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TECHNIQUE OF ORGANIC CHEMISTRY

ARNOLD WEISSBERGER, *Editor*

Volume I:	Physical Methods of Organic Chemistry *Third Edition* — Parts I to IV
Volume II:	Catalytic, Photochemical, and Electrolytic Reactions *Second Edition*
Volume III:	*Second Edition* Part I. Separation and Purification Part II. Laboratory Engineering
Volume IV:	Distillation
Volume V:	Adsorption and Chromatography
Volume VI:	Micro and Semimicro Methods
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Volume VIII:	Investigation of Rates and Mechanisms of Reactions *Second Edition*, in Two Parts
Volume IX:	Chemical Applications of Spectroscopy
Volume X:	Fundamentals of Chromatography
Volume XI:	Elucidation of Structures by Physical and Chemical Methods

TECHNIQUE OF ORGANIC CHEMISTRY

Volume VIII—Part I

INVESTIGATION OF RATES AND MECHANISMS OF REACTIONS

Second Completely Revised and Augmented Edition

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1961

INTERSCIENCE PUBLISHERS, INC., NEW YORK

INTERSCIENCE PUBLISHERS LTD., LONDON

Library of Congress Catalog Card Number 45-8533

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First Edition 1953

Second Revised Edition, 1961

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INTERSCIENCE PUBLISHERS, INC., 250 Fifth Avenue, New York 1, N. Y.

For Great Britain and Northern Ireland:
INTERSCIENCE PUBLISHERS LTD., 88/90 Chancery Lane, London, W. C. 2

PRINTED IN THE UNITED STATES OF AMERICA BY MACK PRINTING CO., EASTON, PA.

INTRODUCTION

Organic chemistry, from its very beginning, has used specific tools and techniques for the synthesis, isolation, and purification of compounds, and physical methods for the determination of their properties. Much of the success of the organic chemist depends upon a wise selection and a skillful application of these methods, tools, and techniques, which, with the progress of the science, have become numerous and often intricate.

The present series is devoted to a comprehensive presentation of the techniques which are used in the organic laboratory and which are available for the investigation of organic compounds. The authors give the theoretical background for an understanding of the various methods and operations and describe the techniques and tools, their modifications, their merits and limitations, and their handling. It is hoped that the series will contribute to a better understanding and a more rational and effective application of the respective techniques. Reference is made to some investigations in the field of chemical engineering, so that the results may be of assistance in the laboratory and help the laboratory chemist to understand the problems which arise when his work is stepped up to a larger scale.

The field is broad and some of it is difficult to survey. Authors and editor hope that the volumes will be found useful and that many of the readers will let them have the benefit of their criticism and of suggestions for improvements.

A. W.

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Rochester, New York

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Investigation of Mechanisms of Reactions

PREFACE TO THE SECOND EDITION

The search for information about the changes which compounds undergo is of the very essence of chemistry, not only because of the end-products formed, but also in view of the intermediates and the transformations which control the over-all reactions. Investigations of the mechanisms of reactions have therefore been undertaken since the beginning of modern chemistry. In recent years they have become one of the most important branches of physical organic chemistry. From a practical point of view, detailed information on the rates and mechanisms of reactions can be most valuable in guiding operations and choosing optimum conditions for synthetic and for analytical work.

This volume is concerned with the theoretical and experimental tools used to establish the mechanisms of reactions. Foremost among these ranks the determination of the rates at which a reaction proceeds as a whole and in its various parts. Several of the physical methods used in the handling of kinetic problems have been discussed in earlier volumes of this series, to which reference is made in order to avoid duplication. But it is the application and adaptation of experimental techniques to the various reactions, as well as the theoretical interpretation of the results, which present the most intricate and highly individual problems. These applications and adaptations, the special methods which have been devised for the study of reaction rates and mechanisms and the relevant theories are discussed in detail; examples of investigations are given as models for related reactions together with appropriate comment on possible variations or refinements.

In the eight years which have elapsed since this was said in the preface to the first edition of this volume, highly significant advances have been made in both the experimental and the theoretical methods for the study of reaction mechanisms, and a new edition rather than a reprinting has become necessary. For this the title of the book has been changed in view of the importance of the non-kinetic methods for the elucidation of reaction mechanisms, and the new edition has been divided into two parts, I dealing with the kinetic methods and II in which very rapid kinetic techniques and the non-kinetic methods are discussed.

TECHNIQUE OF ORGANIC CHEMISTRY

Volume VIII

Investigation of Rates and Mechanisms of Reactions

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CHAPTER I

General Methods of Determining Reaction Mechanisms

E. S. LEWIS, *Rice University*

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I. INTRODUCTION

By the time that structural theory of organic chemistry was well established, it was already clear that the actual number of products from any reaction was far less than could be predicted from the number of atoms of each kind present and the number of structurally satisfactory molecules which could be put together from these atoms. The advent of the application of thermodynamics to chemistry gave grounds for excluding a very large fraction of the conceivable compounds, but even with this limitation the reactions were too specific in that they produced too few products. It became apparent that there were certain pathways from some compounds to others, corresponding to the known reactions, and that the pathways to the substances energetically allowed but not produced are either difficult or nonexistent. The study of these pathways is the study of reaction mechanisms.

Before a more rigorous definition of mechanisms is given it is necessary to describe what is commonly meant by reaction. The term reaction is used in two different senses. Reaction in its first sense is the chemical change represented by a single equation which indicates not only the sub-

stances reacting and produced but also the weight relations between them. This sense is useful for quantitative processes and also for single steps in a multiple step process. Reaction also means the totality of all the changes that occur when the reagents are mixed, or sometimes only the interesting or important changes. In this sense it is proper to say that a reaction produces a mixture of isomers. Since the majority of organic reactions are not quantitative, this usage is common. There will be no attempt here to restrict the term to a single one of these uses.

The description of a geographical pathway between two points can be very complex; a description that would suffice to guide a man would not even mention the major problems of a caterpillar attempting the same route. A more limited set of instructions which might work for either would describe the landmarks along the way, without mentioning the route from one landmark to the next. Similarly, a complete description of the state of a reacting system at every point from start to finish of a reaction is not only impractically complex, but is impossible from the uncertainty principle. We can hope to describe the landmarks on our chemical path, however.

The theory of absolute reaction rates (1) has had a great impact on the study of mechanisms from just this aspect. It defines a state of a reacting system, called the transition state, which is the highest energy point on the path of minimum energy from one stable configuration to the next. Furthermore, a knowledge of the thermodynamic properties for this transition state and those of the preceding stable state suffices to calculate the rate of this process; the path from the stable state to the transition state and the subsequent path is quite immaterial. The landmarks needed to describe the pathway are then the potential minima or stable states along the route which we shall call intermediates, and the transition states between the stable states.

The mechanism can now be defined as a description of all the intermediates and all the transition states passed between the starting reagents and the products. There will be a different transition state for each product containing any particular atom of the reagents, and an additional one for each intermediate. This description may be rather sketchy, with only one intermediate mentioned, or it may go into details about all intermediates and transition states; it will be convenient to call all these descriptions mechanisms and realize that all mechanisms may be improved by being more detailed.

When a mechanism for a reaction is not very detailed, the description of intermediates and transition states may be adequate for more than one reaction; under these circumstances the two reactions may be said to have the same mechanism, or more precisely to have similar mechanisms. Naturally, the more detailed the description, the less will be the chance of apply

ing the mechanism to another reaction. For example, one may start with a general mechanism for aromatic substitution, then go to a more detailed mechanism of nitration of aromatic systems, and finally to a highly detailed mechanism for the nitration of toluene in the *para* position by a nitric–sulfuric acid mixture, which is of very little use in talking about the mechanism of attack by some other electrophile on some other aromatic molecule.

This concept of similar mechanisms has been very fruitful, and is the basis of the understanding of the effect of structure on reactivity. When great detail is sought about a mechanism, one should keep in mind that no two reactions can have exactly the same mechanism. Hence even quite subtle changes in substituents or solvents will change the mechanism in some detail.

II. THE KINETIC APPROACH

1. The Determination of Transition State Properties for Simple Reactions

The transition state has no physical manifestations outside of its influence on the reaction rate. Therefore, only experiments related to rate measurements can give information about the transition state. It will be shown later that rate measurements can also give some information about intermediates in many cases. This accounts for the preeminent importance of rate measurements in mechanism studies.

Reactions can be divided into two groups which may be designated "simple" and "complex" reactions. A reaction can be called "simple" if there is only one transition state between the initial state and the final product. Such reactions are also called "one-step" reactions. All other reactions are then "complex"; these include reactions with intermediates and reactions which yield a variety of products by parallel paths without intermediates.

A simple reaction may be represented by Equation (1),

$$a_1A_1 + a_2A_2 + \ldots + a_iA_i + \ldots \longrightarrow b_1B_1 + \ldots + b_iB_i + \ldots \quad (1)$$

(where a_i is the number of molecules of reagent A_i, etc. One may immediately write the rate law (2) for the reaction (if it is not significantly reversible).

$$d(B_i)/dt = b_ik(A_2)^{a_1}(A_2)^{a_2} \ldots (A_i)^{a_i} \ldots \quad (2)$$

The factor b_i is frequently omitted; its inclusion allows the use of the same rate constant k for the formation of each product and the disappearance of each reagent. Incidentally, a necessary condition for simplicity of a reaction is that the rate law be Equation (2), although this condition is insuffi-

cient. For a simple reaction, then, the only information that can be obtained about the mechanism is contained within the rate constant, and it will therefore be of interest to see what sort of information about the transition state can be obtained from this constant.

The composition of the transition state for a simple reaction is trivial; it contains all the atoms on either side of Equation (1). The thermodynamic properties are obtained from the temperature coefficient of the rate constant using the Eyring equation discussed in another chapter. It is also possible to observe the pressure dependence of the rate and therefore find the volume change on activation. Presumably other less common variables, such as magnetic or electric field, could also be changed to give useful information, although such studies have seldom been made.

A complete knowledge of all structural features of a transition state in principle allows the calculation of the thermodynamic properties, but the calculation of structure from measured properties is not even possible in principle, since there are not enough data. Nevertheless, the structure of a transition state can be approached.

Since the transition state is a minimum energy state with respect to all but one type of motion, many structures can be immediately excluded, and certain others can be excluded because they are obviously too energetic. In this category are specifically those with too few bonds; one attempts to write structures for a transition state containing a maximum number of bonds of a reasonable nature. A simple rule for writing the structure of a transition state is to retain all bonds in the transition state which are present in both the starting reagent and the product, and to give in addition as large a contribution as possible of all the bonds of the reagent which are lost and those of the product which are formed. It is not necessary to abide by the usual rules of valence; in the transition state for the well-known S_N2 reaction one writes carbon with five bonds, for example, and in some atom abstraction reactions a two-bonded hydrogen is written. Rules such as these become less valuable as the activation energy increases, and when the activation energy is sufficient to break several bonds in the reagent there is little justification for writing structures for the transition state strongly resembling the reagent structure. A relation between structure and energy of transition states has been given by Hammond (2). Most of the remaining features of a transition state that can at present be profitably discussed are based on analogies between related reactions, and will be considered later.

2. The Mechanism of Complex Reactions from Kinetics

Rate measurements may also be used to obtain information about the mechanism of complex reactions. Perhaps the first question that should be

asked is whether a reaction is simple or complex, and this can sometimes be unequivocally answered by the kinetic law. If a stoichiometric relation is given by Equation (1) and the rate law is different from Equation (2), then the reaction is certainly complex; if Equation (2) is the rate law then the reaction may be either simple or complex. A rate law often seen for a complex reaction is of the form of Equation (3), in which at least one n_i differs from a_i.

$$d(B_i)/dt = b_i k (A_1)^{n_1}(A_2)^{n_2} \ldots (A_1)^{n_i} \quad (3)$$

In some of these cases one can speak of a rate determining step, a single simple reaction in a complex series, which is slow compared to all the other steps, and alone limits the rate. In this case the transition state for this one step can be treated just like that for an isolated simple reaction, and all the same types of information can be determined. The composition of this transition state is no longer trivial; it is given by the expression $\sum_i n_i A_i$. It should be noted that n may be negative in Equation (3), and that some A which has the coefficient zero in Equation (1) may have an n which is not zero in Equation (3); that substance is then a catalyst.

All the atoms of an intermediate on either side of the transition state are contained within the transition state, therefore the rate law for a reaction with a rate determining step yields information about the composition of the intermediate. For example, the base catalyzed bromination of a ketone (K) obeys the rate equation (4) (Ref. 3).

$$\text{rate} = k(K)(OH^-) \quad (4)$$

The absence of bromine in the rate law shows that the reaction is complex. The transition state for the rate determining step is negatively charged and contains all the elements of the ketone and of the hydroxide ion. One can also conclude that there is an intermediate following the transition state which also does not contain bromine. This intermediate, the enolate ion, need not, and in fact does not, have the same composition as the transition state; it has a molecule of water less. There is one uncertainty about transition state compositions, i.e., if it is not possible to vary the concentration of a reagent (A_i) in the experiments, then the order (n_i) of the reaction with respect to that reagent can not be determined, and therefore the number of molecules of that reagent in the transition state is uncertain. The most common situation of this sort occurs in solution reactions in which the solvent is always of unknown order in the rate law, and the solvent content of transition states is always uncertain.

Many reactions are complex without having a rate determining step. This is the case when successive steps of a reaction go at comparable rates,

and is also the case with chain reactions. In these cases the rate is not always given by an equation like (3), but is often of a complicated form. The rate law is not related to any one step, but is dependent on several. The rate expression does not yield information about a single transition state or intermediate, but by virtue of this complexity a new sort of information is given. It is difficult to derive the mechanism from the rate law, but it is possible to predict the rate law that would result from a particular proposed mechanism. If a proposed mechanism predicts a rate law in agreement with experiment, then the mechanism is worthy of further consideration. If it fails to agree with experiment then it must be discarded, no matter how attractive it may otherwise seem. One can not expect to find the correct series of intermediates by this procedure alone; it very frequently happens that a demonstrably false mechanism will predict the correct kinetic law. The original suggestion of a particular series of intermediates is usually derived from an established series for an analogous reaction, or by the exercise of ingenuity. The final choice between two series of intermediates which predict the same rate law must then be made by nonkinetic methods, or by analogy to other reactions.

3. The Measurement of Rates

There are several serious experimental problems connected with the establishment of the rate law. The desired result is the relation between the rate and the concentration or pressure under a variety of different experimental conditions. No single technique is satisfactory for all reactions. Thus the common method used on solutions of abstracting a sample with a pipet and then titrating the sample for a reagent or product is unsuitable if the reaction occurs to a significant extent during the sampling and the analysis. Normally this method is limited to reactions which do not proceed significantly in a minute or so. Methods in which the extent of reaction is given by the reading of an instrument within the reaction mixture avoid the sampling problem but do not avoid the problem of the mixing of the reagents at the beginning of the reaction. Methods in which the reading of an instrument is made at various times after the start of the reaction can be used on faster reactions; reactions with half lives of a few seconds can be readily followed.

It is more practical for many still faster reactions to resort to a flow system. Then the necessity for fast work disappears and in principle the reaction rate can be directly related to the flow rate, and the only analysis required is an indication of the extent of reaction which often can be obtained with an instrument which need not have a fast response, since it is possible to work with a steady state. Reaction rates can be determined

also by any device which allows comparison of the rate with the rate of some other process. It has been possible to use other reactions, diffusion, heat flow, and nuclear relaxation for the comparison process.

The measurement of the rates of very slow reactions offers special problems. It is usually considered inconvenient to take more than a month or so to conduct an experiment. The measurement of rates for which this period corresponds to a very small extent of reaction then calls for special methods of detection. A particularly ingenious analysis based upon a variant of isotopic dilution has allowed the measurement of a reaction with a half life of up to 10^5 years in experiments lasting only a few weeks (4).

In general, methods for following reactions call for techniques of a varied sort, and each technique includes an analytical procedure which must be suitable for the numerous experiments necessary for a complete kinetic study. There is for this reason a premium on speed and simplicity of analysis, which can often be attained by sacrificing the generality of the more familiar methods. Thus density measurements have almost no use for analyzing a random complex mixture, but when the problem can be reduced to the probing of the extent of completion of one reaction, the dilatometric method has been frequently used. Because of analytical difficulties, there have been very few studies in which the time dependence of the concentration of several different substances in the same reaction have been studied.

Once the experimental problem of measuring the rate or, more usually, measuring concentrations as a function of time is completed, there still remains the problem of converting these data to a differential equation which gives the rate as a function of concentrations. A very general method is to get the rate from the data by a graphical or numerical differentiation. The rate and the reagent concentrations can then be compared and the relations can be seen, especially if each concentration is varied independently. More commonly, the observed concentration dependence on time is compared with that calculated for a few rate laws in integrated form. If a reaction is carried to over 80% completion or more, it is very easy to distinguish by this last method between small integral reaction orders, and the evaluation of the rate constant is more precise than it is by any differentiation method which does not use as many data. When the use of an integrated rate expression is impractical in the general case, it is possible to design the experiment in such a way as to reduce the complexity of any given run by making the concentrations of one or more reagents nearly constant during the run. This can conveniently be accomplished by having these reagents in substantial excess. By this method the use of integrated rate equations becomes very general, and is usually the method of choice, even though it requires extra experiments to determine the rate law.

4. The Significance of the Rate Constant and Its Change with Structure

It has been suggested that knowledge of the rate law leads to many conclusions about the reaction mechanism. In addition further information may be gleaned from the rate constant itself. If, for a given proposed mechanism for a specific reaction, it were possible to calculate the rate constant, then one could compare the calculated constant with the observed one and then get strong confirmation for the assumed mechanism or a clear demonstration that it is wrong. While the theory of absolute reaction rates claims to allow this calculation from first principles, the practice is so involved that it has been carried out only on the simplest reaction, and there is no guarantee that the theory is adequate for the more complicated cases even if it could be applied. Reasonable estimates of reaction rates and activation parameters can now be made for a particular reaction if the corresponding values for a related reaction are known. A related reaction in this sense is often the same reaction except that one reagent is somewhat different in structure. The study of the effect of structural changes on rate of reaction has been extensively pursued recently and the list of examples where good interpolation or extrapolation can be made is steadily growing.

When big changes in structure are made, the calculation of rates may be quite unreliable, but some structural changes will make a particular mechanism impossible, and the observation of a complete lack of reactivity in this case then supports the suggested mechanism for the substances which do react. The inverting attack by nucleophiles on alkyl halides is impossible when the halogen is on the bridgehead of a small bicyclic system; the unreactivity of such molecules to this attack strongly supports the Walden inversion mechanism for the reactive halides (5). As another example, the resistance of *β-tert*-butylacrylic acid to decarboxylation is evidence for a mechanism for the decarboxylation of other α,β-unsaturated acids by way of the β,γ-unsaturated acid, which in this particular case is an impossible isomerization (6). Many other examples in which a mechanism becomes impossible for steric reasons, or because a necessary structural feature (which does not apparently react) is missing, have also been used with success.

Less drastic structural changes can be expected to lead to smaller rate changes. The separation of the effects of changing substituents into a variety of component effects has been fruitful and moderately successful, and the common initial separation has been that of electronic from steric effects (7). In a variety of cases the latter can be ignored and the prediction of rates can now be made by a variety of methods stemming from that of Hammett for many reactions of aromatic systems (8). In aromatic

systems correlations have been extended to highly electron deficient systems (9). Additionally, aliphatic systems are now susceptible to treatment (10), nucleophilic reagents may be varied (11), and solvents for ionic reactions can be changed (12), all with some confidence in the predictive value of the correlations. In this way it is possible to tell if a new reaction has a mechanism similar to that of some related reactions, since the rate will agree with that estimated if the mechanism is similar. The sensitivity of the rate to structural variation (for instance, the Hammett ρ value) will itself give information about the mechanism. The hydrolysis of substituted benzoyl chlorides has a positive ρ (8); one may then conclude that nucleophilic attack by the solvent is important, and the mechanism does not involve the rate determining formation of the oxocarbonium ion. Since water is the solvent this conclusion could not have been drawn from inspection of the rate law. Reactions in solution which involve charge changes have qualitatively understood solvent sensitivity; the intermediacy of ions, for instance, can be suggested when the solvent sensitivity is similar to that for the solvolysis of a tertiary alkyl halide. Actually the conclusion that the transition state is highly polar is well demonstrated by this sort of result, but the conclusion that the products of the rate determining step are ions is less soundly founded.

One of the most subtle substitutions on a molecule is the change from one isotope to another. If it is assumed that the potential energy is unaltered by isotopic substitution, then the effects must be kinetic in nature; one can then hope to get information about the vibrations of the transition state. Since changes in vibrations on activation appear to suffice to explain most isotope effects, the assumption about the absence of potential energy effects seems well justified. The most common reason for a greatly altered vibration on activation is that a bond involving the isotopically altered atom is being broken in the transition state. The location of the bonds which are broken in the rate-determining step is the principle common use of isotope effects in mechanism studies. There is also an improved familiarity with the much smaller secondary isotope effects, i.e., those not involving a breaking bond, so that some mechanistic conclusions can be drawn from the magnitudes of these effects also. A general theory of isotope effects aids greatly in the interpretation of experiments (13).

III. THE NONKINETIC APPROACH

1. Simple Reactions

We have said that the knowledge of the mechanism of simple reactions is complete if we can describe the reagents, the products, and the transition state. The further limitation that only kinetic methods can give informa-

tion on the transition state leaves for any other study only the description of the reagents and the products. Nevertheless, certain studies of these materials are of a type that would seldom be made except to investigate the mechanism. One such study is concerned with the stereochemistry of the product and its relation to that of the reagent; another is concerned with the fate of individual atoms, which can be shown by isotopic or substituent tagging.

As an example of the first of these, the one-step S_N2 reaction was shown to involve the attack of the reagent from the side of the carbon opposite to that of the leaving group, since in the case of optically active secondary alkyl halides the product was shown to have a configuration opposite to that of the starting material. The rearrangement step in the Arndt-Eistert reaction was shown to be a real rearrangement of the carbon skeleton rather than an oxidation-reduction process along the chain by the following demonstration ($C^* = C^{13}$), which is an example of isotopic tagging (14):

$$RC^*OCHN_2 + H_2O \longrightarrow RCH_2C^*OOH + N_2$$

The stereochemical and tracer methods are of particular use in determining the details of structure for individual steps in complex reactions.

2. Complex Reactions

The easiest demonstration that a reaction is complex is to show that a given starting material has more than one ultimate fate, which is to say that the product is a mixture of more substances than can be accounted for on the basis of a single stoichiometric equation. If this is the case, clearly more than one transition state is involved and the reaction is complex. The complexity exists even if two products differ in an extremely subtle manner, such as in stereochemistry or in the distribution of an isotopic tag. The observation that the solvolysis of an optically active alkyl halide yields a partly racemized product shows that there are at least two paths, one leading from *d*-reagent to *d*-product, the other leading to *l*-product. These two transition states may be quite different in nature, and indeed are so unless the product is totally racemic. In this event it is customary to assume the existence of an intermediate incapable of optical activity which leads via mirror image transition states to the two products. It is interesting to note that a transition state can not have more symmetry than the stable states surrounding it and may have less, except in the chemically unimportant reactions (of which the reaction of an alkyl iodide with iodide ion may be an example) where the energy versus reaction coordinate curve is symmetrical about its maximum. Thus the transition states to and from the carbonium ion (with a plane of symmetry) derived from an asymmetric

alkyl halide do not have a plane of symmetry, even though the resulting product is totally racemic.

Complexity is also shown by a multiplicity of fates of tagged atoms. Thus, the fact that terminally tagged benzenediazonium ion reacts with azide ion to give phenylazide containing some but not all of the label of the starting material shows that more than one route is involved. The complete retention of the nitrogen attached to the ring shows that no part of the reaction is a nucleophilic attack on the ring (15). This example illustrates how an examination of the reaction products shows not only that the reaction is complex but also leads to conclusions about the structures of intermediates and transition states.

The study of the nature and distribution of the products gives far more information than merely a demonstration of complexity, which is often not a serious problem. Even a study of the yield of the principle product can be informative. The presence of unreacted starting material in the reaction mixture indicates either that the reaction time was insufficient, or that the extent of reaction was limited by reversibility. Clearly, a new yield determination with a longer reaction time will tell if the limitation is one of rate or equilibrium. When the rate limits the yield, a series of yield measurements under varying initial conditions will give a crude estimate of the influence of the conditions on rate. This method is particularly useful when estimating the effect of structural changes on the rate from literature values of yields determined in the course of a series of preparations. Because the isolation and purification of reaction products is seldom quantitative, such information should be used with caution. The other contributors to poor yields are the destruction of the reagents by side reactions and the destruction of the product wanted by a further step. Under these conditions it is desirable to determine the yields of the by-products, for this is a rich source of quantitative information that is difficult to obtain by kinetic methods. It can be shown that the ratios of the yields of two substances can give the ratios of the rate constants for their formation, even in cases where these steps are not rate determining. This makes product analysis the method of choice for studying relative reactivities of stable intermediates, and for studying relative reactivities of stable molecules when the rates are too fast or too complicated to measure directly. An example is the study of relative reactivities at different points in the same molecule. The principal source of modern knowledge of aromatic substitution comes from a study of the directive effects of groups on the aromatic system. The existence of *ortho-para* orientation in nitration, for example, led to the idea that the attack was by an electron demanding reagent before this or any other electrophile had been identified by kinetic or other methods. The entirely different orientation rules in the Gomberg

reaction (16) showed clearly that this reaction did not involve electrophilic attack. Incidentally, further work of a far more refined nature than a rough product analysis has not yet advanced the mechanistic knowledge very much beyond this point.

It should be noted that the process of determining mechanism by product analysis can be reversed, so that a knowledge of the mechanism can lead to predictions about the yields of all products. Conditions for maximizing the yield of the desired product can thus be selected in advance. An example is the development of the high dilution technique to close large rings. This procedure favors the unimolecular ring closure over the kinetically higher order competing polymerization. The improvement of synthetic methods is one of the important practical applications of studies of mechanisms.

Before quantitative analysis for reaction products can be undertaken, it is clear that a qualitative analysis must be done. The identification of certain types of substances from a reaction mixture can itself lead to mechanistic conclusions. This information is of particular value when a very complicated mixture is encountered, which is often the case in radical chain reactions. The isolation of biacetyl from the photolysis of acetone, for example, gives credence to the suggestion that the acetyl radical is an intermediate (17). Naturally, the conclusions based on observations of this sort are more convincing when the result can be shown to be in quantitative agreement with the proposed mechanism.

3. Intermediate Detection

Evidence showing that an intermediate is present during a reaction is sufficient to prove complexity and will also give information on the nature of the intermediate detected. Since the intermediate plays such a large part in the mechanism, much effort has gone into the problems of detecting and estimating these often elusive substances. When possible, a physical method such as spectrophotometry is desirable since it can characterize as well as give the concentration of the intermediate. The sensitivity of these methods is constantly improving, and the necessary instruments are becoming a more common part of the standard organic chemistry laboratory. We can expect these methods to become increasingly important to intermediate studies. However, many of the intermediates of organic chemistry are so fleeting that their concentrations are far too low to be detected by known physical methods; recourse can still be made to purely chemical methods. The most common technique is to add a new reagent which will react with the intermediate to gave a detectable product. It is then necessary to know the chemistry of the intermediate.

The study of the chemistry of intermediates is a problem in itself. When an intermediate can be isolated from the reaction or from a different reaction, its chemistry can be studied by conventional methods. More commonly, the proposed intermediate is too reactive to be isolated from any reaction, but by the use of the methods outlined earlier, one can estimate the reactivity by extrapolating from the reactions of known stable substances. Thus, the study of the chemistry of triphenylmethyl and its derivatives has greatly facilitated the study of unstable free radicals. Similarly, isolable carbonium ions and carbanions show most of the reactions of the more unstable ionic intermediates in organic reactions (18). Information of this sort can then be used to select a reagent to react with a suspected intermediate and divert it from its usual fate to a more informative one.

The diversion of intermediates has been especially fruitful in free radical chemistry. A classic example was the detection of methyl radicals in various pyrolytic reactions by the reaction with thin metallic mirrors (19); the disappearance of the mirror was a conspicuous indication of the presence of the radicals. The use of stable radicals, such as nitric oxide or oxygen, and substances which react readily with radicals, such as iodine or propylene, have proven very useful as homogeneous radical traps. The more complicated organic inhibitors of chain reactions are also traps for various types of free radicals, but they have been used mostly in kinetic studies to show the interception of the intermediate radical, since the product of the inhibition step is difficult to isolate. Outside the field of free radicals several traps have been used with success. Carbonium ions have been detected with azide ion (20) or halide ions (21,22), carbanions have been trapped with halogens and with isotopic protons (8), divalent carbon reacts with thiophenoxide ion (23) and with olefins (24), the diene intermediate in the *para* Claisen rearrangement was intercepted with maleic anhydride (25) and the benzyne intermediate reacts with dienes (26). It is sometimes necessary to couple such product evidence for interception with kinetic evidence to show that the new product is not formed directly from the starting materials. When an authentic case of intermediate interception has been found, quantitative analysis for the new product will give relative reactivities of the intermediate by its normal route and by its new route with the trap.

IV. CONCLUSION

Several methods for the study of reaction mechanisms have been outlined, using both kinetic measurements and methods which do not involve time. These methods do not constitute a complete list of available tech-

niques; it should be emphasized that any observation which is not completely predictable from the thermodynamic properties of the reagents and the products will give some information about the mechanism. The methods touched upon in this chapter and those described in more detail in subsequent chapters have been the ones which have so far been the most successful. It is hoped that more will be found.

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CHAPTER II

GENERAL THEORY OF RATE PROCESSES

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I. INTRODUCTION

With few exceptions, students of the theory of reaction kinetics have been interested in only those problems for which a reasonably rigorous solution appeared possible. As a result, theoretical progress has been limited largely to uni- and bimolecular, gas-phase interactions between simple molecules, and to a few artificially selected cases (of little general interest) of the influence of media upon reaction velocity. Cases of real chemical interest are usually essentially complex, and their exact analysis is too difficult for available theoretical tools. However, the results obtained for simple reactions constitute an invaluable guide for the more intuitive interpretation of complex reactions. In addition, the theorists have provided us with reasonably dependable solutions of specific problems of immediate practical value. These include the effect upon the rate of isotopic substitution, and, in a more formal way, the effect of changing *m* or *p* substituents of aromatic reactants. A complete systematic interpretation (although not prediction) of the effect of solvents upon reaction velocities is also available.

The kinetics of real reactions of chemical importance are almost invariably complex, in the sense that the observed chemical change is the result of the simultaneous occurrence of a number of reaction steps. Their interpretation is commonly left to the experimentalist, who all too often is content with the use of crude analogies or of empirical rules of uncertain reliability and of doubtful applicability. Reasoning by analogy is probably of greater utility in the study of reaction mechanisms of organic chemistry than of inorganic chemistry (where it is practically worthless), but there is no reliable substitute for a complete kinetic analysis of extensive experimental measurements. Unfortunately, such studies are time-consuming and laborious, and the literature of organic chemistry contains few satisfactory examples of such investigations. The whole subject of organic mechanisms can scarcely be considered to be on a sound basis until at least one example of each type of reaction has been subjected to a careful and exhaustive kinetic study.

II. THE COLLISION THEORY

1. Determination of Collision Frequency

Probably the most direct method of evaluating the rate of a simple reaction is to calculate the number of collisions which the reactant molecules, contained in unit volume, will make per second, and then to attempt to determine the fraction of these collisions which will result in chemical

change. It is not possible to calculate exactly the number, Z, of binary collisions for the general case, where the molecules are nonspherical and attract one another. However, we can obtain some idea of the magnitude of Z in the general case by treating the special case of an ideal gas consisting of spherical molecules which exert no force of attraction upon one another.

To compute the number of collisions which a certain molecule will make with all other molecules in one second, it would be convenient for us to put the origin of our coordinate system at the center of the chosen molecule and to sum up the rates of collisions with all other molecules, taking into account their relative velocities and positions. While this can be done rigorously and without the use of too advanced mathematical methods (1–3), it is probably sufficient for our present purpose to use the following simplified approach (4). Instead of keeping the one molecule fixed (by making it the origin of our coordinate system) and allowing for the normal relative motions of all other molecules, let us assume that all of these other molecules are frozen in their instantaneous positions but that the chosen molecule is moving with such a velocity, u', that it will make the same number of collisions that it would have experienced if it had remained constant and the other molecules had executed their normal motions relative to it. This defines the velocity, u'. The length of the path through which this molecule will move in one second is u' (cm./sec.) $\times$ 1 second. It will simplify the problem, without changing the results, if we assume that all of the fixed molecules are mass points and that the moving molecule has a radius, σ, equal to its actual diameter. The cross section of the moving molecule is thus taken as $\pi\sigma^2$, and it will sweep out a volume of $\pi\sigma^2 u'$ cc. in a time of 1 second. If n is the number of molecules contained in 1 cc., the number whose centers will lie in the volume swept out by the moving molecule is n times the ratio of these volumes or $n\pi\sigma^2 u'$. This is equal to the number of collisions that the chosen molecule makes per second with all other molecules. Since this molecule is in no way distinguished from the others, the total number of molecules colliding per cubic centimeter per second is $n^2\pi\sigma^2\ u'$. However, since two like molecules enter into each collision, the total number, Z, of collisions per cubic centimeter per second is $^1/_2 n^2\pi\sigma^2 u'$. To compute the value of u' would be somewhat more difficult; however, it is approximately equal to the root mean square velocity, $\bar{u}$. $u' \approx \bar{u} = (3RT/M)^{1/2}$ where M is the molecular weight and R is the gas constant in ergs per mole per degree. Therefore:

$$Z \approx (\pi/2)\ (3RT/M)^{1/2}\sigma_i^2 n^2$$

A more exact derivation leads to the following slightly different expression:

$$Z = 2(\pi RT/M)^{1/2}\sigma_i^2 n^2 \qquad (1)$$

The corresponding expression for the total number of collisions per cubic centimeter per second between unlike molecules (A and B), whose concentrations, in molecules per cubic centimeter, are n_A and n_B, is:

$$Z_{AB} = 2[2\pi RT(1/M_A + 1/M_B)]^{1/2}\sigma_{AB}^2 n_A n_B \qquad (2)$$

where σ_{AB} is the mean of the molecular diameters.

In Equations (1) and (2), all the quantities, with the exception of σ_i, the collison diameter, are known or can be readily determined. The most satisfactory way to evaluate σ_i is in terms of measurement of the viscosity of the gas (5). This procedure tends to cancel out any errors that may be present in the equations which relate the molecular diameter to the number of collisions or to the viscosity. The diameters of all ordinary gases lie in the range 2 to 6 $\times$ 10^{-8} cm. Table I lists values typical of Z, computed for the case of HI, taking σ equal to 3.4 $\times$ 10^{-8} cm. The symbol A represents Avogadro's number, 6.023 $\times$ 10^{23}.

TABLE I

Computed Values of Z and $(Z/A) \times 10^3$ for HI

$T°$, K.	n, molecules/cc.	Z, molecules/cc. sec.	$2(Z/A) \times 10^3$, moles/l./sec.
298	2.44×10^{19}[a]	3.4×10^{28}	1.1×10^{8}
596	2.44×10^{19}[a]	4.8×10^{28}	1.6×10^{8}
298	6.02×10^{20}[b]	2.1×10^{31}	6.8×10^{10}
596	6.02×10^{20}[b]	2.9×10^{31}	9.7×10^{10}

[a] Equals 1 atm. at 298°K.

[b] Equals 1 mole per liter.

2. Energy of Activation

The quantity $2(Z/A) \times 10^3$ is the rate in moles/l./sec. which the reaction (in this case $2HI \rightleftharpoons H_2 + I_2$) would have if every collision resulted in chemical change. The inordinately large value of this quantity demonstrates that only a small fraction of all collisions leads to reaction; otherwise all chemical reactions that occur at all would be instantaneous. When it is remembered that the H—I bond must be broken before (or as) the H—H and I—I bonds are formed, it is not surprising that the pair of colliding molecules must have available more than the average thermal energy if they are to react. Another way to state this is that, as the molecules react, their atoms must pass through a configuration which has a higher potential energy than either the reactants or the products. These states and their potential energies are represented crudely by Figure 1. The difference between the potential energies of the reactants and the transi-

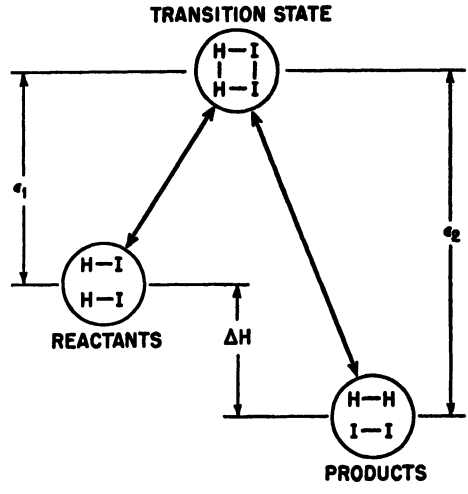


Fig. 1. Potential energy scheme for a bimolecular reaction.

tion state is represented by ϵ_1 on Figure 1. It is called the energy of activation. A necessary condition before a chemical reaction can occur when the two molecules collide is that the pair of molecules have an amount of energy available for the process of activation equal to or greater than ϵ_1. Not all the energy that the colliding molecules possess is available for activation. For example, kinetic energy of the system, which is associated with the components of its momentum at right angles to a line joining the centers of the colliding molecules, will appear after the collision as kinetic energy of the system and is not available for the process of activation. To compute the rate of a chemical reaction, we must be able to determine the fraction of all of the collisions at which the available energy exceeds the energy of activation, ϵ_1.

The larger the energy associated with the quantum state of a molecule the less probable is that state. The relation between the fraction, N_j/N, of the total number of molecules which are in the jth state, the energies ϵ_i, and *a priori* probabilities, p_i, of the several states is given by the Maxwell-Boltzmann equation, which can be written as follows:

$$N_j/N = p_j \exp(-\epsilon_j/kT)/\sum_i p_i \exp(-\epsilon_i/kT) \qquad (3)$$

where k is the Boltzmann constant, R/A (6–8). The *a priori* probability or statistical weight, p_i, of a state is a measure of its degeneracy (9) and is usually equal to unity or a small positive integer. The problem that is of interest in ordinary chemical kinetics is to determine the fraction of the molecules which are in states having energies, ϵ_i, in excess or equal to some

definite value ϵ. If ϵ/kT is large, the following equation is a reasonably accurate approximation.

$$N(\epsilon_i \geqq \epsilon)/N \backsimeq (\epsilon/kT)^{(1/m-1)} \exp(-\epsilon/kT)/(1/2n - 1)! \qquad (4)$$

where n is the number of "square terms" (10) among which the energy is distributed. As an example, in a gas, translational motion contributes three terms (associated with $KE_i = 1/2m(dx_i/dt)^2$); rotational motion contributes three, two, or no terms, depending upon the complexity of the molecules—associated with $KE_i = 1/2I_i\omega_i^2$; and each vibrational degree of freedom contributes two terms—associated with $PE_i = 1/2k_ir_i^2$ and $KE_i = 1/2\mu_i(dr_i/dt)^2$. With the exception of the monomolecular decomposition of complex molecules, it is usually sufficient, for the analysis of chemical kinetics in terms of simple collision theory, to assume that only two square terms contribute to the energy of activation: for example, all the energy of each of the colliding molecules associated with their components of velocity parallel to a line joining their centers at the moment of impact. When the numbers of square terms equals two, the fraction of the molecules having energy equal to or greater than ϵ is given by the following relatively simple expression:

$$N(\epsilon_j \geqq \epsilon)/N = \exp(-\epsilon/kT)$$
$$= \exp(-E/RT) \qquad (5)$$

The product of the total number, Z_{AB}, of collisions between molecules A and B and the fraction, $\exp(-\epsilon/kT)$, of all pairs of molecules which have energies available (in the two pertinent square terms) equal to or in excess of some quantity, ϵ (ergs per molecule), is equal to the number, $Z_{AB}(\epsilon' \geqq \epsilon)$, of such collisions having energy available for activation equal to or greater than ϵ:

$$Z_{AB}(\epsilon' \geqq \epsilon) = Z_{AB} \exp(-\epsilon/kT)$$
$$= 2[2\pi RT(1/M_A + 1/M_B)]^{1/2}\sigma_{AB}^2 \exp(-\epsilon/kT)n_An_B$$

If Z is the value of Z_{AB} when $n_A = n_B = 1$ molecule per cubic centimeter, the proceeding equation may be written as follows:

$$Z_{AB}(\epsilon' \geqq \epsilon) = Z \exp(-\epsilon/kT)n_An_B \qquad (6)$$

If the energy, ϵ, is equal to the *energy of activation* for the reaction, $Z_{AB}(\epsilon' \geqq \epsilon)$ should be equal to or greater than the rate of the chemical reaction expressed as molecules per cubic centimeter per second. Strictly speaking, the *energy of activation* is the difference between the average total energy of all colliding pairs of molecules which react and the average total energy of all corresponding pairs of molecules (11–13).

The results of experimental studies of reaction rates are commonly expressed (14) as moles per liter per second. Equation (6) may be modified to be consistent with this practice:

$$-(d[\mathrm{A}]/dt)_{\max.} = (10^3/A)Z_{\mathrm{AB}} = (A/10^3)Z \exp(-E/RT)[\mathrm{A}][\mathrm{B}]$$

where the quantities in the square brackets, [A][B], etc., represent molar concentrations. It should be noted that while R in the exponent of the preceding equation has the same units as E/T (usually calories per mole per degree), when R occurs under the radical sign of Equations (1), (2), and (6) it must be expressed in ergs per mole per degree.

3. Steric or Probability Factor

Not all of the pairs of molecules which have the necessary energy of activation will react upon collision. Other conditions, such as the relative orientation of the molecules at the moment of impact, must be satisfied before the collision can result in chemical change. To illustrate this, if two HI molecules were oriented as shown in Figure 2a, the breaking of

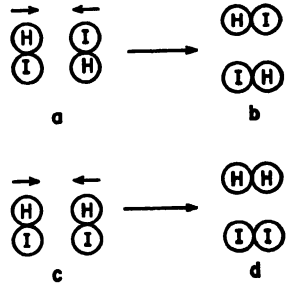


Fig. 2. An illustration of steric effects.

their H—I bonds could lead to only one probable chemical reaction—the formation of two new HI molecules, chemically indistinguishable from the original pair. However, if the orientation were as shown in Figure 2c, the breaking of the original H—I bonds would very probably lead to the formation of an H_2 and an I_2 molecule. While it is very difficult to modify the simple collision theory to take such effects quantitatively into account it is certainly justifiable to introduce an undetermined factor, p, into Equation (6) to allow for such effects:

$$-d[\mathrm{A}]/dt = -p(d[\mathrm{A}]/dt)_{\max.} = p(AZ/10^3) \exp(-E/RT)[\mathrm{A}][\mathrm{B}] \quad (7)$$

The quantity p is called the steric or probability factor. The corresponding empirical rate equation for a bimolecular reaction is:

$$-d[\mathrm{A}]/dt = k[\mathrm{A}][\mathrm{B}] \tag{8}$$

Combining Equations (2), (7), and (8), the following expression for the "rate constant" k is obtained:

$$\begin{aligned} k &= p2A\ 10^{-8}(2\pi RT[M_{\mathrm{A}}{}^{-1} + M_{\mathrm{B}}{}^{-1}])^{1/2}\sigma_{\mathrm{AB}}^{2} \exp\ (-E/RT) \\ &= pAZ\ 10^{-8} \exp\ (-E/RT) \end{aligned} \tag{9}$$

Before we can evaluate k in terms of this equation it is necessary first to determine or estimate values of σ_{AB}, E, and p. Of these quantities, σ is the only one for which there exists a practicable method of evaluation that is completely independent of the kinetic measurements. For the present purpose, σ is best evaluated in terms of viscosity measurement (15). For an ideal gas made up of spherical molecules (16).

$$\sigma^2 = 1.89 \times 10^{-21}(TM)^{1/2}/\eta$$

where η is the measured viscosity in c.g.s. units. Approximate values of σ can also be obtained from determinations of van der Waals' b or from the density of the compound at low temperatures (17). For simple molecules, the experimental values of σ lie in the range 2 to 6 $\times$ 10^{-8} cm. For complex molecules the assumption that the collisions are between spherical non-attractive molecules is so unrealistic as to render Equation (9) useless except as a limiting law.

4. Temperature Coefficient of Reaction Rate

It should be possible to calculate the value of E if complete structural information regarding the reactant molecules and the reaction complex were available. In practice this is never the case, and E is evaluated empirically in terms of the temperature coefficient of the rate constant. Letting B represent its temperature-independent factors, Equation (9) may be written as follows:

$$k = BT^{1/2} \exp\ (-E/RT)$$

Taking logarithms of both sides and differentiating with respect to T, the following equation is obtained:

$$d(\ln k)/dT = {}^1/_2 d(\ln T)/dT + E/RT^2 = ({}^1/_2 RT + E)/RT^2 \tag{10}$$

For most reactions which have been studied ${}^1/_2 RT$ is much less than E, and in these cases the approximate relation:

$$d(\ln k)/dT \approx E/RT^2$$

suffices for the evaluation of E.

From a quantitative viewpoint, the probability factor, p, is little better than an arbitrary correction factor, introduced to render the simple collision theory consistent with the observed reaction rate. In this sense, it is an empirical coefficient defined by the relation:

$$p = (10^3 k/AZ) \exp (E/RT)$$

However, the essential validity of the collision theory is supported by the observation that values of p relatively close to unity occur most commonly for gaseous reactions between simple molecules. For reactions involving more complicated molecules, where more stringent "steric" factors might be expected, values of p many orders of magnitude less than unity have frequently been observed. This subject has been discussed exhaustively by Moelwyn-Hughes (18).

5. Collision Frequency in Condensed Phases

There is relatively little uncertainty in the calculation of the number of collisions between simple molecules existing in a gaseous phase. The kinetic theory of liquids is more complex, and correspondingly there is much greater uncertainty in the calculation of the number of collisions between solute molecules in a liquid solution. For ideal solutions in which the size of the solute molecules is comparable to that of the solvent molecules, it may be shown by a statistical mechanical analysis (19) that the number of collisions between solute molecules and the distribution of energies among these collisions is little affected by the presence of the solvent. It is, therefore, to be expected that the rates of reactions between simple molecules in ideal solutions can be represented by Equation (9). The empirical values of the coefficient, p, do not diverge much more from unity for such solution reactions than they do for the corresponding gas-phase reaction (20).

Although the solvent does not appreciably alter the total number of collisions, it does greatly change their distribution in time. Solvent molecules form a cage around each pair of colliding solute molecules and so tend to prevent them from separating after a single collision. As a result, the collisions between a pair of solute molecules in liquid solutions occur in bursts, separated by periods (21) during which there will be no collisions. If the product $p \exp (-E/RT)$ is so small that the ratio of the total number of collisions to the number of collisions resulting in chemical change is large compared to the average number of collisions in a burst, the time distribution of collisions will not greatly affect the rate of the reaction. The

calculation of the average number of collisions which will immediately follow each encounter of a pair of solute molecules is very difficult, and only crude estimates of this number are at present available (22). However, for all ordinary chemical reactions, the factor $p \exp(-E/RT)$ is such a small number that we can be reasonably sure that the preceding condition is satisfied. There are a few types of reactions (notably the quenching of fluorescence of excited molecules, certain reactions involving atoms or radicals, etc.) for which the probability of reaction at every collision approaches unity. The rates of reactions of these types are proportional to the number of encounters, and are, therefore, governed by the speed of diffusion of the solute molecules (23). Their specific reaction rates do not correspond even crudely to Equation (9), but can be represented to a first approximation by the following relation (23).

$$k_D = 8RT/(3 \times 10^3 \eta) m^{-1} \text{ sec.}^{-1}$$

6. General Solvent Effects

In nonideal solutions, the rates of reaction are strongly influenced by the presence of the solvent. Both the "temperature-independent" factor $10^{-3} pAZ$, and the temperature-dependent factor $\exp(-E/RT)$ are affected. These effects are greatest for reactions involving ions or molecules with permanent dipoles. While these solvent effects can be treated from the viewpoint of the collision theory (24), their analysis is, at least superficially, simpler in terms of the transition state theory. For this reason, their discussion will be postponed to the following section.

III. THE TRANSITION STATE THEORY

1. Concept of the Transition State

In a reaction such as the decomposition of HI, the four atoms, starting from a molecular arrangement which corresponds to the reactants and going to one corresponding to the products, pass through a series of configurations differing from either stable pair of molecules. One of these intermediate configurations, which is less stable than any other occurring on the reaction path, is called the *transition complex*, X. The potential energy of a reacting set of molecules can be represented by a diagram similar to the potential energy diagram of a diatomic molecule. In Figuer 3, which is the diagram of an HI molecule (in its electronic ground state), the coordinate r is a direct measure of the separation of the two atoms. Motion to the right along the

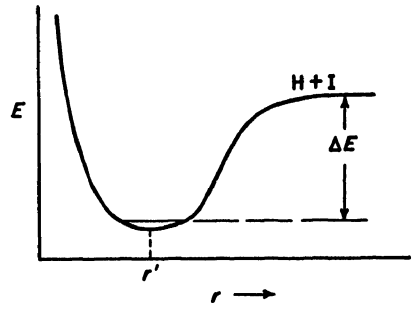


Fig. 3. Potential energy curve for an HI molecule in its electronic ground state.

flat part of the curve represents increasing separation of the two atoms, which are already so far apart that their forces of interaction are negligibly small. The quantity ΔE is the energy of dissociation of the molecule into normal atoms (measured from the oscillational ground state). Figure 4 (page 27) corresponds to the bimolecular decomposition of HI. For this more complex system, a generalized coordinate, representing the configuration of all of the atoms, is plotted as abscissa. This coordinate corresponds to the transition along the reaction path from reactants to products. For example, any point on the flat part of the curve left of the hump represents two HI molecules (with their normal bond lengths, r' of Figure 3), and motion away from the central hump indicates increasing separation of the two molecules, which separation is limited only by the size of the reaction vessel. The thermochemical energy of the reaction corresponds to the length ΔE; the energy of activation, to $\Delta E^{\ddagger}$.

2. Equilibrium between the Reactants and the Transition State

The transition complex, while relatively unstable, consists of a definite configuration of atoms, and as such has a real concentration, [X]. In an equilibrium system, composed of opposing bimolecular reactions, the set of reaction steps which make up the dynamic equilibrium is:

$$A + B \underset{-1}{\overset{1}{\rightleftharpoons}} X \underset{-2}{\overset{2}{\rightleftharpoons}} M + N$$

and the equilibrium concentration of the complex is given by the following relations:

$$[X] = K^{\ddagger}[A][B] = K'^{\ddagger}[M][N] \tag{11}$$

If the concentrations [M] and [N] of the products are very much smaller than their equilibrium concentrations, the rate of the back reaction (step 2) can be neglected and the set of reaction steps may be represented as follows:

$$A + B \underset{-1}{\overset{1}{\rightleftharpoons}} X \xrightarrow{2} M + N \tag{12}$$

Under these conditions it might be expected that the concentration of X would be somewhat less than its equilibrium concentration. However, for all ordinary reactions, where the transmission coefficient (Section III.4) is equal to unity, this has no effect upon the equilibrium concentration.

$$[X] = K^{\ddagger}[A][B] \tag{13}$$

As in the collision theory, it is tacitly assumed (16) that the Boltzmann distribution is maintained in spite of the chemical reaction. The validity of these approximations has been examined theoretically (25,26) and with the exception of the monomolecular decomposition of complex molecules at low pressures, and of reactions occurring during certain types of explosions, the assumption apparently introduces no appreciable error.

The over-all rate, $d[M]/dt$, of the reaction is equal to the rate, v_2, of step 2. For the usual isochoric systems (see Chapter V, II.3), the rate of the unimolecular process, step 2, may be written as follows.

$$d[M]/dt = v_2 = k_2[X] \tag{14}$$

Combining Equations (13) and (14):

$$d[M]/dt = k_2K^{\ddagger}[A][B] \tag{15}$$

The remaining problems are to evaluate k_2 and $K^{\ddagger}$. It is convenient to substitute for $K^{\ddagger}$ its thermodynamic equivalent. The free energy, ΔF of any reaction bears the following relation to the equilibrium constant:

$$\Delta F = -RT \ln K^{\ddagger} + RT\textstyle\sum_i \ln a_i^{\nu_i}$$

where the a_i are the activities of the several reactants and products, and the appropriate exponents, ν_i, are equal to the corresponding coefficients in the stoichiometric equation. Rearranging this equation:

$$K^{\ddagger} = \prod_i (a_i^{\nu_i}) \exp(-\Delta F/RT)$$

When the reactants and products are in their standard states, the activities are each equal to unity and ΔF has the special value of the standard free energy, ΔF^0. Introducing the units commonly used by chemists, the equation for a bimolecular reaction is:

$$K^{\ddagger}(\text{liters/mole}) = \exp(-\Delta F^{\ddagger,0}/RT)(\text{liters/mole}) \tag{16}$$

Written in this form, the equation emphasizes the fact that the units and numerical value of the factor, $\exp(-\Delta F^{\ddagger,0}/RT)$, depend upon the choice of the standard state. Since in the discussion which follows only the

standard free energy will be used, the superscript^0 will be dropped, and $\Delta F^\ddagger$, $\Delta H^\ddagger$, etc., will denote the standard free energy, etc. For an isobaric, isothermal change, $\Delta F = \Delta H - T\Delta S$. Therefore:

$$K^\ddagger = \exp(\Delta S^\ddagger/R) \exp(-\Delta H^\ddagger/RT)$$

and we may write:

$$d[\mathrm{M}]/dt = k_2 \exp(\Delta S^\ddagger/R) \exp(-\Delta H^\ddagger/RT)[\mathrm{A}][\mathrm{B}] \qquad (17)$$

3. Rate of Transformation of the Transition State

To obtain the value of k_2 it is necessary to use the methods of modern statistical mechanics. This can be done most conveniently if $K^\ddagger$ is expressed in terms of partition functions rather than the thermodynamic functions used in Equations (17) (27–32). The following discussion (cf.

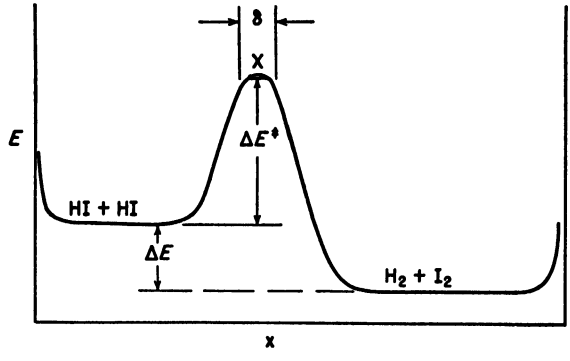


Fig. 4. Potential energy curve representing the bimolecular decomposition of HI.

Glasstone, Laidler, and Eyring (33)) is in no sense a derivation, but may serve to relate the steps of the abstract argument to more familiar intuitive concepts. The rate of the formation of the products is equal to the concentration, $[\mathrm{X}]'$, of the transition state complex multiplied by the mean velocity, $\bar{v}$, with which it moves along the reaction coordinate of the "box," which contains the molecules of the transition complex:

$$d[\mathrm{M}]/dt = [\mathrm{X}]'\bar{v}/\delta \qquad (18)$$

It may be shown that the mean velocity $\bar{v}$, has the following value:

$$\bar{v} = (kT/2\pi m^*)^{1/2} \qquad (19)$$

where k is the Boltzmann constant and m^* is effective mass of the complex. This result is not surprising when it is remembered that the root mean

square velocity of a gas is $\bar{u} = (3kT/m)^{1/2}$. The transition state complex has some unusual properties. There is no restoring force which tends to make it assume a definite position on the reaction coordinate. Therefore, it has one mode of vibration less than might be expected from its known degree of complexity, but in compensation has an extra degree of translational motion—translation along the reaction coordinate. Taking these things into account, it can be shown that the concentration [X]′ of Equation (18) bears the following relation to the concentration [X] of Equation (13):

$$[\mathrm{X}]' = [\mathrm{X}] \frac{(2\pi m^* kT)^{1/2}}{h} \delta \tag{20}$$

Combining Equations (18), (19), and (20):

$$d[M]/dt = [\mathrm{X}] \left\{\frac{(2\pi m^* kT)^{1/2}}{h} \delta\right\} \left(\frac{kT}{2\pi m^*}\right)^{1/2} \frac{1}{\delta} = \left(\frac{kT}{h}\right) [\mathrm{X}] \tag{21}$$

Fortunately, the arbitrary length, δ, which occurs in Equations (18) and (20), cancels out in Equation (21). A comparison of Equations (14) and (21) shows that:

$$k_2 = kT/h \tag{22}$$

This quantity, which has the dimensions of frequency, is a universal constant occurring in the rate equation for all ordinary chemical reactions. Introducing it into Equation (17), we obtain the rate equation for a bimolecular reaction, expressed in terms of thermodynamic quantities:

$$d[\mathrm{M}]/dt = (kT/h) \exp(\Delta S^{\ddagger}/R) \exp(-\Delta H^{\ddagger}/RT)[\mathrm{A}][\mathrm{B}] \tag{23}$$

Formally similar equations may be derived for unimolecular or termolecular reactions, the frequency factor being unchanged and the product of the exponential factors having dimensions and magnitudes consistent with the reaction in question. Since the theory is directly applicable only to simple reactions (see Chapter III.7), other orders of reactions need not be considered here.

4. Transmission Coefficient

The rates of certain types of reactions are less than the values which correspond to Equation (23). This equation is conveniently corrected by introducing a factor (34–36), κ, called the transmission coefficient. For ordinary chemical reactions (in solution or in the gas phase at moderate to high pressures), κ may be set equal to unity. However, there are important classes of reactions for which κ is very small or is a function of pressure.

For example, the collisions of two atoms are practically always elastic; therefore, for the bimolecular combination of two atoms, the value of κ is zero. If allowance is made for the possible emission of a photon during the brief duration of the collision, it has been shown (36) that κ has values in the range between 10^{-12} and 10^{-14}. κ may be much higher for the bimolecular association of radicals, which have many internal degrees of freedom. In a three-body collision, the extra atom or molecule can carry off part of the energy of the quasidiatomic molecule, thereby stabilizing it. By allowing for the occurrence of three-body collisions, it can be demonstrated that κ, corresponding to the formation of a diatomic molecule from its component atoms, is a symbatic function of pressure, ranging from practically zero to a value of the order of magnitude of unity. The transmission coefficients of unimolecular decompositions and isomerizations are, likewise, functions of pressure (37,38). Certain unimolecular *cis-trans* isomerizations involve "forbidden" electronic transitions and have transmission coefficients whose values are small even at high pressures (40).

5. Reactions in Condensed and Nonideal Media

One of the major advantages of the transition state theory of reaction rates is the ease with which it may be applied to reactions occurring in condensed and nonideal systems. In the foregoing discussion, it has been assumed that the reactions were occurring in an ideal system, such as a perfect gas. Equation (11) is exact only when it refers to an ideal system. The corresponding thermodynamic equilibrium constant, $K_o^\ddagger$, is a function of the activities rather than the concentrations:

$$K_o^\ddagger = a^\ddagger/a_A a_B \tag{24}$$

There are several ways in which activities may be defined (41,42). Since the immediate purpose of the present discussion is to compare a nonideal liquid solution with an ideal gas, it is convenient to adopt as the standard state the ideal gas in which the molarity of the solute is equal to unity. It follows from this choice of the standard state that the activity coefficient, α, is equal to the ratio of the molarity of the solute in the ideal gas to its molarity in a solution which is in equilibrium with the gas. Combining this definition with Equation (24) we obtain:

$$K_o^\ddagger = ([X]/[A][B])(\alpha^\ddagger/\alpha_A\alpha_B)$$

or:

$$K_i^\ddagger = K_o^\ddagger(\alpha_{i,A}\alpha_{i,B}/\alpha^\ddagger) \tag{25}$$

where the subscript i refers to the solvent. Introducing this value for $K^\ddagger$ in Equation (15), we may write:

$$d[M]/dt = k_2K_o^\ddagger(\alpha_A\alpha_B/\alpha^\ddagger)[A][B]$$

which leads to either of the following important equations:

$$d[\mathrm{M}]/dt = k_o(\alpha_{i,\mathrm{A}}\alpha_{i,\mathrm{B}}/\alpha_i^{\ddagger})[\mathrm{A}][\mathrm{B}] \tag{26}$$

$$= \kappa(\boldsymbol{k}T/\boldsymbol{h}) \exp(\Delta S^{\ddagger}/R) \exp(-\Delta H^{\ddagger}/RT)(\alpha_{i,\mathrm{A}}\alpha_{i,\mathrm{B}}/\alpha_i^{\ddagger})[\mathrm{A}][\mathrm{B}] \tag{27}$$

where the "activity factor" $(\alpha_{\mathrm{A}}\alpha_{\mathrm{B}}/\alpha^{\ddagger})$, is the ratio of the rate constant for a solution to the rate constant of the same reaction in dilute gas. For regular, ideal solutions, $\alpha_{i,j}$, will not differ greatly from unity. Eyring quotes empirical evidence (43,44) which indicates that 10^2 is a rough average value of $\alpha_{i,j}$ for such solutions. The corresponding value for k_i/k_o (for a bimolecular reaction) is approximately 10^2. In other words, the rate of a reaction should be about the same regardless of whether it occurs in a dilute gas or in an ideal solution. Whenever ions, permanent dipoles, polarizable molecules, etc., are involved, specific effects are to be expected, and the foregoing limited generalization is not even approximately true.

The ratio of rate constants for a monomolecular reaction equals $\alpha_{i,\mathrm{A}}/\alpha_i^{\ddagger}$. Accordingly the ratio will be of the order of magnitude of unity whenever the properties of the transition complex resemble those of the reactant molecule. This is true for nonideal as well as ideal solutions. Examples of this type are the decomposition of N_2O_5 and the "racemization" of pinene (45).

To facilitate the comparison of the rates of reactions in different solvents and at different concentrations in the same solvent, it will be convenient to introduce a new set of conventions. In the so-called "practical system" of activities, the reference state (46,47) is taken as the infinitely dilute solution (in the same solvent), and the concentrations can be expressed as molarities. The corresponding standard state is a solution in which the activity of the solute is equal to unity. The concentration of this solution is $1M$ for an ideal solution. While it may be greater or less for real solutions, depending upon the type of departure from ideality, it is always of the order of magnitude of unity.

If two or more phases are in equilibrium, the fugacities, $f_{i,j}$, of each component in the several phases are equal (48):

$$f_{i,j} = f_{i,k} = f_{i,o}$$

where the first subscript refers to the component and the second to the phase. The fugacity of a component is approximately equal to its partial pressure in a gas or to its partial vapor pressure for a condensed phase. The activity of a component i in a phase j is equal to the ratio of its fugacity in the given solution to its fugacity, $f^0_{i,j}$, in its standard state.

$$\alpha_{i,j} = f_{i,j}/f^0_{i,j}$$

Therefore, if several phases are in equilibrium:

$$f^0_{i,j}\alpha_{i,j} = f^0_{i,k}\,\alpha_{i,k} = f^0_{i,\text{gas}}\alpha_{i,\text{gas}} \approx P^0_{i,\text{gas}}m_{i,\text{gas}}$$

Rearranging, introducing the definition of $\alpha_{i,j} = m_{i,j}/m_{i,\text{gas}}$, and representing the "practical" activity coefficient (46) by γ:

$$(f^0_{i,j}/P^0_{i,\text{gas}})(\gamma_{i,j}/\alpha_{i,j}) = (f^0_{i,k}/P^0_{i,\text{gas}})(\gamma_{i,k}/\alpha_{i,k}) = 1 \tag{28}$$

or:

$$\alpha_{i,j} = (f^0_{i,j}/P^0_{i,\text{gas}})\gamma_{i,j} \tag{29}$$

The factor in parenthesis is independent of concentration, but is a function of the nature of the solute and solvent and of the temperature. It follows from Equation (26) that:

$$d[\text{M}]/dt = k_o(P^{\ddagger,0}{}_{\text{gas}}/P^0_{\text{A,gas}}P^0_{\text{B,gas}})(f^0_{\text{A},j}f^0_{\text{B},j}/f^{\ddagger,0}_j)(\gamma_{\text{A},j}\gamma_{\text{B},j}/\gamma^{\ddagger}_j)[\text{A}][\text{B}] \tag{30}$$

or:

$$d[\text{M}]/dt = k_{j,\infty}(\gamma_{\text{A},j}\gamma_{\text{B},j}/\gamma^{\ddagger}_j)[\text{A}][\text{B}] \tag{31}$$

Equation (31) is in a form convenient for treating the effect of concentration upon the specific velocity for a given solvent and temperature. If it is desired to compare the rate constants for two different solvents, excluding the effect of concentration, the following expression may be obtained directly from Equation (30):

$$k_{j,\infty}/k_{k,\infty} = (f^0_{\text{A},j}f^0_{\text{B},j}/f^{\ddagger,0}_j)(f^{\ddagger,0}_k/f^0_{\text{A},k}f^0_{\text{B},k}) \tag{32}$$

The remaining problem is to predict the numerical values of the activity coefficient ratios of Equations (31) or (32) or at least to relate the results of empirical rate studies to measured thermodynamic properties of solution. This problem is an essentially complex and difficult one. The form of the solution and the order of magnitude of the numerical results depend upon the physical nature of the reactants, solvent, and reaction complex. As might be expected the solvent and concentration effects are least for uncharged nonpolar molecules and greatest for ions. These effects have been studied extensively both theoretically and experimentally (49). An equation similar to Equation (31) was presented, largely on empirical grounds, by Brønsted (50) in 1922 for the special case of ionic reactions in aqueous solution. This special form of the Equation (31) has been tested extensively, in the case of ionic reaction in dilute aqueous solutions, and the results of these tests in general substantiate the predictions of the theory.

IV. A COMPARISON OF THE TRANSITION STATE AND SIMPLE COLLISION THEORIES

1. General Discussion

Both the transition state and collision theories are correct in principle, and when applied properly must yield consistent results. Any attempt to evaluate their relative merits must rest upon a comparison of their usefulness in analyzing real or practical problems. A theory should be able to correlate experimental data in a simple way that is compatible with other accepted theories, and to predict (within limits) the results of other experiments, not yet performed. The two theories appear to be of comparable utility in correlating empirical data. However, in recent years the great majority of the successful, semiquantitative predictions regarding reaction rates have been accomplished with the aid of the transition state theory.

It is interesting to compare the modern transition state theory with a hypothesis regarding reaction rates which was published (51) by Svante Arrhenius in 1889. Arrhenius noticed that the rate of a chemical reaction (inversion of sugar) was an exponential function of temperature, and that, furthermore, the rate increased much more rapidly than the number of collisions of gas molecules or the fluidity (reciprocal of viscosity) of the solvent. From these observations, he was led to postulate that one of the reactants (the sugar) exists in a passive and an active form; that the two forms are in an equilibrium with one another, which is not disturbed by the reaction; that only the active form is capable of reacting; and that the percentage of the reactant in the active form is very small. Under these conditions, the concentration, C'_S, of the active form is related to the total concentration, C_S, of this reactant as follows:

$$C'_S = K_{eq.}(C_S - C'_S) \approx K_{eq.}C_S$$

Introducing the van't Hoff relation:

$$C_S = K^0_{eq.} \exp(-\Delta H/RT)C_S$$

and the rate of the (bimolecular) reaction is:

$$-dC_S/dt = k_A K^0_{eq.} \exp(-\Delta H/RT)C_S C_{H^+}$$

From a strictly empirical viewpoint, this relation closely resembles the basic Equation (15) of the transition state theory. However, the resemblance is more apparent than real. The equilibrium of the Arrhenius hypothesis is an ordinary chemical tautomerism, etc. Obviously, such a postulate is not applicable to a reaction between simple molecules, such as the formation of hydrogen iodide from its elements. In addition, the tempera-

ture-independent factor, k_A, of the Arrhenius hypothesis is not a universal constant, like kT/h, but is an undetermined empirical constant.

One appealing feature of the collision theory is that, in principle, it reduces rate problems to mechanical concepts which can be readily grasped intuitively. While this apparent virtue is largely illusory, the simple theory is advantageous pedagogically and for the qualitative consideration of the reactions of simple systems. Although the statistical concepts of the transition state theory are not easily visualized, at least the operations involved in dealing with the thermodynamic functions (in terms of which the theory can be expressed) are familiar to all chemists.

2. Reaction Rate and Equilibria

The equilibrium constant for a chemical process must be equal to the ratio of the rate constants of the two opposing reactions which constitute the equilibrium. In terms of the transition state theory, this relation can be obtained directly and unequivocally. For simplicity, let us consider two opposing bimolecular reactions:

$$A + B \underset{2}{\overset{1}{\rightleftharpoons}} C + D$$

and further suppose that all of the reactants are present as dilute gases, so that the several activity coefficients can be set equal to unity. For this system:

$$K = k_1/k_2$$

or:

$$\exp(\Delta S^0/R) \exp(-\Delta H^0/RT) = \frac{\kappa_1(kT/h) \exp(\Delta S_1^\ddagger/R) \exp(-\Delta H_1^\ddagger/RT)}{\kappa_2(kT/h) \exp(\Delta S_2^\ddagger/R) \exp(-\Delta H_2^\ddagger/RT)}$$

Since the transmission coefficients must be the same for the two opposing reactions:

$$\Delta S^0 - (\Delta H^0/T) = \Delta S_1^\ddagger - \Delta S_2^\ddagger - (\Delta H_1^\ddagger - \Delta H_2^\ddagger)/T$$

In other words, the standard entropies, enthalpies, and free energies of the reaction are equal to the differences between the entropies, enthalpies, and free energies of activiation, respectively. A similar treatment, starting with the simple collision theory, leads to the following equation:

$$\exp\left(\frac{\Delta S^0}{R}\right) \exp\left(-\frac{\Delta H^0}{RT}\right) = \frac{p_1 Z_1 \exp(-\epsilon_1/RT)}{p_2 Z_2 \exp(-\epsilon_2/RT)}$$

Since the reduced masses and mean collision diameters for the forward and back reactions must be approximately equal, $Z_1 \approx Z_2$. Furthermore, the

difference between the energies of activation is equal to the enthalpy of the reaction. Therefore:

$$\exp(\Delta S^0/R) \approx p_1/p_2$$

While this relation between the entropy and probability factors is certainly not surprising in terms of the transition state theory (52–54), it is hard to justify it from the viewpoint of the simple collision theory.

3. Prediction of the Magnitudes of Reaction Rates

In comparing the application of the two theories to a given reaction, we can write as a close approximation:

$$pZ = \kappa(kT/h) \exp(\Delta S^{\ddagger}/R)$$

For a reaction between two atoms, it can be shown unambiguously that Z as computed from Equation (2) is equal to $(kT/h) \exp(\Delta S^{\ddagger}/R)$, as calculated on the basis of the collision theory (55). The frequency factor, Z, of the simple collision theory, as computed from Equation (2), has values which lie approximately within the range of one order of magnitude, depending only slightly upon the size and complexity of the reactant molecules. In contrast to this, the transition state theory predicts that $\exp(\Delta S^0/R)$ decreases by many orders of magnitude (56) as the reactants increase in complexity from single atoms to polyatomic molecules. While the calculated value of $\Delta S^{\ddagger}$ depends upon the assumed configuration of the transition complex, this value can always be placed within limits even when there is little evidence to guide the theorist in his choice of a structure for the complex. For example, the factor $\exp(\Delta S^{\ddagger}/R)$ for a reaction between two polyatomic molecules should lie within the limits 10^{-5} and 10^{-10} (56). In terms of the collision theory, one might anticipate that bimolecular reactions of complex molecules would require the use of a small steric factor. However, even the estimation of the range of magnitudes to be expected for the steric factor is extremely difficult.

4. Application to Nonideal Systems

As was discussed in the preceding section, a major advantage of the transition theory is the simplicity and ease with which it may be adapted formally to the treatment of reactions in condensed or nonideal systems. While predictions of solvent effects are difficult to make on the basis of either theory, Equations (30), (31), and (32) are particularly useful for the correlation of empirical data.

V. ABSOLUTE CALCULATION OF REACTION RATES

1. Introduction

The ultimate goal of any theory of reaction rates is the quantitative prediction of the rates of reactions from the known physical properties of the reactants. Such prediction involves the calculation, from nonkinetic data, of both the frequency factor and the energy of activation of the reaction. In general, this has proved an impossible task. There are a few simple cases where the prediction can be made fairly rigorously and a moderate number of reactions for which either one or the other of the factors can be calculated with fair approximation. Several more-or-less empirical methods of predicting reaction rates have been published and demonstrated to be reasonably useful. From the viewpoint of organic chemistry, one of the most interesting applications of rate theory is to the absolute calculation of the relative values of the rates of reactions which differ only in some simple way, as in a substituent group on one of the reactants.

2. Predictions Based upon Classical Theory

In some instances, the rate of quenching of the fluorescence of excited atoms by added gases can be computed in a straightforward way. Since these processes are exothermic reactions between excited atoms and normal diatomic molecules, it should be expected that they would not require thermal energy of activation. In other words, their exponential factors, $\exp(-\epsilon/RT)$ should be equal to unity. For reactions of this type for which the energy differences and selection rules are favorable, the frequency factor should be equal to the number of collisions (57). The number of collisions can be computed in terms of the simple collision theory, using molecular and atomic radii obtained from measurements of viscosity or the rate of diffusion. The quenching of excited mercury atoms (Hg^*) by H_2, D_2, or O_2, or of excited thallium atoms (Tl^*) by O_2 or CO_2 are examples for which the predicted and observed rates are in good agreement (compare Tables 14 and 17, Pringsheim, Ref. 57). Chemical equations for two reactions typical of these processes are:

$$Hg^* + H_2 \longrightarrow HgH + H$$

$$Hg^* + O_2 \longrightarrow HgO + O$$

To make similar calculation of the maximum rate of the quenching of fluorescence in liquid solutions, it is necessary to distinguish between encounters and collisions (Section II. 1 and 5), since efficient quenching

occurs at every encounter and is, therefore, independent of the frequency of collision. An approximate analysis (59) leads to the following simple equation for the rate constant of a diffusion-limited reaction:

$$k_D, \text{ liter/mole/second} = 8RT/(3 \times 10^3\eta)$$

More rigorous analyses (60,61) of the problem result in more exact, but much less convenient solutions.

Probably the first successful attempt to calculate the rate of a chemical reaction was made by Strutt in 1912 (58). He formed ozone by allqwing air at low pressure to flow through an ozonizer. After leaving the ozonizer, the gas passed through a porous plug made of oxidized silver, which is an efficient catalyst for the decomposition of ozone. Since the area of the porous plug and the mass of gas flowing through it in one second were known, it was possible to calculate the average number of collisions an ozone molecule would make with the silver oxide surface, on its way through the plug. When the rate of flow was as fast as was consistent with the condition that no ozone could be detected in the effluent gas, calculation based upon simple kinetic theory showed that each ozone molecule in going through the plug made, on the average, 1.6 collisions with the silver oxide surface. In other words, an absolute calculation of the maximum rate of this process corresponded surprisingly closely with the observed rate. It should be realized, however, that the empirical result—that ozone molecules are decomposed at approximately every collision with the silver oxide surface—was not predicted in terms of any theory.

3. Potential Energy Surfaces

The transition state theory has been so widely used in attempts to predict the rates of reactions that this theory is frequently referred to as the *theory of absolute reaction rates.* While in principle either the collision or the transition state theory can be used to predict absolute rates of reaction, it must be admitted that the latter theory has proved much more useful for this purpose. The calculation methods used always involve some approximations, and sometimes are little better than systematic empiricism.

One approach to the problem is to plot the potential energy of the reacting system as a function of the configuration of the constituent atoms. In general, this involves impossibly complex calculations and the use of a diagram in polydimensional space. For a reaction involving only three atoms (X, Y, and Z) the problem is, in principle, relatively simple. For the reaction:

$$X + YZ = XY + Z$$

it is possible to calculate by the methods of quantum mechanics what angle between the atoms X, Y, and Z corresponds to the minimum energy for the close approach of the atom X to the molecule YZ. Should this minimum energy correspond to a linear arrangement of the atoms (as it does for several simple cases (62)) the diagram can be constructed by plotting the distance between X and Y as abscissae and the distance between Y and Z as ordinates. The potential energy of the system can be represented in a three dimensional model on the third perpendicular coordinate. More conveniently, the potential energy surface may be represented by equipotential contour lines on a two-dimensional plot such as shown in Figure 5. In this

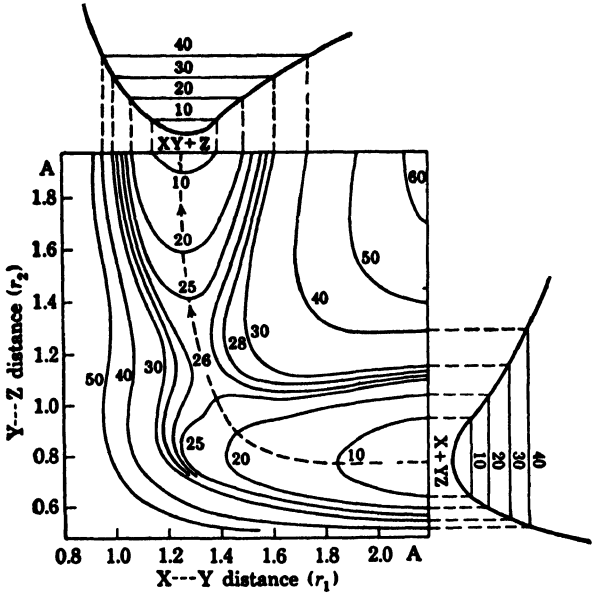


Fig. 5. A typical potential energy contour map for a bimolecular reaction between an atom and a diatomic molecule.

figure, the dotted line running from the point X + YZ to the point XY + Z is the reaction coordinate. A cylindrical surface generated by a straight line perpendicular to the paper and passing through the reaction coordinate, intercepts the potential energy surface in a line curved in three dimensions. (The term cylinder is used here to denote a surface which contains an infinite number of parallel lines all of which are perpendicular to a plane. Such straight lines pass through every point on the cylindrical surface.) If this cylindrical surface is flattened out, the resulting two dimensional curve is the cross section of the potential energy surface along

the reaction coordinate. Such a cross section, corresponding to the surface of Figure 5, is represented in Figure 6a. It is similar to Figure 4. A cross section cut by a plane, which is perpendicular to the paper, parallel to the abscissae, and relatively distant from the origin, is the potential energy curve for the diatomic molecule XY (only slightly influenced by the distant atom Z). A similar potential energy curve for the molecule YZ is cut by a plane parallel to the ordinates. These two cross sections are shown in Figure 5. Figure 6b is the plot of a cross section of the potential energy

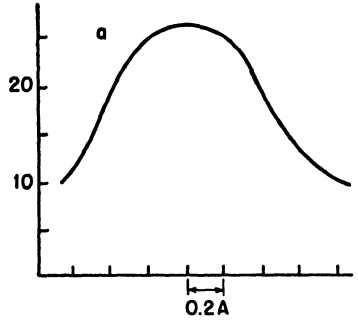


Fig. 6a. A cross section, following the reaction coordinate of the potential energy surface of Fig. 5.

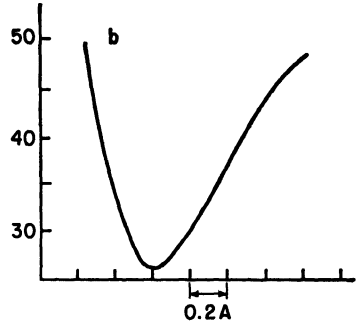


Fig. 6b. A cross section of the potential energy surface of Fig. 5 cut at right angles to this reaction coordinate and representing the transition state.

surface cut by a plane, perpendicular to the cylinder containing the reaction coordinate (at a point corresponding to the transition complex) and to the paper. It represents the potential energy curve of the transition complex in a direction at right angles to the reaction coordinate. Unlike the two potential energy curves in Figure 5 (which are essentially potential energy curves for diatomic molecule), motion along this curve corresponds to motion in space of the three atoms relative to one another.

4. Calculation of Energy of Activation

The chief purpose of constructing potential energy surfaces is the determination of energies of activation. The highest point on the reaction coordinate corresponds to the transition complex. The difference between the potential energy of this point and that of the stable reactants is equal to the energy of activation. For simple reactions, the potential energy surfaces may be calculated from spectroscopic (and other nonkinetic data) using the methods of quantum mechanics. For all real cases, such calculations are approximate. One simplifying assumption which is commonly

used by Eyring and his co-workers (63) is that a fixed fraction (often taken as 0.14) of the total potential energy of the system is due to coulombic interaction. Such calculations have been carried through with a fair degree of approximation for a number of three-atom reactions. The most precise results have been obtained for reactions involving only hydrogen atoms or hydrogen and deuterium atoms (64). Fairly good agreement with experimental data has also been obtained for reactions involving only halogen atoms or hydrogen and halogen atoms. Attempts have also been made to apply the general methods to reactions involving four or more atoms; however, these calculations either involve additional arbitrary assumptions or else apply only to highly specialized cases (compare Westheimer and Mayer (65) and Westheimer (66)).

Frankly empirical methods (particularly the Hirschfelder rules (67)) have been fairly successful in dealing with certain types of reactions. One of the best known of these empirical rules states that, for an exothermic reaction between two diatomic molecules (AB + CD = AD + CB), the energy of activation is equal to one-fourth of the sum of the energies of dissociation of the reactant molecules. Unfortunately, there are relatively few reactions of this type known. The rule has been tested (68) chiefly by showing that it gives values of activation energies greater than the lower limits which can be computed from the known nonoccurrence of these reactions under certain experimental conditions. This rule has also been applied (69) with moderate success to certain second order, gas phase reactions of polyatomic organic molecules.

In principle, a postulated mechanism may be tested by comparing the empirical energy of activation of the reaction to values calculated from the assumed structure of the reaction complex. For actual cases, the difference between calculated energies of activation, corresponding to alternative mechanisms, seldom exceeds the uncertainty of the calculations.

5. Calculation of Entropy of Activation

The calculation of the entropy of activation is a much simpler problem (70,71) than the prediction of the energy of activation. These calculations can be made in terms of partition functions, by using the theories and rules which have been tested by their application to equilibria of stable molecules. An outstanding, successful application of this technic is found in the calculations of Herschbach *et al.* (72) of the pre-exponential factors, $(\mathbf{k}T/\mathbf{h})\ \exp\ (\Delta S^{\ddagger}/R)$ of twelve bimolecular gas reactions between ozone, fluorine, the chlorine oxides and the nitrogen oxides. The agreement between the theoretical and empirical values is, for eleven of these reactions, within one order of magnitude, which is a stringent test of the experimental

data and its interpretation as well as the theory and the methods of calculation. In one instance,

$$2NO_2 = 2NO + O_2$$

the comparison of the calculated and empirical values of $\Delta S^{\ddagger}$ indicates that the transition state does not have a cyclic structure, which was otherwise plausible.

Useful, although relatively crude, approximations can be made to the preexponential factors of reactions involving complex, polyatomic molecules. A re-examination (71) of the older estimates (73) of these factors indicates that they were too small by factors of 10^3 to 10^6, thus demonstrating that such calculations, while relatively simple, are neither obvious nor foolproof.

The theoretical calculation of the entropies of activation of bimolecular reactions in nonideal solutions is a much more difficult problem (70). Particularly for reactions of ions and dipoles in polar solvents the calculations are more nearly semi-empirical than theoretical. Quantitative predictions based upon such calculations should be viewed with some caution.

VI. ABSOLUTE CALCULATION OF RELATIVE RATES

1. Effect of Isotopic Substitution

An important application of the theory of absolute rates is to the prediction of the relative rates of reactions which differ only with respect to some minor factor. This varied factor may be an environmental one, such as a change in the solvent; or it may be an internal one, such as a change in a substituent group of one of the reactant molecules. The effect of isotopic substitution, *e.g.*, deuterium for hydrogen, in a reactant molecule is of special interest.

The potential energy curve for a diatomic molecule, or the potential energy surface for a system of reactants, is, to a very close approximation, independent of the mass numbers of the constituent isotopes which make up the molecule, or molecules. However, the vibrational energy, particularly the *zero point energy*, is an inverse function of the mass of the isotope. These relations are illustrated for a diatomic molecule by Figure 7. In this figure, the horizontal lines represent the total energy (neglecting rotational energy) of the molecule in its several vibrational states, whose quantum numbers are v_i. Even at the absolute zero, the vibrational energy does not go to zero. When the molecule is in its zeroth vibrational level, i.e., $v = 0$, it has an irreducible vibrational energy, E_o, the so-called *zero point energy*.

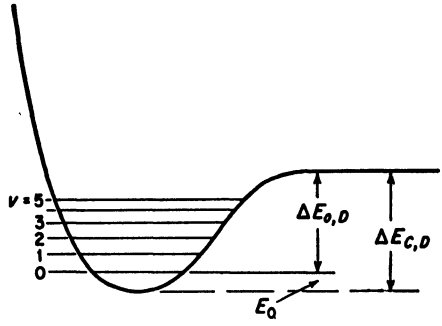


Fig. 7. Potential energy diagram for a diatomic molecule in the ground state.

The zero point energy is equal to $^1/_2h\nu_{\text{osc.}}$, where $\nu_{\text{osc.}}$ is the oscillational frequency of the molecule. This frequency, and therefore the zero point energy, is inversely proportional to the square root of the reduced mass of the oscillator. For example, the (observed) zero point energies of H_2, HD, D_2, and the radicals CH and CD are 6.20, 5.40, 4.42, 4.05, and 2.99 kcal./mole, respectively (74). While the vibrational energies associated with individual bonds in complex molecules are influenced by the molecules as a whole, to a first approximation they may be considered as characteristic of the two atoms and the type of bonding. Values for the zero point energies of such bonds may be obtained from an analysis of infrared spectra. The following values were obtained in this way. The values for the CH and CD bonds are little affected by the rest of the molecule, but the E_0 values for the stretching vibrations for the C—C bond are relatively crude averages (75).

Bond	>C—H	>C—D	>C^{12}—C^{12}<	>C^{12}—C^{13}<
E_0, kcal./mole	4.01	3.14	1 14	1.10

A system of two or more reacting molecules has a zero point energy, both when the molecules are in their stable states and when they exist as a transition complex. This zero point energy is equal to the sum of the terms $^1/_2h\nu_i$ corresponding to each mode of vibration of the system. Just as energy of dissociation, ΔE_D, of a diatomic molecule is influenced by its zero point energy, so the energy of activation, $\Delta E^\ddagger$, and the energy of reaction, ΔE^0, are affected by the zero point energies of the system. This is illustrated by Figure 8. The quantities which should be used in thermodynamic or kinetic calculations are ΔE_o^0 and $\Delta E_o^\ddagger$, respectively. Neither ΔE_c^0 nor $\Delta E_c^\ddagger$ is appreciably affected by changes in the isotopic constituents of

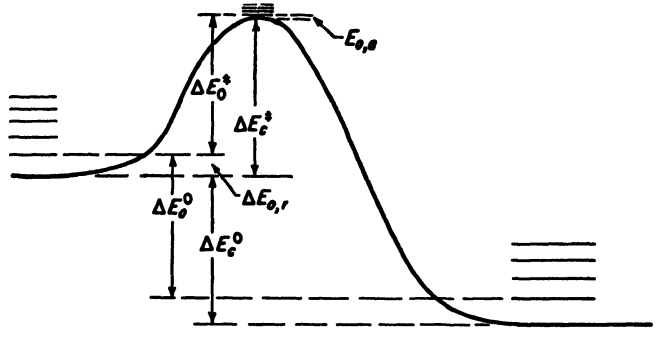


Fig. 8. Potential energy diagram for a reacting system.

the system. Accordingly, if we wish to compare $\Delta E_o^\ddagger$ for two systems which differ only in the substitution of a deuterium for a hydrogen atom, we may write:

$$\Delta E_o^\ddagger(\mathrm{H}) = \Delta E_c^\ddagger - E_{o,r}(\mathrm{H}) + E_{o,a}(\mathrm{H})$$

$$\Delta E_o^\ddagger(\mathrm{D}) = \Delta E_c^\ddagger - E_{o,r}(\mathrm{D}) + E_{o,a}(\mathrm{D})$$

and:

$$\Delta E_o^\ddagger(\mathrm{H}) - \Delta E_o^\ddagger(\mathrm{D}) = E_{o,a}(\mathrm{H}) - E_{o,a}(\mathrm{D}) - E_{o,r}(\mathrm{H}) + E_{o,r}(\mathrm{D})$$

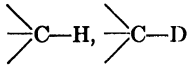
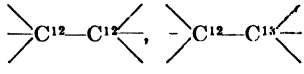
In general $\Delta H^\ddagger$ is not identical with $\Delta E^\ddagger$, but the difference between these quantities does not affect the present considerations. Changes which are produced in the other factors of the kinetic Equation (24) are relatively small and may be neglected in this approximate treatment. Accordingly, we may write:

$$\frac{k_\mathrm{H}}{k_\mathrm{D}} = \exp\left(\frac{E_{o,a}(\mathrm{D}) - E_{o,a}(\mathrm{H}) + E_{o,r}(\mathrm{H}) - E_{o,r}(\mathrm{D})}{RT}\right) \qquad (33)$$

Commonly, the atoms are more loosely bound in the transition complex than they are in the stable reactant molecules. As a result, the vibrational energy levels are closer together for the transition complex and $E_{o,a} < E_{o,r}$. Whenever this condition is true, reactions involving light atoms are faster than those involving heavy isotopes. The difference increases with an increase in the ratio of the isotopic masses. If in the transition complex the atom in question is practically unbonded, $E_{o,a} = 0$ and the ratio, $k_\mathrm{H}/k_\mathrm{D}$, is a maximum. Neglecting those rare but possible cases where the substituted atom is more strongly bound in the reaction complex than in the stable reactant molecules, we may write (76):

$$\frac{k_\mathrm{H}}{k_\mathrm{D}} \leqq \exp\left(\frac{E_{or}(\mathrm{H}) - E_{or}(\mathrm{D})}{RT}\right) \qquad (34)$$

Using this relation and the values of zero point energies listed above, we may compute the maximum values for the ratio of the rate constants for reactions which involve the breaking of the following bonds. In stating the ratio, the constant for the reaction with the lighter isotope is placed in the numerator:

Bonds being broken	Maximum ratio of rate constants
H—H, H—D	3.7
H—H, D—D	19.5
C—H, C—D	5.9
	4 3
	1.07

It should be remembered that these are maximum values. In many reactions involving these bonds, the bond in the transtion complex will be far from broken and the ratio of the rate constants may be much smaller, possibly closer to unity than to the maximum value (77–80). Reactions which involve quantum mechanical "tunneling" of a proton can exhibit abnormally large isotope effects if a deuteron is substituted for the reactive proton (81). In using isotopic tracer atoms in reactions kinetic studies, the possibility that the specific reaction rate may be altered by the isotopic substitution should always be taken into account (78).

2. Kinetic Salt Effect

The ratio of the rates of a given reaction in two different media is dependent only upon the values of the activity coefficients of the reactants and transition complex. If these values of the activity coefficients for the two media are known, the relative rates may be calculated by means of Equation (30). In principle, it is always possible to determine the activity coefficients of the reactants by thermodynamic measurements.

This is not strictly true if the transition complex has a net charge, since the activity of an individual ion is not a thermodynamic concept (see Ref. 42, MacDougall, pp. 372–3). However, it is possible to obtain conventional values for the activities of single ions, and there is reason to believe that these conventional values are satisfactory for the present purpose.

In many cases it is possible to make a reasonable estimate of the activity coefficient of the complex. One such case, which was discussed in a pre-

ceding section (Section III. 5), is the prediction of the activity of a solute in an ideal solution relative to the activity of the same substance in a dilute gas. Although such a prediction is probably not more accurate than one or two orders of magnitude, it is good enough to demonstrate that the rate of a reaction should be roughly the same in an ideal solution as it is in the gas phase. This important prediction is substantiated, in general, by available evidence (82,83).

A medium influence which has been most extensively studied is the effect of ionic strength upon the rates of ionic reactions. It has been widely accepted that the activity coefficients of ions in dilute solutions can be calculated by means of the Debye-Hückel limiting law:

$$-\ln \gamma_+ = (AZ_+^2 / D^{3/2}T^{3/2})\mu^{1/2}$$

where A is a constant made up of universal constants and simple numbers, Z_+ is the charge (in terms of the charge on the electron) on the ion, D is the dielectric constant, and μ is the ionic strength. For aqueous solutions at 25°C.:

$$\log \gamma_+ = -0.509Z_+^2\mu^{1/2}$$

Since the charge on the transition complex is the sum of the charges of the reactant ions (A and B) we may write for a bimolecular reaction:

$$\log (\gamma_A\gamma_B/\gamma^\ddagger) = -0.509\mu^{1/2}[Z_A^2 + Z_B^2 - (Z_A + Z_B)^2]$$
$$= 1.02Z_AZ_B\mu^{1/2}$$

In terms of Equation (31), the rate constant, k_j, of a given reaction occurring in a dilute aqueous solution is related to the rate constant, $k_{j,\infty}$, for the same reaction occurring in infinitely dilute aqueous solution as follows:

$$\log (k_j/k_{j,\infty}) = 1.022Z_AZ_B\mu^{1/2} \qquad (35)$$

For about the last twenty-five years (84,85) this relation has been tested by plotting log k_j against $\mu^{1/2}$ and noting whether the theoretical limiting slopes were realized. In all cases the slopes had the predicted sign and magnitude. There is some disagreement whether the empirical data is uniformly in agreement with Equation (35). In 1922, Brønsted indicated that the activity of an ion is specifically affected by ions of the opposite sign. This concept, called the specific interaction of ions (86), was applied by him to kinetic data in 1925 (87). Olson and Simonson (88) revived this view in 1949 and questioned the general applicability of the Debye-Hückel equation to kinetic and equilibrium data. Probably the most reasonable approach to this controversial subject is the one which has been adopted by Wyatt and Davies (89). These authors use Guggenheim's modified ex-

pression (90) for the activity coefficients of an ion, this expression includes an empirical allowance for the specific interaction of ions, and explains large departures from Equation (35) in terms of the formation of complex ions.

3. Hammett's Rule

The rate at which an organic molecule reacts can be influenced in a number of ways, both steric and energetic, by a change in a substituent group which plays no direct part in the reaction (91,92,93). The effect upon the rate of substitution in an aromatic molecule in a position meta or para to the reacting group follows a particularly simple law. Hammett (94) has shown that a large number of such cases fit the following equations remarkably well (for a detailed critique of this rule, see Jaffé (95), Branch and Calvin (96):

$$\log k_{A,i} = \log k_{A,o} + \rho_A \sigma_i \tag{36}$$

where $k_{A,i}$ is the rate constant for a reaction A. The subscript i designates the substituent group; its special value, o, indicates an unsubstituted

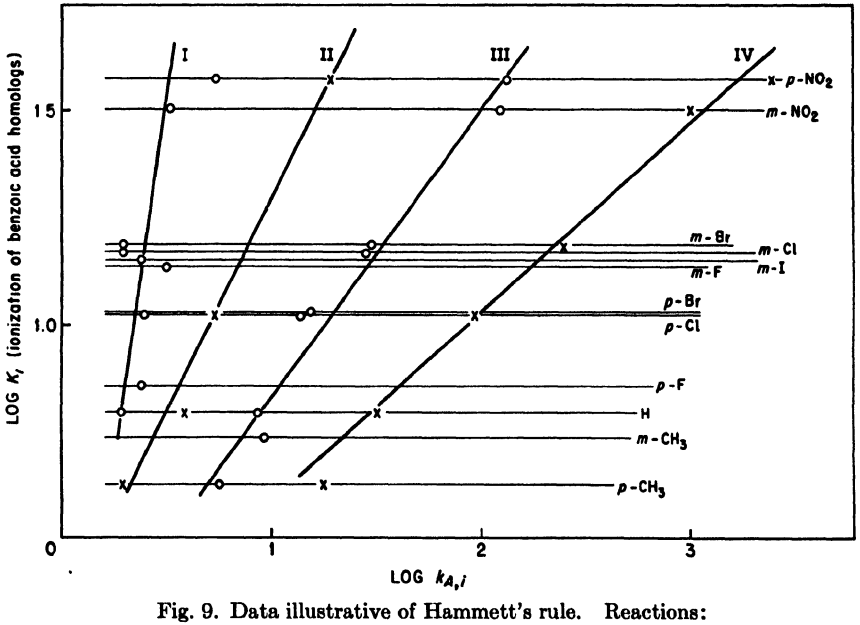


Fig. 9. Data illustrative of Hammett's rule. Reactions:
I. sodium acetate + (substituted) benzophenone.
II. aniline + (substituted) benzoyl chlorides.
III. methanol + (substituted) benzoyl chloride.
IV. NaOH + (substituted) chloride

molecule. The constant, ρ_A, is a function of the nature of the reaction, but not of the substituent. The constant σ_i is characteristic of the substituted group, but is independent of the reaction. A similar equation applies to equilibrium constants, $K_{A,i}$ and $K_{A,o}$. Hammett has used the ionization constants of substituted benzoic acids to determine the values of the σ_i. The values of ρ_A can be fixed in terms of a pair of measured values of $k_{A,i}$ and $k_{A,o}$ (or of $K_{A,i}$ and $K_{A,o}$). The application of this equation to typical data is illustrated by Figure 9 (97). That this equation is a special case of the transition state theory equation for reaction rates can be demonstrated as follows:

If χ is any intensive factor (such as pressure, electric potential, etc.):

$$-RT(\partial \ln K/\partial\chi)_T = (\partial\Delta F^0/\partial\chi)_T$$

where K is the equilibrium constants for a reaction and ΔF^0 is the corresponding standard free energy change. In particular, $\chi_{A,i}$ may be the electrical potential at the reactant group A induced by the substitution in the meta (or para) positions of a group designated by i. If we further assume that, in the range of values of χ to be considered, $\partial\Delta F_A{}^0/\partial\chi_A$ can be taken as constant and equal to g_A, we may write:

$$-RT\int_{\chi_o}^{\chi_i} d \ln K_A = g_A\int_{\chi_o}^{\chi_i} d\chi$$

Integrating this equation between the limits indicated for two reactions, A and B:

$$RT \ln K_{A,i} - (RT \ln K_{A,o} + g_A\chi_{Ao}) = -g_A\chi_{A,i}$$

$$RT \ln K_{B,i} - (RT \ln K_{B,o} + g_B\chi_{B,o}) = -g_B\chi_{B,i}$$

The electric potentials $\chi_{A,i}$ and $\chi_{B,i}$ produced at the similar reacting groups A and B by the common substituent are very probably proportional to one another, i.e., $\chi_{B,i}/\chi_{A,i} = r_{AB}$, where r_{AB} is not a function of χ. Using this relation, we may combine the two preceeding equations to obtain:

$$RT \ln K_{B,i} - RT \ln K_{B,o} - g_B\chi_{B,o} = (g_B/g_A)r_{AB}[RT \ln K_{A,i} - RT \ln K_{A,o} - g_A\chi_{A,o}]$$

which may be simplified as follows:

$$\log K_{B,i} - \log K_{B,o} = [(g_B/g_A)r_{AB}][\log K_{A,i}/K_{A,o}] \qquad (37)$$

The first factor on the right-hand side of the equation is a function of the nature of the reaction (B) only, and the second factor depends only on the substituent groups (i). (Both factors, ρ and σ, depend individually upon the choice of the standard reaction (A).) However, their product is independent of this choice. Accordingly we may substitute the symbols ρ_{AB} and σ_i, respectively, and obtain Hammett's rule (for equilibrium):

$$\log (K_{B,i}/K_{B,o}) = \rho_{AB}\sigma_i$$

An identical expression can be written for equilibria involving the transition states:

$$\log (K_{C,i}^{\ddagger}/K_{C,o}^{\ddagger}) = \rho_{AC}\sigma_i$$

Since:

$$k_{C,i} = (\kappa \cdot kT/h)K_{C,i}^{\ddagger}$$

$$K_{C,i}^{\ddagger}/K_{C,o}^{\ddagger} = k_{C,i}/k_{C,o}$$

and:

$$\log k_{C,i} - \log k_{C,o} = \rho_{AC}\sigma_i$$

Although the numerical values of the constants ρ_{AB} and σ_i must be obtained empirically, the form of this interesting and useful equation has been obtained directly from the transition state theory with the aid of a few reasonable limiting assumptions.

VII. STEPWISE MECHANISMS OF REAL REACTIONS

1. Reaction Steps

Both the collision and transition state theories apply directly only to simple reactions. Unfortunately, such reactions are almost unknown in practice. By far the great majority of organic reactions, which proceed at a measurable rate, are complex in nature. Indeed, the well-established rule that the kinetic *order* of a reaction cannot be predicted from its stoichiometric equation is an admission that most reactions are complex. A complex reaction is the result of the simultaneous occurrence of a number of simple reactions. Even as simple a reaction as the formation of hydrogen bromide from its elements is known to involve the occurrence of at least five simple reactions; and the formation of water from its elements requires twice as many to explain its observed kinetics. The simple reactions which make up the observed process are called *reaction steps.* The complete analysis of a real reaction requires: (*1*) the determination of what reaction steps are involved and how they are interrelated, and (*2*) the application of formal reaction rate theory to each of these steps.

Only three types of reaction steps occur in the homogeneous gas phase. They can be classified as unimolecular, bimolecular, and termolecular reactions. Of these, bimolecular steps are by far the most common. The product of a bimolecular reaction may be one molecule, as in an association process, two molecules, if the process is one of substitution, or three (or more) molecules, as when dissociation occurs:

$$AB + CD \longrightarrow AB \cdot CD$$

$$AB + CD \longrightarrow AD + CB$$

$$AB + CD \longrightarrow A + D + CB, \text{ etc.}$$

Only relatively complex molecules are capable of undergoing monomolecular changes.

If processes involving the emission or adsorption of radiation are included, the number of possible monomolecular steps is much greater. Such processes as the direct optical dissociation of simple or complex molecules, the predissociation of electronically excited molecules, the emission of photons by excited molecules, as well as radioactive changes, are all monomolecular processes.

The product of a monomolecular change may be either an isomer of the original molecule or two free radicals or stable molecular fragments:

$$ABC \rightarrow ACB$$

$$ABC \rightarrow A + CB$$

With the exception of the three-body combination of atoms or radicals:

$$2A + BC \rightarrow A_2 + BC$$

termolecular gas phase reactions are extremely rare.

Reaction steps occurring in solution are in general similar to those taking place in the gas phase. However, in the liquid phase the reactant molecules are caged in by and in constant collision with the solvent molecules. Accordingly, termolecular reactions in which a solvent molecule is a reactant are probably of common occurrence. The rate of a process whose energy of activation is zero or very small is limited, in a condensed phase, by the number of encounters (see Section II.5) rather than by the number of collisions. The rates of such steps, unlike those of all other simple reactions, are determined by the viscosity of the medium.

Reactions in heterogeneous systems can involve all these types of steps which occur in homogeneous systems. In addition the over-all rate may be controlled by diffusion of the reactants to or the products away from a phase boundary. The rates of adsorption or desorption can be important when one of the phases is a solid, as in heterogeneous catalysis. In some cases two-dimensional diffusion on the surface of a solid catalyst may be rate controlling.

2. Reaction Mechanisms

Since in general the rate equation of a chemical reaction does not have the form which would be predicted from the stoichiometric equation, the

products of the rate-determining step must differ from those of the over-all reaction. These intermediate products must undergo further reaction steps, eventually forming the stoichiometric products. A simple example of such a sequence of reactions is illustrated by the oxidation of iodide ion by hydrogen peroxide. In a dilute acid solution, the following reaction occurs at a measurable rate:

$$H_2O_2 + 2H^+ + 3I^- = 2H_2O + I_3^-$$

However, the rate of this reaction, instead of being proportional to the square of the hydrogen ion concentration and the cube of the iodide ion concentration, is represented fairly accurately (98) by the following equation:

$$-d[H_2O_2]dt = k[H_2O_2][I^-]$$

It follows, therefore, that the reaction step which determines the rate of the observed reaction is a bimolecular one involving hydrogen peroxide and iodide ion. The most probable products of this step are water and hypoiodite ion:

$$H_2O_2 + I^- \longrightarrow H_2O + IO^-$$

Hypoiodite ion cannot accumulate in a solution which contains an excess of hydrogen ion and iodide ion. The known occurrence of the following rapidly reversible equilibria explains how the formation of hypoiodite ion can lead to the final product, tri-iodide ion:

$$IO^- + H^+ \rightleftharpoons HIO$$

$$H^+ + I^- + HIO \rightleftharpoons H_2O + I_2$$

$$I^- + I_2 \rightleftharpoons I_3^-$$

The existence of such reaction intermediates must be postulated to explain the course of practically all real reactions. In some cases the transitory existence of the intermediate can be confirmed by direct measurement.

3. Reaction Intermediates

A number of types of chemical entities serve as intermediates in chemical reactions. These include molecular complexes, normal molecules which are unstable in the reacting system, radicals or atoms, diradicals, and unstable ions. A molecular complex is frequently postulated as the primary intermediate in autoxidations. Radicals or atoms serve as intermediates in a wide variety of reactions (99). Their existence and the role which they play in the reaction has been demonstrated unambiguously for reactions occurring in the gas phase.

There is good reason to believe that they play similar roles in solution reactions. The evidence for the occurrence of diradicals (100) and of unstable ions as intermediates in thermal reactions is chiefly indirect. However, it would be difficult to explain the observed course of many organic reactions if these intermediates were not assumed. There can be no reasonable doubt that ions act as intermediates in radiation chemistry (101), and diradicals in photochemistry (102).

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CHAPTER III

Fundamental Operations and Measurements in Obtaining Rate Data

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I. ACCURACY REQUIRED IN RATE MEASUREMENTS

1. General Considerations

To obtain values of rate constants and related quantities it is necessary to determine concentrations at known times and to control the environmental conditions (temperature, etc.) during the course of the reaction. The time and effort which must be spent increase rapidly with the required precision of the measurements. It is advantageous, therefore, to decide in advance what accuracy is necessary for each of the measurements and controls, and to plan the experiment accordingly.

The accuracy of a derived quantity depends on the accuracies of each of the independently measured quantities upon which it is based. It frequently happens that the uncertainty of one of these measurements is great enough to overshadow the combined effects of the uncertainties of the others. Under these conditions it is obviously foolish to attempt to

refine these relatively precise measurements. All available time and effort should be devoted to the improvement of the inaccurate measurement. Likewise, it is useless to make precise measurements of the variables, unless the environmental factors are controlled with corresponding exactness. In rate measurements, with the exception of some fast reactions, it is usually much easier to fix the time accurately than it is to attain corresponding accuracy in the measurement of concentration. Since, in general, reaction rates are sensitive functions of temperature, it is necessary that the reacting system be thermostated with special care.

It is not always necessary or even desirable to strive to obtain the highest possible accuracy in rate measurements. The precision which is required depends upon the use to which the data will be put. If the purpose of the experiment is to compare absolute empirical and theoretical values of a rate constant, the principal uncertainty in the comparison will usually be inherent in the theoretical value of the energy of activation. For this (immediate) use, an uncertainty in the experimental value of 50% could be tolerated. An uncertainty of 5% or less is desirable if an isotopic or solvent effect upon relative rates is to be compared with the predictions of rate theory. In this latter case, the temperature must be controlled within a few hundredths of a degree, but it is unnecessary to know the absolute temperature closer than to the nearest degree.

It should be remembered that all published values of rate constants are part of the literature of chemistry, and, as such, may be used for purposes that were not foreseen by the original experimenter. Some common sense must be used in balancing the accuracy of the result against the time consumed in obtaining it. In the author's opinion, it is preferable to determine rate constants within $\pm 10\%$ at two different temperatures rather than to devote the same effort to obtain the value within $\pm 2\%$ at a single temperature. It should also be borne in mind that precision and accuracy are not synonymous (1). There is no point in taking great pains to reproduce an (unknown) systematic error with great precision.

2. Propagation of Errors in Rate Measurements

The theory of least squares (2) makes it possible to determine the uncertainty of a derived quantity, e.g., a rate constant, in terms of the known random errors of the several measured quantities. It is convenient to use the standard deviation, σ, or the probable error, q, as a measure of uncertainty. For an observed quantity these functions may be defined as:

$$\begin{aligned} \sigma &= q/0.674 \\ &= [(N-1)^{-1} \sum_i r_i^2]^{1/2} \end{aligned} \tag{1}$$

where N is the number of measurements and the r_i are the departures from the mean m. For a function, p, of the variables S_i:

$$p = f(S_1, S_2, S_3, \ldots S_n)$$

the standard deviation, σ, of p is related to the standard deviations, σ_i, of S_i as follows:

$$\sigma = [\sum_i (\partial P/\partial S_i)^2 \sigma_i^2]^{1/2} \qquad (2)$$

It follows from this that the standard deviation, σ_m, of the mean, m, of N measurements is:

$$\sigma_m = \left[\frac{1}{N(N-1)} \sum_i r_i^2\right]^{1/2} \qquad (3)$$

An application of Equation (2) to a typical rate problem will illustrate the magnitudes of the interrelated standard deviations which are commonly encountered in kinetic data.

As an illustrative example, let us assume that it is desired to determine the heat of activation of a first-order reaction with an uncertainty not to exceed $\sigma_{\Delta H} = \pm 200$ cal. The heat of activation is approximately 25,000 cal., and the rate measurements are made at 300 and 330°C. Since:

$$\Delta H = [RTT'/(T' - T)] \ln (\bar{k}'/\bar{k})$$

the partial derivatives are:

$$\partial \Delta H/\partial T = [RT'^2/(T' - T)^2] \ln (\bar{k}'/\bar{k}) = -\Delta HT'/[T(T' - T)]$$

$$\partial \Delta H/\partial T' = -[RT^2/(T' - T)^2] \ln (\bar{k}'/\bar{k}) = -\Delta HT/[T'(T' - T)]$$

$$\partial \Delta H/\partial (k'/k) = [RTT'/(T' - T)]\, \bar{k}/\bar{k} = \Delta H/[(\bar{k}'/\bar{k}) \ln (\bar{k}'/\bar{k})]$$

Introducing these expressions into Equation (2):

$$(\sigma_{\Delta H}/\Delta H)^2 = \{T'/[T(T' - T)]\}^2 \sigma_T^2 + \{T/[T'(T' - T)]\}^2 \sigma_{T'}^2 + [(\bar{k}'/\bar{k}) \ln (\bar{k}'/\bar{k})]^{-2} \sigma_{\bar{k}'/\bar{k}}^2$$

The largest permitted value for the left-hand term is $(200/25{,}000)^2 = 6.4 \times 10^{-5}$. By exerting reasonable care (Section II) the temperature can be controlled so that $\sigma_T = \sigma_{T'} = \pm 0.01$°C. The corresponding contribution to $(\sigma_{\Delta H}/\Delta H)^2$ is:

$$\left[\left(\frac{330}{300 \times 30}\right)^2 + \left(\frac{300}{330 \times 30}\right)^2\right] 10^{-4} = 2.3 \times 10^{-7}$$

Since this is negligible compared to 6.4×10^{-5}, we may write:

$$[(\bar{k}'/\bar{k}) \ln (\bar{k}'/\bar{k})]^{-2} \sigma_{\bar{k}'/\bar{k}}^2 \leqq (\sigma_{\Delta H}/\Delta H)^2$$

or more conveniently:

$$\sigma_{\bar{k}'/\bar{k}}/(\bar{k}'/\bar{k}) \leqq [(T' - T)/(RTT')]\sigma_{\Delta H} = 3 \times 10^{-2}$$

If we make the assumption that $\sigma_{\bar{k}'}/\bar{k}' = \sigma_{\bar{k}}/\bar{k}$, each of these quantities can be as large as $3 \times 10^{-2}/2^{1/2} \approx 2 \times 10^{-2}$.

The quantities, $\bar{k}$ and $\bar{k}'$, are average values of the rate constants. In order to be definite, let us assume that they were determined by the method described in Chapter V, Section IV. 2, and that in all eighteen measurements of concentration were made at each temperature. Nine measurements were made at equally spaced intervals of approximately $\tau_{1/2}/18$, $\tau_{1/2}$ being the half-time. After a lapse of time, τ', of about $3\tau_{1/2}$, nine more measurements of concentration were made, separated by the same constant time interval was used for the first set. The first measurement of the first series is combined with the first of the second series, the second of the first series with the second of the second series, and so forth, to obtain nine independent values of:

$$k_i = (1/\tau') \ln (C_i'/C_i)$$

Since the changes in concentration during each of the series are not too great:

$$\sigma_{k_1} \approx \sigma_{k_2} \approx \sigma_{k_i}$$

By Equation (3):

$$\sigma_{k_i}/k_i = N^{1/2}\sigma_{\bar{k}}/\bar{k} \leqq 3(2 \times 10^{-2}) = 6 \times 10^{-2}$$

The quantities k_i (and k_i') are explicit functions of C_i, C_i', and τ' and implicit functions of temperature. To simplify the procedure, let us consider separately the effect of temperature. Since:

$$k = k^0 \exp(-\Delta H/RT)$$

$$\sigma_k \geqq (\partial k/\partial T)\sigma_T$$

Therefore:

$$\sigma_{k_i}/k_i \geqq (\Delta H/RT^2)\sigma_T = [25{,}000/2(300)^2]10^{-2} \approx 1.5 \times 10^{-3}$$

This indicates that the temperature control of ± 0.01°C. is more than adequate for the present purpose. Taking the partial derivatives of k_i:

$$(\partial k_i/\partial \tau') = -k_i/\tau' \text{ and } (\partial k_i/\partial C_i') = (\tau' C_i')^{-1} \text{ and } (\partial k_i/\partial C_i) = -(\tau' C_i)^{-1}$$

and introducing these relations into Equation (2):

$$\sigma_{k_i}^2 = (k_i/\tau')^2\sigma_{\tau'}^2 + (\tau' C_i')^{-2}\sigma_{C_i'}^2 + (\tau' C_i)^{-2}\sigma_{C_i}^2$$

or:

$$(\sigma_{k_i}/k_i)^2 = (\sigma_{\tau'}/\tau')^2 + (\tau' k_i)^{-2}[(\sigma_{C_i'}/C_i')^2 + (\sigma_{C_i}/C_i)^2]$$

It is reasonable to assume that (even including uncertainties in sample times) $\sigma_{\tau'}$ should not exceed 10 seconds. If in this case the smallest value of $\tau_{1/2}$ is one hour:

$$\sigma_{\tau'}/\tau' = 10/1{,}080 \approx 10^{-2}$$

This shows that $(\sigma_{\tau'}/\tau')^2$ is negligible compared to $(\sigma_{k_t}/k_t)^2$, which is $(6 \times 10^{-2})^2$, and it may be omitted from the preceding equation:

$$(\sigma_{k_t}/k_t)^2 \approx (k_t\tau')^{-2}[(\sigma_{C_t'}/C_t')^2 + (\sigma_{C_t}/C_t)^2]$$

Since in this experiment $\tau' = 3\tau_{1/2} = (3/k) \ln 2$:

$$(k_t\tau')^{-2} = (3 \ln 2)^{-2} \approx 0.22$$

and $C_t' \approx 8C_t$.

Introducing these special values:

$$(\sigma_{k_t}/k_t)^2 \approx 0.22\ [(\sigma_{C_t'}/C_t')^2 + 64\ (\sigma_{C_t}/C_t)^2]$$

When the ordinary methods of chemical analysis are used, the standard deviation of the concentration is practically independent of its absolute value; therefore, we may take $\sigma_{C_t'} = \sigma_{C_t}$. Accordingly, we may obtain the following relation:

$$(\sigma_{k_t}/k_t)^2 \approx 0.22[65(\sigma_{C_t'}/C_t')^2] \tag{4}$$

or:

$$\sigma_{C_t'}/C_t' \approx 0.26\ \sigma_{k_t}/k_t$$

This leads to the conclusion that the largest value of σ_{C_t}/C_t' which is consistent with the desired precision in ΔH is $0.26 \times 0.06 = 0.015$.

It should be realized that there is nothing general about this result. The standard deviations of time and concentration measurements and temperature control are interrelated quantities. They also depend upon the design of the experiment and upon the magnitudes of the measured quantities. The preceding discussion was presented only to illustrate the general simple methods that can be used, and to give examples of the magnitudes involved in a reasonably typical rate study. It should be emphasized that the proper design of an efficient and accurate experimental procedure is only possible after the magnitudes of the several quantities that are to be measured have been determined by preliminary experiments.

II. CONTROL OF ENVIRONMENT

Temperature is the most important environmental factor which affects reaction rate measurements. For some reactions, occurring in solution, it is necessary to hold the pH and ionic strength of the system practically

constant. Approximate constancy of pH is usually maintained by the addition of a buffer to the reacting medium. It is also possible, and in some cases preferable, to regulate the pH by continuous or automatic titration from a microburet (3), using a titrating solution which is relatively so concentrated that the addition of the required amount of reagent produces a negligible change in the volume of the reacting solution. The only feasible way of obtaining an invariant ionic strength is to add such a large excess of a chemically inert salt, e.g., sodium perchlorate, that the effect of the reaction upon the ionic strength can be neglected (4). While pressure control is necessary for isopiestic, gas-phase reactions taking place in static systems, this type of constraint is seldom used in kinetic studies. Rate measurements are nearly always made either in constant-volume static systems or in flow systems at approximately constant pressure.

Temperature control, while frequently vexatious, is seldom a major difficulty in kinetic measurements. Techniques have been developed and adequately described (5–8) which permit the control of temperature within the following maximum limits of variation: 0.001° for moderate temperatures, 0.005° for low temperatures, and approximately 0.1°C. for temperatures up to 900°C. It is more difficult to fix the absolute temperatures within these narrow limits (9), particularly in the high-temperature range.

Essentially, a thermostat is a device which keeps a temperature uniform over a restricted volume and constant during a time interval. Spatial uniformity is obtained by stirring or by using a medium of high thermal conductivity. Temporal constancy is maintained by balancing a suitably varying heat input against a slowly drifting heat loss. The heat input can be varied intermittently, or continuously and proportionately to the demand (10,11). Ordinary laboratory thermostats act on the intermittent principle, chiefly because intermittent regulators are relatively simple and inexpensive. The temperature fluctuation which is characteristic of intermittent regulation can be reduced by minimizing the regulated heat input. This may be accomplished either by lowering the heat loss with the aid of effective insulation or by balancing a large fraction of the heat loss with a steady input. A wide variety of satisfactory thermostats are commercially available, and the theory and practice of thermostat construction has been adequately described (5–8,12).

The active parts of an ordinary (liquid-bath) thermostat are an insulated container, a stirrer, a regulator, a relay, and a heater. At the present time, electrical heating and regulation are used almost universally in laboratory installations. The intermittent (or make-or-break) regulations are usually activated by liquid-in-glass thermometers. For very high or low temperatures or for proportional regulation, thermocouples or resistance

thermometers replace these make-or-break regulators. Because of their high sensitivity, small size, and low heat capacity, the use of thermistors (13) as thermostat regulators is increasing.

While sensitive electromagnetic relays can be used to interrupt the heating current, the use of electronic relays is preferable. The electronic relay can be used to control mechanical switches (frequently of the mercury-in-glass type), or the moving parts can be eliminated by the introduction of a thyratron (6) in a suitable circuit. Resistance heaters in direct contact with the thermostated medium are commonly used; but radiant (infrared) heaters (15) are better suited to some purposes.

Commonly, the reaction vessels are immersed in a stirred and thermostated liquid bath. Water is a very convenient liquid for the room-temperature range. For high temperatures, molten metals, such as lead (14), have been used. High-boiling oils, liquid silicones, and low-melting alloys are available for the intermediate range. A variety of noninflammable fluids has been demonstrated (16) to be useful for the low-temperature range. Metal blocks, which completely surround the reaction vessel, are convenient substitutes for liquid thermostats (12), particularly in the high-temperature range. Because of their high thermal conductivity, they eliminate the necessity for stirring.

The earlier experimenters often kept reaction vessels at fixed temperatures by suspending them in the refluxing vapors of pure liquids. If the vapor bath is properly designed and the system fitted with a barostat, to eliminate fluctuations caused by varying atmospheric pressure, adequate temperature control can be obtained in this way (16). It is relatively easy to keep a system at the melting point of ice or the sublimation point of solid carbon dioxide (16), if suitable precautions are observed.

In an unstirred reacting mixture, the temperature will not be uniform. For ordinary reactions occurring in liquid solutions, the effect of this temperature gradient is commonly negligible. However, it may have a marked effect upon the apparent (i.e., average) rate of fast, exothermic gaseous reactions (17).

III. MEASUREMENTS OF THE LAPSE OF TIME

1. Direct Measurement of Time

While some precautions must be observed in timing a reaction, the direct measurement of time seldom limits the accuracy of a rate determination. The time required for sampling, or for initiating and quenching a reaction, is likely to introduce a much larger uncertainty than is inherent in the performance of a good clock or watch (18).

The accuracy of an electric clock, which is run from a regular a.c. power supply, depends upon the care with which the frequency is monitored at the power station. For intervals of about 10 minutes, the maximum variation of such a clock is probably less than 0.2% (19). The percentage accuracy should be better for longer periods. Unless the highest accuracy is sought for, an electric clock or a good spring-driven clock or watch (18), should be satisfactory for timing reactions whose half-times are 30 minutes or more. Winstein has described (20) an ingenious method of timing moderately fast reactions.

The commonly used stop watches are in general less reliable. For short intervals (~0.5 minute), they may show errors as great as 1% (19). If they are used, care should be taken to keep them properly wound and to compare them frequently with dependable clocks or watches. When feasible two stop watches should be used for each measurement.

2. Instantaneous Analysis at Clocked Intervals

The precision of timing can be greatly improved by determining the concentration of the reactants indirectly, in terms of measurements of certain physical properties (Section IV.3.D,E) of the system. Refractive index and light absorption are ideal for this purpose, since they can be measured in times (1 microsecond or less) which are so short compared to the rate of an ordinary reaction that the analysis may be regarded as practically instantaneous. Continuous records of the changing values of such properties can be obtained by photographic, electrical, or mechanical means. Chronographs (21) which are adapted to a wide range of time scales are available commercially. The use of such methods greatly reduces the drudgery of rate measurements and, when they are properly applied, practically eliminates the contribution of the uncertainty in time to the standard deviation of the measured rate.

3. Initiating and Quenching Reactions

If the initial concentrations of the reactants are to be used in the calculation of a rate, the reaction must be started quickly and with a minimum disturbance of the temperature. Reactions between two or more compounds can be started by mixing solutions which contain the reaction components separately. These solutions can be brought to the temperature of the thermostat before mixing. By the use of a volumetric flask which is specially calibrated to deliver or of a fast-draining pipet (22), the reaction mixture can be prepared in 5 or 10 seconds with a precision of about 0.5%. To insure complete mixing within this time, rapid stirring or vigor-

ous agitation must be employed. Special devices for moderately fast (23) or fast mixing and quenching (24) of reactants have been described.

It is common practice, in the study of high-temperature reactions, to prepare the mixture at a convenient low temperature and then to raise its temperature rapidly to the desired value. This can be accomplished by immersing sealed vessels, containing the reactants, in a thermostat having a high heat capacity and thermal conductivity, or by allowing the reactants to flow rapidly into an evacuated reaction vessel which is situated permanently in the thermostat. If the latter technic is employed, it is advantageous to keep the inlet tubes at a temperature slightly above that of the thermostat. The time required for the equilibrium temperature to be attained approximately depends upon a number of factors: the heat capacity and thermal conductivity of the reaction mixture; the size, shape, and wall material of the reaction vessel; the temperature differential; etc. (25). It is necessary, therefore, to measure directly (as with a thermocouple) the time lag for each experimental set-up.

To follow the course of a reaction, samples may be removed from the reacting mixture with a pipet or similar device. The reaction occurring in the sample can be quenched by chilling, by dilution, by changing the pH, or by adding the sample to a reagent which reacts rapidly and quantitatively with one of the reactants. For example, a reaction between iodine and a reducing agent can be stopped by adding the sample to a suitably buffered arsenite solution, which would reduce the iodine as rapidly as the solutions could be mixed. The excess arsenite can then be titrated, and the iodine which was present in the sample be determined by difference. If the rate is proportional to the hydrogen (or hydroxyl) ion concentration, the reaction can be quenched by adding the sample to an excess of base (or acid) or to an appropriate buffer solution. If the order of the reaction is greater than first, the rate can be greatly decreased by adding the sample to a large volume of solvent. If the solvent is chilled, the rate is further retarded. Unless the reaction is very slow, it is advisable to sacrifice some accuracy in the measurement of the volume of the sample by using a pipet with a short delivery time. For samples of 5 ml. or less, it is convenient to use a hypodermic syringe as a pipet. The quenching solution should be agitated vigorously while the sample is being added.

For high-temperature reactions or for very slow processes, the original reaction mixture can be divided into a number of equal parts and sealed in separate containers. The sealed vessels are placed in the thermostat simultaneously, and removed one at a time after suitable intervals of time. The reaction can be stopped by rapid chilling of the individual containers (15), or by breaking the vessel under an appropriate quenching solution,

4. Flow Systems

A. STRAIGHT TUBES

Flow systems, both of the *straight tube* and of the *stirred reactor* types, have been widely used in the study of reaction rates. The straight tube type is used for very rapid reactions in liquids (Chapter XIV) and more generally for gas reactions. In the latter case the reactant (or mixture of reactants) is introduced at a constant rate at one end of a heated tube. At the other end of the tube, the reaction in the effluent gases is quenched by rapid chilling. The rate of flow of the entering gases is measured with either a metering device or a capillary flow meter (26). The effluent gases are collected and analyzed. The time, τ, which the reactants spend in the thermostated tube can be readily calculated from the measured rate of flow, F, and the dimensions of the tube:

$$\tau = V_r(\text{cc.})/F(\text{cc./sec.}) = \pi r^2 l_r/F(\text{sec.}) \tag{5}$$

where V_r, r, and l_r are, respectively, the volume, radius, and length of the tube.

If there is a change in the number of molecules due to the reaction, this may be taken into account in a fairly simple way, as is illustrated by the following analysis of a first-order reaction:

$$\mathrm{A} = m\mathrm{M}$$

If the entering gas consists of the pure reactant and the number of moles introduced per second is N_A^0, the total number passing (per second) through a cross section of the tube, at a distance l from the entrance is:

$$\begin{aligned} N &= N_A + N_m \\ &= mN_A^0 + (1 - m)N_A \end{aligned}$$

If we make the reasonably good approximation that the drop of pressure along the tube is so small that it can be neglected, an element of volume which was equal to V^0 on entering will expand to V at the point l, and the ratio of these volume elements will be equal to the ratio of the number of moles:

$$V/V^0 = [mN_A^0 + (1 - m)N_A]/N_A^0$$

The initial rate of flow is dV^0/dt (cc./sec.), and the rate at the point l is dV/dt. Therefore:

$$dV/dt = (dV^0/dt)[mN_A^0 + (1 - m)N_A]/N_A^0$$

The corresponding linear rate of flow, dl/dt (cm./sec.), is:

$$dl/dt = (1/\pi r^2)(dV/dt) = (dV^0/dt)[mN_A^0 + (1 - m)N_A]/\pi r^2 N_A^0$$

Since the reaction is first order:

$$-dN_A/dt = kN_A$$

Combining these two equations:

$$-dN_A/dl = [\pi r^2 k/(dV^0/dt)](N_A^0 N_A)/[mN_A^0 + (1 - m)N_A]$$

or:

$$-m\int N_A^{-1} dN_A - [(1 - m)/N_A^0]\int dN_A = [k\pi r^2/(dV^0/dt)]\int dl$$

Integrating between the limits, l_r and 0 and N_A' and N_A^0:

$$m \ln (N_A^0/N_A') + (1 - N_A'/N_A^0)(1 - m) = k\pi r^2 l_r/(dV^0/dt) = kV_r/(dV^0/dt) \quad (6)$$

Since N_A' can be obtained by analysis of the effluent gases, this equation permits the calculation of k in terms of directly measurable quantities. Similar relations may be derived for other reaction orders (27–29). The correction for the change in the number of molecules may be rendered negligible by using a large excess of a chemically inert carrier gas. However, if this is done, it should be remembered that the presence of the inert gas may influence the rate of the reaction.

As applied to homogeneous reactions having moderate or slow rates, the advantages of the straight tube flow method appear to have been exaggerated. There are two important sources of error inherent in the method. The gas does not attain the temperature of the thermostat the instant that it enters the reactor, nor is the reaction quenched immediately when the reactants leave the tube. In any simple analysis (such as the preceding one) of the results of flow experiments, it is assumed that each differential element of volume flows through the reactor as though it were confined, at constant pressure, between two pistons. This neglects the effects of convection and of diffusion upon the observed reaction.

For slow rates of flow, the temperature error can be minimized by equipping the reaction tube with narrow inlet and outlet tubes and surrounding these tubes as well as the reactor by the thermostat (30). A preheater, of relatively small volume, is sometimes used to bring the entering gases quickly to the desired temperature (31).

It is difficult to estimate the effect of convection in a flow system. The usual practice is to avoid, in the design of the apparatus, the more obvious sources of convection, and to assume that the effect of convection is negligible. In principle, the effect of diffusion can be taken into account

in the calculation of the results (32). In practice, such corrections are difficult and uncertain, and are nearly always neglected. This neglect is probably only justified when not more than 5 or 10% of the reactants are used up as they pass through the tube.

B. STIRRED REACTORS

Uncertainties caused by convection and diffusion can be eliminated by stirring the reacting mixture as it flows through the reactor. If the stirring is fast enough the concentrations of reactants and products will be uniform throughout the vessel. After a time, a steady state is reached (approximately) during which the concentrations are determined by a balance between the rate of the reaction and the rates of flow. For example, if the rate of a reaction:

$$A + B = M + N$$

is given by the equation:

$$-d[A]/dt = k[A]^i[B]^j$$

the steady state concentrations of A and of M will be given by the following relations:

$$dN_A/dt = V[A]_0 - V[A]_s - V_r k[A]_s^i[B]_s^j$$

$$V([A]_0 - [A]_s) = V_r k[A]_s^k[B]_s^j \tag{7}$$

or:

$$V[M]_s = V_r k[A]_s^i[B]_s^j \tag{8}$$

In these equations, V_r is the volume of the reactor, in liters; V is the volume rate of flow, in liters per second; N_A and N_M are, respectively, the number of moles of A and of M in the reactor; and the subscripts 0 and s denote, respectively, the initial and steady state molarities. No allowance has been made for the effect of a change in the total number of moles due to the reaction, since it is assumed that the reaction takes place in a (dilute) liquid solution.

In recent years, such stirred reactors have been widely applied in the chemical industries (33), and their usefulness in the study of the kinetics of reactions occurring in liquid solutions has been demonstrated (34). The method is particularly advantageous in the study of complex reactions, since the determination of the rate law (compare Equation 7) involves neither integration of the rate equation (Chapter V, III.2) nor estimation of rates from integrated data. However, these advantages are partially offset by the fact that a separate experiment must be performed to measure the rate corresponding to each set of concentrations of reactants and prod-

ucts. Denbigh (34f) recommends that the usual static measurements (Chapter V,III.2) be used to determine, approximately, the rate equation for a complex reaction and that the stirred-reactor technique be employed to determine the fine details of the mechanism. The rate equation can be evaluated from steady state measurements by making several measurements with different rates of flow, V (or by using two or more reactors in series (34)), and by changing the initial concentrations of the reactants Since the time required to attain the steady state (33c,34c,d) increases with the half-time of the reaction, the direct use of the method appears to be practical only for moderately rapid reactions (whose half-times are in the range of 1 minute to 1 hour). The usual batch method is more convenient for studying the rates of slow reactions, and the straight tube reactor is better adapted to the study of fast reactions (Chapter XIV).

The steady state concentrations can be determined analytically or by the measurement of any of a number of physical properties (Section IV.3 (33c,35)). For slow reactions, a sample of the effluent liquid may be collected and analyzed. For faster reactions, it is preferable to resort to continuous titration in a second reactor (34c), or to stop the reaction in the mixture as it leaves the reactor by mixing it rapidly with a suitable quenching reagent (Section III.3) (36).

IV. MEASUREMENT OF CONCENTRATION OR QUANTITY

1. General Considerations

In addition to beihg accurate, analytical methods that are to be used in kinetic studies should be quick. An ideal method would be practically instantaneous and, preferably, capable of yielding a continuous record of rapidly changing concentration. When the sampling-and-quenching technique is used, speed of analysis is not essential. High reproducibility, i.e., precision, of the results of a series of measurements is not sufficient evidence that the method is accurate. For example, if a McLeod gauge (37) were used to measure the pressure of a gas which was readily adsorbed on the wall of the glass capillary, the results might be highly reproducible but much less accurate. Any new analytical method, or any established method that is used under unusual conditions, should be carefully examined for systematic as well as random errors.

The analytical procedure should not affect the rate of the reaction. A conductivity method using platinized electrodes should not be applied to the study of a reaction that is catalyzed by platinum black. Similarly, a photometric method should not be used on a system that is photochemically labile (to light of the wave length used).

All indirect methods of analysis should be calibrated using known mixtures of the reactants and products, under conditions which duplicate, as closely as feasible, those prevailing in the reacting system. The determination of the reaction rate is simplified if the calibration is not a sensitive function of environmental factors, such as temperature, the nature of the solvent, etc. It is convenient to use properties which are simple, exact functions of the composition of the solution, although properties which are complicated or empirical functions of composition may be employed if sufficient care is taken in the calibration of the method. In using an indirect method of analysis, it is essential that the stoichiometry of the reaction be known as exactly as possible. Failure to take side reactions into account invalidated (38) the results of a number of otherwise careful measurements of reaction rates of gas reactions which were followed by pressure determinations.

2. Direct Measurements

A. CHEMICAL ANALYSIS

The most reliable way of following the course of a chemical reaction is to apply the standard and tested methods of analytical chemistry to samples, withdrawn (and quenched) at suitable intervals. Unless the stoichiometry of the reaction is thoroughly established (38), analysis should be carried out for all probable products as well as for the reactants. Such analytical methods are relatively laborious and time consuming. To avoid this expenditure of time and effort, indirect methods of analysis are frequently used. It should be remembered, however, that the *accuracy* of even the most *precise* of these indirect methods can be no better than the *accuracy* of the standard analytical procedure that was used to calibrate the method. While an indirect method can, in some instances, be calibrated with the aid of synthetic mixtures of pure compounds, the determination of the stoichiometry—including the detection and estimation of the products of side reaction—is always based upon the standard methods of analytical chemistry.

Particularly in the study of gas reactions by the batch method, the samples available for analysis are relatively small. To deal with such small quantities, micro and low-pressure gas burets and special analytical methods have been developed (39). The mass spectrograph is frequently used for the routine analysis (40) of gaseous mixtures. While it must be calibrated with mixtures of known composition, it has the advantage of requiring only very small samples. The use of gas phase chromatographic separation (41) has revolutionized the analysis of complex mixtures of gases and vapors.

B. GAS EVOLUTION METHODS

The rate of a chemical reaction can be evaluated by determining the amount of gas liberated from or absorbed by a liquid reacting system. This old and widely used procedure is applicable whenever one of the reactants or products is a gas. Since the reaction occurs in the liquid and the quantity of matter appearing or disappearing is measured in the gas phase, it is essential that distribution equilibrium between the two phases be maintained (42). It is difficult to establish and maintain equilibrium if the reaction is fast or if the gas is very soluble in the liquid. Since the rate of evolution or absorption of the gas is limited by diffusion in the liquid, the process can be accelerated by stirring the liquid and by creating as large a liquid–gas interface as possible. The change of solubility with temperature requires that the system be very closely thermostated if the gas is appreciably soluble in the reacting mixture.

Gas evolution (or absorption) measurements can be made with relatively simple apparatus, consisting of a thermostated reaction vessel, in which the liquid can be agitated, connected to a gas buret or manometer. The liquid can be agitated by shaking the flask, or by means of a rotary stirrer. Commonly, the flask is attached to a shaker and connected to a fixed buret by a flexible coupling (43), such as a short piece of rubber tubing. Alternately, the flask and buret may be joined rigidly, and the assembly agitated as a unit (43). If a stirrer is used, it can be driven by a shaft passing through a gas-tight stuffing-box (conveniently of the mercury-sealed type (34)), or it can be contained entirely within the reaction vessel and driven from the outside, magnetically (44). To avoid errors due to changing ambient temperature, the buret should be thermostated (42), i.e., water-jacketed. If this is not feasible, the volume of the buret must be kept very small relative to the gas space in the reaction vessel. An elegant modification of the classical apparatus, using a differential manometer and a flexible, glass capillary connection, was described by Brønsted and King (45). Automatic bubble counters (46) have sometimes been used to measure the rate of gas evolution. A constant volume apparatus equipped with a strain gauge (47) has been used to follow the rates of rapid gas-evolving reactions.

To evaluate the changing concentration of a reactant at a time t, in terms of the observed increase in gas volume, ΔV, at constant pressure P, it is necessary to know the stoichiometry of the reaction and the volume, V_l, of the (liquid) reacting mixture. For a reaction:

$$\mathrm{A} + b\mathrm{B} = m\mathrm{M} + \mathrm{N}$$

where only M is gaseous, the concentration of A is given by the following equation:

$$\begin{aligned}[A] &= [A]^0 - x \\ &= [A]^0 - (N_m/mV_l) \\ &= [A]^0 - (P\Delta V/mRT_gV_l) \end{aligned} \quad (9)$$

where N_m is the number of moles of M formed in time t, and T_g is the temperature of the gas in the buret.

As commonly performed, gas evolution measurements are rendered uncertain by the necessity of making vapor pressure corrections. If the reaction occurs in dilute aqueous solution and the evolved gas is confined over water, which is at the same temperature as the reaction mixture, no correction is necessary. If the vapor pressures of the reactants and solvents are negligibly small and the gas is confined over (say) water, the observed change in volume should be multiplied by the factor $(P - P_w)/P$, where P_w is the vapor pressure of the confining liquid. Another way to simplify these corrections is to keep the buret and connecting tubes at a temperature above that of the reaction vessel and to use a nonvolatile liquid, like mercury, in the buret. In this case, the measured change in volume should be multiplied by the factor $(P - P_r)/P$, where P_r is the vapor pressure of the reacting mixture. If a constant-volume, varying-pressure system is employed, it is necessary to know the total volume of the gas space and the solubility coefficient of the gas in the reacting mixture.

C. COLLECTING AND WEIGHING THE PRODUCT

Reactions which either precipitate solids or evolve gases can be studied by collecting and weighing the product. The collection and weighing of a solid precipitate (48) is a cumbersome process and there is little to recommend it, if other analytical methods are available. A continuous record of gas evolution can be made (49) by absorbing the gaseous product on a suitable absorbent which is contained in a vessel suspended from a spring scale or a balance arm.

3. Indirect Measurements

A. GENERAL DISCUSSION

Measurements of physical properties can be used in two different ways to follow the course of a reaction. Samples of the reacting mixture can be taken at suitable times, and these samples can be then analyzed by measuring some physical property. More conveniently, the measurements can be made from time to time on the reacting system as a whole, preferably without disturbing the rate of the reaction. By a proper modification, the latter method can be made to yield a continuous record of the

values of the property, and indirectly of the concentrations, as a function of time.

As an illustration, consider a system whose concentrations can be determined by measuring its absorption of monochromatic light. If the sampling technique is followed, small volumes of the reacting mixture are withdrawn at known times, immediately quenched (Section III.3), and introduced into the cells of a spectrophotometer, where their optical densities (for the particular wave length) are determined. The method of quenching should either produce no change in the optical density, or else should modify the optical densities of all samples to the same extent, and in a known way. Alternatively, the reaction can be allowed to proceed in the cell of the spectrophotometer, and the optical density determined after known intervals without disturbing the reaction. If this procedure is followed, sealed or tightly stoppered cells and a thermostated cell carriage should be used in the spectrophotometer. A continuous record can be obtained by feeding the output of the photocell, which receives the beam of monochromatic light after it has passed through the vessel containing the reaction mixture, to a suitable chronograph. For this purpose, recording spectrophotometers in which the wavelength drive is replaced by a linear time drive are commercially available. While it is relatively simple to obtain a continuous record of a property such as light absorption, continuous records may be made of practically any changing property, if the advantages of such a record warrant the required expenditure of time and effort.

With regard to their usefulness in the study of kinetics, physical properties fall into two major groups, properties of general utility and those of special applicability for particular systems. With very few exceptions, reactions occurring in liquid media produce readily measurable changes in the density and refractive index of the solutions. Pressure changes are commonly used to follow the rates of gaseous reactions which produce changes in the total number of gas molecules. Since practically all reactions are accompanied by the evolution or absorption of heat, the change in temperature of an adiabatic system is a general measure of the course of a reaction. For certain types of reactions, special properties are sensitive functions of the composition of the reacting system. The absorption of light, rotation of the plane of polarized light, conductivity, magnetic susceptibility, and viscosity are useful properties of the latter type.

B. DENSITY OF LIQUIDS

Whenever the partial molar volumes of the reactants and products differ appreciably, there will be a measurable change in the density of the reacting system accompanying the reaction. Since the precise measurement

of density is comparatively simple (50), this property has been widely used for the indirect analysis of reaction mixtures. When the measurements are restricted to dilute solutions, the change in density (or in volume of the sample) is, to a very close approximation, a linear function of the percentage completion of the reaction (51). However, empirical calibration must be employed when the density method is applied to reactions in concentrated solutions or in the absence of a solvent. For example, the density of a binary mixture (over a wide range of composition) is usually a nonlinear—and may even be a multivalued—function of composition.

The progress of a deuterium-hydrogen exchange reaction (Chapter XXVI) can be determined by isolating one of the reaction components, burning it, and determining the density of the resulting water. The *falling drop* and *density gradient* methods (52) of measuring (relative) densities are well adapted to such analyses, since they are precise, relatively rapid, require only small samples, and use comparatively simple apparatus.

The most common use of the density technique in kinetic studies involves the measurement of the change in volume (of the total sample) that is concurrent with the progress of the reaction in the sample. The change in volume can be measured conveniently with a dilatometer (53). A dilatometer is a bulb provided with a side tube through which it can be filled and with an open-end capillary. After the bulb is filled with the reacting mixture, the side tube is closed by means of a stopcock or a mercury cut-off (54) or (for very slow reactions) by sealing off the tube at a thin-walled construction (55). Since the volume of the capillary can be made very much smaller than that of the bulb, an extremely small percentage change in the volume of the liquid results in an easily detectable motion of the meniscus in the capillary. The position of the meniscus can be compared directly to a scale, fastened to or engraved upon the capillary, or it may be read with a cathetometer.

There is no difficulty in obtaining high sensitivity in dilatometric measurements, but it is somewhat more troublesome to render innocuous the effect of systematic errors. Since the dilatometer is a sensitive thermometer, minor variations in temperature result in spurious movement of the meniscus. A maximum variation of the thermostat temperature of 0.01°C. is sometimes allowable, but more often the temperature must be maintained within ±0.001°C. If the heat of the reaction is appreciable, differences in temperature will be set up between the reacting liquid and the thermostat bath and will affect the position of the meniscus (56). This is a serious source of error for fast reactions, but is relatively unimportant for slow reactions. The mixing of the reactants usually results in a noticeable change in temperature. Unless this change is counteracted (54) before the dilatometer is filled, relatively large errors (56) may be introduced into

the first few measurements of the volume. It is also essential that the capillary be of uniform bore, or that any deviations from uniformity be known and corrected for.

To summarize, the dilatometric technique is applicable to most reactions which take place in liquid solutions. It is especially useful for slow and moderately rapid first-order reactions and for slow reactions of any order. If suitable precautions are observed, the measurements can be made as precise as is required for any ordinary kinetic studies. The equipment, aside from a good thermostat, is simple and inexpensive. Readings can be taken visually in one or two seconds and do not disturb the course of the reaction. Automatic records can be obtained with ordinary photographic equipment. For dilute solutions, density or specific volume is a linear function of the composition of the solution, within the required limits of accuracy.

C. REFRACTIVE INDEX

Concentration changes can be followed by measuring the attendant changes in refractive index. This method is, in many respects, quite similar to the dilatometric technique. They are both applicable to a wide variety of reactions; high precision can be obtained by their use; and both density and refractive index are approximately linear functions of concentrations (51) for dilute solutions. Since the changes in refractive index are small, an interferometer (57) is well adapted to their measurement. In the common Raleigh interferometer a light beam is split and passed through two identical cells, and the relative refractive indices of the substances contained in the cells is determined by evaluating the difference between the optical lengths of the two paths. In applying the instrument to a kinetic study, one of the cells is filled with the reacting mixture and the other with a reference liquid whose refractive index is very close to that of the mixture. The difference in refractive index produced by the reaction can be followed by counting fringes or by tilting a compensating plate which is placed in one of the light beams.

As in the use of the dilatometer, the chief experimental difficulties occur in mixing the reactants and introducing the solution into the cell and in insuring that the temperature of the system is uniform. If the reference liquid has (approximately) the same cubic coefficient of expansion as the reacting solution, it is unnecessary to thermostat the system precisely. It is, however, essential that the two cells be, very exactly, at the same temperature. The difficulty of maintaining this condition can be reduced by establishing good thermal contact between the two cells (58).

The use of the interferometer in kinetic studies has about the same advantages and disadvantages as the use of the dilatometer. While the

dilatometer requires a more precise thermostat, the interferometer is a more expensive instrument. Of the two, it is easier to obtain a continuous or automatic record of dilatometer readings. However, a continuously recording interferometer has been constructed (59) and applied to the measurement of rates of moderately fast polymerizations. In these (constant-pressure, liquid) systems the refractive index is affected more strongly by the adiabatic heating than by the change of composition.

D. PRESSURE, PARTIAL PRESSURE, AND DENSITY OF GASEOUS SYSTEMS

The kinetics of homogeneous gas reactions are very commonly studied by measuring the changing pressure of the system at constant temperature and volume. When the reaction results in a change in the total number of gas molecules, its progress can be followed by measuring the total pressure. This can be accomplished without disturbing the rate of the reaction. In some cases, the extent of a reaction can be evaluated by chilling the system and determining the pressure of one or more of the reaction components at a known, low temperature, at which the other reactants and products are frozen out and exert negligible vapor pressure. For example, the synthesis of hydrogen chloride from its elements can be studied by immersing the reaction vessel (after allowing it to react for a known time) in liquid oxygen and measuring the pressure, which is due to hydrogen only. Alternatively, samples of the reacting mixture may be withdrawn and their pressures determined before and after exposing them to a non-volatile reagent which removes one (or more) of the reaction components. When one of the products is quantitatively absorbed by solid reagent which does not otherwise affect the reaction, this reagent may be introduced into the reaction vessel and by its presence cause the reaction to produce a reduction in the number of gas molecules.

A wide variety of pressure-measuring devices exists, and these have been used in rate studies. They have been adequately described elsewhere (47,60) and will not be discussed in detail in this chapter. Special manometers have been developed for the measurement of high, moderate, and low pressures. Some of these can be easily adapted to give continuous records of pressure. Null point pressure indicators of glass, quartz, or metal are useful in the study of corrosive gases or high-temperature systems. By the use of the proper manometric systems, the precision and reliability required in kinetic investigations can be obtained without excessive difficulty. It should be emphasized that manometric measurements of reaction velocity are meaningless unless the stoichiometry of the reaction is known (Section IV), and are no more accurate than the stoichiometric information.

In some instances, the gas density changes although there is no accompanying change in the number of molecules of gas. For example, an exchange reaction may result in the substitution of HD for H_2 molecules. Such processes can be measured conveniently with a gas density balance (61). This is an apparatus by which a sealed, thin-walled glass or silica sphere can be weighed in a gas or a vacuum. From the difference in weight and the known volume of the sphere, the density of the gas can be calculated. Commonly, the balance is used as a null instrument. The pressure of an unknown gas is adjusted until its density is the same as that of a known gas at a definite pressure and at the same temperature. The composition of an unknown mixture of two known compounds can be obtained from such a measurement. If at pressure P and temperature T the density, of a binary mixture of components A and B, is the same as the density of pure gaseous A at the same temperature and at pressure, P^0, and if we may assume that the perfect gas law holds:

$$M_A(P^0/RT) = [M_A M_B(m_A + m_B)/(m_B M_B + m_B M_A)]\ [P/(RT)]$$

or:

$$\text{weight per cent of B} = [M_B/(M_B - M_A)][(P^0 - P)/P^0] \qquad (10)$$

where M_A and M_B denote the molecular weights and m_A and m_B the masses of each component present in a unit volume.

E. TEMPERATURE OF ADIABATIC SYSTEMS

Perhaps the most promising of the generally applicable, indirect methods of studying reaction rates is the one based upon measurement of the changes in temperature of an adiabatic reaction system (62,63). The variation in temperature is due to the heat of reaction. Insofar as the heat capacity, $\bar{C}_p$, of the system and the heat of the reaction, ΔH, may be taken as constant and independent of the progress of the reaction and the corresponding change in temperature, the directly observable change in temperature is a linear function of the extent of the reaction. If x is the number of moles of reactant A disappearing and ΔH is the molar heat of reaction expressed in calories per mole of A consumed:

$$q = x\Delta H$$

Since q is the heat evolved in the reacting system and $\bar{C}_p$ is the heat capacity of the system, including the solvent and calorimeter:

$$q = \bar{C}_p \Delta T$$

or:

$$\Delta T = (\Delta H/\bar{C}_p)x \qquad (11)$$

If, as is common practice, the experiments are performed with dilute solutions, the variation in the temperature is small (less than 0.1°C.) and the preceding equation is a valid approximation within the limits of precision of measurement.

Although these experiments are, strictly speaking, adiabatic processes (Chapter V,II), the total change in temperature can be made so small that it is justifiable to treat the reactions as if they were isothermal, that is, to neglect the change in the rate constant with varying temperature, and therefore with time. For very precise work or for cases where the change in temperature is unusually large (say 0.1° or greater), the change in the rate constant, k, may be allowed for by treating it as a linear function (63) of temperature:

$$k_{T+\Delta T} = k_T[1 + (\epsilon/RT^2)\Delta T] \tag{12}$$

where ϵ is the Arrhenius heat of activation. The use of this approximation greatly simplifies the treatment of an adiabatic reaction (Chapter V.II).

The thermal method of measuring rates of reactions is readily applicable to fast or moderately rapid reactions of first or second order. By the use of straight tube reactors (Section III.4), the rate of fast reactions may be determined from temperature measurements (63,64,65). For slower reactions, Sturtevant has developed and tested a special adiabatic calorimeter which is well adapted to the precise study of reactions whose half times lie in the range from 3 to 200 minutes. Since the measurement is made with a multi-junction thermocouple, it is comparatively simple to obtain a continuous record (68) of the changing temperature. Under favorable circumstances, both the rate constant and the heat of the reaction may be determined from measurements on a single solution.

An ice calorimeter has been used (66) to follow the course of reactions whose rates fall in the intermediate range. For rapid reactions, the transfer of heat from the reacting mixture to the ice mantle is too slow to permit the attainment of a thermal steady state, corresponding to a moderately small temperature differential. The study of slow reactions is limited by the natural fluctuation in the rate of spontaneous melting of ice.

R. Bell has developed (67), and extensively used, an ingenious modification of the thermal method, in which the reaction occurs in a vessel that is in direct contact with a thermostat. In such a system the temperature rises to a maximum and then falls as the rate of the reaction decreases. For first or second order reactions, the rate constant may be calculated from the measured maximum difference in temperature between the thermostat and the reactants. This technique is particularly useful for the study of the catalytic efficiency of a variety of substances upon a given, moderately rapid reaction.

Under proper circumstances the several calorimetric methods of studying reaction rates yield precise results. They are applicable to practically all types of chemical reactions of simple order. It should be remembered, however, that these, like all other indirect measurements, are no more accurate than the analytical methods which are used to determine the stoichiometry of the reactions.

F. LIGHT ABSORPTION

The absorption of light is a specific property of the absorbent (69). Both the magnitudes of the absorption coefficients and the wavelengths at which absorption maxima occur are characteristic of the absorbent compound and, to a lesser extent, of its physical state. If, in a multicomponent solution, there is only one colored, i.e., absorbent, compound present, its concentration can be determined by measurement of the absorption coefficient corresponding to a single wavelength. If two colored substances are present, both concentrations can be evaluated spectrophotometrically by measuring the light absorption of the solution at two suitably chosen wavelengths. The concentrations of n colored components of a solution can, in principle, be similarly evaluated in terms of n measurements of light absorption; however, except in unusually favorable cases, the precision of such measurements, where n is greater than two, is so low that they are of little value. The method can be applied to atoms or simple or complex molecules, and to gaseous or liquid solutions. Approximately, absorption in the visible and in the ultraviolet is a characteristic of the molecule as a whole, while infrared absorption peaks are determined by individual groups, such as:

The basis of spectrophotometric analysis is Beer's law:

$$I = I^0 \exp(-\alpha_\lambda c l) \tag{13}$$

which applies strictly only to the absorption of monochromatic light by a single colored substance. In this equation, I^0 is the intensity of the incident light, I is the intensity of the light transmitted by a layer of a solution of thickness, l, containing a colored substance at a concentration c. The absorption coefficient, α, is a function of the wave length, λ, of the chemical nature of the absorbent, and (to a lesser extent) of such environmental factors as temperature and the nature of the solvent. The numerical value of α depends upon the units in which c and l are expressed, and upon whether e or 10 is used as the base for the exponential. For routine chemical purposes, it is convenient to express c as molarity, [A], and l

as centimeters, and to use the base 10. In these terms, Beer's law may be written as follows:

$$[A] = (1/\alpha_\lambda l) \log (I^0/I)$$

The fundamental equations, when two colored substances A and B are present, are:

$$\alpha_{A,\lambda_1}[A] + \alpha_{B,\lambda_1}[B] = (1/l) \log (I_1^0/I_1) \quad (14)$$

$$\alpha_{A,\lambda_2}[A] + \alpha_{B,\lambda_2}[B] = (1/l) \log (I_2^0/I_2) \quad (15)$$

where the subscripts 1 and 2 refer to the wavelengths of the incident light. It is apparent that, if the absorption coefficients are known for each pure compound corresponding to the two wavelengths, the concentrations may be determined from measurement of (I^0/I) at each wave length.

When there is only a single absorbing substance present, its concentration is approximately proportional to I/I^0 if this quantity is very small. However, it is difficult to make accurate measurements under these conditions. Precise practical measurements are usually limited to a range of values for I/I^0 between 0.2 and 0.9, where the complete form of Beer's law must be retained. The rate of any simple reaction can be expressed directly in terms of I and t, by eliminating c between Beer's law and the rate equation (71). Let us consider, for example, a second-order reaction:

$$2A \longrightarrow 2M + N$$

where only M is colored. Accordingly we may write:

$$[M] = (1/\alpha l) \log (I^0/I)$$

and:

$$1/([A]_0 - [M]) - 1/[A]_0 = kt$$

Eliminating [M] between these equations:

$$\log (I^0/I)/\{\alpha l[A]_0 - \log (I^0/I)\} = [A]_0 kt$$

when $t = \infty$, $[M] = [A]_0$, and $\alpha l[A]_0 = (\log I^0/I_\infty)$. Introducing these relations into the preceding equation, it may be put in the following form:

$$\log (I_0/I)/\log (I/I_\infty) = [A]_0 kt \quad (16)$$

For spectrophotometric purposes, light may be considered monochromatic if α is sensibly constant over the range of wave lengths represented (with appreciable intensity) in the incident light. Monochromatic radiation can be isolated by light filters (72) from line sources, such as low-pressure mercury arcs. Narrow bands of wave lengths that are effectively monochromatic may be isolated from white light sources by properly de-

signed monochromators, or by second-order interference filters. The half-band width of the light transmitted by commercially available interference filters is 70 A. or more, but their transmissivity is very high, 30 to 40%. Monochromators select much narrower bands, but the intensity of the light transmitted is relatively low, necessitating the use of sensitive measuring apparatus. Both manually operated and automatic-recording photoelectric spectrophotometers are available commercially. While relatively expensive, they are very convenient and dependable. A reaction may be studied by transferring samples from the reacting mixture to the spectrophotometer at suitable times or by allowing the reaction to occur in the spectrophotometer cell. If the latter technique is employed, the spectrophotometer cell must be adequately thermostated.

If for reasons of convenience photometric measurements are made with a slight source having a relatively wide range of wave lengths, the applicability of Beer's law should be tested directly with the light source and absorbent which are to be used in the analytical measurements. Values of I^0/I should be determined for all concentrations which are to be used in the rate experiments. The constancy of $c^{-1} \log (I^0/I)$ is a measure of the validity of Beer's law. For a polychromatic source, the appropriate equation is:

$$I/I^0 = \sum_\lambda I_\lambda/I^0 = (I^0)^{-1}\sum_\lambda I_\lambda^0 \exp(-\alpha_\lambda cl) \qquad (17)$$

When I_λ^0 and α_λ are known functions of wavelength, this equation may be solved by integration. Otherwise, a table or plot of I^0/I as a function of c must be prepared empirically.

The concentration of a colored substance in a solution can be determined by matching its color to that of a standard solution. This is commonly done by adjusting the relative thickness of the solutions until they appear identical. At the match point, $c_x l_x = c_s l_s$, where the subscripts x and s refer to the unknown and standard solutions, respectively. Normally, the standard is a solution containing a known concentration of the colored product or reactant. Various colorimeters which facilitate such comparison have been developed (70c,73) and are available commercially. The standard and unknown solutions are matched either visually or photoelectrically. White light is commonly used in visual colorimeters. Some so-called photoelectric colorimeters do not employ an adjustable comparison solution, but measure the optical density ($\log I^0/I$) using a band of wavelengths isolated by a color filter or a simple monochromator. These are in reality not colorimeters but crude spectrophotometers. In spite of the reproducibility of the readings, the corresponding values of concentration may be inaccurate unless the apparent departures from Beer's law are specifically taken into account. Simple colorimeters have

been used in rate studies (74) for a number of years. While convenient, they are not suitable for precise studies.

Colorimetry may be adapted to the study of reactions (75) in which the disappearance of a colored reactant results in the formation of a differently colored product. For this purpose, a colorimeter is used in which one beam of light passes through a fixed thickness of the unknown solution and the other beam passes successively through the standard solutions of the reactant and product. As the colorimeter is adjusted, the total amount of colored substances in the light path is kept constant, but the ratio of the amounts of reactant and product is varied. The precision obtainable with these modified instruments is comparable to that of a simple one-color, visual colorimeter.

Infrared analysis (76) is well adapted to the study of gaseous reactions involving simple molecules or to reactions occurring in condensed phase but yielding a gaseous product, such as carbon dioxide. Quantitative infrared analysis of more complex mixtures is also possible, but must be calibrated empirically under the conditions under which it is to be used.

Measuring the intensity of fluorescence is a convenient and sensitive way to analyze (77) solutions containing a fluorescent reactant or product. While this method has been successfully applied (78) to the study of reaction rates, it should be used with due caution; changing concentrations of substances which can act as either internal filters or quenchers of fluorescence can seriously interfere with the observed intensity of fluorescence.

If the necessary apparatus is available and the experiments are planned to use this apparatus to best advantage, the spectrophotometric method of analysis is well suited to kinetic studies. The measurements can be made precisely and rapidly (79). It is relatively simple to obtain continuous permanent records of measurements made with a photocell, etc. The method can be used in all cases where a marked change in the absorption of the solution occurs at a wave length for which the absorption of the solvent is relatively small.

G. OPTICAL ROTATION

Wilhelmy's study (80) of the catalyzed inversion of sugar is probably the oldest quantitative kinetic investigation. He followed the progress of the reaction by measuring the changing rotation of the plane of polarization of light which passed through the reacting mixture. This technique has been employed a number of times (81) in studying the rates of reactions involving optically active compounds.

For reasonably dilute solutions the observed rotation is very closely a linear function of the concentrations of the optically active substances

present (82). Analyses with the precision required for good kinetic measurements can be obtained with the aid of a well-constructed *polarimeter* (83). Like spectrophotometry, polarimetry has the advantage that the reacting solution need not be thermostated more closely than is required to insure the sensible constancy of the specific reaction rate. Polarimeter readings are nearly always made visually, and several seconds are required for the completion of a single reading. While photoelectric polarimeters have been described (84) and are available, they are specialized and expensive.

H. ELECTRICAL CONDUCTIVITY (CLASSICAL AND HIGH FREQUENCY METHODS)

The rates of ionic reactions occurring in ionizing solvents such as water can be determined by measuring the conductivity (85) of the reacting mixture as a function of time. Obviously, the method is not applicable if the electrodes (usually of platinized platinum) catalyze the reaction. In dilute aqueous solutions, where the ionic conductances, λ_i, are sensibly constant, the conductivity can be regarded as a linear function (86) of the concentrations of the several ions and, therefore, of the extent of the reaction. For all other solutions, the relation between the conductivity and the ionic composition should be determined empirically (87), although the Onsager equation may be used as an interpolation formula for moderately dilute solutions.

This method has been used extensively (88) to determine the rates of hydrolysis of acid anhydrides, the saponification of esters, and similar reactions. If the difference between κ_0 and κ_∞ is relatively large and proper experimental precautions (85) are observed in making the measurements, reasonably precise determinations of reaction rates can be obtained in this way. It is inconvenient that the conductivity is, in general, not a simple function of the ionic composition. Unless special care is taken to establish this function exactly, uncertainty regarding it may lead to major errors in the evaluation of the ionic concentrations. Conductivity measurements, as commonly performed, require manual adjustments of a variable resistance and take 5 or 10 seconds for their completion. They are, therefore, not directly adaptable to measuring rapid reactions (Chapter XIV) in static systems or to recording results automatically.

Measurements can be made rapidly and without introducing electrodes into the reacting solution by the use of high frequency circuits (89). Usually a high frequency oscillator is coupled to the reacting mixture by placing a cell, filled with the mixture, between the plates of a condenser. Changing composition of this solution, due primarily to the formation or disappearance of ions, affects both its conductivity and its dielectric constant. These changes, in turn, affect the characteristics of the oscillator.

These characteristics are, in general, nonlinear functions of the composition of the solution. Therefore, the response of the instrument must be calibrated empirically with the aid of solutions of known composition.

I. MISCELLANEOUS INDIRECT METHODS

Almost every conceivable physical property of solutions has been used at least once as a measure of the progress of reactions. In addition to the measurements of those more commonly used properties which are discussed in the preceding sections, there are several indirect methods which have real merit under special conditions. Among these are the determination of magnetic susceptibility or of dielectric constant and polarographic measurements. Certain types of reactions require special techniques; for example, polymerizations (Chapter XXI) can be studied effectively by determining the viscosity of, or light scattering by, the reacting system. Other methods, such as those based upon the measurement of colligative properties (90) or of the rate of coagulation of colloids (91), seem to be generally worthless.

Galvanic cells can be so designed that their *electromotive force* is a direct measure of the concentrations (or more exactly of the activities) of a wide variety of ions and molecules (93). A precision of 0.2% in the concentration corresponds to a reproducibility of 0.05 millivolt (within a range of factors from 2 to $^1/_2$) in the measurement of the electromotive force, which is readily obtainable under favorable conditions. However, it appears that the method has been seldom used (94). It has some real disadvantages: (*a*) it is limited to ionizing solvents, practically to water; (*b*) the electrodes require some time (from a few seconds to several minutes) to adjust to changes in concentration; and (*c*) a more serious difficulty is that two electrodes, or an electrode and a salt bridge, must be in contact with the reacting solution.

Polarography (95) is an interesting and potentially useful tool for the study of reaction kinetics. It is limited, however, to conducting (chiefly aqueous) solutions, and requires that two electrodes, or an electrode and a salt bridge, be in contact with the reacting mixture. The application of the conventional dropping mercury electrode is further limited, since many organic reactions are catalyzed by mercury. This latter difficulty can be circumvented by the use of a bright platinum electrode in place of the dropping mercury electrode (96). Polarographic apparatus can be readily modified (95a,97) to yield a continuous, automatic record of the course of a reaction. For batchwise analysis of reacting systems, *amperometric titrations* should prove valuable. Information regarding certain rapid reactions (Chapter XIV) has been obtained from analysis of polarographic limiting currents, obtained in the presence of reactive compounds.

Magnetic susceptibility measurements (99) can be used to analyze reacting mixtures. High precision (100) is obtainable when one of the reactants or products is paramagnetic, particularly when no solvent is present. Automatic and continuous records of changing susceptibility can be made with suitable apparatus. Simple apparatus is available (101) for the determination of the oxygen content of gases. One disadvantage of the general method is that it is relatively difficult to thermostat the reacting systems. Furthermore, it requires specialized and comparatively expensive apparatus.

Precise measurements of the *dielectric constants* of liquids (89,102) can be made with presently available apparatus. Rapid and continuous records of changing dielectric constants can be obtained by known and established techniques. While, in general, the relation between dielectric constant and composition of a solution must be determined empirically, it has been claimed (103), for example, that mixtures of the *cis* and *trans* isomers of dichloroethylene can be analyzed with a precision of 0.1% by means of dielectric measurements. Within the limits required for kinetic measurements, thermostating the solution in the dielectric cell should be relatively simple. Since many organic reactions are accompanied by appreciable changes in dielectric constant, it would appear that measurement of this property should be a useful method of following the course of certain reactions.

Measurements of *viscosity* have been employed occasionally (104) to determine the changing composition of reacting solutions. In the study of polymerization or depolymerization occurring in homogeneous liquid solutions (105), this is an effective analytical tool. For other reactions (not involving macromolecules), there is little to recommend the method. As commonly performed, the measurements are relatively inaccurate, slow, and inconvenient. While the common technique of viscosity measurement for the determination of reaction velocity could be greatly improved, it is very probable that this effort would be better spent in improving one of the other methods.

It has been suggested (106) that the course of polymerization reactions in homogeneous solution can be followed by osmotic pressure measurements. For ordinary reactions, such a method of analysis would be practically worthless. The measurement of *surface tension* (107) is a similar, equally unsatisfactory method of determining the rates of ordinary reactions.

Some special analytical methods have proved to be more useful for the *detection of intermediates* and the products of minor side reactions than for the quantitative determination of the major constituents of reacting mixtures. The determination of the *fluorescent spectra* (108) of a reacting gas

is a good example of such a method. *Mass spectrometric* studies (109) of low-pressure flames, etc., while essentially difficult and requiring expensive, specialized apparatus, have yielded important results which are probably obtainable in no other way. The measurement of electron spin resonance (110) is another powerful tool for the detection of free radicals.

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CHAPTER IV

TIME MEASUREMENTS and the RECORDING OF KINETIC DATA

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I. INTRODUCTION

In all measurements that are not carried out under equilibrium conditions a more or less accurate measurement of time is required. In measurements of reaction kinetics time is, of course, an important variable. In addition, some analytical techniques such as microwave spectroscopy and magnetic resonance depend directly upon highly accurate measurements of frequency, which in turn depend upon accurate measurements of time.

Unlike the measurement of length, there was until recently no accurate measurement of time that could be made in terms of a fundamental property of matter which is accessible to an experimenter anywhere. Length can be defined in terms of the wavelength of a particular spectral line emitted from a single isotope under carefully specified conditions. It now appears that time can be similarly defined with equal precision in terms of the frequency of such a spectral line. Until very recently instrumental limitations have precluded the adoption of such a standard; but recent progress in this field has made it very likely that one will be adopted in the near future (1,2).

All civilizations have used the lengths of the day and year as natural standards of time. The day has been subdivided into convenient subunits such as hours, minutes, seconds, and recently milliseconds, microseconds and even smaller units by means of mechanisms that complete some observable repeated action in an accurately reproducible time interval. As technology progressed so did the precision of the auxiliary devices used to subdivide the day into convenient intervals. Thus primitive devices that measured time in terms of the amount of sand or water passing through an orifice, or the amount or burning of a candle were displaced by mechanical clocks that depended upon the repeated oscillation of a pendulum or of a spring and balance wheel. These mechanisms in turn have been replaced by very stable electrical oscillators (1) that use the mechanical vibrations of carefully ground, mounted, and thermostated pieces of quartz. The vibrations of these crystals are coupled to an electrical circuit by means of the piezoelectric effect.

These oscillators are capable of a stability of one part in 10^{10} or better when measured over a period of a day or less. This error is approximately 10 microseconds per day. Furthermore, by means of electronic frequency dividers it is possible to divide the frequency of the oscillator which usually operates at a frequency of 10^5 to 10^7 c.p.s. to any submultiple of the fundamental frequency and to operate an electromechanical clock driven by a synchronous motor at a suitable lowered frequency. Likewise it is possible to multiply the crystal frequency electronically to more than 10^{10} c.p.s. and to use it to measure the whole spectrum of radio frequencies with very great precision.

It is important that the processes of frequency multiplication and division are exact. Whatever frequency is eventually derived from the oscillator has the same precision as that of the oscillator itself. Thus it is possible to compare the oscillator period with a time interval that is many times longer or shorter.

For accurate time measurement the period of a precise oscillator is compared with the length of the day as determined by the interval between two passages of the sun across the meridian. Since the motion of the earth is not entirely constant the length of the day is somewhat variable. The mean solar day is therefore determined by an averaging process. For the most precise work a more constant standard than the day is needed. One of these involves the rotation of the moon about the earth. Successive transits of the moon as measured between fixed positions relative to the background of distant stars are used to remove any effects due to unsteadiness in the earth's rotation. Another precise standard is the tropical year which uses the period of the earth's orbit as a standard. The tropical year is defined as the time of transit of the sun between successive vernal

equinoxes. Since there are slight differences in the duration of different tropical years the year 1900 was chosen as standard and time referred to it is known as *universal time.*

It is only the recent development of very stable oscillators which permits the use of such a long time interval as a standard. In practice several stable oscillators are intercompared and calibrated against astronomical observations. In the United States standard time signals are transmitted by radio stations WWV and WWVH in Maryland and Hawaii where they can be received anywhere in the world. The time kept by WWV's transmitters is compared with the standard oscillators and astronomical observations. Tables of correction are published at regular intervals. Standard time signals are also broadcast by stations in England, Japan, Belgium, Italy, and the Union of South Africa. Thus time measurements of the highest precision obtainable are available to experimenters anywhere on earth. The only equipment required is a short wave radio receiver and suitable auxiliary equipment for making the necessary intercomparisons.

For measurement of long time intervals an accurate watch or clock is all that is necessary. This can be calibrated against the verbal time announcements which are broadcast at regular intervals. For measurements of very short time intervals a crystal oscillator and frequency divider is usually used. This can be calibrated against the standard broadcasts in a number of ways.

1. A harmonic of the oscillator frequency can be made to beat against the carrier frequency of the standard frequency broadcast by injecting the harmonic into the antenna circuit of the receiver. The oscillator can be adjusted to zero beat with the carrier frequency or the number of beats per second can be determined by means of a frequency counter. For example the 10th harmonic of a 1 megacycle oscillator can be made to beat with the 10 megacycle carrier of WWV. Each c.p.s. of beat frequency indicates an error of 1 c.p.s. in 10 megacycles or one part in 10^7.

2. One of the frequency divider stages can be used to trigger an oscilloscope upon which the one-second "ticks" transmitted on WWV are displayed. The rate of drift of the ticks can be determined with a watch. For example the sweep can be triggered at 10 per second and marks derived from the 100 per second divider mixed with the audio output of the radio receiver, and displayed as the vertical deflection on the oscilloscope. If it takes 100 seconds for the tick to drift from one 10 per second mark to the next, the error is one part in 10^3. This method has two advantages. First, it shows the direction of the error. If the oscillator is too fast the tick will drift toward the end of the sweep. Second, it allows a long integrating time and is not affected by fading of the signal.

In general the received frequency will not be exactly the same as that

transmitted by WWV due to changes in the heights of the ionospheric layers that reflect the signal. Motion of the reflecting layer toward the earth increases the frequency and motion away decreases it in accordance with the well-known Doppler effect. Thus the received frequency is not likely to be correct at any particular time but the fluctuations will average out over a long interval. The measurement of drift of the second ticks is an extremely good method of averaging because the position of the tick on the sweep is proportional to the time integral of the frequency difference and is not affected by fading. Loss of the signal for a considerable period will have no effect upon the position of the tick on the sweep when it is again received. This is not the case when cycles of a beat frequency are counted. When the signal is lost those beats that would have occurred are not counted. Thus the apparent beat frequency appears to be less than its actual value.

II. INTERVAL TIMERS

In measuring the duration of any process it is necessary to have some way of comparing the duration of the unknown interval with a known standard. The familiar stopwatch or stopclock does this by providing a shaft that turns steadily at an accurately known rate. At the beginning of the unknown time interval a gear train and dial system that registers the number of revolutions and fractions thereof is connected to the shaft. At the end of the unknown interval the dial system is disconnected so that a reading of the elapsed time is retained. Some provision is usually provided to set the indicating device to zero before a subsequent measurement is started. Stopwatches reading to 0.1 second and electric stopclocks reading to 0.01 second are readily obtainable. They may be operated manually or by means of a solenoid or magnetic clutch. Errors are introduced by variations in the time of operation of the actuating device. The reaction time of a human observer is likely to be greater than 0.1 second depending upon the experimental conditions, although measurements more precise than this can sometimes be made under conditions in which the starting and stopping reaction times are nearly equal.

1. Digital Timers

For short time intervals and when great accuracy is required electronic analogs of the stopclock are available. In these devices an accurate crystal controlled oscillator is connected to an electronic counter train through an electronic switch or "gate." Before the measurement is made the counter is reset to zero. The gate is then opened at the beginning of the unknown time interval and the counter records cycles of the crystal oscillator until

the gate is closed at the end of the interval. As many decades of electronic counter as desired can be provided; and a mechanical register can be used to extend the counting range. Commercial instruments are available that permit the measurement of an arbitrarily long time interval with a resolution of 1 microsecond. The precision of such a device is of course the accuracy of the crystal oscillator, expressed as a fraction of the total interval counted, plus or minus the oscillator period. For example an oscillator having a frequency error of 5 parts per million and a frequency of 1 megacycle when operated with a suitable counter would measure an interval of 1 second with an accuracy of 5 ± 1 microseconds. When great precision is needed the oscillator can of course be calibrated against WWV.

Related to the electronic interval timer is the events per unit time (EPUT) meter. Here the functions of the known and unknown inputs are interchanged. The counter is used to count unknown events for a fixed time determined by a crystal oscillator and frequency divider. Such a device can be used to measure directly an unknown radiofrequency, the speed of rotation of a shaft, or the number of disintegrations of a radioactive source in a convenient time interval. Although such devices have been used for radioactivity measurements they are not the most efficient because they count for a fixed time. To obtain a desired statistical accuracy a fixed number of counts must be obtained. As soon as the requisite number of counts have been received the time is recorded and the next assay can be made. Thus for radioactivity counting of constant accuracy the time to a fixed number of counts should be measured. For this purpose the following sort of device is used. A counter is made to furnish an electrical output at the end of a predetermined number of counts. At the beginning of the counting period, the counter is reset to zero and an electrical stopclock started. At the end of the predetermined number of counts the signal from the counter stops the clock which records the time required for the number of counts. Instruments are available commercially that print the time intervals automatically on paper tape and change the radioactive samples as soon as a count is made. Thus counting is done with constant accuracy in the minimum of time.

2. Analog Timers

Under certain circumstances the inherent accuracy of the digital timers described above is unnecessary. Then, instead of counting discrete events of accurately controlled duration it is possible to measure time by integrating a continuous process. Such timers are the modern counterparts of the ancient water clocks and hour glasses.

The most commonly used analog timer operates by integrating a constant

electric current during the interval being measured. The total charge accumulated is then a measure of the time. This charge may be measured as the voltage across a capacitor into which the current flows. The charge $Q = \int_0^t idt$. The voltage across the capacitor $V = Q/C$ so that $V_{(t)} = (1/C)\int_0^t idt$. If i is made constant, which can be accomplished in a number of ways, and if initially $V = 0$ the relation simplifies to $V_{(t)} = (i \cdot t)/C$, so that $t = (CV)/i$. The timing device consists of a gate to start and stop the charging of the capacitor, a means for providing constant current for charging and a vacuum tube voltmeter for reading the voltage across the capacitor. Charging is usually done through a fixed resistance and the current is kept constant by means of a feedback circuit that is also part of the vacuum tube voltmeter. To give some idea of the capabilities of such a device the following example is illustrative. If a 1 microfarad capacitor is used and 100 volts is picked as the full scale potential the time to obtain a full scale reading is $T = 10^{-6} \times 10^2/i$. If the grid current in the tube is 10^{-9} ampere (a lower figure can be obtained with some types), the leakage rate will be $10^{-9}/10^{-6} = 10^{-3}$ volts per second or full scale in 10^5 seconds. If the leakage error is to be kept to 1% of full scale this places a maximum limit of 10^3 seconds on the time that can be measured with a 1 microfarad capacitor and a charging current of 10^{-7} ampere. A convenient maximum charging rate would be 10^{-2} ampere which with a 1 microfarad capacitor would give a full scale reading of 10^{-2} second. With a 10^{-3} microfarad capacitor it would be possible to have a full scale time of 10^{-5} second but the drift rate due to grid current would be 1 volt per second which means that the meter would have to be read within 1 second of the beginning of the interval to be measured if the error is to be less than 1%.

By the use of rapid recording devices it is possible to extend the range of analog time measuring devices into the submicrosecond range. However, the oscillographic techniques to be described in the next section are more commonly used.

III. RECORDING INSTRUMENTS

Although the interval timers just described are simple and convenient their use presupposes that the time interval to be measured has a precisely defined value and that the process to be measured is capable of furnishing a signal that indicates a definite end point. In the case of radioactivity measurements this end point is unequivocally indicated by the completion of a definite number of recorded disintegrations. It is also possible to define end point when a chemical reaction has reached a state such that the opacity to light of a given wavelength, the electrical conductivity, the redox potential, or some other physical property of the reaction mixture has

reached a predetermined value. This measurement may be useful for routine assays of some chemical system when the kinetics are already known, but for study of the kinetics themselves it is much more satisfactory to be able to follow the entire time course of variation of the measured physical property instead of obtaining only one point on the reaction curve. For this and many other purposes, recorders that indicate the magnitude of a physical quantity as a function of time are widely used. A wide variety of such recorders is available commercially and suitable instruments can be obtained which can record events taking place in intervals from millimicroseconds to years.

1. Mechanical Recorders

Perhaps the simplest and oldest recording device is the smoked drum recorder or kymograph. Here a metal drum is rotated by clockwork or by a synchronous motor locked to the power line frequency. The drum is covered with a uniform layer of soot. The quantity to be measured is converted into the motion of a lever by means of a suitable transducer. The lever carries a stylus which removes the smoke in a sharp line. Thus as the drum turns the stylus writes on it the changes in the magnitude of the quantity to be measured. If very precise timing is needed a second stylus operated by an electromagnet writes a time trace on the drum. The timing marks may be provided by contacts mounted on a pendulum clock or from a photocell actuated when the pendulum interrupts a light beam. For extreme accuracy they may be even derived directly from the time ticks received from WWV. Frequently only the time of occurrence of an event and not its magnitude is needed. In this case an electromagnetically operated stylus is connected to a suitable battery and key. For example an astronomer observes the transit of a star and presses a key which writes the exact instant on a smoked drum. This instant is compared with the time trace derived from an accurate clock suitably calibrated in terms of universal time. Such smoked drum recorders have long been used in astronomy, seismography, physiology, and pharmacology. The time scale may be increased by mounting the drum on a lead screw so that it advances as it turns giving a long spiral trace, or a paper belt may be passed over two drums. The trace on the smoked paper may be made permanent by dipping it in shellac.

Although smoked drum recorders are flexible, inexpensive, and require very little torque to operate the writing levers they suffer from serious drawbacks. The records are messy and difficult to handle, and the writing levers travel in arcs instead of on a straight line making it difficult to determine simultaneous points on different traces. To overcome these limi-

tations strip chart recorders have been developed. These use paper tape ranging in width from 1 to 12 inches and supplied in long rolls. These charts are positively driven through sprocket holes and are printed with grid lines that greatly facilitate measurements. A visible trace is usually made by ink supplied through a capillary pen although a hot stylus on wax covered paper, electrosensitive paper, typewriter ribbons, and various other recording means have been used. The records are clear and permanent. Although many recorders use a pivoted lever to hold the stylus and therefore produce a curved trace several instruments use a rectilinear arrangement.

There are three general types of chart recorders in common use: pneumatic, galvanometric, and potentiometric. The pneumatic recorders are actuated by an air driven servomechanism that can be used to measure pressure, temperature, liquid level, and other quantities important in industrial process control. The servomechanisms provide signals to control valves, alarms, and other instruments used to regulate the process being monitored. Because these recorders require no electricity they are completely explosion proof.

The potentiometric recorders are in many ways equivalent to the pneumatic recorders. They employ a servomechanism which is capable of considerable power output to actuate the pen, and this mechanism can be used to operate cams and switches to actuate process control devices. This class of recorders because of the great efficiency of electrial amplificaton can operate with much weaker signals and from a much wider variety of transducers than the pneumatic recorders. In addition to the usual electrical quantities they may be used to measure pH, optical density, redox potentials, conductivity, high vacuum, and many other properties as well as pressure, temperature, and liquid level. The principle upon which the potentiometric recorder is based is the following: a standard voltage is applied across an electrical resistor and a fraction of it is obtained from a slider which makes contact with the resistor. This fraction is subtracted from the input signal and the difference applied to an electronic amplifier. The amplifier actuates an electric motor which drives the slider over the resistance until the input signal to the amplifier is zero. Under these conditions the voltage at the slider is equal to the input voltage which is in turn equal to a known fraction of the voltage across the resistor. By means of a suitable mechanical system a pen is driven across the recorder chart with a position proportional to that of the slider on the resistor. Some recorders automatically standardize the voltage across the resistor with reference to a standard cell. Others derive the voltage from a mercury cell or an electronically stabilized power supply which gives a very constant output. The resistors can be made to tolerances of 0.1% or less. Hence the potentio-

metric recorder is a very accurate instrument. Commercial units usually have a full scale of 10 millivolts and an input resistance of about 10,000 ohms. The maximum error may be ±0.5% or less. A variety of chart speeds may be obtained by using different interchangeable motors and gears in the chart drive mechanism. Different input ranges can be obtained by means of shunts and voltage dividers according to usual practice with elec trical instruments.

The main disadvantage of the potentiometric recorder is its slowness of response. It requires from 0.5 to about 5 seconds for the pen to travel the width of the chart in different models. Thus, phenomena which change in fractions of a second or less are not faithfully recorded by this class of instrument.

Galvanometric recorders are conventional D'Arsonval meters arranged for recording. The simplest and least expensive of this class of meter is the printer bar recorder. In this instrument a conventional meter movement is used. The indicating needle is periodically pushed against the recording paper by a platen operated by a small synchronous motor. The needle is free to move normally except during the brief instant of clamping. Thus it is possible to use a low torque movement requiring only a few microamperes. Marking of the record is accomplished either by interposing a typewriter ribbon between the needle and recording paper or by using a pressure sensitive paper. Dots are produced at one or 2 second intervals so that it is not possible to follow rapid phenomena. Although this type of instrument is the least expensive and probably the simplest and most reliable, the records are not of good quality and are more difficult to reproduce for publication than those obtained with other recorders.

Ink writing galvanometers are obtainable from a number of manufacturers. By use of a very heavy magnet structure and a coil consisting of many turns of fine wire it is possible to obtain enough torque to actuate a capillary pen with currents as small as 1 milliampere. Although 1 milliampere 1,500 ohm instruments are available with a time constant (critically damped) of as little as 0.2 second they do not give a faithful response to transients of less than a few seconds duration. This is because the torque provided by the movement is marginal. The pen tends to stick on the paper and is eventually brought to the correct position by motion of the chart drive. To obtain reliable kinetic data it is better to use a higher torque meter even though more power is required to drive it. For example a 1 milliampere 1,000 ohm meter has marginal torque and the pen tends to stick on the paper. A 5 milliampere 1,000 ohm meter having the same structure, on the other hand produces sufficient torque to prevent sticking. One manufacturer recommends using a "dither" circuit which adds a low-

frequency alternating current component to the signal applied to a meter having marginal torque. This is at best a makeshift solution.

Another point must be stressed if accurate response to transients is to be obtained. The signal source should present the critical damping resistance recommended by the manufacturer. A smaller resistance will cause sluggish performance and a large resistance may be obtained by inserting a fixed resistance in series with the source if its resistance is too low or a resistance in parallel with the source if it is too high. The former requires more voltage and the latter more current than actually required for the meter. When a vacuum tube or transistor circuit is used the application of feedback of the required type can be used for critical damping. In general recording milliameters are very well made, and a variety of chart speeds and auxiliary event marking pens are available. One manufacturer even offers a pen linkage that permits rectilinear recording.

A. RAPID DIRECT-WRITING INSTRUMENTS

There are a number of ink writing galvanometers available that have very stiff suspensions and require currents of several tens of milliamperes for operation. These instruments have time constants of 0.02 second or less. With driver circuits employing high frequency peaking to make up for the sluggishness of the movement the effective time constant may be decreased to about 0.01 second. Although they tend to spray ink when actuated at high frequency and although they require rather elaborate electronic driver circuits these instruments are rugged and reliable and provide a speed of response nearly two orders of magnitude greater than the galvanometric recorders previously discussed.

One instrument in this class that deserves special mention was originally developed as a direct writing electrocardiograph but the manufacturer has brought out a variety of industrial models using from one to four pens and interchangeable input circuits for alternating or direct current, and linear or logarithmic amplification. A wide variety of transducers will operate directly with these instruments and a wide range of chart speeds can be selected by means of a simple gearshift arrangement. These instruments use a black paper coated with a white wax which is scraped away by a hot stylus. The paper is pulled over a straight edge and the stylus is in the form of a V shaped ribbon whose apex presses the paper against the straight edge. The stylus arm is long enough to give rectilinear recording with a tangent error of less than 1% of full scale. The records obtained are clean and give excellent contrast so that they can be easily reproduced for publication. Where its rather high cost is justified this instrument is to be recommended for all but the most rapid recording.

2. Photographic Recorders

For phenomena that are too fast for direct recording photographic methods must be used. This technique is also applicable for recording directly from highly sensitive galvanometers and electrometers which have insufficient torque for mechanical recording. In galvanometers used for rapid recording it is necessary to make the moving system as stiff and as light as possible. The Dudell loop galvanometer is usually employed for this purpose. In this instrument a single loop of wire is stretched between the pole pieces of a powerful magnet. A small piece of mirror is cemented across the loop. When current is applied the two wires move in opposite directions twisting the mirror and deflecting a beam of light reflected from it. A suitable optical system projects the image of a slit (or straight edge) onto photographic film or paper via the galvanometer mirror. Thus a small spot of light is caused to travel across the photographic material in proportion to the current passing through the galvanometer. A time axis is provided by driving the photographic material at right angles to the direction of motion of the spot. The photographic recording oscillograph is an extremely flexible instrument. The time constant of some galvanometers is only a fraction of a millisecond so that this type of instrument is at least an order of magnitude faster than the fastest direct writing instruments. Since the galvanometers are very compact it is possible to make small portable recorders having over 10 separate channels. The photographic records are permanent and yield good quality reproductions. Portable recording oscillographs are widely used in geophysical exploration and in oil well logging. They have been brought to a high degree of perfection due to the demands of the petroleum industry. Their main disadvantages are that the records must be developed before they can be viewed, and that rapid loop galvanometers have a very low current sensitivity so that they are difficult to drive by means of vacuum tube circuits. The first difficulty has been partially circumvented by an instrument that is designed to use a rapid, "printing out" paper similar to that which has long been used for portrait proofs and which is preexposed to light to increase its sensitivity. Although records produced by this method can be viewed immediately the contrast is not good and the records must be fixed if they are to be made permanent. The equipment is also prohibitively expensive for many uses. The development of power transistors has made possible compact, high efficiency drivers for loop galvanometers so that the second limitation is no longer important.

Since the recording of rapid transients requires a fast paper speed and since rapid starts and stops are required a very constant rate of motion of the photographic material cannot be relied upon for time measure-

ment. Hence, an auxiliary trace should be provided for time marking. This can be an extra galvanometer driven by an a.c. signal of known frequency or a light beam interrupted by a slotted disc driven by a synchronous motor. A simple, ingenious method uses an incandescent lamp having a long, thin filament which is excited at power line frequency and caused to vibrate by placing it in a magnetic field. A very convenient method of time marking uses mixed pulses from successsive divider stages of a crystal controlled time standard and applied to an additional galvanometer. A timing "comb" is produced in which the minute pulses are larger than the second pulses, etc., which makes it easy to measure long intervals accurately.

3. The Cathode Ray Oscillograph

For the most rapid recording the deflection of an electron beam is used. Since the mass of electrons is very small and their velocities can be made extremely high it is possible to record events taking place in 10^{-9} second or less. Commercial instruments are available that have a time resolution of better than 1 millimicrosecond. Because of the low cost, flexibility, and general availability of cathode ray oscilloscopes they are frequently used to record phenomena of long as well as short duration. For recording it is only necessary to add a suitable camera. A wide selection of special recording cameras is available, although standard hand cameras and motion picture equipment may also be used.

In any cathode ray instrument electrons from a heated cathode are accelerated by an electrostatic field and formed into a beam by means of electrostatic or electromagnetic lenses. The beam impinges on a phosphor coated screen and produces a spot of light. The beam and hence the spot can be deflected by the application of electrostatic or electromagnetic fields normal to the direction of the beam. Although electromagnetic deflection is usually used in television and radar, electrostatic deflection is almost universally used in oscilloscopes because it is easier to obtain a wide range of deflecting speeds. Electromagnetic deflection permits a smaller spot size and better focus over the whole face of the tube but is only easy to use for repetitive deflection at a constant frequency in both coordinates, a condition unusual in oscillography.

In the electrostatic cathode ray tube the deflecting fields are set up between two pairs of plates at right angles. Thus, one pair moves the spot horizontally and the other pair vertically. Both pairs of deflecting plates are driven from vacuum tube amplifiers. In the simplest form of oscillographic recording the amplified signal is applied to one pair of deflecting plates. The spot is imaged on moving photographic film or paper by means

of a camera lens. The photographic material moves at right angles to the direction of spot deflection and provides the time axis. Time markers can be provided by intensity modulating the cathode ray beam by an auxiliary time marker, or by using a double beam oscilloscope that displays impulses from a crystal controlled time standard on a separate trace. This method of recording has several advantages. The record can be of indefinite length and the focus is usually much better since the spot is kept near the center of the tube. The photographic material moves continuously and is not subject to the rapid acceleration that would be required for motion pictures. The main disadvantage of this method is the high speed with which the photographic material must be moved and its wastefulness when very rapid phenomena are to be followed. In general film motion faster than 1 meter per second is impractical. Since it is difficult to get a projected image of the cathode ray spot much less than 0.1 mm. in diameter on film of normal size (35 mm.) the time resolution of this method is normally limited to about 0.1 millisecond.

By applying a potential that changes linearly with time to a pair of deflecting plates at right angle to those carrying the signal a time axis can be provided directly on the cathode ray tube itself. Thus a direct display of the signal is provided for viewing or it may be photographed with a stationary film camera.

The signal that rises linearly to form the time trace is known as the sweep. In early oscilloscopes and some of the less expensive ones currently produced the sweep only runs continuously. That is, it causes the spot to traverse the face of the tube and then return to the beginning and start over again. Such a sweep can be synchronized with and used to view repetitive electrical signals but is quite useless for observing single phenomena. In modern instruments the sweep also can operate in a "triggered" mode that causes the spot to traverse the face of the cathode ray tube once each time a triggering signal is received. When no trigger is received the spot rests at the beginning or end of the trace. For satisfactory observation of single phenomena a circuit should also be provided to cut off the electron beam when the spot is stationary. This is necessary to prevent flooding of the screen with stray light which renders both photographic and visual observation difficult. To make visual observation of single transients possible phosphorescent screens with a long afterglow have been developed. With some of these the image can be observed for nearly a minute in a darkened room. Other phosphors have been developed which have a high photographic brightness and a very short persistence. These are of great advantage for rapid photography. Still other phosphors have a high visual efficiency and a short persistence for visual observation of rapidly repeating phenomena. Table I shows the characteristics of some common phosphors.

TABLE I*
Characteristics of Fluorescent Screens Suitable for Cathode Ray Oscillographs

Phosphor	Color	Persistence	Use
P-1	Yellow green	Medium	High efficiency for visual observation of repetitive phenomena.
P-2	Yellow green	Long	Good visual efficiency for repetitive phenomena; long phosphorescence for observing nonrepetitive phenomena.
P-4	White	Medium-short	Television
P-7	Blue flash Yellow	Very short Very long	Best for observing nonrepetitive phenomena visually. Blue component efficient photographically.
P-11	Blue	Very short	Best photographic efficiency.

* Table prepared from material supplied by courtesy of the Radio Corporation of America and the Allen B. Dumont Company.

TABLE II*
Photographic Materials Suitable for Oscillographic Recording

Material	Resolving power, lines/mm.	Exposure index		Relative speed for P-11 phosphor	Contrast	Use
		Daylight	Tungsten			
Kodak Linograph Pan Film	70	250	200		Medium	General high speed photography. Very high speed recording in conjunction with P-11 phosphor. Can also be used with all others.
Kodak Linograph Ortho Film	95	125	64		Medium	General high speed photography where red sensitivity is not required. High speed recording in conjunction with P-11 phosphor. Also records well with P-1. Can be developed with red safe light.

TABLE II* (*continued*)

Material	Resolving power, lines/mm	Exposure index		Relative speed for P-11 phosphor	Contrast	Use
		Daylight	Tungsten			
Kodak Spectrographic Film Type 1-D(2) (Panchromatic)	Very coarse grain	1,600		55	Medium	Highest speed photography and oscillography when fastest writing rates are required. Resolving power is sacrificed for speed.
Kodak Photoflure Blue Sensitive				35	Very high	For recording from X-ray fluorescent screen but useful with P-11 Phosphor. A green sensitive material is also available which should give good results with P-1 and P-2 Screens.
Kodak Royal X Pan Recording Film	Coarse grain	1,600		100	High	Fastest film available for Cathode Ray photography and general high speed recording.
Kodak Tri-X Pan (135)	Medium	320	250	45	Medium	Readily available material for general purpose recording where extreme speed or extreme contrast are not needed.

* Material for table supplied by courtesy of the Eastman Kodak Company.

For best results careful attention should be paid to the selection of a phosphor for a given application. It is also important to be sure that the electron beam in a given oscilloscope has sufficient energy to excite a particular phosphor efficiently. This is determined by the total accelerating voltage. Some CRT's have post-deflection acceleration and it is the sum of the pre- and post-deflection accelerating voltages that determine the energy of the electrons.

Likewise the selection of the proper photographic material for use with a particular phosphor and writing rate is also important. Table II indicates the properties of typical photographic emulsions that are particularly adapted for oscillographic work.

It should be mentioned that oscilloscopes using "storage" cathode ray tubes are available. One type of direct view storage tube produces two separate beams, a "write" beam and a flood beam. The write beam charges up an insulated grid behind the viewing screen. The flood beam passes through the grid only where it has been charged by the write beam and hence causes illumination only along the path of the writing spot. The image persists until the grid is discharged by applying a pulse to it. The tube can be viewed indefinitely at high ambient illumination and can be erased instantly. However due to the coarseness of the grid, the resolution does not compare with that of conventional tubes.

A. SYNCHRONIZATION

In any cathode ray oscillographic recording a timed sequence of operations must be performed. This can be accomplished manually or more or less elaborate automatic mechanisms can be employed. In at least one make of recording camera many of the synchronizing functions are built into the camera itself. Electronic or synchronous motor operated timing and sequencing devices may also be used. At the other extreme of complexity a hand camera may be employed with the shutter opened and closed manually before and after the expected event.

Whatever the programming mechanism the following sequence of operations must somehow be performed:

1. Camera shutter opens, and photographic material is brought up to speed if a film sweep is employed.
2. Oscilloscope sweep is started if used.
3. Phenomenon to be recorded is initiated.
4. Sweep terminates; travel of photographic material is stopped; camera shutter closes.
5. Photographic material is advanced if film sweep is not employed.

Additional elaborations are possible. A clock or counter and a data card may be photographed in one corner of the record by means of a mirror or prism system. The clock is best illuminated by means of a brief flash of light that occurs the instant the camera shutter is fully open A commercial photographic strobe light operated in the conventional way from contacts on the camera shutter is entirely satisfactory for this purpose. The duration of the flash is small enough to record a sharp picture on moving film.

To conserve film when events requiring a great deal of time are to be recorded they may be sampled at intervals either by taking single sweeps on single frames of film or by running the film at constant speed for brief intervals. When it is necessary to record the phenomena at all times photographic material may be saved by advancing it continuously at a slow rate while the oscilloscope sweep is operating continuously across the film. The record then appears as a series of diagonal traces, the signal deflection being in the direction of film travel and no longer at right angles to the trace. If this feature is objectionable a small amount of signal from the sweep can be applied to the signal plates of the oscilloscope. This causes the trace to move upward at the same rate that its image is carried downward by the moving film. The resulting photograph will show a series of traces directly across the film with the signal deflection accurately at right angles to the traces. With sweep rates of less than 100 kilocycles the time for the beam to return is at most a few percent of the sweep time in modern oscilloscopes. Hence little information is lost in using this method of operation. Great economy of photographic material can be realized particularly if signals on adjacent traces are allowed to overlap. If in addition the camera is programmed to sample the data only at intervals records of minimal length can be obtained. This method of operation has been employed to particular advantage in neurophysiological investigation.

B. X-Y PLOTTING

Although this chapter is concerned primarily with the measurement of quantities as a function of time no description of oscilloscopic methods would be complete without mentioning X–Y or "phase plane" plots. It is frequently more illuminating to plot one quantity directly in terms of another rather than plot both as functions of time and then compare them. For example in a rapid scanning spectrophotometer absorption is plotted directly as a function of wavelength rather than as a function of time. This is accomplished by mounting a suitable transducer such as a potentiometer on the wavelength drive of the spectrophotometer and applying it to the horizontal axis of the oscilloscope. Recording is accomplished by opening the shutter of the camera during one or more complete cycles of operation.

Certain mathematical methods in analyzing kinetic data depend upon plotting the time derivative of a variable as a function of the variable itself. This can be accomplished by putting the variable on the X axis of an oscilloscope and by passing it through an electronic differentiator and applying the result to the Y axis. Oscillatory systems in particular lend themselves to this type of presentation. A damped sinusoidal oscillation

would be represented as a spiral trace. To indicate the time on such a record the trace may be interrupted periodically by means of timing pulses applied to the blanking circuit of the oscilloscope.

C. MULTIPLE TRACE DISPLAYS

Often it is desired to present two or more phenomena simultaneously as a function of time. This may be accomplished in several ways. 1. By using several separate oscilloscopes and combining their images by suitable optical means. 2. By multibeam oscilloscope tubes. 3. By time sharing using an electronic switch.

The first of these methods is simple and straightforward but is also cumbersome and wasteful of space. While satisfactory for photography it is generally unsatisfactory for visual display. If traces can be restricted to narrow bands which do not overlap cathode ray tubes having a long, narrow rectangular face are available. These can be stacked vertically to give any number of traces desired.

The multibeam oscilloscope is the most flexible multiple trace device. Traces are displayed on a single screen and each trace can cover the entire face of the tube. Two types of tube are available. In one type a single electron gun is used to form two beams which pass between common horizontal deflecting plates but separate vertical ones. This method provides excellent alignment of the two traces but requires that both are driven at the same horizontal rate.

In the other type of tube an entirely separate electron gun and deflecting system is provided for each trace. Tubes having as many as four guns are commercially available. This arrangement is very flexible. Entirely separate data can be displayed by each trace. On the other hand it is difficult and expensive to make tubes in which the axes of the different deflecting systems are accurately parallel. The traces also tend to drift out of alignment so that the time of occurrence of events displayed on separate traces can no longer be compared.

The electronic switch method of presentation is the least flexible of the various methods, but within its limitations it possesses some real advantages. A standard cathode ray tube is used and exact horizontal alignment is preserved at all times. In operation the signals from the various input channels are connected in sequence to the vertical deflecting system of the oscilloscope. If the sampling period is less than the time required for the spot to move its own width the separate channels appear as continuous traces. Unfortunately the spot cannot switch instantaneously from one signal to the next but the rate of transition is limited by the rise time of the deflecting circuits. When switching is used the deflecting system must

have a much greater bandwidth (smaller rise time) than that required for the signal alone. This requires more elaborate and expensive deflecting circuits. On the other hand these can often be simpler and more reliable than the duplicate deflection circuits necessary for multigun tubes. A further disadvantage of switching is that during the time the spot travels from one signal level to another it produces a trace on the screen which appears as a smear of light and reduces the contrast in the image. In some oscilloscopes a blanking circuit is provided that turns the beam off during switching. This improvement is highly desirable.

In dual trace oscilloscopes that employ switching there is a provision for either rapid switching of the beam or for presenting the signals on alternate traces. The latter mode of operation permits the viewing of repetitive phenomena without obscuring any details of the signals that might be lost in the switching transients.

At least one manufacturer offers a dual beam oscilloscope incorporating plug-in input circuits. Dual trace switching units are available for this instrument so that it is possible to display two phenomena on each beam and thus to display four separate phenomena simultaneously.

4. Magnetic Recording

Magnetic tape presents a flexible and economical method of recording data. Several channels can be recorded simultaneously by using as many recording heads mounted side by side as needed. A great flexibility in speed is permitted. The data can be recorded at high speed and played back slowly for analysis. The maximum frequency that can be recorded is somewhat in excess of 1,000 c.p.s. per inch per second of tape speed. This is limited by the width of the gap in the recording head. The tape will not permit the recording of very low frequencies or of d.c. levels directly. Where slowly changing quantities must be presented they can be used to frequency or time modulate a carrier frequency which is in turn impressed upon the tape. This somewhat restricts the bandwidth of the system because the modulation process requires a periodic sampling of the signal and at least two samples per cycle of the highest frequency component in the signal are required. In such a case the carrier frequency must be at least twice as high as the highest frequency to be recorded. On the other hand frequency or pulse time modulation systems do not require accurately linear response from the tape. Hence the signal can be recorded at a much higher level than if it were put on the tape directly, and a much greater dynamic range and signal to noise ratio can be achieved. The principal disadvantage of magnetic tape lies in the lack of a directly visible record. The tape acts as a data storage device and one of the other

types of recorder described above must be used for display purposes. Recently some ingenious methods have been worked out in which a magnetized spot is caused to move across the width of the tape in proportion to the strength of the input signal. The magnetized trace thus generated can be made visible by dusting the tape with magnetic powder. Hence visible oscillograms can be generated directly on magnetic tape. It is to be hoped that this method will be developed further and made commercially available in the near future.

5. Digital Methods

Instead of recording a function continuously it is possible to sample it at regular intervals and to convert the samples thus obtained to numerical form. The numerical data can be displayed as decimal digits by means of an automatic printer or they may be kept in binary form and stored on punched cards, punched tape, or magnetic tape. Although such methods lack the intuitive value of graphical methods the data can be much more precise and compact. Where computation is to be done the data are in a form in which they can be used directly for manual or electronic computation. Digital recording will probably become increasingly important as electronic computation becomes more widely used.

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CHAPTER V

EVALUATION AND INTERPRETATION OF RATE DATA

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I. RELATION OF REACTION RATES TO KINETIC MECHANISMS

From the viewpoint of organic chemistry, the two most important applications of the study of reaction kinetics are the determination of: (*1*) reaction mechanisms and (*2*) the relative reactivities of certain compounds. Since the relative reactivities of two or more compounds cannot be properly recognized without a knowledge of the reaction step involved, it follows that in the second application (as in the first) an investigation of reaction mechanism is of primary importance. Every student of kinetics recognizes that the unequivocal determination of the mechanism of a reaction is extremely difficult and a goal which has been reached in very few cases. It is imperative, therefore, that in the investigation of the mechanism of a complex reaction every available tool be used. Chief among these is the evaluation of the empirical rate equation for the reaction. A comparison of the observed rate equation with the equations obtained from the analysis of postulated mechanisms makes possible the rejection of a number of mechanisms which otherwise might appear to be reasonable explanations of the reaction. While it is scarcely to be expected that only one mechanism will be consistent with the empirical rate equation, it is usually possible to make a choice between those which pass this test, in terms of the energetics of the system, and by means of special methods and critical experiments.

There are a large number of classes of reactions which are of interest to organic chemists, and an almost infinite variety of compounds can undergo each of these types of reactions. Faced with the obvious impossibility of making a careful study of each of this enormous array of possible reactions, it has become customary for chemists to assume certain mechanisms for the prototype reactions and to assign, by analogy, mechanisms to supposedly related reactions. This is not a safe procedure. In the field of kinetics, reasoning by analogy may be very helpful, but it is never trustworthy. The marked difference in the mechanisms of formation of hydrogen iodide and of hydrogen bromide from their respective elements is a striking example of the danger in blind dependence upon apparently safe analogies. While it is not practicable to eliminate entirely the method of analogies from the study of the mechanisms of organic reactions, at least every effort should be made to establish on a firm basis the mechanisms of the prototype reactions. The importance of careful and extensive measurements of the kinetics of such reactions is second only to the determination of their stoichiometry.

II. EMPIRICAL RATE EQUATIONS

1. Simple Relations in Isochoric, Isothermal Systems

Laboratory studies of the rates of reactions are usually conducted at constant temperature and volume in a closed system. For the present purpose, a closed system may be defined as one in which any change in the quantity of the reactants and solvent is due solely to the chemical reaction. As an introduction to the subject, let us consider only *simple reactions*, where a simple reaction is defined as one whose rate is determined exclusively by the rate of a single reaction step. In a simple reaction the concentrations of intermediates, if any are formed, do not affect the rate of the over-all reaction. In general, the rate of a *simple reaction* whose stoichiometric equation is:

$$aA + bB + cC + \ldots = lL + mM + \ldots$$

can be represented by a differential equation of the following form:

$$dx/dt = k(A_0 - x)^j[B_0 - (b/a)x]^k[C_0 - (c/a)x]^l \ldots \qquad (1)$$

In this equation, the exponents (j, etc.) are the simple positive integers 0, 1, 2, or 3, the coefficients (b/a, etc.) are determined by the stoichiometric equation, x is the decrease in the concentration of A due to the reaction, and the quantities A_0, etc., are the initial concentrations of the several reactants. It follows from these definitions:

$$dx/dt = -d[A]/dt = -(a/b)d[B]/dt = (a/m)d[M]/dt, \text{ etc.}$$

The sum of the exponents ($j + k + l$) is called the *order of the reaction.* Similarly, j is the *order of the reaction with respect to the substance A*, k is the order with respect to B, etc.

In general, the *rate constant*, k, is a function of temperature, pressure, and the composition of the reacting mixture, and, therefore, indirectly a function of time. However, for most homogeneous reactions occurring at constant temperature and volume, k will not vary significantly with time.

The outstanding exceptions to this statement are ionic reactions whose progress produces a marked change in the ionic strength of their media. Such reactions have been discussed extensively by Scatchard (1,2).

Whenever k can be taken as independent of time, Equation (1) can be integrated in terms of simple functions, the form of the integrated equation depending upon the numerical values of the exponents (j, etc.) and of the coefficients (b/a, etc.).

A second-order reaction involving one reactant will serve to illustrate

the process of integration and the several useful forms of the integrated equation. In this case, where $j = 2$ and k and $l = 0$:

$$dx/dt = k(A_0 - x)^2$$

The corresponding indefinite integral is:

$$1/(A_0 - x) = kt + I$$

where I is the constant of integration. This equation clearly indicates that the reciprocal of the concentration of the reactant is a linear function of the elapsed time. Since $x = 0$ when $t = 0$, $I = 1/A_0$, and:

$$1/(A_0 - x) = kt + 1/A_0$$

or:

$$x/A_0(A_0 - x) = kt$$

It is apparent from this equation that t approaches infinity as x approaches A_0. In other words, there is no finite time of completion for a reaction of this order, or, for that matter, for any reaction whose order is first or higher. The rate of a reaction may be characterized by the rate constant (in this case $k \equiv$ sec.$^{-1}$ l. mole^{-1}). For some purposes, it is more convenient to represent the intrinsic speed of a reaction by its *half-time*, $\tau_{1/2}$, the time required for half of the reactant to disappear. For the present example, the relation between the half-time and the rate constant and initial concentration is:

$$^1/_2A_0/A_0(^1/_2A_0) = k\tau_{1/2}$$

$$\tau_{1/2} = 1/kA_0$$

Similar integrated expressions can be obtained for each of the possible special cases of Equation (1). A few of the more important special cases are summarized in Table I.

The quantities listed in the first three groups of columns indicate the kinetic and stoichiometric classifications of the reactions. The differential equations, and the indefinite and definite integrated forms of these equations, are summarized in the next three columns. The values for the half-times given in the next to the last column are all in terms of the concentration of the first reactant, A. This is, of course, possible only when the concentrations of all other substances participating in the reaction are greater than $A_0/2$. The final column contains the "dimensions" of the rate constants expressed in terms of seconds and moles per liter. The several integrated equations can be written in different but equivalent forms. For example, the definite integrated equation for a first-order reaction is often written:

$$(A_0 - x) = A_0 e^{-kt} \text{ or } x = A_0(1 - e^{-kt})$$

and the equation for the third-order reaction as:

$$1/(A_0 - x)^2 - 1/A_0^2 = kt$$

If the initial concentrations of the substances taking part in a second or higher order reaction (such as the examples given in the third and sixth rows) are identical, the equation degenerates to that of a reaction of the same order but involving only one reactant. While empirical equations can be written and integrated for a vast number of reactions of different orders, the infrequency with which such reactions occur makes such a procedure of doubtful value.

2. Temperature Coefficients and Heats of Activation

The rates of most reactions which have been studied increase rapidly with increasing temperature. For simple reactions, the rate constant obeys, to a very good approximation, the Arrhenius equation:

$$k = k_0 \exp(-\epsilon/RT) \tag{2}$$

where ϵ and k_0 are constants. In terms of the simple collision theory (Chapter II), k_0 is proportional to the square root of the absolute temperature. For more complex reactions, whose activation involves more than two square terms, the rate constant would be expected (Chapter II) to be a more complex function of temperature. However, even for these cases, Equation (2) holds approximately. The transition state theory leads to an equation of the form of Equation (2) in which k_0 is directly proportional to the absolute temperature, at least insofar as the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ can be taken as independent of temperature. This linear, or square-root, dependence upon the temperature is usually negligible compared to the exponential factor.

For the empirical evaluation of ϵ it is convenient to put Equation (2) in logarithmic form:

$$\ln k = \ln k_0 - \epsilon/RT$$

The slope of a plot of $\log k$ against $1/T$ is equal to $-0.434\epsilon/R$.

3. Simple Reactions in Nonisochoric and Nonisothermal Systems

Laboratory measurements of the rates of gaseous reactions are commonly made at constant temperature and volume. Although the rates of reactions occurring in liquid solutions are usually studied under constant

TABLE I.a

Special Cases of Integrated Rate Equations, Corresponding to $dx/dt = k(A_0 - x)^j\{B_0 - (b/a)x\}^k\{C_0 - (c/a)x\}^l$ at Constant Volume and Constant Temperature

Order $j+k+l$	Suborder $j\,k\,l$	Stoichiometric coefficients $a\,b\,c$	Differential equation	Indefinite integral
1	1 0 0	1 — —	$\frac{dx}{dt} = k(A_0 - x)$	$\ln (A_0 - x) = I - kt$
2	2 0 0	1 — —	$\frac{dx}{dt} = k(A_0 - x)^2$	$\frac{1}{(A_0 - x)} = I + kt$
2	1 1 0	1 1 —	$\frac{dx}{dt} = k(A_0 - x)(B_0 - x)$	$\frac{1}{(B_0 - A_0)} \ln \frac{(B_0 - x)}{(A_0 - x)} = I + kt$
2	1 1 0	1 2 —	$\frac{dx}{dt} = k(A_0 - x)(B_0 - 2x)$	$\frac{1}{(B_0 - 2A_0)} \ln \frac{(B_0 - 2x)}{(A_0 - x)} = I + kt$
3	3 0 0	1 — —	$\frac{dx}{dt} = k(A_0 - x)^3$	$\frac{1}{(A_0 - x)^2} = I + 2kt$
3	1 1 1	1 1 1	$\frac{dx}{dt} = k(A_0 - x)(B_0 - x)(C_0 - x)$	$\frac{(C_0 - B_0)}{\text{Den}^*} \ln (A_0 - x) + \frac{(A_0 - C_0)}{\text{Den}^*} \ln (B_0 - x) + \frac{(B_0 - A_0)}{\text{Den}^*} \ln (C_0 - x) = I + kt$
> 1	j 0 0	1 — —	$\frac{dx}{dt} = k(A_0 - x)^j$	$\frac{1}{(A_0 - x)^{j-1}} = (j-1)kt + I$
0	0 0 0	1 — —	$\frac{dx}{dt} = k$	$-(A_0 - x) = I + kt$
$1/2$	$1/2$ 0 0	1 — —	$\frac{dx}{dt} = k(A_0 - x)^{1/2}$	$-(A_0 - x)^{1/2} = I + \frac{kt}{2}$

* Den $= (A_0 - B_0)(A_0 - C_0)(B_0 - C_0)$.

TABLE I.b

Special Cases of Integrated Rate Equations, Corresponding to $dx/dt = k(A_0 - x)^j\{B_0 - (b/a)x\}^k\{C_0 - (c/a)x\}^l$ at Constant Volume and Constant Temperature

Order $j+k+l$	Suborder $j\,k\,l$	Stoichiometric coefficients $a\,b\,c$	Definite integral	Half-time $\tau_{1/2}$	Units of k
1	1 0 0	1 — —	$\ln \frac{A_0}{(A_0 - x)} = kt$	$\frac{1}{k} \ln 2$	sec.$^{-1}$
2	2 0 0	1 — —	$\frac{x}{A_0(A_0 - x)} = kt$	$\frac{1}{kA_0}$	sec.$^{-1}(M)^{-1}$
2	1 1 0	1 1 —	$\frac{1}{(B_0 - A_0)} \ln \frac{A_0(B_0 - x)}{B_0(A_0 - x)} = kt$	$\frac{1}{k(B_0 - A_0)} \ln \frac{2(B_0 - A_0)}{B_0}$	sec.$^{-1}(M)^{-1}$
2	1 1 0	1 2 —	$\frac{1}{(B_0 - 2A_0)} \ln \frac{A_0(B_0 - 2x)}{B_0(A_0 - x)} = kt$	$\frac{1}{k(B_0 - 2A_0)} \ln \frac{2(B_0 - A_0)}{B_0}$	sec.$^{-1}(M)^{-1}$
3	3 0 0	1 — —	$\frac{2A_0x - x^2}{A_0^2(A_0 - x)^2} = 2kt$	$\frac{3}{2kA_0^2}$	sec.$^{-1}(M)^{-2}$
3	1 1 1	1 1 1	$\frac{(B_0 - C_0)}{\text{Den}^*} \ln \frac{A_0}{(A_0 - x)} + \frac{(C_0 - A_0)}{\text{Den}^*} \ln \frac{B_0}{(B_0 - x)} + \frac{(A_0 - B_0)}{\text{Den}^*} \ln \frac{C_0}{(C_0 - x)} = kt$	$\frac{(B_0 - C_0)}{k\ \text{Den}^*} \ln 2 + \frac{(C_0 - A_0)}{k\ \text{Den}^*} \ln \frac{B_0}{B_0 - (A_0/2)} + \frac{(A_0 - B_0)}{k\ \text{Den}^*} \ln \frac{C_0}{C_0 - (A_0/2)}$	sec.$^{-1}(M)^{-2}$
$j > 1$	j 0 0	1 — —	$\frac{1}{(A_0 - x)^{j-1}} - \frac{1}{A_0^{j-1}} = (j-1)kt$	$\frac{2^{j-1} - 1}{kA_0^{j-1}}$	sec.$^{-1}(M)^{1-j}$
0	0 0 0	1 — —	$x = kt$	$\frac{A_0}{2k}$	sec.$^{-1}(M)$
1/2	1/2 0 0	1 — —	$A_0^{1/2} - (A_0 - x)^{1/2} = \frac{kt}{2}$	$\frac{(2 - 2^{1/2})A_0^{1/2}}{k}$	sec.$^{-1}(M)^{1/2}$

* Den. $= (A_0 - B_0)(A_0 - C_0)(B_0 - C_0)$.

(atmospheric) pressure, the change in volume which such a solution undergoes due to the progress of the reaction is relatively small—frequently less than 1%. The volumes of liquids are not appreciably affected by ordinary changes in pressure. Therefore, reactions taking place in condensed systems at constant pressure may be treated as constant volume processes. The rates of all simple, constant volume, constant temperature reactions can be adequately represented by equations of the type of Equation (1).

Sometimes it is more convenient to make rate measurements in *open systems* (Chapter III, III.4) or closed systems under other conditions of restraint. A gaseous reaction proceeding at constant pressure and temperature is an example of the latter type. The quantities of the reactants and products may be expressed in terms of their number (n_i) of moles (or molecules) in the system, of their partial pressures (P_i) (for a gaseous system), or of their mole fractions (X_i), instead of by the usual concentration units $[R_i]$. The form of the differential equation which represents the rate of a particular reaction is influenced both by the conditions of restraint and by the units in which the quantities of the reactants are specified. It is probably worth while, therefore, to consider a few of the modified forms of the rate equation which correspond to the principal units and to some of the simple conditions of restraint.

Strictly speaking, Equation (1) applies only to simple reactions occurring in isochoric systems. If reactions taking place in systems in which the volume varies with time are to be included, Equation (14) of Chapter II should be replaced by the following expression:

$$-dn^{\ddagger}/dt = k_2 n^{\ddagger} \tag{3}$$

since the rate at which the transition state complex breaks up into product molecules is a property of the nature of the individual complex, not of its concentration. The general form of the rate equation for a bimolecular reaction can be obtained by combining Equation (3) with Equation (13) of Chapter II:

$$-dn_A/dt = k_2 K^{\ddagger} n_A [B]$$

This may be generalized to include all orders of simple reactions as follows:

$$-dn_1/dt = k n_1 [R]^{n-1} \prod_{i=2}^{i=l} [R_i]^{\nu_i} \tag{4}$$

where the ν_i are the exponents (j, k, and l of Equation 1) and R_i represents the ith reactant. Equation (4) may be derived with equal simplicity in terms of the simple collision theory (Chapter II).

There appears to be no theoretical justification for the opinion (3) that reaction rates (for ideal systems) should be expressed as follows.

$$-dn_1/dt = k\prod_i X_i^{n_i}$$

It should be remembered that (for ideal systems) K_c and K_p are functions of temperature only, while K_x is a function of pressure as well as of temperature. Considerations of the deviation from ideality and of the choice of the standard state do not enter into the determination of the proper form of the fundamental rate equation.

Since n_i, $[R_i]$, X_i, and P_i are related either in general or in terms of the perfect gas law, Equation (4) may be written as a function of time and of any one of these groups of variables. In general:

$$n_i = V[R_i] = nX_i$$

where n is the total number of moles in the system at any time. For a perfect gas:

$$n_i = (nRT/P)[R_i] = n(P_i/P) = (V/RT)P_i = (RT/PV)X_i \quad (5)$$

where P is the total pressure. Differentiating these equations with respect to time, we obtain for isothermal, isochoric systems:

$$dn_1/dt = V(d[R_i]/dt) = (V/RT)(dP_i/dt) = n(dX_i/dt + X_1(d \ln n/dt)) \quad (6)$$

Similarly, for isothermal, isopiestic systems:

$$dn_i/dt = (nRT/P)[d[R_i]/dt + [R_i](d \ln n/dt)] = (n/P)[dP_i/dt + P_i(d \ln n/dt)] = n[dX_i/dt + X_i(d \ln n/dt)] \quad (7)$$

the $d \ln n/dt$ terms may be eliminated since the change in the total number of molecules (for a closed system) is proportional to the change in the number of molecules of any reactant, R_i. The constant of proportionality (for the first reactant, R_1) may be defined as:

$$a = (n^0 - n)/(n_1^0 - n_1) \quad (8)$$

where the superscript zero refers to the initial conditions.

The following derivation of the rate equation of an isopiestic process expressed in terms of mole fraction illustrates the derivations of the several equations of Table II. Differentiating Equation (8) with respect to time:

$$d \ln n/dt = (a/n)(dn_1/dt)$$

Combining this with Equation (7):

$$d \ln n/dt = a[dX_1/dt + X_1(d \ln n/dt)]$$

Rearranging this expression:

$$-n[dX_1/dt + X_1(d \ln n/dt)] = -[n/(1 - aX_1)]dX_1/dt$$

Since the left-hand term is equal to $-(1/n)(dn_t/dt)$, we may substitute in Equation (4) to obtain:

$$-dX_1/dt = k(1 - aX_1)X_1[\mathrm{R}_1]^{\nu_1 - 1} \prod_{i=2}^{i=l} [\mathrm{R}_i]^{\nu_i} \tag{9}$$

For a perfect gas $[\mathrm{R}_i] = (P/RT)X_i$; accordingly:

$$-dX_1/dt = k\,(1 - aX_1)\,(P/RT)^{\nu - 1} \prod_{i=1}^{i=l} X_i^{\nu_i}$$

This equation and its seven analogs are presented in Table II. Five of these equations, which are marked with asterisks, were derived upon the assumption that the perfect gas law applies to the system, and accordingly are valid only for gas reactions. Those marked with a dagger are applicable to nonisothermal, constant pressure (or constant volume) systems; but in integrating the differential equation the variation of k with temperature (and therefore with time) must be taken into account. The equations designated by a double dagger can be applied directly to systems under arbitrary restraints, providing that P or V is known as an explicit function of time.

Each of the tabulated equations reduces to the simple form:

$$dy/dt = k' \prod_i y_i^{\nu_i}$$

when $a = 0$, that is, when the reaction produces no change in the total number of mols. For isothermal reactions the integration of the several equations in terms of simple functions is possible, being easiest for first order reactions.

TABLE II

Differential Rate Equations for Simple Reactions Occurring in Closed Isothermal System

Units	Isochoric systems	Isopiestic systems
n_i	‡† $-\frac{dn_1}{dt} = \left(\frac{1}{V}\right)^{\nu - 1} k \prod_t n_i^{\nu_i}$	‡†* $-\frac{dn_1}{dt} = \left(\frac{P}{nRT}\right)^{\nu - 1} k \prod_t n_i^{\nu_i}$
$[\mathrm{R}_i]$	† $-\frac{d[\mathrm{R}_i]}{dt} = k \prod_t [\mathrm{R}_i]^{\nu_i}$	* $-\frac{d[\mathrm{R}_1]}{dt} = k\left(1 - \frac{aRT}{P}[\mathrm{R}_1]\right) \prod_t [\mathrm{R}_i]^{\nu_i}$
P_i	* $-\frac{dP_1}{dt} = \left(\frac{1}{RT}\right)^{\nu - 1} k \prod_t P_i^{\nu_i}$	†* $-\frac{dP_1}{dt} = \frac{k}{(RT)^{\nu - 1}}\left(1 - a\frac{P_1}{P}\right) \prod_t P_i^{\nu_i}$
X_i	‡† $-\frac{dX_1}{dt} = k\left(\frac{n}{V}\right)^{\nu - 1}(1 - aX_1) \prod_t X_i^{\nu_i}$	‡†* $-\frac{dX_1}{dt} = \left(\frac{P}{RT}\right)^{\nu - 1} k(1 - aX_1) \prod_t X_i^{\nu_i}$

* Perfect gas only.

† Applicable to nonisothermal system, allowing for variation of k with time.

‡ Applicable to nonisochoric, nonisopiestic systems if proper allowance is made for variations, in V, P, and n.

The coefficient k of these equations is the following function of temperature (Chapter II, III.2):

$$k = \kappa(\boldsymbol{k}T/\boldsymbol{h}) \exp(\Delta S^{\ddagger}/R) \exp(-\Delta H^{\ddagger}/RT)$$

For reactions in adiabatic systems (and in all other nonisothermal systems) T must be known as an explicit function of time if the rate equation is to be integrated. The mathematical treatment of these equations is comparatively difficult and, in general, they cannot be integrated in terms of simple functions. Fortunately, it is seldom if ever necessary to use nonisothermal systems in the laboratory study of reaction kinetics (4–8).

For all ordinary variations of pressure, k may be considered to be independent of pressure. However, useful information concerning the transition complex may be obtained by comparing the empirical values of k at ordinary and at high pressures (9–11).

4. Rate Equations for Complex Reactions

The rates of many reactions of chemical interest correspond to differential equations more complex than Equation (1), even when the measurements are made under isothermal, isochoric conditions. One of the best-known examples is the formation of hydrogen bromide from its elements, the rate of which can be represented quite accurately by the following expression (12):

$$d[\mathrm{HBr}]/dt = k[\mathrm{H_2}][\mathrm{Br_2}]^{1/2}/\{1 + (k'[\mathrm{HBr}]/[\mathrm{Br_2}])\}$$

The general form of this equation, (10), fits (to the best of the authors knowledge) all published rate data for steady-state reactions occurring in homogeneous, isothermal, isochoric systems.

$$-d[\mathrm{R}_i]/dt = \sum\{k_j\Pi_i[\mathrm{R}_i]^{\nu_i}/(\beta + \sum_i k_{ji}\Pi_i[\mathrm{R}_i]^{\nu_i})\} \qquad (10)$$

where $\beta = 0$ or 1 and the ν_i are positive or negative small integers, half integers, and possibly third integers. As usual (Chapter II, II.6) the several rate constants, k, are functions of temperature, pressure, the nature of the solvent (which may change with time), the surface-to-volume ratio, and the nature of the walls. In this equation, R_i may represent a product of the reaction or a catalyst (Section VII.3), as well as a reactant. Equations of this form are commonly derived by an approximate method (the so-called steady state method) (Section V.3) from a postulated set of reaction steps, i.e., the *reaction mechanism* (Section V). Accordingly, it may be expected that there will be instances when equations of this type will not agree exactly with very precise experimental data.

III. DETERMINATION OF THE ORDERS OF SIMPLE AND COMPLEX REACTIONS

1. Direct Evaluation of the Orders of Simple Reactions

The most obvious method of determining the order of a reaction is to compare the data, concentrations and corresponding times, with the several integrated rate equations. If the data fit an equation, in the sense that the values of the rate constant, k, are independent of time, it may be concluded (within the limits of precision of the data) that the reaction and the equation have the same order. If the reaction is a simple one, and particularly if it involves only one reactant, there are several practicable ways by which such a comparison can be made.

A graphic comparison is perhaps the simplest and most useful of these methods. The order of the reaction can be determined by ascertaining what function of the concentration is linearly dependent upon time. As shown in Table I, these functions are the concentration, the logarithm of the concentration, the reciprocal of the concentration, and the reciprocal of the square of the concentration for zero-, first-, second-, and third-order reactions, respectively. The test is made by plotting several of these functions of concentration against time and finding which set of points lies closest to a straight line. This method cannot be conveniently applied to reactions whose rates are influenced by more than one reactant.

In place of the graphic comparison, the rate coefficients, k, may be calculated and tabulated, using successive pairs of points for each of the pertinent integrated equations, and the several sets of values may be inspected for constancy. For example, to test whether a set of data are consistent with a second-order equation, values $k_{i,\ i+1}$ of the rate coefficients should be computed from each successive pair of points by means of the following equation:

$$([\mathrm{A}]_i - [\mathrm{A}]_{i+1})/\{[\mathrm{A}]_i[\mathrm{A}]_{i+1}(t_{i+1} - t_i)\} = k_{i,\ i+1}$$

where the $[\mathrm{A}]_i$ represent concentrations of the reactant at the time t_i. If the values of the $k_{i,\ i+1}$ show no trend when listed in the order of the time of measurement, the data are compatible with the postulate that the reaction is second order.

It must be remembered that experimental data are never exact. Small trends in the values of the rate coefficients, or small departures from linearity in the corresponding plots, can easily be obscured by the random errors of the measurements. This is especially true when the data are restricted to a small part of the possible extent of the reaction, say, to the disappearance of the first 5 or 10% of the reactant. Under these conditions

the rate is nearly constant and fits any of the simple, integrated equations approximately. It is necessary, therefore, to compare (by graphic or analytical methods) the data to all plausible integrated equations, and to show that the data fit one of these equations much better than they do the others.

Some students of kinetics prefer to evaluate the order of a reaction in terms of measurements of its half-time. When this procedure is followed, it is necessary to make measurements of the half-time corresponding to two (or preferably more) different initial concentrations of the reactant, and to determine from these results the functional relation between the half-time and the initial concentration. The order of the reaction can be identified, by comparing the empirical function with a table of half-time functions, such as is listed in Table I. This method can be applied to the determination of the several partial orders for reactions whose rates depend upon the concentrations of more than one substance. It is not convenient when the reaction is complex.

A method, similar in principle to the preceding one, requires the measurement of the rate of the reaction corresponding to two or more different initial concentrations of the reactant (13,14). An order is assumed for the reaction, and rate coefficients based upon this assumption are computed for the first part (approximately 20%) of the data of each of the experiments. If the assumed order is the same as that of the actual reaction, the values of the rate coefficient will be independent of the initial concentration of the reactant. But if the wrong order is assumed in making the computation, the ratio of the values of the coefficients would be directly proportional to some power of the initial concentrations. This method has the advantage that it is not influenced appreciably by kinetic effects of the products, changing ionic strength, etc. As in the previous methods, it is of course essential to show, not only that the data are consistent with some particular rate equation, but also that they are inconsistent with all other plausible rate equations.

In principle it is possible to determine the order of a reaction in terms of a single experiment, without comparing the data directly to the several plausible integrated rate equations. One such procedure was suggested by van't Hoff in 1884. The general differential rate, for a simple reaction involving only one reactant, can be written in the following form:

$$\log (dx/dt)_i = \log k + j \log (A_0 - x_i) \qquad (11)$$

where j is the order of the reaction, and the subscript i refers to any particular value of t and x. The values of $(A - x_i)$ are measured at the successive times t_i. The corresponding values of the rate, $(dx/dt)_i$, can be determined graphically or by some approximate method. If the reaction is a simple one involving only one reactant, a plot of log $(dx/dt)_i$ against log $(A - x)_i$ is a straight line with a slope of j, the order of the reaction.

Several more sophisticated methods of determining the order of simple reactions have been described (15–18). They commonly involve the use of functions of dimensionless ratios, such as $(A - x)/A$. While these procedures are mathematically elegant, their usefulness (like that of the van't Hoff method) is more apparent than real. They are unnecessary for simple reactions and insufficient for complex reactions.

2. Determination of the Rate Laws of Complex Reactions

The determination of the rate law, or differential rate equation, (10), of a complex reaction is more difficult and requires many more measurements than does the evaluation of the order of a simple reaction. A convenient and generally applicable way of solving this problem requires the evaluation of the *initial rate* of the reaction at a number of different initial concentrations of the several reactants. The differential rate equation can be determined directly from these data. Since rates are not directly measurable, the initial rate must be evaluated from measurements of concentrations and times by graphic or numerical methods.

The initial rate can be evaluated graphically by the following procedure. The measured values of the concentration are plotted on rectilinear coordinate paper as a function of time, using scales (19) which are consistent with the precision of the data. A smooth curve, which in the experimenter's judgment best represents the points, is drawn on the plot. At any desired point, a transparent straight edge is placed in contact with the curve and rotated until it appears to be tangent to the curve. The value of the tangent, expressed in appropriate units, is an estimate of the rate of the reaction at that time which corresponds to the chosen point. Although this procedure involves two subjective steps, its results are reasonably reproducible if the several steps are made carefully. Unfortunately, the initial rate which is fixed by the slope at the start of the line is more difficult to estimate than the rates at later times.

Both the precision and the ease of estimation of the slope can be improved by the use of a device consisting of a plane mirror mounted at right angles to a straight edge. When the edge of the mirror is placed on the curve, the curve and its image meet at a point common to the mirror and the paper. Unless the curve is at right angles to the plane of the mirror, the line made up of the curve and its image appears to have a kink at the point of junction. When the mirror is in such a position that the line appears to be continuous, the straight edge which is attached to the mirror is parallel to the tangent to the curve at the selected point, and so measures the rate of the reaction at the corresponding time. This device is particularly useful in determining the initial rate, since the procedure does not

lose precision when the mirror is placed at the "end" of a curve. Other optical (20) and mechanical devices (21) which facilitate the determination of the slope of curves are available.

An analytical approximation, which avoids the subjectivity of the graphic method, consists in setting x_1/t_1 equal to $(dx/dt)_0$. This approximation is equivalent to the assumption that concentration is a linear function of time in the first time interval, t_1. The error involved in this approximation can be decreased by shortening the time interval. However, as the time interval becomes small, the effect of random errors in x_1 and t_1 upon their ratio becomes greater, thereby decreasing the reliability of the determination. One way of avoiding this dilemma is to make several measurements of concentration at increasing times, to plot these values, and to use values of x_1 and of t_1 taken from a smooth curve which was drawn "through" the experimental points. This semigraphic method has the disadvantage that it introduces a subjective step—the construction of the smooth curve.

The initial rate can be determined by fitting an empirical equation to the experimental data and evaluating its first derivative at zero time, in terms of the constants of the equation. If the measurements are limited to the first 10 or 20% of the reaction, the data should fit a cubic equation with reasonable accuracy:

$$x = Bt + Ct^2 + Dt^3$$

where x is the measured change in the concentration of the reactant and t is the elapsed time, measured from the start of the reaction. If x_i is measured after each of three equal, successive time intervals, t_1, the initial rate, $(dx/dt)_0$, may be expressed directly in terms of measured values x_i and t_1:

$$(dx/dt)_0 = B = (1/t_1)[3x_1 - (3/2)x_2 + x_3/3] \tag{12}$$

There is no single, ideal method of determining the value of the initial rate from the experimental data. The method adopted should conform to the precision of the data, the accuracy required of the results, and the preference (or prejudice) of the experimenter.

The rates of many reactions can be represented by the following relatively simple equation:

$$dx/dt = k \prod_{i=1}^{i=n} [A_i]^{\nu_i} \tag{13}$$

where the symbols $[A_i]$ represent the concentrations of all substances which influence the rate, i.e., the reactants, products, and catalysts. The exponents ν_i of this equation can be evaluated from a minimum of $(n + 1)$ measurements of the initial rate. The initial rate:

$$(dx/dt)_{0,\,\mathrm{I}} = k \prod_{i=1}^{i=n} [\mathrm{A}_i]_{0,\mathrm{I}}^{\nu_i}$$

should be measured for some convenient set (I) of the initial concentrations of the substances, A_i. If one of these initial concentrations, say $[\mathrm{A}_j]$, is increased by a factor r, and the others are left unchanged, the corresponding value of the initial rate is:

$$(dx/dt)_{0,\,\mathrm{II}} = k\, r^{\nu_j} \prod_{i=1}^{i=n} [\mathrm{A}_i]_{0,\mathrm{I}}^{\nu_i} = r^{\nu_j}(dx/dt)_{0,\,\mathrm{I}}$$

The exponent ν_j corresponding to the reactant A_j can then be obtained by comparing (as follows) the initial rates of these two experiments:

$$r^{\nu_j} = (dx/dt)_{0,\,\mathrm{II}}/(dx/dt)_{0,\,\mathrm{I}}$$

or:

$$\nu_j = [\log (dx/dt)_{0,\,\mathrm{II}} - \log (dx/dt)_{0,\,\mathrm{I}}]/\log r \qquad (14)$$

Proceeding in this way, one additional experiment suffices to determine the exponent, ν_i, corresponding to each of the n substances, A_i. Whenever it is feasible, values of r equal to or greater than two should be used.

The foregoing simple procedure should never be trusted to determine completely the form of the rate equation for a reaction. In general, the experimenter can have no *a priori* assurance that the rate of the reaction will fit the simple Equation (13) rather than requiring the more general form of Equation (10). Equation (14) is applicable only when the rate equation has the form of Equation (13), in which the exponents may be negative as well as positive. If there are additive terms in either the numerator or denominator of the rate equation, the method breaks down.

In practice, the initial rates should be determined for all practicable combinations of the initial concentrations of the substances present in the system. These concentrations should be varied over as wide a range as possible. Equation (14) can then be applied to groups of experiments in various parts of the studied range. The form of the equation which is compatible with all of the data is usually determined by a process of "trial and error." The differential equation so obtained should be integrated and its integral form compared to values of the concentrations and time corresponding to a large fraction of the possible extent of the reaction, for experiments with widely different initial concentrations.

It should always be remembered that apparent departures from the simpler rate laws may be due to salt or solvent effects (Chapter II). Many of the earlier studies of the kinetics of inorganic reactions were hopelessly confused by the neglect of the effect of changing environment—usually varying ionic strength.

Several methods which do not involve the evaluation of the initial rate have been proposed for the determination of rate equations. The best known of these is the Ostwald isolation method (22), which is directly applicable only to reactions whose rates fit Equation (13). In applying this method, the initial concentration of one of the reactants, A_j, is made much smaller than those of all the other reactants. When the condition is satisfied, the rate can be expressed as follows:

$$dx/dt = k \prod_{i=1}^{i=n} [A_i]^{\nu_i} \approx k\{[A_j]^{\nu_j}/[A_j]_0^{\nu_j}\} \prod_{i=1}^{i=n} [A_i]_0^{\nu_i} = k'[A_j]^{\nu_j} \qquad (15)$$

Since $[A_j]_0$ is much smaller than the other initial concentrations, the coefficient k' is practically constant during the course of the reaction, and may be taken as equal to:

$$k[A_j]_0^{-\nu_j} \prod_{i=1}^{i=n} [A_i]_0^{\nu_i}$$

The exponent ν_j may be determined by comparing the empirical values of x and t to the integrated forms of Equation (15) (Table I). Possible values of ν_j are the small integers and half integers of either sign, lying between $+3$ and -3. The values which occur most commonly are $+1$, $+2$, and 0. When the natural limitations of the system, e.g., solubilities, absolute rates, etc., permit, each of the several exponents, ν_i, may be determined by making (successively) the initial concentrations of each of the reactants much smaller than all of the other initial concentrations. This method of analysis can only be used when the variables $[A_i]$ are separable, that is, for reactions whose rates fit Equation (13), rather than requiring the more general form of Equation (10).

In a useful modification of this method, $[A_j]_0$ is kept smaller than the other initial concentrations in all of the experiments. The first experiment serves to determine ν_j, as described in part 1 of this section. A second experiment is then performed in which the initial concentration of one of the reactants, A_1 (not A_j), is increased by a factor r and the other concentrations are left unchanged. The ratio of the values of k' for these two experiments fixes the value of ν_1:

$$k'_{II}/k'_{I} = r^{\nu_1}$$

$$\nu_1 = (\log k'_{II} - \log k'_{I})/\log r$$

This modified isolation method is analogous to the method of initial rates, and is applicable whenever $[A_j]$ is separable from the other variables $[A_i]$.

IV. CALCULATION OF RATE CONSTANTS

Representative values of the rate constants may be obtained, for simple reactions, by methods similar to those used in determining the order of the reaction. Indeed, the procedure can be designed to yield both order and rate constant as the result of a single set of computations. Since, in general, more experimental data are available than are required to establish the value of the constant, some method of averaging is necessary. Methods varying from simple graphic procedures to analytical treatments based upon formal statistical theory have been used, depending upon the precision required and the preference of the experimenter.

1. Graphic Methods

A relatively quick and convenient way of evaluating the rate constant of a simple reaction is to plot an appropriate (rectifying) function of the concentration of a reactant against time, draw a representative straight line through these points, and compute the rate constant in terms of the slope of this line. For each order, that function is chosen which makes the plotted points correspond to a straight line. For the commoner cases, these functions are listed in column five of Table I. The relation between the slope and the rate constant can easily be deduced from the integrated rate equation, as is illustrated by the two following examples. For a first-order reaction:

$$\ln [A]_0/[A]_t = kt_j$$

and the constant is equal to -2.30 times the slope, when $\log [A]_t$ is plotted against time:

$$k = -2.30(\log [A]_1 - \log [A]_j)/(t_1 - t_j) \tag{16}$$

Similarly for a second-order reaction:

$$1/[A]_t - 1/[A]_0 = kt_i$$

and the constant is equal to the slope when the reciprocal of concentration is plotted against time.

$$k = ([A]_1^{-1} - [A]_j^{-1})/(t_1 - t_j) \tag{17}$$

The graphic procedures are equally simple for other orders, as long as the concentration of only one reactant changes appreciably during the reaction. When the changing concentrations of two or more reactants enter into the rate equation, graphic methods, while still possible (23), are less convenient and are seldom used.

These graphic procedures are perhaps the most practical and useful of the simple methods of determining a value for the rate constant that is representative of a given set of data. Although the drawing of a straight line to represent the plotted data is a subjective process, if reasonable care is taken the results obtained by different computers, from a given set of measurements, are surprisingly similar. In plotting, scales should be chosen which make the smallest coordinate division approximately equal to the known or estimated uncertainties (standard deviation of a single value) of the quantities being plotted. If the use of such a scale requires an inconveniently large sheet of coordinate paper, the graphic method should be used only to obtain an approximate value of the rate constant. One of the more formal analytical methods (see Section 3) should be used to determine its "best value." Since the subjective fitting of the line to the data appears to be influenced by the magnitude of the slope and the apparent scatter of the points, it is customary to use 1 mm. or $^1/_{20}$ in. graph paper and to adjust the relative scales so that the slope is roughly 45°. The most representative line need not pass through any of the points, but should be chosen intuitively to make the sum of the residuals equal to zero. Frequently, the errors of the concentration measurements are much greater than those of the time measurements. When this is true, the residuals should be thought of as parallel to the concentration axis, i.e., vertical, rather than as perpendicular to the line. If the uncertainties vary from point to point and are known, it is helpful to indicate their values by the length of short lines having their centers at the plotted points. When this is done, the fitted line should intersect, or at least pass close to, all of these short vertical lines.

2. Simple Analytical Methods

Simple analytical methods are widely used for the determination of the "average" value of a rate constant. Two common procedures of this type are the *long-interval* and the *short-interval methods*. While these simple analytical schemes avoid the subjective weighting of the several experimental points which is inherent in the graphic method, they have the disadvantage that they weight the points in an arbitrary and, in general, illogical manner.

The long-interval method involves the computation of values of k by combining the initial concentration successively with each of the other measured concentrations and times. If there are $(n + 1)$ measurements of the concentration (including the initial value), the procedure yields n values of k. Their arithmetic mean:

$$\bar{k} = (1/n) \sum_{i=1}^{i=n} k_{0,i}$$

is taken as the representative value of the rate constant. A second-order reaction will serve to illustrate the detailed steps. The several values of the rate constant for a second-order reaction are:

$$k_{0,1} = (1/t_1)(1/[\mathrm{A}]_1 - 1/[\mathrm{A}]_0)$$

$$k_{0,2} = (1/t_2)(1/[\mathrm{A}]_2 - 1/[\mathrm{A}]_0)$$

$$k_{0,t} = (1/t_t)(1/[\mathrm{A}]_t - 1/[\mathrm{A}]_0)$$

The arithmetic mean of these values is:

$$\bar{k} = \frac{1}{n}\sum_{i=1}^{i=n}\frac{1}{t_i[\mathrm{A}]_i} - \frac{1}{n[\mathrm{A}]_0}\sum_{i=1}^{i=n}\frac{1}{t_i}$$

It is apparent from this equation that the first point receives a much greater weight than any succeeding one. For reasons of experimental convenience, concentration measurements are commonly made after equal time increments, that is, $t_i = it_1$ or $t_{i+1} - t_i = t_1$. For this (common) special case.

$$\bar{k} = \frac{1}{nt_1}\sum_{i=1}^{i=n}\frac{1}{i[\mathrm{A}]_i} - \frac{1}{nt_1[\mathrm{A}]_0}\sum_{i=1}^{i=n}\frac{1}{i}$$

$$\backsimeq \frac{1}{nt_1}\sum_{i=1}^{i=n}\frac{1}{i[\mathrm{A}_i]} - \frac{2.303\log n + 1/2n + 0.5772}{nt_1[\mathrm{A}_0]} \qquad \text{(see Ref. 24)} \quad (18)$$

It is reasonable to follow this system of analysis when the initial concentration is known much more accurately than any of the succeeding values. This condition is realized when the initial mixture can be made exactly, the time of mixing is short compared to the interval t_1, and the analytical determination of $[\mathrm{A}]_i$ is relatively inaccurate. More commonly the standard deviation of $[\mathrm{A}]_0$ is approximately equal to the standard deviations of $[\mathrm{A}]_i$, in which case the use of the long-interval method of averaging is inappropriate.

In the short-interval method, values of $k_{i,\,i+1}$ are computed for each successive pair of values of concentration and time. For example, the values for a second-order reaction are:

$$k_{0,1} = (1/t_1)(1/[\mathrm{A}]_1 - 1/[\mathrm{A}]_0)$$

$$k_{1,2} = \{1/(t_2 - t_1)\}(1/[\mathrm{A}]_2 - 1/[\mathrm{A}]_1)$$

$$k_{n-1,n} = \{1/(t_n - t_{n-1})\}(1/[\mathrm{A}]_n - 1/[\mathrm{A}]_{n-1})$$

The corresponding value of the "average" rate constant is:

$$\bar{k} = \frac{1}{n}\left[\frac{1}{[A]_n}\cdot\frac{1}{t_n - t_{n-1}} - \frac{1}{[A]_0}\cdot\frac{1}{t_1} + \frac{1}{[A]_1}\cdot\frac{t_2 - 2t_1}{t_1(t_2 - t_1)}\right.$$
$$\left. + \frac{1}{[A]_2}\cdot\frac{t_3 + t_1 - 2t_2}{(t_3 - t_2)(t_2 - t_1)} + \frac{1}{[A]_3}\cdot\frac{t_4 + t_2 - 2t_3}{(t_4 - t_3)(t_3 - t_2)} + \ldots\right]$$

When the time interval between measurements is constant, all but the first two terms of the polynomial vanish, and $\bar{k}$ is given by the following equation:

$$\bar{k} = (1/nt_1)(1/[A]_n - 1/[A]_0)$$

In other words, when the time interval is constant, the use of the short-interval method of computing the average is equivalent to rejecting all but the first and last measurements (25). When the time intervals are approximately but not exactly equal, the result is not much different; the greatest weights are placed upon the initial and final measurements and small, varying weights upon the others. In spite of its apparent absurdity, this method of averaging has appeared a number of times in the chemical literature. It was pointed out by Kassel (26) that the short-interval method of averaging places equal weight upon the several points when the measurements of time correspond to a constant decrement in the concentration. This latter condition exists when the "clock reaction" technique is used, but it is uncommon practice in kinetic measurements.

The detailed application of the long- and short-interval methods of averaging to simple reaction of orders other than second is similar to, and as simple as, the preceding examples. These methods can be applied to complex as well as to simple reactions, in terms of the proper integrated rate equations. Inspection of a plot of k_t against t_1 (or of a table in which the k_t values are arranged in the order of increasing time) frequently reveals systematic trends, which may indicate significant departures from the assumed rate law.

A good simple method of determining rate constants depends upon the planning of the experiment. A series of $(n + 1)$ measurements of the concentrations $[A]_t$, are made at times t_0, t_1, $2t_1$, $3t_1$, ..., nt_1. The total interval nt_1 should not exceed the half-time, $\tau_{1/2}$. After a known lapse of time τ', which should be as great or greater than $\tau_{1/2}$, a second series of $(n + 1)$ measurements of the concentrations are made at times which differ by the constant increment t_1. A value, k_t, of the rate constant is then calculated for each pair of points corresponding to the times t_0 and τ', t_1 and $(\tau' + t_1)$, $2t_1$ and $(\tau' + 2t_1)$, ..., nt_1 and $(\tau' + nt_1)$. The arithmetic mean of these values, k_t, is a good representative value of the rate constant. In its calculation each point is used once and only once, and the probable

errors of the quantities which are averaged are all of the same order of magnitude. The following equations symbolize the computations required by the foregoing method for first- and second-order reactions. The concentrations belonging to the first and second series of measurements are denoted, respectively, by $[A]_i$ and $[A]_i'$:

$$\text{(first order) } \bar{k} = \{2.303/(n+1)\tau'\} \sum_{i=0}^{i=n} (\log [A]_i - \log [A]_i')$$

$$\text{(second order) } \bar{k} = \{1/(n+1)\tau'\} \sum_{i=0}^{i=n} (1/[A]_i' - 1/[A]_i)$$

The preceding plan for an experiment lends itself equally well to the graphic determination of a representative value of the rate constant.

3. Formal Analytical Methods

The *method of averages* (27) is superior to those averaging procedures which are based upon either the long-interval or the short-interval methods. It is based upon the assumption that the best value of k is the one which renders the sum of the residuals, ρ_i, equal to zero. If we again take a second-order reaction as an illustration, the residuals are defined by:

$$\rho_i = 1/[A]_i - 1/[A]_0 - kt_i$$

Since the value of $\bar{k}$ is to be adjusted to make the sum of the residuals equal to zero, we may write:

$$\sum_{i=1}^{i=n} 1/[A]_i - n/[A]_0 - \bar{k} \sum_{i=1}^{i=n} t_i = 0 \tag{19}$$

If, for a particular set of measurements, the initial concentration is known much more accurately than are the succeeding concentrations, we may introduce the known value of $[A]_0$ into the foregoing equation and obtain $\bar{k}$ as follows:

$$\bar{k} = \left(\sum_{i=1}^{i=n} 1/[A]_i - n/[A]_0\right) \Big/ \sum_{i=1}^{i=n} t_i$$

If, as is generally true, the probable error of the value of the initial concentration is as great or greater than the probable errors of the other values of the concentrations, it is more logical to eliminate $[A]_0$ from the equation which determines $\bar{k}$. To accomplish this it is necessary to divide the data into two groups, 1 to l and $(l+1)$ to n. Introducing the corresponding sums into Equation (19), we obtain two equations:

$$\sum_{i=1}^{i=l} 1/[A]_i - l/[A]_0 - \bar{k}\sum_{i=1}^{i=l} t_1 = 0$$

$$\sum_{i=l+1}^{i=n} 1/[A]_i - (n-l)/[A]_0 - \bar{k}\sum_{i=l+1}^{i=n} t_1 = 0$$

Eliminating $[A]_0$ between these equations:

$$\bar{k} = \left\{\sum_{i=1}^{i=l} 1/[A_i] - l/(n-l)\sum_{i=l+1}^{i=n} 1/[A_i]\right\} \Big/ \left\{\sum_{i=1}^{i=l} t_i - l/(n-l)\sum_{i=l+1}^{i=n} t_i\right\} \quad (20)$$

In applying this equation the data should be divided into two equal (or nearly equal) groups, the first sum containing the first half of the values and the second sum the remainder of the terms. The data should not be grouped in any other way (such as, including all the terms with even valued i's in one sum and with odd valued i's in the other). Any such special grouping or any marked disparity between l and $n/2$ reduces the reliability of the resultant $\bar{k}$. Application of the method to reactions of other orders can be made directly by setting $\sum \rho_i = 0$ and evaluating $\bar{k}$ or $\bar{k}$ and $[A]_0$ from the resulting equations. For a first-order reaction the corresponding equations are:

$$\rho_i = \ln [A]_i - \ln [A]_0 + kt$$

$$\bar{k} = 2.303\left(\sum_{i=1}^{i=l} \log [A]_i - \sum_{i=l+1}^{i=n} \log [A]_i\right) \Big/ \left(\sum_{i=l+1}^{i=n} t_i - \sum_{i=1}^{i=l} t_i\right) \quad (21)$$

The most commonly used of the so-called sophisticated methods of curve fitting is the (unweighted) least squares procedure (27,28). The basic postulate of this method is that the best values of the adjustable constants of the empirical equation are those which make the sum of the squares of the residuals a minimum. The following application of this postulate to a second-order reaction should serve to illustrate the details of this procedure for any simple reaction. When the sum of the squares of the residuals:

$$\sum\nolimits_{\rho i}^2 = \sum(1/[A]_i - 1/[A]_0 - \bar{k}t_i)^2$$

is a minimum, its partial derivatives with respect to the adjustable constants are each equal to zero. To take the more general case, let us assume that the probable error of $[A]_0^{-1}$ is of the same order of magnitude as the probable errors of the $[A]_i^{-1}$. Under these circumstances both $\bar{k}$ and $[A]_0^{-1}$ should be treated as adjustable constants of the equation, and:

$$(\partial/\partial[A]_0^{-1}) \sum \rho_i^2 = 0 \text{ and } (\partial/\partial\bar{k}) \sum_i \rho_i^2 = 0$$

Performing these operations:

$$(\partial/\partial[A]_0^{-1}) \sum_i \rho_1^2 = -2 \sum_{i=1}^{i=n} (1/[A]_i - 1/[A]_0 - \bar{k}t_i) = 0$$

$$\sum_{i=1}^{i=n} 1/[A]_i - n/[A]_0 - \bar{k} \sum_{i=1}^{i=n} t_i = 0 \tag{22}$$

$$(\partial/\partial\bar{k}) \sum_i \rho_1^2 = -2 \sum_{i=1}^{i=n} (1/[A]_i - 1/[A]_0 - \bar{k}t_i)\, t_i = 0$$

$$\sum_{i=1}^{i=n} t_i/[A]_i - 1/[A]_0 \sum_{i=1}^{i=n} t_i - \bar{k} \sum_{i=1}^{i=n} t_1^2 = 0 \tag{23}$$

Combining Equations (22) and (23) to eliminate $[A]_0$:

$$\bar{k} = \{(1/n)\sum_i t_i \sum_i 1/[A]_i - \sum_i t_i/[A]_i\} / \{(1/n)(\sum_i t_i)^2 - \sum_i t_i^2\} \tag{24}$$

where sums are taken from $i = 1$ to $i = n$. In applying Equation (24), it is necessary to tabulate the t_i and $[A]_i$ values, to compute and tabulate $[A]_i^{-1}$, $t_i[A_i]^{-1}$, and t_i^2, to take the indicated sums, and finally to enter these numerical values in Equation (24). The use of an automatic computing machine greatly reduces the labor involved in these steps.

For a first-order reaction, the equations corresponding to (22), (23), and (24), are (25), (26), and (27), respectively:

$$\sum_{i=1}^{i=n} \ln [A]_i - n \ln [A]_0 + \bar{k} \sum_{i=1}^{i=n} t_i = 0 \tag{25}$$

$$\sum_{i=1}^{i=n} t_i \ln [A]_i - \ln [A]_0 \sum_{i=1}^{i=n} t_i + \bar{k} \sum_{i=1}^{i=n} t_i^2 = 0 \tag{26}$$

$$\bar{k} = 2.303\{(1/n) \sum_i t_i \sum_i \log [A]_i - \sum \log [A]_i\} / \{\sum_i t_i^2 - (1/n)(\sum_i t_i)^2\} \tag{27}$$

4. Statistical Treatment of Rate Data

Contrary to the view held by some experimenters, the theory of least squares is not supported by a rigorous theoretical foundation (29). This is particularly true for data whose distribution does not correspond to a normal Gaussian curve. When the distribution is markedly skewed there is no reasonable justification for the direct application of the ordinary least squares treatment. It is, of course, possible to treat even skewed distributions by more general statistical methods. Physical and chemical data are usually adjusted by the standard least squares procedure, partly because it has become conventional, but chiefly because no better simple method is known.

Regardless of whether the least squares method is the best one to apply generally to physical data, it should be apparent that the *unweighted least squares* solutions which are outlined in the preceding section do not yield the best possible values for the rate constants. First, all points were assigned equal weights, and, second, functions of the measured concentrations were introduced into the equations defining the residuals. According to the general theory of least squares, the quantity which should be minimized is not the sum of the squares of the residuals but the sum of the *weighted* squares of the residuals (30–32). The appropriate weights are proportional to the reciprocal of the squares of the standard deviations (of single values). If the original measured data (and not functions thereof) are introduced into the equation defining the residuals, it is frequently true that the unweighted least squares solution is appropriate, since the standard deviations of the several measurements are approximately constant. This is not the case when a function of the measured quantity is used. For example, in the derivation of Equation (27), the residuals were defined by the following equation:

$$\rho_t = \ln [A]_t - \ln [A]_0 + kt_t$$

If the standard deviations, $\sigma_{A,t}$, of the $[A]_t$ were constant and equal to σ_A, the standard deviation of $\ln [A]_t$ would be:

$$\sigma_t = (d \ln [A]_t/d[A]_t)\sigma_A = \sigma_A/[A_t]$$

If, for example, $[A]_n$ were equal to $[A]_1/10$, the ratio of the squares of the standard deviations of their logarithms would be:

$$\sigma_n^2/\sigma_1^2 = 10^{-2}$$

and the weight of $\ln [A]_n$ should be 1% of that of $\ln [A]_1$; whereas, Equation (27) makes these two weights equal.

Statisticians have developed general calculating procedures which avoid this difficulty. These procedures, while laborious, are not excessively time-consuming if a fully automatic calculating machine is available. Generally, it is necessary to find approximate values of the adjustable constants by the method of selected points or by some graphic procedure. The method of least squares is then used to obtain correction terms for these estimated constants. The labor is considerably lessened if it is assumed that the measurements of one of the quantities are free from error. For rate measurements it is sometimes reasonable to assume that the measured times are known much more accurately than are the corresponding concentrations, and to attribute the random residuals entirely to the errors in the concentration measurements. The application of this method to a few special cases (where the measurements of one quantity are assumed to be

free from error and the error of the other quantity is independent of its value) was presented in detail by Bond (30). One of these cases was applied to kinetic data by Guggenheim and Wiseman (33). More general methods, which are capable of treating cases in which both measured quantities are subject to random error and in which the weights vary from point to point, are given in outline form by Deming (31).

It has sometimes been questioned whether statistical adjustments ought to be applied to kinetic data. In particular, Kassel (34) made the following statement:

"Now there is no use in adopting sophisticated methods to find the 'most probable' values of these constants unless equally sophisticated methods are first used to find the form of the equation. But if we do this we shall never have reactions of the first order, but only of the 0.97836 ± 0.00258 order; etc."

This criticism appears to be without reasonable justification. We are surely justified in accepting the theoretical result that the order of a *simple* reaction occurring in a homogeneous solution is always integral. This is a *condition of restraint* which should be applied to the statistical analysis of kinetic data, just as the condition that the sum of the angles of a triangle is exactly 180° is applied to least squares solutions of surveying problems. If, on the other hand, the rate measurements are afflicted with a systematic error, this is most likely to be revealed by statistical adjustment of the data. Typical systematic errors are caused by a slowly drifting temperature caused by a faulty thermostat, the assumption of an erroneous value for the initial concentration, an unsuspected changing solvent effect, or a minor side reaction. The determination of the best values of the constants belonging to the rate law of a complex reaction is a much more difficult problem, but in principle it is similar to the analysis of a simple reaction. As pointed out earlier, (33,35) careless analysis of even quite precise data is likely to lead to erroneous conclusions.

Directions for the application of weighted least square techniques to the evaluation of the energy of activation, from measurements of the specific reaction rates at different temperatures, have been published. Unfortunately, it is assumed in these papers (36) that the Arrhenius equation,

$$k(T) = k_0 \exp(-\Delta E/RT)$$

is exact and that the value of k_0 and ΔE are independent of temperature. There is no theoretical justification for this assumption. One of the time-saving simple methods of averaging (e.g., a graphical method) would be consistent with the use of this frankly approximate equation. If the apparent precision of the data warrant the labor, the weighted least squares technique should be applied to an equation which is consistent with the rate theory of the type of reaction being studied (37).

5. Indirect Measurement of Concentration

Instead of determining analytically the changing concentration of a reactant, the course of a reaction can be followed by measuring some physi-

cal property which is a function of the composition of the system (38). When the functional relation between this property and the composition of the solution is a simple one, it is convenient to replace the concentration, where it occurs in the rate equation, by the directly measured quantity. As an illustration, let us consider a first-order reaction whose rate is determined by measuring a quantity r which is a linear function of the concentration of the reactant:

$$r = a + b[\mathrm{A}] \tag{28}$$

where a and b are constants. Since $[\mathrm{A}]_\infty = 0$, a and b can be eliminated, and:

$$[\mathrm{A}]_t/[\mathrm{A}]_0 = (r_t - r_\infty)/(r_0 - r_\infty) \tag{29}$$

Introducing this expression into the first-order rate equation:

$$\ln (r_0 - r_\infty)/(r_t - r_\infty) = kt_t$$

or:

$$r_t = r_\infty + (r_0 - r_\infty) \exp (-kt_t) \tag{30}$$

The values of the three adjustable constants (r_0, r_∞, and k) of this equation can be fixed in terms of a set of measured values of r_t and t_t by the method of least squares (30–33) or approximately by the method of selected points. If this same method of indirect analysis is applied to a reaction of higher order, it is necessary to determine the value of a fourth adjustable parameter. In general, the problem is more complicated if the relation between the concentration and the measured quantity is nonlinear.

Guggenheim (39) has described the following convenient and effective design of an experiment for the determination of the rate constant of a first-order reaction. A series of n measurements ($r_1, r_2, \ldots, r_n$) are made at times ($t_1, t_2, \ldots, t_n$). After an interval τ' a second series of measurements ($r_1', r_2', \ldots, r_n'$) are made at times $\tau', \tau' + t_1, \tau' + t_2, \ldots, \tau' + t_n$. The interval τ' between the two series should be greater than t_n and preferably should exceed the half-time, $\tau_{1/2}$. It is convenient, although unnecessary, to keep this short interval, $t_{i+1} - t_i$, constant. The observed times and readings may be introduced into Equation (30):

$$r_t = r_\infty + (r_0 - r_\infty) \exp (-kt_t)$$

$$r_1' = r_\infty + (r_0 - r_\infty) \exp [-k(\tau' + t_t)]$$

Subtracting the second from the first equation:

$$r_t - r_t' = (r_0 + r_\infty)[1 - \exp (-k\tau')] \exp (-kt_t)$$

Putting the equation into logarithmic form:

$$\ln (r_t - r_t') = \ln \{(r_0 - r_\infty)[1 - \exp(-k\tau')]\} - kt_t$$

Since the quantity, $\ln \{(r_0 - r_\infty)[1 - \exp(-k\tau')]\}$, is a constant, k can be evaluated graphically by plotting $\log (r_t - r_t')$ against t_t. A representative value of k can be obtained from the slope of the resulting straight line:

$$k = 2.303\ \Delta \log (r_t - r_t')/\Delta t_t$$

This is an interesting and simple example of the advantage which can be obtained by planning a rate experiment, rather than allowing its design to be dictated entirely by experimental convenience and laboratory convention (40).

V. COMPARISON OF A POSTULATED MECHANISM TO OBSERVED DATA

To determine whether an empirical rate law is consistent with a postulated mechanism, it is necessary to derive a rate equation based on the mechanism. In principle, it is only necessary to write a differential equation for each step postulated in the mechanism, to reduce the number of variables by introducing the stoichiometric conditions, and to solve the resulting simultaneous differential equations. For all but the very simplest cases (41–49) the analysis is difficult, and frequently it is impossible to obtain a closed solution. Accordingly, approximations are commonly used.

1. Exact Solutions

The following mechanism illustrates a case simple enough to be solved completely:

$$\begin{aligned} A &\longrightarrow B & v_1 &= k_1[A] \\ B &\longrightarrow C & v_2 &= k_2[B] \\ C &\longrightarrow B & v_3 &= k_3[C] \\ B &\longrightarrow E & v_4 &= k_4[B] \end{aligned}$$

In this and the following discussions, the symbols v_t refer to the rates of the several reaction steps. For example, $v_1 = -d[A]/dt$, etc. If we consider the condition where $[A]_0 = a$ and $[B]_0 = [C]_0 = [E]_0 = 0$, and introduce the following symbols:

$$a - x = [A] \qquad y = [C] \qquad z = [E]$$

We may write the following simultaneous equations:

$$dx/dt = k_1(a - x)$$

$$dx/dt - dy/dt - dz/dt = k_1(a - x) - k_2(x - y - z) + k_3y - k_4(x - y - z)$$

$$dy/dt = k_2(x - y - z) - k_3y$$

$$dz/dt = k_4(x - y - z)$$

The first of these equations may be integrated directly, yielding

$$x = a[1 - \exp(-k_1t)]$$

If this value is substituted into the other three equations, the resulting differential equations are first order in three variables and can be solved simultaneously by standard methods. The following integrated equations constitute their solution:*

$$[A] = a \exp(-k_1t)$$

$$[B] = [ak_1(k_3 - k_1) \exp(-k_1t)]/De + (m_1C_1/k_4) \exp(m_1t) + (m_2C_2/k_4) \exp(m_2t)$$

$$[C] = [ak_1k_2 \exp(-k_1t)]/De - (m_1/k_4 + 1)C_1 \exp(m_1t) - (m_2/k_4 + 1)\, C_2 \exp(m_2t)$$

$$[E] = a + [ak_4(k_1 - k_3) \exp(-k_1t)]/De + C_1 \exp(m_1t) + C_2 \exp(m_2t)$$

Where the special symbols have the following significance:

$$De = k_1^2 - k_1(k_2 + k_3 + k_4) + k_3k_4$$

$$m_1 = (-k_2 - k_3 - k_4 + [(k_2 + k_3 + k_4)^2 - 4k_3k_4]^{1/2})^1/_2$$

$$m_2 = (-k_2 - k_3 - k_4 - [(k_2 + k_3 + k_4)^2 - 4k_3k_4]^{1/2})^1/_2$$

$$C_1 = [ak_1/(m_1 - m_2)]\,[k_4(k_1 - k_3) + m_2(k_1 - k_2 - k_3)]/De$$

$$C_2 = [ak_1/(m_2 - m_1)]\,[k_4(k_1 - k_3) + m_1(k_1 - k_2 - k_3)]/De$$

Figure 1 is a plot of data which were computed upon the illustrative assumption that the values of the parameters were: $a = 16$, $k_1 = 5$, $k_2 = 4$, $k_3 = 3$, and $k_4 = 3$. These values were chosen to show the simultaneous changes in the several concentrations. They correspond to relatively stable intermediates, not to the usual unstable intermediates.

* This solution and the numerical values plotted in Figure 1 were presented by Dr. F. T. Wall as part of a term paper in a course on reaction kinetics, in 1933, while he was

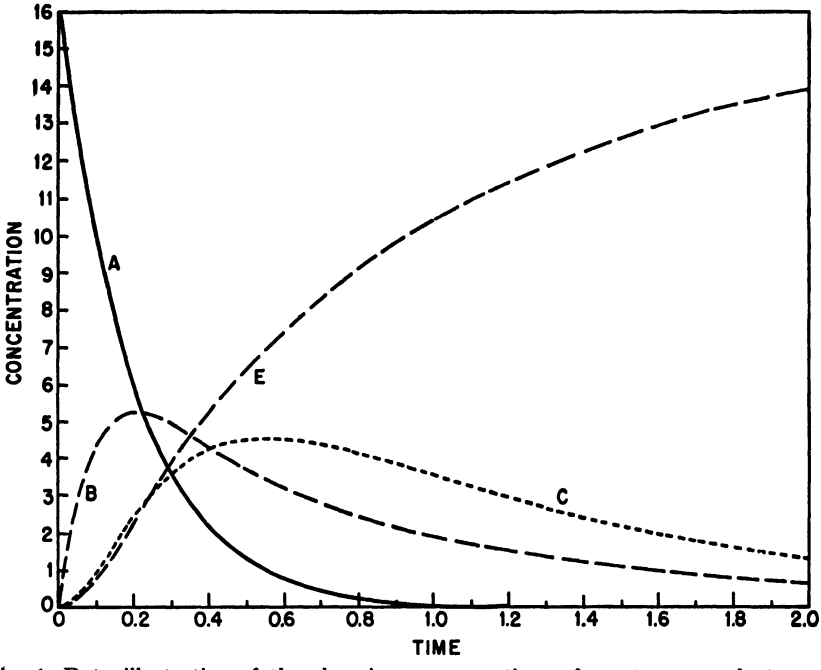


Fig. 1. Data illustrative of the changing concentrations of reactants, products, and intermediates in a complex reaction.

2. Approximate Numerical Solutions

The solution of sets of simultaneous differential equations corresponding to reaction mechanisms can always be obtained in terms of infinite series. While the numerical evaluation of the rate constants in terms of such a series solution is practicable, at least for the simpler cases, it is laborious and the method has seldom been used. The analysis of the kinetics of rearrangement of α-methoxystyrene (50) is an interesting and instructive example of the successful application of this method. The numerical analysis of problems of this type can be greatly expedited by the use of modern electronic computers (51–53).

3. The Bodenstein Steady State Approximation

The method which is used almost universally in comparing postulated mechanisms to empirical rate data is the *Bodenstein steady state approximation* (54). This method is applicable only to those cases in which the intermediates are unstable and, therefore, their concentrations are at all

times much smaller than those of the reactants. For such cases, it is reasonable to postulate that, after a time which is very short relative to the half-time of the reaction, a steady state is attained and that during this steady state the rates of change of the concentrations of the intermediates are negligibly small. On the basis of this assumption, we may set the time derivatives of the concentrations of each of the intermediates equal to zero. This permits us to eliminate algebraically the concentrations of all of the intermediates from the over-all rate equation.

The validity of this postulate has been submitted to careful scrutiny (55–60) and there appears to be no reason to doubt its correctness and usefulness as applied to ordinary reactions, whenever the concentrations of all the intermediates are very small compared to the concentrations of the reactants. When this condition is not satisfied the approximation is unnecessary, since the appreciable concentrations of the intermediates are then susceptible to direct measurement. If the changing concentrations of the reactants and intermediates are all known, the rate of each reaction step can be determined directly from the experimental data. The set of hypothetical data of Figure 1 is an example of this latter type.

As an illustration of the use of this approximate method, it may be applied to the following mechanism, which was proposed by Ogg (61) to explain the observed first-order kinetics of the decomposition of N_2O_5:

$$N_2O_5 \longrightarrow NO_2 + NO_3 \qquad v_1 = k_1[N_2O_5] \qquad (1)$$

$$NO_2 + NO_3 \longrightarrow N_2O_5 \qquad v_2 = k_2[NO_2][NO_3] \qquad (2)$$

$$NO_2 + NO_3 \longrightarrow NO_2 + O_2 + NO \qquad v_3 = k_3[NO_2][NO_3] \qquad (3)$$

$$NO + NO_3 \longrightarrow 2NO_2 \qquad v_4 = k_4[NO][NO_3] \qquad (4)$$

In this system both NO_3 and NO can be considered unstable intermediates; NO, because it is known (62) to react very rapidly with N_2O_5. Accordingly, the steady state conditions are:

$$d[NO_3]/dt = v_1 - v_2 - v_3 - v_4 = 0$$

and:

$$d[NO]/dt = v_3 - v_4 = 0$$

Solving these equations for the concentrations of the intermediates:

$$[NO] = (k_3/k_4)[NO_2]$$

and:

$$[NO_3] = k_1[N_2O_5]/\{(k_2 + k_3)[NO_2] + k_4[NO]\}$$
$$= k_1[N_2O_5]/(k_2 + 2k_3)[NO_2]$$

The rate of decomposition of N_2O_5 may be written:

$$-d[N_2O_5]/dt = v_1 - v_2$$
$$= k_1[N_2O_5] - k_2[NO_2][NO_3]$$

Eliminating the concentrations of the intermediates:

$$-d[N_2O_5]/dt = k_1[N_2O_5] - k_1k_2[N_2O_5]/(k_2 + 2k_3)$$
$$= \{2k_1k_3/(k_2 + 2k_3)\}[NO_5]$$

This shows that the assumed mechanism is consistent with the observed first-order kinetics. This agreement is not in itself proof that the mechanism is correct, since other plausible mechanisms also lead to the first-order law. Additional examples of the use of this steady state approximation are presented in Section VII.

Christiansen (63) has presented a useful procedure for abbreviating the algebra involved in the steady state approximation. For steps which are first order with respect to the unstable intermediate, it is convenient to substitute first-order rate equations (with time-dependent rate constants, w_i) for the rates of the bimolecular steps. For instance, if the mechanism involved in the reaction between a radical, r·, and an oxygen molecule:

$$O_2 + r\cdot \longrightarrow rO + O\cdot$$

the rate of the step may be written as:

$$v_j = w_j[r\cdot]$$

instead of the usual:

$$v_j = k_j[O_2][r\cdot]$$

If there are several ways in which an intermediate can react, the probability P_j that it will follow a certain path j is equal to the ratio of the "first-order rate constant," w_j, to the sum of the first-order rate constants for all the possible reactions involving this constant:

$$P_j = w_j/\sum_i w_i$$

The rate of formation of the products of step j may be written as the product of the rate of formation of the intermediate r_j and the probability that it will undergo the specified reaction:

$$v_j = v_{+r_j}P_j$$

The use of these functions can be illustrated by applying them to the preceding example, the decomposition of N_2O_5. In the modified terminology the rates of steps (2) and (3) are:

$$v_2 = w_2[NO_3] \qquad v_3 = w_3[NO_3]$$

The rate of decomposition of N_2O_5 is equal to the rate of step (1) minus that of step (2):

$$-d[N_2O_5]/dt = v_1 - v_2$$

This mechanism contains only one reaction involving NO; therefore, the probability that NO will undergo step (4) is unity, and:

$$v_3 = v_4 \text{ and } k_4[NO] = w_3$$

The probability that NO_3 will react with NO_2 to reform N_2O_5 is:

$$P_2 = w_2/(w_2 + w_3 + k_4[NO]) = w_2/(w_2 + 2w_3)$$

Accordingly the rate of step (2) is:

$$v_2 = v_1P_2 = v_1w_2/(w_2 + 2w_3)$$

and the observable rate of decomposition of N_2O_5 is:

$$-d[N_2O_5]/dt = v_1\{1 - w_2/(w_2 + 2w_3)\} = 2v_1w_3/(w_2 + 2w_3)$$
$$= \{2k_1k_3/(k_2 + 2k_3)\}[N_2O_5]$$

While the advantage is scarcely demonstrated by this simple example, the use of this modified procedure in the analysis of more complex reactions often effects a considerable saving of labor.

When it is necessary to postulate that a number of intermediates participate in a reaction and that a relatively large number of reaction steps influence its velocity, the application of the steady state approximation can be troublesome and time consuming. Not infrequently, a step in such a mechanism which is required by the "materials balance" can occur by any of several different reaction paths. For example, atoms or radicals can disappear by a second-order (3-body) gas phase encounter, by a first-order diffusion to the walls, or by a process which is catalyzed by one of the reactants or products. The straightforward application of the Bodenstein approximation to such a system requires that the complete analysis of the system of equations be carried out for each possible variant of this step. It is often possible to set the rate of such a step equal to some unknown function, F_j, and to carry through the analysis of the mechanism retaining this undetermined function. Finally, the function can be evaluated by comparing the theoretical equation to the observed rate law.

While it is entirely unnecessary, and scarcely useful, for so simple a case, the decomposition of N_2O_5 will serve to illustrate the procedure. The basic postulate in the mechanism of this reaction is that the reversible dissociation of N_2O_5 into NO_3 and NO_2 occurs at an appreciable rate, so that the first two steps of the mechanisms are:

$$N_2O_5 \longrightarrow NO_3 + NO_2 \qquad v_1 = k_1[N_2O_5] \qquad (1)$$

$$NO_2 + NO_3 \longrightarrow N_2O_5 \qquad v_2 = k_2[NO_2][NO_3] \qquad (2)$$

A molecule of NO_3, if it does not recombine with NO_2, must react to form the stable products of the reaction. This latter reaction, which could be the "spontaneous" dissociation of NO_3 or its dissociation catalyzed by O_2, NO_2, or N_2O_5, may be written in the following unspecified form:

$$NO_3 \rightarrow\rightarrow NO_2 + {}^1/_2O_2 \qquad v_3' = F_3' \tag{3'}$$

where the double arrow indicates that this step may in reality be complex, consisting of two or more simple reactions. As a first trial, let us assume that the rate of step (3') is proportional to the first power of $[NO_3]$ and to some unknown function of the concentrations of the several reactants and products:

$$v_3' = [NO_3]f_3'([N_2O_5], [NO_2], [O_2]) = [NO_3]F_3'$$

The probability that NO_3 will undergo step (3') is:

$$P_3' = F_3'/(k_2[NO_2] + F_3')$$

and the rate of this step, which yields the stable products of the reaction, is:

$$v_3' = v_1P_3' = k_1[N_2O_5]F_3'/(k_2[NO_2] + F_3')$$

This equation is compatible with the observed rate law,

$$-d[N_2O_5]/dt = 2(d[O_2])/dt = k[N_2O_5]$$

only if:

$$F_3' = k_3[NO_2]$$

Accordingly, the indefinite step (3') must be replaced by the only energetically feasible step involving NO_2:

$$NO_2 + NO_3 \longrightarrow NO_2 + NO + O_2 \tag{3}$$

Since it is known (62a) that NO reacts rapidly with N_2O_5, a reaction step like (4') must be added to complete the mechanism:

$$NO + N_2O_5 \longrightarrow\longrightarrow 3NO_2 \tag{4'}$$

This mechanism consisting of steps (1), (2), (3), and (4') is consistent with the first-order kinetics of the N_2O_5 decomposition, which are observed at all but very low pressures. However, the kinetics of the rapid reaction between NO and N_2O_5 have been studied directly (61b,62b) and it has been demonstrated that reaction (4') is complex, consisting of step (1) followed by step (4). In the light of this additional information, step (4') should be replaced by step (4).

By the use of this modification of the Bodenstein approximation, we have demonstrated that, once steps (1) and (2) are (arbitrarily) assumed, the as-

sumption of steps (3) and (4) (or 4′) is the only way in which the mechanism can be completed that is consistent with the experimental information. Alternative possibilities, such as:

$$NO_3 \longrightarrow NO + O_2$$

or:

$$2NO_3 \longrightarrow N_2O_4 + O_2$$

are ruled out.

4. More Intuitive Methods

Some reaction mechanisms are so complicated, involving many intermediates and interlocking cycles of steps, that the application of the Bodenstein approximation or even of its generalized approximations is so cumbersome and unwieldy as to be practically useless. More intuitive (and less reliable) methods are commonly employed in attempts to gain some information about such processes. Since these "methods" are rather vague, it is difficult to present a satisfactory outline of them. Usually the first act is to postulate a set of reaction steps that appear to be compatible with available stoichiometric, kinetics, and energetic data. Each of these steps must be consistent with the known or assumed properties of the chemical entities involved. The whole mechanism must be carefully examined for internal consistency. Equilibria must satisfy the criterion of the principle of detailed balancing, i.e., of microscopic reversibility (64). Use is frequently made of the treacherous concepts of rate-determining reactions and rate-limiting processes. The procedure is difficult, and few research men are capable of carrying out such an analysis without introducing tacit assumptions and hidden inconsistencies. Because of the extreme complexity of biological reactions, this type of reasoning has been most commonly applied to them.

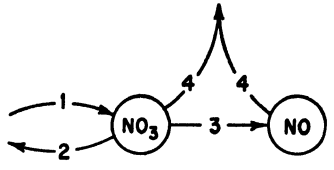


Fig. 2. Flow sheets for the intermediates involved in the decomposition of N_2O_5.

It is usually helpful to construct a flow sheet showing the interrelations of the intermediates. An extremely simple example, shown in Figure 2, is based upon the N_2O_5 decomposition mechanism which was discussed in the preceding section. This diagram shows at a glance that the inter-

mediate, NO, is derived only from the first intermediate, NO_3, and in turn can undergo only one reaction. Since this case is too simple to show the possible use of such a diagram, let us consider an example of moderate complexity—a probable mechanism for the formation of water from its elements. Kinetic evidence (65) indicates that probably only the following ten reaction steps are of importance:

$$H_2 + O_2 \xrightarrow{\text{wall}} H_2O_2 \quad (1)$$

$$H + O_2 + H_2O_2 \longrightarrow H_2O + O_2 + \dot{O}H \quad (2)$$

$$\dot{H} + O_2 \longrightarrow \dot{O}H + \dot{O} \quad (3)$$

$$H + O_2 + M \longrightarrow H\dot{O}_2 + M \quad (4)$$

$$\dot{O}H + H_2 \longrightarrow H_2O + H \quad (5)$$

$$\dot{O} + H_2 \longrightarrow \dot{O}H + H \quad (6)$$

$$2H\dot{O}_2 \xrightarrow{\text{wall}} H_2O_2 + O_2 \quad (7)$$

$$H\dot{O}_2 + H_2O_2 \longrightarrow H_2O + O_2 + \dot{O}H \quad (8)$$

$$H\dot{O}_2 + H_2 \longrightarrow H_2O_2 + \dot{H} \quad (9)$$

$$H_2O_2 \xrightarrow{\text{wall}} H_2 + {}^1/_2O_2 \quad (10)$$

Figure 3, which is a flow sheet based upon this mechanism, shows clearly the interrelations of the four postulated intermediates. While such a diagram is unnecessary for this example, which has been carefully examined

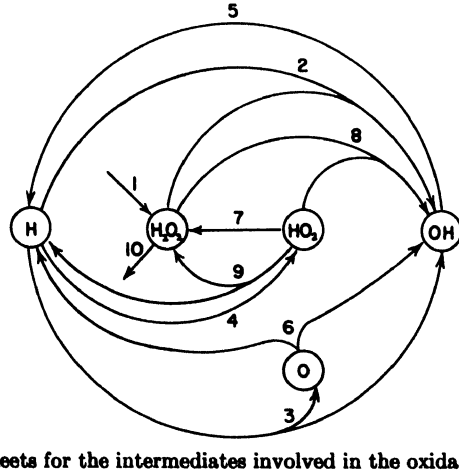


Fig. 3. Flow sheets for the intermediates involved in the oxidation of hydrogen.

by the steady state method, it does help the kineticist to get a general view of the reaction. A number of interesting schemes of this sort, dealing with the singularly intricate processes of photosynthesis, are given by Rabinowitch (66).

VI. DETERMINATION OF REACTION MECHANISM

1. Necessary Data

Published chemical mechanisms are often based upon entirely inadequate evidence. In general, the minimum information which justifies placing any credence in a postulated reaction mechanism is knowledge of the stoichiometric equation, the rate law, and the energy of activation. The number of possible reaction steps can be reduced if the energies, or better the free energies, corresponding to each of the possible reaction steps are known or can be reliably estimated.

Unfortunately, there are relatively few reactions for which all of these basic data are available. In some cases their determination may be laborious or intrinsically extremely difficult. Biologists sometimes attempt to establish reaction mechanisms upon measurements of response times of intact organisms, without having any definite knowledge of the chemical nature of the reactants or products involved in the reaction. While some information can be gained in this way (67), any conclusions arrived at (even with regard to the order of the reaction) should be considered highly unreliable. Stoichiometric information is less important if the concentration of reactants, disappearing to form unknown products, or of known products, formed from unknown precursors, can be measured as functions of time. In such cases, the orders of the reactions can be determined unambiguously, and it is probably justifiable to speculate about the reaction mechanisms. Organic chemists sometimes postulate mechanisms for reactions whose rate laws are wholly unknown. The only defense of this practice is that it saves time and effort. Mechanisms arrived at in this way should be considered only as temporary working hypotheses resting upon very shaky foundations.

2. Critical Experiments

After a mechanism has been devised to fit the basic data (or has been postulated intuitively or by analogy) it can be subjected to any of a number of special tests. These special tests or *critical experiments* are designed to answer specific questions. The following questions are typical of those for which one could reasonably expect to obtain the answers from critical

experiments. Are radicals or atoms present in the reacting system? Does a proton ionize from a particular position on the molecule with a velocity great enough to be consistent with the mechanism? Is a given intermediate present in detectable quantities? Does the transition state have some property which is demanded by the mechanism?

Usually critical experiments are so designed that a positive result is strong confirmatory evidence for the mechanism which is being considered. Sometimes a negative result gives equally strong support to an alternative hypothesis. More commonly, a negative result is relatively meaningless, at best eliminating only a few possibilities from a large field of mechanisms. In the absence of systematic information, i.e., the basic required data, critical experiments are, in general, of little use in the establishment of reaction mechanisms.

The detection or isolation of intermediates was one of the first special methods used in the study of reaction kinetics. As far as chemical isolation is concerned, this method fell into disrepute in the first decade of the present century. It was realized that most intermediates are unstable substances whose steady state concentrations cannot be great enough to permit their isolation by ordinary means. Compounds other than reactants or products which are readily isolated from a reacting mixture are more likely to be the products of side reactions than reaction intermediates. It is unfortunate that in the application of reaction kinetic studies to some related fields (notably biology) this outmoded and untrustworthy approach is still followed.

Occasionally, intermediates have intense, characteristic visible or ultraviolet absorption bands, by which they can be detected at relatively low concentrations, 10^{-6} M or less. Spectroscopic detection, and even quantitative determination of the concentration, of intermediates has been successfully applied to solution (68) as well as to gas-phase (69) reactions. More crudely, the presence of intermediates is sometimes detected by the appearance of transient colors.

Radicals and atoms (and, in principle, other intermediates) can be detected by the addition of special reagents which react with radicals, etc., to form colored or otherwise easily detectable products. The removal of mirrors of As, Pb, etc. (70,71), by atoms and radicals is a widely used and valuable method for the detection of radicals in gaseous systems. The addition of inhibitors which react with radicals to remove them from the system to a reacting mixture is a technique (72) commonly employed when it is suspected that a chain reaction is occurring. In a set of beautifully executed experiments (71,73), a group of radicals which were present during a gas-phase reaction were identified by the direct use of a mass spectrometer.

At the present time, tracer atoms (stable or unstable isotopes) are very commonly used in the study of reaction kinetics. Since they are adequately discussed in Chapter XXVI, 1, they need not be outlined here. Possibly it is not out of place to emphasize the fact that the common use of tracers in critical experiments supplements but does not replace a more systematic study of the reaction kinetics and stoichiometry. The disappointingly meager results of the earlier tracer studies was largely due to lack of appreciation, by overly zealous experimenters, of this important distinction.

Some reactions which occur at a measurable rate in the dark can be accelerated by illumination with light of suitable wave length. If the absorbing compound is a simple molecule, both the products and efficiency of the primary photochemical act (74) will be known. In this way it is possible to introduce into the system a definite reaction intermediate at a determinable rate. Valuable information about the mechanism can be obtained by measuring the rate of the reaction in the dark and in light of several known intensities. This technique was used very effectively in the study of the formation of hydrogen bromide from its elements (Section VII.3).

3. Estimation of the Reliability of a Mechanism

The estimation of the reliability (or probable correctness) of a given mechanism is made difficult by the fact that no one has succeeded (or possibly even attempted) in formulating the entire process of devising and testing a mechanism as a coherent, logical routine. No matter how well a given mechanism fits the basic observations and specific tests, it is always possible that some different mechanism, which represents the data just as well, will be discovered later. For reactions involving only simple compounds, it is possible to list all the intermediates whose existence is compatible with our knowledge of physics and chemistry. If these intermediates are not too numerous, it is feasible to write down all of the uni-, bi-, and termolecular reactions which they can undergo. This group of steps can be treated as a mechanism, and a rate law can be derived with the aid of the Bodenstein approximation. Finally, the rate law (and the individual steps) can be compared with existing experimental facts, and the rate equation and mechanism be reduced to as simple terms as are consistent with the available data. Chemists usually prefer to select a set of steps from the larger group of possibilities, and to test this set as a possible mechanism, repeating the process with other sets until all the apparently plausible mechanisms have been compared with the data. Even when only this intuitively limited group of mechanisms is examined, it is exasperating how often apparently mutually exclusive mechanisms lead to the same rate law

(within the limits of precision of the measurements). In more formal terms: there exist m possible mechanisms for a reaction, the kineticist considers n of these possible mechanisms, and by comparing them with the experimental data eliminates all but o mechanisms. While o is usually smaller than n, it is seldom equal to unity. Even if o equals one, there is always the possibility that one of the $m - n$ mechanisms which were not tested might be consistent with all of the data. Published statements to the effect that a given mechanism has been proven are evidence chiefly of the scientific immaturity of the writer and of the laxity of the editor.

The confidence which can be placed in the correctness of a mechanism increases with the number, variety, and accuracy of the measurements upon which it is based. The evidence supporting the mechanisms of a few relatively simple reactions (some of which are outlined in Section VII) is so reliable that these mechanisms are generally accepted as correct. These mechanisms are based upon very extensive and accurate rate measurements; the energies of formation of all of the intermediates are known; and they are confirmed by a number of special experiments.

When it is necessary or desirable that a mechanism be established as firmly as possible, it is suggested that the following rules be observed. Rate measurements should be made as accurately and extended over as wide a range of initial concentrations and environmental conditions as is practicable. These measurements should not be limited to those starting conditions which insure maximum precision. Important (and unexpected) information about a reaction can often be obtained by extending the rate measurements to extreme conditions under which the reproducibility of the observations is relatively poor. When possible, the energetics of the system should be examined. The energies of activation of endothermic steps must be equal to or greater than their thermochemical heats of reaction. The empirical frequency factors of the individual steps must fall within the limits (Chapter II) set by reaction rate theory. If a step is common to the mechanisms of more than one reaction, the value of its rate constant must be independent of the mechanism in which this step occurs. As many special tests and critical experiments should be performed as appear pertinent to the case under consideration.

VII. TYPICAL COMPLEX REACTIONS

From a kinetic viewpoint, the important classes of complex reactions are: equilibria, cyclic reactions, catalyzed reactions, induced reactions, straight-chain reactions, branched-chain reactions, and polymerization. This classification is arbitrary and not entirely logical. It is introduced only for

convenience. Reactions frequently have properties which are characteristic of more than one class; for example, polymerizations are special cases of straight- or branched-chain processes, and frequently are induced reactions as well. The following illustrations of the several classes were chosen either because they are relatively simple cases or because they have been studied with unusual care.

1. Equilibria

The simplest type of complex reaction is an equilibrium which involves only two reaction steps. The decomposition of hydrogen iodide is a classic example of such a process, in which both the forward and backward steps are simple reactions corresponding exactly to the stoichiometric process:

$$2HI = H_2 + I_2$$

The rates of decomposition and of synthesis of hydrogen iodide and the concentrations at equilibrium have been studied (75) at temperatures ranging from 566 to 781°K. The rate of decomposition has been studied over an unusually wide range of initial concentrations, 0.02 to 7.0 moles per liter. Both the forward and backward reactions appear to be strictly bimolecular (76), except at very (77) high temperatures where an atomic chain mechanism becomes important.

Since it is not necessary to assume that reaction intermediates exist, the rate equation may be obtained directly without using the Bodenstein approximation. When the initial concentrations of hydrogen and iodine are equal to zero, the rate of decomposition of hydrogen iodide may be represented by the following equation:

$$dx/dt = k_1 (a - x)^2 - k_2(x/2)^2$$

where $a = [HI]_0$ and $x/2 = [H_2] = [I_2]$. Introducing the equilibrium constant:

$$K = k_2/k_1 = [HI]^2_{eq.}/[H_2]_{eq.}[I_2]_{eq.}$$

k_2 may be replaced by Kk_1 and:

$$dx/[a^2 - 2ax + (1 - K/4)\, x^2] = k_1\, dt$$

Integrating this equation between the limits 0 and x and 0 and t:

$$\frac{1}{K^{1/2}} \ln \frac{(1 - K/4)[(1 - K^{1/2}/2)(x/a) - 1]}{(1 - K/4)[(1 + K^{1/2}/2)(x/a) - 1]} = k_1 at$$

or:

$$k_1 = \frac{1}{K^{1/2}at} \ln \frac{(1 - K^{1/2}/2)(x/a) - 1}{(1 + K^{1/2}/2)(x/a) - 1}$$

A similar expression involving k_2 and K may be obtained for the reverse reaction, in which the initial concentration of hydrogen iodide is zero (75, 78). The numerical values, obtained from the empirical data for k_1, k_2, and K, satisfy the two rate equations and the equilibrium relation for all temperatures at which measurements were made. The rate data, including a correction term which becomes important at high concentrations, are consistent with both the simple collision theory (76) and the transition state theory. More recent measurements (28) of the equilibrium constant as a function of temperature are somewhat divergent from the classical values (75). However, this does not appear to invalidate any of the conclusions about the nature of the reaction. The rates of reaction and equilibrium for deuterium iodide have also been measured (78,79). These results, while not in quantitative agreement with predictions based upon the transition state theory, are certainly consistent with it.

2. Cyclic Reactions

The classic case of a carefully studied, complex reaction is the formation of hydrogen bromide from its elements:

$$H_2 + Br_2 = 2HBr$$

Bodenstein and Lind, who studied this reaction in 1906 (80), demonstrated that its rate was in agreement with the following equation:

$$d[HBr]/dt = k[H_2][Br_2]^{1/2}/\{1 + ([HBr]/k'[Br_2])\}$$

where k' is independent of temperature (and is approximately equal to 10) and k has a temperature dependence corresponding to an energy of activation of about 41,400 cal. Since the square root of the bromine concentration occurs in the expression for the rate law, it was suggested by the original authors that reversible dissociation of bromine must play a part in the reaction. However, the detailed interpretation of the mechanism was not worked out for 13 years, after which it was presented independently by Christiansen, Herzfeld, and Polanyi (81).

In this chemically simple system, the only probable intermediates are the bromine and hydrogen atoms. They could undergo the following bimolecular reactions with the reactants or products:

$$Br\cdot + H_2 \longrightarrow HBr + H\cdot \qquad \Delta H = 16.7 \text{ kcal.}$$

$$Br\cdot + HBr \longrightarrow Br_2 + H\cdot \qquad \Delta H = 40.6 \text{ kcal.}$$

$$H\cdot + Br_2 \longrightarrow HBr + Br\cdot \qquad \Delta H = -40.6 \text{ kcal.}$$

$$H\cdot + HBr \longrightarrow H_2 + Br\cdot \qquad \Delta H = -16.7 \text{ kcal.}$$

The two reactions of hydrogen atoms are exothermic and, therefore, should have small (or zero) energies of activation (Chapter II). The bromine atom reactions are both endothermic. The rate of the second should be smaller than that of the first by a factor of about:

$$\exp(-40{,}600/2T)/\exp(-16{,}200/2T) = \exp(-24{,}400/2T)$$

In the range of temperatures (220 to 300°C.) in which the experiments were performed, this factor is very small (2×10^{-11} to 6×10^{-11}) and the second reaction may be justifiably neglected. In addition to reacting with the diatomic molecules, the atoms can disappear by combining with one another:

$$2Br\cdot + M \longrightarrow Br_2 + M$$

$$2H\cdot + M \longrightarrow H_2 + M$$

$$H\cdot + Br\cdot + M \longrightarrow HBr + M$$

These recombination reactions are all exothermic, and could occur either as three-body collisions (as written above) or by diffusing to and combining on the walls. Their relative rates are determined largely by the concentrations of the atoms. Since no hydrogen atoms are produced directly, and, furthermore, the reactions of hydrogen atoms producing bromine atoms are exothermic while these of bromine atoms producing hydrogen atoms are endothermic, the concentration of hydrogen atoms must be much less than the concentration of bromine atoms. Accordingly the only atomic combination reaction which must be considered is the recombination of bromine atoms. On the basis of these arguments we may postulate the following mechanism:

$$Br_2 \longrightarrow 2Br\cdot \qquad v_1 = k_1[Br_2] \qquad (1)$$

$$Br\cdot + H_2 \longrightarrow HBr + H\cdot \qquad v_2 = k_2[H_2][Br\cdot] \qquad (2)$$

$$H\cdot + Br_2 \longrightarrow HBr + Br\cdot \qquad v_3 = k_3[Br_2][H\cdot] \qquad (3)$$

$$H\cdot + HBr \longrightarrow H_2 + Br\cdot \qquad v_4 = k_4[HBr][H\cdot] \qquad (4)$$

$$M + 2Br\cdot \longrightarrow Br_2 + M \qquad v_5 = k_5' P_c[Br\cdot]^2 = k_5[Br\cdot]^2 \qquad (5)$$

The symbol P_c represents a linear function of the partial pressures in the system. Introducing the steady state approximations $d[Br]/dt = 0$ and $d[H]/dt = 0$, it follows that:

$$2v_1 + v_3 + v_4 - v_2 - 2v_5 = 0 \qquad \text{and} \qquad v_2 - v_3 - v_4 = 0$$

Adding these equations:

$$v_1 = v_5 \qquad \text{or} \qquad [\text{Br}\cdot] = \{(k_1/k_5)[\text{Br}_2]\}^{1/2}$$

Combining the second and fourth of this series of equations, we obtain:

$$[\text{H}\cdot] = (k_1/k_5)^{1/2}k_2[\text{H}_2][\text{Br}_2]^{1/2}/(k_3[\text{Br}_2] + k_4[\text{HBr}])$$

In terms of the present mechanism, the rate of formation of hydrogen bromide is given by the following equation:

$$\begin{aligned} d[\text{HBr}]/dt &= v_2 + v_3 - v_4 \\ &= k_2[\text{H}_2][\text{Br}\cdot] + (k_3[\text{Br}_2] - k_4[\text{HBr}])[\text{H}\cdot] \end{aligned}$$

Introducing the values for the concentrations of the intermediates and simplifying, we obtain:

$$d[\text{HBr}]/dt = 2(k_1/k_5)^{1/2}k_2[\text{H}_2][\text{Br}_2]^{1/2}/\{1 + [\text{HBr}]/(k_3/k_4)[\text{Br}_2]\}$$

Comparison of this equation with the empirical rate law shows that if the mechanism is correct:

$$2(k_1/k_5)^{1/2}k_2 = k \qquad \text{and} \qquad k_3/k_4 = k'$$

Since steps (3) and (4) are exothermic reactions between atoms and simple molecules, their energies of activation must be small, probably between zero and 2 kcal. The ratio of the corresponding constants must be practically independent of temperature, since:

$$k_3/k_4 = (k_3^0/k_4^0) \exp [(\Delta H_4^\ddagger - \Delta H_3^\ddagger)/RT]$$

where the difference $(\Delta H_4 - \Delta H_3)$ would be expected to be small relative to RT. Since k_1/k_5 is equal to the equilibrium constant, K, for the dissociation of molecular bromine:

$$2(k_1/k_5)^{1/2}\, k_2 = 2(K^0)^{1/2}k_2^0 \exp [(-\Delta H_{\text{Br}_2}/2 - \Delta H_2^\ddagger)/RT]$$

The thermochemical heat of dissociation of bromine is 45,200 cal. Therefore, the mechanism requires that the heat of activation corresponding to k be greater than 22,600 cal.; the empirical value is 41,400 cal. We may conclude that the mechanism is consistent with the stoichiometric, kinetic, and energetic measurements.

A further and more exacting test of the mechanism can be made by comparing the rate of the thermal (dark) reaction with that of the photochemical process. When light is absorbed by bromine it is dissociated into atoms:

$$h\nu + \text{Br}_2 \longrightarrow 2\text{Br}\cdot$$

If a mixture of hydrogen and bromine is illuminated with light which is

absorbed by bromine the rate of formation of hydrogen bromide is increased. In the temperature range between 100 and 200°C., where the rate of the thermal reaction is negligible, the observed rate law for the photochemical reaction (82) is:

$$d[\mathrm{HBr}]/dt = k_\varphi[\mathrm{H_2}]I_{\mathrm{abs.}}^{1/2}/\{1 + ([\mathrm{HBr}]/k'[\mathrm{Br_2}])\}$$

where k' has the same value as in the thermal reaction, k_φ is a temperature-dependent constant, and I_{abs} is the number of einsteins absorbed per second per liter. If step (1) of the mechanism is replaced by the photochemical primary act (83).

$$h\nu + \mathrm{Br_2} \longrightarrow 2\mathrm{Br}\cdot \qquad n_1' = I_{\mathrm{abs.}} \tag{1'}$$

and the steady state approximation applied as before, the resulting rate equation is:

$$d[\mathrm{HBr}]/dt = 2(k_2/k_5^{1/2})[\mathrm{H_2}]I_{\mathrm{abs}}^{1/2}/\{1 + [\mathrm{HBr}]/(k_3/k_4)[\mathrm{Br_2}]\}$$

As before $k_3/k_4 = k'$, which is in agreement with the observation that k' has the same value for the photochemical and thermal reactions. Since the recombination of bromine atoms in the gas phase almost certainly has zero heat of activation, the heat of activation of k_2 should be equal to that of the empirical rate constant, k_φ; this value is 17,600 cal. We are now in a position to calculate the value of the heat of activation of k (for the thermal reaction) in terms of the photochemical measurements and of the thermochemical heat of dissociation of bromine:

$$k = 2K^{1/2}k_2 = 2(K^0)^{1/2}k_2^0 \exp\,[(-45{,}200/2 - 17{,}600)/RT]$$
$$= 2(K^0)^{1/2}k_2^0 \exp\,(-40{,}200/RT)$$

This value of 40,200 cal. is in satisfactory agreement with the empirical value of 41,400 cal.

There are several other facts (84) which tend to increase our confidence in this mechanism. In the temperature region in which both the thermal and photochemical rates are appreciable, the (nonadditive) total rate is consistent with the predictions of the mechanism. The effects of chemically inert gases upon the photochemical rate are compatible with the mechanism. The rate constants for the individual steps may be calculated upon the assumption that the empirical observations and the postulated mechanisms are both correct. The values of these several rate constants are all consistent with the requirements of rate theory. There are no apparent inconsistencies in the interpretation of the unusually extensive and careful measurements of the rate of this reaction. The success of the analysis of this case does a great deal to strengthen our confidence in the reliability of this general method of analysis of reaction mechanisms.

3. Catalyzed Reactions

The only important difference between catalyzed and noncatalyzed reactions is that the concentration of some nonreactant occurs with a positive exponent in the numerator of the expression for the rate law of the catalyzed reaction. The rate is increased by the presence of the catalyst, a substance which does not undergo any permanent change during the course of the reaction. Catalysis may be given a kinetic definition in terms of the rate law expressions of the individual steps or a more general definition (85) in terms of the acceleration of the over-all process. It appears to be impossible to state a reasonable and coherent definition that is consistent with both of these viewpoints. Since this divergence of opinion is largely a matter of nomenclature, it does not cause any real confusion among students of kinetics. The only purpose of the present section is to illustrate methods of obtaining information about mechanisms from rate data. The principles and applications of homogeneous catalysis are discussed in Chapter XII.

In 1928, Abel (86) predicted the rate of a catalyzed reaction in terms of information which was available about the rates of certain noncatalyzed reactions. Hydrogen peroxide and thiosulfate ion react very slowly, but the reaction is greatly accelerated by the addition of a soluble iodide. In slightly acid (buffered) solutions, hydrogen peroxide oxidizes iodide ion at a moderately rapid rate. The rate law expression for this reaction is:

$$d[I_2]/dt = k'[H_2O_2][I^-]$$

Iodine, the product of this reaction, oxidizes thiosulfate ion at an immeasurably fast rate. Since the rates of all other possible reactions of iodine are much slower, the rate of the catalyzed oxidation of thiosulfate by peroxide must be equal to the rate of the reaction between hydrogen peroxide and iodide, which can be measured directly in the absence of thiosulfate. Therefore:

$$-d[S_2O_3^{2-}]/dt = k'[H_2O_2][I^-]$$

This prediction is in complete agreement with the rate measurements. Since the mechanism of the iodide-peroxide reaction is known, the following detailed mechanism for the catalyzed reaction may be assumed:

$H_2O_2 + I^- \longrightarrow H_2O + IO^-$	($v_1 = k[H_2O_2][I^-]$, rate determining)
$H^+ + IO^- \rightleftharpoons HIO$	(rapid, reversible)
$HIO + H^+ + I^- \rightleftharpoons I_2 + H_2O$	(rapid, reversible)

$$I_2 + 2S_2O_3^{2-} \rightarrow\rightarrow S_4O_6^{2-} + 2I^- \quad \text{(complex, rapid)}$$

$$2H^+ + H_2O_2 + 2S_2O_3^{2-} = S_4O_6^{2-} + 2H_2O \quad \text{(stoichiometric)}$$

The stoichiometric equation is the sum of the four reaction steps.

In the analysis of this process we have made use of the concept of the *rate-determining step*. It is assumed that the reaction consists of one slow, rate-determining step which is followed by several relatively rapid, consecutive steps whose kinetics do not affect the observed rate or kinetic law. While this concept must be used with caution, its application to the present case appears to be trustworthy. The steady state approximation could be applied to this case, assuming that the unstable intermediates are IO^-, HIO, I_2, and I_3^-, and possibly $S_2O_3^-$ and I_2^-, but is doubtful if any further information could be obtained from such an analysis.

A somewhat similar and intrinsically interesting case is the silver ion catalyzed reduction of peroxysulfate ion by vanadyl or chromic ions (87). These reactions:

$$7H_2O + 3S_2O_8^{2-} + 2Cr^{3+} = Cr_2O_7^{2-} + 6SO_4^{2-} + 14H^+$$

$$4H_2O + S_2O_8^{2-} + 2VO^{2+} = 2HVO_3 + 2SO_4^{2-} + 6H^+$$

are very slow in the absence of a catalyst. In the presence of a soluble silver salt they occur at rapid but measureable rates. The rate law expressions for the two reactions are identical, even the value of the rate constant, k', being the same:

$$-d[S_2O_8^{2-}]/dt = k'[S_2O_8^{2-}][Ag^+]$$

The only conclusion which appears to be compatible with these results is that the peroxysulfate and silver ions react to form some intermediate, X, which is capable of rapidly oxidizing either chromic or vanadyl ions. A generalized mechanism which corresponds to this conclusion may be written as follows:

$$S_2O_8^{2-} + Ag^+ \text{——} X + M \qquad v_1 = k_1[S_2O_8^{2-}][Ag^+] \text{ (rate determining)}$$

$$kH_2O + lX + mCr^{3+} \rightarrow\rightarrow nCr_2O_7^{2-} + oAg^+ \quad \text{(fast)}$$

$$k'H_2O + l'X + m'VO^{2+} \rightarrow\rightarrow n'HVO_3 + o'Ag^+ \text{ etc.} \quad \text{(fast)}$$

The kinetics give no direct information about the nature of the intermediate X. It was originally postulated that it was a trivalent compound of silver. However, later measurements (88) make it appear very probable that the intermediate is divalent silver, perhaps Ag^{2+}. Assuming this to be true, we may write (for the vanadyl reaction) the following mechanism which is consistent with the available information, although far from

proven in detail:

$$S_2O_8^{2-} + Ag^+ \longrightarrow Ag^{2+} + SO_4^{2-} + SO_4^- \quad \text{(rate determining)}$$

$$SO_4^- + Ag^+ \longrightarrow Ag^{2+} + SO_4^{2-} \quad \text{(fast)}$$

$$Ag^{2+} + VO^{2+}\cdot 2H_2O \longrightarrow Ag^+ + HVO_3 + 3H^+ \quad \text{(fast)}$$

It should be noted that in these catalyzed redox reactions the catalyst is alternately oxidized and reduced. Usually, as in the two preceding examples, either the oxidized or reduced form predominates at the steady state. In the case of the bromine-bromide catalyzed decomposition of hydrogen peroxide (89), the steady state concentrations have been measured directly and shown to be consistent with predictions based upon the mechanism and the rate data.

From the viewpoint of organic chemistry, acids and bases are by far the most important homogeneous catalysts (90). A wide variety of chemical reactions are catalyzed by either (or both) H_3O^+ or OH^-. Limiting the discussion to those reactions which occur in aqueous solution and neglecting the kinetic salt effects (compare Chapter II, VI.2), their rates may be represented by equations of the following form (91).

$$-d[R_1]/dt = (k_H[H^+] + k_0 + k_{OH}[OH^-]) \times f([R_i], \text{etc.})$$

$$= k \times f([R_i], \text{etc.})$$

where $f([R_i], \text{etc.})$ is a function of the concentrations of the reactants only. When $k_H[H^+] \gg k_0 + k_{OH}[OH^-]$,

$$\log k \approx \log k_H - \text{pH}$$

and when $k_{OH}[OH^-] \gg k_H[H^+] + k_0$

$$\log k \approx \log k_{OH} + \log K_w + \text{pH}$$

where K_w is the ionization constant of water, k_0 represents the rate constant of the uncatalyzed (or solvent catalyzed) reaction. Figure 4 is a diagrammatic representation of the specific reaction rates, k, of typical reactions as functions of pH. The relative positions of the lines are arbitrary, but their general forms (especially their slopes) are significant.

The rates of some reactions which occur in buffered solutions, at constant pH and ionic strength, increase with increasing concentration of the buffer. The clearest and most convincing explanation of this and related phenomena was given by Brönsted (92) in terms of his generalized theory of acids and bases. This theory defines an acid as any substance which can yield a proton and a base as any substance which can accept a proton. Many reactions are catalyzed by general acids and bases as well as by H_3O^+ and

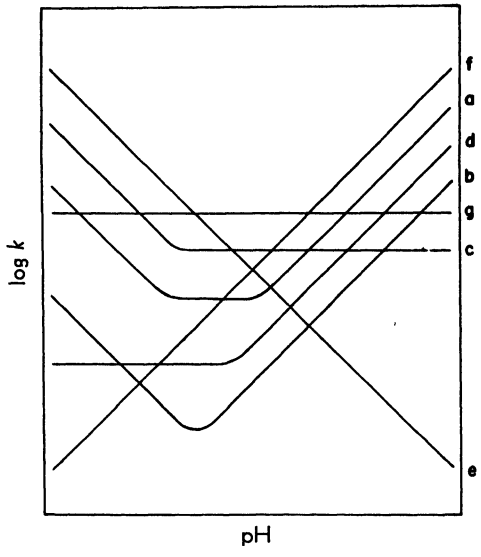


Fig. 4. The logarithms of the specific reaction rates of typical acid-base catalyzed reactions as functions of pH

OH^-. For example, the mutarotation of glucose (93) is catalyzed by acids, such as H_3O^+, CH_3COOH, NH_4^+, etc., and by generalized bases, including OH^-, NH_3, CH_3OO^-, SO_4^{2-}, etc. The rate of such a reaction can be represented (if we neglect primary kinetic salt effects) as follows (91):

$$-d[G]/dt = (\sum_i k_{Ai}[A_i] + k_w + \sum_i k_{Bi}[B_i])[G]$$

where the symbols A_i and B_i indicate generalized acids and bases, respectively. The values of the several rate constants, k_{Ai} and k_{Bi}, are related to the ionization constants K_{Ai} and K_{Bi}, of the respective acid and bases. These, the Brönsted relations (92–95), may be written as

$$k_{Ai} = G_A K_{Ai}^{\alpha} \quad \text{and} \quad k_{Bi} = G_B K_{Bi}^{\beta}$$

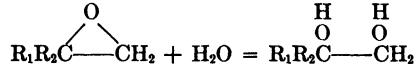
The values of the coefficients G_A and G_B and of the exponents α and β depend upon the nature of the reaction, the solvent and the temperature. Like Hammett's rule (Chapter II,VI.3), the Brönsted relations can be derived from the transition state theory, in terms of reasonable assumptions.

G. N. Lewis defined an acid as a molecule which is "capable of receiving an electron pair (from a basic molecule) into the shell of one of its atoms" (96). So defined, acids include, in addition to the Brönsted acids, substances such as H^+, Ag^+, $AgClO_4$, BF_3, $AlCl_3$ and SO_3^{2-}. The catalytic

activity of many of these compounds (particularly in dry, base-free solvents) has been recognized by organic chemists for many years. However, the Lewis concept of acids has helped to systematize this mass of information and has been a useful basis for prediction and a guide to new experimental studies (97).

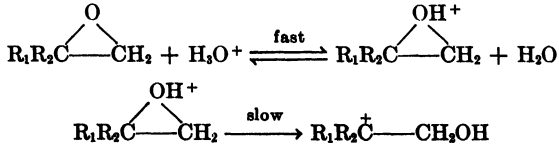
A variety of detailed mechanisms of acid and base catalysis have been proposed and enthusiastically advocated by their authors, and as vigorously attacked by inventors of rival mechanisms. Commonly, the alternative mechanisms are consistent with the same steady-state kinetics. Since the supporters of each type of mechanism insisted that it be applied to all examples of acid-base catalysis, the resulting polemics were prolonged but indecisive. More recently, the use of critical experiments (particularly, the use of tracers, the measurement of the effect of isotopic substitution upon the rate, and comparison of the rates of homologous reactions involving variously substituted reactants) has introduced some order into the formerly prevailing chaos. With the accumulation of definite information, it has become obvious that no one mechanism fits all reactions.

The hydrolysis of the epoxides,

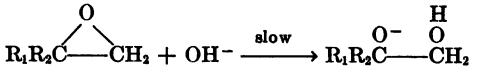


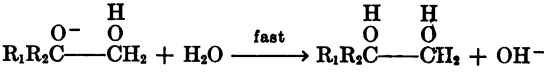
is an interesting example of an acid- and base-catalyzed reaction whose detailed mechanism appears to have been established with a fair degree of certainty. In acid solutions, this reaction is catalyzed by H_3O^+; in the pH range from 7 to 11, its rate is constant; but it is catalyzed by OH^- in more basic solutions (98). The substitution of D_2O for H_2O as the solvent accelerates the acid catalyzed reaction about two fold but has no effect upon the reaction occurring in basic solutions (99). When the hydrolysis occurs in water enriched with O^{18}, the tracer atom goes predominantly to the branched carbon atom in acid solutions but, to the primary carbon atom in basic solutions (100). The entropies and enthalpies of activation of these reactions have been determined and compared to the same quantities for analogous reactions (101). As has been stated by F. A. Long and his coworkers (99–101), all of these results are consistent with the following mechanisms.

In acid solution there is a rapid reversible equilibrium, followed by a slow isomerization and, then, by a rapid reaction with water.



In alkaline solution, the rate determining step is the addition of an OH^-.

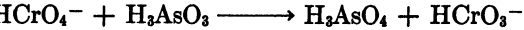




4. Induced Reactions

Some redox reactions are accelerated if a second reducing (or oxidizing) agent is present. A simple example is the oxidation of manganous ion by chromate ion in the presence of arsenious acid. The direct oxidation of manganous ion by chromate is very slow, while the oxidation of arsenious acid by chromate is relatively rapid. If a soluble chromate is added to a solution containing manganous ion as well as arsenious acid, both reducing agents are oxidized and at comparable rates. The oxidation of manganous ion in this system is an *induced reaction* (102). It is induced by the simultaneous occurrence of the reaction between arsenite and chromate. The arsenious acid is called the *inductor* and the manganous ion the *acceptor*. The relative amounts of the two reducing agents which are oxidized depend upon their initial concentrations. As the ratio of the concentration of manganous ion to that of arsenious acid is increased indefinitely, the ratio (called the *induction* factor) of the number of equivalents of manganous ion oxidized to the number of equivalents of arsenious acid oxidized approaches a limiting value of one-half (103).

Some conclusions regarding the mechanisms can be derived from these simple observations: (*1*) The direct reaction between manganous ion and chromate ion is negligibly slow compared to the reaction between arsenite and chromate ions. (*2*) An intermediate is formed, as the result of the (primary) reaction between arsenite and chromate, which is capable of oxidizing either arsenious acid or manganous ion. (*3*) This intermediate is presumably (although not necessarily) a partially reduced form of chromate. The maximum value (one-half) of the induction factor indicates that the intermediate is a compound of tetravalent chromium. One possible generalized mechanism which is consistent with these three conclusions may be written as follows:



$$HCrO_3^- + Mn^{2+} + 5H^+ \rightarrow \rightarrow Mn^{3+} + Cr^{3+} + 3H_2O$$

The second and third reactions must be complex; but in the absence of kinetic information it is useless to speculate about the intimate details of the process. The sum of the first two reactions is the stoichiometric equation for the primary reaction, in the absence of manganous ion:

$$2HCrO_4^- + 3H_3AsO_3 + 8H^+ = 3H_3AsO_4 + 2Cr^{3+} + 5H_2O$$

If a great excess of manganous ion is present, so that the limiting value (one-half) of the induction factor is realized, the stoichiometric equation for the over-all reaction is the sum of the first and third equations:

$$HCrO_4^- + H_2AsO_3 + Mn^{2+} + 5H^+ = H_2AsO_4 + Mn^{3+} + Cr^{3+} + 3H_2O$$

A similar induced reaction, involving chromate ion, isopropyl alcohol, and manganous ion, was studied extensively and carefully by Westheimer and co-workers (102c,104). A detailed mechanism for this process has been based upon measurements of the induction factor, an unusually complete kinetic study, an analysis of the energetics, and special experiments using a deutero-substituted compound.

This mechanism involves the rapid, reversible formation of a neutral ester of isopropanol and chromic acid. The decomposition of this ester into acetone and quadrivalent chromium is a base-catalyzed reaction and is relatively slow in acidic aqueous solutions. In the presence of an excess of Mn^{2+}, the quadrivalent chromium is rapidly reduced to Cr^{3+}; the resulting trivalent manganese dismutes into MnO_2 and Mn^{2+}. If no Mn^{2+} is present, the quadrivalent chromium is reduced by the isopropanol, which is oxidized to acetone. This latter reaction probably involves divalent and pentavalent chromium as intermediates. The occurrence of this reaction approximately doubles the overall rate of oxidation of the isopropanol. The mechanism can be accepted with considerable confidence.

There is one important class of induced reactions for which the induction factor does not approach a finite limit, but continues to increase as the ratio of concentration of acceptor to that of inductor is increased indefinitely. In these cases, the induced reaction is a chain process (Section 5 below). The inducing reaction acts as a chain starter, usually by forming radicals as intermediates. Polymerization chains induced by redox reactions (Section 6 below) are important examples of this type. There is some tendency in the current literature to refer to such processes as catalyzed reactions. This seems unfortunate, since the distinction between catalyzed and induced reactions is a clear and definite one. Not only is there a typical difference between the mechanisms of these classes of reac-

tions, but also catalysts can act without undergoing any permanent chemical change while inductors must be continuously used up in order to induce a reaction.

5. Chain Reactions and Inhibition (105)

The distinguishing characteristic of a chain reaction is that for each molecule activated many react. This can be directly demonstrated by photochemical measurements. The quantum yield, φ, of a photochemical reaction is the ratio of the number of molecules reacting in a system in unit time to the number of photons absorbed in the same system and time. Since one molecule is activated for each photon absorbed, the quantum yield is a direct measure of the ratio of the number of molecules reacting to the number being activated. For simple photochemical reactions, the observed values of φ are of the order of magnitude of unity. For example, the quantum yields for the photochemical decompositions of hydrogen iodide and of bromphosgene are equal, respectively, to 2.00 and 1.0. In contrast to this, the quantum yields for the photochemical chlorinations of hydrogen, carbon monoxide, and certain hydrocarbons are large numbers, reaching values as great as 10^6. The absorption of a single photon initiates a chain of events resulting in the formation of a great number of product molecules. The original activation can be brought about thermally or can be the result of an inducing reaction.

The synthesis of hydrogen chloride is a superficially simple reaction which possesses many properties characteristic of chain reactions. The activation process is the dissociation of chlorine. At moderately elevated temperatures, this may occur as the result of an energy-rich collision:

$$M + Cl_2 \longrightarrow 2Cl\cdot + M$$

it may be due to the absorption of a photon:

$$h\nu + Cl_2 \longrightarrow Cl\cdot + Cl\cdot^*$$

or it may be caused by reaction with atomic sodium:

$$Na\cdot + Cl_2 \longrightarrow NaCl + Cl\cdot$$

Regardless of how the chloride atoms are produced, they can react readily with molecular hydrogen:

$$Cl\cdot + H_2 \longrightarrow HCl + H\cdot$$

The resulting atomic hydrogen reacts in turn with molecular chlorine:

$$H\cdot + Cl_2 \longrightarrow HCl + Cl\cdot$$

regenerating a chlorine atom. If there were no other reaction steps involved, the chain length would be infinite and the introduction of a single chlorine atom would bring about the complete consumption of the reactants. The chain could be broken by the combination of atoms, for example, the recombination of chlorine atoms. Since chlorine atoms are very reactive, they can be removed by reacting with any of a number of possible impurities. Traces of oxygen are difficult to remove from chlorine, and are commonly responsible for chain breaking. Impurities which act in this way are called *inhibitors.*

The following over-simplified mechanism for the photochemical synthesis will serve as an illustration of a chain reaction:

$$h\nu + Cl_2 \longrightarrow 2Cl\cdot \qquad \text{(chain-initiating step)} \qquad (1)$$

$$Cl\cdot + H_2 \longrightarrow HCl + H\cdot \qquad \text{(chain-propagating step)} \qquad (2)$$

$$H\cdot + Cl_2 \longrightarrow HCl + Cl\cdot \qquad \text{(chain-propagating step)} \qquad (3)$$

$$Cl\cdot + O_2 \rightarrow\rightarrow [H_2O,HCl] \qquad \text{(chain-terminating step)} \qquad (4)$$

Making the usual steady state approximations, that $d[Cl\cdot]/dt = 0$ and $d[H\cdot]/dt = 0$, we can obtain the following rate equation which corresponds to the four-step mechanism:

$$d[HCl]/dt = 4k_2(I_{abs.}/A)([H_2]/k_4[O_2])$$

where $I_{abs.}$ represents the number of photons absorbed by chlorine per liter per second and A is Avogadro's number. Although the mechanism is obviously incomplete, the equation derived from it is consistent with the observed rate over a reasonably wide range of initial concentrations. While there is some uncertainty about the complete mechanism (106) of this reaction, there can be no reasonable doubt that the four steps presented here play important roles.

It is interesting to compare this mechanism to that of hydrogen bromide synthesis. While the mechanisms are formally very similar, the observed characteristics of the reactions differ widely. These differences are due chiefly to the fact that step (2) is endothermic for the bromine case and exothermic for the chlorine case. The chlorine reaction is much more sensitive to the presence of impurities, probably because chlorine atoms are far more reactive than bromine atoms. From a kinetic viewpoint both reactions should be classed as chain processes. However, experimentally the hydrogen bromide synthesis does not exhibit many of the properties which are considered symptomatic of chain reactions. In the lower temperature range its quantum yield is small, going to values less than unity. It is also relatively insensitive to the presence of traces of impurities.

Some compounds, such as ammonia, inhibit the chlorine reaction much more strongly than does oxygen. Concentrations of ammonia which are scarcely detectable by ordinary means reduce the quantum yield from a value of many thousands to one of less than ten. The inhibitor acts by reacting with a chain carrier, and in removing the atom is itself destroyed. In this system oxygen is converted to water and ammonia to nitrogen trichloride. If a trace of ammonia is present in a mixture of hydrogen and chlorine, the photochemical reaction exhibits an *induction period.* During the induction period the reaction is scarcely detectable, but as soon as the inhibitor is used up the rate rises rapidly to its normal value.

Another classic example of a chain reaction is the autoxidation of sulfite ion in aqueous solution. Since any of a large variety of organic compounds (particularly alcohols and amines) retard this reaction, it was first studied (107) as a case of negative catalysis. At that time, it was believed that negative catalysts acted by combining with, and so removing, traces of positive catalysts, which were adventitiously present. While it is undeniable that this type of negative catalysis exists, in the present instance the alcohols, etc., function as chain-breaking inhibitors (108). It was postulated by Haber and Franck (109) that hydroxyl and perhydroxyl radicals are intermediates in this and similar reactions. The following mechanism for the copper-catalyzed, alcohol-inhibited reaction is based upon this suggestion. but it contains detailed steps for which there is only very scanty evidence:

$$HSO_3^- + Cu^{2+} \longrightarrow Cu^+ + H\dot{S}O_3 \qquad \text{(chain initiating)} \qquad (1)$$

$$O_2 + H_2O + Cu^+ \longrightarrow Cu^{2+} + OH^- + H\dot{O}_2 \qquad \text{(chain initiating)} \qquad (2)$$

$$O_2 + H_2O + H\dot{S}O_3 \longrightarrow H_2SO_4 + H\dot{O}_2 \qquad \text{(chain propagating)} \qquad (3)$$

$$H\dot{O}_2 + HSO_3^- \longrightarrow HSO_4^- + \dot{O}H \qquad \text{(chain propagating)} \qquad (4)$$

$$\dot{O}H + HSO_3^- \longrightarrow H\dot{S}O_3 + OH^- \qquad \text{(chain propagating)} \qquad (5)$$

$$2H\dot{S}O_3 \longrightarrow H_2S_2O_6 \qquad \text{(chain breaking)} \qquad (6)$$

$$2H\dot{O}_2 \rightarrow\rightarrow H_2O + {}^3/_2\, O_2 \qquad \text{(chain breaking)} \qquad (7)$$

$$H\dot{O}_2 + ROH \rightarrow\rightarrow [ROOH + H_2O] \qquad \text{(chain breaking)} \qquad (8)$$

Figure 5 presents a flow sheet of the intermediates corresponding to this mechanism.

The chain length of this reaction was determined (108) photochemically and found to reach values as high as 40,000 when carefully purified reagents and water were used. The chain length can also be estimated from simultaneous measurements of the rates of oxidation of sulfite and of the inhibi-

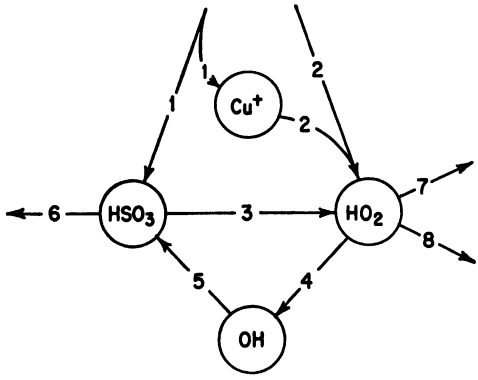


Fig. 5. Flow sheet for the intermediates involved in the copper-catalyzed oxidation of the sulfite ion.

tor. When the concentration of the inhibitor is high enough, practically every chain is broken by a reaction between an intermediate (HO_2) and an inhibitor molecule, resulting in the oxidation of the latter. Under these limiting conditions the rate of oxidation of the inhibitor, $-d[\text{Inh}]/dt$, should be equal to the rate, v_i, at which chains are started. Since the rate of oxidation of sulfite is equal to the product of the rate of chain starting, v_i, and the average chain length, Z:

$$-d[HSO_3^-]/dt = v_i Z$$

in the presence of a high concentration of inhibitor:

$$Z = (-\text{d}[HSO_3^-]/dt)/(-d[\text{Inh}]/dt)$$

Bäckstrom (108) compared values of the chain length obtained in this way with the directly determined quantum yields and found satisfactory agreement, thus confirming the general mechanism of inhibition.

6. Polymerization

Polymers are formed as the result of chain reactions. Polymerization involves chain-initiating, chain-propagating, and chain-terminating steps. The intermediates which react in the chain-propagating and -terminating steps are growing polymers of widely differing molecular weights. The participation of such a vast number of different intermediates in the reaction mechanism is more an apparent than a real complication, since the reactivities of the growing polymer molecules are only slightly affected by their molecular weights. The average chain length of a polymerization reaction is simply related to the number average of the molecular weight

of the polymers formed. Since this latter quantity can be measured directly, it offers an additional and useful method of obtaining kinetic information about this class of reactions.

Polymers can be formed by condensation or addition reactions. The bonds between the units of condensation polymers are formed by the elimination of water, etc., between two unlike reacting groups. An esterification reaction between molecules of hydroxycarboxylic acids is a simple example of this type. Like other esterifications, these reactions are catalyzed by acids. Addition polymers are formed by reactions between unsaturated molecules, the double bond being broken in the process, but no matter being eliminated. In this type of polymerization, the chain-propagating intermediates are usually free radicals (or diradicals). These may be produced photochemically or chemically. For theoretical studies it is convenient to liberate the radicals photochemically at known and easily controlled rates, by optical dissociation of the monomer or of an added sensitizer. In commercial practice, polymerizations are commonly induced by redox reactions. An oxidizing agent, usually a peroxide, is added to the system and, by reacting with the monomer or an added (more reactive) reducing agent, generates radicals which initiate the polymerization.

In the literature of a polymerization, such induced reactions are frequently referred to as catalyzed polymerizations and the peroxide is called a catalyst. This is an unfortunate usage. While reactions of this general type were classically designated as examples of *induced catalysis* (102b), in view of our present knowledge of chain processes they are clearly *induced* chain reactions.

Some addition polymerizations go by way of ionic rather than radical mechanisms, and are *catalyzed* by generalized (Lewis) acids (Section VII.3).

While the detailed kinetics of polymerization reactions show almost infinite variety, there are certain basic characteristics which are common to all such reaction mechanisms. The chain-initiating steps may be second or first order with respect to the monomer, or may be photochemical reactions which are directly proportional to the "intensity" (photons per liter per second) of the absorbed light and zero order with respect to the monomer. The propagating step is invariably second order, involving a growing polymer molecule and a monomer (or "dead polymer") molecule. The chain-terminating step may be either a first-order spontaneous reaction of a growing polymer or a second-order disproportionation or addition reaction between two polymeric radicals. For condensation polymerization it is unnecessary to assume any special chain-breaking step.

The following mechanism is typical of a simple, photochemically initiated addition polymerization. The chain-breaking step is assumed to be one of disproportionation. The special symbols have the following significance: M, a monomer R′—CH=CH_2; P_r, a polymeric radical containing

r monomer units R′—(CHR—CH_2)$_{r-1}$—CHR—$\dot{C}H_2$; M_r, a stable polymer molecule containing r monomer units R′—(CHR—CHr)$_{r-1}$—CR=CH_2 or R′—(CHR—CH)$_{r-1}$—CHR—CH_3; φ the quantum yield; and $I_{abs.}$ the number of einsteins absorbed per liter per second. For simplicity, let us assume that only a small fraction of the incident light, I_0, is absorbed; and, therefore, $I_{abs.} \approx I_0[M]$:

$h\nu + M \longrightarrow P_1$, etc.	$v_i = \varphi I_0[M]$	(initiation)
$P_1 + M \longrightarrow P_2$	$v_{p,1} = k_{p,1}[M][P_1]$	(propagation)
$P_n + M \longrightarrow P_{n+1}$	$v_{p,n} = k_{p,n}[M][P_n]$	(propagation)
$P_n + P_s \longrightarrow M_n + M_s$	$v_{t,ns} = k_{t,ns}[P_n][P_s]$	(termination)

Since the chains are terminated by disproportionation, half of the polymers will have double bonds and, therefore, can undergo reactions similar to those of the monomer. However, if we restrict our consideration to the first part of the reaction, the total concentration of the polymers will be negligible compared to the monomer concentration. If, as is generally the case, the half-life of a growing polymer is relatively very short, we may apply the steady state assumption that:

$$d[P_r]/dt = 0$$

Considering the radical P_1, we write:

$$v_i - k_{p,1}[M][P_1] - k_{t,11}[P_1]^2 - k_{t,12}[P_1][P_2] - k_{t,13}[P_1][P_3]\ldots = 0$$

$$v_i - k_{p,1}[M][P_1] - [P_1]\sum_{r}^{r=\infty} k_{t,1r}[P_r] = 0$$

For the radical of two units, P_2, the corresponding equation is:

$$k_{p,1}[M][P_1] - k_{p,2}[M][P_2] - [P_2]\sum_{1}^{\infty} k_{t,2r}[P_r] = 0$$

and similar equations can be written for each of the other P_r:

$$k_{p,n-1}[M][P_{n-1}] - k_{p,n}[M][P_n] - [P_n]\sum_{1}^{\infty} k_{t,nr}[P_r] = 0$$

Since the reactivities of the polymeric radicals should not be appreciably dependent upon their molecular weights, the following simplifying assumption appears reasonable:

$$k_{p,1} = k_{p,2} = k_{p,r} = k_p$$

$$k_{t,11} = k_{t,1r} = k_{t,nr} = k_t$$

Introducing these simplifying approximations into the preceding equations, we obtain the following group of n equations:

$$v_i - k_p[M][P_1] - k_t[P_1] \sum_r [P_r] = 0$$

$$k_p[M][P_1] - k_p[M][P_2] - k_t[P_2] \sum_r [P_r] = 0$$

$$k_p[M][P_2] - k_p[M][P_3] - k_t[P_3] \sum_r [P_r] = 0$$

$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$

$$k_p[M][P_{n-1}] - k_p[M][P_n] - k_t[P_n] \sum_r [P_r] = 0$$

If these equations are added, the second term of each equation cancels the first term of the equation immediately following and:

$$v_i - k_p[M][P_n] - k_t \left(\sum_r [P_r]\right)^2 = 0$$

Since P_n corresponds to the largest polymeric radical in the system, its concentration must be negligibly small and the second term of this equation may be dropped. Therefore:

$$\sum_r [P_r] = (v_i/k_t)^{1/2}$$

The rate of disappearance of the monomer is:

$$-d[M]/dt = v_i + \sum_{r=1}^{r=n} v_{p,r} = v_i + k_p[M] \sum_{r=1}^{r=n} [P_r]$$

Since n is a large number, the rate of initiation may be neglected relative to the sum of the rates of the propagating steps. Combining the last two equations and introducing the value:

$$v_i = \varphi I_0[M]$$

we can obtain the following expression for the rate of disappearance of the monomer:

$$-d[M]/dt = k_p[M](I_0\varphi[M]/k_t)^{1/2} = k_p(\varphi/k_t)^{1/2} I_0^{1/2}[M]^{3/2}$$

Empirical rate equations of this general type are commonly observed (110) for addition polymerization.

An additional check on the mechanism can be obtained by comparing the *number average of the molecular weight* as predicted by the mechanism with the experimental value obtained from osmotic pressure measurements.

The number average of the molecular weight, $\bar{m}$, is defined as:

$$\bar{m} = \sum_{r=1}^{r=\infty} n_r m_r \Big/ \sum_{r=1}^{r=\infty} n_r$$

where m_r is the molecular weight of a polymer of r units and n_r is the number of moles of this particular polymer occurring in a liter of solution. The kinetic chain length, Z_t, of this (or any chain) reaction may be defined as:

$$Z_t = -(d[\mathrm{M}]/dt)/v_i \qquad \text{or} \qquad -(d[\mathrm{M}])/dt = v_i Z_t$$

Since Z_t is a function of the monomer concentration, it is also a function of time. The problem is greatly simplified if we restrict our consideration to a time short enough to justify treating Z_t as a constant average value, $\bar{Z}$. Under these conditions $\bar{Z}$ is the average extent of polymerization:

$$\bar{Z} = \bar{m}/m_1$$

where m_1 is the molecular weight of the monomer. Equating the two values for the rate of disappearance of the monomer:

$$v_i\bar{Z} = k_p(\varphi/k_t)^{1/2} I_0^{1/2}[\mathrm{M}]^{3/2} = \varphi I_0[\mathrm{M}]\bar{Z}$$

$$\bar{Z} = k_p[\mathrm{M}]^{1/2}/(k_t\varphi I_0)^{1/2}$$

or:

$$\bar{m} = k_p[\mathrm{M}]^{1/2} m_1/(k_t\varphi I_0)^{1/2}$$

The preceding simplified derivation would be applicable if the measurements were restricted to the first 10% of the reaction. More general solutions of this problem for each of the several types of addition polymerization have been obtained and are presented in the specialized literature of polymerization (110). Equations containing the *molecular weight distribution* can also be obtained from the postulated mechanisms (111). However, it is so difficult to obtain reliable experimental values of the distribution, that these equations are chiefly of academic interest.

The kinetics of polymerization have been studied extensively and effectively from a theoretical as well as from an experimental standpoint. Some of the special methods used in these investigations are presented later (Chapter XXI) in this volume.

7. Branching Chain Reactions and Explosions

The chain reactions discussed in the preceding sections are all of the *straight-chain* or *nonbranching* type. Each chain-propagating step produces one, but not more than one, radical. In a *branching-chain* reaction, there exists the possibility that one chain-carrying radical can react (in a single step) to form two (or more) radicals, thereby continuing the chain and simultaneously starting a new one. In polymerization, chain branch-

ing results in the formation of branched-chain polymers. If the probability of branching is high, the polymer produced is a three-dimensional net work, differing distinctly in its physical properties from a straight-chain polymer of the same molecular weight. Chain-branching steps commonly occur in strongly exothermic reactions, particularly at high temperatures. The mechanism postulated (Section IV.4) for the hydrogen-oxygen reaction contains the two following steps which initiate new chains:

$$O_2 + \dot{H} \longrightarrow \dot{O}H + \dot{O}$$

$$H_2 + \dot{O} \longrightarrow \dot{O}H + \dot{H}$$

Such steps are almost invariably endothermic, and become of importance at elevated temperatures.

Reactions are greatly accelerated by the occurrence of chain branching. If the average chain length of a straight-chain reaction were Z, the observed rate of this reaction would be:

$$-d[\mathrm{R}]/dt = v_i Z$$

where v_i is the velocity of the chain-starting step. However, if each cycle started a new chain (that is, if the efficiency of branching were equal to one) the rate of this reaction would be increased by a factor β (112):

$$\beta = (1 + 2 + 2^2 + 2^3 + \ldots + 2^z)Z^{-1} = (2^{z+1} - 1)/(2 - 1)Z$$

The effect of branching increases with the length of the chain. Even for a moderate length (such as 99) the increase is inordinately large:

$$\beta = (2^{100} - 1)/99 \approx 10^{28}$$

Under all ordinary conditions, chain branching cannot occur with such a high probability. Even if the efficiency were as low as 1%, the increase due to branching would be far from negligible:

$$\beta = \left[1 + \sum_{i=2}^{i=Z} (1.01)^i\right] Z^{-1}$$

for Z equal to 99 this factor is 1.74, and for Z equal to 999 it is 2×10^3.

Some information concerning the kinetics of chain reactions can be obtained from theoretical analyses of typical reactions, without specifying the detailed reaction mechanisms (113). While the following case is simpler than any which have been observed, its formal analysis illustrates some of the characteristics of chain reactions. The reaction is assumed to be a bimolecular process:

$$R_1 + R_2 = P_1 + P_2$$

in which the only unstable intermediate is an activated molecule, R_1^*. Molecules R_1^* can be activated by thermal collisions with a molecule of R_1, R_2, P_1, or P_2. The activated molecules can be deactivated by collision with any molecule or can react with R_2. Accordingly, the mechanisms are:

$$R_1 + M \longrightarrow R_1^* + M \qquad v_1 = k_1[M][R_1]$$

$$R_1^* + M \longrightarrow R_1 + M \qquad v_2 = k_2[M][R_1^*] = w_2[R_1^*]$$

$$R_1^* + R_2 \longrightarrow P_1 + P_2 \qquad v_3 = k_3[R_2][R_1^*] = w_3[R_1^*]$$

It is further assumed that a certain fraction, α, of the reaction steps (3) result in the activation of one or more molecules of R_1. The average number of activated molecules, R_1^*, resulting from those steps which produce one or more activated molecules is β. Assuming that a steady state exists, where $d[R_1^*]/dt = 0$, we may write:

$$v_1 - v_2 - v_3(1 - \alpha\beta) = 0$$

or (Section V.3):

$$v_1 = [R_1^*](w_2 + w_3[1 - \alpha\beta])$$

which can be written in the following form:

$$[R_1^*] = (v_1/w_3)/[(w_2/w_3) + 1 - \alpha\beta]$$

The rate of formation of the products is:

$$d[P_1]/dt = v_3 = w_3[R_1^*] = v_1/[(w_2/w_3) + 1 - \alpha\beta]$$

If the probability of propagating the chain, α, were zero, the observed rate would be v_t:

$$v_t = v_1 P_3 = v_1[w_3/(w_2 + w_3)]$$

Since:

$$w_2/w_3 + 1 - \alpha\beta = [(w_2 + w_3)/w_3][1 - \alpha\beta/(1 + w_2/w_3)] = P_3^{-1}[1 - \alpha\beta/(1 + w_2/w_3)]$$

The rate of formation of the product may be written as follows:

$$d[P_1]/dt = v_1 P_3/[1 - \alpha\beta/(1 + w_2/w_3)] = v_t/[1 - \alpha\beta/(1 + w_2/w_3)]$$

Since the rate of the chain reaction is also equal to $v_t Z$ where Z is the average chain length:

$$Z = [1 - \alpha\beta/(1 + w_2/w_3)]^{-1}$$

When $\beta = 1$ and $\alpha \leqq 1$ the process is a straight-chain reaction. When $\beta > 1$, chain branching occurs. When $\alpha\beta > (1 + w_2/w_3)$, the original

assumption of a steady state is impossible, that is, a steady rate is impossible or the system is an explosive one.

Gas phase explosions have been studied very extensively (114). It has shown, for all cases, that there exists a limited region of temperature, pressure, and composition in which explosions take place. At constant temperature and composition, there is an upper as well as a lower limit to the range of pressures in which explosions can occur. It is well established that the lower limit is due to chain-breaking steps occurring on the walls of the vessel, and that the upper limit is due to three-body chain-breaking steps occurring in the gas phase. The kinetics of all of these systems are very complicated, and it is difficult experimentally to obtain reproducible results. In spite of these great, inherent difficulties, considerable progress has been made in the study of the kinetics of a number of these reactions (114).

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CHAPTER VI

THE INTERPRETATION OF RATE DATA

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I. EVALUATION OF THE KINETICS EXPERIMENT

Ideally, the chemist engaged in rate measurements might be supposed to first make his measurements and then interpret them. Practically, the research seldom develops in this tidy way. Interpretation starts as soon as the first run is completed and guides even the planning of the second run. Thereafter, each new experiment is planned with reference to what has been learned from earlier runs; indeed, sometimes the entire direction of the research is changed owing to some surprising discovery. Thus, the interpretation and the planning of kinetics experiments are closely interdependent, and it is appropriate to deal first with those aspects of interpretation which most directly affect the design of future experiments.

The first question to be asked is whether the data are satisfactory for the purpose intended. Or perhaps the question should be put more bluntly: Are the data any good at all? Such a crude question is justified because there are many kinetic data in the literature which are worthless, and many more which are wrong in some important respect. These faulty data can be found in papers old and new, authored by chemists of small reputation and by some of the best known kineticists of all time, and in the journals of many countries. One can be sure that in many other instances faulty data were recognized as such before they reached the stage of publication, and that the labor of many months had to be discarded when the decision was made either to repeat the work properly or to abandon it. A frank, direct statement is now needed: *other good chemists have gotten into trouble in kinetics work, and you can too if you aren't careful.*

Kinetics work is deceptively simple. Once a reaction is known, all one has to do is to measure the concentration of a product or reactant as a function of time under defined conditions. If the reaction is properly recognized, the conditions are properly defined, and the measurements of concentration and time are properly made, the data (at least the raw data) cannot be incorrect. In most of the faulty work alluded to above, the specification, "properly," was not met. In place of proper definition of conditions and of the reaction itself, or of proper determination of concentrations or times, assumptions were made or inadequate evidence for the quality of the experiment was accepted. Probably the assumptions were

largely at fault. The temptation to assume, for instance, that a certain reaction occurs as expected, or that a certain analytical method is reliable in the system under study, or that the solvent at hand is of adequate purity, can be very strong. This writer's plea is that such assumptions should be verified experimentally wherever possible, or that they be rendered unnecessary through, for example, careful purification of materials before measurements are started. A few days of careful preparation for rate measurements can save months of extra work.

In the following pages, a number of aspects of kinetics experiments that need to be carefully checked are discussed. Each is introduced by a question which the experimenter is urged to put to himself.

Is the Reaction Under Study Properly Identified?

It might seem an affront to ask a chemist whether the reaction whose rate he is studying is actually the reaction he thinks it is. Yet the question needs to be asked. The literature contains several examples of the incorrect identification of reactions studied kinetically. During the 1930's the kinetics of reactions of ethanolic sodium or potassium hydroxide with alkyl halides were studied in several laboratories, and it was generally assumed that the products were alcohols resulting from the displacement of halogen by hydroxide ion. In at least one instance this assumption was elaborately justified. Yet J. U. Nef (1) had shown more than thirty years previously that the predominant products were ethers resulting from attack of ethoxide ion on the halides. Other instances of mistakes in the identification of reactions have been detected and revealed by Brown and Nelson (2), by de la Mare and Robertson (3), and by Hughes, Ingold, and co-workers (4).

How can such mistakes be avoided? The best way is to properly identify the reactants and the products. Often one reactant is an organic compound whose identity can be checked by measurement of physical constants, preparation of solid derivatives and/or quantitative analysis for elements. The identity of such a reactant is usually easy to verify; all the more reason for doing it. Often one reactant is a chemical obtained in reagent grade from a reliable supply house; such chemicals are usually of good quality but one should remember that even the most reliable packager can occasionally put an incorrect label on a bottle. Product isolation is equally important. Even though the reaction under study may be found in all the text books, isolation and identification of the products *from a reaction run under the conditions of the rate measurement* is still strongly advised. Text books are sometimes wrong, and they tend to copy errors one from another.

Sometimes isolation of a product is impractical because of its physical

properties, or its susceptibility to further change under the reaction conditions, or because the reaction itself was run at very low concentrations. In such cases it is advisable to isolate what one can and to perform various types of "infinity" analyses. The latter involve waiting until the reaction has gone substantially to completion, and then making chemical or physical measurements capable of showing whether the desired product has been formed and/or whether the reaction has gone quantitatively. In photometric kinetics, which are usually run at very low concentrations, a spectrum run on the infinity solution is sometimes satisfactory as both a qualitative and a quantitative analysis for the product.

Does the Reaction Occur Quantitatively, and Is Its Stoichiometry Properly Represented?

Even though authentic reactants have given the expected product in, say, 65% isolated yield, side reactions may nevertheless be of significant magnitude. Also, the stoichiometry may not be as expected. These questions can only be answered by quantitative analyses, certainly on infinity samples, and in special cases on samples taken during the course of the reaction. The latter are necessary in consecutive reactions to follow the rise and decay of an intermediate product. The failure of a reaction to occur quantitatively according to some set equation is not, however, necessarily a reason to shun kinetic study of it. There are good, convenient ways to handle both competing and consecutive reactions so that rate constants for both the component reactions can be determined accurately (see Chap. VIII).

An example of unexpected stoichiometry was encountered by Chapman and Parker (5). Aniline reacts with 2,4-dinitrochlorobenzene according to the equation, $ArCl + 2C_6H_5NH_2 \rightarrow ArNHC_6H_5 + C_6H_5NH_3Cl$, which (since the reaction is of second order) requires use of the expression, $dx/dt = k(a - 2x)(b - x)$, for the calculation of rate constants. Of the two equivalents of aniline required, the first effects displacement of chlorine and the second neutralizes the hydrochloric acid produced in the first step. However, the reaction of aniline with 2,4-dinitro*fluoro*benzene in ethanol conforms to the equation, $ArF + C_6H_5NH_2 \rightarrow ArNHC_6H_5 + HF$, and rate constants must be calculated with use of the expression, $dx/dt = k(a - x)(b - x)$. Here only one equivalent of aniline is consumed because hydrofluoric acid does not neutralize aniline in the medium used. Thus it is necessary to use different expressions to calculate rate constants for two very closely related reactions.

Does the Analytical Method Properly Represent the Extent of Reaction?

The importance of an affirmative answer is obvious. A method of analysis can be tested by analyzing known mixtures having compositions similar to those expected for reaction samples. However, even if an excellent check is obtained, one should not be entirely satisfied. This is because the actual reaction may be accompanied by an unexpected side reaction which consumes reactants or produces products in such a way as to distort the meaning of the analytical values.

The most general protection against being misled by analytical information is to follow the progress of the reaction by two or more entirely different analytical methods. If one method is faulty, viewed as analytical chemistry, there is a good chance that the second method will not be. If a side reaction affects the values obtained by one method of analysis, there is a fair chance (but not a certainty) that it will not affect values obtained by the other. If the rate of reaction as represented by the second method is the same as by the first, confidence in the work is increased. If yet a third method confirms the results of the other two, the possibility that some disturbing feature has gone undetected is reduced to a very low level.

An example of a system susceptible to three independent methods of analysis, and in which side reactions have been detected, is the reaction of an amine with an aryl chloride such as 2,4-dinitrochlorobenzene in an alcoholic solution. The expected reaction is of the amine with the aryl chloride:

$$ArCl + 2R_2NH \longrightarrow ArNR_2 + R_2NH_2^+Cl^- \qquad (1)$$

However, the interaction of the amine with the alcohol

$$R_2NH + R'OH \rightleftharpoons R_2NH_2^+ + R'O^-$$

enables a side-reaction of alcoholysis to occur

$$R'O^- + ArCl \longrightarrow ArOR' + Cl^- \qquad (2)$$

The sum of these two side reactions is then

$$ArCl + R_2NH + R'OH \longrightarrow ArOR' + R_2NH_2^+Cl^- \qquad (3)$$

This reaction can be followed by any one of three convenient methods: acid-base titration, argentometric titration for chloride ion, or photometric determination of $ArNR_2$. If the appearance of chloride ion is determined, the apparent rate represents both the aminodechlorination (Equation 1) and the alkoxydechlorination (Equation 2) reactions. If the disappearance

of amine is determined by acid-base titration, the apparent rate again represents both reactions but one is represented less strongly than the other. This is because reaction (1) consumes two equivalents of amine while reaction (2) consumes only one. Thus, both chemical methods are obscured by the competing reaction, but to different extents. Finally, if photometric analysis is used, only formation of $ArNR_2$ is measured. The infinity absorbance is less than theoretical, and the complication is thus revealed. From the photometric data, rate constants for both the main reaction and the competing reaction can be determined. This phenomenon and methods of treating it are discussed in several papers (6–9).

An example of a reward gained by analyzing both for reactant disappearance and for product formation has been reported by Burchfield and Storrs (10). In a study of the kinetics of reaction of 2,4-dinitrofluorobenzene with cysteine, the formation of the ultimate product, *N*-(2,4-dinitrophenyl)cysteine, was found to lag behind consumption of 2,4-dinitrofluorobenzene. Investigation revealed that dinitrophenylation occurred first on the sulfur atom of cysteine, and that the dinitrophenyl group then shifted to the nitrogen atom. A less careful study might have failed to detect the intermediate *S*-dinitrophenyl derivative.

Larsson (11) used an unusual but effective analytical method in his study of the hydrolysis of *Tabun* (dimethylaminoethoxyphosphoryl cyanide), the nerve gas. The eventual hydrolysis product is monoethyl phosphate. He determined the rates of formation of cyanide ion and of dimethylamine by standard chemical methods and compared them with the rate of destruction of *Tabun* determined by following the decrease in toxicity to mice. The latter measurements gave good first order kinetic plots, and enabled a more penetrating analysis of the reaction than would otherwise have been possible. The overall picture was that the cyano and dimethylamino groups were hydrolytically displaced in separate steps with cyano being the first to go from most *Tabun* molecules.

Complications may be encountered in reactions involving hydroxide ion owing to reaction with the glass of containing vessels. Solutions of sodium hydroxide in aqueous dioxane are notoriously reactive with glass. If disappearance of base is measured, falsely high rates may be observed, while if a product is determined the apparent rate may be falsely low. The experience of Foster and Hammett (12), who encountered and then circumvented this complication, is instructive.

When a physical method of analysis is used, gross errors stemming from events not directly connected with the reaction under study are possible. If photometric analysis is used, the formation of a highly colored substance from, say, a side reaction involving the solvent can distort the measurement of reaction rate. In manometric kinetics, spurious results can be

caused by a leak. In kinetics by dilatometry, cases are known in which the reaction under study occurred so rapidly that it was nearly finished before measurements of meniscus level could be started; measurements of volume change pertained, therefore, to some subsequent reaction involving a product of the first reaction. Benkeser, Hoke, and Hickner (13) have described such a case; the writer can recall another from his own experience.

The most dependable protection against such gross errors, as well as against distortions due to side reactions, etc., is again determination of reaction rate by some independent method of analysis, preferably a chemical method. The taking of this precaution is commonplace in first class kinetics work, and many illustrative examples could be cited. Just two will be mentioned. Hughes, Ingold, and Reed (14), in their renowned study of the kinetics of aromatic nitration, used dilatometry as their principal analytical tool but checked occasional reactions by chemical determination of nitro groups in the water-insoluble fraction of their reaction solutions. Long, Dunkle, and McDevit (15), in studying salt effects on the hydrolysis of γ-butyrolactone, again used dilatometry but did occasional runs by titration of the product, γ-hydroxybutyric acid, with standard base. Rate constants determined by the two different methods agreed well.

In manometric kinetics, trouble can be caused by the slowness of evolution of a gas from a liquid in which it is insoluble. An "induction period" is observed, for example, in the evolution of carbon dioxide from acidified aqueous solutions (16). A most surprising illustration is that methane is not instantaneously evolved when formed in concentrated sulfuric acid solutions (17). Rapid stirring was necessary in order to avoid the formation of supersaturated solutions with resultant lag in gas evolution.

Are the Forms of the Reactants in the Reaction Solution Accurately Known?

Have the reactants undergone reversible change preceding the reaction of kinetic interest? If so, what has been formed, and to what extent? There are both simple and complex cases, and even the simple cases call for comment. The simple cases include those in which no reactant undergoes reversible chemical change during preparation of the reaction solution and those in which, as when a carboxylic acid is dissolved in aqueous sodium hydroxide, a reactant is immediately and quantitatively converted into some other form. The situation is straightforward if the reactant as introduced, or a totally converted form, is directly involved in the rate determining step of the reaction whose rate is measured. It is also relatively straightforward if the form present in massive amount is in equilib-

rium with a small amount of a highly reactive form which is responsible for the reaction of kinetic interest. (For example, diazo coupling with phenols in acid solution occurs via the tiny amount of phenoxide ions present in such solutions (18,19).) In such cases, the measured rate constant is composite, frequently the product of an equilibrium and a rate constant.

The complex cases are those in which the reactant introduced is *partially* converted to some other form. The converted form may be either more or less reactive than the original. If the conversion is recognized, the situation may in principle be untangled although in practice the required equilibrium constants may be difficult to evaluate. If the conversion is not recognized, the kinetic results may be grossly misleading.

If rates of reactions of a series of compounds under standard conditions are to be compared, and if these conditions are such as to bring about partial conversion of the compounds to other forms, the comparison must take account of the degree of conversion in each case if it is to be meaningful.

Complexities from partial conversion are frequently encountered in kinetics in strongly acidic media. Compounds not usually thought of as basic may be extensively protonated by very strong acids. Carboxylic amides, for instance, have pK_a values about -1.7; this means that they are almost totally protonated in $5M$ hydrochloric acid. A plot of the rate constant for the acid catalyzed hydrolysis of benzamide against [HCl] has a maximum at about $4.5M$ (20). Interpretation: the rate determining step involves reaction of the protonated amide with water; at low acid concentration, increasing acidity causes increasing protonation, but the amide is substantially all protonated by $4.5M$; beyond this point the principal effect of increasing acid concentration is to decrease the activity of the water and thus to decrease the hydrolysis rate.

The situation is even more complex in the decarboxylation of 2,4,6-trialkylbenzoic acids and the decarbonylation of 2,4,6-trialkylbenzaldehydes. These reactions have been studied in detail by Schubert and his associates (21–23); their papers are a model of the way in which a really complex situation can be resolved.

The kinetics of nitration of nitrobenzene are complicated by partial protonation of the substrate in nearly anhydrous sulfuric acid. This is a contributing cause of a rate maximum in *ca.* 90% sulfuric acid, a phenomenon upon which false conclusions concerning the nitration mechanism were at one time based. The complications have been discussed by Gillespie and Norton (24).

Are the Conditions of the Experiment Properly Established?

No chemist would deny the importance in kinetics of using pure materials, of controlling and measuring temperatures accurately, and of recording times properly. Yet many a chemist has succumbed to the temptation to "save time" by using reactants or solvents not properly purified, and many otherwise worthy studies are of limited value because of inadequate control of temperature.

The best practice is to purify all chemicals and solvents as highly as possible. But clearly it would be unwise to purify all materials to the ultimate degree for every rate study; so much time would be spent in purification that there would be no time left for the experiments proper. Thus one does, in practice, accept chemicals and solvents at a certain stage of purification as satisfactory, but always with the reservation that further purification might be called for by the results of the experiments. Solid organic compounds are recrystallized to constant melting point and liquid reactants are fractionated, center cuts being taken. Physical properties of the purified compounds are checked against literature values; if discrepancies exist, they are resolved either by further purification or by experimental demonstration that the substance is of proper identity and satisfactory purity. Vapor phase chromatography is especially useful in determining the purity of a volatile compound. Reagent grade inorganic chemicals are frequently used as packaged by a reliable firm, but often require redrying before use. Solvents always require treatment, redistillation at the very minimum, and often rather elaborate purification sequences (25).

The painstaking purification of reactants and solvents in preparation for kinetics work often takes a week or two, and this can be frustrating to the chemist eager to get on with rate measurements. But such careful work is well justified on grounds of efficiency. One of the most productive laboratory workers in this writer's acquaintance refuses to take any short cuts in purification of materials for kinetics; this phase of his work takes considerable time, but he saves time in the long run because he seldom needs to repeat experiments (except for duplicate checks as originally planned).

In some cases the method of analysis requires special precautions in the purification of the solvent. For example, in a study of the kinetics of the reaction of *n*-butylamine with ethyl formate (26), the reaction was followed by the change in optical density at 220 mμ, at which wavelength the product (*n*-butylformamide) absorbs much more strongly than does ethyl formate. Absolute ethanol was the solvent, but commercial absolute ethanol could not be used because the traces of benzene it contains absorb too strongly at 220 mμ. A special sequence of drying procedures, starting

from 95% ethanol, had to be devised. Another example concerns a study of the reactions of several nucleophiles with ethyl *p*-toluenesulfonate (27). The solvent was 60.72% aqueous dioxane. When iodide ion was the reagent, traces of peroxides in the solvent interfered with the determination, and it was necessary to use fresh dioxane for each run. However, this special precaution was not necessary in reactions involving the reagents bromide ion, chloride ion, or hydroxide ion.

Temperature control for most reactions in solution is provided by a liquid bath the temperature of which can readily be held constant to $\pm 0.02°$ in the range 0–70°C. and to $\pm 0.1°$ in the range 70–200°C. (However, closer control of temperature is needed for dilatometry.) In practice, the desired constancy of temperature is readily obtained by use of commercially available equipment. Indeed, thermostat baths can be held at constant temperature for periods of weeks or months. This very dependability can, however, lull the kineticist into the dangerous luxury of failing to read the temperature during a run. Temperature control apparatus not only can fail, but usually does sometime in the course of a rate study. A relay may cease to function properly, a chill draught from an open window may cool the bath beyond the heater's capacity to warm it, or room temperature may rise above bath temperature on an unusually warm afternoon. To guard against the simple oversight of neglecting to check bath temperature, one should set for himself a schedule for temperature observation. Temperature should be read and noted before the start of a run, at its completion, and at intervals between depending on the amount of time elapsed. If samples are taken at intervals of 5 minutes or longer, it is good practice to read and note the temperature as each sample is taken.

The thermometers used to read bath temperatures must be checked occasionally against a standard thermometer certified by the National Bureau of Standards or an equivalent agency in another country. It is probable that when kinetic data of different laboratories disagree slightly, failure to establish temperatures properly is often the cause of disagreement.

Keeping of a good time record, as discussed elsewhere in this volume (Chap. III), is also important. One point to be added is that for many kinetic experiments knowledge of the true zero time, the time of starting the reaction, is not necessary. Commonly the rate constant is determined from the slope of a plot of $1/(a - x)$, $\log (a - x)$ or other function against time; the slope is determined by the differences between time points but not by their absolute values. Since the true zero time is always somewhat uncertain owing to uncertainties in the time required for mixing or to unavoidable irregularities in temperature while the reaction solution is being installed in the thermostat bath, it is often better to choose an arbitrary zero time after the solution is all mixed and thermally equilibrated with

the bath, and to relate all remaining time readings to this arbitrary zero. It must be borne in mind, however, that for some kinetic problems (such as treatment of consecutive reactions; see Chap. VIII) knowledge of time with respect to the true zero time is required.

Is the Reaction Sensitive to Trace Impurities?

Some reactions are and the kinetic effects of the trace impurities may be profound. Sometimes the chemist has reason to suspect trace impurity effects; in such a case he can systematically explore the question. He can determine whether the rate is affected by the intentional addition of the suspected impurity. Also, he can see whether the rate depends on the history of the reactants and solvent. Thus, is the rate with ultra-purified materials different than with materials purified with ordinary care? Unexpected trace impurity effects often are revealed by lack of reproducibility between experiments. Many important kinetic effects have been discovered by tracking down the cause of irreproducibility of runs.

Oxygen has a great effect on some reactions, particularly radical reactions. An amusing and yet serious case was discovered by Bauer and Daniels (28). The addition of bromine to cinnamic acid is relatively slow under ordinary conditions, and is catalyzed by light. Its kinetics had been studied by several workers including Bauer and Daniels. In their second publication, however, these workers reported that in the absence of oxygen the reaction occurs very rapidly *in the dark*. Thus, all the earlier work pertained more to the inhibition by oxygen than to the addition reaction itself.

Another reaction strongly retarded by traces of oxygen is the decomposition of benzenediazonium acetate in methanol to give, mainly, benzene, formaldehyde, nitrogen, and acetic acid (29). The kinetics under both oxygen-free conditions and in the presence of oxygen have been studied.

Yet other reactions are accelerated by oxygen in small concentrations. An example is the addition of hydrogen bromide to propyne (30).

Metal ions in minute concentrations sometimes exert strong catalytic effects. An instance concerns the oxidation, by hydrogen peroxide, of *o*-mercaptophenylacetic acid to the corresponding disulfide (31). This reaction is powerfully catalyzed by ferrous ion, and even when efforts were made to purify materials so as to eliminate traces of this ion, ferrous ion catalysis still prevailed. However, addition of ethylenediaminetetracetic acid, which tightly complexes ferrous ion, caused both a drop in rate and a change in the overall kinetic law. This use of a strong chelating reagent to suppress traces of a metal ion is a technique of general value. Another instance is described by Ball and Edwards (32).

Traces of water in supposedly anhydrous media sometimes have a big effect on reaction rate. There are two general ways in which such an effect can be revealed. The easier is to perform a run or two in which small amounts of water are deliberately added; if the added water has no effect on the rate, as is frequently the case, much comfort is gained. The more rigorous and more difficult way is to study the reaction under strictly anhydrous conditions. The absolute exclusion of water is difficult to attain; usually an elaborate apparatus must be built so that no dried material is ever exposed to the laboratory atmosphere for even an instant. However, there are special cases in which traces of water can be destroyed chemically without adverse effect on the system; for example, strictly anhydrous acetic acid can be made by treating ordinary glacial acetic acid with acetic anhydride, and is a satisfactory anhydrous solvent as long as acetic anhydride does not interfere (33).

The isomerization of *n*-butane, catalyzed by aluminum chloride or bromide, is a reaction in which dramatic trace impurity effects have been demonstrated. Leighton and Heldman (34) found that this well-known reaction did not occur if absolutely dry materials were used and all transfers were made in a vacuum system. Traces of water or hydrogen bromide activated the system, and rate measurements on the HBr-induced reaction were made. A few years later, Pines and Wackher (35) made another surprising discovery: absolutely olefin-free *n*-butane is not isomerized by aluminum bromide even when hydrogen bromide is added. Both these discoveries were made as the result of efforts to track down the cause of irreproducibility of rates in early measurements. And both were of considerable importance in elucidating the mechanism of the isomerization reaction.

Trace impurities may also be contributed by the containers used for the experiments. Cases are known in which traces of acid or base or other catalytically active species from glass surfaces exerted large effects on rate (36,37).

Is the Order of the Reaction Properly Established?

The chemist usually anticipates some particular order of reaction before he starts rate measurements. He usually plots the results of the first few experiments in the fashion appropriate for the expected order. If straight lines result, he is tempted to consider the order of reaction settled and to move on to other aspects of the work. This is not a defensible procedure. It can allow unusual reaction orders to escape detection, and completely fails to reveal dependence of rate on any species which is not consumed in the reaction.

Proper definition of kinetic order always involves a series of runs in which initial concentrations of the several reactants are varied. If the proper rate expression is used, experiments at all concentrations give the same rate constant. (With this exception: if the changes in concentration are great enough to change the medium appreciably, the rate constant may vary on this account.) The reader is referred to some recent researches in which the proper definition of kinetic order, including some unusual orders, is exemplified (38–45).

Is the Experiment Properly Organized to Provide Significant Data?

The chemist measuring reaction rates is in fact not doing that; actually, he measures something else, such as the change in a titration value, in an optical density value, or the meniscus level in a dilatometer, as a function of time. He then derives a reaction rate constant from his original measurements.

If the rate measurement is to be significant, there must be significant differences in the quantities measured at various times during a run. If titrations are made with a common buret, differences in titration values of 0.05 cc. are not very significant since the expectable error of measurement is nearly that large. If a dilatometer is used, differences in meniscus level on the order of differences caused by fluctuation of the temperature of the thermostat bath are again of limited value.

These matters usually lie within the control of the chemist. If titration is the method of analysis, all of the following magnitudes may within wide limits be set as desired: the concentrations of reactants, the size of samples taken for analysis, the times between samples, the concentration of the titration reagent and the precision of the buret. Other methods of analysis offer similar ranges of choice. In the well-designed experiment, these several magnitudes are set so as to provide differences between successive samples that are many times greater than the expectable error of measurement. The choice of appropriate magnitudes, of concentrations, sample size, etc., is not difficult but it does require careful consideration of the several quantitative variables and their interaction with one another. Thus, if differences in titration values are too small, the trouble might be remedied by increasing the concentration of reactants, by increasing the size of the sample taken for analysis, by decreasing the concentration of titrant, by using a microburet instead of a common one, or by a combination of these changes. But if the concentration of reactants is increased, the reaction will in general go faster and this may require sampling at shorter intervals.

Closely related is the matter of the number of samples to be taken, or

the number of observations to be made, during a run. The rate constant is usually derived from the slope of a plot of an appropriate function of concentration against time. The question is, therefore, how many points does it take to establish the linearity and the slope of the line.

Mathematically, two points define a straight line. If one of these is for zero time, at which concentrations are known from the method of preparation of the reaction solution, one point at a later time based on analysis of the reacting solution would appear to suffice. One can indeed find rate "constants" in the literature which have been determined in just this way, but such values are not usually accepted as having much significance. A principal difficulty is that two points may as well be joined by a curved as by a straight line. A "two point" experiment gives no information as to whether the function which is plotted really is linearly dependent on time, and thus gives no indication of the order of the reaction. Furthermore, such a procedure cannot reveal any of the experimental defects or complications which are called to one's attention by a curved or scattered plot, as discussed below. Finally, any error in either of the two observations is embodied in the "constant" obtained.

Three completely accurate points would provide a test of the linearity of the function which is plotted. But complete accuracy is never obtained; three points as obtained in a typical kinetic experiment provide a very uncertain test of linearity. Four points in a straight line are fairly convincing, but it is hard to decide whether nonlinearity is a result of scatter or of determined curvature, or of both. Indeed, when one makes allowance for the chance that one or two points in a run may be either spoiled by experimental mishap or rejected because of their gross deviation from the line established by the rest, one finds that eight to ten points per run are desirable. This number is usually sufficient to allow curvature to be distinguished from linearity even when there is scatter or need to reject one or two points. In this writer's work, eight to ten points per run is standard practice.

Does the Kinetic Plot Reveal any Defects or Complications in the Experiment?

It is wise to plot an appropriate function of concentration, such as log $(a - x)$ or $1/(a - x)$, against time for every run even if the slope is not determined graphically. Such a plot is very informative about the experiment.

One desires to obtain a straight line. Curvature indicates trouble. But one's delight at obtaining a straight line must be restrained, especially if the points plotted represent no more than 50 or 60% completion of the

reaction. Any function approximates linearity if taken over a sufficiently small interval. In order to call forth any latent deviations from linearity, one should, therefore, perform at least one run for each reaction in which points are taken covering 80 or 90% of the entire reaction. Even if the line is straight to 90% of completion, deviations from the assumed rate expression may still lie concealed (46). Full confidence in a rate expression is gained only after a series of runs with varying initial concentrations support it.

The causes of deviations from linearity in the kinetic plot will now be considered. Most dismaying of all is a hopeless scatter of points or a pattern suggesting that the reaction is going in a backwards direction. Such behavior shows that something is seriously wrong in the experiment. Most often the method of analysis is at fault. Or, in a run performed in sealed ampoules, trace impurity effects, varying from one ampoule to another, may be responsible. The reaction may not be following the expected chemical equation. And sometimes poor experimental technique is the source of trouble. Whenever hopeless scatter or a reverse trend is encountered, the entire experiment must be reconsidered and re-examined before additional rate measurements are made.

Curvature may be due to an incorrect assumption of the order of the reaction. If first order is assumed but the reaction is in fact of second order, downwards curvature (curve D in Figure 2) will be observed. If second order is assumed but the reaction is really first order, upwards curvature (curve A in Figure 1) will result. Fractional orders, third or higher orders, and mixed orders of reaction are also possible; methods of defining the true reaction order are discussed elsewhere in this volume (Chap. V).

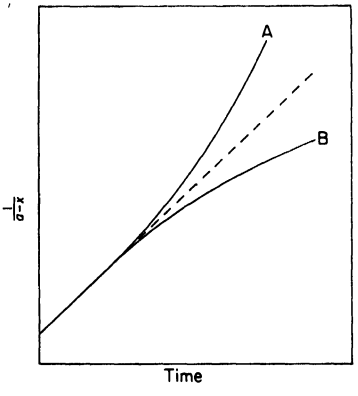


Fig. 1. Second-order kinetic plots showing upwards (A) and downwards (B) curvature.

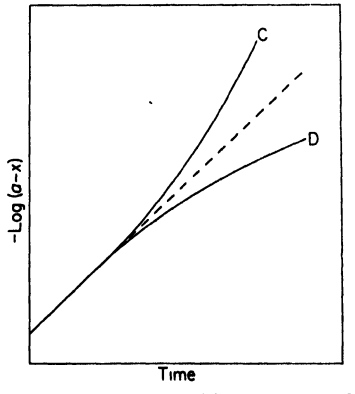


Fig. 2. First-order kinetic plots showing upwards (C) and downwards (D) curvature.

In working with second-order reactions, chemists often set the initial concentrations of the critical reactants equal so that the simple expression, $1/(a - x) = kt + C$, can be used in calculation of rate constants. If a is the initial concentration of one reactant, correctly known, and if the concentration of the second reactant is by mistake higher than a, the result will be upward curvature in the kinetic plot (curve A of Figure 1). If the concentration of the second reactant is by mistake less than a, downward curvature (curve B of Figure 1) is caused.

In first order kinetics, the rate constant is usually obtained from the slope of a plot of $-\log(r_\infty - r)$ against time, where r is some property of the system linearly dependent on the extent of reaction (see Chap. V). Such a plot is equivalent to Figure 2. If the infinity value (r_∞) is incorrectly known, curvature results. Use of an infinity value higher than the true one causes downward curvature (curve D of Figure 2) while use of an erroneously low infinity value causes upward curvature (curve C).

If a reaction progresses to a state of equilibrium instead of to completion, the kinetic plot shows downwards curvature with eventual zero slope. Although sometimes unexpected, reversibility of the reaction is usually easy to recognize. By use of appropriate expressions, rate constants can be derived for a reaction progressing to a state of equilibrium (see Chap. V).

Curvature can be caused by change in temperature during a run. Decreasing temperature causes downward curvature, and increasing temperature the opposite. Change in temperature can be due to faulty thermostat operation. Also, the temperature of the reacting solution may change during the early part of a run if the method of preparation of the reaction solution does not insure thermal equilibrium with the thermostat from the very start. If the reaction is exothermic and is run at high reactant concentrations, the heat liberated by the reaction may cause a temporary rise to higher than thermostat temperature.

Other complications in runs at high reactant concentrations have to do with the considerable change in the medium that may occur as the run progresses. If ions are produced, the ionic strength will change with possible resultant increase or decrease in instantaneous rate constant and therefore upwards or downwards curvature. If acid or base is produced or consumed, and the reaction is acid or base catalyzed, curvature may be caused. When runs are made at lower concentrations such complications are obviously less serious and they can be substantially eliminated by, for example, adding salts to maintain substantially constant ionic strength or buffers to maintain essentially constant pH.

Impurities in the reactants ordinarily cause downward curvature. The most common impurities are those of similar chemical character; such are most likely to be retained during purification steps. The impurity may be

more or less reactive than the reactant proper. In either case the instantaneous rate constant is high at the start and then drops as the more reactive compound is consumed. Whether the impurity is fast- or slow-reacting, the kinetic plot may nevertheless be linear over a considerable part of the reaction, and the linear portion may often be used to define a rate constant. Indeed, if one is dealing with a mixture of a fast- and a slow-reacting compound, he can in favorable cases derive rate constants for both reactions from a single kinetic plot (47–49).

Catalysis by a product, known as autocatalysis, causes upward curvature. This is a fairly common phenomenon (45,50–53), and is discussed in Chap. XII. In some cases a reaction is so strongly dependent on catalysis by a product that there is scarcely any chemical change during the early part of the reaction; only when the slow uncatalyzed reaction has formed a significant amount of product does the reaction rate become appreciable. This is the phenomenon of an "induction period."

An induction period is also observed for certain consecutive reactions, A $\rightarrow$ B $\rightarrow$ C, when the formation of the ultimate product (C) is measured and when the rate constants of the two steps are such that the intermediate product (B) accumulates during the early part of the reaction (54). The kinetic curve is again curved upwards.

Curvature in the kinetic plot can also be due to side reactions. The particular way in which a side reaction affects the kinetic plot depends on what the side reaction is and on what method of analysis is used. In many cases a side reaction does not cause deviations from linearity (55); this is a further reason for not deriving too much satisfaction from a linear plot. An exhaustive discussion of the ways in which side reactions can cause curvature is beyond the scope of this chapter. Reference is made, however, to instances in which such complications have been encountered (6–8,56–59).

Are the Data Reproducible?

This question is relevant to all scientific observations, and the asking of it infers no disrespect to the investigator. The kineticist must ask it of himself, and he can answer the question best by performing a repeat run under the same or similar conditions.

The two principal causes of irreproducibility of kinetic data are human error and unsuspected variation in the materials used for the experiments. Chemists sometimes make mistakes. A mistake in weighing may be made, or the wrong chemical may be taken from the shelf, or a manipulative error may escape notice, or a simple mistake in arithmetic may be made. Any of these can be the cause of an erroneous rate constant. The chance that the

same error would be made in successive experiments is small, especially if the two experiments are independent of each other. (Thus, they should be based on independent weighings, etc.)

A chemist in this writer's acquaintance, a careful and methodical worker, once found that rate constants for supposedly identical runs differed considerably from one another. When a third and then a fourth run were made, the rate constant drifted farther and farther from its original value. Eventually he found that in preparing a standard solution, he had not swirled it long enough to ensure thorough mixing; the solution was more concentrated at the bottom than at the top. In embarrassment and chagrin, he prepared a new standard solution and made further runs; reproducibility was now excellent. This is representative of the kind of human error which can be caught by repeating a determination.

Unsuspected variations in the materials, insofar as they have kinetic significance, usually concern trace impurities. The method of purification often is not uniformly efficient in removing such impurities, and one batch of material may contain them in different amounts from another. Runs based on the two batches may therefore give different rate constants. As discussed above (p. 187), many important kinetic effects have been discovered from irreproducibility owing to trace impurities.

Trace impurities have some tendency to be time-variable. Thus, they may form or disappear as a solvent or reactant sets on the shelf. Again, at a later time another batch of reactant may be in use. Factors due to simple mistakes sometimes also vary with time. A mistake in the standardization of one batch of standard solution is usually not repeated when another batch is standardized. A leak in a manometric apparatus may appear or disappear during the passage of weeks, and so forth. For these reasons it is wise to check for reproducibility not only between runs, say, on successive days, but also between runs performed weeks or months apart.

When small differences in rate are being measured, the question of reproducibility is especially important. The work of Reinheimer *et al.* (60) represents careful attention to reproducibility in such a case.

It is common practice to perform each run in duplicate and to be satisfied if the two constants agree. This is commendable, but repetition of every run is not always necessary. Thus, if one is determining the variation of rate constant with respect to some variable such as temperature or the concentration of a reactant, he can do a series of single runs under regularly varied conditions and then plot the constants obtained against the variable whose effect is under study. If a smooth curve can be drawn through the set, reproducibility is judged to be satisfactory. Any runs which deviate from the smooth curve are repeated.

Is the Rate Constant Properly Derived From the Data?

The literature contains numerous values that were not. In most of the instances known to this writer the difficulty was that an incorrect mathematical operation was performed uniformly throughout a set of runs. In one case, it is said, the slopes of plots of $-\log(a - x)$ versus time were all *divided* by 2.30 to obtain first-order rate constants. They should have been *multiplied* by this figure, and so the reported figures are all too low by a factor of $(2.30)^2$ or 5.29.

It is common to record time in whatever unit is convenient and to reckon rate constants initially in terms of that unit. If the minute or the hour was the unit of time, the initial rate constants are then, for publication, converted to constants based on the second by dividing by 60 or 3,600, respectively. In one paper from a distinguished kinetics laboratory, division by 60 was performed once too often on a set of data and the reported constants are 60-fold too low.

Sometimes when a large number of runs are to be made by a standardized experimental procedure, it is convenient to reckon rate constants by use of a special expression into which the numbers directly observed, such as cubic centimeters of titrant, can be inserted. This saves time and lessens the chance of arithmetic mistakes. An expression of this type was devised by Steger (61) for use in his studies of aromatic nucleophilic displacements induced by alkoxide ions. However, his expression was wrong; the figure 50 should appear where he wrote 100. Lulofs (62) used the same wrong expression. The rate constants in both papers are twice too large. The mistake was finally discovered by Lorang (63) and by Talen (64).

What can be done to avoid such blunders? An effective protection is to have another person calculate the rate constant from the raw data for some representative run. If he does the entire calculation with reference only to basic principles, and not to any short-cut expressions that may be in use in the laboratory, and gets the same rate constant as was originally calculated, one can have confidence that no systematic mistake of the type just mentioned has been made.

Another safeguard is to compare rate constants determined experimentally with literature values. Usually the new data do not exactly correspond to data in the literature but often they may be compared with data for the same reaction at a different temperature or in another solvent or with data for a closely related reaction. With reference to well-known effects of temperature, solvent change, or structural change on reaction rate, one can judge whether the new data have a reasonable relationship to the other values. A departure from expected relationships may constitute a discovery of considerable significance, but it also obliges the investigator to be particularly certain of his own work.

A most valuable method of checking calculations is that of making rough estimates or comparisons from the raw data. For instance, if one reaction has a rate constant three times that of another, it is usually possible to see in the raw data that the amount of chemical change in a given time interval early in the one reaction is about three times that in the other. If the calculated rate constant for a reaction indicates a half-life of, say, 30 minutes, one can inspect the raw data to see if the reaction was about half complete in 30 minutes. In comparing data for the same reaction at different temperatures, the old rule-of-thumb that rate doubles for every 10° rise in temperature is a helpful guide. Rough estimates such as these have helped the writer discover many a mistake in kinetic data.

If the Reaction Is Complex, Is the Experiment Designed to Allow the Complexities to be Dealt with Easily?

Because of the mathematical simplicity of rate expressions for first-order kinetics, it is desirable that experiments on complex reactions be set up so that first-order rate expressions can be used. The great majority of reactions of interest to the organic chemist are first order in some principal reactant known as the "substrate"; in addition, the rate may depend on the concentrations of the "reagent," of acids or bases, and/or of other species such as halide ions. Whatever the total order, if the reaction is set up so that all constituents of the reaction mixture are in great excess over the substrate, then the reaction will obey first order expressions. This is known as pseudo-first-order kinetics. The "great excess" of other constituents over the substrate may be as little as 10:1, but it is better to have an excess of 40:1 or even 100:1.

Pseudo-first-order rate constants are functions of the concentrations of those species in excess which do affect the reaction rate. The nature of the function with respect to any species can be determined by performing a series of runs in which the concentration of that species is systematically changed although always held in great excess over the substrate. This procedure can be repeated for each constituent of interest. Sometimes it is practical to change the reactant which is in minor amount and then to perform additional runs to determine the effect of varying the concentration of the former "substrate."

Mathematically, if the rate of a reaction is governed by the expression

$$dx/dt = k[\mathrm{A}]\ [\mathrm{B}]^n\ [\mathrm{C}]^m$$

the pseudo-first-order expression is

$$dx/dt = k_\psi[\mathrm{A}]$$

in which

$$k_\psi = k[\mathrm{B}]^n\,[\mathrm{C}]^m$$

k_ψ, the pseudo-first-order rate constant, is seen to be a function of the concentrations of B and C. As mentioned, the nature of the function can be determined. When it is known, the proper rate constant can be calculated from the expression

$$k = k_\psi/[\mathrm{B}]^n[\mathrm{C}]^m$$

Probably the greatest advantage of first-order kinetics is the simplicity of the kinetic expressions for treating complex reactions: consecutive and competing reactions, etc. This subject is treated elsewhere in this volume (Chap. VIII).

When a physical method of analysis is used, another outstanding advantage is that one does not need to know the proportionality factor relating concentration of reactant or product to the physical property which is measured. In second-order kinetics, on the other hand, knowledge of such proportionality factors is vital. Let us see why this is so; we shall for simplicity assume that some property proportional to the concentration of a reactant is measured. Thus, $(a - x) = gr$, where g is a proportionality constant and r is the physical property measured. If we calculate the rate constant from two representative points on the linear kinetic plot, we have for first-order kinetics

$$k(t_2 - t_1) = -\ln gr_2 - (-\ln gr_1) = \ln (r_1/r_2)$$

The proportionality constant, g, has been cancelled out. On the other hand, for second-order kinetics

$$k(t_2 - t_1) = 1/gr_2 - 1/gr_1 = (r_1 - r_2)/gr_1r_2$$

Here, the proportionality constant remains and must be evaluated if the method is to be used.

Other advantages of the pseudo-first-order procedure have to do with the fact that the substrate is used at very low concentration. This is necessarily so, if the other reactants are to be present in large excess. Typically, the substrate might be 10^{-3} or $10^{-4}M$ with other reactants from 10^{-2} to $10^{-1}M$. One consequence is that the reaction itself causes negligible change in the ionic strength or solvent properties of the medium. Another advantage is that very little of the substrate is needed for a pseudo-first-order run; this economy feature is attractive when the substrate is accessible only by a difficult synthesis. When photometric analysis is used, it is decidedly convenient to have the substrate at low concentration since optical extinction coefficients are very high at the wavelengths most suitable for photometric analysis.

First-order runs have another advantage in that they are generally complete earlier than second-order runs on the same reactions. The half-life of a first order reaction is a constant, and the reaction can be considered complete upon the passage of ten half-lives. (Mathematically, 99.9% reaction should occur within ten half-lives.) On the other hand, the half-life of a second-order reaction increases with decreasing concentration of the reactants; each half-life is longer than the preceding one, and a very long time is required to reach 99.9% reaction especially if the initial concentrations of the reactants were equal. Consequently, infinity samples from first order runs are much more accessible for routine checking or for yield determination (9,65) than are infinity samples from second-order runs.

There are also some disadvantages to pseudo-first-order kinetics. Perhaps the most serious is that the pseudo-first-order rate constant is very sensitive to highly reactive impurities in the reactants in excess. If, for example, the reaction of a substrate with a moderately reactive amine is under study, small amounts of a highly reactive amine impurity could cause a falsely high rate early in the reaction with resulting curvature in the kinetic plot. With still larger amounts of the highly reactive amine, conceivably the whole of the observed reaction could involve that reactive impurity. The chemist using the pseudo-first-order technique therefore has a special obligation to purify reactants with care.

Another disadvantage is that isolation of products is difficult because of the very small concentrations used. If absorption characteristics of the species involved are favorable, this difficulty can be circumvented by comparing the ultraviolet spectrum of the infinity solution with that of a mock infinity solution (a solution containing the expected products in the concentrations expected from a quantitative reaction). It is clearly worthwhile to isolate the product from the same reaction at higher concentrations, but not entirely safe to assume that the reaction is the same as at lower concentrations. However, if product isolation from a reaction at higher concentrations is coupled with a second-order run which gives the same second-order rate constant as derived from pseudo-first-order data, the reaction can be considered to be correctly identified.

A significant limitation on the pseudo-first-order procedure is the difficulty of using chemical methods to follow a reaction at such low concentrations. The absolute amount of chemical change in, say, a 25 cc. aliquot is very small and usually below the reach of chemical methods such as acid-base titration, Volhard titration, etc. This denies to the investigator the use of some very convenient analytical methods and obliges him to use a physical method of analysis. Even if a convenient physical method is available, the limitation is still serious because of the need for

a check kinetic run with chemical analysis. As mentioned in the preceding paragraph, a check run can however be performed under second-order conditions.

Because of its simplicity and flexibility, the pseudo-first-order procedure has come to be widely used in modern kinetic investigations. Reference is made to a number of recent studies in which this procedure has been used; these papers also represent excellent kinetic research in other respects (9,38,45,46,48,54,65,66).

Does the Infinity Value Remain Constant?

In first order kinetics the rate constant is most commonly reckoned from the slope of log $(r_\infty - r)$ versus time. This practice depends vitally on the accuracy of the infinity value, r_∞, which must therefore be determined with care. Sometimes infinity values drift with time owing to chemical or physical changes in the infinity solution. The infinity value may, for example, be affected by deterioration of the reaction product, by a reaction involving the solvent or by a defect in the apparatus. It is wise to determine the stability of the "infinity" value of a mock infinity solution and also the stability of the infinity values in actual runs, as a function of time. If the infinity value drifts but not too seriously, the situation can be handled by making infinity readings at the earliest possible time, at about ten half lives. If the infinity value changes rapidly owing to a further reaction of the product, the matter can sometimes be handled by the equations for consecutive reactions (8,67).

If it is inconvenient or impractical to determine the infinity value, but there is nevertheless reason to believe that the meaning of analytical observations is not distorted by side reactions, the Guggenheim method of determining rate constants (Chap. V) may be used. The Guggenheim method does not require knowledge of initial or of infinity values. But caution must be observed in interpretation of a linear Guggenheim plot (68). Roseveare has pointed out that reactions complicated by reversibility, by a side reaction, or by a subsequent reaction may give perfectly straight Guggenheim plots. A linear Guggenheim plot is therefore not assurance of simple first-order kinetics.

II. CALCULATION OF ENERGY AND ENTROPY OF ACTIVATION

1. Methods of Calculation

The Arrhenius equation (Chap. II) in its integrated form is

$$k = Ae^{-E/RT} \tag{4}$$

Taking logarithms

$$\ln k = \ln A - E/RT \tag{5}$$

or

$$\log k = \log A - E/2.303RT$$

This equation is in accord with the empirical fact that for most reactions a plot of log k versus $1/T$ is a straight line. The slope of this line is then $E/2.303R$; E calculated in this way is called the Arrhenius activation energy.

The slope may be determined graphically, but if data for three or more temperatures are available the points may not fall precisely on a line. In such a case it is best to calculate the slope by the method of least squares with the rate constant for each good run being given equal weight in the least squares computation. The slope, however determined, is multiplied by $2.303R$ to get E. R has the value 1.987 cal./deg., and so $2.303R$ is 4.576 cal./deg.

If data for only two temperatures are available, it is convenient to use the equation

$$\log k_2 - \log k_1 = (E/2.303R)]\,[(T_2 - T_1)]/[T_2T_1] = (E/4.576)/[(T_2 - T_1)/T_2T_1] \tag{6}$$

in which k_2 and k_1 are rate constants at, respectively, absolute temperatures T_2 and T_1.

Very careful studies have shown that the Arrhenius energy of activation is not completely independent of temperature as implied by Equation (4). Modified Arrhenius equations of the type

$$k = AT^n \exp(-E/RT) \tag{7}$$

have been proposed on empirical grounds.

Transition state theory gives the equation

$$k = kT/h \exp(-\Delta H^{\ddagger}/RT) \exp(\Delta S^{\ddagger}/R) \tag{8}$$

It is obvious that this has the same mathematical form as (7) if $n = 1$. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are, respectively, the enthalpy and the entropy of activation. Equation (8) is based on the necessarily incorrect assumption of equilibrium between reactants and transition state and therefore is at best an approximation to the truth. Nevertheless, it has served to stimulate much fruitful thought about kinetic problems. Also, it has become customary to analyze rate constants into temperature-dependent and temperature-independent parts in terms of the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively, of Equation (8).

Equation (8) can be expressed as

$$\ln k = \ln (k/h) + \ln T - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$$

Differentiating,

$$d(\ln k)/dT = 1/T + \Delta H^{\ddagger}/RT^2 = (RT + \Delta H^{\ddagger})/RT^2$$

Comparison with the differential form of the Arrhenius equation,

$$d(\ln k)/dT = E/RT^2$$

shows that

$$E = \Delta H^{\ddagger} + RT \tag{9}$$

It follows that $\Delta H^{\ddagger}$ can be obtained from the Arrhenius activation energy simply by subtracting RT. In the vicinity of room temperature RT is about 600 calories. The uncertainty in energy of activation is often of this magnitude. Thus there is relatively little difference between the Arrhenius activation energy, E, and the enthalpy of activation, $\Delta H^{\ddagger}$.

With reference to Equation (9), Equation (8) can be rewritten

$$k = (e\, k\, T/h) \exp (-E/RT) \exp (\Delta S^{\ddagger}/R)$$

Taking common logarithms,

$$2.303 \log k = 2.303 \log (ek/h) + 2.303 \log T - E/RT + \Delta S^{\ddagger}/R$$

Rearranging,

$$\Delta S^{\ddagger}/2.303R = \log k - \log ek/h - \log T + E/2.303RT \tag{10}$$

The value of k is 1.3803×10^{-16} erg deg.$^{-1}$ molecule^{-1} and of h is 6.6238×10^{-27} erg sec.$^{-1}$ molecule^{-1} (69). Therefore ek/h is 5.6645×10^{10} deg.$^{-1}$ sec.$^{-1}$. Taking the logarithm and substituting into Equation (10), one gets

$$\Delta S^{\ddagger}/4.576 = \log k - 10.753 - \log T + E/4.576T \tag{11}$$

$\Delta S^{\ddagger}$ has units of cal. deg.$^{-1}$ mole^{-1}, sometimes referred to as entropy units (e.u.). It should be noted that Equation (11) is valid only if the rate constant is based on the second as the unit of time. Corresponding equations can be devised if rate constants are based on the minute or the hour, but it is better to convert rate constants to the basis of the second before calculating $\Delta S^{\ddagger}$. To calculate $\Delta S^{\ddagger}$ by Equation (11), one inserts a good experimental rate constant, the corresponding absolute temperature and E, the Arrhenius activation energy calculated as described above.

The energy of activation can be calculated equally well from, for example, the pseudo-first-order or the second-order rate constant for a reaction. This is because it is derived from the rate of change of rate with temperature

and not from the absolute values of the rate constants. $\Delta S^{\ddagger}$, on the other hand, depends on the absolute values of rate constants. In general a different value of $\Delta S^{\ddagger}$, for the same reaction under the same conditions, is obtained from the pseudo-first- as from the second-order rate constant. Since $k = k_{\psi}/[B]$ where k amd k_{ψ} are, respectively, the second-order and the pseudo-first-order constants and B is the reagent in excess; k (and therefore $\Delta S^{\ddagger}$ calculated from k) will be higher than k_{ψ} (or than $\Delta S^{\ddagger}$ calculated from k_{ψ}) if $[B] < 1$ and lower if $[B] > 1$. Furthermore, $\Delta S^{\ddagger}$ derived from rate constants of order greater than one depends on the unit of concentration used; units of moles per liter have been arbitrarily chosen as standard.

2. Variation of Energy of Activation with Temperature

For complex reactions the Arrhenius energy of activation sometimes is strongly dependent on temperature and cannot be considered a simple characteristic of the reaction. The matter is perhaps best discussed with reference to a hypothetical specific case. Suppose that reactant A undergoes two competing reactions, $A \rightarrow B$ and $A \rightarrow C$, with rate constants k_B and k_C. The total rate constant for the consumption of A, k_{tot}, is then equal to k_B plus k_C. Suppose that the Arrhenius activation energies for the two reactions are 15 kcal. and 30 kcal., respectively, and that at 300°K. k_B is 10 and k_C is 1 (in some arbitrary units). By use of Equation (6), one reckons that at 330°K. k_B is 98.7 and k_C is 97.8, and that at 360°K. k_B is 661 and k_C is 4,470. The values of k_{tot} at the three temperatures are then 11, 196.5, and 5,131. From these k_{tot} values one can reckon the Arrhenius activation energy for the destruction of A to be 18.8 kcal. for the interval 300 to 330°K. and 25.7 kcal. for the interval 330 to 360°K. Thus the apparent energy of activation lies between the energies of activation of the two component reactions and is strongly dependent on temperature. A familiar group of reactions conforming to this pattern are electrophilic substitutions in monosubstituted benzenes to give mixtures of *ortho* and *para* products.

For other complex reactions the energy of activation is no more dependent on temperature than for a simple reaction. Again let us consider a specific situation:

$$A + B \rightleftharpoons C \longrightarrow D$$

Let us assume the first step to be rapidly reversible with equilibrium constant K and the second step, with rate constant k, to be rate-determining. This is a common situation. The overall rate constant, k_{tot}, is the product of k times K. From thermodynamics, $K = \exp(-\Delta H/RT) \exp(\Delta S/R)$;

k is similarly analyzed into thermodynamic components by Equation (8). It follows that

$$kK = \exp(-\Delta H/RT) \exp(\Delta S/R)\ \boldsymbol{k}T/\boldsymbol{h} \exp(-\Delta H^{\ddagger}/RT) \exp(\Delta S^{\ddagger}/R)$$

or

$$kK = (\boldsymbol{k}T/\boldsymbol{h}) \exp[-(\Delta H + \Delta H^{\ddagger})/RT] \exp[(\Delta S + \Delta S^{\ddagger})/R]$$

Thus, $\Delta H^{\ddagger}$ for the overall reaction is simply the sum of ΔH for the equilibrium step and $\Delta H^{\ddagger}$ for the slow step. Its only dependence on temperature is that arising from temperature variation of its component enthalpies.

We have seen that for some complex reactions the energy of activation can vary strongly with temperature and that for others it must be substantially temperature-independent. Let us now consider the origin of the distinction.

Mathematically, variation of energy of activation with temperature can arise when the overall rate constant is comprised in whole or in part of rate constants for individual steps combined *additively*. Chemically, this means that some reactant or intermediate is effectively partitioned between two different reaction pathways. If the energies of activation of the two alternate pathways are different, the proportion of the total reaction going by one pathway or the other will vary with temperature and so also will the apparent overall activation energy. It should be noted, however, that if the two alternate pathways have the same or nearly the same activation energy then the overall activation energy will be substantially independent of temperature. Another point to be noted is that the partition between two pathways must be real if overall energy of activation is to vary. For instance, if the activation energy for *ortho* substitution were so much higher than for *para* substitution that an electrophilic substitution gave almost entirely the *para* product at any temperature, the overall activation energy would not be noticeably temperature-dependent.

Mathematically, if the overall rate constant is comprised of rate and equilibrium constants combined only through multiplication and division, the overall enthalpy of activation is simply the sum of the ΔH or $\Delta H^{\ddagger}$ values of the component steps. The only variation of energy of activation with temperature is that arising from temperature variation of the component enthalpies. Chemically, such a situation usually means one or more rapidly reversible steps followed by a slow rate-determining step. The rate of vinyl polymerization is also governed by an expression of this type (see Chap. XXI).

From the above it can be seen that variation of activation energy with temperature can be a criterion of mechanism. It is a one-way criterion, however, significant if there is a substantial variation with temperature,

but not significant if the activation energy is essentially temperature-independent. This is because even when the overall rate constant is comprised of individual rate constants combined additively, the overall activation energy may nevertheless not change with changing temperature. In recent years Bender, Ginger, and Unik (70), Bensley and Kohnstam (70a), and Salomaa (71) have used this criterion of mechanism.

III. THE ISOKINETIC RELATIONSHIP

1. The Idea of a Reaction Series

The organic chemist can learn a good deal about the mechanism of a reaction from its products and its kinetics under various conditions. But there are limitations to how much can be learned from study of a single reaction. Often additional information can be gained from studying reaction rate as a function of structure in a *series* of related reactions. Even when the mechanism is known, study of the effect of structure on reactivity is of interest and value.

All such studies involve the assumption that closely related reactions tend to have the same mechanism. *A priori*, there is no justification for such an assumption. There is no reason why apparently similar reactions should not differ widely in mechanism; indeed, the literature contains many instances in which modest changes in structure or solvent cause deep-seated changes in mechanism. However, the opposite assumption—that each reaction has its own unique mechanism—is far less attractive. It is possible to conceive, for example, an infinite number of alkyl chlorides and therefore an infinite number of reactions of alkyl chlorides with sodium ethoxide, but it is not possible to conceive that these reactions take place in an infinite number of ways sufficiently different from one another to warrant classification as different mechanisms. To assume a unique mechanism for every reaction is also contrary to the fundamental assumption of natural science that there are basic regularities in nature. Moreover, there is by now abundant evidence for constancy of mechanism through many series of closely related reactions.

A group of closely related reactions is called a *reaction series*. The change from one reaction to another in a series is most often a structural change in one reactant. This change may, for example, be in the identity and/or the position of a substituent in a benzene ring, in the length of an aliphatic chain or in the number of atoms in a ring structure. A reaction series may also comprise the same reaction in a series of solvents. Actually, there is no limit to the degree of change permitted within a reaction series.

It is generally most profitable, however, to assemble series of reactions of demonstrably identical mechanism or which differ from one another in some obviously regular fashion. In the latter case, the assumption is made that the several reactions are either of the same mechanism throughout or that a single change in mechanism may occur somewhere within the series.

2. The Enthalpy-Entropy Relationship

Variation in rate within a reaction series may be caused by changes in either or both the enthalpy (or energy) and the entropy of activation. Four categories can be recognized:

1. Changes in rate are due chiefly to changes in enthalpy of activation; $\Delta S^{\ddagger}$ is substantially constant. This is a common situation. Many reaction series which follow the Hammett $\rho\sigma$ relationship (see p. 213) fall within this category.
2. Changes in rate are due chiefly to changes in the entropy of activation; $\Delta H^{\ddagger}$ is substantially constant. This is less common, but cases are known.
3. Changes in rate are due to random changes in both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.
4. Changes in rate are due to changes in both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, but these quantities vary in a parallel fashion. A plot of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ is linear. A typical plot is shown in Figure 3.

The fourth category is extensive. That there is a linear relationship between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for many reaction series is an empirical fact. It has important implications the recognition of which is chiefly due to Leffler (72). The present discussion is largely based on a major paper of his. The subject has also been treated, from a somewhat different point of view, by Wilmarth and Schwartz (73).

Linear relationships between ΔH and ΔS, from equilibrium constants, are also found for certain equilibrium reaction series. Leffler's paper (72) concerns both rate and equilibrium processes, but the present discussion is restricted to the phenomenon in kinetics.

Leffler emphasizes that numerous reaction series do not give linear plots of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$. He also points out that a linear plot can be obtained as a consequence of random experimental error. Let us imagine a reaction series in which the kinetic effect of structural or solvent change is negligible at all temperatures, that is, in which the rate constant at every temperature (and therefore the free energy of activation, $\Delta F^{\ddagger}$) is constant for all reactions in the series. In such a case the measured values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the several reactions would differ randomly from each other owing to experimental error, and a plot of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ would be linear.

This is because

$$\Delta\Delta F^{\ddagger} = 0 = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger}$$

Rearrangement gives $\Delta\Delta H^{\ddagger} = T\Delta\Delta S^{\ddagger}$, in which T is an experimental temperature. For this reason little significance should be attached to a linear plot of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ if the variations in these quantities are of the order of magnitude of the uncertainties which might arise from experimental error and if the slope of the plot (see below) is within the temperatures of experimentation.

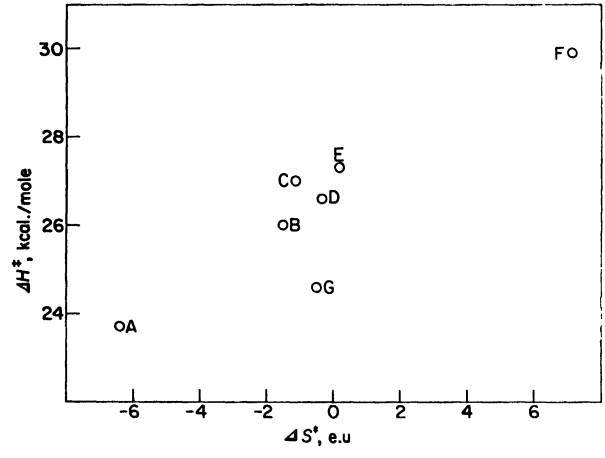


Fig. 3. Plot of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ for solvolysis of some cyclic arenesulfonates in acetic acid. A, cyclopentyl *p*-toluenesulfonate; B, endo-norbornyl *p*-bromobenzenesulfonate; C, cyclohexyl *p*-toluenesulfonate; D, cyclohexyl *p*-bromobenzenesulfonate; E, bornyl *p*-toluenesulfonate; F, menthyl *p*-toluenesulfonate; G, neomenthyl *p*-toluenesulfonate. The slope of the best line through all points but G is 450°K.; this is the isokinetic temperature. Data of S. Winstein *et al.* (71a).

A linear plot of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ implies the following algebraic relationship:

$$\Delta H^{\ddagger} = \beta\Delta S^{\ddagger} + \text{constant}$$

Let us choose two points on the line and designate them 1 and 2. It follows that

$$\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger} = \beta(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger})$$

From the relationship, $\Delta H^{\ddagger} = \Delta F^{\ddagger} + T\Delta S^{\ddagger}$

$$\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger} = T(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}) + (\Delta F_2^{\ddagger} - \Delta F_1^{\ddagger})$$

Therefore

$$\beta(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}) = T(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}) + (\Delta F_2^{\ddagger} - \Delta F_1^{\ddagger})$$

It is obvious that if $\Delta F_2^{\ddagger} = \Delta F_1^{\ddagger}$, then $\beta = T$. β, the slope of the plot, is thus the absolute temperature at which the reactions corresponding to points 1 and 2 have equal free energies of activation which means equal rates. This is true regardless of which points on the line are labelled 1 and 2. Therefore, *the slope of a linear plot of $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ is the absolute temperature at which all reactions which conform to the line occur at the same rate.* This temperature is called the isokinetic temperature.

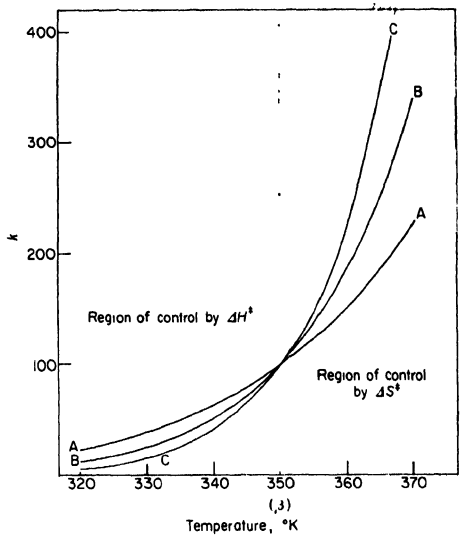


Fig. 4. Plot of rate constant versus temperature for three reactions in a hypothetical reaction series whose isokinetic temperature (β) is 350°K. Reactions A, B, and C have $\Delta H^{\ddagger}$ of 10, 15, and 20 kcal./mole, respectively.

The significance of the isokinetic relationship lies not so much in the interesting fact that plots of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ are often linear, nor in the consequence that the slope of this line is a temperature at which all reactions in the series have equal rates, but in the fact that the isokinetic temperature is a point of inversion of relative reactivity within the series. Passing a reaction series through the isokinetic temperature is like passing a beam of light through an ordinary lens; the image is inverted. That reaction which is slowest below the iokinetic temperature is fastest above, and vice versa.

The phenomenon of inversion of relative rates is best seen in a graphic presentation. In Figure 4 the rate constants of three reactions from a

hypothetical reaction series are plotted as a function of temperature. The isokinetic temperature is 350°K. (77°C.) and the three reactions, labelled A, B, and C, have enthalpies of activation of 10, 15, and 20 kcal., respectively. All three reactions were assigned a rate constant of 100 (in some arbitrary units) at the isokinetic temperature, and the other rate constants were computed from these values by use of Equation (6).

Reaction A was the fastest of the three below the isokinetic temperature, but it is the slowest above. Reaction C, the slowest below the isokinetic temperature, is the fastest above. This is the inversion phenomenon.

Reaction series which conform to the isokinetic relationship are not rare. Leffler listed 81 reaction series which gave good isokinetic plots from the literature prior to 1954, and numerous additional examples have since been found. Figure 4 therefore carries a clear and important message: *great care must be observed in the interpretation of rate data from a reaction series at only one temperature.* Especially if changes in reactivity are small, it is possible that the one temperature chosen for rate measurements may be close to the isokinetic temperature for the series, and that a change of reaction temperature of a few degrees might invert the apparent affect of structure or solvent on reactivity. Thus, the same set of reactions might be accelerated by electron-attracting substituents below the isokinetic temperature and retarded (relatively) above. A reaction might be favored by nonpolar solvents below the isokinetic temperature and by polar solvents above.

In Figure 4, it can be seen that *below the isokinetic temperature* the reaction (A) of lowest energy of activation has the highest rate. This may be called the region of control by $\Delta H^{\ddagger}$. It is the more familiar; in the majority of reaction series lower energy of activation does mean higher rate. *Above the isokinetic temperature* the reaction (C) of highest entropy of activation has the highest rate. This is the region of control by $\Delta S^{\ddagger}$. Control by $\Delta S^{\ddagger}$ is less familiar, but is often encountered in the effects of solvents on reaction rate (74).

Because many, many reaction series do conform to the isokinetic relationship, generalizations for predicting the effect of structure or solvent on reaction rate must be regarded with reserve. However correct a generalization may be in predicting relative rate below the isokinetic temperature, it will be correspondingly incorrect above.

Generalizations concerning the effects of structure or solvent on reactivity have played a major role in the development of theoretical organic chemistry. It is therefore necessary to ask whether the existence of the isokinetic relationship jeopardizes the whole structure of organic theory. Fortunately it does not, because in most cases conclusions from structural or

solvent effects on reactivity at a single temperature have been re-enforced by other types of evidence. Only in the absence of re-enforcing evidence do conclusions call for reconsideration. But even then they are frequently correct. Often rates in both the reaction series on which the generalization was based and in the reaction series to which it was applied were both governed largely by changes in $\Delta H^{\ddagger}$. In other cases both were responsive mainly to changes in $\Delta S^{\ddagger}$. False conclusions would be expected only if a generalization based on rates below the isokinetic temperature were applied to rates in another series above the isokinetic temperature for that series, or vice versa.

Of the 81 reaction series following the isokinetic relationship tabulated by Leffler, somewhat more than half had an isokinetic temperature well above the temperature region investigated experimentally. Another quarter had an isokinetic temperature well below the temperatures of experimentation. When the isokinetic temperature was high it was often very high; in 32% of Leffler's examples, the isokinetic temperature is more than 100° above the mid-point of the experimentally investigated temperature region. It can be seen that most of Leffler's cases were in the familiar region of control by $\Delta H^{\ddagger}$, that is, below the isokinetic temperature.

Cases in which the isokinetic temperature lies within or close to the temperatures of experiment are fairly common. The writer encountered one such case in his own research (75). A most interesting example has been described by Saunders and Ware (76). These authors studied the thermal rearrangement of (*p*-substituted phenyl) diphenylmethyl azides to *p*-substituted benzophenone anils, making measurements at 169, 180, and 190°C. The data (in dibutyl carbitol solvent) gave a good isokinetic plot with slope (isokinetic temperature) 461°K. which is 188°C. And indeed the rates at 190° were nearly the same for *p*-substituents as different in electronic effect as the methoxy group and the nitro group. The rates at 180° showed some tendency to spread in the fashion expected if electron-releasing substituents facilitate reaction; it is clear that at room temperature the spread would be even greater. On the other hand at a higher temperature, say 250°C., the spread would be in the opposite fashion. Saunders and Ware discussed the electronic effects with commendable restraint in view of their small magnitude as measured. Had the temperatures of measurement been well below the isokinetic temperature with resultant greater spread in individual rate constants, restraint would have been equally justified.

Another interesting feature of the data of Saunders and Ware is that the short reaction series comprising the rearrangement of triphenylmethyl azide in three solvents not only gave an isokinetic plot but had almost

the same isokinetic temperature (194°C.) as did the other series. Thus solvent effects were small as measured, but would have been greater in opposite senses at higher or lower temperatures.

The question arises: What is the chemist to do if he is not allowed to draw conclusions from rate data at one temperature? The answer is: make measurements at one or more additional temperatures. The chemist is than in a position to calculate $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and to see how these two factors contribute to the reaction rate. He may find that rate is governed mostly by the enthalpy of activation, either because the isokinetic temperature is high or because the entropy of activation is essentially constant through the series. (The latter is the extreme case of the former.) Or he may find that the entropy of activation dominates the determination of rate. In either case he can check the literature to see whether the effects with which he wishes to compare his own data arose mostly from $\Delta H^{\ddagger}$ or mostly from $\Delta S^{\ddagger}$. When he does so he will find that most of the electronic effects on rate concern the enthalpy of activation and that many kinetic solvent effects are embodied in the entropy factor.

But what if the changes in rate are so small that differences in $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ are within experimental error? Then obviously only the rate constants themselves can be used in discussion of the factors affecting reactivity. But even here measurements at two or more temperatures are necessary; the chemist cannot know that differences in $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ are small until rates at at least two temperatures have been determined. In an investigation of the subtle effects of London forces on reactivity in aromatic nucleophilic substitutions, J. D. Reinheimer and the writer (77) were obliged to consider rate constants themselves for the reasons cited.

IV. LINEAR FREE ENERGY RELATIONSHIPS

1. Introduction

It is an empirical fact that a plot of log k for the saponification of m- or p-substituted ethyl benzoates against log K for the ionization of the corresponding benzoic acids is approximately linear (78). The plot is shown in Figure 5. ("Corresponding" means that log k for saponification of ethyl m-chlorobenzoate is plotted against log K for ionization of m-chlorobenzoic acid, etc.) That a straight line is obtained indicates a relationship between the effects of the substituents on saponification rates and their effects on the extent of ionization.

The mathematical expression of the linear plot is

$$\log k = a \log K + \text{constant}$$

Since $\log k = -\Delta F^{\ddagger}/2.303RT + \log kT/h$, and $\log K = -\Delta F/2.303RT$, the linear plot can also be expressed

$$-\Delta F^{\ddagger}/2.303RT = a(-\Delta F)/2.303RT - \log kT/h + \text{constant}$$

At constant temperature, this becomes

$$\Delta F^{\ddagger} = a(\Delta F) + \text{constant}$$

That is, the free energy of activation for the saponification reaction is linearly related to the free energy of the ionization reaction. This is consequently a *linear free energy* relationship.

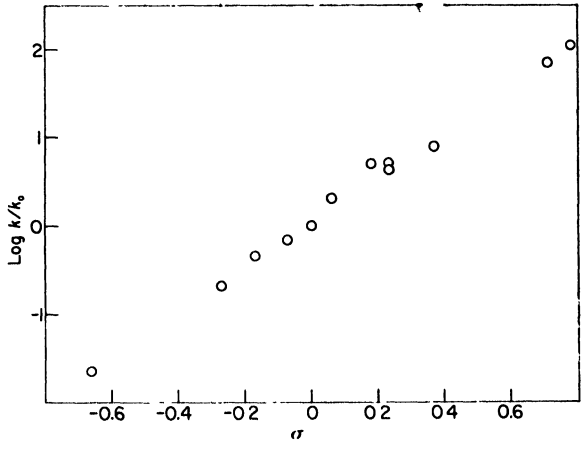


Fig. 5. Plot of $\log k/k_0$ for saponification of *m*- and *p*-substituted ethyl benzoates in 85% ethanol against Hammett σ values of the substituents. The slope, ρ, is +2.54. Data of C. K. Ingold and W. S. Nathan, and of D. P. Evans, J. J. Gordon, and H. B. Watson (78a).

Linear free energy relationships have been found between rate and/or equilibrium constants for many types of reaction series. The effects of *m*- and *p*-substituents on the rates and equilibrium constants of side-chain reactions of benzene derivatives are correlated by the Hammett $\rho\sigma$ relationship. The Hammett relationship has been extended to the correlation of rates of aromatic substitution reactions and of other reactions which have exceptionally large electronic demands. Electronic effects of *ortho* substituents and of substituents in aliphatic systems have been correlated in a group of linear free energy equations developed by Taft. The catalytic activities of acids and bases are correlated with their ionization constants through the Brönsted catalysis law. Rates of nucleophilic displacement reactions are represented in linear free energy relationships due to Swain

and to Edwards. Effects of solvents on the rates of solvolysis reactions are correlated in equations developed by Winstein and Grunwald.

All of these relationships are based on the empirical observation that plots of log k (or log K) for one reaction series against log k (or log K) for another series involving the same changing factor are linear or approximately so. Considering for the moment only relationships between rates, let us designate rate constants for the first series by k and for the second series by k'. The fact of a linear plot implies that

$$\log k - \log k_0 = a(\log k' - \log k'_0)$$

Here, k_0 and k'_0 are rate constants of corresponding reactions chosen as a standard of reference because of their simplicity or familiarity. The second (k') series is considered as a standard reaction series, chosen as such because it is simple or common or blessed with an abundance of good data. The differences ($\log k' - \log k'_0$) within the standard series define a parameter which is designated by a Greek or Roman letter. Each particular ($\log k' - \log k'_0$) value is characteristic of that particular representative of the factor (substituent, solvent, etc.) which changes within the standard series. The proportionality constant a is a parameter characteristic of the subsidiary (k) reaction series. (This proportionality constant is represented by various Greek or Roman letters in the several linear free energy equations.) In general, many subsidiary reaction series obey the relationship and each has its own characteristic a value. Clearly, a for the standard reaction series is 1.00.

Thus these linear free energy relationships involve two parameters: one ($\log k' - \log k'_0$) characteristic of the various representatives of the factor which changes through the reaction series, the other (a) characteristic of the reaction series themselves.

There are also some four-parameter linear free energy relationships. These are more flexible than the two-parameter equations and tend to give more precise correlations. On the other hand, the chemical significance of four-parameter relationships is less clear unless some of the parameters are defined in such a way that their meaning is inescapable.

Linear free energy relationships are useful in various ways. The fact that data from a reaction series are correlated by some linear free energy equation establishes a correspondence between the new reaction series and all the others which obey the relationship. This indicates that the effects of the variable factor (substituent, solvent, etc.) are regular within the new series. Lack of correlations, on the other hand, indicates that some special influences operate in the reaction series which does not fit.

Linear free energy relationships are useful for the prediction of rates (or equilibrium constants) for reactions which have not been subjected to

quantitative study. In favorable cases, fifty or a hundred rate constants can be predicted after only six have been measured with the expectation that the predicted values are accurate to ±20%. The magnitudes of the various parameters are useful as numerical indices of the factors they represent. Furthermore, it has been possible to dissect some of these parameters into components which represent finer aspects of the effect of structure on reactivity. Deductions (sometimes questionable) about reaction mechanism have been made from the magnitude of various parameters or from the fact that reaction series do or do not obey a linear free energy relationship. Linear free energy equations have even been used for the determination of structure (79). Their utility is wide.

The ways in which linear free energy relationships are customarily used by chemists are mathematically very simple. In many circumstances these simple mathematical methods are quite sufficient. In some cases, however, it is desirable or even imperative that more sophisticated procedures be used. If a bifunctional or polyfunctional reactant, transition state (for rate processes) or product (for equilibrium processes) is involved in the chemical reaction, account need be taken of the symmetry numbers of the species involved (80). Statistical procedures valuable in judging the quality of any correlation of a set of data with a linear free energy relationship have been developed by Jaffé (81,82). Such a statistical analysis can be particularly serviceable in the extreme case in which an apparent correlation is found, on analysis, to have practically no statistical significance. Methods for correlating dependence of rate on more than one variable have been presented by Miller (83).

2. The Hammett $\rho\sigma$ Relationship

This is the best known and most widely used of the linear free energy relationships. It is based on the empirical observation that plots of the logarithms of rate or equilibrium constants for many side-chain reactions of *meta*- or *para*-substituted benzene derivatives against the logarithms of the dissociation constants of the corresponding *meta*- or *para*-substituted benzoic acids are linear or nearly so. An example of such a linear plot is discussed at the beginning of this section (p. 210) and is displayed in Figure 5.

The equation for the linear plot is

$$\log k - \log k_0 = \rho(\log K - \log K_0) \qquad (12)$$

Here, K and K_0 are dissociation constants in water at 25°C. for, respectively, a *m*- or *p*-substituted benzoic acid and for benzoic acid itself, and k and k_0 are rate (or equilibrium) constants for the reaction of the *m*- or

p-substituted benzene derivative and for the parent benzene derivative lacking *m*- or *p*-substituents. ρ is a proportionality constant. The difference ($\log K - \log K_0$) is taken to define a parameter *sigma* which represents the (electronic) effect of each *meta* or *para* substituent.

$$\sigma \equiv \log K - \log K_0 \tag{13}$$

Sigma (σ) is a *substituent constant*, characteristic (supposedly) only of the substituent and its position (*meta* or *para*). As will soon be mentioned, *sigma* constants are not constant for *all* reactions, though their range of constancy is great.

Equation (12) is thus transformed into

$$\log k - \log k_0 = \rho\sigma \tag{14}$$

This is the Hammett $\rho\sigma$ relationship. *Rho* (ρ) is a *reaction constant*, characteristic only of the reaction series and not dependent on the particular substituents represented.

Sigma values are representative of the electronic effects of *m*- or *p*-substituents. Since electron-attracting substituents increase the strength of benzoic acids, they have positive σ values. Electron-releasing substituents, which decrease the strength of benzoic acids, have negative σ values. Hammett chose dissociation constants of benzoic acids to define substituent constants because of the availability of especially good data concerning that reaction series.

Rho values represent the susceptibility of the various reaction series to the electronic influence of *meta* or *para* substituents. A positive ρ value indicates that the reaction is accelerated, or that the equilibrium is shifted to the right, by electron-attracting substituents. A negative ρ value indicates the opposite. The magnitude of ρ is indicative of the sensitivity of the reaction to electronic effects; a high ρ value (positive or negative) indicates high sensitivity. The definition of σ values (Equation 13) implies that ρ is $+1.00$ for the dissociation of *m*- or *p*-substituted benzoic acids in water at 25°C.

Hammett's presentation of the $\rho\sigma$ relationship in his classic book of 1940 includes a list of σ values for several common substituents (78). Jaffé, in a thoroughgoing review and re-examination of the relationship, presented a much more extensive table of values (81). Jaffé's σ values are of mixed origin. His procedure was as follows: (*a*) Hammett's σ constants were accepted without change, and (*b*) were used to reckon reaction (ρ) constants for numerous reaction series; (*c*) with ρ values established, σ constants for additional substituents were then calculated and finally (*d*) each σ value for a substituent not listed by Hammett was averaged from data from several reaction series. Jaffé felt that ideally *sigma* for

any substituent should be the value which best fits the entire body of experimental data. The computation of such "best total fit" σ values would require the use of electronic computing equipment; the procedure Jaffé adopted was an approximation to his ideal consistent with resources available to him at the time.

As Jaffé himself pointed out, his procedure makes σ values to some extent dependent on the body of data available at the time of their evaluation. This is, of course, a shortcoming of all scientific knowledge. McDaniel and Brown (84), while admitting the value of "best total fit" *sigmas* for purposes of empirical correlation and prediction, advocated a return to the Hammett definition of σ constants, as per Equation (13), especially for their employment in evaluation of structural effects on re-

TABLE I
Hammett Sigma Values

Substituent	*meta* σ(84)	*para* σ(84)	*para* σ^+(91)	*para* σ^-(81)
—$N(CH_3)_2$		−0.83		
—NH_2	−0.16	−0.66		
—OH	0 12	−0 37		
—OC_6H_5	0 25	−0.32		
—OCH_3	0 12	−0 27	−0.78	
—CH_3	−0.07	−0.17	−0.31	
—$Si(CH_3)_3$	−0 04	−0.07	0.02	
—C_6H_5	0 06	−0.01	−0.18	
—H	(0 00)	(0.00)	(0.00)	
—COO^-	−0.1	0.0		
—$NHCOCH_3$	0.21	0.00		
—SCH_3	0.15	0.00	−0.60	
—F	0.34	0.06	−0.07	
—SO_3^-	0.05	0.09		
—I	0.35	0.18	0.14	
—Cl	0.37	0.23	0.11	
—Br	0.39	0.23	0.15	
—PO_3H^-	0.2	0.26		
—$COOC_2H_5$	0.37	0.45	0.48	0.68
—$SOCH_3$	0.52	0.49		0.73[a]
—$COCH_3$	0 38	0.50		0.87
—CF_3	0 43	0.54	0.61	
—SO_2NH_2	0.46	0.57		
—CN	0.56	0.66	0.66	1.00
—SO_2CH_3	0.60	0.72		1.05
—NO_2	0.71	0.78	0.79	1.27
—$N(CH_3)_3^+$	0.88	0.82		
—$S(CH_3)_2^+$	1.00	0.90		

[a] From Reference 85.

activity. Provided the data are good, σ constants derived from benzoic acid dissociation constants are not time-dependent.

The σ constants listed in Table I are taken from McDaniel and Brown (84). (The σ^+ and σ^- values have a special meaning as will be explained presently.)

If one has obtained kinetic data for a reaction series in which the identity of *meta* and/or *para* substituents is the variable factor, he can easily determine whether the data are correlated by the Hammett $\rho\sigma$ relationship by plotting the logarithms of the several rate constants against the ap-

TABLE II
Some Representative Hammett ρ Values[a]

Jaffé's reaction series no.	Reaction series	ρ value
8	Dissociation (equilibrium) of phenylacetic acids	+0.49
23a	Dissociation (equilibrium) of phenols	+2.11
46c	Saponification (rate) of methyl benzoates	+2.23
77	Reaction (rate) of phenoxide ions with ethylene oxide	−0.95
93a	Reaction (rate) of benzyl chlorides with OH^-	−0.33
95b	Reaction (rate) of benzyl chlorides with I^-	+0.79
121a	Reaction (rate) of dimethylanilines with CH_3I	−2.14
186a	Decomposition (rate) of benzoyl peroxides	−0 20
204	Condensation (rate) of 4-substituted-2-nitrochlorobenzenes with $NaOCH_3$	+3.94
[b]	Chlorination (rate) of monosubstituted benzenes by chlorine in acetic acid	−8.06
[b]	Solvolysis (rate) of α,α-dimethylbenzyl chlorides in 90% aqueous acetone	−4.50

[a] Taken from Jaffé's review (81) except as noted.
[b] Taken from Reference 91.

propriate σ constants chosen from Table I. If a linear plot is obtained, the slope is *rho* for the reaction series under the conditions of the kinetic measurements. Unless there are at least four linear points in such a plot, *rho* is not considered to be very well established.

Rates and equilibria of reactions of 3,4- and 3,5-disubstituted, as well as 3,4,5-trisubstituted, benzene derivatives are also well correlated by the Hammett equation (86). The equation used is:

$$\log k - \log k_0 = \rho\Sigma\sigma \qquad (15)$$

That is, the electronic influence of each substituent is separately exerted. This is not true, however, if one substituent interferes sterically with the

mesomeric effect of another, *ortho* to itself. Equation (15) can also be used if the two or more substituents are in different rings having an equivalent relationship to the reaction site, as in diphenylacetic acids.

Rho values generally vary with temperature. For many reaction series which follow the Hammett equation, the entropy of activation is essentially constant. If so, ρ is expected to be inversely related to absolute temperature. This relationship may be arrived at in various ways (87,88) of which the following is the simplest. From Equation (8), and if $\Delta S^{\ddagger} = \Delta S_0^{\ddagger}$

$$\log k - \log k_0 = (\Delta H_0^{\ddagger} - \Delta H^{\ddagger})/2.3RT = \sigma\rho$$

Rearranging,

$$\rho = ([(\Delta H_0^{\ddagger} - \Delta H^{\ddagger})]/2.3R) \; (1/T) \qquad (16)$$

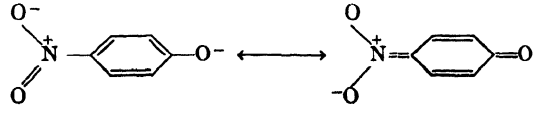
As a first approximation, none of the quantities on the right side of Equation (16) changes with temperature except the temperature itself; thus the inverse dependence.

Other reaction series which are correlated by the Hammett equation have variable $\Delta S^{\ddagger}$, but in such a fashion that a plot of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ is linear. That is, they obey the isokinetic relationship (see p. 205). For such reaction series, the absolute magnitude of ρ necessarily decreases as the isokinetic temperature is approached from below. At the isokinetic temperature ρ is zero, and above the isokinetic temperature the sign of ρ is reversed and its absolute magnitude *increases* with temperature. Leffler (72) and Wilmarth and Schwartz (73) have discussed this matter critically. Jaffé's review (81) lists instances of both increasing and decreasing ρ with increasing temperature.

From the above discussion it is obvious that theoretical arguments based on the magnitude or even the sign of *rho* can be misleading unless proper account is taken of the temperature factor (88).

3. Extended Hammett $\rho\sigma$ Relationships

In some reaction series there is an exceptional opportunity for *para*-substituents to accept or release electrons mesomerically in the initial and/or the transition (or final) state. For example, in the acidic ionization of phenols, a *p*-nitro group can enter into very strong mesomeric interaction with the ionized hydroxy group in the phenolate anion:



(17)

The corresponding resonance in the *p*-nitrophenol molecule is of much less importance. It is apparently for this reason that in attempting to correlate ionization constants of *m*- or *p*-substituted phenols, Hammett found that the *p*-nitro group behaved as though its σ constant were +1.27 instead of +0.78 as defined by Equation (13). The exalted σ value implies exalted powers of electron-acceptance. Consistent with this interpretation is the fact that the effect of the *m*-nitro group on the ionization of phenols is satisfactorily correlated with use of the ordinary σ value; resonance similar to that shown in Equation (17) is not conceivable for the *m*-nitrophenolate ion. This same exalted σ value for the *p*-nitro group was also required in other reaction series involving reactions of phenolate ions, of anilines, and of aniline derivatives.

Since 1940 several other *para* substituents with capacity for mesomeric electron acceptance have been found to require two substituent constants, one for most reaction series, another for those reaction series in which there is a special opportunity for mesomeric acceptance of electrons by the substituent. The special *sigma* value is designated σ^- and it is required in reactions of aniline and phenol derivatives and in nucleophilic substitution reactions at ring positions (89,90). σ^- values for several *p*-substituents, mostly from Jaffé's review, are listed in Table I.

Special *sigma* values are also useful for reactions that have a heavy demand for electron release by *para* substituents. These special values are designated σ^+ and are required for *para* substituents capable of mesomeric electron release. Brown and Okamoto (91) have used a single reaction series, the rates of solvolysis of *m*- and *p*-substituted α,α-dimethylbenzyl chlorides, to evaluate σ^+ values. The rates of solvolysis for a number of *meta*-substituents and their standard Hammett σ values were used to establish *rho* (−4.54) for this reaction series, and σ^+ values for *p*-substituents were then reckoned with use of the expression, $\log k/k_0 = \rho\sigma^+$. σ^+ values obtained in this way are listed in Table I. Brown and Okamoto have shown that with use of these special σ^+ constants, one may obtain good Hammett correlations of the rates of electrophilic substitution reactions at ring positions and of the rates or equilibria of a number of "electrophilic" side chain reactions. The latter are mostly nucleophilic substitutions in which the transition state involves considerable carbonium ion character at the α-carbon to the benzene ring.

In one reaction series, the acid dissociation of 1-hydroxypyridinium salts, the use of both σ^+ and σ^- values is necessary to obtain a good Hammett correlation (92). This is because of the dual electronic character of the heterocyclic *N*-oxide group.

We have seen that the special σ^- or σ^+ values are called for when the reaction series has a large demand for mesomeric electron release or ac-

ceptance by *p*-substituents, while the ordinary σ constants are preferred when the electronic demands of the reaction series are more moderate. *Sigma*, the substituent constant, is thus not truly a constant; it is a function of the electronic demands of the reaction series. It is, therefore, surprising that but two *sigma* values suffice to give reasonably good correlations of the rates and equilibrium constants of most reaction series. (In general, *p*-substituents which have σ^- values do not have σ^+, and vice versa.) One might expect that a continuous series of special *sigma* values would be needed according to the varying electronic requirements of the various reaction series. There is, indeed, some evidence that one special *sigma* value is not enough. Jaffé found, for instance, that the acid dissociation of thiophenols required the use of *sigma* values for *p*-$COCH_3$ and *p*-NO_2 between σ and σ^- in order for good correlation to be obtained (81). Again, he found that several σ values were required to properly correlate the effects of the *p*-hydroxy and the *p*-dimethylamino groups in various reaction series. Thus representation of substituent effects by the three types of *sigma* values, σ, σ^-, and σ^+, derives its justification from the circumstance that it works pretty well most of the time rather than from any powerful theoretical consideration or neat experimental evidence.

Indeed, van Bekkum, Verkade, and Wepster (92a) have strongly challenged representation of substituent effects by the three parameters, σ, σ^-, and σ^+. Regarding many *para*-σ values given by Equation (13) as possibly exalted because of mesomeric interaction with the carboxyl group, they based their analysis on the σ values (from Equation 13) of certain "primary" substituents (e.g., *m*-Br) which could not engage in such mesomerism. They constructed plots of log k versus σ for various reaction series, and assigned "secondary" substituents whatever σ values were necessary to assure linearity. This approach gave each "secondary" substituent a characteristic σ value for each reaction. The σ values for "secondary" substituents were in general broadly scattered; those for *p*-NO_2, for example, were almost evenly distributed between +0.78 and +1.4. This analysis deprives the customary σ, σ^-, and σ^+ values of much of the theoretical significance which has been assigned to them, but leaves them as valuable as ever for the empirical correlation of data.

The success of the Hammett relationship in correlating effects of meta and para substituents in reactions of benzene derivatives suggests its extension to the effects of substituents in other aromatic ring systems. Some progress has been made in this direction, especially for the naphthalene and quinoline systems, but relatively few *sigma* and *rho* values are as yet available (93–99).

In reactions of certain derivatives of polynuclear aromatic hydrocarbons, good correlations of rates with localization energies given by quantum me-

chanics have been obtained in several instances. For example, log k for solvolysis of α-arylethyl chlorides are linearly related to localization energies (100). So also are log k for reactions of arylmethyl chlorides with potassium iodide (101). Similar observations have been made concerning the rates of hydrolysis of ethyl esters and acid chlorides of arenecarboxylic acids (102,103) and the rates of reactions of arylamines with 2,4-dinitrochlorobenzene (104). Rates of aromtaic nucleophilic substitution in *aza* derivatives of polynuclear aromatic hydrocarbons show, however, only a qualitative correlation with quantum-mechanically calculated energies (105,106). Like other linear correlations of logarithms of rate constants, these also are linear free energy relationships.

4. Taft's Equations

A plot of log k for saponification of *ortho*-substituted ethyl benzoates against log K for dissociation of the corresponding benzoic acids *does not* approximate a straight line. This was shown by Hammett (78). Nor is a plot of log k for saponification of esters of aliphatic acids against log K for dissociation of these acids sufficiently regular to be called linear. The reason for scatter in such plots is that the effects of *ortho* substituents and aliphatic substituents on saponification rates are partly steric whereas the dissociation of carboxylic acids is comparatively insensitive to steric effects of neighboring substituents. Thus log K for dissociation of aliphatic or *o*-substituted benzoic acids represents principally polar (or electronic) effects while log k for ester saponification reflects the operation of both polar and steric effects. Since steric effects have no particular relationship to polar effects, it is small wonder that the plots are not linear. *meta* and *para* substituents are so far removed from the reaction sites that their effects on reaction rates and equilibria are almost entirely electronic; hence the success of the original Hammett relationship.

Robert W. Taft, Jr., has performed a powerful analysis of the effects of *ortho* and aliphatic substituents on rates and equilibria. He has developed procedures for separating polar (or electronic) effects from steric effects. He has evaluated parameters representing, separately, the polar effects and the steric effects of many *ortho* and aliphatic substituents. He has also made a convincing separation of the *sigma* constants of *meta* and *para* substituents into inductive and mesomeric components. Taft's contributions are of such significance, and so much interwoven with one another, that they are presented separately in this section. They are, however, properly to be regarded as extensions of the Hammett $\rho\sigma$ relationship.

This section is limited to a presentation of Taft's principal equations, of the way in which they have been employed to evaluate various parameters,

and of the manner in which other investigators can use these equations and parameters in the correlation of data. Taft has presented a thoroughgoing review and recapitulation of the development of his relationships (107). His more recent contributions are described in a review article (108) and in research papers (108–113).

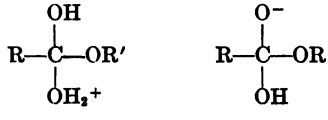
A. ALIPHATIC REACTIONS

In essence, Taft assumed that the change in free energy of activation within a reaction series may be represented as the sum of polar, steric, and resonance contributions. That is

$$\Delta\Delta F^{\ddagger} = \Delta\Delta F_P^{\ddagger} + \Delta\Delta F_S^{\ddagger} + \Delta\Delta F_R^{\ddagger} \tag{18}$$

Taft used the term "polar" to designate electron displacement effects, by either the inductive or the mesomeric mechanism, and "resonance" to designate effects of conjugation of the functional group with other parts of the molecule. The resonance factor is not primarily concerned with whether electrons are supplied to or taken from the functional group, but rather with changes in resonance stabilization as the reactants form the transition state. Equation (18) is not represented as being complete; Taft has acknowledged that hydrogen-bonding free energy terms should be included in special cases. An there is evidence that London forces affect the free energy of activation independently of the other factors (77).

With reference to Equation (18), if one compares reactions in which the conjugation ("resonance") effect is negligible and steric effects are constant, then differences in rate should reflect only polar factors. The acid and base catalyzed hydrolyses of an ester were selected as reactions meeting these specifications. Bender (114) had shown that both reactions proceed through intermediates such as (I) and (II) which differ only in the number of pro-



(I) (II)

tons. Since the proton is small, the steric requirements of acid and base catalyzed ester hydrolysis should be nearly identical and the ratio of rates, k_B/k_A, should depend only on polar factors. This idea was originated by Ingold (115) in 1930, but it received little attention until Taft took it up.

With the ratio of base to acid catalyzed ester hydrolysis rates as a measure of the polar effect of a substituent, it was then assumed that differences in this ratio in a series of esters were determined by differences in the polar factor and by the sensitivity of the ratio to the polar effects of

substituents. This was stated in equation form,

$$\log (k_B/k_A) - \log (k_B/k_A)_0 = \rho^* \sigma^* \tag{19}$$

Here σ^* is a parameter representing the polar effects of substituents and ρ^* is a parameter representing the sensitivity of the ratio to polar effects. Taft defined ρ^* as 2.48, and rearranged Equation (19) to the following form for the purpose of defining σ^* constants:

$$\sigma^* = (1/2.48) (\log (k/k_0)_B - \log (k/k_0)_A) \tag{20}$$

Essentially, the hydrolyses of ethyl esters of structure R—$COOC_2H_5$ were used for the evaluation of σ^* values although the actual procedure was refined so as to incorporate other series of esterification and ester hydrolysis rates and thereby to broaden the definition of σ^* values. The refined σ^* values do not, however, differ much from those based only on ethyl ester hydrolysis rates. σ^* was defined as equal to zero for R=CH_3; that is, k_0 refers to the hydrolysis of ethyl acetate. σ^* values for a number of aliphatic substituents are displayed in Table III; other values may be found in Taft's publications.

For reaction series in which the conjugation effect does not operate, Taft then assumed

$$\log k - \log k_0 = \rho^*\sigma^* + E_s \tag{21}$$

This can be considered as a modification of Equation (18) with $\Delta\Delta F_P^{\ddagger}$ being represented in a *rho-sigma* fashion as in the original Hammett equation. E_s is $\Delta\Delta F_S^{\ddagger}$; it is called a steric substituent constant but clearly is dependent on the steric requirements of the reaction as well as on the size of the substituent. For reaction series in which $\Delta\Delta F^{\ddagger}$ is not influenced by the size of substituents, this equation simplifies to

$$\log k - \log k_0 = \rho^*\sigma^* \tag{22}$$

For the evaluation of E_s values, the assumption was made that rates of acid-catalyzed ester hydrolysis and esterification are influenced by polar factors to a negligible extent. That is, ρ^* is zero. This assumption is justified by the fact that *rho* for acid-catalyzed hydrolysis of *m*- and *p*-substituted benzoate esters or esterification of benzoic acids is very small (between -0.2 and $+0.5$). Also, the absolute rates of acid-catalyzed hydrolysis of ethyl propionate and ethyl chloroacetate are nearly the same in spite of the great difference between the polar effects of the chlorine atom and the methyl group; the two groups are, however, similar in size. E_s was defined

$$E_s \equiv \log (k/k_0)_A \tag{23}$$

TABLE III
Aliphatic Substituent Constants

A. Alkyl and Aryl Substituents

Substituent name	Formula	σ^*	E_s
Phenyl	C_6H_5	+0.60	[a]
Hydrogen	H	+0.49	+1.24
Diphenylmethyl	$(C_6H_5)_2CH$	+0.40	−1.76
Benzyl	$C_6H_5CH_2$	+0.22	−0.38
β-Phenylethyl	$C_6H_5CH_2CH_2$	+0.08	−0.38
Methyl	CH_3	(0.00)	(0.00)
Ethyl	CH_3CH_2	−0.10	−0.07
n-Propyl	$CH_3CH_2CH_2$	−0.12	−0.36
n-Butyl	$CH_3CH_2CH_2CH_2$	−0.13	−0.39
Isobutyl	$(CH_3)_2CHCH_2$	−0 12	−0.93
Neopentyl	$(CH_3)_3CCH_2$	−0.16	−1.74
Isopropyl	$(CH_3)_2CH$	−0.19	−0.47
sec-Butyl	$CH_3CH_2CH(CH_3)$	−0.21	−1.13
tert-Butyl	$(CH_3)_3C$	−0.30	−1.54

B. Substituents of the Type X—CH_2—

Substituent	X of XCH_2—	σ^*	E_s
$(CH_3)_3\overset{+}{N}—CH_2$	$(CH_3)_3\overset{+}{N}$	+1.90	
$CH_3SO_2CH_2$	CH_3SO_2	+1.32	
$NCCH_2$	CN	+1.30	
FCH_2	F	+1.10	−0.24
$ClCH_2$	Cl	+1.05	−0.24
$BrCH_2$	Br	+1.00	−0.27
CF_3CH_2	CF_3	+0 92	
ICH_2	I	+0.85	−0.37
$C_6H_5OCH_2$	C_6H_5O	+0.85	−0.33
CH_3COCH_2	CH_3CO	+0.60	
$HOCH_2$	HO	+0.56	
CH_3OCH_2	CH_3O	+0.52	−0.19
$ClCH_2CH_2$	$ClCH_2$	+0.38	−0.90
CH_3	H	(0.00)	(0.00)

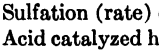
[a] E_s for phenyl cannot be obtained via Equation (23) because the resonance factor intervenes.

Again, k_0 refers to the hydrolysis of ethyl acetate; that is, E_s is arbitrarily set as equal to zero for $R=CH_3$. It should be emphasized that E_s values defined in this way refer to the acid-catalyzed ester hydrolysis reaction. If another type of reaction series were used to evaluate E_s, the values obtained would in all likelihood follow the same qualitative order as Taft's but they might not parallel Taft's values quantitatively.

E_s values for several substituents are also listed in Table III.

With a large number of σ^* constants at hand, Taft was in a position to test the general validity of Equation (22). This equation may be considered to be the aliphatic version of the Hammett relationship, applicable in reaction series in which steric and conjugation factors do not cause differences in rate. This equation survived the test very well; good linear plots of log k against σ^* were obtained in a number of series. A representative plot is shown in Figure 6. ρ^* values for a number of aliphatic reaction series correlated by Equation (22) are listed in Table IV. If rates within a reaction series are correlated by Equation (22), it is implied that differences in rate do not arise to any significant extent from steric or conjugation factors.

TABLE IV
Some Representative Taft ρ^* Values for Aliphatic Reactions[a]

Taft's reaction series no.	Reaction series	ρ^* value
3	Ionization (equilibrium) of carboxylic acids, RCOOH	+1.72
4	Acid catalyzed hydrolysis (rate) of acetals, $RCH(OEt)_2$	−3.65
10	Sulfation (rate) of alcohols, ROH	+4.60
25	Acid catalyzed hydrolysis (rate) of ethylene oxides, 	−1.83
28	Solvolysis (rate) of toluenesulfonate esters, RCH_2OSO_2Ar, in ethanol	−0.74
29	Substitution (rate) in reactions of alkyl bromides, RCH_2Br, with thiophenoxide ion	−0.61

[a] Selected from Table IX of Reference 107.

The assumption that ρ^* is zero for acid-catalyzed ester hydrolysis implies that the ρ^* of Equation (19) is identically ρ^* for the saponification of ethyl esters. As was mentioned above, this ρ^* was arbitrarily assigned the value of +2.48; all the ρ^* values in Table IV are relative to it. This asssignment was made because it put ρ^* for aliphatic reactions on about the same scale as the Hammett ρ for corresponding reactions of *m*- and *p*-substituted benzene derivatives. Thus, this value of +2.48 compares with ρ for the saponification of *m*- and *p*-substituted ethyl benzoates varying between +2.3 and +2.6, depending on the conditions of temperature and solvent. Also, when ρ^* are defined with respect to this standard, then ρ^* values for the (equilibrium) dissociation of aliphatic acids and for the

general acid catalyzed dehydration of acetaldehyde hydrate by aliphatic acids are nearly the same as ρ values for the corresponding reactions of *m*- and *p*-substituted benzoic acids.

The substituent constants of Table III show several features in accord with long standing concepts of electronic effects in aliphatic systems. The electron-releasing effect of the ethyl group is but slightly greater than that of the methyl group, and the further increase in electron-release on going to the *n*-propyl and *n*-butyl groups is so slight as to be hardly distinguishable. In the series methyl, ethyl, isopropyl, *tert*-butyl, electron-release increases in the order mentioned (the inductive order). In groups of type XCH_2, the intervening CH_2 group is expected to filter out mesomeric effects and transmit only inductive effects. It is therefore reasonable that the

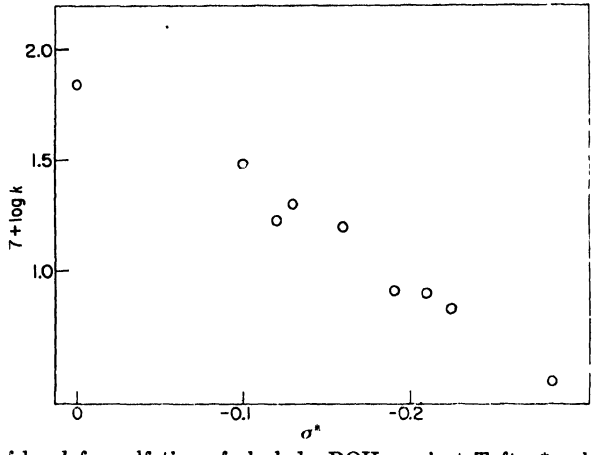


Fig. 6. Plot of log k for sulfation of alcohols, ROH, against Taft σ^* values for the R groups. Data of N. C. Deno and M. S. Newman (115a).

order of electron attraction by the halogens is the inductive order, F > Cl > Br > I. The fact that the CH_3OCH_2 and $HOCH_2$ groups attract electrons more than does CH_3 is understood on the same grounds. The trimethylammonio, methylsulfonyl and cyano groups have long been considered to have strong electron-attracting inductive effects, and it is reassuring to see high σ^* values for the corresponding XCH_2 groups.

It was recognized years ago that methylene groups act as insulators towards transmission even of inductive effects; inductive effects are known to damp out rapidly as they pass along a saturated chain. The σ^* values in Table III give quantitative expression to this effect. Comparison of $\sigma^* = +1.05$ for $ClCH_2$ with $\sigma^* = +0.38$ for $ClCH_2CH_2$ shows that the extra methylene group has cut σ^* by a factor of 1.05/0.38 or 2.8. Similarly,

σ^* for C_6H_5 (+.60) divided by σ^* for $C_6H_5CH_2$ (+.22) is 2.7, and σ^* for $C_6H_5CH_2$ divided by σ^* for $C_6H_5CH_2CH_2$ (+.08) is 2.8. The introduction of a methylene group thus has reduced σ^* by about 2.8-fold in three instances; Taft has cited other instances in which the same factor operates.

The fact that Taft's σ^* values are so strongly in accord with previous conceptions robs them of novelty but increases confidence in them. One does not hesitate to use them to represent electronic (polar) effects in aliphatic systems just as one uses Hammett σ values to represent electronic effects of *meta* and *para* substituents.

Taft's steric substituent constants (E_s) are also in harmony with evidence from other sources. For example, the expected orders of size, *tert*-butyl > isopropyl > ethyl > methyl, and neopentyl > isobutyl > *n*-propyl, are correctly represented by E_s values.

B. REACTIONS OF *ortho* SUBSTITUTED BENZENE DERIVATIVES

Essentially the same procedure was used as with aliphatic reactions. Equation (20) was again used for the evaluation of σ^* values, and Equation (23) for the evaluation of E_s. It should be noted, though, that a different ester is used as a standard for evaluation of σ^* than for evaluation of E_s. σ^* values are relative to zero for H, as are Hammett σ values for *m*- and *p*-substituents; that is, ethyl *benzoate* is the standard ester. (This is a change from the procedure followed in most of Taft's publications, and was suggested in a personal communication from Professor Taft.) E_s values are relative to zero for CH_3; that is, ethyl *o-toluate* is the standard ester. Ethyl benzoate cannot be used as a standard for the evaluation of E_s values because its hydrolysis rates are affected by resonance contributions to the free energy of activation much more than are rates of hydrolysis of *o*-substituted ethyl benzoates. (Almost any *ortho* substituent interferes with resonance between the carbethoxy group and the benzene ring.) Equation (20) makes allowance for the resonance factor, but Equation (23) does not.

Taft's values of σ^* and E_s for *ortho* substituents are listed in Table V. Hammett's σ values for the corresponding *para* substituents are, for comparison, also tabulated. In view of the generally recognized parallelism of polar effects from *ortho* and *para* positions, it is reassuring that the σ^* values for *ortho* substituents are very near to the σ values of the same substituents in the *para* position. Confidence in the E_s values is also supported by comparison with other data; the order of size indicated by the E_s values is qualitatively similar to that indicated by racemization rates of optically active biphenyl derivatives (117).

TABLE V
Substituent Constants for *Ortho* Substituents

Substituent	σ^{*}[a]	E_s[b]	σ_p[c]
OCH_3	−0.41	+0.99	−0.27
OC_2H_5	−0.23	+0.90	−0.24
CH_3	−0.17	(0.00)	−0.17
H	(0.00)	[d]	(0.00)
F	+0.24	+0.49[e]	+0.06
Cl	+0 20	+0.18	+0.23
Br	+0.21	0.00	+0.23
I	+0.21	−0.20	+0.18
NO_2	+0.78	−0.75	+0.78
C_6H_5		−0.90	

[a] σ^{*} values are relative to zero for H, and are taken from Reference 116.

[b] E_s values are relative to zero for CH_3.

[c] From Reference 84.

[d] E_s for H cannot be calculated by Equation (23) owing to the intrusion of resonance factors.

[e] The E_s given for F is considered less reliable than the rest.

C. FURTHER DEVELOPMENTS

Taft has shown that a linear steric energy relationship applies within a

$$\log k - \log k_0 = \delta E_s \tag{24}$$

restricted group of reaction series. If this equation applies, differences in rate must be almost wholly due to steric effects. A more general equation represents both electronic and steric effects:

$$\log k - \log k_0 = \rho^{*}\sigma^{*} + \delta E_s \tag{25}$$

This equation has been found to give a good account of data in one extensive reaction series (112).

For reaction series in which steric effects are negligible but conjugation (resonance) effects are not, it is, in principle, possible to evaluate the conjugation effect by use of the equation

$$\log k - \log k_0 = \rho^{*}\sigma^{*} + \Delta\Delta F_R^{\ddagger}$$

This equation can be used if the reaction series includes enough nonconjugating substituents to establish the value of ρ^{*} and if there is some means of evaluating σ^{*} for the conjugating substituents. Kreevoy and Taft (118) used an equation of this type to evaluate deviations from linearity in a simple $\rho^{*}\sigma^{*}$ plot which were ascribed to hyperconjugation.

It is mentioned above that σ^{*} values for XCH_2 groups (see Table III) represent the operation of the inductive but not of the mesomeric effects

of the substituents X. With reference to an important paper by Roberts and Moreland (119), Taft has taken $0.45\sigma^*_{XCH_3}$ as representing the inductive component of the Hammett σ value for either *meta* or *para* substituents. $0.45\sigma^*_{XCH_3}$ is labelled σ_I. The mesomeric component of the Hammett σ value is then obtained by subtracting σ_I from σ:

$$\sigma_R = \sigma - \sigma_I$$

This constitutes an analysis of the Hammett σ values into their inductive and mesomeric components. The results of this analysis are qualitatively in harmony with evidence from other sources.

D. USE OF TAFT'S EQUATIONS AND PARAMETERS

When kinetic data for a series of reactions of aliphatic or *o*-substituted benzene derivatives become available, it is interesting to see whether they can be correlated by use of Taft's equations and parameters. This is similar to the common practice of seeing whether a new set of data concerning *m*- and *p*-substituted benzene derivatives can be correlated by the Hammett equation. But there is a difference: there is but one Hammett equation (complicated it is true by a duality of *sigma* values for some substituents), but there are several Taft equations.

Probably the best approach is to start with a plot of log k against σ^* for the several substituents represented in the series. A linear plot indicates the applicability of Equation (22); the slope is ρ^*. If this first plot is not linear, a plot of log k against E_s should next be tried; if it is linear, Equation (24) is shown to be applicable, and the slope is δ. If neither is linear, a plot of log $(k/k_{CH_3}) - E_s$ against σ^* might be tried; if it is linear, Equation (21) prevails. If nonlinearity persists, it is possible that Equation (25) would give a good account of the data; the paper by Pavelich and Taft (112) should be consulted. All the while one should bear in mind that deviations from linearity may be due to conjugation of some substituents with the reacting functional group.

A note of caution is now necessary. One must be on guard against a coincidental fit. If the plot comprises only a few points (say four or five), representing small changes in steric and/or polar effects, it is possible that linearity will be approached not because of any fundamental adherence to the relationship being tested but rather because of random variations of individual constants. The possibility of a coincidental fit is much diminished if a larger number of points is plotted, or if wide variations in structure are represented in the plot.

If Equation (22) applies, it is implied that steric effects do not cause differences in rate within the series. If Equation (24) prevails, electronic

effects are shown not to cause changes in rate. If Equation (21) or (25) leads to good correlation of the data, both steric and electronic effects are shown to be important in determining relative reactivity.

The sign of ρ^* reveals whether the reaction is accelerated or retarded by electron-withdrawing substituents, and the magnitude of ρ^* indicates the sensitivity of the reaction to electronic effects. In interpreting ρ^*, one must bear in mind that if the reaction series obeys the isokinetic relationship the sign of ρ^* will change at the isokinetic temperature. If data for only one temperature are available and the magnitude of ρ^* is small, its sign has questionable significance.

If for one reason or another a linear plot according to Equation (21), (22), (24), or (25) is expected but not obtained, the deviation from linearity may signify a change in mechanism. For example, in the otherwise linear plot of log (k_B/k_A) against σ^* for the hydrolysis of alkyl acetates in water, the point for *tert*-butyl acetate deviates sharply. It is known from other evidence that the mechanism of acid-catalyzed hydrolysis of *tert*-butyl esters is different from that of primary and secondary alkyl esters (120).

An important application of Taft's substituent parameters is their use for the quantitative representation of electronic and steric effects in aliphatic systems and in *o*-substituted benzene derivatives. Related to this is Taft's own use of substituent parameters for the detailed analysis of substituent effects on reactivity, particularly in his later papers.

E. JUSTIFICATION OF TAFT'S EQUATIONS

A careful examination of Taft's derivations shows that many assumptions are involved. Several of the assumptions, although reasonable, are difficult to support through rigorous argument. Also, some of the procedures used to define parameters might be questioned; indeed Taft has made small changes in his assumptions and definitions of parameters during the development of his relationships. This lack of rigor is repeatedly pointed out by Taft. His case for the worth of his methods rests not so much on the absolute validity of his assumptions and definitions as on the fact that the results are so eminently sensible with respect to other knowledge of steric and electronic effects. The results are sensible not only qualitatively, but also with respect to fine quantitative detail. It is also to be noted that, although the fundamental assumptions and definitions are to some extent based on intuition, the rest of Taft's procedures allow no scope for the exercise of subjective choice; the various parameters are derived with mathematical objectivity from the data.

5. The Brönsted Catalysis Law

A. GENERAL ACID CATALYSIS AND SPECIFIC LYONIUM ION CATALYSIS

The rate of an acid catalyzed reaction in water solution obviously depends on the acid concentration. But there are different kinds of acid concentration to consider, and different kinds of dependence on acidity. Acid concentration is often adequately represented by the concentration of oxonium ions, or pH, and the rates of many acid catalyzed reactions are dependent only on this factor. In such cases it matters not what buffer system governs the pH. This is known as *specific oxonium ion catalysis.* The other principal category is dependence of the rate on the concentration of each and every acid species present in the solution. Each acid species catalyzes the rate according to its own ability, described by its catalytic constant. This is known as *general acid catalysis.*

Recognition of these two forms of acid catalysis, of their scopes and of their significance with respect to reaction mechanism is due to a number of investigators among whom H. M. Dawson, J. N. Brönsted, L. P. Hammett, and C. G. Swain are especially to be cited. Currently the leading researcher and writer in this field is R. P. Bell (121,122).

Let us imagine that the acids HA_1, HA_2, . . . HA_i are present in the aqueous solution, and that (as is frequently but not always so) rates depend on the first powers of acid concentrations. Also, let us suppose that, aside from the participation of acids, the reaction is first order in substrate S. Then, for specific oxonium ion catalysis,

$$\text{rate} = k_{obs}[S] = k[H_3O^+][S]$$

And for general acid catalysis

$$\text{rate} = k_{obs}[S] = k[H_3O^+][S] + k_1[HA_1][S] + k_2[HA_2][S] + \ldots k_i[HA_i][S]$$

The best way to determine whether a reaction is general acid catalyzed or specific oxonium ion catalyzed is to determine the reaction rate in a series of buffers of constant pH but varying absolute concentration of the buffer constituents. If possible, the several buffer solutions should be adjusted to constant ionic strength by compensation with an inert salt. If the reaction rate depends only on pH (specific oxonium ion catalysis), it will be constant throughout the series of buffers. If the reaction rate depends on the concentration of each and every acid present it will increase with increasing concentration of the acid constituent of the buffer. For example, a series of acetate buffers, containing sodium acetate and acetic acid in 1:1 ratio, might be used with the absolute concentration of each

constituent being 0.01M (HOAc 0.01M, NaOAc 0.01M), 0.04M, 0.07M, 0.10M, and 0.13M. If the reaction is general acid catalyzed, the apparent rate constants for the several buffers will be related by the equation

$$k_{obs} = k[H_3O^+] + k'[HOAc]$$

k and k' are the catalytic constants for oxonium ion and for acetic acid respectively. Their values can be determined from a plot of k_{obs} against [HOAc]; the slope is k' and the intercept $k[H_3O^+]$.

Specific oxonium ion catalysis is observed when a proton is transferred to the substrate in equilibria preceding some slow reaction of the conjugate acid of the substrate:

$$H_3O^+ + S \rightleftharpoons SH^+ + H_2O \quad (26)$$

$$HA + S \rightleftharpoons SH^+ + A^- \quad (27)$$

$$A^- + H_3O^+ \rightleftharpoons HA + H_2O \quad (28)$$

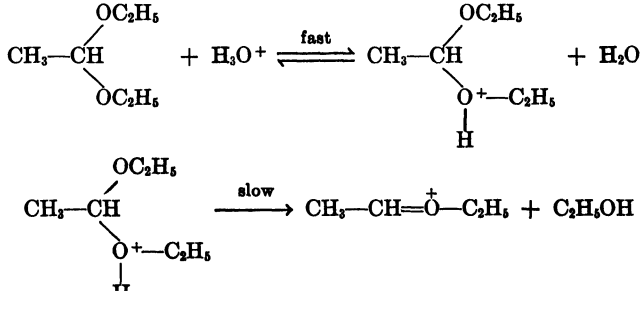
$$SH^+ \xrightarrow{\text{slow}} \text{products} \quad (29)$$

(Other reversible steps may also precede the slow step.)

Here either oxonium ion (Equation 26) or some other acid HA (Equation 27) can furnish a proton to the substrate. However, owing to the existence of equilibrium (28), the sum of Equations (27) and (28) is Equation (26), and it is *mathematically* sufficient to represent protonation of the substrate by Equation (26) alone. If K is the equilibrium constant of reaction (26) and k the rate constant for reaction (29), the overall rate constant is

$$k_{obs} = kK[H_3O^+] \quad (30)$$

Reaction (29) may be unimolecular, as written, or it may involve combination of SH^+ with some other species. The hydrolyses of acetals, of carboxylic amides, and of 4-(*p*-sulfophenylazo)-1-naphthyl methyl ether (123) are examples of specific oxonium ion catalyzed reactions. The accepted mechanism for acetal hydrolysis is



$$CH_3CH{=}\overset{+}{O}C_2H_5 + 2H_2O \xrightarrow{\text{fast}} CH_3C(OC_2H_5)(OH)H + H_3O^+$$

General acid catalysis is observed when, one way or another, the whole of the catalyzing acid is present in the rate-determining transition state. Three principal cases can be recognized:

1. Transfer of a proton from the acid to some other species is rate-determining:

$$S + HA \xrightarrow{\text{slow}} SH^+ + A^-$$

The overall rate constant is defined by:

$$k_{obs} = k_{HA}[HA]$$

k_{HA} is a catalytic constant characteristic of the acid HA. S may be either the substrate as introduced or some other species in equilibrium with the original reactants. An example is the reconversion of the nitroethane anion to nitroethane (124):

$$CH_3-\overset{-}{C}H-NO_2 + HA \rightarrow CH_3CH_2NO_2 + A$$

2. The acid and the substrate combined reversibly to form a complex which reacts slowly to form products. Reaction (31) may be unimolecular,

$$S + HA \rightleftharpoons S\cdot HA \qquad \text{equil. const., } K$$

$$S\cdot HA \xrightarrow{\text{slow}} \text{products} \qquad \text{rate const., } k \qquad (31)$$

as written, or it may involve combination of S·HA with some other species. The overall rate constant is defined: $k_{obs} = kK[HA]$.

3. A proton is transferred reversibly to the substrate and the conjugate acid of the substrate undergoes a slow proton transfer reaction with the conjugate base A of the catalyzing acid.

$$HA + S \rightleftharpoons SH^+ + A \qquad \text{equil. const., } K \qquad (32)$$

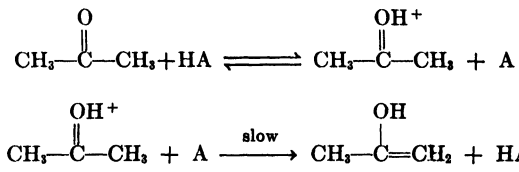
$$SH^+ + A \xrightarrow{\text{slow}} \text{products} \qquad \text{rate const., } k \qquad (33)$$

The overall rate constant is given by:

$$k_{obs} = kK[HA] \qquad (34)$$

A common variation involves formation of the species S by some prior reversible reaction. In another variation, SH^+ combines reversibly with some other reactant prior to the rate-determining step (33). Though seemingly indirect, this is a common type of general acid catalysis. Exam-

ples include the dehydration of acetaldehyde hydrate, the mutarotation of glucose and the enolization of ketones (122,125–127). The acid catalyzed enolization of acetone occurs as follows.



It is doubtful whether any major chemical phenomena have been blessed with names more confusing than specific oxonium ion catalysis and general acid catalysis. The pH-dependent type of acid catalysis is called specific oxonium ion catalysis because, it is said, the only effective catalyst is oxonium ion. This is true in a mathematical sense (see Equation 30), but it is not true that oxonium ion is the only acid which can furnish a proton to the substrate (see Equations 26–28). Since the catalyzed rate is determined by a *general* property of the medium, the pH, the pH-dependent type could just as reasonably be called general acid catalysis. As for the type dependent on the concentration and the catalytic power of each and every acid in the solution, called general acid catalysis, it could equally well be called specific acid catalysis because it depends on the *specific* concentration and catalytic ability of each acid present. The chemist is therefore advised to depend on rote memory rather than reason in keeping the names of these two types of catalysis straight in his mind.

This discussion of acid catalysis has so far concerned only water solutions. The principles are also applicable in other basic solvents, such as alcohols, carboxylic acids, and amines. In these solvents one distinguishes, using the conventional names, general acid catalysis from *specific lyonium ion catalysis*. The lyonium ion is that ion formed by addition of a proton to a solvent molecule; in ethanol, the lyonium ion is $C_2H_5OH_2^+$.

Distinguishing the two types of acid catalysis in a nonaqueous solvent is not as simple as in water. The diagnostic experiment, it will be remembered, involves determining reaction rate in a series of buffers of constant buffer ratio although varying absolute concentration of the buffer constituents, and at constant ionic strength. The difficulty is with the concept of ionic strength in solvents such as ethanol. Because ion pairing is extensive in ethanol, salt effects tend to be specific and they are not adequately represented by the ionic strength (26,128,129). One procedure is to add no salt other than the buffer constituent and to judge whether the variation in rate between the several buffer concentrations is within the range of salt effects. If the variation is well beyond the magnitude of salt effects, general acid catalysis may be confidently recognized. If it is within the magnitude

of salt effects, a firm decision must await a detailed understanding of the kinetic salt effects of the salts involved in the experiments.

B. GENERAL BASE CATALYSIS AND SPECIFIC LYATE ION CATALYSIS

These are the exact counterparts of the two forms of acid catalysis just described. The category of base catalysis in which rate (in water solution) is dependent only on pH is called *specific hydroxide ion catalysis.* The category in which rate depends on the concentration and catalytic power of each and every base in the solution is called *general base catalysis.* The one is distinguished from the other by the same type of diagnostic experiment: the catalyzed rate is measured in a series of buffer solutions of constant pH and constant ionic strength but varying absolute concentrations of the buffer constituents. If the catalyzed rate is constant in the several runs, specific hydroxide ion catalysis is at hand. If it increases linearly with the concentration of the buffer constituents, one has general base catalysis.

Since the same type of experiment is used to diagnose both acid and base catalysis, the question arises: How is one to know whether increased rate with increased absolute buffer concentration indicates general acid or general base catalysis? Is it the increased concentration of the acidic or the basic constituent of the buffer which is responsible for the increase in rate? Often this equation can be answered very simply; many acid catalyzed reactions are strongly catalyzed by sulfuric acid and not at all by sodium hydroxide, and vice versa. But there are cases in which such a blunt approach will not work. For example, an acid catalyzed reaction of an amine may be stopped dead by addition of a strong acid which ties up the amine as the corresponding ammonium ion. A more subtle method is to study the dependence of rate on buffer concentration at more than one pH (130). Imagine that acetate buffers are being used; for pH 4.75 (the half-neutralization pH) one might use solutions in which [HOAc] and [OAc^-] were, respectively, 0.005 and 0.005M, 0.01 and 0.01M, 0.02 and 0.02M, etc. For pH 5.75, [OAc^-] would have to be ten times [HOAc]; [HOAc] and [OAc^-] might be, respectively, 0.005 and 0.05M, 0.01 and 0.1M, 0.02 and 0.2M, etc. If the reaction were general *acid* catalyzed, a plot of the catalyzed rate versus [HOAc] would have the same slope at both pH values. However if it were general *base* catalyzed the slope of a plot of rate versus [HOAc] at pH 5.75 would be much greater than at 4.75 because in the buffers at the higher pH [OAc^-] increases in absolute magnitude much faster than it does at the lower pH.

Specific hydroxide ion catalysis is observed when the bases effect an initial reversible proton removal from the substrate followed by a slow

reaction of the conjugate base of the substrate:

$$OH^- + SH \rightleftharpoons S + H_2O \quad (35)$$

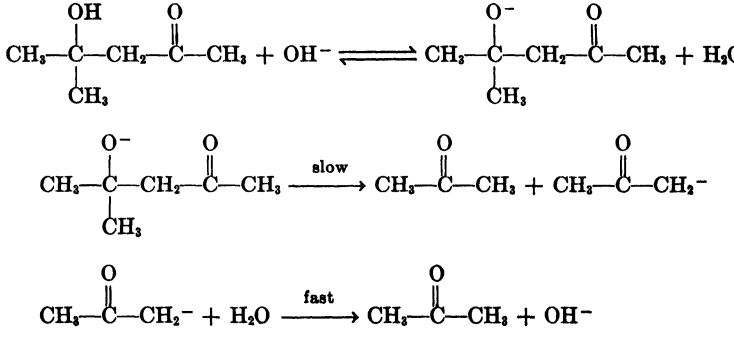
$$B + SH \rightleftharpoons BH + S \quad (36)$$

$$BH + OH^- \rightleftharpoons B + H_2O \quad (37)$$

$$S \xrightarrow{\text{slow}} \text{products} \quad (38)$$

(Other reversible steps may also precede the slow step.)

Just as specific oxonium ion catalysis does not mean that the oxonium ion is the only effective acid in the system, so also specific hydroxide ion catalysis does not mean that hydroxide ion is the only effective base. What it does mean is that the base catalyzed reaction rate is mathematically dependent only on hydroxide ion concentration because the sum of Equations (36) and (37) is equal to Equation (35). The overall rate constant is defined: $k_{obs} = kK[OH^-]$. Here, K is the equilibrium constant of Equation (35) and k is the rate constant for Reaction (38). It is understood that Reaction (38) may be unimolecular, as written, or bimolecular. An illustrative example of specific hydroxide ion catalysis is the depolymerization of diacetone alcohol:



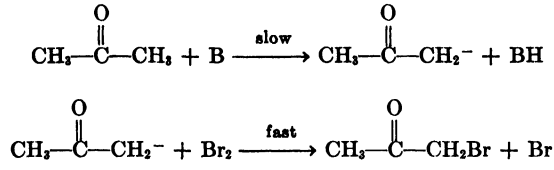
General base catalysis is observed when, one way or another, the whole of the catalyzing base is present in the rate-determining transition state. Three principal cases can be recognized:

1. Transfer of a proton to the base is rate-determining:

$$B + SH \xrightarrow{\text{slow}} BH + S$$

The overall rate constant is defined: $k_{obs} = k_B[B]$, where k_B is the catalytic constant of the base B. SH may be either the substrate as introduced or some species in reversible equilibrium with the original reactants. This case is exemplified by the many reactions in which removal of a proton

from a carbon atom is the slow step, among which are the neutralization of nitroparaffins (131) and the conversion of ketones to their enolate ions. The general base catalyzed halogenation of ketones is illustrative:



2. The base and the substrate combine, reversibly, to form a complex which reacts slowly to form products.

$$\mathrm{B} + \mathrm{SH} \rightleftharpoons \mathrm{SH \cdot B} \qquad \text{equil. const., } K$$

$$\mathrm{SH \cdot B} \xrightarrow{\text{slow}} \text{products} \qquad \text{rate const., } k \qquad (39)$$

Reaction (39) may be unimolecular, as written, or it may involve combination of SH·B with some other species. The overall rate constant is defined: $k_{obs} = kK[\mathrm{B}]$.

3. A proton is removed reversibly from the substrate and the conjugate base of the substrate undergoes a slow proton transfer reaction with the conjugate acid BH of the catalyzing base.

$$\mathrm{B} + \mathrm{SH} \rightleftharpoons \mathrm{BH} + \mathrm{S} \qquad \text{equil. const., } K$$

$$\mathrm{S} + \mathrm{BH} \xrightarrow{\text{slow}} \text{products} \qquad \text{rate const., } k \qquad (40)$$

The overall rate constant is defined: $k_{obs} = kK[\mathrm{B}]$. An important variation of this case involves formation of the species SH by some prior reversible reaction. In another variation, S combines reversibly with some other reactant prior to the rate-determining step (40). This apparently indirect but entirely legitimate type of general base catalysis appears to obtain in the reaction of *n*-butylamine with ethyl formate (26). The preferred mechanism is presented in Equations (58–60), page 272.

C. THE BRONSTED CATALYSIS LAW

It has been shown that for a general acid catalyzed reaction, the catalytic activity of any acid can be represented by a catalytic constant, k_A. It is an empirical fact that plots of log k_A against log K_A, K_A being the dissociation constant of the acid, are linear when a series of acids of a single type (carboxylic acids, anilinium ions, etc.) are considered. The line can be represented by the equation.

$$\log k_A - \log k_{A,0} = \alpha (\log K_A - \log K_{A,0}) \qquad (41)$$

which is of the same form as the typical Hammett and Taft *rho-sigma* equations. It is clear that if a series of *m*- and *p*-substituted benzoic acids are under consideration, ($\log K_A - \log K_{A,0}$) is σ and α is ρ. However, it is customary to use another representation of the linear plot:

$$\log k_A = \alpha \log K_A + \log G \tag{42}$$

or

$$k_A = GK_A^{\alpha} \tag{43}$$

Whichever way the line is represented, α is its slope. Comparison of (41) and (42) shows that

$$G = k_{A,0}/K_{A,0}^{\alpha}$$

Most discussions of general acid catalysis ignore G and its value and focus attention on α. α is always positive, and its magnitude is between zero and 1.00. α indicates the degree of dependence of the reaction on the strength of the catalyzing acids.

Similarly, the catalytic efficiencies of bases in general base catalysis can be represented

$$\log k_B = \beta \log K_B + \log G$$

or

$$k_B = GK_B^{\beta}$$

Again, G is pretty much ignored and β is emphasized. β has positive values between zero and 1.00.

Just as for acids, the Brönsted Catalysis Law for bases holds only so long as bases of similar type are under consideration. For example, in the general base catalyzed decomposition of nitramide, the points in a plot of $\log k_B$ versus $\log K_B$ for carboxylate ions fall on one line and those for nuclear substituted anilines fall on another. The two series require slightly different β and G values (132).

General acid (or base) catalysis is difficult to observe if the value of α (or β) is near to either extreme of its possible values, that is, near to zero or near to 1.00. This limitation is most easily seen with reference to a specific case. Let us consider some reaction catalyzed by acetic acid in water solution. Three acids must be considered, H_3O^+, HOAc, and H_2O^+; their K_A values are 55.6, 1.8×10^{-5}, and 1.8×10^{-16}, respectively. (One might suppose K_A for H_3O^+ to be 1.0 and for water to be 1×10^{-14}. But since K_A is defined as the equilibrium constant of the reaction, $HA \rightleftharpoons H^+ + A^-$, namely as $[H^+][A^-]/[HA]$, the concentration of water must appear in the numerator when in reckoning K_A for H_3O^+ and in the denominator

for H_2O.) The catalytic efficiencies of oxonium ion and acetic acid are related by

$$\log k_{H_3O^+} - \log k_{HOAc} = \alpha[\log 55.6 - \log (1.8 \times 10^{-5})] = 6.48\alpha$$

When α is 0.5, oxonium ion is then 1.74×10^3 times as effective a catalyst as acetic acid. If $[H_3O^+]$ is set at $10^{-5}M$ and [HOAc] at $0.1M$ by use of a simple acetate buffer system, the acetic acid catalyzed rate is then $0.1/(10^{-5})(1.74 \times 10^3)$ or 5.7 times the oxonium catalyzed rate. General acid catalysis is thus easily demonstrable. But if α is 0.9, oxonium ion is 6.9×10^5 as effective a catalyst as acetic acid and it is necessary to have acetic acid 6.9×10^4 times as concentrated as oxonium ion if the acetic acid catalyzed reaction is to be even one tenth as fast as that catalyzed by the oxonium ion. Now, if $[H_3O^+]$ is set at 1.8×10^{-6} by use of a 10:1 acetate:acetic acid buffer, [HOAc] must be $(6.9 \times 10^4)(1.8 \times 10^{-6})$ or $0.12M$ and $[OAc^-]$ must then be $1.2M$. One would predict, then, that in a solution $1.2M$ in sodium acetate and $0.12M$ in acetic acid the acid catalyzed rate would be 10% greater than in, say, a solution $0.06M$ in sodium acetate, $0.006M$ in acetic acid and $1.14M$ in sodium chloride. The effect would be barely detectable even with use of these extreme conditions. Moreover the 10% increase would be suspect because it might also be ascribed to nonuniformity of salt effects at concentrations as high as $1.2M$ (15). Thus general acid catalysis by acetic acid is not detectable with certainty when α is as high as 0.9.

It sould be noted, though, that the common diagnostic experiment with dilute buffers can allow general acid catalysis with α of around 0.8 to escape unnoticed while the use of more concentrated buffers will reveal the effect (133).

The difficulty of detecting general acid catalysis when α is very low has to do with competition between added acids and the solvent acting as an acid. The catalytic efficiencies of acetic acid and water are related by

$$\log k_{HOAc} - \log k_{H_2O} = \alpha[\log(1.8 \times 10^{-5}) - \log (1.8 \times 10^{-16})]$$
$$= 11\alpha$$

When α is 0.5, acetic acid is 3.16×10^5 times as effective a catalyst as water; if [HOAc] is $0.1M$, the acetic acid catalyzed reaction is $(3.16 \times 10^5)(0.1)/56$ or 560 times as fast as the water catalyzed reaction. However, if α is 0.1, acetic acid is only 13 times as effective a catalyst as water (on a molar basis) and the acetic acid catalyzed rate in $0.1M$ HOAc is only $(13)(0.1)/56$ or about 2% that of the water catalyzed reaction. Such a small contribution is not detectable with certainty. The same type calculation shows that, with $\alpha = 0.1$, the reaction would go about 10% faster in $0.1M$

HCl and about twice as fast in 1.0*M* HCl as in water alone. Thus a reaction which was no longer recognizable as general acid catalyzed because of its low α value could still respond to catalysis by a very strong acid.

Significance of the Magnitude of α or β. A Brönsted acid consists of a proton and its carrier (or base). The magnitude of α is interpreted as indicating the degree of separation of the proton from its base in the trans tion state for the slow step in the reaction. A high α (near 1.00) indicates a large degree of separation of the proton from its old base and of attachment to its new base, and a low α (near zero) represents a low degree of detachment of the proton. Similarly, a high β indicates a high degree of transfer of a proton to the catalyzing base in the transition state and a low β indicates a low degree of proton transfer.

The foregoing statements properly apply to categories 1 and 2 of general acid or base catalyzed mechanisms (pp. 232 and 235) and not to category 3. Let us examine the latter case, with special reference to the situation represented in Equations (32) and (33) (page 232). Equation (34) shows that the catalytic constant, k_{HA}, is equal to kK. Let us suppose that such a reaction shows a rather high α value, say 0.8. It is easily shown that

$$K = K_{HA}/K_{SH^+}$$

That is, the equilibrium constant of Reaction (32) is the ratio of the acid dissociation constants of the species HA and SH^+. The rate constant for the slow step is, by the Brönsted Catalysis Law,

$$\log k_{A^-} = \beta \log K_{A^-} + \log G$$

K_{A^-} is the basic dissociation constant of the base A^-, and is equal to $10^{-14}/K_{HA}$. Then,

$$\log k_{HA} = \log K_{HA} - \log K_{SH^+} - 14\beta - \beta \log K_{HA} + \log G$$

Since only K_{HA} of the quantities on the right will vary from one acid to another, the other terms can be combined with log G into a new constant, log G'. This equation then becomes

$$\log k_{HA} = (1 - \beta) \log K_{HA} + \log G'$$

Thus α for the overall acid catalyzed reaction is equal to $(1 - \beta)$, β being the Brönsted parameter for the rate-determining general base catalyzed step. The high α of 0.8 stems from a low β of 0.2 for the slow step.

Nucleophilic Catalysis. Bender and Turnquest (134) and Bruice and Schmir (135) have shown that bases such as acetate ion and tertiary amines catalyze the hydrolysis of *p*-nitrophenyl acetate in the mathematical fashion of general base catalysis. They have given persuasive evidence that the function of the catalyzing base is to effect a nucleophilic displacement of the

p-nitrophenoxy group to form an intermediate which is then rapidly hydrolyzed to acetic acid and the regenerated base.

$$CH_3\overset{O}{\overset{\|}{C}}\!-\!OAr + B \xrightarrow{\text{slow}} CH_3\overset{O}{\overset{\|}{C}}\!-\!B + Ar\!-\!O^- \xrightarrow[H_2O]{\text{fast}} CH_3COOH + B$$

Of a group of tertiary amines investigated by Bender and Turnquest, all but trimethylamine (sterically hindered) obeyed a Brönsted type plot of log k_B against log K_B. The slope was +1.62. This apparent β is far higher than the generally accepted limit of unity for this parameter.

Bender termed this phenomenon general base catalysis in his original report, but in a later paper (136) the name *nucleophilic catalysis* was proposed as more appropriate. The reason for the change in terms is that in the reactions with *p*-nitrophenyl acetate the various amines were acting not as bases, or nucleophilic reagents towards hydrogen, but rather as nucleophilic reagents towards carbon. That a linear plot was observed is not surprising; it is much like a Hammett correlation. That the slope was higher than unity indicates that the formation of a carbon-nitrogen bond is more dependent on electron supply to nitrogen than is the formation of any hydrogen-nitrogen bond.

6. The Grunwald-Winstein *mY* Relationship

As Hughes and Ingold (137) have shown, the solvolysis (reaction with solvent) of alkyl halides and related compounds often involves an initial rate-determining ionization to form a carbonium ion and an anion.

$$R - X \xrightarrow{\text{slow}} R^+ + X^-$$

The carbonium ion may then react in several ways: it may recombine with X^-, it may combine with some other nucleophile (a solvent molecule, for example), it may eliminate a proton to form an olefin or it may rearrange to another carbonium ion with eventual formation of stable substitution, elimination or recombination products. Substitution occurring by this mechanism is symbolized S_N1 (substitution, nucleophilic, unimolecular).

The other principal mechanism for nucleophilic substitution at saturated carbon is the S_N2 mechanism in which the nucleophile mounts a rate-determining attack on the substrate with displacement of the group X. (For substitution at unsaturated carbon, yet another mechanism prevails (138).) Whether the S_N1 or the S_N2 mechanism is followed depends in part on the structure of the substrate: tertiary alkyl halides and diphenylmethyl halides, which can yield *relatively* stable carbonium ions, tend to

react by S_N1 while primary alkyl and methyl halides, which would give rise to highly unstable carbonium ions, tend to undergo S_N2 substitution. There are also in-between mechanisms which represent a blend of S_N1 and S_N2 (139); these are encountered with substrates such as secondary alkyl or benzyl halides which give rise to carbonium ions of intermediate stability.

The rates of S_N1 reactions depend on the ionizing power of the solvent. S_N1 reactions (of initially neutral substrates) go fast in good ionizing solvents such as water and formic acid, and slow in solvents such as ethanol.

Grunwald and Winstein (140) showed that plots of log k for the solvolysis of various alkyl halides against log k for the solvolysis of *tert*-butyl chloride

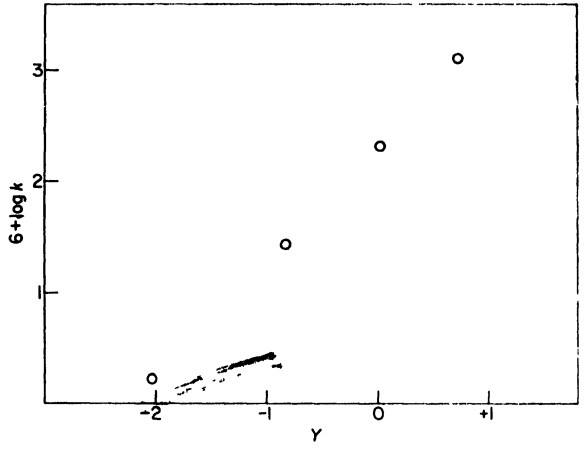


Fig. 7. Plot of log k for solvolysis of diphenylmethyl chloride in aqueous dioxane solutions against Grunwald-Winstein Y values (145).

in the same solvents were linear. A typical plot, concerning solvolysis of diphenylmethyl chloride in dioxane–water mixtures, is shown in Figure 7. In this plot, log k for solvolysis of diphenylmethyl chloride in any solvent is plotted against log k for *tert*-butyl chloride solvolysis in that same solvent. Plots of this type obey the equation

$$\log k - \log k_0 = m(\log k - \log k_0)_{t\text{-BuCl}} \tag{44}$$

k_0 was arbitrarily chosen as the rate constant for solvolysis in "80%" ethanol (a mixture of four volumes of absolute ethanol with one volume of water). A parameter Y was defined:

$$Y \equiv (\log k - \log k_0)_{t\text{-BuCl}} \tag{45}$$

Equation (44) was then rewritten

$$\log k - \log k_0 = mY \tag{46}$$

This is the Grunwald-Winstein relationship. Y is a solvent parameter, defined by Equation (45). Y represents the capacity of the solvent to facilitate ionization of a covalent halide, *p*-toluenesulfonate ester, or related substrate. m is a substrate parameter; it is the slope of the plot of log k versus Y. m represents the sensitivity of the substrate's solvolysis reactions to changes in the ionizing power of the solvent. Ideally each substrate would have its own characteristic m value which would suffice to correlate its rates of solvolysis in all solvents.

Since the original publication, the Grunwald-Winstein relationship has been extended and subjected to intense scrutiny in a series of researches in Winstein's laboratory (141–145).

Y values for a selection of common solvents, and the manner in which Y varies with the water content of the solvent, are presented in Table VI.

The Grunwald-Winstein relationship has been successful in that it has led to good linear correlations of the rates of solvolysis of many substrates in many solvents. But the relationship is not so general as might be hoped. Thus, although the rates of solvolysis of diphenylmethyl chloride in dioxane–water (Fig. 7), in ethanol–water and in acetone–water mixtures are all linearly correlated with Y, the data for all the solvents do not fall on a single line (145). The data for dioxane–water fall on one excellent line (Fig. 7), those for ethanol–water on another and those for acetone–water on a third line. The three lines have different slopes (m values). The reason for the dispersion of points is presumably that the manner in which solvents act to stabilize a strictly alkyl carbonium ion, the *tert*-butyl cation, is somewhat different from the way they act to stabilize a cation in which the positive charge is partly diffused around an aromatic ring.

Use of the Grunwald-Winstein relationship is nevertheless superior to an older practice of correlating solvolysis rates with the dielectric constant of the medium (146). Both theoretical considerations and limited sets of experimental data indicated that log k should be linearly related to $(D - 1)/(2D + 1)$, where D is the dielectric constant. Fainberg and Winstein (142) have shown, however, that when a wider range of dielectric constant is considered log k is not linear with $(D - 1)/(2D + 1)$. They emphasize that dielectric constant alone is a poor guide to solvolysis rate and quote examples of greatly differing solvolysis rates in solvents of similar dielectric constant.

A significant deviation from the Grunwald-Winstein relationship is encountered with solvolyses which partake of S_N2 character. In contrast to strictly S_N1 solvolyses, the rates of such reactions depend on the nucleo-

TABLE VI

Y Values of Solvents and Solvent Mixtures

%[b] Component of lower *Y*[c]	*Y* values[a]							
	HCOOH–H_2O	CH_3OH–H_2O	CH_3COOH–H_2O	C_2H_5OH–H_2O	Acetone–H_2O	Dioxane–H_2O	CH_3COOH–HCOOH	Dioxane–HCOOH
100	2.05	−1.09	−1.65	−2 03	—	—	−1.65	—
90	2.22	−0.30	−0.13	−0 75	−1.86	−2.03	−0.93	—
80	2.32	0.38	0.55	(0.00)	−0 67	−0.83	−0.42	−2.30
70	2.42	0.96	1 08	0.60	0 13	0.01	0.05	−1.37
60	2.52	1.49	1.52	1.12	0 80	0.72	0.41	−0.68
50	2.64	1.97	1 94	1 66	1 40	1.36	0.76	−0.09
40	2.83	2.39	2.31	2.20	1.98	1.94	1.07	0.40
30	3 02	2.75	2.66	2.72	2.48	2.46	1.34	0.88
20	3.17	3.02	2.99	3.05	2 91	2.88	1.61	1.29
10	3.33	3.28	3.25	3.31	3.23	3.22	1.86	1.72
0	3.49	3.49	3.49	3.49	3.49	3.49	2.05	2.05

[a] Data of Fainberg and Winstein (142) with interpolation by means of a large-scale plot where necessary.

[b] Per cent by volume; *X* volume per cent CH_3OH (in CH_3OH mixtures) means x volumes of CH_3OH plus 100-*x* volumes of H_2O.

[c] In water–organic solvent mixtures the organic component has lower *Y*; in dioxane–formic acid and acetic–formic acid mixtures dioxane and acetic acid have lower *Y*.

philic reactivity of the solvent. Although the rates of some solvolysis reactions of considerable S_N2 character are surprisingly well correlated by the mY relationship for restricted series of solvents (for example, ethyl bromide in water–ethanol mixtures), great deviations are encountered when solvents of dissimilar character are considered. This is shown by comparison of rates in a carboxylic acid solvent (acetic or formic acid) and in an ethanol–water mixture of equal Y value. The ratio $(k_{ROH}/k_{AcOH})_Y$ is close to unity for tertiary halides and for other substrates expected to undergo ionization without nucleophilic participation of solvent molecules. But for isopropyl, ethyl and methyl bromides, $(k_{ROH}/k_{AcOH})_Y$ is, respectively, 40, 80, and 300 (145). Ethanol is much more nucleophilic than acetic acid, and its relative effectiveness increases with increasing S_N2 character of the solvolyses. This perturbation owing to nucleophilic participation of the solvent certainly marks a limitation of the Grunwald-Winstein relationship but it is not to be considered a deficiency. Indeed, the relationship was of value in giving quantitative expression to the phenomenon of nucleophilic participation.

Some degree of generality for the Grunwald-Winstein relationship is indicated by the fact that log k for solvolyses of 9-decalyl perbenzoate and of *tert*-butyl pertosylate in methanol–water mixtures are linearly related to Y (147). In these reactions heterolysis of oxygen-oxygen bonds rather than carbon-halogen or carbon-oxygen bonds occurs. The line for *tert*-butyl pertosylate broke sharply as absolute methanol was approached and log k plunged to very low values; this deviation was a clue to deeper aspects of the solvolysis mechanism.

Certain solvent effects on spectra have also been correlated with Y values. Kosower (148) has shown that in particular the transition energy for a prominent band in the spectrum of 1-ethyl-4-carbomethoxypyridinium iodide is linearly related to Y. The transition energies in methanol–water mixtures, when plotted against Y, form an excellent straight line. So also do the transition energies in ethanol–water and acetone–water mixtures, but the three lines have somewhat different slopes. The correlation is so good that Kosower has suggested the transition energies as a new parameter, Z, representing solvent ionizing power. Two advantages of the Z parameter are that it is easily determined, by recording the spectrum of 1-ethyl-4-carbomethoxypyridinium iodide in the solvent in question, and that it can be determined for solvents in which *tert*-butyl chloride undergoes no chemical reaction. At the time of this writing, the Z parameter is so new that there has not been time for a thorough testing and criticism of it by other investigators. It appears, though, to have real possibilities.

Swain and coworkers (149–151) have approached the correlation of solvolysis rates through the use of a modified Grunwald-Winstein equation

and of new linear free energy relationships of their own devising. They have achieved many excellent empirical correlations. Swain's solvolysis equations have not come to be widely used, however. They have been discussed critically by Winstein, Fainberg, and Grunwald (145).

7. Equations for the Correlation of Rates of Nucleophilic Displacements

A. THE SWAIN-SCOTT EQUATION

The philosophical origin of this equation is Swain's view that all polar displacement reactions involve the concerted action of a nucleophilic reagent (N) attacking the substrate (S) as an electrophilic reagent (E) pulls off the group which is displaced:

$$N + S + E \rightleftharpoons [\text{transition state}] \rightarrow \text{products}$$

This view led to the expectation that displacement rates could be correlated by the four parameter equation

$$\log k - \log k_0 = sn + s'e \tag{47}$$

Here, n is a nucleophilic constant characteristic of N, and e is an electrophilic constant characteristic of E. s and s' measure the discrimination of S among different N and E reagents. k is the rate of reaction of the substrate under consideration with nucleophile N and electrophile E. k_0 is the rate of reaction of the same substrate with water, in which both N and E are H_2O, and for which both n and e are defined as zero.

Swain and Scott (152) regard the Grunwald-Winstein relationship and the Brönsted Catalysis Law as corollaries of Equation (47). The Grunwald-Winstein relationship is said to be the special case in which sn is negligibly small compared to $s'e$; s' then corresponds to m and e to Y. This view gains some support from the fact, discussed above, that solvolyses of partial S_N2 character show widely different rates in solvents of different nucleophilic reactivity but equal Y value. In the Swain-Scott view, these are cases in which the sn term is not negligible.

The corollary of most interest to Swain and Scott concerns cases in which $s'e$ is negligible compared to sn. Equation (47) than becomes

$$\log k - \log k_0 = sn \tag{48}$$

This is the Swain-Scott equation. The arbitrary definitions for this linear free energy relationship are that $n = 0.00$ for water and that $s = 1.00$ for reactions of methyl bromide. n values for other reagents are determined

from their rates of reaction with methyl bromide:

$$(\log k - \log k_0)_{MeBr} \equiv n \tag{49}$$

As mentioned above, both k and k_0 in Equation (48) refer to reactions of the same substrate.

Equation (48) implies that, for a series of reactions of a substrate with various nucleophilic reagents, a plot of log k against the corresponding n values will be linear. Such plots have indeed proved to be linear in a considerable number of cases. A typical plot is shown in Figure 8. The slope of the line is s for that substrate. s values reported by Swain and Scott varied from 0.66 for ethyl p-toluenesulfonate to 1.43 for benzoyl chloride. A high s value indicates great susceptibility to the nucleophilic power of reagents as measured by n.

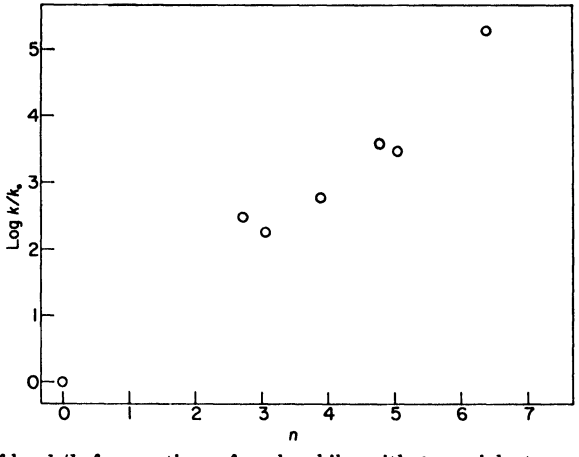


Fig. 8. Plot of log k/k_0 for reactions of nucleophiles with β-propiolactone against Swain-Scott n values (152).

n values for a number of common reagents are listed in Table VII.

The fact that plots of log k versus n are linear for a large number of reaction series makes the Swain-Scott relationship useful for the empirical correlation and prediction of reaction rates. It has received considerable use in this way. But the relationship has its shortcomings too.

An obvious limitation is that differences in steric interaction between substrate and reagent should cause deviations from linearity. Perhaps because most of the reagents considered by Swain and Scott were quite small, they could not find any definite evidence for this effect in the data they treated.

Swain and Scott, in their original publication (152), observed that reac-

TABLE VII[a]
Swain-Scott Nucleophilic Constants, n

Nucleophile	n	Nucleophile	n
$S_2O_3^{2-}$	6 4	Thiourea	4.1
HS^-	5.1	N_3^-	4.0
CN^-	5 1	Br^-	3.9
I^-	5.0	Pyridine	3.6
SCN^-	4 8	Cl^-	3.0
Aniline	4 5	Acetate ion	2.7
OH^-	4 2	H_2O	0.0

[a] This table is taken from Reference 139.

tions of certain substrates with hydroxide ion deviated greatly from the linear relationship. They also found their n values, as determined by Equation (49), not to serve well for the correlation of rates of nucleophilic displacement on hydrogen; they suggested that it might be bettter to set up a special scale of n values for displacements on hydrogen.

Although Swain and Scott applied their relationship to a relatively small number of substrates, in most of which the site of substitution was a saturated carbon atom, Equation (48) implies general applicability as long as the electrophilic contribution to reactivity is small. It implies, for example, that nucleophilic reagents should stand in a constant order of reactivity towards all substrates. Bunnett and Bassett (153) have, however, described instances in which even this qualitative prediction is not borne out. In view of this and of the other short comings which Swain and Scott themselves point out, their equation is seen to be more an empirical approximation than an expression of fundamental principles. As a means for correlating data, for predicting rate constants or for expressing reactivity (as n or s values), the Swain-Scott equation is quite useful. But it is not sufficiently well grounded to justify theoretical arguments based on deviations from linearity in plots of log k versus n.

B. EDWARDS' EQUATIONS

Edwards (154,155) has devised two four-parameter equations which give a better correlation of rates of nucleophilic displacements than does the two-parameter Equation (48) of Swain and Scott. It is well known that the availability of four parameters rather than two enables a better fit of data to be attained. Edwards' success might therefore be regarded as a mere demonstration of mathematical finesse were it not that two of his parameters are derived directly from external physical data. Moreover, it is possible to attach some physical significance to the separate terms of Edwards' equations.

It has long been recognized that nucleophilic reactivity has some tendency to be related to basicity. Thus, strong bases such as the hydroxide methoxide and amide (NH_2^-) ions are also strong nucleophiles. Also, within limited series of nucleophiles, such as substituted anilines or substituted phenoxide ions, a linear correlation of nucleophilic reactivity with basicity has been achieved through the Hammett $\rho\sigma$ relationship. However, it has also been recognized (156,157) that the correlation of nucleophilic reactivity with basicity is far from absolute. For example, the weakly basic thiophenoxide ion is much more reactive with many substrates than is the hydroxide ion. Other weakly basic species of high nucleophilic reactivity include iodide ion, thiosulfate ions, and thiourea. It has long been believed that the high nucleophilic reactivity of these species stems from their high polarizability (152,158).

Edwards' treatment gives separate expression to the basicity and the polarizability components of nucleophilic reactivity. His original equation was

$$\log k - \log k_0 = \alpha E_n + \beta H \tag{50}$$

E_n and H are reagent constants representing, respectively, the polarizability and the basicity characteristics of the reagent. α and β are substrate constants representing the susceptibility of the substrate to these reagent traits. E_n is obtained from the oxidation potential of the couple:

$$2 \text{ reagent} \rightleftharpoons (\text{reagent})_2 + 2e$$

E_n is defined:

$$E_n \equiv E_0 + 2.60 \tag{51}$$

H is obtained from pK_a of the reagent:

$$H \equiv pK_a + 1.74 \tag{52}$$

The factors 2.60 and 1.74 (which is log 55.6) are introduced in order to make E_n and H zero for water. α and β for any series of reactions of one substrate with several reagents are calculated by means of a least squares analysis; this gives the values of α and β which result in the best overall fit to Equation (50). It should be noted that Edwards' procedure involves no arbitrary assignment of constants other then $E_n = 0.00 = H$ for water.

Values of E_n and of H for a number of common reagents are tabulated in Edwards' first paper (154).

Edwards was able, by means of Equation (50), to achieve good correlations of the rates of a large number of nucleophilic displacements on carbon, hydrogen, oxygen, and sulfur. His equation was superior to that of Swain and Scott even for correlation of the data which they used for the development of their relationship. The same set of E_n and H values,

defined by Equations (51) and (52), which gave good correlation of displacements on carbon, served equally well for correlation of rates and equilibria of displacements on several other elements, including certain metals. It will be recalled that Swain and Scott suggested a special set of n values be used for displacements on hydrogen.

Edwards' second equation (155)

$$\log k - \log k_0 = AP + BH \tag{53}$$

differs from his first in the origin of the reagent polarizability parameter (now symbolized P). H is again the reagent basicity parameter, defined as before. A and B are substrate parameters, roughly equivalent to but not exactly the same as α and β in Equation (50). P is reckoned from polarizability as determined through refraction measurements:

$$P \equiv \log (R_\infty / R_{H_2O})$$

where R_∞ and R_{H_2O} are molar refractions of the reagent and water, respectively, at infinite wavelength.

With use of his second equation, Edwards was able to achieve correlations equal in quality to those obtained with his first. One disconcerting feature of his first equation was that it required negative β values for some reaction series. Negative β implies that nucleophilic attack is hindered by the basicity of nucleophiles; there is no independent evidence supporting such an idea. The β values required for good correlations by his second equation are all positive.

A difficulty with Edwards' second equation is that of evaluating P for reagents of complex structure. For many polyatomic anions, molar refractions are not available in the literature. Moreover, even when the molar refraction of a polyatomic ion or molecule is known, one does not know just how much of it to count as contributing effectively to its P value. Edwards has pointed out that the polarizability of more than just the first atom of the reagent is significant to nucleophilic reactivity, but on the other hand R_∞ for the entire ion cannot appropriately be used for the reckoning of the reagent parameter P.

Bunnett and co-workers (77,153,159) have discovered certain structural effects on reactivity in nucleophilic displacements which are most reasonably interpreted as being due to London forces in the transition state. London forces are forces of attraction which are proportional to the product of the polarizabilities of the atoms concerned and inversely proportional to the sixth power of the distance of separation. Because of the latter feature, they operate only at very short range. It is probable that much of the importance of the polarizability term in Edwards' equations is traceable to London forces.

V. KINETIC DEDUCTIONS FROM YIELD DATA

Since product yields are routinely recorded in preparative organic chemistry and since there is generally some connection between reaction rates and product yields, it is worthwhile to inquire when and how reliable kinetic conclusions can be derived from yield data. In certain situations yields are reliably indicative of relative reaction rates. In very special cases, rate constants can be deduced from yields. But in many, many, cases no definite kinetic conclusions can be drawn from yield data. Because the preparative literature seldom provides the information needed to decide whether yields are indicative of rates, most of the comments in this section pertain to evaluation of one's own experiments.

1. Cases in Which Yields Do Indicate Relative Rates

If yields are limited by the failure of reactions to go to completion, if the reactions are not reversible and if side reactions are negligible, then yields do indicate relative reaction rates. If, for example, a 30% yield is obtained from compound A and a 60% yield from compound B in the same period of time, and if about 70% of A and about 40% of B remained unreacted, it can be concluded that B reacts faster than A (though not exactly twice as fast). This situation is fairly common, but conclusions about relative rates cannot be justified unless a material balance and a test for reversibility show that slowness of reaction actually is the yield-limiting factor. If such data are to be used to compare the reactivity of A with that of B, the same conditions need have been used in the two experiments. The extreme case is that in which B reacts to a measurable extent and A is unaffected under the same conditions; the obvious conclusion that B is more reactive than A is sound and often important.

Even though the extent of reaction is limited by the reactivities of A and B, isolated yields may nevertheless fail to indicate relative reactivity correctly. This is because isolated yields also reflect the efficiency of isolation procedures. If the product from A is obtained in 60% yield and that from B in 50% yield, B may nevertheless be more reactive. It may be that isolation of the former product was almost quantitative and of the latter only 60% efficient.

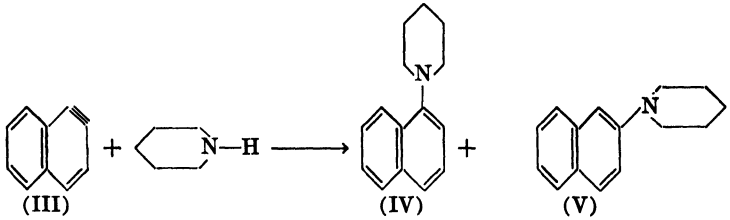
In the special case that yield is limited by the slowness of the reaction, isolation is efficient and the rate law for the reaction is known, a rate constant can be calculated from the yield. This case is almost trivial since the rate law can only be established by kinetic measurements.

The other principal case in which kinetic conclusions can be drawn from yields is that in which two or more products are formed competitively in

a system in which the same competitive situation prevails throughout the experiment. Efficient isolation or other accurate determination of true yields is also necessary. This situation is often deliberately created in order to measure comparative reactivities in reactions not amenable to direct determination of rate constants. A simple example is determination of the relative rates of nitration of alkylbenzenes in the *ortho*, *meta*, and *para* positions by accurate determination of the yields of *ortho*, *meta*, and *para* mononitration products. The conclusion that rates of substitution at the three positions are proportional to yields (statistically adjusted, because there is but one *para* position) involves the assumption, which seems unchallengeable, that all three reactions involve interaction of the alkylbenzene molecule with the same nitration reagent according to the same rate law. The conclusion is valid only if dinitration is insignificant; the three mononitrotoluenes do not, for example, undergo nitration at identical rates (160,161).

The same principle is exemplified in the reactions of 2,4-dinitrophenyl *p*-toluenesulfonate with nucleophilic reagents. This ester is cleaved either by attack on sulfur or by attack on carbon in the dinitrophenyl group with formation of, respectively, *p*-toluenesulfonyl or 2,4-dinitrophenyl derivatives of the nucleophilic reagents (153). Yields of the two types of cleavage products were determined for reactions with several nucleophiles in experiments in which material balances were excellent. Relative rates of attack at carbon versus sulfur were deduced from the yields. To illustrate, from the fact that reaction with aniline forms 88% of 2,4-dinitrodiphenylamine and 10% of *p*-toluenesulfonanilide, it was deduced that the rate of attack of aniline on carbon is about nine times as great as on sulfur.

Certain reactive intermediates may react in diverse ways, each of which forms a characteristic product. If neither product is formed in any other way and if neither product undergoes further change under the conditions of the reaction, the comparative yields of the products indicate the comparative rates of reactions by the different pathways. α-Naphthalyne (III)



(III) (IV) (V)

is such an intermediate and it reacts with piperidine, in the presence of sodium amide or lithium piperidide, to form α- and β-naphthylpiperidines (IV and V) in about a 1:2 ratio (162,163). This indicates that the rate

of C—N bond formation at the α-position is half that at the β-position. The necessary condition that the products do not undergo further change is amply satisfied in these experiments. Furthermore, since the 1:2 ratio of products is obtained under diverse conditions of reaction, the same rate law appears to govern C—N bond formation at both of the two positions, and therefore the *rate constants* for reaction at the two positions also stand in the ratio 1:2.

Another type of competition experiment was employed to determine relative rates of nitration of pairs of aromatic compounds (164). These experiments involved allowing a small amount of the nitrating reagent to react with such a large excess of a known mixture of two aromatic compounds that the amounts consumed by nitration did not sensibly alter the ratio of the two aromatic compounds in the mixture. More recently, as a consequence of better understanding of the kinetics of nitration, relative reactivity has been determined through direct determination of rate constants (14).

In the case of aromatic phenylation via phenyl radicals, direct determination of rate constants is not possible, but relative rates have been determined for many pairs of aromatic compounds by the competition method (165–167). A typical experiment concerned the relative rates of phenylation of fluorobenzene and of nitrobenzene, and was performed as follows: 6 g. of benzoyl peroxide (a source of phenyl radicals) was allowed to decompose in solution in 200 cc. of an equimolar mixture of fluorobenzene and nitrobenzene. The relative yields of fluoro- and nitrobiphenyls, on a molar basis, were taken to represent the relative rates of reaction of phenyl radical with fluorobenzene and nitrobenzene. (This involves the assumptions that once a phenyl radical attacks a benzene derivative the formation of a biphenyl is assured, which is probably not strictly correct (168), and that the small amounts of biphenyls formed are not further phenylated in the presence of so much fluorobenzene and nitrobenzene, which is probably correct within experimental error.)

2. Cases in Which Yields Do Not Indicate Relative Rates

Prominent among these are cases in which a product once formed is lost either by (a) conversion to another product whose yield can be determined, by (b) conversion to undefinable or difficultly isolable products (tars, gaseous oxidation products, very soluble products, etc.) or by (c) inefficiency of isolation procedures. All three are common but the first (a) case is the most insidious because it can lead to false conclusions even from painstaking experimental work. Thus, the isolated yields of two products from a given reaction may total nearly 100%, but these yields may have

no simple relationship to the rates of formation of the two products or indeed they may have no relationship whatsoever.

The extreme case is that of thermodynamic control of reaction products. This is the case in which two or more products (frequently isomers) are readily interconvertible under the reaction conditions so that the yields determined represent the position of the equilibrium between the products rather than their rates of formation. Reactions exemplifying thermodynamic control of products include the high temperature sulfonation of naphthalene (the kinetically favored product, α-naphthalenesulfonic acid, is obtained at low temperatures), the addition of hydrogen halides and halogens to 1,3-dienes (169) and the Friedel-Crafts methylation of toluene in the presence of excess HF and BF_3 (170). In other cases the shift from product ratios determined kinetically to ratios determined thermodynamically is slow. Such a case is the mercuration of toluene in acetic acid with perchloric acid catalysis (171); during the first hour of reaction at 25°C., products were formed in the approximate ratio 20% *ortho*, 10% *meta*, and 70% *para*, but during a period of days the product ratio shifted to 30–35% of each isomer. It is clear that measurements made after long reaction times would not properly represent the relative rates of mercuration at the three positions.

Yields may be wholly unrepresentative of rates if the reactions under consideration proceed to a state of equilibrium between reactants and products. In such a case, yield is governed by the equilibrium constant between reactant and product and not by the rate constant for transformation of reactant to product. This is an insidious case because an excellent material balance indicating the absence of side reactions will fail to disclose the factor which governs yields. Reversibility can usually be detected, though, by exposing the isolated product to the conditions of the reaction. If there is no evidence for reversion to "reactant" in significant amount, reversibility is shown not to be a yield-limiting factor.

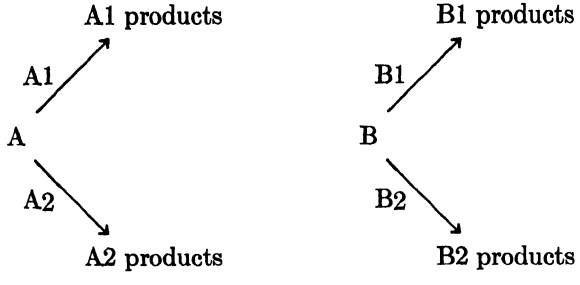
If poorly defined by-products are formed in large amount, or if a good material balance cannot be obtained, yield figures are of dubious value as indications of relative reactivity. A highly reactive compound may give a poor yield because of a voracious side reaction or post reaction while a less reactive compound may give a better yield because the side and/or post reactions are less destructive. For example, a better yield is obtained in the nitric acid nitration of benzene than of aniline although the latter is more reactive. In the von Richter reaction (172) (exemplified by the action of KCN in aqueous ethanol on *p*-chloronitrobenzene to form *m*-chlorobenzoic acid), the yield is low with nitrobenzenes carrying either electron releasing substituents or strongly electron-attracting substituents, and relatively high with substituents of intermediate character. Substituent

of the former class decrease reaction rate (much starting material is recovered) and thereby lower the yield while substituents of the latter class cause a rapid reaction (no recovery of starting material), which, however, leads to very little substituted benzoic acid. To be sure, some insight has been gained into factors influencing rate in this reaction, but only from as complete a material balance as possible and not from yield figures alone.

Even when a product once formed does not undergo further change, yields may still be of little value as indices of reactivity. One such case is that in which yields for several reactions under uniform conditions are all in excess of 90%. Let us suppose that the reactions were first order. A reaction which passed through four half-lives during the standard period of reaction would form 94% of product while one twice as fast would pass through eight half-lives forming 99% of product. In view of the lack of quantitative character in the usual isolation procedures, the isolated yield might well be 92% from the former reaction and 90% from the latter. Only if the reactions were exceptionally clean and the method of isolation or analysis exceptionally precise could the difference in rates be recognized from yield data when the reactions had gone so nearly to completion.

Instances in which all yields are very low (say, less than 5%) must also be regarded with reserve. One must be on guard against the possibility that the small yield of product formed was derived from an impurity in the reactants and not from the reactants proper.

Another case in which few conclusions about relative reactivity can be reached from yields even though reactions are clean and well described is that involving comparison of two reactions each of which is split into two pathways. The situation is as follows:



Let us imagine that A and B are related substrates and that reactions A1 and B1 are of one type and that A2 and B2 are of another. Now if A gives principally A1 products and B gives principally B2 products, the temptation is strong to consider reaction A1 to be faster than B1, and B2 to be faster than A2. In actuality no such conclusion is warranted. All the

results show is that A1 is faster than A2 and B2 faster than B1. It is quite possible that reaction B1 is twice as fast as A1 but that B forms B2 products because reaction B2 is twice again as fast.

A case of this type involves reactions of 1-bromo-2-methylnaphthalene (let us call it "A") and of 1-fluoro-2-methylnaphthalene ("B") with sodium amide in boiling piperidine. Two reactions are possible: reductive dehalogenation to 2-methylnaphthalene (A1 or B1) and piperidino-dehalogenation (A2 or B2) to 1-piperidino-2-methylnaphthalene. The products were 81% of 2-methylnaphthalene from the bromo compound (A1 >> A2) and 84% of 1-piperidino-2-methylnaphthalene from the fluoro compound (B2 >> B1). Bromine was principally dehalogenated and fluorine was principally replaced by a piperidino group. The temptation is strong to say that bromine undergoes reductive dehalogenation faster than fluorine and that fluorine undergoes piperidinodehalogenation faster than bromine. Although these statements are probably true, the evidence cited does not in the least support them (162).

VI. DEDUCTION OF STRUCTURAL EFFECTS ON REACTIVITY FROM KINETIC DATA

1. Introduction

The ultimate stage in a kinetics research, the derivation of chemical significance from the assembled data, requires scientific judgment and insight of a high order. This is the concern of the present and the following sections. Probably only in the selection of new experiments to be performed is there greater opportunity for the exercise of creative ingenuity.

The topic of this and the following sections is thus, in a sense, "how to do excellent kinetics research." It is immediately obvious that any treatment of this topic will of necessity be incomplete. One can no more tell a scientist how to do creative research of the highest quality than he can tell an artist how to paint a masterpiece. Techniques can be described and taught, to be sure, but real creative insight cannot. The chemist can be instructed how to go about determining a rate constant and the artist can be instructed how to achieve realistic perspective in the representation of a house. But the inspired insight involved in the best kinetics research is as unteachable as the creative instinct of Rembrandt or Picasso.

The approach of this section will, therefore, be something like that used in the schooling of the creative artist. Certain definable principles will be presented, and considerable attention will be given to noteworthy achievements in the realm of deductions from kinetics. The kineticist, like the

artist, can gain insight and inspiration from study of the works of the masters.

Since we are still enormously far from the absolute reckoning of reaction rates, the recognition of structural effects on reactivity always involves comparing the reactivity of related structures. All such comparisons involve the assumption that related reactions have the same mechanism; that is, that the change in reactivity stems from the effect of the new structural feature on the same mechanism. Fundamentally, this assumption underlies the whole systematization of organic chemistry, the consideration, for example, of aldehydes as a class rather than individually. Yet the assumption is sometimes wrong, as in the change from S_N2 for most substitution reactions of ethyl bromide to S_N1 for corresponding reactions of *tert*-butyl bromide or the change from the S_N2 mechanism for the alkaline hydrolysis of methyl chloride to the α-elimination mechanism for the reaction of chloroform with strong bases (173). Therefore as one compares the reactivities of related compounds, he must be constantly alert for evidence of a change in mechanism.

The deduction of structural effects on reactivity may be considered in two principal aspects. The more common is that of recognizing what well-known effects are operating, and in what fashion, in a particular reaction series. Recognition of the manner in which reaction rate is affected by electron-attracting substituents, for example, may provide a clue to the reaction mechanism. Again, it may suggest to the synthetic chemist a way in which he can improve the yield of a desired product. The more erudite aspect is that of discovering previously unrecognized structural effects on reactivity.

2. Recognition of Well-Known Effects in a New System

The general approach is to correlate changes in rate with the known characteristics associated with the changes in structure. These characteristics may be steric or polar effects of substituents, conjugation effects, changes in general molecular geometry or local effects such as hydrogen bonding, London forces or electrostatic interactions. If each structural change altered but one of these factors, the problem would be much simpler than it is. A newly introduced methyl group, for example, has bulk and therefore a steric effect, a tendency to release electrons, and polarizability which can give rise to London forces interactions. Which of these several properties is responsible for its effect on reaction rate can sometimes be reasoned from consideration of the general molecular structure; thus a methyl group in the para position to a reactive side chain is likely to be too far away to exert any but an electronic effect. But in general the effects

of substituents are best recognized by studying the effects of a number of substituents of widely varying characteristics. There is, for example, no general tendency for electronic effects to vary in parallel fashion with steric effects. Thus the methyl group and the bromine atom are similar of size but opposite in sign of electronic effect.

In years past correlations of rate changes with the electronic, steric or other effects of substituents were usually made qualitatively. But in recent years, with the availability of the Hammett equation in highly developed form and of Taft's equations, it is often feasible to try a quantitative correlation by plotting log k against an appropriate substituent parameter. If such a plot is linear or nearly so, a correlation with the characteristic represented by the parameter is strongly indicated. One's degree of confidence in the correlation is greater the larger the variation in electronic or steric effect among the substituents considered and the greater the slope of the plot. If the slope is small, the correlation may be fortuitous.

In this connection a certain paper in the recent literature, better not cited specifically, is of interest. In this paper rate constants are reported for a group of reactions which represent changes in substituents, in solvents, and in the groups displaced in a substitution reaction. The maximum variation in rate in the whole set of data is only about two-fold. The measurements were essentially all at one temperature. From the delicate trends in rate which could be distinguished by scrutiny of the data, the authors drew conclusions about the mechanism of the reaction! Actually, such small changes in rate could arise from minor perturbations. Also, it is possible that the temperature of measurement was the isokinetic temperature of reaction series in which structural effects are considerable. The data warrant hardly any conclusions at all.

There is also a need for caution in the interpretation of strongly positive correlations. This difficulty is sometimes encountered when an effect varies regularly as a halogen atom is varied from F to Cl to Br to I. There are many properties of the halogens which vary regularly in this series—electronegativity, polarizability, radius, etc.—and it may not be easy to tell which is the cause of the observed effect. The series of alkyl groups: methyl, ethyl, isopropyl, *tert*-butyl, presents a similar problem.

If a linear plot according to one of the Hammett or Taft equations is obtained, the sign of the slope indicates whether reaction rate is increased or decreased by the characteristic plotted horizontally, and the magnitude of the slope indicates the sensitivity of reaction rate to that characteristic. Such conclusions are straightforward, except that a small slope must be treated with caution. The reaction series may obey the isokinetic relationship (p. 205), and a few degrees change in temperature may reverse the sign of the slope.

If the operation of some specific effect such as hydrogen-bonding or neighboring group participation (174) is suspected, the matter may be further tested by determining the kinetic effect of a specific alteration of the substrate. Thus, whether hydrogen bonding by a hydroxy group plays a part in determination of rate may be discovered by converting it to a methoxy group by methylation. The methoxy group has nearly the same electronic effect as hydroxy and is usually not much greater in effective size. A large change in rate would support the idea that hydrogen bonding or some closely allied effect was important in the case of the hydroxy compound. Neighboring group participation has definite steric requirements. Sometimes its possible importance in determining rate can be tested by altering the substrate structure in such a way as to render neighboring group participation structurally impossible but without affecting polar influences on the reaction site. Thus while neighboring group participation can be strong in *trans*-2-substituted cyclohexyl *p*-toluenesulfonates, it is geometrically impossible in the *cis* isomers (174).

Some of the other specific effects which may operate in a particular case are presented in the next few pages.

3. Recognition of New or Unusual Effects

The discovery of a new factor affecting reactivity, or of the novel operation of a known factor, usually stems from observation of rate effects which do not appear to be explicable in terms of current theory. These deviations from the predictions of theory may immediately suggest an interpretation or they may stand unexplained for years until some chemist gets a flash of insight as to their cause. The interpretive hypothesis, however conceived, requires supporting evidence before it is accepted. In a few cases the supporting evidence has been found in the existing literature but more often new experiments have been performed specifically to test the hypothesis.

Less commonly a new effect has been predicted from theory and then sought in experimental data. Again, new experiments have usually been necessary to provide an adequate test of the hypothesis.

These steps in the development of new theory of structural effects on reactivity are, or course, essentially those involved in the development of any scientific generalization. The vital flash of insight cannot be taught or even systematically described; indeed, often the originator of an idea cannot accurately describe its genesis. But procedures for testing a hypothesis can be described and certain essential characteristics of evidence and proof can be discussed.

A. THE NEED FOR SUPPORTING EVIDENCE

In the era preceding the electronic theory of valency, the generalizations of organic chemistry were mostly empirical rules. "Rules" like the Markownikoff rule of addition to olefins and the Crum Brown-Gibson rule of orientation in aromatic substitution (175) come to mind. These "rules" usually made no attempt at interpretation of the effects which they concerned. In that era there was little true understanding of the factors which govern reactivity, and a reliable empirical generalization was a welcome contribution.

Today, however, the empirical recognition of a tendency for reactivity to depend on structure or medium in some definable fashion is accorded a lowly status. Such empirical rules continue to serve a useful role in some complex fields of organic chemistry, but they are regarded as having only pragmatic value as temporary expedients until the effects in question can be described in fundamental terms. For a new "effect" to be properly accepted today, it must be given a reasonable theoretical interpretation. Frequently, quantitative correlation of kinetic data with thermodynamic data or physical properties plays an important part in the verification of a new "effect."

In the earlier days of theoretical organic chemistry, roughly between 1925 and 1950, it was not uncommon for chemists to propose new structural effects on reactivity without offering either a sound interpretation in terms of fundamental theory or supporting physical or thermodynamic evidence. This unfortunate practice tended to give theoretical organic chemistry a bad reputation in the eyes of scientists not well acquainted with the field, with men not sufficiently informed to distinguish the sound from the unsound. The consequence was to delay acceptance of many substantial advances made in this period. Fortunately the proportion of poorly supported proposals of new effects has dropped sharply in recent years.

Inadequately supported proposals of steric effects were notably abundant in earlier years. That the size of groups could influence organic reactivity was correctly recognized about 1890 by Kehrmann (176) and by Victor Meyer (177), but at that time there was no true understanding of these effects. A tendency developed to classify, uncritically, any deviation from expected reactivity as a steric effect. Steric effects consequently fell into disrepute. Then, following the tremendous success of electronic theories of reactivity in the late 1920's, the pendulum of shallow thinking swung towards interpretation of all rate phenomena in electronic terms. A proper appreciation of steric effects did not come until about 1947. It was a combination of good measurements, such as determination of racemization rates of optically active biphenyls by Roger Adams and co-workers (178)

and of equilibrium constants for association of trimethylboron with amines by H. C. Brown (179), and of careful theoretical calculations, such as those of Westheimer and Mayer (180) and of Dostrovsky, Hughes, and Ingold (181), that finally conferred respectability on steric effects.

The preceding paragraphs stress the value of rational interpretation and of correlation with physical measurements in the establishing of a new structural effect on reactivity. Equally important is the design and execution of good experiments to demonstrate the existence of the effect. These often call for a high degree of ingenuity and originality, often exceeding that involved in conception of the original hypothesis. One powerful way of demonstrating a new structural effect involves comparing rates for analogous compounds which are nearly alike in all respects except the feature under consideration. Another principal method involves comparison of reactivities in two reaction series with attention to deviations from the sort of correlation which might be expected on the basis of existing theory. The latter method requires a larger number of data than the former and a greater degree of caution in their interpretation.

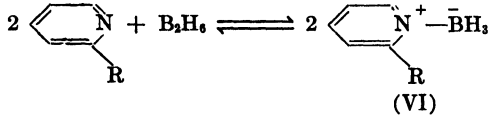
The first great success of the electronic theory as applied to organic chemistry was the interpretation of the reactivity and physical properties of aromatic compounds in terms of mesomeric and inductive effects. Some of the important early contributions were made by Robinson but the greatest part of the theory is due to Ingold. Of the several phenomena unified by their theories of electronic effects, the orientation rules in aromatic substitution had provoked the interest of chemists for the longest time. In the years preceding the electronic theory of valency many interpretations of these rules were offered but none were truly satisfying. The successful interpretation was based on fundamental understanding of the nature of the atom and of chemical bonding. That the theory of inductive and mesomeric effects should give a good account of orientation rules was an important achievement but its real success was that it also explained the acidities of substituted benzoic acids, the dipole moments of monosubstituted and *p*-disubstituted benzenes, the lengths of bonds between ring substituents and ring carbon atoms, and other physical and chemical properties. Since Robinson and Ingold and their associates were developing not an "effect" but rather a whole new theory of organic chemistry, the burden of proof was heavy. Their work is a classic illustration of the manner in which supporting evidence from other types of measurements can help to build a powerful case for a new theory concerning the effect of structure on reactivity. A good account of this theory as it had been developed by 1940 has been given by Watson (182).

A case in which a structural effect on reactivity was predicted from theory, confirmed by physical measurements and last of all recognized in

chemical phenomena was the discovery of steric inhibition of resonance. Hampson (183,184) reasoned, from the theory of mesomerism in aromatic compounds as developed by Ingold and others, that the condition of mesomerism or resonance in, for example, nitrobenzene should require the nitro group to approach coplanarity with the ring. This followed, as he said, from simple ideas of stereochemistry. He further reasoned that large substituents *ortho* to a nitro group should interfere with mesomerism and therefore alter its physical and chemical consequences. He then measured dipole moments of selected compounds and found support for his ideas in facts such as that nitrodurene has a significantly lower dipole moment than does nitrobenzene.

These developments were soon followed by chemical evidence showing that *ortho* substituents interfere with the normal activating effects of nitro groups and of dimethylamino groups, whose mesomeric interaction with an aromatic ring has similar steric requirements. It was shown that *ortho* substituents inhibit acid catalyzed hydrogen isotope exchange, an electrophilic aromatic substitution, in dimethylaniline (185). Also, *ortho* substituents were shown to decrease the activating effect of the nitro group in a typical nucleophilic substitution, the displacement of bromine by piperidine (186). Subsequently, steric inhibition of resonance has been recognized in many other chemical and physical manifestations (187).

H. C. Brown's researches on steric effects are another good example of reliance on independent physical measurements to establish a factor of kinetic importance. Brown's studies, which he summarized in a lecture to The Chemical Society (188), are based on thermodynamic measurements, principally of equilibrium constants for the association of amines with BH_3 and its derivatives. A typical association reaction is



(VI)

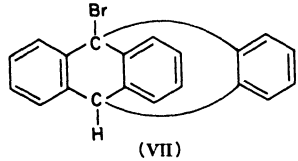
Brown and his co-workers measured association constants for many sets of amines and boron compounds, and they were able to show convincingly that steric interactions were a major factor determining the free energies of such association reactions.

Brown's application of these ideas to kinetic phenomena may be illustrated with respect to bimolecular nucleophilic substitution at saturated carbon (189). That S_N2 reactions are subject to steric hindrance had been recognized by other workers, notably by Dostrovsky, Hughes, and Ingold (181); Brown's contribution was to confirm and greatly extend knowledge of such effects. He reasoned that the steric requirements of

boron, carbon and nitrogen atoms are about the same, and that the steric strain in, say, $(CH_3)_3\overset{-}{B}—\overset{+}{N}(CH_3)_3$ should therefore be about the same as in hexamethylethane, $(CH_3)_3C—C(CH_3)_3$. He also reasoned, in the same vein, that the steric strain in a 2-alkylpyridine-BH_3 complex of type (VI) should resemble that in the transition state for the reaction of the same 2-alkylpyridine with methyl iodide. In support of this view, the energies of activation of such reactions were found to correlate excellently with the heats of reaction of the corresponding bases with BH_3. Similar correlations of theory, thermodynamic measurements and kinetic data were obtained in numerous other reaction series. The total effect was to build a powerful case for Brown's views of steric hindrance effects.

B. THE USE OF SUBSTRATES OF RIGID OR RESTRICTED GEOMETRY

The importance of resonance in the triphenylmethyl carbonium ion in contributing to the S_N1 reactivity of triphenylmethyl halides was demonstrated in an elegant experiment by Bartlett and Lewis (190). These authors prepared bromotriptycene (VII) which is constitutionally the same as triphenylmethyl bromide but for one feature. In both compounds three



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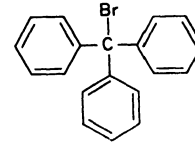
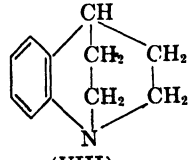


aryl groups are bonded to the carbon which carried the bromine atom. The difference is that in bromotriptycene the three aryl groups are tied together by the attachment of their three *ortho* positions to a carbon atom. Since the polar effect of an alkyl substituent is small, one might expect bromotriptycene to be highly susceptible to nucleophilic substitution as is triphenylmethyl bromide. In actual fact, bromotriptycene is inert to nucleophilic reagents. Although the structural difference between the two compounds is slight, it has the effect of making bromotriptycene a rigid structure unable to undergo any change in geometry about the carbon atom which carries the bromine. It is inferred, therefore, that the S_N1 reactivity of triphenylmethyl bromide depends vitally on the ability of this molecule to assume, as it forms the transition state, some conformational arrangement of the phenyl groups which is prohibited in bromotriptycene. This essential conformational arrangement is deduced to be one in which the phenyl groups and the central carbon approach coplanarity so that the developing carbonium ion can be stabilized by resonance.

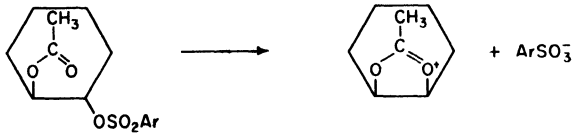
Aromatic tertiary amines are known to couple readily with diazonium salts, to be much weaker bases than aliphatic amines, and to have certain spectral features associated with the amino group as a ring substituent. These characteristics had been regarded on good evidence as consequences of resonance between the amino group and the ring. An elegant confirmation of this view was provided by Wepster (191), again with use of a rigid structure which defined the geometrical relationship of functional group to aromatic ring. Wepster showed that benzoquinuclidine (VIII), although formally an aromatic tertiary amine, does not couple with diazonium salts,



(VIII)

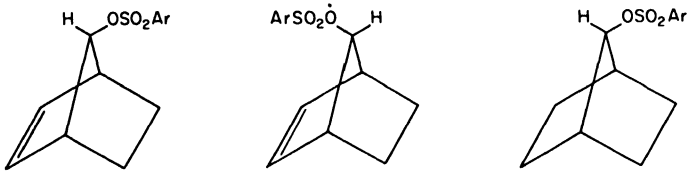
is a relatively strong base and lacks the spectrum characteristic of aromatic amines. Wepster explained that in benzoquinuclidine, the two unshared electrons of the nitrogen atom occupy an orbital which lies in the plane of the benzene ring and has no opportunity to overlap with the *p* orbital of the adjacent ring carbon, and therefore no opportunity to enter into resonance with the aromatic ring. The principle is the same as that involved in steric inhibition of resonance (p. 261).

Winstein's recognition of neighboring group effects also made use of experiments in which molecular geometry was intentionally restricted. Neighboring group participation involves, essentially, intramolecular nucleophilic attack by a neighboring substituent on a carbon atom bearing a displaceable group; products of this displacement are an anion (if the displaceable group was originally neutral) and a complex cation which quickly undergoes some further reaction, such as capture of a solvent molecule or loss of a proton. The phenomenon has been reviewed (192). One of Winstein's important experiments involved studying the rates of solvolysis of 2-substituted cyclohexyl *p*-bromobenzenesulfonates, from which the *p*-bromobenzenesulfonoxy group is displaceable. It was found that *trans*-2-acetoxycyclohexyl *p*-bromobenzenesulfonate solvolyzes about three thousand times faster than the *cis* isomer (174). Since polar effects of the *cis*- and *trans*-2-acetoxy groups are the same, the much higher rate with the *trans*-2-acetoxy compound must arise from something the *trans* acetoxy group can do which the *cis* acetoxy group cannot do because of geometrical restrictions. The involvement of the *trans* acetoxy group is represented in the following way, described as "participation":



This representation was supported by product studies of various sorts.

Carbon-carbon double bonds can also act as "participating" groups. A dramatic illustration again involved substrates of fixed geometry (193). The rates of solvolysis of *anti*-7-norbornenyl *p*-toluenesulfonate (IX), its *syn* stereoisomer (X) and its saturated analog, 7-norbornyl *p*-toluenesulfonate (XI), were found to stand in the order 10^{11} to 10^4 to 1, respec-



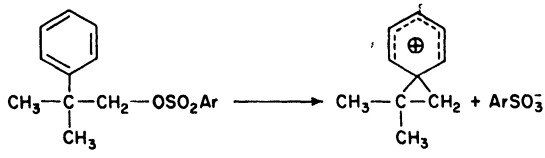
(IX) (X) (XI)

tively. The ten million-fold greater reactivity of the *anti* (IX) as compared to the *syn* (X) isomer stems from the ability of the π-electrons of (IX) to approach the back side of the carbon atom bearing the *p*-toluenesulfonoxy group with resultant expulsion of that group and formation of an unusual homoallylic carbonium ion. This ion then reacts with acetic acid on the front side to form an acetate ester of retained configuration. The π-electrons of the *syn* isomer (X) are not suitably located for such participation. The ten thousand-fold greater reactivity of (X) over the saturated analog (XI) assertedly stems from participation by a methylene group: this is a more complex case; for details the reader should consult the original publications (193).

In gaining evidence of the participating power of substituents, Winstein was several times able to show that the rate of solvolysis of a β-substituted alkyl arenesulfonate was far in excess of what one would expect from the conventional polar effect of the substituent on ordinary S_N1-type ionization. For example, *trans*-2-iodocyclohexyl *p*-bromobenzenesulfonate underwent solvolysis in acetic acid a thousand times *faster*, and the *trans*-2-chloro analog five thousand-fold *slower*, than unsubstituted cyclohexyl *p*-bromobenzenesulfonate (174). The deceleration by chlorine represents its normal polar effect on an S_N1-type ionization. Since iodine has about the same polar effect as chlorine, as judged from Taft σ^* values, the fact that the iodine compound solvolyzes five million times faster than its chlorine analog shows that a new effect, neighboring group participation, is operating

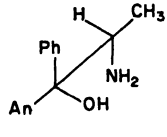
in the case of iodine. Iodine has much greater participating power than chlorine because of its greater size and greater polarizability.

The same principle was used in establishing the ability of β-phenyl groups to participate. A β-phenyl group is electron-attracting and would be expected to decelerate S_N1-type ionization. Actually, 2-phenyl-2-methylpropyl (familiarly known as neophyl) *p*-toluenesulfonate solvolyzes in acetic acid 460 times faster than 2,2-dimethylpropyl (familiarly neopentyl) *p*-toluenesulfonate (194). The large *increase* on replacing a methyl by a phenyl group indicates participation, represented as follows:



The several substrates of fixed geometry cited above have mostly involved rigid three-dimensional molecular frameworks. Fixed geometry can also be achieved in ordinarily flexible systems by the introduction of large groups which will fit only in one conformation. In the ordinarily flexible cyclohexane system, the introduction of a *tert*-butyl group effectively freezes the molecule in that conformation in which this very large group is equatorial. Eliel (195,196) and Winstein (197) have used this conformation-freezing device in studying the reactivity of various functional groups as a function of their equatorial or axial situation on a cyclohexane ring. In *trans*-4-*tert*-butylcyclohexanol, for instance, the hydroxy group is necessarily equatorial and in the corresponding *cis* isomer the hydroxy group is necessarily axial. It was found, for example, that an equatorial hydroxy group is esterified by acetic anhydride in pyridine about four times as fast as an axial hydroxy group. With information of this type at hand, it was then possible to calculate conformational equilibrium constants ([*e* - OH]/[*a* - OH]) from rates of esterification of cyclohexanol itself, of 4,4-dimethylcyclohexanol, etc.

One of the best ways to isolate a steric effect, to be sure that all other things are equal, is to study the reactions of a pair of stereoisomers, This device was used with great success by Curtin (198,199) in his elucidation of the "cis effect." The cis effect is illustrated by the action of nitrous acid on *erythro*- and *threo*-1-*p*-anisyl-1-phenyl-2-aminopropanol (XII and XIII, respectively). In each case the elements of ammonia are re-



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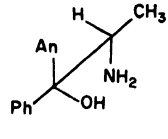
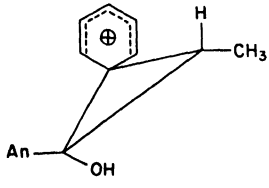


(XIII)

moved by the nitrous acid, an aryl group migrates to the position vacated by the amino group, and the product is an aryl 1-arylethyl ketone. The mechanism is assuredly diazotization of the amino group, loss of N_2 with migration of an aryl group, and finally loss of a proton. From the *erythro* isomer (XII) 87% of *p*-anisyl 1-phenylethyl ketone, representing phenyl migration, was formed. From the *threo* isomer, 92% of phenyl 1-(*p*-anisyl) ethyl ketone, a product of *p*-anisyl migration, was formed. Clearly migration tendency is determined more by *where* the aryl group is than by *what* it is. Consideration of the probable transition state for the migration indicates the origin of the effect. From the *erythro* isomer (XII), the transition states for phenyl migration and for *p*-anisyl migration resemble (XIV) and (XV), respectively. In each the nonmigrating groups (CH_3,



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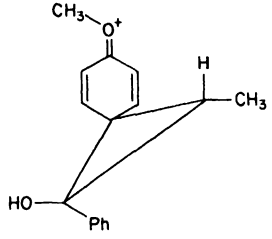


(XV)

H, OH, and one aryl group) approach coplanarity as in an olefin. The larger groups, CH_3 and aryl, approach a *cis* arrangement in (XV) with consequent crowding and strain. In (XIV), on the other hand, each of the larger groups is *cis* to one of the smaller; there is less crowding and less strain. Transition state (XIV) is therefore favored, and phenyl migration from the *erythro* isomer predominates.

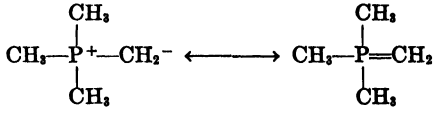
Curtin (198) has cited numerous instances in which the cis effect operates in elimination reactions, ring closures and rearrangements. In most cases the effect was recognized by comparing the behavior of stereoisomers much as described above.

C. DIVERSE WAYS OF KEEPING CONSTANT ALL INFLUENCES BUT THE ONE UNDER INVESTIGATION

Bordwell (200) recognized a steric effect by using vinylogy to keep electronic effects nearly comparable. The problem was to discover why α-halosulfones are rather unreactive with nucleophilic reagents in contrast to α-haloketones and α-halonitriles which are exceptionally reactive. Chloromethyl phenyl sulfone is, to illustrate, less than one-fiftieth as reactive as *n*-butyl chloride with potassium iodide in acetone whereas chloroacetonitrile is three thousand times more reactive. The problem

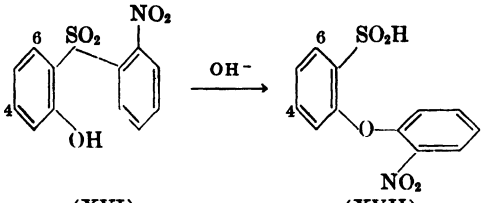
was solved by comparing the reactivity of γ-(*p*-toluenesulfonyl)allyl chloride, $C_7H_7SO_2CH{=}CHCH_2Cl$, with that of allyl chloride itself. The former was fourteen times more reactive with potassium iodide in acetone. This shows that *electronically* sulfonyl groups are activating, as expected. It follows that the deactivating influence in α-halosulfones is of nonelectronic origin, probably steric. This conclusion is theoretically reasonable; the large sulfonyl group would be expected to block attack on the backside of the carbon to the C—Cl bond just as such attack is blocked in neopentyl chloride.

Doering's recognition of *d*-orbital resonance in sulfonium and phosphonium salts involved comparison with ammonium salts in which factors other than the one under study could be expected to be nearly constant (201,202). It was shown that tetramethylphosphonium ion and trimethylsulfonium ion exchange hydrogen with deuteroxide ion in heavy water more than a million times faster than does tetramethylammonium ion. The kinetic acidity of an α-hydrogen is surely related to the capacity of the remainder of the ion to accommodate the developing negative charge. The inductive effects of the positive poles in these three ions can be considered roughly constant. The much greater acidity of the phosphonium and sulfonium ions must therefore be due to some special effect which cannot influence the removal of protons from tetramethylammonium ions. This special effect is postulated to be *d*-orbital resonance; in the case of the phosphorus species, this resonance may be pictured as follows:



This resonance involves a canonical structure in which phosphorus is pentacovalent. Such is denied to nitrogen by the Pauli Exclusion Principle.

It has long been known that an *ortho* substituent generally exerts about the same electronic effect as the same substituent in the *para* position. With reference to this generalization, comparison of the reactivities of *ortho* and *para* isomers has made possible the definition of certain steric and other local effects of *ortho* substituents. Bunnett and Okamoto (203) used this principle in recognizing and verifying a colossal steric acceleration effect in the base-induced Smiles rearrangement of 2-hydroxy-2′-nitrodiphenyl sulfones (e.g., (XVI) → (XVII)). The rearrangement involves intramolecular nucleophilic attack by the ionized hydroxy group on the 1′-carbon atom leading to formation of a carbon-oxygen bond and scission of a carbon-sulfur bond. That a 6-methyl group accelerates the rearrangement was observed by Smiles (204) and interpreted as an electronic effect.



(XVI) (XVII)

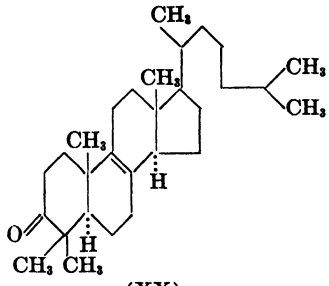
Bunnett and Okamoto studied the rates of rearrangement of isomeric 4- and 6-methyl-, bromo-, and chloro-substituted derivatives of (XVI) and found that each 6-substituted derivative rearranged 10^5 to 10^6 times as fast as the isomeric 4-substituted derivative. This is far beyond the magnitude of the difference in electronic effects of *ortho* and *para* isomers;

(XVIII) (XIX)

The right hand ring in these formulas is imagined to be perpendicular to the plane of the paper.

also, the same degree of acceleration is produced by the electron-releasing methyl group as by the electron-attracting chlorine and bromine atoms. Interpretation as a steric effect is therefore suggested, and this is reasonable from consideration of the mechanics of the system. The ionized 2-hydroxy group must approach the 1′-carbon, as in conformation (XIX), in order for rearrangement to occur. In the absence of 6-substituents (R = H) the favored conformation is the fruitless one (XVIII) in which the 6-position is near the 1′-position; introduction of a large 6-substituent obliges the left-hand ring to rotate (to avoid crowding of R against the right hand ring) into a conformation (XIX) in which the ionized hydroxy group is close to its optimum position.

Barton's discovery and definition of long-range conformational effects on the reactivity of triterpenoid and steroid compounds (205–208) is another illustration of the principle of keeping constant all factors but the one under study. An example of these conformational effects is the fact that lanost-8-enone (XX) condenses with benzaldehyde, at the 2-position to form a benzylidene derivative, six times as fast as does the isomeric lanost-7-enone (XXI). The only difference between these two isomers is the position of a double bond. One would not expect much difference in the electronic effects of the double bonds in the two positions in view of the initially small polar effect of C=C and of the long saturated chain between



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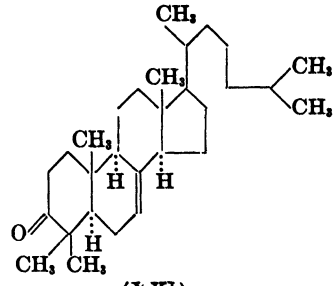


(XXI)

it and the site of reaction in either ketone. Barton cited other evidence indicating that the effect observed is not polar in origin; for instance, a carboxylate group ($—COO^-$) and a carbomethoxy group ($—COOCH_3$), which are quite different in polar character, exert almost the same effect on reaction rate. Straightforward steric hindrance can be excluded by consideration of the known geometries of the molecules. After rejecting these and other improbable causes of the phenomenon, Barton concluded: "We are, therefore, forced to admit a new effect which we have defined as follows: the differences in rate...probably arise, in main part, from conformational distortion produced by unsaturated substituents. We imagine that this distortion is transmitted through the saturated molecule by a slight flexing of valency angles and alteration of atomic coordinates.....The new effect may, therefore, be described as 'conformational transmission.'"

D. INTERPRETATION OF DEVIATIONS FROM REGULAR RELATIONSHIPS

Most of the examples of the recognition of new effects so far considered have involved comparisons in which the ideal of holding constant all factors but the one under study has been closely approached. A rather different approach is the detection of new effects from deviations in linear free energy plots. Taft's evaluation of steric substituent constants (E_s), (see p. 222) involves essentially this approach. Other instances can be found elsewhere in Taft's work (118).

An excellent example of the use of deviations from linear free energy plots to recognize structural effects is McDaniel and Brown's study (209) of *ortho* effects on the strengths of diverse types of aromatic acids. These authors recognized that *ortho* substituents might affect acid strength by direct steric hindrance, steric inhibition of resonance, hydrogen bonding or other means. They chose dissociation of the conjugate acids of 2-, 3-, and 4-substituted pyridines as a standard reaction series in which none of these effects would be expected to be important. They then plotted pK_a

for other series of aromatic acids against the corresponding pK_a values for pyridinium ion dissociation. Most of the points for *m*- and *p*-substituted acid ions fell on a line, while most of the points for *ortho* substituted acids deviated from that line. All *ortho* substituents but fluorine caused positive deviations in the acidity of benzoic acids, and among both halogens and alkyl groups the deviations were greater the larger the group. These deviations were attributed to steric inhibition of the acid-weakening resonance of the carboxyl group with the benzene ring. All *ortho* halogens caused negative deviations in the acidity of phenols and thiophenols, and the deviations were greater the more electronegative the halogen. These were ascribed to acid-weakening hydrogen-bonding with the *ortho* halogen atoms. Other series of acids were also probed.

Reinheimer and Bunnett (77) used a somewhat similar approach in their recognition of London forces effects on the reactions of nucleophilic reagents with 2-substituted-4-nitrofluorobenzenes. Having determined rates of reactions of several reagents with the 2-hydrogen, 2-methyl, 2-bromo, and 2-nitro substrates, they considered the ratio, k_Y/k_{OH^-}, as a function of the group in the 2-position. Such ratios were taken to compensate for the differing polar effects of 2-substituents; differences in the ratios were then representative of local interactions such as steric effects and London forces. For reagents of polarizability greater than hydroxide ion (ammonia, piperidine, thiophenoxide ion), such ratios were found to increase with increasing polarizability of the *ortho* substituent, the extent of increase being greater with the polarizability of the reagent concerned. (Steric hindrance effects could also be discerned for piperidine.) Reinheimer and Bunnett showed that the trends in k_Y/k_{OH^-} were consistent with a hypothesis of London forces interactions between *ortho* substituents of high polarizability and reagents of high polarizability, but not with conventional steric or electronic effects.

One of the most convincing ways of demonstrating that a new effect is at hand is to show that the kinetic effect of a change in structure is qualitatively opposite to what would be expected on the basis of known effects. There is an example in the work of Reinheimer and Bunnett: The introduction of a 2-methyl group causes a small absolute *increase* in the rate of reaction of 4-nitrofluorobenzene with sodium thiophenoxide. Since both the steric and the polar effects of the methyl group decelerate such a reaction, the observation of an actual increase in rate shows that something else is involved. The "something else" is indicated to be London forces.

Another example of the same principle of evidence is Winstein's demonstration of neighboring group participation by β-iodo and β-phenyl substituents, both of which cause large rate accelerations although their polar

effects would oppose straightforward S_N1 ionization. This matter has been discussed on pp. 264–265.

VII. DEDUCTION OF REACTION MECHANISMS FROM KINETIC DATA

Since there are other chapters of this book devoted in large part or in their entirety to this subject, only certain general principles will be presented here.

1. The Uncertainty of Kinetics as a Criterion of Mechanism

The first thing to be said about the deduction of a reaction mechanism from kinetic data is that in general it cannot be done. That is, an absolute answer cannot be obtained. This is not to deny the value of kinetics as evidence for reaction mechanisms. Indeed, of all the methods for study of reaction mechanisms, only determination of product identities and yields is more generally significant.

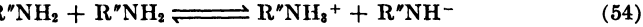
The chief contribution of reaction kinetics is the rejection of conceivable mechanisms. Providing the data are good and the reasoning sound, the rejection is final. Frequently several mechanisms remain compatible with the kinetics, and its is often impossible to choose between them on the basis of kinetic data. (However, if the kinetic data are incomplete or inferior, more or better data may provide a basis for distinction.) Of the mechanisms allowed by the kinetics, some may be discarded on other grounds such as stereochemical evidence or results of experiments with isotopic tracers, and others may be substantially eliminated on the basis of structural effects on reactivity or other principles of analogy. Frequently the field is so narrowed by these several forms of evidence and argument that there is essentially no choice left. The remaining mechanism is said to be "established" or "proved." In other cases, two or more substantially different mechanisms remain compatible with all available data.

Even when all but one of the conceivable mechanisms have been discarded, the remaining "established" mechanism cannot be accepted as final. With the passing of time, advances in chemical thought may lead to the conception of new mechanisms which are fully compatible with the data. The mechanism originally favored may have to be discarded on grounds of new evidence. Or, it may be susceptible of refinement with advances in technique and theory. The recent literature contains many examples of both types of modification of mechanisms once considered "established."

The qualification that kinetic evidence does not finally establish a mechanism is often explicitly stated in papers dealing with the deduction of mechanism from kinetics. In others it is not explicitly stated, but this qualification is implicit in all.

Studies of the mechanism of aminolysis of esters illustrate the way in which a mechanism once considered well established has required to be revised in the light of subsequent work. Ester aminolysis is base catalyzed and the amine itself can act as catalyst. Consequently the order of reaction is greater than one in amine, indeed, 3/2 order in amine under certain

conditions. These facts were discovered by Betts and Hammett (210) who proposed the following mechanism to account for them:



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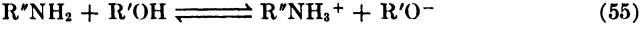

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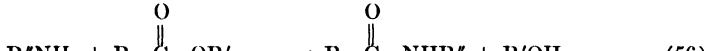

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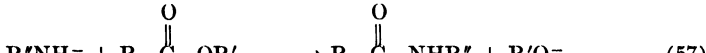
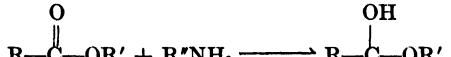


(57)

The interaction of amine with alcoholic solvent, Equation (55), was considered to establish $[R''NH_3^+]$, and $[R''NH_3^+]$ should be proportional to $[RNH_2]^{1/2}$. Insertion of this into the equilibrium expression for Equation (54) results in the prediction that $[RNH^-]$ should be proportional to $[RNH_2]^{3/2}$. Therefore, insofar as Reaction (57) was involved, the overall reaction was expected to be 3/2 order in amine. Betts and Hammett showed that their mechanism also accounted for the kinetic effects of added RHN_3^+ salts and of substituents in the acyl group. Their mechanism was generally accepted for more than twenty years.

Bunnett and Davis (26) showed that the results of Betts and Hammett could also be accounted for by either of the following mechanisms:



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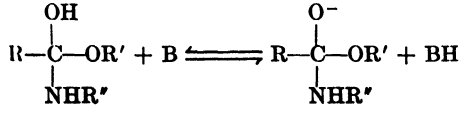

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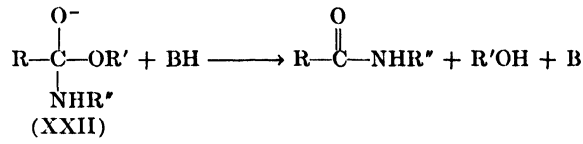
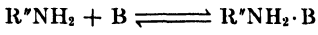


(60)

(XXII)

or



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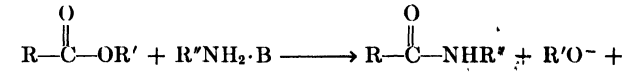


(62)

In each of these the catalyzing base is symbolized B. The mechanism of Equations (58–60) involves a series of pre-equilibria involving amine, ester, and base followed by general acid catalyzed removal of an alkoxide ion from tetrahedral intermediate (XXII). The second mechanism (Equations 61–62) is much like Betts and Hammett's; the difference is that whereas theirs postulated $R''NH^-$ as an especially reactive reagent, this postulates a "carrier" of $R''NH^-$, namely, a hydrogen-bonded complex of amine with base. With either mechanism the base might be an amine molecule or an alkoxide ion generated according to Equation (55); in the former case the reaction would be second order in amine and in the latter 3/2 order in amine. Kinetics mixed 3/2 to second order in amine had been observed (211).

A fundamental difference between the mechanism of Betts and Hammett and those of Bunnett and Davis is that the former requires specific lyate ion catalysis and the latter general base catalysis. Which variety of base catalysis prevails had not previously been tested; Bunnett and Davis showed that the catalysis is *general*. The mechanism of Equations (54–57) is therefore not tenable. Of the two compatible with general base catalysis, that of Equations (61–62) is disfavored because the reactions of primary and secondary amines with 2,4-dinitrochlorobenzene are insensitive to catalysis by hydroxide ion (212,213). The mechanism of Equations (58–60) is therefore preferred.

This tale demonstrates both the power and the limitations of kinetics as a tool for the establishment of reaction mechanisms. It is difficult to see how anything like this degree of understanding of ester aminolysis mechanism could have been attained without the use of kinetics. Yet Betts and Hammett knew and said that their mechanism was not necessarily the final answer, and Bunnett and Davis are aware that their favored mechanism may also required revision or even rejection in future years.

A similar story can be told concerning the kinetics and mechanism of iodination of phenol. Studies by Soper (214,215) and by Berliner (216)

established the two term rate expression

$$\text{rate} = k_0[\text{PhOH}][\text{I}_2]/[\text{H}_3\text{O}^+][\text{I}^-] + k_{\text{HA}}[\text{PhOH}][\text{I}_2][\text{HA}]/[\text{H}_3\text{O}^+]^2[\text{I}^-]$$

With attention to the equilibria

$$\text{I}_2 + 2\text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{I}^- + \text{HOI}$$

$$\text{H}_3\text{O}^+ + \text{HOI} \rightleftharpoons \text{H}_2\text{O} + \text{H}_2\text{OI}^+ \rightleftharpoons 2\text{H}_2\text{O} + \text{I}^+$$

$$\text{HA} + \text{I}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{AI} + \text{I}^-$$

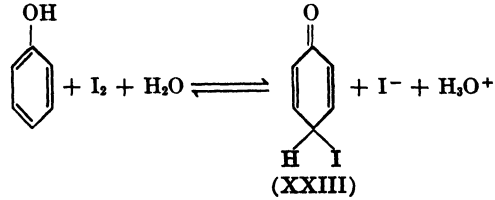
(HA is an acid, and AI an acyl hypoiodite)

$$\text{PhOH} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{PhO}^-$$

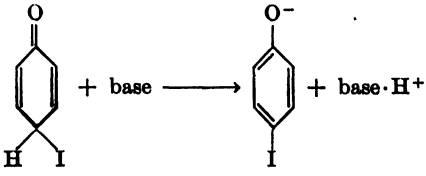
$$\text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{H}_3\text{O}^+ + \text{A}^-$$

Berliner observed that the kinetics were compatible with mechanisms involving any of the following combinations of rate-determining steps: (*a*) reaction of phenol with hypoiodous acid (first term) and of phenoxide ion with acyl hypoiodite (second term); (*b*) reaction of phenoxide ion with I^+ or H_2OI^+ (first term), and of phenoxide ion with acyl hypoiodite (second term); (*c*) reaction of phenoxide ion with hypoiodous acid with oxonium ion catalysis (first term) or with general acid catalysis (second term); and (*d*) reversible combination of phenoxide ion with I^+ or H_2OI^+ to form a complex which then releases a proton slowly to water (first term) or A^- (second term). Considering that the iodination of phenol should resemble the iodination of aniline, and taking account of the results of a kinetic study of the latter reaction (217), Berliner chose mechanism (*c*) as best in accord with all evidence. Berliner regarded mechanism (*d*) with disfavor because of then-recent evidence that proton loss from aromatic carbon was not kinetically significant in aromatic nitration and bromination; he considered it likely that the same would be true for iodination.

Some five years later Grovenstein (218) revived mechanism (*d*), which he pictured



(XXIII)



This mechanism bears a close similarity to the probable mechanism of some bromodecarboxylation reactions studied by Grovenstein. He then showed (219) that 2,4,6-trideuterophenol is iodinated only one fourth as fast as phenol; of the four mechanisms, only (*d*) is compatible with this result. Grovenstein observed that the mechanism of formation of complex (XXIII) is left undecided because measurements of an equilibrium do not reveal the pathway between initial and final states.

Here, as in the ester aminolysis example, the mechanism originally favored has been discarded on the basis of new evidence. As in the aminolysis case, doubts about the mechanism originally favored were raised by discoveries made in intervening years. And as in the other case, the conclusions from kinetics have at no stage been offered as absolute.

2. The Advisability of a Manifold Attack

In the determination of reaction mechanisms, the most effective research utilizes many types of experimentation. This is a matter of record. Seldom has a mechanism been defined to the extent of being considered "established" on the basis of evidence of a single type.

It sometimes happens that studies of a particular sort are highly productive of evidence of mechanism up to a point, but that further work of the same sort furnishes little additional insight. When such a point has been reached, it is advisable to reconsider the whole problem with special attention to new types of experiments which might furnish new types of information. Even though a new mode of experimentation may be unfamiliar or inconvenient with respect to available laboratory resources, the time and effort required to obtain the necessary facilities or to master the new technique are often warranted. Whatever other justification there may be for the monotonous application of a certain mode of experimentation to case after case, this cannot be defended on grounds of efficiency in the definition of reaction mechanisms.

The rewards to be gained from a manifold attack are illustrated in this volume by Bender (Chapter XXV) in his analysis of the forms of evidence for the formation of intermediates in chemical reactions. A glance at the Table of Contents of his chapter reveals the many forms of evidence, the many types of experimentation, which have contributed vitally to the

solution of some of the most critical problems in reaction mechanisms. The several case histories of important achievements in reaction mechanisms given by Frost and Pearson (220) also demonstrate the variety of forms of evidence which have constituted the substance of real progress in this field of research.

3. The Value of the Unique Experiment

Sherlock Holmes once said, with reference to a bizarre murder, "It is a mistake to confound strangeness with mystery. The most commonplace crime is often the most mysterious, because it presents no new or special features from which deductions may be drawn. This murder would have been infinitely more difficult to unravel had the body of the victim been simply found lying in the roadway without any of those *outré* and sensational accompaniments which have rendered it remarkable. These strange details, far from making the case more difficult, have really had the effect of making it less so" (221).

Holmes' statement is equally true of reaction mechanisms. Sir Christopher Ingold put the matter in these words with reference to the mechanism of aromatic nitration: "The second-order nitration in sulfuric acid and the first-order nitration in nitric acid could be held to be consistent with many theories of mechanism. The kinetics indicate nitration either by the nitric acid molecule itself, or by any reactive entity whose concentration throughout nitration bears a constant ratio to the stoichiometric concentration of nitric acid. . . . .That is all that can be said on the basis of these particular kinetic results: they are of *too normal* [italics mine] a type to give any specific indication of mechanism.

"On the other hand, the observation of zeroth-order kinetics for nitration in nitromethane and in acetic acid is highly significant. It has for nitration the same kind of importance as Lapworth's discovery of the first-order bromination of acetone had for prototropy. . . ." (14).

The zeroth-order nitration to which Ingold refers is the fact that, with nitric acid in large excess, the rate of nitration of several benzene derivatives is independent of the concentration or even of the identity of the compound being nitrated. As he pointed out, this means that the rate of nitration depends on some preliminary process which does not involve the aromatic compound. He showed that the preliminary change must be in the nitric acid itself. Actually, it has to do with the slow production of nitronium ion from nitric acid. The strange experimental result of zeroth order nitration was vital evidence for the nitronium ion as the effective nitrating species in organic solvents.

Understanding of the mechanism of aromatic nucleophilic substitution

reactions has also benefited from a unique experimental result. This is the fact that the reaction of *N*-methylaniline with 2,4-dinitrofluorobenzene, *but not with 2,4-dinitrochlorobenzene or 2,4-dinitrobromobenzene*, is subject to general base catalysis (65). The conclusion drawn from this and associated results was that this aromatic nucleophilic substitution goes through a metastable intermediate complex. In combination with other lines of evidence indicating the same conclusion, the unique base catalysis observation made the intermediate complex mechanism highly probable for aromatic nucleophilic substitution reactions in general.

Winstein's observation of the "special salt effect" of lithium perchlorate in certain solvolysis reactions is another unique kinetic result of high significance. Normally a plot of solvolysis rate constant against salt concentration is a straight line of positive slope, but with lithium perchlorate and some substrates such a plot is exceptionally steep at very low salt concentrations and then settles down to a line typical of a normal salt effect. The initial steep rise accounts for as much as a three-fold increase in solvolysis rate with increase in $LiClO_4$ concentration from zero to $0.001M$. The interpretation given, for example, with respect to the acetolysis of *threo*-3-*p*-anisyl-2-butyl *p*-bromobenzenesulfonate, is that lithium perchlorate interferes with "return" from the external ion pair to the original (though racemic) substrate. Perchlorate ion displaces *p*-bromobenzenesulfonate ion from the external ion pair, and the resulting carbonium perchlorate can only proceed to solvolysis products. The strange phenomenon of the special salt effect has thus exposed important details of ionization processes (222–225).

Sommer (226–228) has made good use of substrates of unique geometry to gain information about the mechanism of nucleophilic substitution at silicon. Whereas bimolecular substitution at "bridgehead" carbon (in bromotriptycene (VII), for example) is extremely slow owing to bond angle fixation and hindrance of attack on the backside of the carbon (190, 229), nucleophilic substitution at bridgehead silicon goes considerably faster than in corresponding noncyclic silicon compounds. Sommer reasoned that a transition state analogous to that for S_N2 at saturated carbon is therefore impossible. On the other hand, the data are consistent with a mechanism in which the nucleophile attacks at right angles to the bond to be broken to form a 5-coordinate silicon intermediate. Though this conclusion could no doubt have been reached from evidence of other types, Sommer's experiments with bridgehead silicon compounds are probably the most decisive tests of the question that could have been devised.

It may seem that unique observations, such as Ingold's zeroth-order nitration or Winstein's special salt effect, are a matter of luck. Can an investigator tackling a new mechanism problem depend on finding such a

unique result? Of course he cannot, but he can be alert to unusual observations. The odd result, which may seem annoying at first, may be the key to unlock the problem. In other cases, as in Sommer's work with bridgehead silicon componds, the unique experiment was the result of deliberate planning. Sommer and his co-workers worked long and hard to prepare suitable bridgehead compounds; their labors were well rewarded by the decisiveness of the conclusions reached.

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CHAPTER VII

USE OF COMPUTERS

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I. INTRODUCTION

In this chapter, we shall discuss the use of computers as a tool for the investigation of reaction mechanisms. While computers can be used to study any mathematical problems which may arise, we shall concern ourselves only with their use in relating the kinetics to the reaction mechanism, at present the most important application of computers in this field. This is an exceedingly difficult problem both experimentally and theoretically, but its solution is greatly enhanced by the use of computers.

The basic properties of the computer as an instrument are given in Section II, with particular emphasis on the types, design, and characteristics of interest. The experimental and theoretical problems involved in relating the kinetics to the reaction mechanism are summarized in Section III. The general principles and techniques of computer analysis and the applications to the problem are presented in Section IV, while in Section V, these techniques are illustrated with specific examples: The most important uses of the computer for the investigation of reaction mechanisms are briefly reviewed in Section VI.

II. COMPUTERS

Computers are basically used as an aid in correlating experimental and theoretical results. Their design and application depend on the particular subject being studied and the extent of theoretical knowledge which exists in the field.

1. Nature of Computers

In the crudest sense, any physical model can be considered a computer, as for example, the water flow model (1) or resistance model (2) for representing chemical reactions. The water flow model uses a series of buckets at different levels with connecting pipes such that water can flow down the chain from one bucket to another. When water is pumped into the upper bucket at some fixed rate, the water level in each of the other buckets will adjust itself so that the rate of inflow of water in each bucket is just equal to the rate of outflow, the water level depending on the relative sizes of the pipes. When the water level in each bucket remains constant, the system is said to be in a steady state. A similar situation occurs for a sequence of chemicals forming a reaction chain as: $A \rightarrow B \rightarrow C \rightarrow D$. When the first chemical in the reaction sequence is introduced at a constant rate, the concentrations of the other chemicals, called intermediates, will adjust themselves so that the rates of each reaction step are equal. The basis of the water flow model for a reaction sequence rests on an analogy between water level and chemical concentration, rate of flow of water and chemical reaction rate, and pipe sizes and chemical rate constants. A similar analogy between voltage and concentration, electrical current and rate of reaction, and electrical conductance and rate constant is taken for the electrical model.

Although these models may be interesting and instructive, their usefulness depends on the validity of the analogies involved. The analogy can

be established by demonstrating a correspondence between every quantitative and qualitative property of the model and the chemical system. In this case, studies of the model's properties should be considered as checks on the analogy. If the properties of the model and the real system disagree, then the analogy is incorrect. If they agree, one has only shown that the analogy is correct without any understanding of the physical reasons why it should be so. This particular use of models is generally of little value and should only be undertaken if the theoretical foundations of the subject are unknown.

However, if the theory of the subject is known or even assumed, then the analogy can be established by showing that the model satisfies the same theory in terms of its physical variables. In this case, the model may be considered a computer. Specifically, we may define a computer as a model whose physical principles of operation are understood and which therefore can be used to calculate the logical implications of those principles or any equivalent set of principles which differ only in the choice of physical variables. Now, if the computer predictions do not agree with those observed in the real system, it is the theory of the real system which is in question and not the analogy with the computer system. For example, it can be shown for a simple waterflow model that the rate of flow of water from a given bucket is proportional to the water level of that bucket. Thus it obeys the same laws in terms of its physical variables as do the analogous chemical variables for a linear chain reaction sequence ($A \rightarrow B \rightarrow C$) obeying the law of mass action, and may be used as a computer for such systems. If the behavior of the model does not agree with the chemical experiments, then it is the reaction scheme or the law of mass action which is in question, not the analogy to the waterflow model. For bimolecular reaction steps ($A + B \rightarrow C + D$), which according to the law of mass action have a non-linear rate law, the water flow model cannot be used as a computer since it is limited to a linear rate law.

The theory of any set of phenomena can generally be expressed in terms of mathematical equations, and the model may be considered a computer for solving the particular mathematical equations it obeys. Any other phenomena which satisfy the same type of equations (i.e., where the variables can be related to those of the computer system by a proportionality factor) can be studied on this particular computer. Mathematical equations are the common basis relating computers, models, and phenomena. Any phenomena with the same equations may be considered as models for each other and any model may be used as a computer to study these equations. The term "mathematical equations" is used here in its broadest sense and requires no more than some logical relationship between the variables. For example; the theory of a chemical re-

action is ultimately expressed in terms of interactions on the molecular level. The equations for the net reaction rate in these terms are cumbersome to write down and difficult to simplify. However it is not necessary to know these reaction rate equations since a computer can be constructed which represents each molecule (although for practical reasons the computer may be limited to a total of about one thousand molecules). This computer can then be used to compute the net reaction rate or the concentration of the chemicals as a function of time.

2. Characteristics and Design of Computers

We shall list and discuss the most important characteristics by which particular computers can be classified, and which determine the best computer to use for a given problem.

A. ABILITY

The "ability" of a computer refers to the different types of mathematical equations the computer is capable of solving. Because of the particular model chosen, some computers are limited to a very narrow class of equations, such as very special types of differential equations. This is satisfactory if the particular problem to be studied is also limited to these special equations. However, with modern techniques, it is easy to construct components which can perform elementary mathematical operations such as addition, multiplication, integration, comparison, matrix addition, etc. The complete computer is then capable of solving any equations which can be written in terms of the elementary operations it can perform, and the ability of the computer is determined by the number of different operations available.

B. PROGRAMMING

Programming consists of combining the elementary operations to form a particular equation or a more complex operation. The simplicity and speed with which the programming can be effected is important in determining the computers usefulness for certain problems.

C. CAPACITY

The capacity is measured by the total number of any particular elementary operations available to the computer. For example, a computer with ten multipliers has a greater capacity than one with five. The capacity may determine the total number of independent variables for simultaneous algebraic or differential equations or the degree of the equa

tions which can be solved (at least two multipliers are required for a quartic equation).

D. RANGE

This refers to the total range of the variables and parameters which can be studied without the computer running off scale (i.e., outside the allowable size of its physical variables) or into accuracy and stability problems. It is not the maximum value of any one variable which is important, since this can be brought into the range of computer variables by appropriate adjustment of a scale factor (e.g., one second of computer time may represent 10^6 or any number of seconds so far as the equations are concerned). Rather it is the relative size of any two variables which is limited by the physical properties of the computer and defines the range.

E. SPEED

This can be the time it takes to perform any particular operation, elementary or complex, or to solve a particular equation. Any one of these times can be used to compare computers, but it is the time it takes to solve a particular problem that is most pertinent.

F. ACCURACY AND STABILITY

Since a computer is itself a real physical system, a calculation is actually an experiment and is subject to the same general problems as any experiment. The accuracy with which the initial conditions can be specified and the solution measured is important. The stability of the solution for short times and for long times (repeatability of the experiment) must also be considered.

G. INPUT AND OUTPUT

Input refers to the manner and ease with which the initial conditions of a given problem can be inserted into the computer, while output refers to the manner and ease of obtaining the solution in a useful form. For many problems, such as solutions of differential equations, a graphical output is essential.

H. COST AND AVAILABILITY

The cost of a computer varies greatly according to its characteristics and for economic reasons this often determines its availability. However, in many cases, a computer owned by one institution may be used by others.

Computer design usually reduces to finding the best model capable of providing all the characteristics required for study of a particular subject. In general, the characteristics of a computer are interrelated and one cannot be obtained without affecting the others. Also, these characteristics must be coordinated with the characteristics of the real system such as the experimental accuracy, type of theoretical equations, and number of variables.

Within these requirements, the computer is usually designed to give maximum accuracy, stability, and ease of programming for a reasonable cost. At present, there are two conditions which have considerably enhanced the development of computers: first, the widespread use of electronics as an efficient and convenient means of representing a wide variety of mathematical problems; second, the breakdown of computers into elementary mathematical operations. The latter development has the advantage that once a particular operation is designed, it can often be used in other electronic computers to solve different problems or equations; the effort of design is not wasted and the cost is reduced. There are, two basic types of computers, the digital and the analog, which differ from each other considerably. Either type may be mechanical or electronic, but we shall emphasize the electronic versions since the mechanical computers are rapidly becoming obsolete.

3. Electronic Analog Computers (3,4)

An analog computer is a model the physical variables of which are known to satisfy a certain set of equations. The value of the physical variable is taken to be proportional to the mathematical variable of the equations that the computer represents. The characteristics, such as accuracy, depend on the properties of the model. A familiar example is the slide rule where the analog is between the physical variable of distance on the rule and the mathematical variable of the logarithm of a number (although for convenience, the number itself is written on the rule). For any given slide rule, these variables are proportional to each other. The operation of the slide rule satisfies an equation of addition, a given distance on the fixed rule being added to a given distance on the movable rule to form the sum of their distances, and corresponds to addition of logarithms, i.e., multiplication of the numbers. The accuracy is limited by the total length of the rule and the stability is determined by the uniformity and temperature dependence of the material.

For electronic analog computers, the physical variables are time and voltage, corresponding mathematically to an independent variable and

dependent variable respectively. With modern circuitry, it is not difficult to develop components which can perform many mathematical operations such as addition, subtraction, integration, and comparison. These give the analog computer considerable ability to study a variety of equations important in physics and chemistry. However, there are many problems which an analog computer cannot be used to solve, such as those encountered in partial differential equations or matrix calculus. The abilities are primarily limited to problems which have only one independent variable. Programming requires only the coupling of the appropriate operations by wires to form the equation desired. The initial conditions are obtained by adjustment of potentiometers. The solution is usually displayed graphically on an oscilloscope. The speed of solution is measured in milliseconds or seconds for any problem which the computer can solve. The capacity, accuracy, stability, range, and cost are all interrelated and depend on the particular computer, but some rough limits can be given. The accuracy is rarely better than one tenth per cent. The capacity is limited to about one hundred elementary operations, although this can be extended to about one thousand for certain types of operations. The maximum range may vary from ten to ten thousand and is closely related to the short time stability, depending on both the computer design and the mathematical stability of the equations being solved. The long time stability depends on the d.c. level drift which may be as much as one percent per hour but can be eliminated by automatic zeroing devices or a.c. circuitry; in addition, instability arises due to changes in the properties of the vacuum tubes and resistors of about one percent per year. The cost of an analog computer varies from one thousand to fifty thousand dollars.

4. Electronic Digital Computers (5)

Although all digital computers are based on some physical phenomena, they are not models in that the physical variables are not directly related to the mathematical variables. A simple example is the abacus, on which the operation of addition is performed by moving the appropriate beads from one side to the other. The physical properties of the beads and the frame are unimportant, as is the exact position of the bead; it is only necessary to know whether the bead is on the right side or left side of the frame. The principle of operation is simply that of counting and the abacus itself is just a convenient instrument for notation.

The high speed electronic digital computers operate on the same principles. A vacuum tube is considered to represent the number zero when it is not conducting current and the number one when it is conducting a large current; the exact current is not important any more

than the exact position of the bead in the abacus. Many vacuum tubes, like many beads, can represent larger numbers. Basically, these computers can perform only the elementary operations of addition, subtraction, multiplication, division, and comparison. However they also have a memory, a device which can store information for later use, and the ability to move information in and out of the memory. As with a a human being who is likewise limited, the combination of these features provides essentially an unlimited ability and capacity. Thus, while the computer has only one adder component, any number of additions can be carried out one at a time by storing the information for each one in the memory. All higher mathematical operations such as integration, are carried out by numerical techniques, which require only a procedure and arithmetical operations. Digital computers have already been used to solve partial differential equations and problems of matrix calculus, and can in principle be used to study any problem for which a logical procedure can be given.

All information pertaining to data or procedure is given to the computer by means of code words impressed on magnetic tapes (in some cases, punch cards are used) by special typewriters, and the results from the computer are printed as words or numbers by a machine which can read magnetic tapes. The programming of the digital computer is done in two steps. The first step involves the basic programming of the procedures for all the higher mathematical operations necessary for a particular type of problem; this corresponds to the actual construction of the analog computer, although the method is that of typing code words onto magnetic tapes. It should be noted that once an operation has been programmed, it may be utilized in any new problem with little more effort than copying the tape. The second step in the general programming is the joining of the various operations for a specific problem, and corresponds to the programming of the analog computer.

There is no inherent limitation of practical value on the accuracy, range, or stability of the computer operations. Numbers having ten to twelve digits are represented and more digits can be included. All calculations are exact. The only important physical property is the speed of the computer operations, since the total time to solve any given problem is the product of the total number of computer operations required times the speed for these operations. The effective characteristics of the computer are determined by the particular numerical procedures used. For a given procedure, a greater accuracy, range, or stability requires a greater number of computer operations and hence a longer time. The time for a solution is usually measured in minutes or hours.

The cost of an electronic digital computer is about one million dollars.

and for that reason they are only owned by large groups or institutions. Individuals may rent the use of a computer at from one hundred to five hundred dollars per hour usually for a limited period. An average maximum between one and ten hours per week is common. The cost of programming will depend on whether the mathematical operations required are already available, but is usually between one and fifty thousand dollars.

To summarize the relative advantages and disadvantages of electronic analog and digital computers: because of accuracy, ability, or capacity requirements, the digital computer is often the only one capable of solving the problem. In cases where both computers are capable, the costs of basic programming (digital) or construction (analog) are likely to be comparable; however the cost of further operation is negligible for the analog, but not for the digital. The analog computer is available to small groups, thus offering ample time for elaborate investigation. The solutions are obtained graphically and rapidly (milliseconds to seconds), and the effects of changes in initial conditions or parameters are immediate. The digital computer is of limited availability to the individual. Solutions can be obtained graphically but are slower (minutes to hours) and may require an intermediate step (use of printer) to be observed. However the digital computer affords the advantage of automatic and convenient data processing. Thus if various features of the graphs such as slopes or maxima, must be highly accurate, they can be better obtained from the digital computer. However both types of computers have an important role in the study of reaction mechanisms.

III. KINETICS AND THE REACTION MECHANISM

1. General Principles

The study of the reaction kinetics of a chemical system is one of the important methods used to elucidate the reaction mechanism. The kinetics of a reaction are completely determined by (*1*) the stoichiometry, (*2*) the rate law, and (*3*) the values of the constants involved in the rate law, together with the initial experimental concentrations. The stoichiometry expresses the possible reaction steps allowed between a set of distinct chemicals; it is not necessary to know the chemical composition of the chemicals involved. Conversely, experimental studies of the reaction kinetics can be expected to give information concerning these three aspects of the reaction mechanisms.

In practice there is no way of interpreting the reaction mechanism directly from the kinetic data. The usual procedure is one of trial and error. A

mechanism consistent with all the known physical and chemical data is hypothesized for the system, and the kinetic predictions of this mechanism are tested against the experimental kinetics. If there is agreement, the mechanism is satisfactory; if not, the mechanism is modified and the procedure repeated. The testing of any particular mechanism requires a detailed study of the kinetics and involves many difficult theoretical and experimental problems which are discussed below. Consequently, it is important to make a good first choice for the proposed reaction mechanism. Any known physical and chemical properties of the system will aid considerably in limiting the likely reaction mechanisms. Equally important, the qualitative and crude quantitative features of the kinetics can be used directly to limit the possibilities.

In all that follows, we shall assume that we are dealing with systems of dilute soluble chemicals. For this case, there is much experimental and theoretical evidence (6) to support the use of the law of mass action as the rate law. Thus the determination of the reaction mechanism is reduced to finding the stoichiometry and the rate constants. While the determination of the rate constants plays an important role in testing the mechanism, it should be pointed out that the rate constant itself has no meaning until the stoichiometry and the rate law are known. In the next sections we shall discuss the experimental and theoretical problems in relation to the testing and determination of the mechanism.

2. Experimental Problems

The application of the law of mass action to the stoichiometry produces a set of differential equations. In principle these equations are solved to obtain formulas relating the concentrations at any time, the initial concentrations, the time, and the rate constants. Experimentally, all quantities can conceivably be measured directly except the rate constants. The testing of the mechanism requires qualitative and quantitative agreement between the formula and the experimental results. Quantitative agreement means that there exists one set of values for the rate constants such that the formula exactly expresses the experimental results at every time (t) and for all initial conditions. It is not the actual values of the rate constants which are important, but the fact that one set of values explains all the experimental data. We shall call this test the test for "invariance of the calculated rate constants." Basically, this is a decisive test for the mechanism, but in practice it cannot be carried through completely. The experimental data have a limited accuracy, as well as limited range of possible initial conditions and times for which the kinetics can be measured. Often, some of the chemicals involved in the reaction cannot be observed at

all. As a result the critical value of the test is reduced. With the best practical conditions, kinetic studies alone can only show that a mechanism is satisfactory, not that it is the only mechanism which can explain the data. But to be satisfactory, it must be shown that the rate constants are invariant for *all* the available experimental data.

A simple example will help to illustrate some of these points. Consider the irreversible reaction

$$A \xrightarrow{k} B \tag{1}$$

for which an application of the law of mass action yields the differential equation

$$da/dt = -ka \tag{2}$$

which describes the reaction kinetics, where a is the concentration of chemical A, t is the time, and k is the rate constant. The solution of this equation is

$$a = a_0 \exp(-kt) \tag{3}$$

where a_0 is the initial concentration of a. The solution indicates that qualitatively the concentration of A is always decreasing in time from the initial concentration and approaches zero as the time approaches infinity; there are no minima or maxima. If the experimental data do not fit these conditions, the mechanism is obviously incorrect and no further study is warranted. If the qualitative test is satisfied, the solution indicates that a plot of the natural logarithm of a versus t should yield a straight line whose slope is $-k$. That is, plotting the experimental data in this way should yield a curve (in this case a straight line) such that the measured rate constant (the slope of the curve in this case) at every time (t) is the same; this is one example of the invariance of the measured rate constant. But this curve is only a straight line within the accuracy of the experimental data and over the range of time studied. It might actually be slightly bowed in this range or break sharply from a straight line at larger times, indicating that this mechanism is incorrect. This would occur for example, if the reaction were slightly reversible. By carrying out the same plot for different initial conditions, this possibility might be reasonably eliminated or definitely demonstrated, as by studying the kinetics of A in the presence of a large amount of B.

In some cases, very special formulas must be used because of the experimental limitations or difficulties in solving the differential equations. For instance, in our example the rate constant can be given by

$$k = 0.693/t_{1/2} \tag{4}$$

where $t_{1/2}$ is the time at which the concentration is one half of its initial value (i.e., $a = {}^1/_2 a_0$). If for various physical and chemical reasons, it is known that the particular reaction follows this mechanism, then the formula (4) is convenient for evaluating the rate constant. If the mechanism is not known, such a number has no meaning. For no matter what the mechanism, if the experimental data have the same qualitative features, this formula can be used to produce a calculated rate constant. However if this calculated rate constant has the same value for all initial conditions, then its invariance is a partial test of the mechanism. Generally speaking, it is important that the experimental data studied be as accurate as possible and cover the greatest range of conditions available, in order that the mechanism can be reasonably considered as satisfactory.

3. Theoretical Problems

As well as the experimental difficulties already discussed, there are theoretical difficulties. Except for extremely simple stoichiometry, as in our example, the application of the law of mass action will lead to a set of simultaneous non-linear differential equations. These equations cannot generally be solved in closed form and any approximate solutions are extremely involved and impractical to apply. Even the qualitative features of the solutions are difficult to obtain. Often, any simple formulas which can be deduced are questionable because of the mathematical assumptions involved, or are of little value because their region of validity is not accessible to experimental study (e.g., formulas for the initial slopes of the kinetic curves). An especially useful assumption is that of the steady state which is more easily studied experimentally; this assumption reduces the differential equations to non-linear algebraic equations. Though simpler, these equations are also difficult to analyze, and in addition the conditions necessary for the steady state to hold are not easily derived from the differential equations.

The theoretical problems can be summarized in the following questions. (*1*) Given a particular reaction mechanism, what are the qualitative features of the kinetics, what practical experiments can be given to test the validity of this mechanism, and how can the values of the rate constants be determined if the mechanism is known? (*2*) To what extent can the stoichiometry be deduced from kinetic studies alone? That is, rather than use the method of trial and error to determine the stoichiometry, can the possibilities be narrowly limited by certain general but critical tests? (*3*) How many different mechanisms are consistent with the experimental data for a given accuracy and range of initial conditions?

These last two questions differ primarily in detail, and the answer to the

second question already gives a partial answer to the third. Also, it is clear that the answers to both these questions could be obtained by organizing and classifying the answers to question (1) for all conceivable reaction mechanisms. While this is impossible, certain general types of reaction mechanisms can be studied, leading to positive conclusions. These three questions reflect deeply on the value of kinetic studies as a tool for determining the reaction mechanism. In the next sections we shall see that the use of computers is particularly helpful in obtaining the answers.

IV. USE OF COMPUTERS

1. General Principles

There is one important point to be kept in mind when computers are used to study complicated equations. The computer deals with numbers, not mathematical variables. Any solution obtained must be for specific numerical values of the parameters; the solution itself is only a set of numbers which may be graphically portrayed. In some cases, this is all that is desired, but in order to obtain properties of the equations which are independent of the parameters the procedure is more complicated. Consider the problem of determining by means of a computer the properties of the equation

$$y = mx \tag{5}$$

where m is a parameter, x the independent variable, and y the dependent variable. The most elementary mathematical analysis shows immediately that this is the equation of a straight line through the origin with slope m for any value of m; we shall assume that such analysis is impossible for the moment. For a specific numerical value of m, say 0.5, the computer can calculate and plot the values of y for specific values of x; only a finite number of different values of x can be used and these should be chosen close enough so that the resulting curve would not be expected to change radically for values in between. In our example, a graph would show a straight line through the origin with slope 0.5. Repeating the calculation for different values of m chosen close together would allow one to assert that "for all values of m and x studied on the computer, the equation represents a straight line of slope m passing through the origin." Such an assertion will be called a "computer theorem." Nothing can be said about the nature of the equation outside the range of values studied on the computer. The limitations of using the computer alone are apparent.

However, the realization that this equation is a straight line over the

range of the computer is of considerable benefit to the mathematical analysis of the equation. In our example, the analysis is trivial, but in the general case the use of the computer to give insight should not be underestimated. Difficult mathematical analysis is always facilitated by an appreciation of the answer which one should obtain. Time is not wasted trying to prove impotent or incorrect theorems. The combination of computer studies and mathematical analysis creates an extremely powerful method for the study of complicated equations.

2. Applications to the Problems of Kinetics

With these features in mind, we may list the particular applications of the computer to the various aspects of the kinetics.

A. CALCULATION OF RATE CONSTANTS

If the stoichiometry and rate law of the mechanism are known and good experimental data are available, the computer may be used to calculate the rate constants. For a particular set of initial conditions, the computer rate constants are varied until the graphical solutions from the computer match those of the experiment. Any information which limits the range of the rate constants will reduce the number of trials needed to produce the best fit. If the experimental data are very inaccurate or incomplete, then it is possible to find more than one set of rate constants which will match the curves equally well, but for reasonably good data this does not occur.

B. TEST OF MECHANISM

If the stoichiometry and rate law of the mechanism are only assumed, the procedure is the same as in application (A) and can be used to test the proposed mechanism. But in addition, the kinetic curves for different sets of initial conditions should match the corresponding experimental curves using the same set of rate constants throughout. If one set of rate constants does not allow a fitting of curves over all initial conditions for which data are available, the mechanism is incorrect. If the curves do fit, the mechanism is satisfactory, though there may be other mechanisms which can fit the data equally well.

C. STUDY OF QUALITATIVE FEATURES

The prominent qualitative features of the kinetics of any mechanism can be readily observed on the computer. These should be studied for their dependence on the rate constants, initial conditions, and changes in

the stoichiometry. This is an important use since the existence of any particular qualitative feature is extremely difficult to prove analytically even if, in the rare cases, it is suspected to exist. Once knowing that a property exists, it is relatively easy to study it by mathematical analysis.

D. QUANTITATIVE FORMULAS

Computer theorems can be developed to give formulas for the rate constants or relations between the chemical concentrations. Such theorems are primarily limited to mechanisms with only a few parameters since otherwise a quantitative study over the range of all parameters requires too much time. The use of the computer as an analytical tool is more important for the larger systems.

E. PRACTICAL TEST OF FORMULAS

In many cases, correct formulas can be derived by mathematical analysis alone, but the accuracy required for the experimental data, in order that the formulas have any practical value, is not known. The computer is then used as a model for the chemical system and the formulas applied to the computer data. For example, the Equation (2) shows that $k = 1/a(da/dt)$ gives the rate constant in terms of the concentration and the slope of the kinetic curve at any time (t). Since slopes are in general difficult to measure, the formula is of questionable value, but it can be tested by using the computer curves; the calculated value of the rate constant being compared with the known value used in the computer. The accuracy of the computer measurement should be made comparable to the experimental accuracy for the chemical system.

V. EXAMPLES

In this section we shall give specific examples of different applications already carried out on two particular computers; the Johnson Foundation Electronic Analog Computer and the Univac I Electronic Digital Computer. The problems studied are of particular concern in the theory of enzyme reactions, but the mechanisms have applications in other fields of chemistry. The computer techniques will be amply illustrated.

1. The Johnson Foundation Electronic Analog Computer

The Johnson Foundation Electronic Analog Computer shown in Figure 1 was constructed in 1950 for the specific purpose of studying the problems

of chemical kinetics. It consists of electronic adders, variable multipliers, and integrators which carry out the mathematical functions. Also there are purely electronic components which have no effect on the mathematics, such as power supplies, choppers, and detectors; the latter allow the use of a.c. circuitry which increases the long time stability by eliminating many of the d.c. drift problems. The input of initial conditions is by means of potentiometers, called "input adders," and the rate constants are set by resistance dividers, called "constant multipliers." The output is obtained as a trace on an oscilloscope, with equipment provided for enlarging and photographing the results. The computer is able to solve the non-linear differential equations which arise in the study of reaction kinetics. The capacity is limited to mechanisms with about 8 or 10 different chemi-

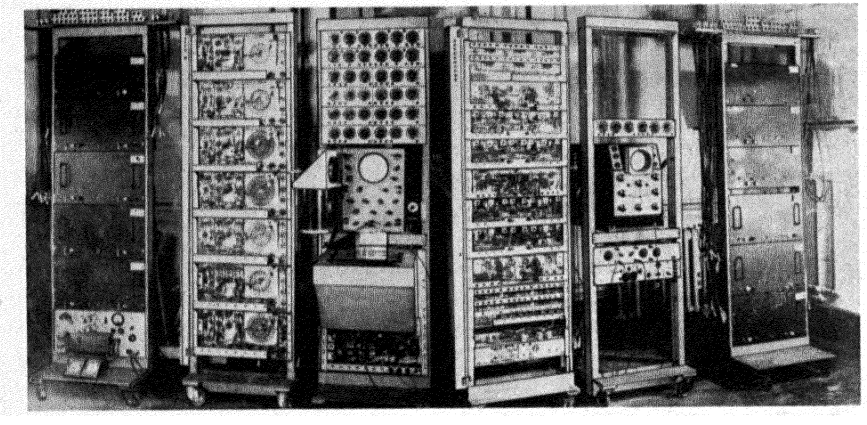


Fig. 1. The Johnson Foundation Electronic Analog Computer.

cals, depending on the stoichiometry. The accuracy is comparable to the experimental accuracy for enzyme reactions, i.e., between one and five percent. The total time for a solution can be varied from 60 to 500 milliseconds, after which the solution is automatically repeated so that a persistent trace is observed on the oscilloscope. For these total times and a maximum relative range of about 100, there are no major stability problems, although the integrators must be rezeroed about once every hour for accurate results. For longer solution time or greater ranges, the computer will usually develop short times instabilities depending on the problem. The total cost of the computer, exclusive of labor and design, is about twelve thousand dollars; it required about five man-years to complete.

The programming of the computer is illustrated by Figure 2b, which is a schematic diagram of the computer arrangement for representing the

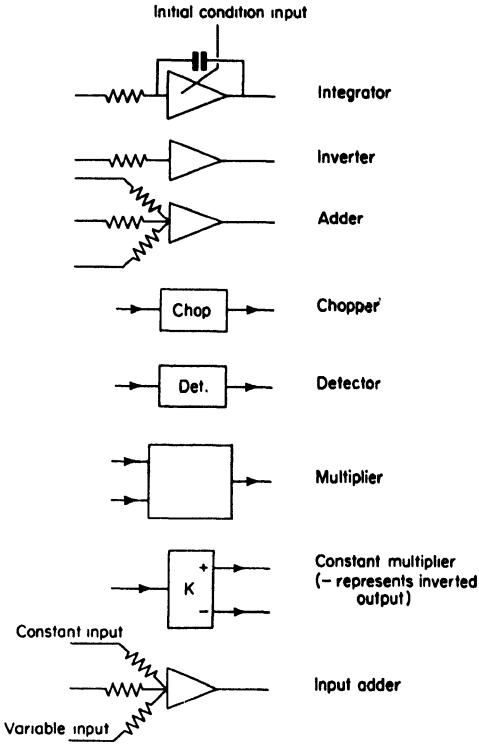
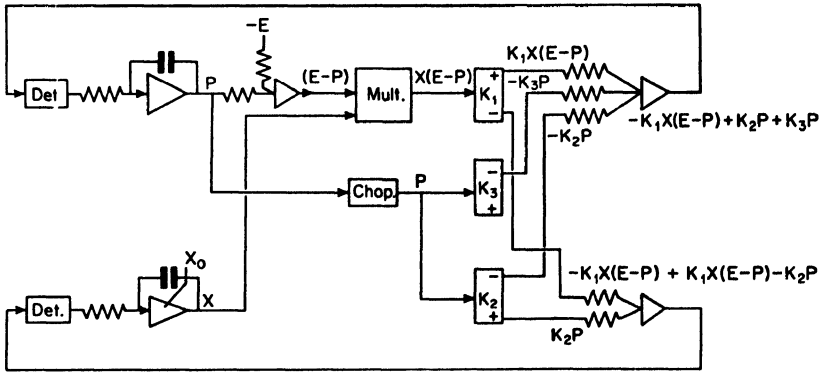


Fig. 2a. Symbols for computer elements.



g. 2b. Schematic diagram of the analog computer program for Michaelis-Menten mechanism.

following differential equations:

$$(10/RC_P)(dX/dt) = -K_1[X(E - P)/25] + K_{-1}P \quad (6a)$$

$$(10/RC_X)(dX/dT) = K_1[X(E - P)/25] - K_{-1}P - K_2P \quad (6b)$$

where X and P are variable voltages which depend on the computer time T, while E and X_0 are constant voltages. The constants K_1, K_{-1}, and K_2 are obtained by constant multipliers and have values between zero and one. The factor $10/RC_P$, where RC_P is the time constant for the P integrator, is due to the gain of the integrator. Electronically, it is necessary to limit all voltages to a maximum of 25 volts; consequently, a constant factor of $^1/_{25}$ is introduced in the variable multiplication. All integrators and adders perform electronic inversion which corresponds to multiplication of the input by minus one. The constant multipliers have two outputs, one inverted and the other not inverted. The choppers and detectors have no net mathematical value; the multiplier has a built-in chopper. It is most easy to see that the computer arrangement produces the corresponding differential equations by assuming that the outputs of the integrators are the variable voltages, P and X. These are then carried through the appropriate operations of addition and variable and constant multiplication to form the terms on the right hand side of the differential equations. According to the differential equations, the appropriate sums of these terms give the right hand side of Equations (6a) and (6b); i.e., the respective derivatives $\dot{P}$ and $\dot{X}$. When these derivatives are introduced into the integrators, the output will be P and X respectively. This is consistent with our original assumption and the electronic feedback properties of the circuitry will insure that the equations are satisfied. In operation, the computer is started with $X = 0$, $P = 0$, and $(E - P) = E$. At time $T = 0$, X is suddenly raised to its initial value X_0. The solution of P and X proceeds from this set of initial conditions for the total computation time (60–500 msec.); then X and P are automatically reset to zero and the solution repeated in the same manner.

2. Study of the Michaelis-Menten Mechanism

A. GENERAL FEATURES

This particular computer circuit solves the equations which represent the Michaelis-Menten mechanism (7) for enzyme reactions. The stoichiometry is

$$\begin{array}{ccccc} \mathrm{E} & + & \mathrm{S} & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & \mathrm{ES} \\ (e-p) & & x & & p \end{array} \quad (7)$$

$$\begin{array}{ccccc} \mathrm{ES} & \xrightarrow{k_2} & \mathrm{E} & + & \text{product} \\ p & & (e-p) & & \end{array}$$

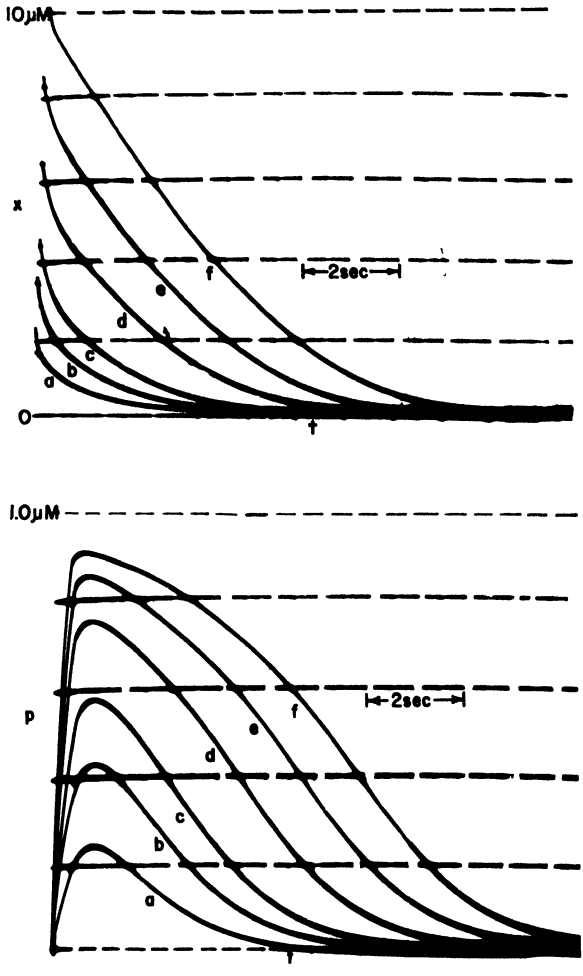


Fig. 3. Computer solutions for the effect of initial substrate concentration (x_0) on the kinetics of the substrate (x) and the intermediate (p) of the Michaelis-Menten mechanism, with: $k_1 = 0.9 \times 10^6 M^{-1}\,\text{sec.}^{-1}$; $k_{-1} = 0$; $k_2 = 1\ \text{sec.}^{-1}$; $e = 1\mu m$. For curve (a) $x_0 = 2.5\mu M$; (b) $x_0 = 3\ 6\mu M$; (c) $x_0 = 4.5\mu M$; (d) $x_0 = 6.6\mu M$; (e) $x_0 = 8.3\mu M$; (f) $x_0 = 10.0\mu M$.

and the application of the law of mass action shows that the concentrations x and p satisfy the differential equations

$$dx/dt = -k_1x(e - p) + k_{-1}p \tag{8a}$$

$$dp/dt = k_1x(e - p) - k_{-1}p - k_2p \tag{8b}$$

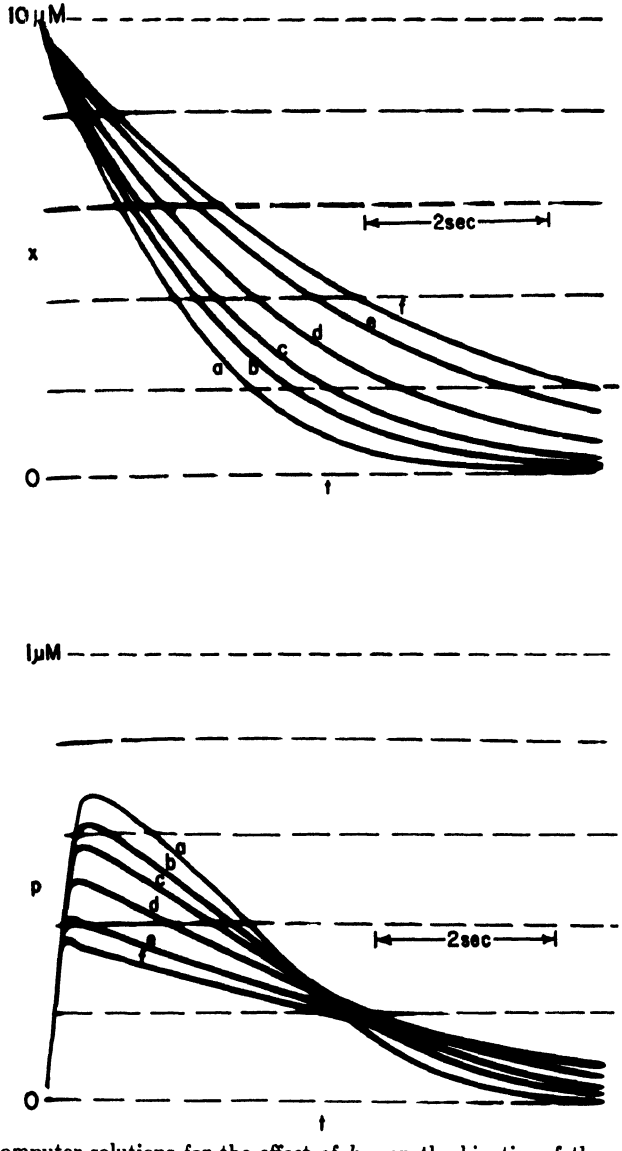


Fig. 4. Computer solutions for the effect of k_{-1} on the kinetics of the substrate (x) and the intermediate (p) of the Michaelis-Menten mechanism with: $k_1 = 0.8 \times 10^6 M^{-1}\text{sec.}^{-1}$; $k_2 = 3$ sec.$^{-1}$; $e = 1\ \mu M$; $x_0 = 10\ \mu M$. For curve (a) $k_{-1} = 0$ sec.$^{-1}$; (b) $k_{-1} = 1$ sec.$^{-1}$; (c) $k_{-1} = 2$ sec.$^{-1}$ (d) $k_{-1} = 4$ sec.$^{-1}$; (e) $k_{-1} = 7$ sec.$^{-1}$; (f) $k_{-1} = 10$ sec.$^{-1}$

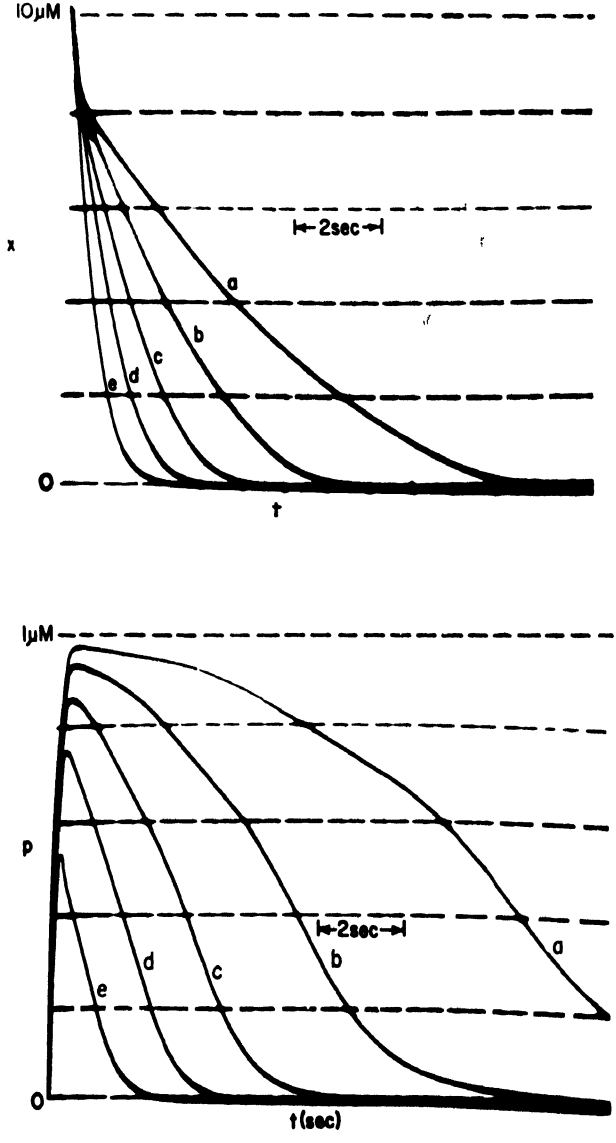


Fig. 5. Computer solutions for the effect of k_2 on the kinetics of the substrate (x) and the intermediate (p) of the Michaelis-Menten mechanism, with: $k_1 = 0.8 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_{-1} = 0$; $e = 1\mu M$; $x_0 = 10\mu M$. For curve (a) $k_2 = 0.5$ sec.$^{-1}$; (b) $k_2 = 1$ sec.$^{-1}$; (c) $k_2 = 2$ sec.$^{-1}$; (d) $k_2 = 4$ sec.$^{-1}$; (e) $k_2 = 10$ sec.$^{-1}$

where k_1, k_{-1}, and k_2 are rate constants; x, p, and e are the concentrations of substrate, intermediate, and total available enzyme, respectively; and t is the real time observed by the experimenter. The chemical system is started with $x = 0$, $p = 0$, and $e - p = e$; then at $t = 0$ an initial amount of substrate $x = x_0$ is added, and the reaction proceeds. Comparing the differential Equations (8a) and (8b) with those for the computer circuit (Equations 6a and b) we see that the equations are identical if we set

$$\begin{aligned} x &= X \times \bar{x}/25 \\ p &= P \times \bar{p}/25 \\ k_1 &= (10s/RC_P\bar{x})K_1 \\ k_{-1} &= (10s/RC_P)K_2 \\ k_2 &= (10s/RC_P)K_3 \\ T &= st \\ \bar{x}/\bar{p} &= RC_XR/C_P \end{aligned} \tag{9}$$

where $\bar{x}$ and $\bar{p}$ are constant scale factors representing the chemical concentrations associated with 25 volts of X and P; the constant s represents the scale factor between computer time and real time. The RC's, K's, and s must be chosen to give the chemical quantities desired. As all the relationships are linear, the correlation of computer solutions to chemical solutions is simply a matter of proportionality. Setting $\bar{p} = e = 1M$, $\bar{x} = 10M$, $RC_X = 0.2$, $RC_P = 0.02$, and $s = 0.02$ gives $k_1 = 10^6M^{-1}$ sec.$^{-1}$ for $K_1 = 1.0$; $k_{-1} = 10$ sec.$^{-1}$ for $K_{-1} = 1.0$; $k_2 = 10$ sec.$^{-1}$ for $K_2 = 1.0$; and $t = 50T$ so that ten milliseconds of computer time is equivalent to 0.5 seconds of real time. Using these values for the scale factors, typical computer solutions of the kinetics of substrate (x) and intermediate (p) for the Michaelis-Menten system are shown in Figures 3, 4, and 5, where in Figure 3, x_0 is varied; in Figure 4, k_{-1} is varied; and in Figure 5, k_2 is varied to illustrate the effect of these parameters. The horizontal lines in these graphs are 5 volts apart and the spaces in the lines indicate 10 milliseconds of computer time. These figures readily demonstrate the dependence of the qualitative features of the kinetics on the various parameters.

For experimental and theoretical reasons it is useful to divide the kinetics into distinct regions. These are shown accentuated in Figure 6. The "on" region represents the transition from the initial state to the steady state and is characterized by rapidly changing intermediate and substrate concentrations, though the total change in substrate is small. For some mechanisms, there may be an overshoot with respect to the steady state as shown in the lower graph. Experimentally, the "on" region is difficult to study because of the short time involved. Usually rapid flow techniques are required.

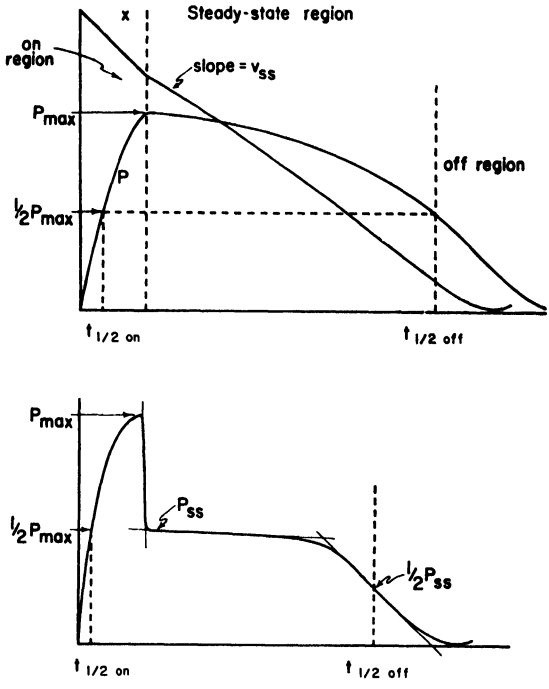


Fig. 6. General types of substrate (x) and intermediate (p) curves as a function of time. These figures show the definition of the more important features. In the upper figure the steady state region is determined by the time at which the maximum occurs and the $t_{1/2\ off}$. In the lower figure it is determined by the intersection of the maximum and minimum slopes and $t_{1/2\ off}$ as shown.

The steady state region is characterized by a slowly changing intermediate concentration. This region is the most easily studied experimentally, but it shows no striking qualitative features. Theoretically, the steady state is studied by assuming that the derivative of the intermediate is zero. A look at the computer solutions shows that this is not true, which observation has stimulated considerable research into the nature of the theoretical conditions for the steady regions (8). It can be shown that the steady state equations obtained by setting $\dot{p} = 0$ are approximately valid so long as $\dot{p}/\dot{x} \ll 1$ and also $\dot{p}/\dot{p} \ll 1$ (a dot $(\cdot)$ means time derivative, i.e., $\dot{p} = dp/dt$). These conditions are always satisfied for $x \gg e$, as well as more special cases. They indicate that the steady state region is characterized by an intermediate curve which is approximately a straight line with a slope ($\dot{p}$) not necessarily zero. Thus a steady region exists for the curves of Figure 4 for $x_0 \gg e$ even though many of them do not have a zero slope for the intermediate in this region. Except for special cases,

when $x_0 < e$, the steady state region does not exist as can be seen in curve (a) of Figure 3.

Finally we define the "off" region for the reaction. This is the region in which the intermediate decays from its steady state to its final equilibrium value. For the irreversible reactions discussed here, the equilibrium state has all concentrations (x,p) equal to zero, except for the products which are not considered. Whenever the conditions discussed in the previous paragraph are no longer valid, the steady state region ceases to exist. These conditions are not always qualitatively obvious. For purposes of discussion, the end of the steady state region and the beginning of the "off" region is defined, somewhat arbitrarily, as the time point at which the intermediate has dropped to half its steady state value (i.e., the $t_{1/2\ \mathrm{off}}$; see below). Experimentally, quantitative measurements in the off region are difficult to make because of the low concentrations for the substrates and intermediates. Again there are nc important qualitative features in the region.

In addition to the different regions, it is useful to define certain distinct quantitative properties. These are the steady state concentrations denoted by p_{ss} and x_{ss}, the steady state slope of the intermediate curve $(\dot{p}_{ss})$ and the net reaction velocity $(v_{ss} = x)$ in the steady state. The maximum values of the intermediate are denoted by p_m; for the upper graph of Figure 6, $p_m \approx p_{ss}$, while for the lower figure there is a great difference. As we have already pointed out, the concentrations of both substrate and intermediate will change somewhat in the steady state region so that p_{ss} and x_{ss} are actually variables in time. We will also define the half times of the reaction: $t_{1/2\ \mathrm{on}}$ is the time in the "on" region at which the intermediate concentration has risen to one half its maximum value (i.e., $p = {}^1/_2\, p_m$), and $t_{1/2\ \mathrm{off}}$ is the time in the "off" region at which the intermediate has dropped to one half its steady state concentration (i.e., $p = {}^1/_2 p_{ss}$).

B. SPECIFIC RESULTS

Historically, the first application of computers to the investigation of the reaction mechanism was made (9) in 1940. The Michaelis-Menten reaction mechanism for enzymes was studied with the aid of a differential analyzer (a mechanical analog computer). The results were compared with the experimental data for the reaction of peroxidase.

First it was noted that by adding together the differential equations (8a and b) and integrating the resulting equation from $t = 0$ to $t = \infty$, the equation

$$x_0 = k_2 \int_{t=0}^{t=\infty} p\, dt \tag{10}$$

is obtained. The integral in this equation is just the total area under the intermediate curve. The shape of the computer solutions (Fig. 3) indicates that this might be approximated by the area of a rectangle whose height is p_m and whose length is $t_{1/2\ off}$, giving the formula

$$x_0 = k_2 p_m t_{1/2\ off} \qquad (11$$

This derivation is only suggestive; it has no mathematical rigor. However, the Equation (11) can be tested on the computer data. Figure 7 shows a plot of $k_2 p_m t_{1/2\ off}$ versus the value of x_0 used in the computer for several different values of k_2 and for $k_{-1} = 0$; the values of p_m and t_{off} are

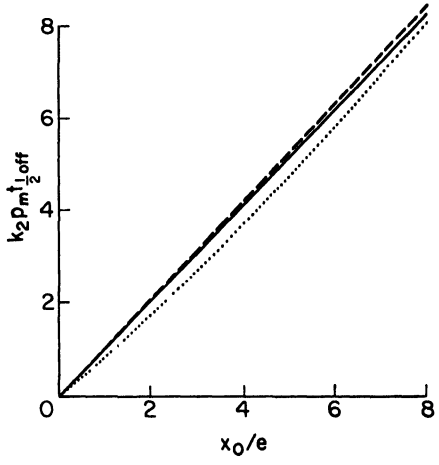


Fig. 7. Computer (differential analyzer) test of the equation: $x_0 = k_2 p_m t_{1/2\ off}$ for the Michaelis-Menten mechanism with $k_1 = 10^6 M$ sec.$^{-1}$; $k_{-1} = 0$; $e = 1\mu M$. The values of k_2 are: 0.5 sec.$^{-1}$ for the curve (– – –), 1.0 sec.$^{-1}$ for the curve (———), and 2.0 sec.$^{-1}$ for the curve (. . .). In all three cases, the initial substrate is varied over the values $x = 1,2,4,8\mu M$.

taken from the differential analyzer solutions. The graph shows that Equation (11) is valid within a few percent over a wide range of the parameters. Further studies have shown that it is most accurate when $k_2/k_1 x_0$ is small, but it is remarkable that it holds quite well (within 6 percent) even when this quantity is fairly large and the kinetic curves no longer have a rectangular shape (see curve b in Fig. 3). The effect of the reverse reaction (k_{-1}) on the $t_{1/2\ off}$ has also been studied (8) and a more complicated formula developed; but for $k_{-1} \ll k_1 x_0$ as is usually the case, its effect is negligible (as can be seen in Fig. 4). Formula (11) is an excellent example of a computer theorem. So far no rigorous mathematical analysis has been able to justify its wide range of validity.

For this mechanism, it is also easy to prove mathematically that

$$t_{1/2\ \mathrm{on}} = 0.693/(k_1x_0 + k_{-1} + k_2) \tag{12}$$

and

$$p_m = k_1x_0e/(k_1x_0 + k_{-1} + k_2) \tag{13}$$

under the condition that $x_0 \gg e$.

By using rapid flow and spectrophotometric techniques, the experimental values of $t_{1/2\ \mathrm{on}}$, p_m, and $t_{1/2\ \mathrm{off}}$ were measured as a function of the initial substrate concentration (x_0). One set of rate constants was found which satisfied these formulas within the experimental accuracy over the range

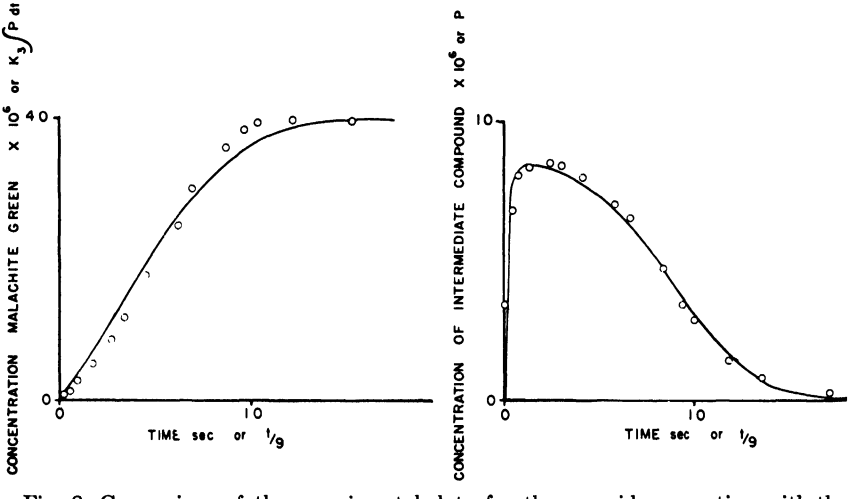


Fig. 8. Comparison of the experimental data for the peroxidase reaction with the computer (differential analyzer) solutions for the Michaelis-Menten system. The computer values are: $k_1 = 1 \times 10^7 M$ sec.$^{-1}$; $k_{-1} = 0$; $k_2 = 5$ sec.$^{-1}$; $e = 1\mu M$; $x_0 = 4\mu M$. The experimental values of e and x_0 are the same.

studied. In addition, the entire experimental kinetic curve for the intermediate was compared with a differential analyzer solution for this set of rate constants. The comparison is shown in Figure 8 and the good agreement indicated that the mechanism was satisfactory for the available experimental data.

More recent studies (10) have shown that the Michaelis-Menten mechanism is not adequate to explain the peroxidase system. Using modern techniques, more difficult initial conditions were studied, and the presence of a second, very transient intermediate was discovered spectrophotometrically. The mechanism was modified and the experimental data were shown to satisfy a type I mechanism of second order (see Section V.3.A.). This

new mechanism explains all the early data just as well as the Michaelis-Menten mechanism. Even if the second intermediate could not be observed, experiments carried out over the wider range of initial conditions and with greater accuracy would have indicated that the Michaelis-Menten mechanism was not satisfactory.

3. Study of General Types of Reaction Mechanisms

We shall now study the application of the computer to general types of mechanisms. The generalizations are all related to the Michaelis-Menten mechanism and are of interest in the study of enzyme reactions. While we shall limit ourselves to systems without reverse reactions, the effects of reversibility have been studied elsewhere (8).

A. THE TYPE I MECHANISM

The type I mechanisms are defined as a system with only one enzyme but any number of intermediates. If there are n intermediates, the system is called "the type I system of order n." The stoichiometry for a fourth-order system is

$$\begin{array}{lll} \mathrm{E} + \mathrm{S} \xrightarrow{k_1} \mathrm{ES}_1 & & \\ p_0 \quad x \qquad\quad p_1 & & \\ \mathrm{ES}_1 \xrightarrow{k_2} \mathrm{ES}_2 & & \\ \qquad\quad p_2 & & \\ \mathrm{ES}_2 \xrightarrow{k_3} \mathrm{ES}_3 & & \\ \qquad\quad p_3 & & \\ \mathrm{ES}_3 \xrightarrow{k_4} \mathrm{ES}_4 & & \\ \qquad\quad p_4 & & \\ \mathrm{ES}_4 \xrightarrow{k_5} \mathrm{E} + \text{product} & & \end{array}$$

where the concentrations of the intermediates are labeled p_i for $i = 1, 2, 3, 4$, (in general, $i = 1, 2, \ldots, n$) and p_0 is the concentration of the free enzyme. The stoichiometry for the nth order system follows the same pattern; the mechanism can be schematically drawn as a cycle (see Fig. 9). The type I system of order one is just the Michaelis-Menten system. The differential equations for the kinetics of this system are readily obtained from the law of mass action and have been studied on the electronic analog computer. The procedure is the same as for the Michaelis-Menten mechanism.

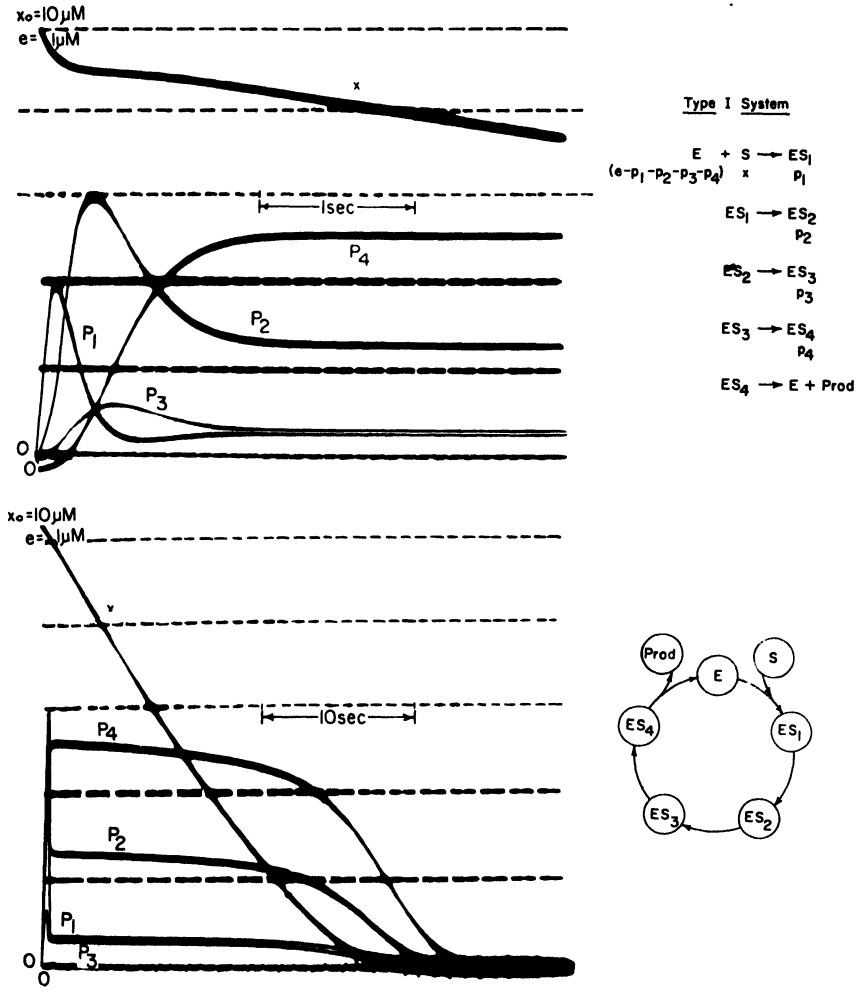


Fig. 9. Typical computer solutions for the fourth-order type I system with $x_0 >> e$. The upper and lower figures have exactly the same parameters except for the time scale. $x_0 = 10\mu M$; $e = 1\mu M$; $k_1 = 0.9 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_2 = 9$ sec.$^{-1}$; $k_3 = 1$ sec.$^{-1}$; $k_4 = 9$ sec.$^{-1}$; $k_5 = 2$ sec.$^{-1}$

Typical computer solutions for this system with $x_0 \gg e$ are shown in Figure 9 where the upper and lower figures differ only in the time scale, the upper showing the "on" region in more detail. The qualitative features of these solutions are quite striking. In the "on" region, all the intermediates except the last one (p_4) show an overshoot, and in some cases an additional undershoot with respect to the steady state. In the steady

state and off regions all the intermediates have the same qualitative features, which closely resemble those for the Michaelis-Menten system (with $k_{-1} = 0$). Computer studies of second- and third-order systems show that these features do not depend on the order of the system, nor are they particularly sensitive to the values of the rate constants so long as x_0 is large.

A detailed study of the computer solutions suggested mathematical approximations which could be used to develop mathematical properties of the qualitative features. For example, when the ith intermediate reaches its peak (p_{im}), the $i + 1$st intermediate is still approximately at a zero level. The mathematical development of this approximation leads to explicit formulas for the values of the p_{im} and shows that for the last intermediate in the cycle (p_n) there will be no overshoot (i.e., $p_{nm} = p_{nss}$). In addition the following ordering theorem can be proved:

$$p_{im}/p_{iss} > p_{i+1m}/p_{i+1ss} \tag{15}$$

This theorem states that the ratio of the maximum to the steady state value for a given intermediate is smaller the further the intermediate is from the substrate (i.e., the greater the i); the ratio for the last intermediate in the cycle (p_n) is one. Thus, if it is known that a particular system must have a type I mechanism, the application of this theorem to the experimental data will show the order of the intermediates in the cycle. This should be considered a mathematical theorem because the validity of the assumption required can be tested directly on the experimental data. It illustrates the use of the computer as an analytical tool.

The steady state equations are obtained by setting all the derivatives of all the intermediates to zero, simultaneously. The resulting algebraic equations are easily solved and give the steady state values as

$$p_{iss} = a_i x_0 e/(bx_0 + c) \tag{16}$$

where a_i, b, and c are functions of the rate constants with a_i depending on the particular intermediate while b and c are the same for all, for a system of any particular order. The values of the a_i are related by the equation

$$k_{i+1}a_i = k_i a_{i-1} \tag{17}$$

The suggestive reasoning applied to the study of the $t_{1/2\ off}$ for the Michaelis-Menten system can also be applied to the type I system, and a computer theorem was developed, namely

$$x_0 = k_{i+1}p_{i\ ss}t_{i\ 1/2\ off} \qquad \text{for } i = 1, 2, 3, \ldots, n \tag{18}$$

within a few percent, for $x_0 \gg e$. Inserting the steady state equations into these formulas proves that all the $t_{i\ 1/2\ off}$ are approximately equal

(i.e., $t_{i\ 1/2\ off} \backsimeq t_{j\ 1/2\ off}$ for $i, j = 1, 2, \ldots, n$) as can be observed in Figure 9. A detailed analysis of the computer solutions shows that while the $t_{i\ 1/2\ off}$ are approximately equal for large x_0, the differences are such that the $t_{i\ 1/2\ off}$ are ordered

$$t_{i\ 1/2\ off} < t_{i+\ 1/2\ off} \tag{19}$$

This theorem has since been proved mathematically though it is difficult to apply for large x_0 because of the small differences in the $t_{1/2\ off}$'s. At low x_0 (i.e., $x_0 < e$) the ordering of the $t_{1/2\ off}$'s becomes quite apparent as shown in Figure 10.

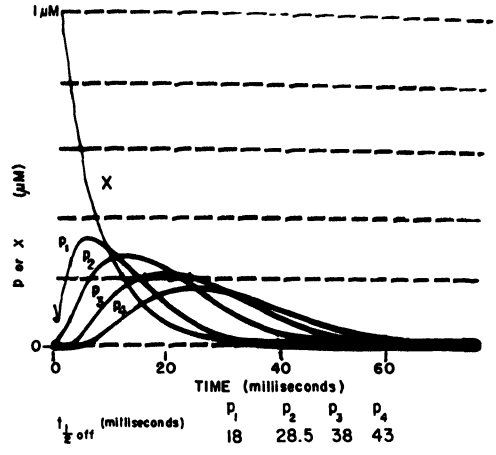


Fig. 10. Typical solutions of the fourth-order type II mechanisms for low initial substrate concentration. $x_0 = 1\mu M$; $e = 1\mu M$; $k_1 = 10^8 M^{-1}\text{sec.}^{-1}$; $k_2 = 1.2 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_3 = 1.2 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_4 = 1.2 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_5 = 1.2$ sec.$^{-1}$

When the substrate concentration is very low ($x_0 \ll e$) the non-linear differential equations reduce to approximately linear differential equations which can be solved exactly by mathematical methods. Various interesting formulas can be derived. For instance, a method was developed by which the kinetic curve of the product alone could be analyzed to give the total number of intermediates in the system as well as the values of all the rate constants. However, it was not known if the method had any practical value for the usual experimental accuracy. The computer was used as a test system and the method applied to the computer solutions. Unfortunately, it was found that for a system with more than two intermediates, the method could not resolve the total number of intermediates and even the ability to resolve second-order systems depended critically

on the relative size of the rate constants. Consequently, the method is impractical.

With these results, it is now easy to understand how the revised peroxidase mechanism (type I of second order) could explain the early peroxidase experiments as well as the Michaelis-Menten mechanism. First, except for an induction period in the "on" region, the second intermediate (which is also the last in the second-order cycle) has the same qualitative features as the Michaelis-Menten intermediate; the induction period could not be observed because of transients due to the initial mixing of the substrate and enzyme. The $t_{1/2\,off}$ equations, 18 and 11, show the same functional form and cannot be used to distinguish the mechanisms. *A priori*, there is a difference in the steady state equations which could be used to distinguish the mechanism, namely, $a_2 = b$ (Equation 16) for the second-order system, while $a = b$ for the Michaelis-Menten system (Equation 13). However, if the rate constant (k_2) for the breakdown of the first intermediate to the second is very large ($k_2 \gg k_3$), then $a_2 \approx b$ and the steady state equations are approximately identical as a function of x_0. Also, with this condition on the rate constants, $p_{1\,ss} \approx 0$, so that the first intermediate would not be detected. The $t_{1/2\,on}$ Equation (12) is the only critical test. For the Michaelis-Menten intermediate, $t_{1/2\,on} \to 0$ for $x_0 \to \infty$, while for the second intermediate of the type I system, $t_{2\,1/2\,on} \to 0.693/k_2 e$ as $x_0 \to \infty$. Unfortunately, for large k_2, the $t_{2\,1/2\,on}$ will be so small when x is sufficiently large that it could not be measured experimentally, and for smaller x_0 it will behave approximately as the $t_{1/2\,on}$ for the Michaelis-Menten intermediate, as a function of the x_0. Thus it is not a practical test.

Except for a fortunate occurrence, the distinction between these two mechanisms could not be experimentally established even now. The actual peroxidase system involves an acceptor (A) which is usually held in excess ($a_0 \gg x_0$). The first-order reaction steps that we have discussed are actually pseudo-first-order reactions as

$$ES_I + A \xrightarrow{k_2'} ES_{II}A$$

This makes no difference in our previous analysis and solutions if we set $k_2 = k_2' a_0$ which is also a constant. By varying the concentration of a_0 (still keeping it in excess), the effective value of k_2 can be changed. It was only when experiments could be carried out with low values of a_0, leading to an effectively small k_2 value, that the presence of the first intermediate could be detected by kinetic experiments. It is of course possible that this mechanism is still not the correct one; for instance, it might well be a type I system of third order under certain conditions. However the pres-

ent mechanism is satisfactory for the entire range of initial conditions and within the experimental accuracy which is now available. This particular problem illustrates the importance of carrying out the experimental study over the greatest range of initial conditions and with the best accuracy, as well as the usefulness of the computer for such investigations.

B. TYPE II SYSTEMS

The technique for studying generalized mechanisms and the importance of the computer in these studies will become more apparent from a brief discussion of two other types of mechanisms. The type II mechanism is a generalization of the Michaelis-Menten system in which there are any number of enzymes, but each having only one intermediate. The number of enzymes is called the order of the system. The stoichiometry for the fourth-order type II system is

$$\begin{array}{rcl} \mathrm{E} + \mathrm{S} & \xrightarrow{k_1} & \mathrm{E_1S} \\ (e_1 - p_1)\ x & & p_1 \end{array}$$

$$\begin{array}{rcl} \mathrm{E_1S} + \mathrm{E_2} & \xrightarrow{k_2} & \mathrm{E_2S} + \mathrm{E_1} \\ (e_2 - p_2) & & p_2 \end{array}$$

$$\begin{array}{rcl} \mathrm{E_2S} + E_3 & \xrightarrow{k_3} & \mathrm{E_3S} + \mathrm{E_2} \\ (e_3 - p_3) & & p_3 \end{array}$$

$$\begin{array}{rcl} \mathrm{E_3S} + \mathrm{E_4} & \xrightarrow{k_4} & \mathrm{E_4S} + \mathrm{E_3} \\ (e_4 - p_4) & & p_4 \end{array}$$

$$\mathrm{E_4S} \longrightarrow \mathrm{E_4} + \text{product}$$

where e_1, e_2, e_3, e_4 are the total enzyme concentrations for each enzyme. The generalization to the nth-order system follows the same pattern. A mechanism of this type has been proposed as a possible explanation of the kinetic data for the reaction of cytochromes (11). For $n = 1$, we obtain a Michaelis-Menten system.

The differential equations for this system are easily written down and have been studied on the analog computer for the case where all enzyme concentrations are equal ($e_i = e_j = e$ for all i and j). Figures 11 and 12 show typical computer solutions for the substrate and intermediate kinetics for large x_0, with two different sets of rate constants. The qualitative features for the intermediates are less striking than for the type I systems; there are no overshoots for the type II systems. The first intermediate is qualitatively identical with the Michaelis-Menten intermediate in every respect. For the other intermediates ($i > 1$) the only difference is an in-

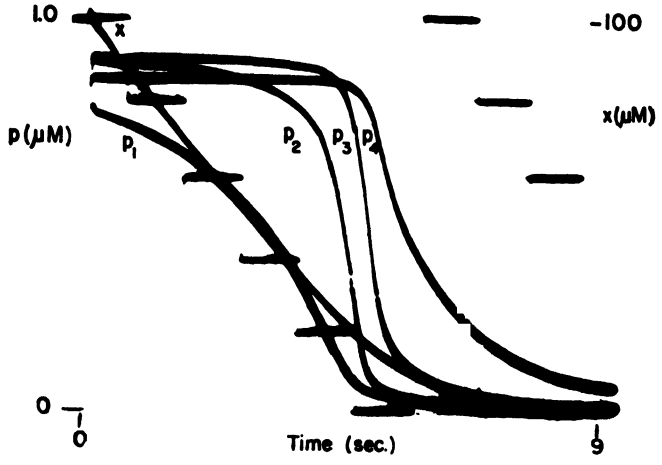


Fig. 11. Typical computer solutions for the fourth-order type II mechanism for large x_0. $x_0 = 100\mu M$; $e = 1\mu M$; $k_1 = 0.75 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_2 = 2.3 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_3 = 1.8 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_4 = 1.2 \times 10^8 M^{-1}$ sec.$^{-1}$; $k_5 = 20$ sec.$^{-1}$

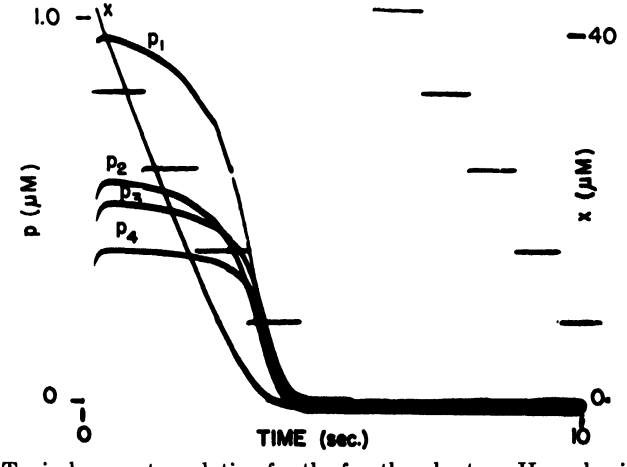


Fig. 12. Typical computer solution for the fourth-order type II mechanism for large x_0. $x_0 = 40\mu M$; $e = 1\mu M$; $k_1 = 0.5 \times 10^6 M^{-1}$ sec^{-1}; $k_2 = 3.0 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_3 = 4.5 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_4 = 4.0 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_5 = 3.0$ sec.$^{-1}$

duction period in the "on" region and a considerable flattening of the steady state slopes. Detailed computer studies over a wide range of rate constants and initial conditions show that when the steady state region exists, the steady state slopes are ordered; that is

$$\dot{p}_{t+1\,ss} < \dot{p}_{t\,ss} \tag{22}$$

Also, the $t_{1/2\ off}$'s are always ordered

$$t_{i+1\ 1/2\ off} > t_{i\ 1/2\ off} \tag{23}$$

Both these computer theorems have been studied mathematically and sufficient conditions can be given for their validity (see Appendix Section 6). It is curious that when these conditions are not met, the computer still indicates that the theorems are valid; however, only a few exceptions to the mathematical theorems have been observed since they lie at the limits of the computer range. For $x_0 < e$, the solutions are identical with those for the type I system (see Fig. 10), as can be easily proved mathematically.

C. TYPE III SYSTEMS

The type III systems represent a combination of the type I and type II systems. There can be any number of distinct enzymes (e_i for $i = 1, 2, \ldots, n$) and each enzyme may have any number of intermediates (p_{ij} for $j = 0, 1, 2, \ldots, m_i$). The intermediates for a given enzyme form a type I cycle and the cycles for different enzymes are joined by the type II coupling. The system is completely described by a set of numbers (n; $m_1, m_2, m_3, \ldots, m_n$). Both the type I system given as (1; m_1) and the type II system given as (n; 1, 1, . . ., 1) are special cases of this mechanism. For example, the stoichiometry relations for the system (4; 1, 3, 1, 1) and (4; 2, 2, 1, 1) are shown in Figures 13 and 14 respectively (the labeling of the index j is done by primes, i.e., $p_{21} = p_2$; $p_{22} = p_2'$; $p_{23} = p_2''$); an acceptor has been included in the last step. We shall define a "linear intermediate" as one whose breakdown reaction is either first order or pseudo-first order. Thus all intermediates are linear except the last intermediate of each type I cycle, but the very last intermediate of the system (p_{nm_n}) is also linear. If there is only one intermediate in any cycle, then it is considered as the last intermediate of that cycle. So far, only the systems with all $e_i = e_j = e$ have been studied.

Typical computer solutions for these mechanisms with $x_0 \gg e$, are shown in Figures 13 and 14. Many other mechanisms of this type have been studied over a wide range of the parameters. The qualitative features we shall now discuss are independent of the rate constants for $x_0 \gg e$, and depend on the order of the reaction mechanism only as indicated.

In the "on" region every cycle (fixed i) behaves as an independent type I cycle no matter where that cycle occurs in the chain (except for a small induction period in all but the very first intermediate, p_{11}, of the system). Thus all the intermediates of a given cycle have an overshoot except the last one of that cycle. The ratio of the maximum to the steady state

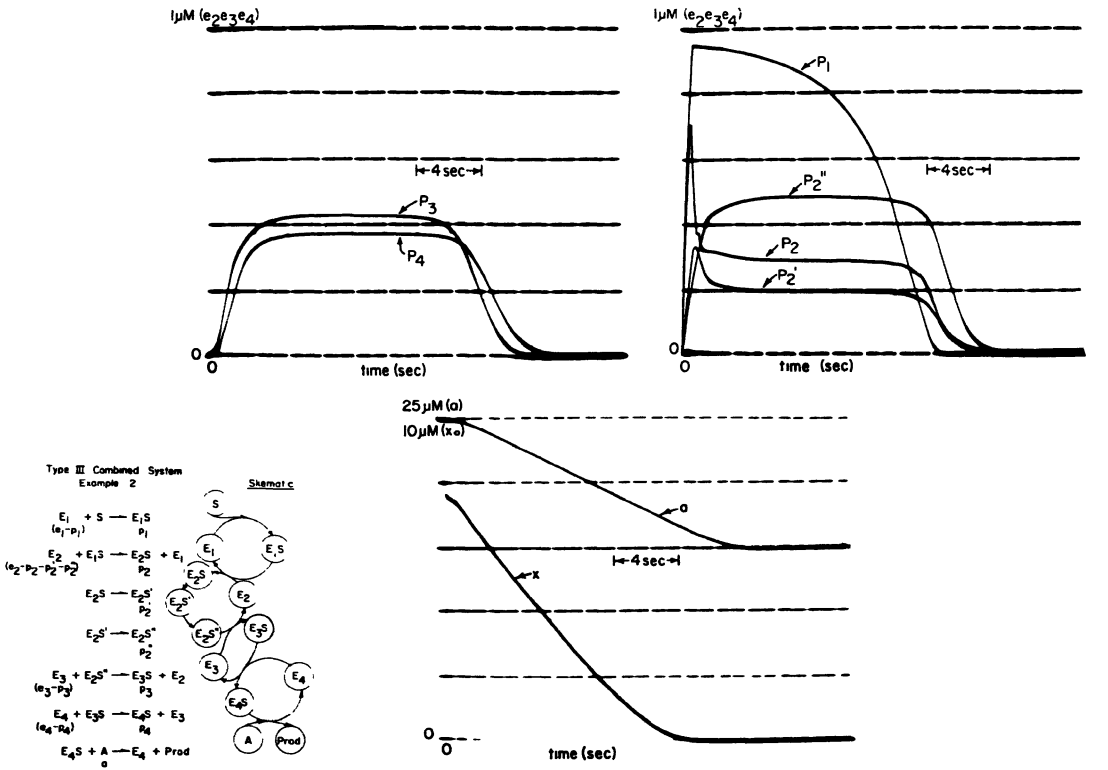


Fig. 13. Typical computer solution for the type III system (4;1,3,1,1) for large x_0. $x_0 = 10\mu M$; $a_0 = 25\mu M$; $e = 1\mu M$; $k_1 = 0.9 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_2 = 18 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_3 = 2$ sec.$^{-1}$; $k_4 = 3$ sec.$^{-1}$; $k_5 = 2 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_6 = 2 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_7 = 6 \times 10^6 M^{-1}$ sec.$^{-1}$

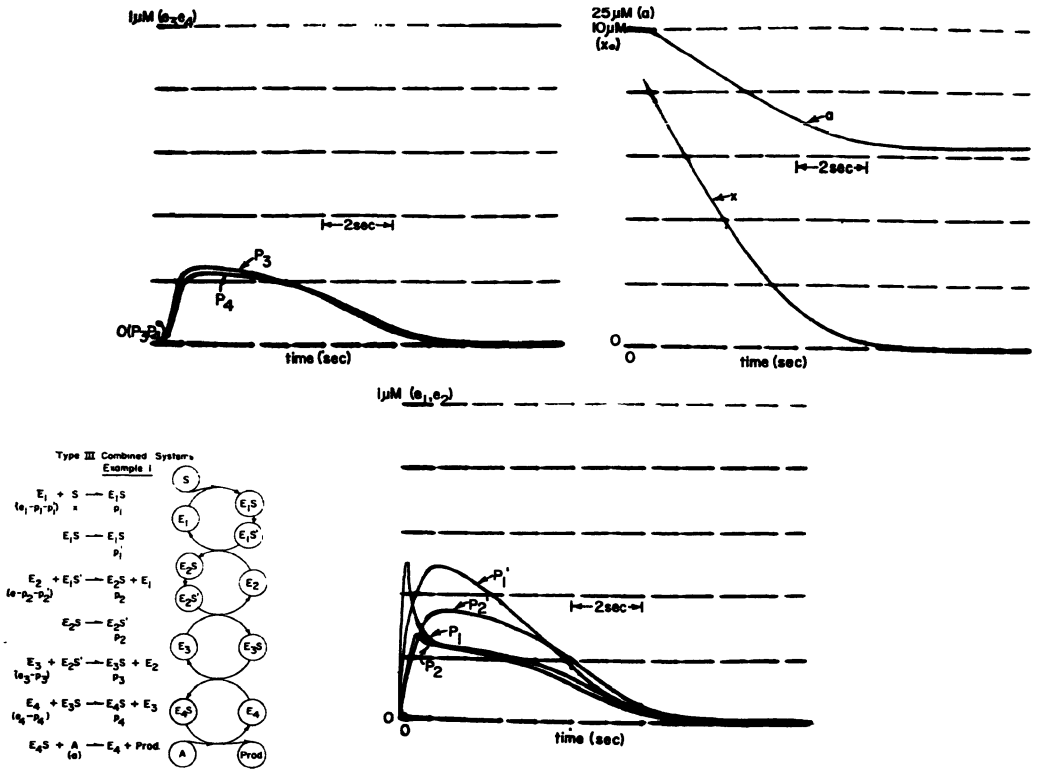


Fig. 14. Typical computer solutions for the type III system (4;2,2,1,1) for large x_0. $x_0 = 10\mu M$; $a_0 = 25\mu M$; $e = 1\mu M$; $k_1 = 0.9 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_2 = 8$ sec.$^{-1}$; $k_3 = 8 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_4 = 8$ sec.$^{-1}$; $k_5 = 7 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_6 = 9 \times 10^6 M^{-1}$ sec.$^{-1}$; $k_7 = 3.2 \times 10^6 M^{-1}$ sec.$^{-1}$.

values satisfies the ordering theorem (Equation 15) for all the intermediates of that cycle, but *not* between intermediates of different cycles.

In the steady state region and "off" region all the intermediates except the last one of any given cycle show the same qualitative features as for the separate type I system, for example, their steady state slopes. The last intermediate of each cycle (p_{tm_t}) demonstrates the qualitative features of the intermediates of a type II system both in its own kinetics and in its relationship to the kinetics of the last intermediate of different cycles. This property is observed in the decreasing steady state slopes of the last intermediates in each cycle as one goes further down the chain (i.e., for greater i). Finally it is possible to give a general $t_{1/2\ off}$ theorem for the linear intermediates; the $t_{1/2\ off}$'s for the linear intermediates are all approximately equal for large x_0 and satisfy an equation of the form

$$x_0 = k\, p_{ss} t_{1/2\ off} \tag{24}$$

but the small differences satisfy the ordering theorem

$$\begin{gathered} t_{ij\ 1/2\ off} < t_{kl\ 1/2\ off} \\ \text{for } i = k \text{ and } l > j \\ \text{and for } k > i \text{ and any } j \\ \text{but not for } j \text{ or } l = m_t. \end{gathered} \tag{25}$$

That is, the $t_{1/2\ off}$'s are ordered for all the linear intermediates in the entire chain, the $t_{1/2\ off}$ being greater the further any particular linear intermediate is from the substrate. The $t_{1/2\ off}$'s for the last intermediates of any cycle (except for the last cycle in the chain) do not satisfy any simple ordering theorem. For low x_0 the kinetics of all the intermediates take the form shown in Figure 10.

These statements are all true when the acceptor is in excess ($a_0 \gg x_0$), but some of them are not apparent from the computer solutions (Figs. 13 and 14) because the acceptor, though in greater amount than the substrate, was not in excess. This does not affect the "on" region of any intermediate or the steady state and "off" region properties of the linear intermediates. However, any intermediate whose breakdown depends on the acceptor is involved in a second-order reaction and cannot be considered as a linear intermediate. In our example, the effect of the decreasing acceptor concentration shows up primarily on the last intermediates of each cycle; the maximum of these curves occurs inside the steady state region. These effects are explained quantitatively in the appendix, Section 6.

We are now in a position to make a rather general statement based on the properties discovered by the use of the computer and mathematical analysis. If it is known or assumed that a system is of the class of type III

mechanisms, it is possible to determine the exact mechanism from the qualitative and semi-qualitative features of the experimental kinetics, or if the data are incomplete, definite limits can be put on the possible stoichiometry. The method is as follows: Equation (24) is tested as a function of x_0 for all the intermediates; those which satisfy it are linear intermediates. These intermediates occur in the stoichiometry in the same order as their $t_{1/2\ off}$'s (Equation 15). The remaining intermediates have no overshoots and do not satisfy Equation (24). They are the last intermediates of the different cycles and are placed in the appropriate cycle according to the ordering of their steady state slopes. For very low x_0 all the intermediates of the system will have their $t_{1/2\ off}$'s ordered, but it is not possible to distinguish between the type I, II, and III systems.

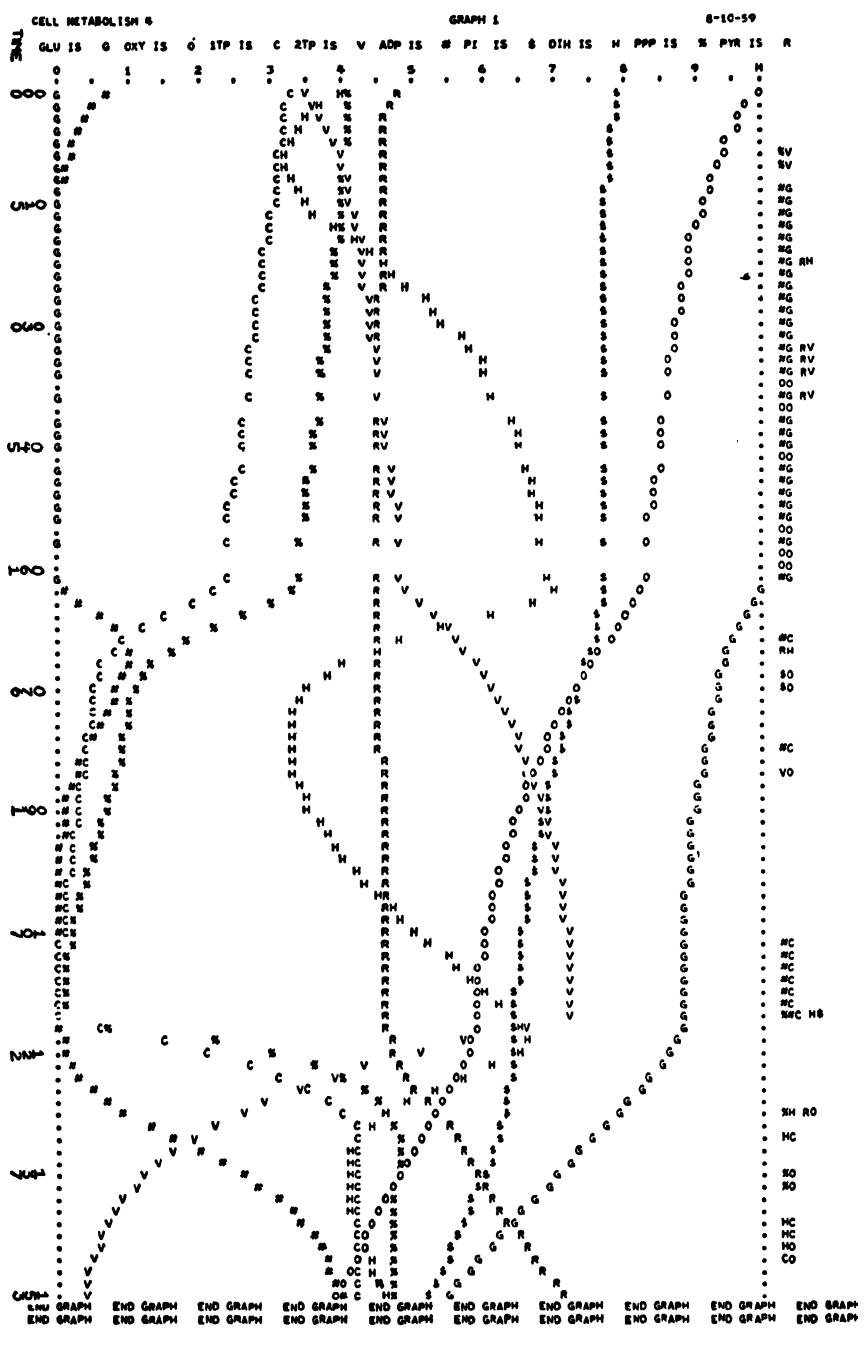
Other tests for the mechanism are presented in the appendix, in which the theory of stoichiometric reflection coefficients is discussed. This theory was developed by a detailed study of the computer solutions combined with mathematical analysis. It represents a highly refined use of the computer as both an intuitive stimulant and an analytical tool. Finally, the practical value of theory was determined by the computer.

4. Use of the Digital Computer

In 1956, the studies of reaction kinetics indicated the need of a computer with greater accuracy, considerably increased capacity, and the ability to do data processing. These features are beyond the scope of analog computers, but fortunately, at about the same time, the University of Pennsylvania opened its computing center based on a Univac I electronic digital computer donated by the Remington Rand Corporation. A program, recently completed, was developed to utilize this computer for the study of reaction kinetics (12). This program gives the computer the ability to solve non-linear simultaneous differential equations using numerical integration techniques, but for reaction mechanisms involving up to forty different chemicals. The accuracy can be varied from 1 to 0.0001 percent, better accuracy requiring a longer solution time. As a basis of comparison, the digital computer requires about three minutes to give one solution of the fourth-order type II system with the same accuracy as the analog computer which requires only 100 milliseconds. The maximum relative range of the digital program is one million. To program the computer for a specific problem, it is only necessary to type the reaction stoichiometry, as normally written, onto a magnetic tape; the computer automatically generates the corresponding differential equations to be solved. The values of the initial conditions and rate constants in chemical units are typed on tape with only an additional symbol to indicate the particular

Phosphorylation of glucose	1	$0 \rightarrow 3 \times 10^{-2}$ 3×10^{-2}	GLU +	1×10^{-6} 1.02×10^{-6}	ENZ	$\xrightarrow{3 \times 10^{9}}$	ENG − GLU − ENZ		
	2	0 1.02×10^{-6}	ENG +	5×10^{-4} 1.5×10^{-3}	1TP	$\xrightarrow{1 \times 10^{10}}$	ADP + GLP + ENZ − ENG − 1TP		
	3	0 1×10^{-3}	GLP +	1×10^{-6} 1×10^{-6}	ETZ	$\xrightarrow{4 \times 10^{10}}$	ETG − GLP		
	4	0 1×10^{-6}	ETG +	5×10^{-4} 1.5×10^{-3}	ITP	$\xrightarrow{4 \times 10^{10}}$	GPP + ETZ + ADP − ETG − 1TP		
	5	0 1×10^{-3}	GPP			$\xrightarrow{1 \times 10^{4}}$	GAP + DHA − GPP		
Glycolytic phosphorylations of ADP	6	0 1.3×10^{-3}	DHA +	1×10^{-4} 2×10^{-4}	DPH	$\xrightarrow{2 \times 10^{9}}$	AGP + DPN − DHA − DPH		
	7	0 1.3×10^{-3}	AGP +	1×10^{-4} 2.5×10^{-4}	DPN	$\xrightarrow{8 \times 10^{7}}$	DHA + DPH − AGP − DPN		
	8	0 2×10^{-4}	GAP +	5×10^{-5} 5×10^{-5}	MOD	$\xrightarrow{6 \times 10^{11}}$	MOB + DPH − GAP − MOD		
	9	0 1×10^{-4}	MOB +	4×10^{-2} 5×10^{-2}	PIΔ	$\xrightarrow{4 \times 10^{9}}$	DGA + MOX − MOB − PIΔ		
	10	0 5×10^{-5}	MOX +	1×10^{-4} 2.5×10^{-4}	DPN	$\xrightarrow{6 \times 10^{9}}$	MOD − MOX − DPN		
	11	0 2×10^{-4}	DGA +	1×10^{-4} 1×10^{-2}	ADP	$\xrightarrow{1 \times 10^{10}}$	1TP + PGA − DGA − ADP		
	12	0 2×10^{-4}	PGA +	1×10^{-4} 1×10^{-2}	ADP	$\xrightarrow{5 \times 10^{9}}$	1TP + PYR − PGA − ADP		
	13	1×10^{-2} 2×10^{-2}	PYR +	1×10^{-4} 2×10^{-4}	DPH	$\xrightarrow{5 \times 10^{8}}$	LAC + DPN − PYR − DPH		
	14	1×10^{-2} 1.2×10^{-2}	LAC +	1×10^{-4} 2.5×10^{-4}	DPN	$\xrightarrow{1 \times 10^{7}}$	PYR + DPH − LAC − DPN		
Oxidative phosphorylations of ADP	15	1×10^{-2} 2×10^{-2}	PYR +	3×10^{-6} 7×10^{-6}	4DIN	$\xrightarrow{2 \times 10^{7}}$	4DIH − PYR − 4DIN		
	16	3×10^{-6} 7×10^{-6}	DIH +	2×10^{-6} 6×10^{-6}	3X I	$\xrightarrow{7.5 \times 10^{10}}$	3XSI + DIN − DIH − 3X·I − DIH		
			+	5×10^{-4} 5×10^{-4}	OXY				
	17	2×10^{-6} 6×10^{-6}	XSI +	4×10^{-2} 5×10^{-2}	PIΔ	$\xrightarrow{4 \times 10^{9}}$	XSP − XSI − PIΔ		
	18	2×10^{-6} 6×10^{-6}	XSP +	1×10^{-4} 1×10^{-2}	ADP	$\xrightarrow{1.5 \times 10^{10}}$	2TP + X I − XSP − ADP		
	19	2×10^{-6} 6×10^{-6}	XSI +	$0 \rightarrow 2.5 \times 10^{-2}$ 2.5×10^{-2}	DBP	$\xrightarrow{1.2 \times 10^{9}}$	X I − XSI		
ATP utilization and transfer	20.	5×10^{-4} 1.5×10^{-3}	2TP +	$0 \rightarrow 2.5 \times 10^{-2}$ 2.5×10^{-2}	DBP	$\xrightarrow{4 \times 10^{9}}$	1TP − 2TP		
	21	5×10^{-4} 5×10^{-3}	1TP +	2×10^{-6} 3.06×10^{-6}	PUE	$\xrightarrow{3 \times 10^{9}}$	PPP − 1TP − PUE		
	22	1×10^{-6} 3.06×10^{-6}	PPP			$\xrightarrow{2 \times 10^{9}}$	ADP + PUE + PIΔ − PPP		

Fig. 15. Chemical equations representing the reactions of glucose and oxygen metabolism in irreversible form: separate equations representing their reverse can be easily formulated. For abbreviations, see Reference 13. The initial concentration of each reactant is written on the upper left, and the maximal concentration used in plotting the computer solutions on the lower left. Where an initial concentration of zero is increased during the course of the reaction, the change is indicated, as in the case of glucose (GLU), by the symbol $0 \rightarrow 1 \times 10^{-3}$. The reaction velocity constants, written above the arrows, are of such dimensions that the products of the concentrations and the constants give the fluxes in moles/liter/second. In each case the symbols for the reactants appear again on the right-hand side of the equation, preceded by a minus sign, to indicate that they have been expended in the reactions (DC-9).


CELL METABOLISM 4
GRAPH 1
8-10-59
TIME
GLU IS
G OXY IS
G 1TP IS
C 2TP IS
V ADP IS
PI IS
$ DIH IS
H PPP IS
% PYR IS
R
END GRAPH

chemical and reaction step. All scale factors are automatically calculated before the solution is started and removed before the final results are put out. The solution is given as a table of concentration values versus time to the accuracy specified or as a typewritten graph with an accuracy of one percent. Finally, the computer can process the solutions automatically. Graphs or tables may be obtained giving the dependence of many quantities of interest, such as the $t_{1/2\ off}$'s or the steady state concentrations, on the initial conditions or rate constants.

One problem (13) has already been studied on the digital computer. This concerned the development of a minimum reaction mechanism capable of explaining the experimental data for the interaction of the glycolytic and respiratory systems of the cell. The mechanism hypothesized is illustrated by the equations of Figure 15. While some of these reaction steps were hypothesized, others had been studied independently; for these, the total enzyme concentrations and rate constants could be given from the experimental data. The problem was to show that there existed values of the unknown rate constants and enzyme concentrations which would be of reasonable magnitude and produce results consistent with the experimental data for the complete system. In particular it was necessary to show that certain qualitative effects, such as the Crabtree effect, could be explained by the mechanism.

Because there are twenty-seven chemicals involved, the problem required the use of the digital computer. The chemical equations, essentially as they appear on this page, were typed on the magnetic tape along with the known parameters and a first estimate of the unknown parameters. Figure 16 shows a typical typewritten graph for some of the chemicals of this system. The first estimate did not work, but after several improved estimates a satisfactory choice of parameters was found, proving that this mechanism was sufficient to explain the available experimental data. Undoubtedly other values of the parameters or even other mechanisms can explain the data equally well; only future experiments can begin to limit the possibilities. However, the mechanism given is relatively simple and certainly satisfactory at present.

Fig. 16. A solution of the reaction kinetics of the equations of Fig. 15 for the various components for three types of metabolism: (a) time units 0-064, metabolism of endogenous substrate; (b) time units 064-119, metabolism of added glucose, illustrating the activated and inhibited phases of glucose and oxygen metabolism; (c) time units 119-153, relief of glucose and oxygen inhibition by the addition of an uncoupling agent. The maximal values for the concentration scale of each reactant plotted are given in Fig. 15. Since the velocity constants are inserted to give metabolic rates on the order of moles/liter/second, the numbers along the bottom of the trace indicate μsecond time intervals. The abscissa can be read as seconds and the rates of utilization of the components as μmoles/liter/second (DC-11).

VI. CONCLUSIONS

The examples discussed in the previous section demonstrate the importance of computers in the study of both specific and general problems of reaction mechanisms. When the mechanism is known, the determination of the rate constants by the computer is trivial. Detailed computer studies are especially important to distinguish specific mechanisms when several are proposed to explain the experimental data. Finally, the determination of the rate constants and the stoichiometry can be separated by the computer study of general types of reaction mechanisms. In this respect, the computer is an expedient tool for realizing the qualitative and semi-qualitative properties of the reaction kinetics which are relatively independent of the values of the rate constants. The positive results already obtained in formulating a procedure to relate the kinetic data directly to the stoichiometry warrant the computer study of still other types of general mechanisms.

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APPENDIX

Stoichiometric Reflection Coefficients

The relationship between the qualitative features of the kinetics and the mechanism has already been developed in previous sections with the aid of computers. In this section we shall develop similar relationships for the steady state. The technique is centered about a quantity called the "stoichiometric reflection coefficient," which is easily measured experimentally. Also the theoretical value of this quantity can be readily calculated for many types of reaction mechanisms; it is sensitive to the stoichiometry of the mechanism but independent of the values of the rate constants. The reader is assumed to be familiar with the terminology, notation, and discussion of mechanisms given in sections III and V. Again we shall limit ourselves primarily to irreversible sequential reactions though reversible reactions have also been considered (8).

1. Steady State Experiments

It is convenient to resolve any chemical reaction into two types of chemicals. The chemicals which are required to initiate the reaction and the major net products of the reaction will be called the "fundamental chemicals of the reaction." The concentrations of these chemicals can usually be directly controlled experimentally. The second type are called "intermediates." These chemicals are produced in the course of the reactions; they do not have to be supplied initially, and they do not remain in any appreciable amount at the end of the reaction. Usually, their concentrations are controlled indirectly by the concentrations of the fundamental chemicals. Thus for enzyme reactions the fundamental chemicals are the substrate, acceptors, and products, while the intermediates are the enzyme substrate or enzyme acceptor complexes. For the linear sequential reaction

$$A \rightharpoonup B \rightharpoonup C \rightharpoonup D \qquad (1)$$

the chemicals A and D are fundamental chemicals while B and C are intermediates.

A. KINETIC STEADY STATES

There are two types of experiments which can be discussed in terms of the steady state. The first is the approximate steady state (i.e., the steady state region, see Section V) which arises as part of the kinetic response of a system as it proceeds from its initial state to its final equilibrium state.

This will be called a "kinetic steady state." It is characterized by intermediates whose concentrations vary slowly in time. The concentrations of the fundamental chemicals are not constant, but change at a rate determined by the net reaction rate (v). These concentrations and reaction rates approximately satisfy the steady state equations which are obtained from the differential equations for the kinetics by setting the time derivatives of all the intermediates simultaneously to zero. In general, the kinetic steady states will exist only if the concentrations of the fundamental chemicals, not including the products, can be made large compared to the steady state concentrations of the intermediates; whether or not this can be done will depend on the mechanism. When the steady state does exist, it is clear from the chemistry or from the steady state equations that the concentrations of the intermediates as well as the net reaction rate (v) will be determined by the concentrations of the fundamental chemicals for any particular mechanism. These statements may be written in functional notation

$$p_i = p_i(x_1, x_2, \ldots, x_n; k_1, k_2, \ldots, k_l) \tag{2}$$

$$v = v(x_1, x_2, \ldots, x_n; k_1, k_2, \ldots, k_l) \tag{3}$$

where p_i is the steady state concentration of the ith intermediate, x_j (j = 1, 2, . . ., n) is the steady state concentration of the fundamental chemicals, v is the steady state reaction velocity and the k's are the rate constants. The functional form will depend on the specific stoichiometry of the mechanism.

When the kinetic steady state exists two different measurements can be performed. The values of the p_i, v, and x_j can be measured at some specific point, such as at the start of the steady state region. When the initial conditions for the experiment are changed, these values will change and the initial condition can be used as a parameter to determine a different steady state. This is called an "initial condition experiment." Or, for a given set of initial conditions, the entire steady state region can be studied as a function of the time. Here the time is used as a parameter and every time corresponds to a different steady state since the concentrations of the fundamental chemicals and the intermediates have changed due to the net reaction rate. It is important to keep in mind that in both cases these are only approximate steady states.

B. INDUCED STEADY STATES

The second type of experiment is called an "induced steady state." In this case the concentrations of the fundamental chemicals are maintained constant by supplying them at the same rate they are consumed or

removing them at the rate at which they are produced. This can be done by reservoirs of the fundamental chemicals in contact with the reacting system by means of semi-permeable membranes. These reservoirs can be made so large that the concentrations of the fundamental chemicals will be maintained at the fixed values of the reservoirs even though there is a net reaction rate. When the reservoir concentrations are changed, a different steady state will be obtained. We call this a "reservoir induced steady state." However it is also possible to obtain an induced steady state by supplying or removing the fundamental chemicals at the fixed rate (v), consistent with the stoichiometry. Thus if three molecules of X_1 are required for every one of X_2, then X_1 must be supplied three times faster than X_2. Also, for some reactions, such as those for enzymes, there is a maximum reaction rate (v_M) determined by the rate constants and the total enzyme concentration, and the supply rate (v) must always be less than this maximal rate. If these conditions are met, the concentrations of all the chemicals will adjust themselves to produce a steady state whose flux is identical with that of the supply rate. Such steady states will be called "velocity induced steady states." Again, if the supply rate is changed, the system will attain a different steady state.

It is also possible to have a mixed induced steady state in which some of the fundamental chemicals are maintained constant by reservoirs, while others are supplied at some fixed rate. In practice many of the fundamental chemicals can often be ignored. For instance, the products play no role when the reactions are irreversible, and reservoirs are not needed for chemicals which are in such excess that there is no appreciable change in concentration in the time required to attain and measure the steady state.

For all the induced steady states, the steady state equations are satisfied exactly, and there are no inherent limitations on the concentrations or mechanisms for which steady states can be attained as in the kinetic case. The relationship between the induced and kinetic steady states can be summarized in the statement: *So long as the kinetic steady state exists, there corresponds an induced steady state having approximately identical concentrations and reaction rates for all chemicals.*

The converse of this statement is not true, and the experimental use of induced steady states provides a much wider range for application of the steady state equations.

C. CHANGE OF STEADY STATES

We shall refer to the concentrations of the fundamental chemicals *and* the steady state flux (v) as the "fundamental variables." In view of the

preceding discussion all the fundamental variables can, in principle, be directly controlled by the experimenter. For a given system the concentrations of all the intermediates are determined from the steady state equations, e.g., Equation (2), when the values of the fundamental variables are specified. In addition, the fundamental variables satisfy the steady state rate equation (3). It is important to note that the flux is treated on an equal basis with the concentrations of the fundamental chemicals.

Now consider an experiment in which one of the fundamental variables is changed. Provided at least one other fundamental variable is free to change, Equation (2) can still be satisfied and the system will attain a new steady state characterized by new values for the concentrations of intermediates and whatever fundamental chemicals were free to change. For example, in a reservoir induced steady state, if only one of the reservoir concentrations is changed, the concentrations of the intermediates and the flux will change, but there will be no change in the concentrations of the other fundamental chemicals. For a mixed induced steady state, when the supply rate (v) is changed, all the concentrations will change except those maintained by the reservoirs. With regard to the kinetic steady states, the initial condition experiment is effectively the same as a reservoir induced steady state for which the products are maintained at zero. Since the steady state equations are approximately valid, the steady state region can be interpreted in a similar manner as all the fundamental variables will change in a time (Δt) due to the chemical conservation condition.

Whatever fundamental variables are used to motivate the transition from the original to the new steady state will be referred to as the "primary variables." Usually only one primary variable is changed at a time, but two or more primary variables are of interest for studies of kinetics of the steady state region.

2. The Stoichiometric Reflection Coefficients

A. DEFINITION

It is convenient to give a more dynamic description of the steady state experiments discussed in the previous section. We can interpret these experiments by saying that when one of the fundamental variables is changed, it *causes* changes in all the other variables of the system. Or conversely, all the variables in the system *reflect* the changes in the primary variable. We shall define the coefficient of reflection between any two variables as the ratio of the relative changes in the two variables. Thus if a, b, and c denote the values of these variables in the original steady state and a', b', and c' denote their values in the new steady state, then the change is given as

$$\Delta a = a' - a \tag{4}$$

and the relative change by

$$r_a = \Delta a/a \tag{5}$$

Similarly for b and c. And the reflection coefficient of a into b is defined as

$${}^aR_b^\Delta = r_b/r_a = (\Delta b/b)/(\Delta a/a) \tag{6}$$

The Δ in the upper right of R denotes the fact that this is the coefficient for finite changes in the variables. For the moment we shall be more concerned with the reflection coefficient for infinitesimal changes given as

$${}^aR_b = \lim_{r_a \to 0} {}^aR_b^\Delta = (a/b)(db/da) \tag{7}$$

From the definition, it follows that

$$r_b = {}^aR_b r_a \tag{8}$$

A reflection coefficient can be defined between any two variables of the system regardless of how the transition to the steady state was motivated. However, the values of the reflection coefficients will in general depend on the particular fundamental variables which are allowed to change. For the moment, we shall only consider cases in which the reaction rate and one fundamental chemical can change, all the others being maintained constant. If it is necessary to distinguish between the reflection coefficients when different fundamental chemicals can change, we shall place a forescript on the lower left of R. Thus ${}_a^xR_y$ and ${}_b^xR_y$ are the reflection coefficients between x and y when the fundamental chemical a is the only one allowed to change in the first case, and only chemical b in the second case. When no forescript is used, it is understood that the reflection coefficients are for a particular fundamental chemical.

B. ELEMENTARY PROPERTIES

The following elementary properties are easily proven by the application of mathematical limit theorems. Although there are exceptions when these theorems do not apply (8), we shall not encounter them in the problems discussed here.

(1) The reflection coefficient of b into a is the reciprocal of the reflection coefficient of a into b, i.e.,

$${}^bR_a = 1/{}^aR_b \tag{9}$$

(2) The reflection coefficient of a into c is the product of the reflection coefficients of a into b and b into c, i.e.,

$$ {}^{a}R_{c} = {}^{a}R_{b} \times {}^{b}R_{c} \tag{10} $$

(3) If the variables depend on a parameter such as time (t) then the reflection coefficients can be written in terms of the derivatives of the variables, i.e.,

$$ {}^{a}R_{b} = (\dot{b}/b)/(\dot{a}/a) \tag{11} $$

where the dot ($\cdot$) refers to the time derivative ($\dot{a} = da/dt$). This property follows by dividing the numerator and the denominator of Equation (6) by Δt and taking the limit. It is particularly important for the study of the kinetics of the steady state region in which $\dot{a}$ and $\dot{b}$ become the steady state slopes.

3. Theoretical Values of the Reflection Coefficients

We shall now derive the theoretical values of the reflection coefficients for various mechanisms. Though we shall limit ourselves to sequential reactions with irreversible reaction steps, the results have been extended to more general cases (8).

A. FIRST- AND SECOND-ORDER REACTION STEPS

For sequential reactions, all reaction steps have the same flux (v) in the steady state. For any first order or pseudo-first-order reaction step of the mechanism,

$$ \mathrm{A} \xrightarrow{k} \mathrm{B} \tag{12} $$

the steady state equation is

$$ v = ka \tag{13} $$

Differentiating this equation gives

$$ dv = kda \tag{14} $$

and dividing Equation (14) by Equation (13) yields

$$ dv/v = da/a \tag{15} $$

or

$$ r_{v} = r_{a} \qquad \text{and hence } {}^{a}R_{a} = 1 \tag{16} $$

For any second-order reaction step of the mechanism

$$A + B \xrightarrow{k} C \tag{17}$$

we have

$$v = kab \tag{18}$$

Differentiating gives

$$dv = kadb + kbda \tag{19}$$

and dividing Equation (19) by Equation (18) yields

$$dv/v = da/a + db/b \tag{20}$$

which states that

$$r_v = r_a + r_b \tag{21}$$

and hence

$$1 = {}^vR_a + {}^vR_b \tag{22}$$

The application of this technique to a given mechanism produces the velocity reflection coefficients. Other reflection coefficients can be calculated by applying the elementary properties 1 and 2. However, it is important to note that the equations we have just derived are completely general; it does not matter where these reaction steps occur in the sequence of the mechanism or what other reaction steps are present.

When the reactions are reversible, it is necessary to use a more complicated approach which requires solving the steady state equations for the general variables in terms of the fundamental variables. But even in this case it is often possible to simplify the algebraic calculations.

B. SPECIFIC TYPES OF MECHANISMS

Using Equations (16) and (22), the reflection coefficients for specific mechanisms can be easily written down.

(1) The Linear Chain. For the linear chain

$$\underset{a_1}{A_1} \rightarrow \underset{a_2}{A_2} \rightarrow \underset{a_3}{A_3} \rightarrow \ldots \rightarrow \underset{a_{n-1}}{A_{n-1}} \rightarrow \underset{a_n}{A_n}$$

where A_1 and A_n are considered the fundamental chemicals and A_i for $i \neq 1,n$ the intermediates (the a_i are the concentrations), it follows from Equation (13) that

$${}^vR_{a_i} = 1 \tag{23}$$

Applying property 1 and 2, we can show that

$${}^{a_i}R_v = 1/{}^vR_{a_i} = 1 \tag{24}$$

and

$$^{at}R_{aj} = {}^{at}R_{v} \times {}^{v}R_{aj} = 1 \tag{25}$$

This result is valid even if all the reaction steps are reversible except the very last one in the chain.

(2) The Michaelis-Menten System. For the Michaelis-Menten mechanism

$$\begin{array}{c} \mathrm{E} + \mathrm{S} \rightharpoonup \mathrm{ES} \\ q \quad x \\ \\ \mathrm{ES} \rightharpoonup \mathrm{E} + \mathrm{P} \\ p \end{array} \tag{26}$$

we have from Equations (16) and (22) that

$$^{v}R_{x} + {}^{v}R_{q} = 1 \tag{27}$$

and

$$^{v}R_{p} = 1 \tag{28}$$

From the conservation condition for the total enzyme

$$e = q + p$$

it follows that

$$r_q = dq/q = -dp/(e - p) = -\,[p/(e - p)] \times r_p \tag{30}$$

and

$$^{p}R_{q} = -p/(e - p) \tag{31}$$

From property 2, we can set

$$^{v}R_{q} = {}^{v}R_{p} \times {}^{p}R_{q} \tag{32}$$

in Equation (27) and obtain

$$^{z}R_{v} = 1/{}^{v}R_{x} = (e - p)/e \tag{33}$$

And we also have that

$$^{z}R_{p} = {}^{z}R_{v} \times {}^{v}R_{p} = (e - p)/e \tag{34}$$

(3) Type I, II, and III Mechanisms. For the generalized mechanisms discussed in Section V, the reflection coefficients are obtained in the same manner.

For the type I system of order n, we have

$$^{z}R_{v} = (e - P)/e \tag{35}$$

$$^{p_i}R_{p_j} = 1 \qquad \text{and} \qquad {}^{P}R_{p_i} = 1 \tag{36}$$

$$^{v}R_{p_i} = 1 \tag{37}$$

where

$$P = \sum_{i=1}^{n} p_i \tag{38}$$

While the coefficients for the type II and type III systems can be easily written down (8), we shall only give explicitly the results for the 2nd order type II system. These are

$$^{x}R_{p_1} = \frac{1}{[e_1/(e_1 - p_1)] - (p_2/e_2)} \tag{39}$$

$$^{p_1}R_{p_2} = (e_2 - p_2)/e_2 \tag{40}$$

$$^{v}R_{p_2} = 1 \tag{41}$$

Of course, in any case Equations (16) and (22) can be applied directly.

Though we have limited ourselves to sequential reactions, branched reactions pose no difficulties. The reflection coefficients can be derived in terms of the flux (v) in each branch of the reaction.

4. Principles of Application

The most important features of the technique of reflection coefficients are now apparent. Since the reflection coefficient was defined in terms of the steady state experiments, its experimental application is immediate. The experimenter need only measure the relative changes in any chemicals that can be detected and then determine what reflection coefficient equations are satisfied. The equations used may be those relating the reflection coefficients (Equations 10 and 22), or those giving the individual reflection coefficients in terms of the concentrations (such as Equation 35). In practice, it is necessary to use the finite reflection coefficients since the changes in concentrations must be finite and usually on the order of several percent. However it is not difficult to show that the infinitesimal and finite reflection coefficients are approximately equal when the relative changes (r) are small (i.e., $r \ll 1$). Thus, the equations we have derived may be applied directly. The convenience of the reflection coefficient lies in the simplicity of these equations and the fact that they can be directly tested experimentally.

The second important feature of the reflection coefficients is that they are sensitive to the stoichiometry of the mechanism without regard to the magnitude of the rate constants. In all the equations which we have

derived for the reflection coefficients, the rate constants do not appear. The equations are only in terms of the concentrations of the various chemicals and the flux which can be determined experimentally. Basically, the reflection coefficient equations represent a special differential form of the steady state equations which eliminates the rate constants. If the reflection coefficient equations are integrated, the rate constants will reappear as the constants of integration. However the ease with which the coefficients can be derived for many types of mechanisms makes this approach especially convenient for setting up tests of proposed mechanisms. In addition, it is important to observe that the reflection coefficient equations (16 and 22) for irreversible first- and second-order reactions apply regardless of any other reactions involved in the mechanism. Consequently, it is possible to directly deduce some aspects of the stoichiometry from the experimentally measured values of the reflection coefficients.

Finally, the theoretical values of the reflection coefficients show immediately the conditions necessary in order to distinguish different mechanisms. For wherever the reflection coefficients for one mechanism are approximately equal to those for another, the mechanism cannot be distinguished by steady state experiments. Thus, if $P \approx 0$ for a type I mechanism, then ${}^{z}R_{s} \approx 1$ and the system cannot be distinguished from that of the linear chain (Equation 24). Consequently, to avoid misinterpretation of the mechanism, it is important to experimentally test the reflection coefficient equations over the greatest possible range of the fundamental variables.

5. Experimental Techniques and Problems

A. INDUCED STEADY STATE—COMPUTER EXAMPLE

To illustrate the experimental application of reflection coefficients, a reservoir-induced steady state was set up in the computer for a second-order type II system. The analog computer is particularly appropriate here because the errors involved in setting and measuring the "concentrations" are comparable to those involved in enzyme experiments (about 2 percent). In this particular experiment the concentrations of the intermediates were measured as a function of the concentration of the substrate; the substrate was changed by a sufficient amount to cause a 10 percent change in the concentration of the particular intermediate being studied. This was done for each different value of the substrate from low values to values which saturated the intermediate near its maximal value. The same experiment was repeated using 20 percent changes in the intermedi-

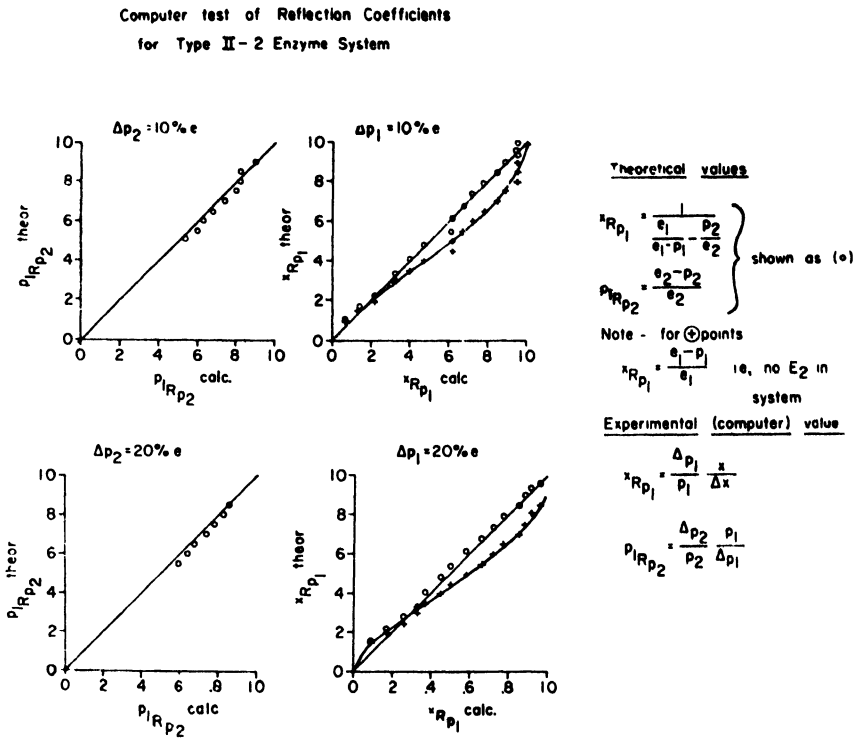

Fig. A. Practical application of the techniques of reflection coefficients to computer solutions of the second-order type II system.

ates. Figure A shows a plot of the measured reflection coefficients given by ${}^{a}R_b = r_b/r_a$ against the theoretical values (Equations 39 and 40) for which the measured concentrations were used. The results are shown as circles in Figure A and should satisfy a straight line of slope one as indicated.

The curve marked by crosses demonstrates a practical application of reflection coefficients for distinguishing the stoichiometry. In this case the same data were used, but it was assumed that only the first intermediate could be detected so that a first-order type II system was hypothesized. The curve plots the measured reflection coefficient against $(e_1 - p_1)/e_1$, the theoretical value for a first-order system (same as Michaelis-Menten). The deviation from the straight line is quite apparent and demonstrates that the system could not be first order. The near agreement at the upper and lower ends of the curve, corresponding to low and high substrate concentrations, is predicted from the theory. In those cases the reflection coefficient ${}^{z}R_{p_1}$ approaches the same value for both a first- and second-order type II system.

B. INITIAL CONDITION EXPERIMENTS

For the study of kinetic steady states, the application of the reflection coefficients to the initial condition experiments is the same as for a reservoir induced steady state. However there will be additional error terms over those discussed for the induced steady states since the steady state equations are only approximately valid for the kinetic case. But these error terms can be ignored when the relative derivatives ($s = \dot{a}/a$) are small ($s \ll 1$); that is, essentially when the kinetic steady state can be said to exist. A more important limitation in the kinetic case is due to the fact that the reflection coefficients can only be studied over a range of initial conditions for which the steady state exists and this range may not be sufficient to discriminate between mechanisms.

6. Semitheoretical Applications—The Kinetics of the Steady State Region

A. GENERAL PROBLEMS

The application of reflection coefficients provides an extremely powerful method for understanding the kinetics of the steady state region. In this case, we interpret the relative changes (r_a) as being the relative slopes, defined as the ratio of the steady state slopes ($\dot{a}$) to the concentration (a). An application of property 3 of the reflection coefficients enables us to apply all our previous equations to the steady state region. Thus Equation (36) means that for a type I system all the intermediates will have the same relative slopes, implying that their qualitative features will be approximately identical in the steady state region. Since the $t_{1/2\ off}$'s can be roughly included in the steady state region, the approximate equality of the $t_{1/2\ off}$'s for this mechanism follows from the same equation. Similarly, for the type II systems, the ordering of the relative steady state slopes and the $t_{1/2\ off}$'s follows from the condition that ${}^{p_1}R_{p_i+1} < 1$. A study of the reflection coefficient equations for the nth order system show that this condition will certainly be satisfied for $p_i^* > 1/2$ or for $p_i^* > p_{i+1}^*$ where $p_i^* = p_i/e_i$. This can be verified by Equations (39) and (40) for the second-order system. All these results have already been observed in the computer solutions discussed previously. A more interesting example that will serve to illustrate the technique of reflection coefficients is discussed below.

B. SUPERPOSITION PRINCIPLE

Thus far we have considered problems for which only one of the fundamental chemicals can change. This is generally sufficient for induced

steady states since all the fundamental variables are controlled by the experimenter. However, for the kinetic steady states it is sometimes not possible or desirable to limit the system to changes in only one fundamental chemical at a time. For enzyme systems, both the substrate and acceptor may change considerably throughout the course of the reaction. Both of these are taken as the primary variables which motivate the changes from one steady state to the other.

When two of the fundamental chemicals are allowed to change, there is no difference in the net result if both change simultaneously or separately, where first one changes and then the other; so long as the changes are infinitesimal. The net effects are additive. If a and b represent the concentrations of two fundamental chemicals while c is any other variable of the system, then the net change in c is given by

$$r_c = r_a {}^{a}_{a}R_b + r_b {}^{b}_{b}R_c \tag{42}$$

where the lower forescript on the R indicates which of the fundamental chemicals is allowed to change, the other being considered constant. We call this the "Superposition Principle." The effects of different infinitesimal relative primary changes are additive according to Equation (42).

C. KINETICS OF REACTIONS WITH TWO VARIABLE SUBSTRATES

As an example of the application of the superposition principle, we shall study the second-order type II system with a variable acceptor in the last reaction step; i.e.,

$$\begin{aligned} E_1 + S &\rightarrow E_1S \\ E_1S + E_2 &\rightarrow E_2S + E_1 \\ E_2S + A &\rightarrow E_2 + \text{Product} \end{aligned} \tag{43}$$

We have already calculated the reflection coefficients for this system due to changes in the substrate (Equations 39–41); i.e., ${}_{x}R$. The coefficients for changes in the acceptor (${}_{a}R$) are calculated in the same way, but assuming that the substrate is maintained constant. Comparing the values of the ${}_{a}R$ with the ${}_{x}R$, then applying the superposition principle, the net changes can be written as

$$r_{p_1} = {}^{z}_{z}R_{p_1}\left[r_x - \frac{p_2}{e_2} r_a\right] \tag{44}$$

$$r_{p_2} = {}^{z}_{z}R_{p_2}\left(r_x - \frac{e_1}{e_1 - p_1} r_a\right) \tag{45}$$

$$r_v = {}_x^zR_v\left(r_x + \frac{p_1}{e_1 - p_1} \times \frac{p_2}{e_2 - p_2}\, r_a\right) \tag{46}$$

where ${}_x^zR_{p_1}$, ${}_x^zR_{p_2}$, and ${}_x^zR_{v2}$ are given by Equations (39–41).

In the study of the steady state region, it must be noted that the changes in the primary variables are dependent since all changes are controlled by the net reaction rate (v). In our case, we have

$$\Delta x = \Delta a \tag{47}$$

If the initial steady state concentrations are x_0 and a_0, and if $a_0 \geq x_0$ then

$$r_x = dx/x \qquad \text{and} \qquad r_a = da/a = dx/(a' + x) \tag{48}$$

where $a' = a_0 - x_0$ is a constant. It is clear that as the reaction proceeds and x runs from x_0 to 0, then r_x will become very large ($\rightarrow \infty$) while r_a remains finite. And the ratio of r_x to r_a will increase from a_0/x_0 at $x = x_0$ to ∞ at $x = 0$. Recalling that the reflection coefficients themselves do not change appreciably in the steady state region we can immediately deduce the qualitative properties of the intermediates. Equation (44) shows that the effect of r_a on r_{p_1} is reduced by a factor p_2/e_2 relative to the effect of r_x, and since $r_a < r_x$, the steady state slope of the first intermediate will always be negative after the start of the steady state region (both r_a and r_x are negative quantities). In fact the maximum of p_1 will mark the onset of the steady state region.

However, for the second intermediate, Equation (45) shows that the effect of r_a is increased by the factor $e_1/(e_1 - p_1)$ relative to the effect of r_x. Depending on the size of p_1, the effect of r_a may be greater than r_x, making r_{p_2} positive. Since $r_x \rightarrow \infty$ as the reaction proceeds, r_x will eventually dominate and r_{p_2} must become negative. As a result, the maximum of p_2 may occur inside the steady state region. The quantitative expansion of this effect is obtained by replacing r_a in terms of r_x in Equation (45). This yields

$$r_{p_2} = {}_x^zR_{p_2}r_x\left(1 - \frac{e_1}{e_1 - p_1} \times \frac{x}{a' + x}\right)$$

from which it is easy to demonstrate that the maximum in p_2 will occur at

$$x/x_0 = [(e_1 - p_1)/e_1]\,[(a_0/x_0) - 1]$$

So if $x_0/a_0 < (e_1 - p_1)/e_1$, then p_2 will be negative throughout the steady state region and the maximum will occur at the start of the steady state region.

The qualitative features we have just described for the second-order type II system with variable acceptor can be extended to the nth-order

type II and type III systems (see Fig. A). A study of the reflection coefficients shows that for type II mechanisms, the first intermediate always has its maximum at the start of the steady state region when $x_0 < a_0$. For both type II and type III mechanisms all other intermediates involved in second-order reaction steps may have the maximum within the steady state region depending on the values of the reflection coefficients. Since the intermediates involved in linear reaction steps are entirely controlled by the reaction rate (i.e., ${}^{r}R_p = 1$) and the rate is always negative, these intermediates have a negative steady state slope throughout the steady state region. The computer solutions shown in Figures 13 and 14 illustrate these qualitative features. The fact that all the intermediates in Figure 14 show no maximum within the steady state region is easily demonstrated for these steady state concentrations.

7. Summary

The study of reflection coefficients provides a useful experimental and theoretical technique for the investigation of reaction mechanisms. For many mechanisms, the theoretical values of the reflection coefficients depend only on the measured concentrations of the chemicals involved and not on the rate constants. Consequently, the experimental determination of the reflection coefficients yields data which can be directly interpreted in terms of the stoichiometry of the reaction mechanism. The experimental conditions required are practical and the equations are simple. In addition the reflection coefficients offer a dynamic description of the kinetics of the steady state region. Their analytic study quickly yields many theorems relating the stoichiometry and the qualitative and semiqualitative properties of the steady state region. The conditions necessary for the theorems are automatically expressed in terms of the concentrations so that their effectiveness can be determined from the experimental data.

CHAPTER VIII

COMPETING REACTIONS

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I. INTRODUCTION

Numerous examples are known wherein a single reactant or reaction intermediate participates in two or more simultaneous and competitive reactions. Such processes are often undesired in synthetic organic chemistry and in the functional group analysis of difficultly separable materials of similar reactivity. On the other hand, the quantitative analyses of specifically designed competitive reactions have provided valuable information in regard to chemical reactivity in numerous systems where other kinetic methods are either unreliable, too tedious or completely unavailable. In general this method involves the comparison of the specific rate constants of some reactant or reactive intermediate with a group of different substrates. A series of relative reactivities are thus determined without resort to the actual measurement of any absolute values of the specific rate constants.

Competing reactions are usually encountered in most reactions proceeding by complex kinetics, including all chain processes, and occasionally in consecutive reactions. Qualitative kinetic analysis of such systems can often be of value by ruling out certain mechanisms and giving credence to other mechanisms.

II. MATHEMATICAL TREATMENT OF COMPETING REACTIONS

1. Simple Competing Reactions

Competing reactions of this type fall into two groups: (*1*) the kinetic equations for the two competing reactions are identical except that the values of the specific rate constants differ; and (*2*) the kinetic equations are different. The former are called homocompetitive and the latter heterocompetitive reactions (1). Reactions in which a reagent or intermediate simultaneously reacts with two compounds containing the same functional (or reactive) group are usually homocompetitive because they proceed by the same mechanism and hence conform to analogous kinetic expressions. Competition of two reagents, A and B, for an intermediate, C, gives the following equations:

$$-d[\mathrm{A}]/dt = k_1[\mathrm{A}][\mathrm{C}]^n \tag{1}$$

$$-d[\mathrm{B}]/dt = k_2[\mathrm{B}][\mathrm{C}]^n \tag{2}$$

Division of Equation (1) by Equation (2) and integration yields:

$$k_1/k_2 = \log ([\mathrm{A}]/[\mathrm{A}]_i)/\log ([\mathrm{B}]/[\mathrm{B}]_i) \tag{3}$$

where the subscript i refers to the initial concentration. This treatment can be applied to three or more reagents competing for C (2). A nondifferential equation for second-order competing reactions (n = unity), which gives the concentration of A, B, or C as a function of time, involves an infinite series of converging terms, and is algebraically complicated.

Reaction of reagent A with a reagent or intermediate B to give two products X and Y by kinetically similar paths yields the equation:

$$d[\mathrm{X}]/dt = k_1[\mathrm{A}]^m[\mathrm{B}]^n \tag{4}$$

$$d[\mathrm{Y}]/dt = k_2[\mathrm{A}]^m[\mathrm{B}]^n \tag{5}$$

Division of Equation (4) by Equation (5) and integration yields:

$$k_1/k_2 = [\mathrm{X}]/[\mathrm{Y}] \tag{6}$$

If $m = n = 1$:

$$-d[\mathrm{A}]/dt = -d[\mathrm{B}]/dt = (k_1 + k_2)[\mathrm{A}][\mathrm{B}] \tag{7}$$

By combination of the ratio k_1/k_2 and the sum $k_1 + k_2$ obtained from the conventional integrated second-order rate equation, the absolute values of k_1 and k_2 can be obtained even if the concentration of X and Y as a function of time cannot be followed.

Competition of first- and second-order rate reactions gives rise to more complicated expressions. The following competitive processes:

$$A \xrightarrow{k_1} \text{products}$$

$$A + C \xrightarrow{k_2} \text{products}$$

give rise to the equation:

$$d[A]/d[C] = (k_1/k_2[C]) + 1 \tag{8}$$

which can be integrated to:

$$[A] = [A]_t - (k_1/k_2) \ln ([C]_t/[C]) - ([C]_t - [C]) \tag{9}$$

An equation correlating k_1, k_2, A or C, and time is complicated algebraically.

When competition gives two products (X and Y) which can be analyzed:

$$A \xrightarrow{k_1} X$$

$$A + B \xrightarrow{k_2} Y$$

It follows that:

$$d[X]/d[Y] = k_1/k_2[B] \tag{10}$$

and if:

$$[B] = [B]_t - [Y] + [Y]_t \tag{11}$$

it follows that:

$$[X] - [X]_t = (k_1/k_2) \ln \{([B]_t + [Y_t])/([B]_t - [Y] + [Y]_t)\} \tag{12}$$

or if $[X]_t = [Y]_t = 0$:

$$[X] = (k_1/k_2) \ln \{[B]_t/([B]_t - [Y])\} \tag{13}$$

If B is also consumed in the first step of the reaction but does not enter kinetically into that step:

$$[B] = [B]_t - [Y] - [X] + [Y]_t + [X]_t \tag{14}$$

and if $[Y]_t = [X]_t = 0$:

$$[X] = \frac{k_1}{k_2} \ln \frac{k_1/k_2 + [B]_t}{k_1/k_2 + [B]_t - ([X] + [Y])} \tag{15}$$

Since:

$$-d[A]/dt = k_1[A] + k_2[A][B] \tag{16}$$

if $[A]_t = [B]_t$ and if B is consumed in the first step of the reaction the concentrations of B and A are equal at all times and

$$k_1 t = \ln \frac{(k_1/k_2 + [A])[A]_i}{(k_1/k_2 + [A]_i)[A]} \tag{17}$$

Competition between two second-order reactions which are different order in one of the reagents, for example,

$$A + A \xrightarrow{k_1} \text{products (second-order reaction)}$$

$$A + C \xrightarrow{k_2} \text{products (second-order reaction)}$$

can also be imagined. Since:

$$d[A]/d[C] = (k_1[A]/k_2[C]) + 1 \tag{18}$$

integration yields:

$$[A] = [A]_i([C]/[C]_i)^{k_1/k_2} + \{[C]_i/(1 - k_1/k_2)\}\{1 - ([C]/[C]_i)\}^{k_1/k_2} \tag{19}$$

Again equations involving time are complicated algebraically.

2. Consecutive Reactions Involving Competition for a Common Reagent

A rather common kinetic situation is the occurrence of two consecutive second-order processes involving a common reagent.

$$A + B \xrightarrow{k_1} C$$

$$C + B \xrightarrow{k_2} D$$

Here A, and its reaction product C, compete for reagent B. Such a process is involved in the basic hydrolysis of an ester of a dibasic acid or in disubstitution reactions. If $k_2 \gg k_1$, k_1 can be readily obtained from the equation:

$$-d[A]/dt = k_1[A][B] \quad \text{or} \quad -d[B]/dt = 2k_1[A][B] \tag{20}$$

or if $k_1 \gg k_2$:

$$-d[A]/dt = k_1[A][B] = -d[B]/dt \tag{21}$$

However, when k_2 and k_1 are of equal magnitude, or k_2 somewhat greater than k_1, kinetic analysis is very difficult. Often k_1 can be measured by working at high [B] whence a pseudo-first-order reaction is observed. In many cases C can be isolated in pure state and its further reaction with B studied in the absence of A. In addition, the initial rate of disappearance of A or B can provide a measure of k_1.

When a large excess of B cannot be tolerated, and C cannot be prepared

free from A, an exact measurement of k_1 and k_2 is difficult. One method developed by French (3) involves the substitution of the parameter $\theta = \int_0^t [B]dt$ into the expressions:

$$-d[A]/dt = k_1[A][B] \tag{22}$$

$$-d[B]/dt = k_1[A][B] + k_2[C][B] \tag{23}$$

$$d[C]/dt = k_1[A][B] - k_2[C][B] \tag{24}$$

Since $d\theta/dt = [B]$:

$$-d[A]/d\theta = k_1[A] \quad \text{and} \quad \ln([A]_t/[A]) = k_1\theta \tag{25}$$

The relationship between θ and t is readily established by plotting B against time and integrating graphically. A somewhat more complicated process involving curve matching was suggested for the measurement of k_2 which is defined by the equations:

$$[B] = [B]_t - [A]_t \times \left\{2 - 2\exp(-k_1\theta) - \frac{\{k_1\exp(-k_2\theta) + \exp(-k_1\theta)\}}{k_1 - k_2}\right\} \tag{26}$$

$$[C] = k_1[A]_t\left\{\frac{\exp(-k_1\theta) - \exp(-k_2\theta)}{k_2 - k_1}\right\} \tag{27}$$

This method has been applied to the periodate oxidation of the Schardinger dextrins (4). Further treatment of this problem have been given by Frost and co-workers (5).

As pointed out by McMillan, it is considerably easier to determine the value of the ratio k_2/k_1 than k_2 and k_1 themselves (6). Provided that values of [A] and [C] can be measured, the ratio of Equations (21) and (24) can be integrated to give the equation:

$$[C] = \frac{[A]}{(k_2/k_1) - 1}\{1 - ([A]/[A]_t)^{(k_2/k_1)-1}\} \tag{28}$$

A variation of the procedure has been given by Wells (7). Since:

$$d[D]/dt = k_2[C][B] \tag{29}$$

$$d([C] + [D])/dt = k_1[A][B] \tag{30}$$

$$d[D]/d([C] + [D]) = (k_2/k_1)([C]/[A]) \tag{31}$$

substituting:

$$[A]/[A]_t = a, \quad [C]/[A]_t = x, \quad [D]/[A]_t = y, \quad x + y = z, \quad k_2/k_1 = k$$

it can be shown that:

$$dy/dz = k(z - y)/(1 - z) \tag{32}$$

with:

$$1 - z = ([A]_i - [C] - [D])/[A]_i = [A]/[A]_i \tag{33}$$

Since $y = z = 0$ at $t = 0$:

$$y = 1 + k(1 - z)/(1 - k) - (1 - z)^k/(1 - k) = 1 + ka/(1 - k) - a^k/(1 - k) \tag{34}$$

If the initial concentrations are restricted to $[A]_i = [B]_i$ it follows at the completion of the reaction ($[B] = 0$) that:

$$[A] = [D] \text{ or } a = y$$

since:

$$[B]_i - [B] = [A]_i - [A] + [D] \tag{35}$$

Equation (34) at the end of the reaction thus reduces to:

$$y^k + y(1 - 2k) + k - 1 = 0 \tag{36}$$

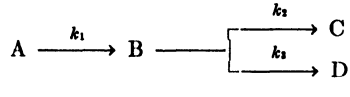
Values of k_1/k_2 consistent with observed values of y are given by Wells (7). By measurement of [D], [A], or [C] at the end of the reaction the value of $[D]/[A]_i = y$ at the completion of the reaction can be calculated from the relations:

$$[A]_f = [D]_f, \quad [C]_f = [A]_i - [D]_f - [A]_f = [A]_i - 2[A]_f \tag{37}$$

where the subscript f indicates final concentrations. The ratio k_1/k_2 is thereby defined. As the value of y approaches 0.50 the value of k_1/k_2 approaches zero.

3. Consecutive Reactions Involving Competing Reactions of a Reactive Intermediate

A reaction of the type:



where B is a reactive intermediate never present at high concentrations is readily treated since:

$$\ln ([A]_i/[A]) = k_1 t \tag{38}$$

and

$$[C]/[D] = k_2/k_3 \tag{39}$$

The absolute values of k_2 and k_3 are not readily obtained. A more complicated situation results when one of the steps is reversible. The simplest example of this type:

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_3} C$$

gives rise to an extremely complicated expression, from which k_1, k_2, k_3 or ratios of these constants cannot be easily evaluated when [A], [B], or [C] are expressed as functions of time (5). If k_1 and k_2 are greater than k_3 an equilibrium assumption can be made:

$$[A]/[B] = k_2/k_1 \tag{40}$$

Thus it follows that:

$$-d[A]/dt = d[C]/dt = k_3[B] = (k_1k_3/k_2)[A] \tag{41}$$

and:

$$\ln [A] = -(k_1k_3/k_2)t + \text{constant} \tag{42}$$

An improvement in this treatment is to obtain $d[B]/dt$ by differentiation of Equation (40):

$$k_1d[A]/dt = k_2d[B]/dt \tag{43}$$

Since:

$$d[A]/dt + d[B]/dt + d[C]/dt = 0 \tag{44}$$

it follows that:

$$d[A]/dt + (k_1/k_2)(d[A]/dt) + (k_3k_1/k_2)[A] = 0 \tag{45}$$

and:

$$-d[A]/dt = k_3k_1[A]/(k_2 + k_1), \quad \ln [A] = -\{k_3k_1/(k_2 + k_1)\}t + \text{constant} \tag{46}$$

Another approach, when [B] is very low, is to make the steady state assumption that $d[B]/dt = 0$ from which it follows that

$$k_1[A] = k_2[B] + k_3[B], \quad [B] = k_1[A]/(k_2 + k_3) \tag{47}$$

and:

$$-d[A]/dt = d[C]/dt = \{k_3k_1/(k_2 + k_3)\}[A], \quad \ln [A] = -\{k_3k_1/(k_2 + k_3)\}t + \text{constant} \tag{48}$$

A refined steady assumption (8) can be made by solving Equation (47) for:

$$d[\mathrm{B}]/dt = k_1/(k_2 + k_3)(d[\mathrm{A}]/dt) \tag{49}$$

Using Equation (49) in the solution of Equation (44) yields:

$$-d[\mathrm{A}]/dt = \{k_3k_1/(k_1 + k_2 + k_3)\}[\mathrm{A}],\ \ln [\mathrm{A}] = -\{k_3k_1/(k_1 + k_2 + k_3)\}t + \text{constant} \tag{50}$$

Equation (50) reduces to Equation (48) when $k_2 + k_3 \gg k_1$, to Equation (46) when $k_1 + k_2 \gg k_3$, and to Equation (42) when $k_2 \gg k_1 + k_3$. The integration constants in Equations (42), (46), (48), and (50) have not been specified since the boundary conditions of $[\mathrm{A}] = [\mathrm{A}]_i$ at $t = 0$ are not useful (8). Boundary conditions at $t = 0$ of $[\mathrm{A}]_i = [\mathrm{A}] + [\mathrm{B}]$ where [B] is given by Equations (40) or (47) are more valid.

Using the "normal" steady state assumption Table I summarizes the rate expressions derived and the constants that can be evaluated for a number of possible reaction sequences.

For more complicated reaction schemes where the steady state treatment becomes awkward a general treatment by Christiansen can be applied (9). In a system containing $n - 1$ reactive intermediates (X_1, X_2 ..., X_{n-1}):

$$\mathrm{A} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{X}_1 + \mathrm{C}$$

$$\mathrm{X}_1 + \mathrm{D} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{X}_2 + \mathrm{E}$$

. . . . . .

$$\mathrm{X}_{n-1} + \mathrm{M} \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} \mathrm{N} + \mathrm{P}$$

A series of quantities w may be defined as the rate of a given step (v) divided by the concentration of any reactive intermediate involved.

$$w_1 = v_1 = k_1[\mathrm{A}][\mathrm{B}]$$

$$w_{-1} = v_{-1}/[\mathrm{X}_1] = k_{-1}[\mathrm{C}], \text{ etc.}$$

If the total concentration of reactive intermediates is negligible compared to the reactants and products, the rate of reaction will be equal to the rate of any step. Thus a series of n simultaneous equations can be written

$$v = w_1 - w_{-1}[\mathrm{X}_1]$$

$$v = w_2[\mathrm{X}_1] - w_{-2}[\mathrm{X}_2], \text{ etc.}$$

These equations can be solved by eliminating the unknowns (X_1, X_2, etc.) and v expressed as the difference between the rates of forward (v^+) and reverse (v^-) reactions.

$$1/v^+ = 1/w_1 + w_{-1}/w_1w_2 + \ldots + (w_{-1}w_{-2} \ldots w_{-(n-1)})/(w_1w_2 \ldots w_n) \quad (51)$$

$$1/v^- = 1/w_{-n} + w_n/w_{-n}w_{-(n-1)} + \ldots + (w_nw_{(n-1)} \ldots w_2)/(w_{-n}w_{-(n-1)} \ldots w_{-1}) \quad (52)$$

4. Induced Reactions

A simple type of induced reaction is represented by the scheme:

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X + C$$

$$X + B \xrightarrow{k_3} Y + \text{products}$$

$$X + D \xrightarrow{k_4} Z + \text{products}$$

where X is a reactive intermediate and the other reactants and products are stable molecules or ions. The characteristic feature of the induced reaction is that D does not, to an appreciable extent, react directly with either A or B, but only with the intermediate formed by their reaction.

Three reaction steps compete for the intermediate; steps 2, 3, and 4. Although the rate of the overall reaction may depend on the rates of all steps, especially step 1, the stoichiometry of the reaction is dependent only on the ratio of the velocities of steps 3 and 4 (v_3 and v_4), these steps being simple second-order competitive reactions:

$$d[Y]/d[Z] = k_3[B]/k_4[D] \quad (53)$$

It is evident that if $v_3 \gg v_4$ the stoichiometry is

$$A + 2B \longrightarrow \longrightarrow Y + C + \text{products}$$

while if $v_4 \gg v_3$

$$A + B + D \longrightarrow \longrightarrow Z + C + \text{products}$$

The induction factor—in this example the number of equivalents of D reacted divided by the number of equivalents of B reacted—provides a means of expressing quantitatively the stoichiometry of the induced reaction. The induction factor can vary from zero to unity, depending on the relative velocities of steps 3 and 4. It may be mentioned incidentally that the state of oxidation of the intermediate of an induced reaction can often be adjusted so that the induction factor attains a maximum value, i.e., $v_3 \ll v_4$. As demonstrated by Westheimer a logical analysis of the induction factor can thus provide valuable information even if the induced reaction involves many reaction steps (10).

If the velocities of steps 3 and 4 are comparable, or if they can be made

TABLE I
Kinetics Based on Steady State Assumption

Reaction	Mechanism	Rate, $-d[A]/dt$	Constants that can be evaluated[a]
1	$A \underset{2}{\overset{1}{\rightleftharpoons}} X$ $X \xrightarrow{3}$ products	$k_1[A]/(r+1)$	$k_1/(r+1)$
2	$A + B \underset{2}{\overset{1}{\rightleftharpoons}} X$ $X \xrightarrow{3}$ products	$k_1[A][B]/(r+1)$	$k_1/(r+1)$
3	$A \underset{2}{\overset{1}{\rightleftharpoons}} X + C$ $X \xrightarrow{3}$ products	$k_1[A]/(r[C]+1)$	k_1 and r
4	$A + B \underset{2}{\overset{1}{\rightleftharpoons}} X + C$ $X \xrightarrow{3}$ products	$k_1[A][B]/(r[C]+1)$	k_1 and r

5	$A \underset{2}{\overset{1}{\rightleftharpoons}} X$ $X + D \xrightarrow{3}$ products	$k_1[A]/\{r([D] + 1)\}$	k_1 and r
6	$A \underset{2}{\overset{1}{\rightleftharpoons}} X + C$ $X + D \xrightarrow{3}$ products	$k_1[A]/\{r[C]/([D] + 1)\}$	k_1 and r
7	$A + B \underset{2}{\overset{1}{\rightleftharpoons}} X + C$ $X + D \xrightarrow{3}$ products	$k_1[A][B]/\{r[C]/([D] + 1)\}$	k_1 and r
8	$A \underset{2}{\overset{1}{\rightleftharpoons}} X$ $X \underset{4}{\overset{3}{\rightleftharpoons}} Z$	$(k_1[A] - rk_4[Z])/(r + 1)$	$k_1/(r + 1)$ and $rk_4/(r + 1)$

[a] Constants that can be evaluated, if v_2 is of the same order of magnitude as v_4, by studying rate of disappearance of A as a function of initial composition of mixture; $r = k_1/k_2$

comparable by suitable adjustment of the concentrations of B and D, the stoichiometry of the overall reaction is intermediate between the two extremes cited. Such a condition is especially favorable for testing the validity of the postulated mechanism and for evaluating k_3/k_4. A plot of the ratio of initial rates of formation of Y and Z for a number of reaction mixtures against the ratio of initial concentrations of B and D should be a straight line with zero intercept, according to Equation (53). Experimental confirmation of this relation would testify to the existence of competing steps 3 and 4, and the slope of the line would be equal to k_3/k_4. An alternative treatment of the data is to plot the initial rates of disappearance of A and D or of B and D against the initial ratio of concentrations of B and D. These plots should be straight lines with intercepts of unity in accordance with the following equations:

$$d[\mathrm{A}]/d[\mathrm{D}] = 1 + (k_3/k_4)([\mathrm{B}]/[\mathrm{D}])$$

and (54)

$$d[\mathrm{B}]/d[\mathrm{D}] = 1 + (2k_3/k_4)([\mathrm{B}]/[\mathrm{D}])$$

The equations are derived from Equation (53) and the stoichiometric relations between A, B, D, Y, and Z. In principle, k_3/k_4 can also be evaluated from the initial and final composition of a single reaction mixture (or from the induction factor). The equation for this purpose is derived by integration of Equation (53) or (54). The resulting expression is not easy to work with, however.

If a substance, E, which reacts with the intermediate is substituted for D, and if the ratio of rate constants of the competing steps is again determined, the relative rates of reaction of the intermediate with D and E are thus determined. In this way the relative reactivity toward the intermediate of each member of a series of substances D, E, etc., can be found.

5. Chain Processes

All chain processes involve at least two competing reactions of the active intermediate, one leading to propagation of the chain and one leading to termination. If propagation is favored over termination, the kinetic chain length (number of molecules reacting for each original active intermediate generated) will be high; if termination is favored the kinetic chain length will be low. The kinetic expression describing a chain process invariably involves the ratio of rate constants for these competing reactions. For example, a simple chain process such as the following:

$$\text{initiating step} \longrightarrow X$$

$$\left.\begin{aligned} X + A &\xrightarrow{k_1} B + X_1 \\ X_1 + C &\xrightarrow{k_2} X + D \end{aligned}\right\} \text{propagation}$$

$$2X \xrightarrow{k_3} E \qquad \text{termination}$$

wherein X and X_1 are active intermediates can be readily treated kinetically if the steady state assumption:

$$d[X]/dt = d[X_1]/dt = 0$$

can be made. Since:

$$-d[A]/dt = k_1[X][A]$$

and from the steady state assumption:

$$k_1[X][A] = k_2[X_1][C]$$

$$R_i = \text{rate of initiation} = 2k_3[X]^2, \quad [X] = (R_i/2k_3)^{1/2}$$

it follows that:

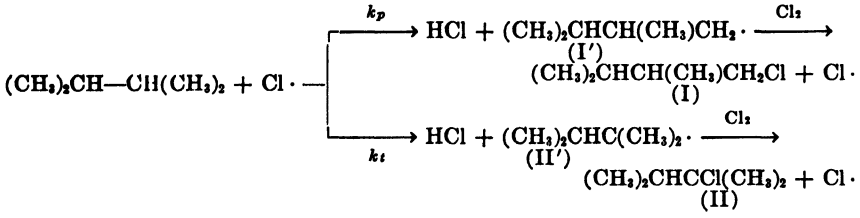
$$-d[A]/dt = k_1[A](R_i/2k_3)^{1/2} \tag{55}$$

for the reaction approaching the stoichiometry, A + C ⟶ B + D. Equation (55) involves the ratio, $k_1/k_3^{1/2}$, of the competing reactions which are kinetically first- and second-order in X. If R_i is known from independent measurement the value of this ratio can be readily obtained.

III. EXPERIMENTAL METHODS

1. Determination of Relative Rates of Reaction

The simplest, and probably the most important, type of competitive process involves the reaction of some reagent (B) with a substrate (A) to give two or more products, the kinetics of both reactions being first-order in [A] and of the same kinetic order in [B]. Aromatic and aliphatic substitution reactions leading to isomeric products are examples of this type of process. Much of our knowledge of directive effects in aromatic and aliphatic substitutions are based upon a knowledge of the products of such competitive processes. For example, the photochlorination of a large excess of 2,3-dimethylbutane in the liquid phase at 40°C. leads to the formation of 60% of I and 40% II (11).



From an analysis of the ratio of products the ratio of rate constants for attack of a chlorine atom on the primary (k_p) and tertiary (k_t) hydrogen atoms can be calculated to be (60/12)/(40/2) = 1:4 since the expressions:

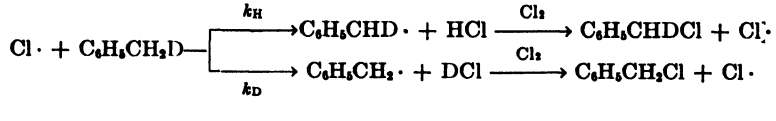
$$d[\mathrm{I}]/dt = 12k_p[\mathrm{A}] \qquad d[\mathrm{II}]/dt = 2k_t[\mathrm{A}]$$

lead to Equation (6′) where:

$$([\mathrm{I}]_f - [\mathrm{I}]_i)/([\mathrm{II}]_f - [\mathrm{II}]_i) = 12k_p/2k_t \qquad (6')$$

Before much faith can be placed in such a calculation several requirements must be met. For example, it must be shown that I and II are stable under the reaction conditions and that facile rearrangement is absent. Moreover it must be shown that I and II are not consumed in a further step in the reaction (in this case by polychlorination) or if they are consumed in a further step that they are both consumed to the same degree. Such a requirement can usually be achieved by use of such a large excess of a reagent that only a small percentage is actually consumed and the ratio of unreacted reagent to product is large at the end of the reaction. The criterion which must be satisfied for an exact determination of a ratio of rate constants is that the ratio of products measured must be a true measure of the relative rates of the competing reactions. In the case of photochlorination experiments this has been demonstrated by isotopic labeling experiments which have shown that every attack of a chlorine atom on a primary carbon-hydrogen bond produces I and only I while every attack of a chlorine atom upon a tertiary carbon-hydrogen bond produces II and only II (11). Thus interconversions between I′ and II′ or I and II can be eliminated and the ratio of k_p/k_t as measured from the product ratio accepted as valid.

A special example of the use of this type of competitive process is the determination of deuterium isotope effects in aliphatic substitutions. This can be achieved by using a substrate which has hydrogen and deuterium in equivalent positions, such as α-deuteriotoluene (12).



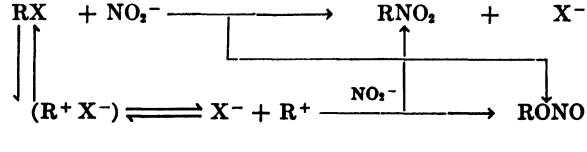
An analysis for the ratio of deuterium to hydrogen chloride will give the ratio k_H/k_D provided that it is known that the first step of the reaction is not reversible. In the case of chlorination this step is indeed not easily reversed. However, when α-deuteriotoluene is photobrominated reversal of the hydrogen or deuterium abstracting step does occur and the ratio k_H/k_D can be determined only under special conditions wherein the hydrogen and deuterium halides are rapidly removed from the reaction zone to prevent the reverse reaction between benzyl radical and hydrogen or deuterium bromide from occurring (13).

A further example of the versatility of such a simple system of competitive reactions in determining relative reactivities is the determination of the deuterium isotope effect for the attack of chlorine atoms upon the tertiary position of isobutane. From two experiments, one using isobutane and one using 2-deuterio-2-methylpropane it is possible to arrive at the relative reactivities of $k_{t-H}/k_{p-H} = 4.5$ and $k_{t-D}/k_{p-H} = 3.2$ at $-15°$ (11). If it is assumed that the primary hydrogen atoms have the same reactivity in both hydrocarbons it follows that in 2-methyl-2-propane the deuterium isotope-effect for attack of a chlorine atom at the tertiary position is $k_{t-H}/k_{t-D} = 1.4$.

Another area in addition to aliphatic and aromatic substitution reactions wherein the study of such simple competitive processes has been a fruitful approach has been the study of the reaction products of resonance stabilized anions, such as the nitrite ion (14).

$$RX + NO_2^- \begin{cases} \xrightarrow{k_1} RNO_2 + X^- \\ \xrightarrow{k_2} RONO + X^- \end{cases}$$

The ratio k_1/k_2 can be calculated from the ratio of nitro compound to nitrite ester provided the reaction follows the scheme shown above. In this regard it should be pointed out that the calculation of relative reactivities from product composition without a detailed knowledge of the mechanism or kinetic order is often of little value, at least from a quantitative sense. The knowledge of mechanism becomes more important when the nature of the two or more products becomes more diverse. For example, in the example cited above what real quantitative significance can be derived from the ratio of the two isomeric products determined in an experiment if the actual process involved is as shown below:



Another example of the importance of a knowledge of mechanism and kinetic order, as well as stoichiometry, can be drawn from our knowledge of the solvolysis of alkyl halides. By inspection, the following equations:

$$\mathrm{RX} + \mathrm{OH^-} \begin{cases} \xrightarrow{k_S} \mathrm{ROH} + \mathrm{X^-} \\ \xrightarrow{k_E} \text{olefin} + \mathrm{H_2O} + \mathrm{X^-} \end{cases}$$

might be expected to yield the reactivity ratio, k_S/k_E = ROH/olefin. This is not necessarily the case since the substitution reaction can occur by the S_N1 path with first-order kinetics ($-d[\mathrm{RX}]/dt = k_S[\mathrm{RX}]$) and the elimination reaction by an E_2 process with second-order kinetics ($-d[\mathrm{RX}]/dt = k_E[\mathrm{RX}][\mathrm{OH^-}]$). This would yield the equation:

$$d[\mathrm{ROH}]/d[\text{olefin}] = k_S/(k_E[\mathrm{OH^-}]) \tag{56}$$

which upon integration ($[\mathrm{OH^-}]_i - [\mathrm{OH^-}]_f = [\mathrm{ROH}] + [\text{olefin}]$) yields:

$$[\mathrm{ROH}] = (k_S/k_E) \ln \frac{(k_S/k_E) + [\mathrm{OH^-}]_i}{(k_S/k_E) + [\mathrm{OH^-}]_i - ([\mathrm{ROH}] + [\text{olefin}])} \tag{57}$$

A more complex determination of relative reactivities involves the interaction of some reactant or reactive intermediate (C) with two or more other reagents (A and B) to give products which are either different or the same.

$$\mathrm{A} + \mathrm{C} \xrightarrow{k_A} \text{products}$$

$$\mathrm{B} + \mathrm{C} \xrightarrow{k_B} \text{products}$$

Provided that the order of reaction can be ascertained from inspection of the above reactions, Equation (3′) applies:

$$(\log [\mathrm{A}]_i - \log [\mathrm{A}]_f)/(\log [\mathrm{B}]_i - \log [\mathrm{B}]_f) = k_A/k_B = (\log [\mathrm{A}]_i/[\mathrm{A}]_f)/(\log [\mathrm{B}]_i/[\mathrm{B}]_f) \tag{3′}$$

Under the special conditions that the ratio of [A]/[B] remains constant during the reaction (for example when A and B are present in large excess over C) Equation (6′) can be used:

$$([\mathrm{A}]_i - [\mathrm{A}]_f)/([\mathrm{B}]_i - [\mathrm{B}]_f) = k_A/k_B \tag{6″}$$

In both Equations (3′) and (6″) the units used to express the concentration of A and B are immaterial. Equation (6″) is best applied when the products of the two reactions are different (P_A and P_B) and an accurate measure of the amount of A and B consumed can be made from a knowledge of $[\mathrm{A}]_i - [P_A]$ and $[\mathrm{B}]_i - [P_B]$. In this event it must again be ascertained that the amounts of products found are a true measure of the rates of the

reactions with rate constants k_A and k_B. Application of the more exact Equation (3′) has the advantage that further reaction of the first formed products, even interconversion of products, need not interfere with the determination of the ratio k_A/k_B since here it is possible to use a reasonably large concentration of C in respect to A and B and to measure the fraction of A and B consumed without detailed information concerning the products formed.

The use of competitive experiments to determine relative reactivities of A and B toward a common reagent or reactive intermediate C would not be used when the specific rate constants, k_A and k_B, could be measured directly. Instead competitive experiments are of value in the numerous instances where either the rates of the individual reactions are too fast for convenient measurement or where the overall kinetics are too complex to allow k_A or k_B to be established. In the case of two very similar reactants A and B, competitive experiments often can yield relative reactivities with less effort than a complete kinetic study, although such an approach is fraught with danger unless some evidence in regard to mechanism or kinetics is available. In certain cases competitive methods may present less experimental difficulties and yield relative reactivities with less experimental uncertainty than two separate determinations of k_A and k_B. For example, k_A and k_B may be rate constants in a free radical chain process whose values can be absolutely determined by appropriate techniques but whose values in reality are considerably affected by trace impurities which give rise to catalysis or inhibition. Problems of mixing of reaction mixtures wherein very fast reactions are expected are usually less serious for the measurement of competitive experiments than for the determination of a specific rate constant and, in fact, reagent C can be added or generated slowly or at varying and unknown rates in a competitive process. In certain cases the experimental problem of following the extent of the individual reactions as a function of time may be too tedious due to lack of suitable analytical methods. Here one relative reactivity calculated by a single analysis is probably more accurate than the ratio of two rate constants each calculated from only one kinetic point. It should be mentioned that experimental errors in analysis or in the preparation of reagent solutions often cancel in competitive experiments. Thus, in competitive experiments of the type under discussion the actual concentration of A, B, and C need not be known but only an accurate measure of the fraction of A and B reacting is required. Advantages in the case of a reaction wherein C cannot be easily handled are obvious. Errors due to change in solvent character with reaction, or to autocatalysis by a reaction product, are usually absent from competitive processes due to cancellation of terms. However, for the accurate determination of the ratio k_A/k_B in a competitive process, methods

must be available for the accurate measurement of A and B in the presence of each other, or of the products of reactions from A and B in the presence of each other. Gas-liquid chromatography has proved to be a valuable tool for such analyses of chemically similar substances and it is expected that in the future, studies of competitive reactivities will become increasingly popular due to the ease of analysis by this method.

As an example of the application of Equations (3′) and (6″) let us consider the Diels-Alder reaction for which precise rate studies have been reported in only a few instances. Reaction of 0.5 mmole of radioactive maleic anhydride (C) with 5 mmole of 1-phenyl-1,3-butadiene (A) and 5 mmole of 1-*p*-chlorophenyl-1,3-butadiene (B) in an appropriate solvent produced the Diels-Alder adduct of A (0.355 mg.) and the Diels-Alder adduct of B (0.208 mg.) as determined by the radio-assay and isotope dilution techniques (15). Since the ratio of A/B did not vary appreciably during reaction ($[A]_i = 10[C]_i$, $[B]_i = 10[C]_i$), the relative reactivity of B to A toward maleic anhydride can be directly calculated from Equation (6″) to be 0.586. Independent experiments indicated that the formation of the adducts was not reversible. By this general procedure a series of relative reactivities of substituted 1-phenyl-1,3-butadienes toward maleic anhydride has been easily and accurately determined. In this regard it should be mentioned that the most accurate reactivity series involve competitive experiments where one compound has been used as a standard throughout. Reactivity series based on the comparison of relative reactivities of A to B, B to C, C to D, etc., are apt to involve an accumulation of errors when the relative reactivities of A to D are compared.

In the Diels-Alder reaction the diene could have been used in a deficiency. For example, when 2,4-cyclopentenedione (A), maleic anhydride (B), and cyclopentadiene (C) are mixed in equal molar quantities in an appropriate solvent the diene will be rapidly and quantitatively consumed (16). Analysis of the products can be readily achieved since the Diels-Alder adduct of A is enolic and its ferric chloride complex follows a Beers-Lambert plot whereas A is not enolic and gives no coloration with ferric ion. Analysis of the reaction products from a variety of initial concentrations indicate that 25% of the enedione had reacted and by difference 75% of the maleic anhydride must have reacted. Since $[A]_i/[A]_f = 1.33$ and $[B]_i/[B]_f = 4.33$ it follows from Equation (3′) that $k_B/k_A = 4.85$.

The foregoing kinetic analysis has been based on the assumption that the Diels-Alder reaction is a one-step second-order process between A or B and C. If it should be shown that the actual process is more complicated, for example,

$$A + C \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{complex} \xrightarrow{k_3} \text{adduct}$$

where k_1, k_2, and k_3 are of approximately equal magnitude, then the foregoing kinetic analysis of relative reactivities has little theoretical significance although this knowledge could still be put to practical use.

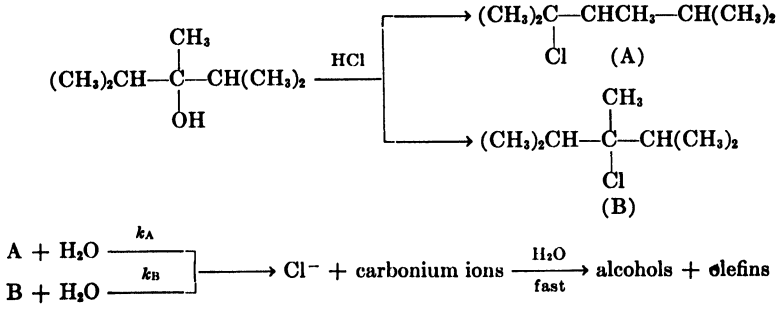
Electrophilic aromatic bromination is another reaction which possesses kinetic uncertainties. For example, in acetic acid the order with respect to bromine is dependent on temperature, dilution and type of compound, and is usually experimentally found to be nonintegral (17). Such a reaction is well suited to investigation by competitive methods if a series of relative reactivities of various aromatics is desired (18). A similar procedure has been employed in aromatic nitration (19). Since, in the case of bromination, the rate of reaction can be readily followed by consumption of bromine, whereas accurate analyses for the consumption of aromatic materials in a competitive process were difficult before the advent of gas-liquid chromatography, relative reactivities in aromatic substitution by bromine have often been determined by some arbitrary manner, for example by measuring the time for 10% reaction under conditions of identical initial concentrations of reagents (20). However, for the more reactive aromatic substrates the reactions become quite fast and problems concerned with mixing and following the rate are apt to appear. In these cases competitive processes are certainly preferred since the bromine can be added very slowly or actually generated *in situ*. In an ingenious approach Francis *et al.* generated bromine slowly in the presence of two aromatic compounds by the slow reaction of potassium bromate and bromide in the presence of acid (21). By this technique development of regions in which A and B are locally depleted can be avoided and adequate mixing assured. The question of local depletion of reagents in a competitive reaction can, of course, be experimentally checked by varying the speed of mixing or stirring.

In cases where the synthesis of A or B invariably gives rise to a mixture of the two, the values of k_A and k_B can still be determined even if reaction with C gives only a common product (D), provided the course of the reaction can be followed as a function of time by measurement of the decrease in [C] or increase in [D].

$$A + C \xrightarrow{k_A} D$$

$$B + C \xrightarrow{k_B} D$$

An example of this type of process is the formation of *tert*-alkyl chlorides from reaction of 2,3,4-trimethyl-3-pentanol with hydrogen chloride followed by the determination of k_A and k_B for hydrolysis from the rate of hydrogen chloride formation (see Section III.2) (22).



Competitive processes are particularly valuable in studies of free radical or atomic processes since here kinetics are often difficult to observe or reproduce. For example, photochemical chlorination of an alkane generally occurs so rapidly that the kinetics and rate of the free radical chain process:

$$Cl_2 \xrightarrow{h\nu} 2Cl\cdot$$

$$Cl\cdot + RH \xrightarrow{k_H} HCl + R\cdot$$

$$R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot$$

$$2Cl\cdot \xrightarrow{\text{wall}} Cl_2$$

$$R\cdot + Cl\cdot \longrightarrow RCl$$

$$2R\cdot \longrightarrow R{-}R$$

are not easily measured. Kinetic chain lengths (molecules of RH consumed per quanta of light absorbed) have been measured, but reproducibility is poor due to inhibition by trace impurities. Moreover, kinetic chain length is a composite measure of all the rate constants in the propagation and termination reactions and would be a poor measure of the effect of the structure of RH on k_H, the rate constant for the hydrogen abstraction step. However, relative reactivities are readily measured by competitive methods with no interference from trace impurities which so drastically influence the kinetic chain length. Walling and Miller in a study of directive effects in hydrogen abstraction competitively photochlorinated α-deuteriotoluene and a series of meta- and para-substituted toluenes (23). From a knowledge of the isotope effect in the photochlorination of α-deuteriotoluene alone it was possible to obtain a series of relative reactivities based on the amounts of deuterium and hydrogen chloride formed by use of Equation (3).

Numerous other free radical processes in which hydrocarbons A, B, etc. compete for a radical or atom, C, have been studied and most of our concepts in regard to the reactivity and selectivity of radicals and atoms are

based on such experiments. In addition to numerous chlorination results (24), data are presently available on competition of this type using bromine atoms (25), *N*-succimidyl radicals (25), trichloromethyl radicals (26), trifluoromethyl radicals (27), methylene (27), and *tert*-butoxy radicals (28). A somewhat different technique has also been used in the case of *tert*-butoxy radicals, conveniently generated from the thermal decomposition of di-*tert*-butyl peroxide. At elevated temperatures (*ca.* 140°C.) a significant proportion of *tert*-butoxy radicals usually decompose by a unimolecular process even in the presence of fairly active hydrogen donors.

$$(CH_3)_3CO\cdot \xrightarrow{k_1} (CH_3)_2C{=}O + CH_3\cdot$$

$$(CH_3)_3CO\cdot + RH \xrightarrow{k_2} (CH_3)_3COH + R\cdot$$

$$R\cdot + CH_3\cdot + (CH_3)_3CO\cdot \longrightarrow \text{a variety of other products}$$

As long as acetone and *tert*-butyl alcohol result only in the manner shown the ratio of k_1/k_2 can be calculated from a knowledge of the amounts of acetone and *tert*-butyl alcohol formed (29). A test of whether acetone or *tert*-butyl alcohol are being formed in other ways is to measure the ratio of acetone to *tert*-butyl alcohol produced in the presence of a large excess of RH at varying *tert*-butoxy radical concentrations (30). Constancy in the ratio indicates that these products are not formed in processes more than first order in total radical concentration. The calculation of the ratio k_1/k_2 then follows from the equation:

$$d[\text{acetone}]/d[t\text{-butyl alcohol}] = k_1/k_2[RH]$$

which integrates to:

$$[\text{acetone}]/[t\text{-butyl alcohol}] = k_1/k_2[RH]$$

when [RH] is large enough to be considered constant and when acetone and *tert*-butyl alcohol are absent initially. Again, measurement of k_1/k_2 for a number of hydrocarbons gives rise to a relative reactivity series (relative values of k_2) for the hydrocarbons toward the *tert*-butoxy radical.

Vinyl polymerization in the presence of a chain transfer agent can be treated as a competitive second-order process involving the ratio of k_{tr}/k_p:

$$\sim\!\!\sim M\cdot + RH \xrightarrow{k_{tr}} \sim\!\!\sim MH + R\cdot$$

$$\sim\!\!\sim M\cdot + RCH{=}CH_2\ (M) \xrightarrow{k_p} \sim\!\!\sim M\cdot$$

This ratio is readily obtained if the average degree of polymerization ($\overline{DP}$) (number average molecular weight of polymer/molecular weight of monomer) is measured.

$$\frac{1}{\overline{DP}} = \frac{\text{rate of formation of polymer chains}}{\text{rate of consumption of monomer}}$$

In general when $\overline{DP} > 40$ it can be assumed that more than 95% of the monomer is consumed in the propagation step ($-d[M]/dt = k_p[M\cdot][M]$). Polymer molecules are formed in transfer with RH ($d[\text{polymer}]/dt = k_{tr}[RH][M\cdot]$), by chain transfer with monomer ($d[\text{polymer}]/dt = k_{tm}[M][M\cdot]$), and in termination processes. If the termination is a bimolecular coupling process:

$$2 \sim\!\!\sim M\cdot \xrightarrow{k_t} M{-}M$$

it follows that the total rate of polymer molecule formation is:

$$d[\text{polymer}]/dt = k_{tr}[RH][M\cdot] + k_{tm}[M\cdot][M] + k_t[M\cdot]^2 \quad (58)$$

and that:

$$1/\overline{DP} = (k_{tr}[RH]/k_p[M]) + (k_{tm}/k_p) + (k_t[M\cdot]/k_p[M]) \quad (59)$$

Equating the rate of initiation, R_i, and termination (steady state assumption) yields:

$$[M\cdot] = (R_i/2k_t)^{1/2} \quad (60)$$

and:

$$1/\overline{DP} = (k_{tr}/k_p)([RH]/[M]) + (k_{tm}/k_p) + \{(k_tR_i/2)^{1/2}/k_p[M]\} \quad (61)$$

The ratio k_{tr}/k_p can be obtained by holding [M] and R_i constant and varying the ratio of [RH]/[M] (an inert diluent must be used) whence a plot of $1/\overline{DP}$ as a function of [RH]/[M] yields a straight line whose slope is k_{tr}/k_p. A more suitable method is to vary R_i (particularly easy in an initiated polymerization) but hold [RH] and [M] constant. This yields a linear relationship when $1/\overline{DP}$ versus $R_i^{1/2}$ is plotted and the intercept is $(k_{tr}/k_p)([RH]/[M]) + (k_{tm}/k_p)$. The value of k_{tm}/k_p can be determined in a similar manner in the absence of RH, or the value of R_i can be varied at a number of [RH]/[M] ratios and the resulting intercepts replotted as a function of [RH]/[M]. Somewhat different expressions can be derived if termination occurs by a first-order process or if termination involves disproportionation of polymer radicals. Since k_p is independent of the structure of RH a series of related reactivities of polymer radicals toward hydrogen transfer agents can be determined from the relative values of k_{tr}. In this way relative reactivities of various hydrocarbons have been determined toward the polymer radicals of styrene, methyl methacrylate, methyl acrylate, acrylonitrile, and methacrylonitrile (31).

Relative reactivities toward methyl radicals have been ascertained in

several ways. In the vapor phase the photochemical decomposition of d_6-acetone yields the trideuteriomethyl radical which can abstract either a deuterium atom from the acetone to give tetradeuteriomethane or a hydrogen from an added hydrocarbon to give trideuteriomethane.

$$CD_3COCD_3 \xrightarrow{h\nu} CD_3\cdot + CD_3CO\cdot$$

$$CD_3\cdot + D_3CCOCD_3 \xrightarrow{k_A} CD_4 + \cdot CD_2COCD_3$$

$$CD_3 + RH \xrightarrow{k_R} CD_3H + R\cdot$$

$$CD_3\cdot, CD_3CO\cdot, R\cdot, \cdot CD_2COCD_3 \longrightarrow \text{a variety of products}$$

As long as the deuteriomethanes do not arise in any other manner the ratio k_A/k_R can be readily determined (32). The ratio $[CD_4]/[CD_3H]$ can be obtained from mass spectral analysis. If $[RH]$ and $[CD_3COCD_3]$ are so large that their ratio is constant during the reaction,

$$CD_4\text{-formed}/CD_3H\text{-formed} = k_A[CD_3COCD_3]/k_R[RH]$$

The reactivities of numerous hydrocarbons relative to acetone-d_6 toward methyl radicals have been reported. In the liquid phase methyl radicals generated from acetyl peroxide have been allowed to compete for hydrocarbons and carbon tetrachloride (33). Methane and methyl chloride formed under conditions of high and constant concentration of the hydrocarbon and carbon tetrachloride yield the relative reactivities.

$$(CH_3CO_2)_2 \xrightarrow{\Delta} \longrightarrow 2CH_3\cdot + 2CO_2$$

$$CH_3\cdot + CCl_4 \xrightarrow{k_C} CH_3Cl + CCl_3\cdot$$

$$CH_3\cdot + RH \xrightarrow{k_R} CH_4 + R\cdot$$

$$CH_3\cdot, CCl_3\cdot, R\cdot \longrightarrow \text{a variety of products}$$

$$CH_3Cl\text{-formed}/CH_4\text{-formed} = k_C[CCl_4]/k_R[RH]$$

If $[CCl_4]$ had decreased during reaction, but only by the reaction shown, and if RH had decreased, but only by the reaction shown, the ratio k_C/k_R could be evaluated from the equation:

$$\{d[CH_3Cl]/([CCl_4]_t - [CH_3Cl])\}/\{d[CH_4]/([RH]_t - [CH_4])\} = k_C/k_R \quad (62)$$

which yields:

$$\ln\{[CCl_4]_t/([CCl_4]_t - [CH_3Cl])\}/\ln\{[RH]_t/([RH]_t - [CH_4])\} = k_C/k_R \quad (63)$$

Szwarc and co-workers have developed an extremely versatile method of measuring the methyl affinities of a wide variety of substances including olefins (34), dienes (35), quinones (36), aromatics (37), and aralkyl hydrocarbons (38). The general method involves the measurement of methane and carbon dioxide produced in the partial (about 5%) decomposition of a dilute solution of acetyl peroxide in the presence of a standard solvent and in the presence of an added substance whose methyl affinity is to be measured. In the presence of only a hydrogen donor (SH) methane and ethane both result but the ratio of $(C_2H_4 + 2CH_6)/CO_2$ is nearly unity (39). The ethane results from a "cage" reaction of methyl or acetoxy radicals (39,40). When the decomposition is performed in the presence of an unsaturated or an aromatic material (A) the ratio of $(CH_4 + 2C_2H_6)/CO_2$ can be less than unity. If the stationary concentration of radicals is sufficiently low that all methyl radicals which diffuse into solution are consumed by the following reactions:

$$CH_3\cdot + SH \xrightarrow{k_S} CH_4 + S\cdot$$

$$CH_3\cdot + A \xrightarrow{k_A} CH_3\text{—}A\cdot$$

$$S\cdot + CH_3A\cdot + A + SH \longrightarrow \text{a variety of products}$$

and if [SH] and [A] are large enough to be considered constant (only small amounts of acetyl peroxide are decomposed):

$$CH_4\text{-formed}/\cdot ACH_3\text{-formed} = k_S[SH]/k_A[A] = CH_4\text{-formed}/CH_4\text{-"lost"}$$

The value of CH_4-formed can be experimentally measured while CH_4-"lost" is equal to $(CO_2$-formed$) - (2C_2H_6$-formed$) - (CH_4$-formed$)$. The value for CH_4-"lost" can also be derived from the difference between $CH_3\cdot$-formed and CH_4-formed. Since in the absence of A it has been shown that CH_4-formed = $CH_3\cdot$-formed and that $(CH_4 + 2C_2H_6)/CO_2 = 1$, (39,41) it follows that in the presence of A, $CH_3\cdot$-formed = $CO_2 - 2C_2H_6$. The ratio of CH_4-formed to CH_4-"lost" is conveniently expressed as:

$$(CH_4/CO_2)/\{1 - (CH_4 + 2C_2H_6)/CO_2\} \qquad (64)$$

In the event that methane can also be formed by the attack of methyl radicals upon A

$$CH_3\cdot + A \xrightarrow{k_{AS}} CH_4 + A'\cdot$$

it follows (42) that:

$$\begin{aligned} CH_4\text{-formed}/CH_4\text{-"lost"} &= k_{AS}/k_A + (k_S/k_A)([SH]/[A]) \\ &= (CH_4/CO_2)/\{1 - (CH_4 + 2C_2H_6)/CO_2\} \end{aligned} \qquad (65)$$

or:

$$([A]CH_4/CO_2[SH])/\{1 - (CH_4 + 2C_2H_6)/CO_2\} = (k_{AS}[A]/k_A[SH]) + (k_S/k_A) \quad (66)$$

The ratios k_S/k_A and k_{AS}/k_A and hence k_S/k_{AS} are easily evaluated by graphical methods from experiments performed at a variety of [A]/[SH] ratios. It should be noted that by using the ratios CH_4-formed/CO_2 and CH_4-"lost"/CO_2 that the loss of potential methyl radicals by the reactions of acetoxy radicals does not interfere with the kinetic treatment. In the presence of a vinyl monomer (M) it is difficult to maintain [M] at a constant value due to polymerization. Here, competition of a standard aliphatic hydrocarbon (SH), such as isooctane, and M for methyl radicals leads to equation

$$\{1 - (CH_4 + 2C_2H_6)/CO_2\}/(CH_4/CO_2) = (k_M/k_S[SH])(1/t)\int_0^t [M]dt \quad (67)$$

If it is assumed that n molecules of M are polymerized for each initiation step, and that only methyl radicals initiate polymerization,

$$CH_3\cdot + M \xrightarrow{k_M} CH_3M\cdot \xrightarrow{(n-1)M} \text{polymer molecule}$$

it follows that at any time ($[CH_4,l]$ = methane-"lost"):

$$[M] = [M]_i - n[CH_4,l]$$

and:

$$d[CH_4]/d[CH_4,l] = k_S[SH]/k_M([M]_i - n[CH_4,l]) \quad (68)$$

or:

$$[CH_4]_f/(1/n)\ln\{[M]_i/([M]_i - n[CH_4,l]_f)\} = k_S[SH]/k_M = [CH_4]_f/(1/n)\ln([M]_f/[M]_i) \quad (69)$$

Substitution for n yields

$$[CH_4]_f/[CH_4,l]_f = (k_S[SH]/k_M[M]_i)\{[M]_i/([M]_i - [M]_f)\}\{\ln([M]_i/[M]_f)\} = (CH_4/CO_2)/\{1 - (CH_4 + 2C_2H_6)/CO_2\} \quad (70)$$

from which k_S/k_M can be calculated if the fraction of M polymerized is measured. Slightly more complex equations result if it is assumed that every radical not appearing as methane ($CH_3\cdot$ and $S\cdot$) initiates polymerization. The assumption that n molecules of M are polymerized for each initiating step certainly cannot be exactly correct since polymer chain length should be a function of total radical concentration which itself decreases as the concentration of acetyl peroxide decreases. However, fairly consistent values of k_M/k_S are obtained as the ratio [SH]/[M] is varied.

In the last example of the use of competitive reactions some approximations had to be made in order to arrive at an equation which could be solved by the use of experimental data. An intriguing example of a competitive process wherein the theoretical kinetic equations are not easily solved by use of experimental data but which is still amenable to an approximate solution has been given by Kooyman (43). Various aralkyl hydrocarbons (RH) inhibit the free radical addition of carbon tetrachloride to olefins (O) presumably by reacting with trichloromethyl radicals to form relatively stable benzyl radicals. The fate of the trichloromethyl radicals in such a system can be described approximately by:

$$CCl_3\cdot + RCH_2{-}CH{=}CH_2 \xrightarrow{k_A} CCl_3H + R\dot{C}H{-}CH{=}CH_2$$

$$CCl_3\cdot + RCH_2{-}CH{=}CH_2 \xrightarrow{k_O} RCH_2{-}\underset{\displaystyle CH_2CCl_3}{\underset{|}{C}}H{-}CH_2CCl_3$$

$$CCl_3\cdot + RH \xrightarrow{k_R} CCl_3H + R\cdot$$

Although values of k_R can best be determined by two hydrocarbons competing for trichloromethyl radicals derived from bromotrichloromethane (26), the three equations given above can be solved to yield values of k_O/k_R. Kooyman first demonstrated that in the absence of RH the addition of an excess of CCl_4 to 1-cetene, catalyzed by benzoyl peroxide, followed the equation

$$CCl_4 \text{ bound to olefin/peroxide decomposed} = [CCl_4]_O/\Delta P = k$$

where CCl_4 bound to olefin represents 1:1 adduct as well as telomer formed by the process

$$RCH_2\dot{C}HCH_2CCl_3 \xrightarrow{CCl_4} RCH_2CHClCH_2CCl_3 + CCl_3\cdot$$

$$\xrightarrow[(2)\ CCl_4]{(1)\ n\text{-}RCH_2{-}CH{=}CH_2} R{-}CH_2{-}\underset{\displaystyle CH_2CCl_3}{\underset{|}{C}}H{-}(CH_2{-}\underset{\displaystyle CH_2R}{\underset{|}{C}}H)_n{-}Cl + CCl_3\cdot$$

The value of $[CCl_4]_O$ can be readily determined from the chlorine content of the high boiling residue of the reactant while ΔP can be determined by titration. Under steady state conditions the carbon tetrachloride bound to olefin $[CCl_4]_O$ would be determined by the rate of addition step, $d[CCl_4]_O/dt = k_O[CCl_3\cdot][O]$ and the rate of peroxide (P) decomposition would most likely follow the first-order expression, $-d[P]/dt = k_P[P]$. Combination leads to the expression:

$$dd[CCl_4]_O/d[P] = -k_O[CCl_3\cdot][O]/k_P[P] \qquad (71)$$

If the formation of an allyl radical by hydrogen abstraction always leads to chain termination

$$\mathrm{RCHCH{=}CH_2 + CCl_3\cdot \longrightarrow R{-}\overset{\displaystyle CCl_3}{\overset{|}{C}}H{-}CH{=}CH_2}$$

it follows that:

$$2fk_P[P] = 2k_A[CCl_3\cdot][O] \tag{72}$$

and:

$$d[CCl_4]_O/d[P] = -f(k_O/k_A) \tag{73}$$

or that:

$$[CCl_4]_O/([P]_t - [P]_f) = k_O f/k_A \tag{74}$$

where f is a stoichiometric efficiency factor for the formation of trichloromethyl radicals by the decomposition of the benzoyl peroxide. In the presence of high concentrations of an active chain transfer agent (RH),

$$d[CCl_4]_O/d[CCl_3\cdot]_{RH} = -k_O[CCl_3\cdot][O]/(k_R[CCl_3\cdot][RH] + k_A[CCl_3\cdot][O]) \tag{75}$$

where $[CCl_4]_O$ and $[CCl_3\cdot]_{RH}$ represent carbon tetrachloride adding to the olefin and trichloromethyl radicals abstracting a hydrogen atom from RH or the allylic position of the olefin. When retardation by RH is large, $k_R[CCl_3\cdot][RH] \gg k_A[CCl_3\cdot][O]$ and:

$$-d[CCl_3\cdot]_{RH}/k_R[RH] = d[CCl_4]_O/k_O[O] \tag{76}$$

When RH is large and constant:

$$-[CCl_3\cdot]_{RH}/k_R[RH] = (1/k_O)\int_{[O]_i}^{[O]_f} d[CCl_4]_O/[O] \tag{77}$$

The amount of trichloromethyl radicals abstracting a hydrogen atom from a benzyl position will be proportional to the retardation and to the amount of additional peroxide $(\Delta P)_{RH}$ that will have to be decomposed in the presence of RH to bring about the same amount of addition of CCl_4 to the olefin in the presence and absence of RH. This follows from the rate of initiation being equal to the rate of termination under steady state conditions:

$$\text{peroxide} \longrightarrow \longrightarrow 2f\,CCl_3\cdot \quad \text{initiation}$$

$$\left.\begin{aligned} CCl_3\cdot + RH &\longrightarrow CCl_3H + R\cdot \\ CCl_3\cdot + R\cdot &\longrightarrow RCCl_3 \end{aligned}\right\} \text{termination}$$

Thus:

$$2f(\Delta P)_{RH} = 2[CCl_3\cdot]_{RH} \text{ and } f(\Delta P)_{RH} = [CCl_3\cdot]_{RH}$$

The following expression results:

$$-f(\Delta P)_{RH}/k_R RH = (1/k_O)\int_{[O]_i}^{[O]_f} d[CCl_4]_O/[O] \quad (78)$$

If carbon tetrachloride gave only a 1:1 adduct with olefin the olefin concentration at any time would be $[O]_t - [CCl_4]_O$ and Equation (78) would reduce to:

$$-f(\Delta P)_{RH}/k_R[RH] = (1/k_O)\ln\{[O]_i/([O]_i - [CCl_4]_O)\} = (1/k_O)\ln([O]_i/[O]_f) \quad (79)$$

From a knowledge of f, ΔP, [RH], and % olefin converted to 1:1 adduct the rate k_O/k_R could be determined.

However, since telomers are also found $[O]_f$ is less than $[O]_i - [CCl_4]_O$. Experimentally, a plot of $1/[O]$ versus $[CCl_4]_O$ was prepared and graphically integrated to give values of $\int d[CCl_4]_O/[O]$ under standard conditions of $[O]_i$ and $[CCl_4]_i$. A plot of $[CCl_4]_O$ versus $\int d[CCl_4]_O/[O]$ was then prepared so that from a given experiment in the presence of RH if $[CCl_4]_O$ was known (from the amount of CCl_4 in the nonvolatile residue) and the amount of peroxide decomposed known (by titration) $\int d[CCl_4]_O/[O]$ could be found and $(\Delta P)_{RH}$ calculated by comparison with the experiments performed in the absence of RH having an identical $[CCl_4]_O$. Although this is a rather complicated technique based on a number of assumptions and dubious kinetic techniques, relative reactivities determined toward the trichloromethyl radical by a series of hydrocarbons (relative values of k_H) appear quite reasonable in view of knowledge of similar processes. By similar techniques the relative reactivities of numerous polynuclear aromatic materials toward trichloromethyl radicals have been determined (44). In this case the peroxide-catalyzed addition of bromotrichloromethane to 1-cetene was employed as the standard reaction. Because of its higher reactivity no telomerization was observed and $\int d[CCl_3Br]_O/[O]$ was taken as $\ln\{[O]_i/([O]_i - [CCl_3Br]_O)\}$. However, in the case of polynuclear hydrocarbons (Ar) the reactivity toward trichloromethyl radicals is so high that addition of bromotrichloromethane to 1-cetene can be observed only in the presence of small amounts of Ar and the concentration of Ar therefore decreased during reaction. Thus:

$$-\int d[CCl_3\cdot]_{Ar}/k_{Ar}[Ar] = (1/k_O)\ln\{[O_i]/([O]_i - [CCl_3Br]_O)\} \quad (80)$$

and since:

$$[Ar] = [Ar]_O - x[CCl_3\cdot]_{Ar} \text{ and } 2f(\Delta P)_{Ap} = x[CCl_3\cdot]_{Ar}$$

where x is the total number of trichloromethyl radicals consumed by each Ar molecule in retardation, it follows that:

$$-(x/k_{Ar})\ln[Ar]_0/\{[Ar]_0 - 2f(\Delta P)_{Ar}\} = (1/k_0)\ln\{[O]_i/([O]_i - [CCl_3Br]_0)\} \quad (81)$$

If x and f are known the ratio of k_O/k_{Ar} can be calculated. If x is unknown, but assumed to be constant, relative values of k_{Ar} for different hydrocarbons can still be calculated. If termination products ($RCCl_3$, etc.) are high boiling and cannot be physically separated from the olefin-halomethane adducts, Equations (78), (79), and (81) can be applied only when $k_O[O] \gg k_R[RH]$ or $k_{Ar}[Ar]$.

The relative reactivities of various olefins toward the trichloromethyl radical has been measured by allowing a deficiency of bromotrichloromethane to react with a mixture of two olefins and determining the composition of the product (45):

$$\left.\begin{matrix}CH_2{=}CHR_1\\ CH_2{=}CHR_2\end{matrix}\right\} + CCl_3\cdot \begin{cases}\xrightarrow{k_1} CCl_3CH_2CHR_1\cdot \xrightarrow{BrCCl_3} CCl_3CH_2CHR_1Br + CCl_3\cdot\\ \xrightarrow{k_2} CCl_3CH_2CHR_2\cdot \xrightarrow{BrCCl_3} CCl_3CH_2CHR_2Br + CCl_3\cdot\end{cases}$$

From the structure of the product formed by adding trichlorobromomethane or an aldehyde to an unsymmetrical olefin:

$$R_1CH{=}CHR_2 + BrCCl_3 \xrightarrow{\text{catalyst}} \begin{cases}\xrightarrow{k_1} R_1CH(CCl_3)—CH(Br)R_2\\ \xrightarrow{k_2} R_1CH(Br)—CH(CCl_3)R_2\end{cases}$$

$$R_1CH{=}CHR_2 + RCH{=}O \xrightarrow{\text{catalyst}} \begin{cases}\xrightarrow{k_1} RCOCH(R_1)—CH_2R_2\\ \xrightarrow{k_2} R_1CH_2—CH(R_2)COR\end{cases}$$

the values of the ratio k_1/k_2 have been determined as a function of the structure of R_1 and R_2 (46).

Often in competitive chain processes two reagents compete for two active intermediates. This process has been most thoroughly studied in the case of copolymerization of two monomers, wherein the monomers M_1 and M_2 compete for the polymer radicals ending in $M_1\cdot$ and in $M_2\cdot$ (47). A similar situation exists in the autoxidation of two hydrocarbons, R_1H and R_2H, by a chain process involving $R_1OO\cdot$ and $R_2OO\cdot$. The conversions of R_1H and R_2H to R_1OOH and R_2OOH are determined by the following four equations:

$$R_1OO\cdot + R_1H \xrightarrow{k_{11}} R_1OOH + R_1\cdot$$

$$R_1OO\cdot + R_2H \xrightarrow{k_{12}} R_1OOH + R_2\cdot$$

$$R_2OO\cdot + R_2H \xrightarrow{k_{22}} R_2OOH + R_2\cdot$$

$$R_2OO\cdot + R_1H \xrightarrow{k_{21}} R_2OOH + R_1\cdot$$

When kinetic chain lengths are > 40 the following equations are approximately correct:

$$-d[R_1H]/dt = k_{11}[R_1OO\cdot][R_1H] + k_{21}[R_2OO\cdot][R_1H] \quad (82a)$$

$$-d[R_2H]/dt = k_{12}[R_1OO\cdot][R_2H] + k_{22}[R_2OO\cdot][R_2H] \quad (82b)$$

$$d[R_1H]/d[R_2H] = (k_{11}[R_1OO\cdot][R_1H] + k_{21}[R_2OO\cdot][R_1H]) \div (k_{12}[R_1OO\cdot][R_2H] + k_{22}[R_2OO\cdot][R_2H]) \quad (83)$$

Under steady state conditions:

$$d[R_1OO\cdot]/dt = d[R_2OO\cdot]/dt$$

$$k_{12}[R_1OO\cdot][R_2H] = k_{21}[R_2OO\cdot][R_1H]$$

and:

$$[R_2OO\cdot] = k_{12}[R_1OO\cdot][R_2H]/k_{21}[R_1H]$$

Substitution into Equation (83) yields:

$$\frac{d[R_1H]}{d[R_2H]} = \frac{k_{11}[R_1OO\cdot][R_1H] + k_{12}[R_1OO\cdot][R_2H]}{k_{12}[R_1OO\cdot][R_2H] + k_{22}k_{12}/k_{21}[R_1OO\cdot][R_2H]^2/[R_1H]} \quad (84)$$

Cancellation of $[R_1OO\cdot]$ and rearrangement yields:

$$\frac{d[R_1H]}{d[R_2H]} = \frac{k_{11}/k_{12}(1 + [R_1H]/[R_2H])}{k_{22}/k_{21}(1 + [R_2H]/[R_1H])} \quad (85)$$

If $[R_1H]$ and $[R_2H]$ are essentially constant during reaction (small % reaction or by constant replenishment), or if the ratio of $[R_1H]/[R_2H]$ remains constant, $[R_1H]$ (consumed)/$[R_2H]$ (consumed) or $[R_1OOH]$ (found)/$[R_2OOH]$(found) can be substituted for $d[R_1H]/d[R_2H]$. Equation (85) can be solved by two experiments wherein the ratio of $[R_1H]/[R_2H]$ is varied. In practice it is usually easier to plot values of k_{22}/k_{12} versus k_{11}/k_{12} for each experiment. Intersection of these two linear plots yields values of the ratios of the rate constants. In case the hydrocarbon concentrations or ratios change during reaction an integrated form of Equation (85):

$$\frac{k_{22}}{k_{21}} = \frac{\log ([R_2H]_i/[R_2H]_f) - (1/p) \log \dfrac{1 - p[R_1H]_f/[R_2H]_f}{1 - p[R_1H]_i/[R_2H]_i}}{\log ([R_1H]_i/[R_1H]_f) + \log \dfrac{1 - p[R_1H]_f/[R_2H]_f}{1 - p[R_1H]_i/[R_2H]_i}} \quad (86)$$

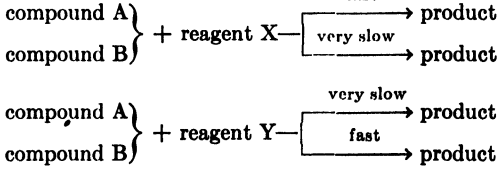
can be employed where $p = (1 - k_{11}/k_{12})/(1 - k_{22}/k_{21})$. Again two experiments will yield values of k_{22}/k_{12} and k_{11}/k_{12} by graphical solution of the simultaneous equations. In general, experiments should be planned so

that the intersection of plots correlating possible values of k_{22}/k_{21} and k_{11}/k_{12} have slopes as far apart as possible. Experimental uncertainties and the choice of experimental conditions are discussed further by Mayo and Walling (47).

When the competitive autoxidation of cumene and tetralin was studied under conditions wherein hydroperoxides were formed in nearly quantitative yields it was found that at 90°C. the oxidation of a mixture containing 0.68 mole fraction of cumene produced tetralyl hydroperoxide and cumyl hydroperoxide in a 7.7 to 1 mole ratio while a similar oxidation of a mixture containing 0.915 mole fraction of cumene produced the hydroperoxides in a 1.15 to 1 ratio, the hydroperoxides being analyzed by infrared absorption after reduction to the alcohols by lithium aluminum hydride (48). Knowing the oxygen absorption, and hence the total yield of hydroperoxides, the amounts of tetralin and cumene consumed were available and Equation (86) could be solved. The results indicate that tetralin is 16 times more reactive toward a tetralyl-peroxy radical than cumene, while a relative reactivity of 23 toward the cumyl-peroxy radical was observed. On the basis of only two experiments these values are probably identical indicating little difference in the selectivity of cumyl- and tetralyl-peroxy radicals. In other systems, particularly copolymerization, k_{11}/k_{12} and k_{21}/k_{22} can vary widely. If $k_{11}/k_{12} \gg 1$ and $k_{21}/k_{22} \ll 1$ a definite alternating tendency occurs of which the copolymerization of α-methylstyrene and oxygen to give a 1:1 copolymer of alternating α-methylstyrene and oxygen units is an extreme example (49).

2. Competition Reactions in Quantitative Analysis

Most successful functional group analyses of mixtures of organic materials based on the consumption of reagents X and Y can be described kinetically by



Successful analyses are thus usually based on the fact that the competing reactions have widely different rates or that actual competition does not occur. In a few instances analyses have been performed wherein compounds A and B have similar reactivity and both react with a given reagent at comparable rates, to produce a common product whose concentration

versus time can be readily followed, e.g., acid or halide ion. Alternately the disappearance of the reagent may be followed. One general procedure for such an analysis is to follow the reaction by a kinetic method which allows the specific rate constant for the slower reacting compound to be measured and its initial concentration calculated by extrapolation. The point at which the faster reacting substance has been essentially completely destroyed in a second-order or pseudo-first-order process depends on the ratio of rate constants k_A/k_B:

$$A + \text{reagent} \xrightarrow{k_A} \text{product}$$

$$B + \text{reagent} \xrightarrow{k_B} \text{product}$$

Since:

$$-d[A]/dt = k_A[A][\text{reagent}] \text{ and } -d[B]/dt = k_B[B][\text{reagent}]$$

it follows that:

$$d[A]/d[B] = k_A[A]/k_B[B] \qquad (\ln[A]/[A]_i)/(\ln[B]/[B]_i) = k_A/k_B$$

and:

$$[A]/[A]_i = ([B]/[B]_i)^{k_A/k_B}$$

TABLE II
Fractional Conversion of Two Competing Reagents in a First-Order Process

k_A/k_B	% A reacting	% B reacting
100	98	3.8
50	98	7.5
20	98	17.8
10	98	32.4
5	98	54.3
4	98	62.4
3	98	72.8
2	98	85.9

In Figure 1 the % B reacting as a function of % A reacting is given for a number of k_A/k_B ratios greater than 1. Thus, if k_A/k_B is 4, only 50% of B will have reacted when 94% of A has been consumed and if k_A/k_B is 5, 97% of A will have reacted by the time B is 50% consumed.

If the reaction of a mixture of A and B, under conditions such that the rate of reaction is first-order or pseudo-first-order, is followed by the concentration of a common product (x) produced in part from A (y) and in part from B (z):

$$dx/dt = k_A([A]_i - y) + k_B([B]_i - z) \qquad x = y + z \qquad (87)$$

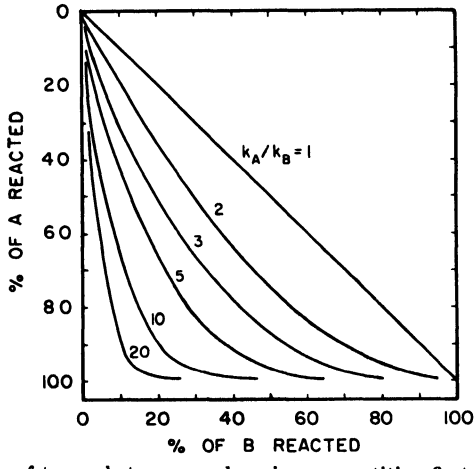


Fig. 1. Conversions of two substances undergoing competitive first-order reactions as a function of relative reactivity.

As y approaches $[A]_t$, dx approaches dz and:

$$\ln ([B]_t - z) = -k_B t + \ln [B]_t = \ln ([B]_t + [A]_t - x) \qquad (88)$$

A plot of $\log ([B]_t + [A]_t - x) = \log (x_\infty - x)$ versus time will give a straight line of slope $-k_B/2.303$ after the point where A has been consumed (see Fig. 2). Extrapolation to $t = 0$ gives $\log [B]_t$. The value of $[A]_t$ can be obtained by difference, and if so desired, values of $[A]_t - y$ can be obtained from the differences between the curved line ($\log ([A]_t + [B]_t - y - z)$) and straight line of Figure 2 ($\log ([B]_t - z)$). Values of k_A may be determined from plots of $\log ([A]_t - y)$ as a function of time. In this type of analysis great care must be exercised that the value of x_∞ is quite accurate since the value of $[B]_t$ is much more sensitive to the value of x_∞ than is the value of k_B. This type of analysis has been applied to isomeric 3°-alkyl chlorides (22,50) and to mixtures of other halides and dihalides (51). This method could be applied to competing second-order processes. However, a more accurate kinetic analysis seems likely if the reaction can be reduced to pseudo-first-order kinetics and followed by the appearance of a common product.

If the values of the rate constants k_A and k_B are known other experimental approaches are possible. For example, Roberts and Regan used the reaction with diphenyldiazomethane (DDM) to determine mixtures of carboxylic acids (52):

$$\left.\begin{matrix} R_1CO_2H \\ R_2CO_2H \end{matrix}\right\} + \text{DDM} \xrightarrow[k_2]{k_1} \begin{matrix} R_1CO_2CH(C_6H_5)_2 + N_2 \\ R_2CO_2CH(C_6H_5)_2 + N_2 \end{matrix}$$

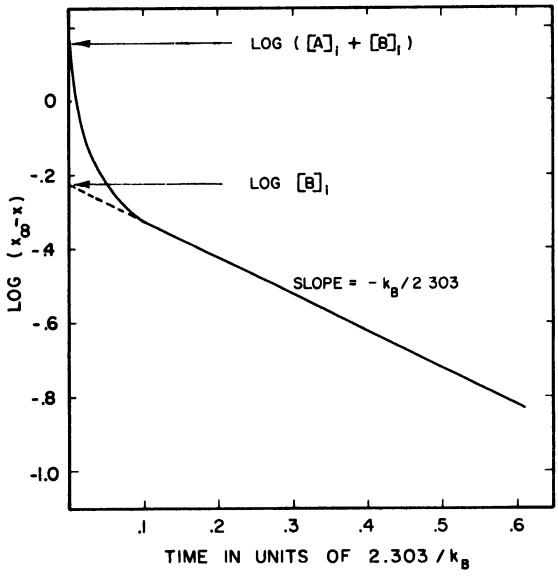


Fig. 2. Kinetic analysis of an equimolar mixture of A and B (total concentration, 1.2 units) undergoing competitive first-order reactions to produce x with $k_A/k_B = 20$.

For certain experimental reasons it was necessary to use an excess of the carboxylic acids. The rate of disappearance of DDM, which could be followed spectrophotometrically, should in the presence of a large excess of the acids follow the equation:

$$-d[\mathrm{DDM}]/dt = k_1[\mathrm{R_1CO_2H}][\mathrm{DDM}] + k_2[\mathrm{R_2CO_2H}][\mathrm{DDM}] \quad (89)$$

and:

$$\ln ([\mathrm{DDM}]/[\mathrm{DDM}]_i) = -(k_1[\mathrm{R_1CO_2H}] + k_2[\mathrm{R_2CO_2H}])t \quad (90)$$

Since $[\mathrm{R_1CO_2H}] + [\mathrm{R_2CO_2H}] = [\mathrm{RCO_2H}]_{\mathrm{total}}$ can be determined by titration it follows that if k_1 and k_2 are known from experiments using pure acids:

$$2.303 \log ([\mathrm{DDM}]/[\mathrm{DDM}]_i) = -\{k_1[\mathrm{R_1CO_2H}] + k_2([\mathrm{RCO_2H}]_{\mathrm{total}} - [\mathrm{R_1CO_2H}])\}t \quad (91)$$

Lee and Kolthoff have developed an essentially empirical method of analysis of two compounds undergoing a common reaction (k_A and k_B known) which depends upon the determination of the total percent reaction at a single time interval (53). Plots of $([\mathrm{A}]_t + [\mathrm{B}]_t)/([\mathrm{A}]_i + [\mathrm{B}]_i)$ versus $[\mathrm{A}]_t/([\mathrm{A}]_i + [\mathrm{B}]_i)$ yield straight lines (for first-order reactions, competing second-order processes give a slight curvature) whose slopes depend on the value of t selected, and upon the ratio of k_A/k_B. After selection of the opti-

mum reaction period, which depends upon the values of k_A and k_B, a plot of the above functions can be made and if conditions are carefully controlled an accurate analysis can be obtained by measuring $[A]_t + [B]_t - x = [A]_t + [B]_t$ at time t. Experimentally the reaction time must be carefully controlled and care must be taken to avoid the usual kinetic interferences such as solvent changes, trace catalysis, temperature variation, etc. This method has been applied to reactions in which $k_A/k_B = 4$ with an average error of 2% (absolute) (53). The single point method has been successfully applied to second-order reactions, for example the basic hydrolysis of esters (53):

$$\left.\begin{matrix}R_1CO_2C_2H_5\\R_2CO_2C_2H_5\end{matrix}\right\rangle + OH^-/H_2O \xrightarrow{\begin{matrix}k_A\\k_B\end{matrix}} \begin{matrix}R_1CO_2^-\\R_2CO_2^-\end{matrix} + C_2H_5OH$$

epoxidation of double bonds (54):

$$\left.\begin{matrix}RCH{=}CH_2\\RC(CH_3){=}CH_2\end{matrix}\right\rangle + C_6H_5\overset{O}{\overset{\|}{C}}OOH \xrightarrow[C_6H_6]{CHCl_3} \begin{matrix}\xrightarrow{k_A} RCH(O)CH_2 + C_6H_5CO_2H\\\xrightarrow{k_B} R{-}C(O)(CH_3){-}CH_2 + C_6H_5CO_2H\end{matrix}$$

and to the second-order reaction of alkyl bromides with ethoxide ion (55):

$$\left.\begin{matrix}R_1Br\\R_2Br\end{matrix}\right\rangle + CH_3CH_2O^-/CH_3CH_2OH \xrightarrow{\begin{matrix}k_A\\k_B\end{matrix}} \begin{matrix}R_1OC_2H_5 + \text{olefin} + Br^-\\R_2OC_2H_5 + \text{olefin} + Br^-\end{matrix}$$

A crude kinetic analysis can be obtained in any competitive first-order or pseudo-first-order process by expressing k_A and k_B as percent reaction in a specific time interval (e.g., the half-life of a substance involved in a first-order reaction is $\ln 2/k$). If, in the selected time interval, A has reacted to the extent of 30% and B to the extent of 50%, the value of $0.3[A]_t + 0.5[B]_t$ can be approximated. Such a method cannot be easily applied to second-order processes.

A somewhat similar empirical method had been used earlier for the analysis of mixtures of cis-trans olefins by methoxymercuration (56):

$$>C{=}C< + Hg(OAc)_2 \xrightarrow{CH_3OH} >C(OCH_3){-}C(HgOAc)< + HOAc$$

A plot of the log of the $1/3$ life period (the time to consume $1/3$ of the total olefin when mercuric acetate and total olefin concentration were initially equal) versus per cent ethyl elaidinate in a mixture of ethyl elaidinate and

ethyl oleate gave a straight line from which the per cent ethyl elaidinate in an unknown mixture could be estimated to within about 4%. Again experimental conditions had to be carefully controlled and the standard and unknown reaction mixtures prepared in such a manner as to give the same initial concentration of total olefin.

Further discussions of the application of competitive reactions in quantitative analyses are given by Fritz and Hammond (57), Laitinen (58), and Lee (53).

3. Identification of Reaction Intermediates

One of the few ways of obtaining direct information about short-lived reaction intermediates is to allow the reaction to occur in the presence of a substance to which the intermediate adds, or otherwise reacts, yielding a product by means of which the intermediate can be identified. The intermediate, which would normally participate in other reactions, is accumulated in the form of an unreactive derivative.

For example, by using the Paneth mirror technique (59), Pearson, Robinson, and Stoddart (60) were able to develop methods for detecting hydrogen atoms in the presence of alkyl radicals and vice versa. Hydrogen atoms do not remove a lead mirror while alkyl radicals react, whereas both hydrogen atoms and alkyl radicals react rapidly with an antimony mirror. If a stream of gas is passed over a thin lead mirror, a heavy lead mirror (to remove all alkyl radicals), and a thin antimony mirror, alkyl radicals can be detected by the removal of the thin lead mirror while the presence of hydrogen atoms will be shown by the removal of the antimony mirror.

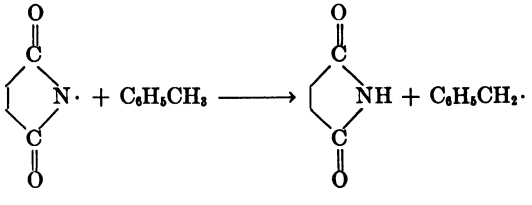
If the relative reactivity of two reagents toward some reactive species is known, competition experiments can often either eliminate this substance as a possible reaction intermediate or support a mechanism formulating such an intermediate. In the event that in a process occurring by an unknown mechanism, competition for an intermediate gives relative reactivity data similar to that observed in some other reaction; it is often assumed that the two reactions involve a common intermediate. Coupled with other information concerning the reaction in question this experiment often serves to define the nature of the intermediate. For example, the chlorination of hydrocarbons by *N*-chlorosuccinimide has been suggested to proceed by the formation of molecular chlorine followed by the usual free radical chain reaction (61). In testing this hypothesis Wiberg (13) found that the chlorination of α-deuteriotoluene ($C_6H_5CH_2D$) by *N*-chlorosuccinimide at 110°C. gave $C_6H_5CH_2Cl$ and C_6H_5CHDCl in a ratio indicating a deuterium isotope effect in the reaction of 1.59 ± 0.05 which presumably is connected with some active intermediate (Z).

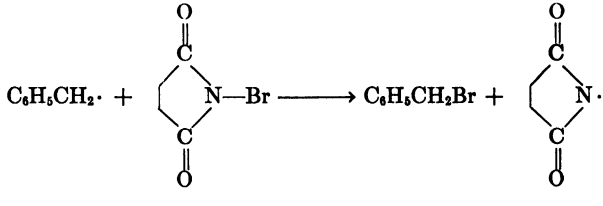
$$C_6H_5CHDH + Z \xrightarrow{k_H} \longrightarrow C_6H_5CHD{-}Cl$$

$$C_6H_5CH_2D + Z \xrightarrow{k_D} \longrightarrow C_6H_5CH_2{-}Cl$$

$$2k_H/k_D = C_6H_5CHDCl/C_6H_5CH_2Cl$$

The deuterium isotope effect in the photochlorination of toluene at 110°C. was found to be 1.47 ± 0.02. It thus appears that both reactions involve a common intermediate and since photochlorination is recognized as involving a chlorine atom as the hydrogen abstraction species it follows that chlorination by *N*-chlorosuccinimide does also, at least under the conditions used. Further substantiation for this hypothesis is the observation that the *N*-succinimidyl radical (often the active intermediate in bromination by *N*-bromosuccinimide) gives a deuterium isotope effect of 3.59 ± 0.05 in. attack upon α-deuteriotoluene at 110°C. Since photobromination involves a significantly lower isotope effect than bromination by N-bromosuccinimide it follows that bromine atoms are not the hydrogen abstracting species in the latter reaction, and the reaction with toluene follows the path suggested by Bloomfield (62).





A further illustration of this technique can be drawn from the data on the solvolysis of various *tert*-butyl derivatives. The data of Table III support the conclusion that all these reactions involve a common intermediate, usually formulated as the *tert*-butyl carbonium ion:

$$(CH_3)_3C{-}Y \xrightarrow{k_1} Y^- + (CH_3)_3C^+ \begin{cases} \xrightarrow{H_2O} (CH_3)_2C{=}CH_2 + H^+ \\ \xrightarrow[H_2O]{} (CH_3)_3COH + H^+ \end{cases}$$

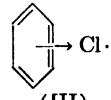
since the proportion of olefin is independent of Y (63). Similarly, the hydrolysis of benzhydryl chloride in 90% aqueous acetone at 50°C. in the presence of 0.101*M* sodium azide gave 34.0% azide and 66.0% alcohol

TABLE III
Effect of Structure on the Rate and Products of Solvolysis of *tert*-Butyl Compounds

Solvent	Temp.	Y	10^5k_1, sec.$^{-1}$	% Olefin
80% aq. ETOH	65.3	SMe_2^+	11 8	35.7
80% aq. ETOH	65.3	Cl	89.7	36.3
60% aq. ETOH	25.0	Cl	0.85	16.8
60% aq. ETOH	25 0	Br	37.2	12.6
60% aq ETOH	25 0	I	90.1	12 9

(first-order rate constant 12.4×10^{-5} sec.$^{-1}$) while benzhydryl bromide (first-order rate constant 416×10^{-5} sec.$^{-1}$) gave 34.5% azide and 65.5% alcohol, supporting the conclusion of a common intermediate, the diphenylmethyl carbonium ion (64).

Studies of competitive reactions offer a powerful tool for investigating the effect of nonreacting solvents upon the reactivity of active intermediates. For example, the addition of aromatic solvents to a branched-chain hydrocarbon gives rise to a more selective photochlorination (11). This specific solvent effect increases with the concentration of the aromatic material and with the basicity of the aromatic nucleus. Thus the nature of the hydrogen abstracting species is being altered by the aromatic solvent, presumably by the formation of III, a hydrogen-abstracting species



(III)

less reactive and more selective than the "free" chlorine atom. Comparison of sulfuryl chloride and chlorine as chlorinating agents in the photochemical chlorination of a branched-chain hydrocarbon has indicated that in an aliphatic solvent different hydrogen-abstracting species are present, and that the sulfuryl chloride chlorination proceeds at least partly in the following manner (65):

$$SO_2Cl\cdot + RH \longrightarrow R\cdot + HCl + SO_2$$

$$R\cdot + SO_2Cl_2 \longrightarrow RCl + SO_2Cl\cdot$$

However, when photochemically initiated chlorinations of a branched-chain hydrocarbon were investigated in the presence of a large amount of an aromatic solvent no difference was noted between chlorine and sulfuryl chloride as the chlorinating agent. Here it seems likely that both reagents give rise to the same reaction intermediate, the complexed chlorine atom (III).

4. Evaluation of Rates of Competing Steps in Complex Reactions

When a substance undergoes reaction with another reagent by competing first- and second-order reactions, which yield a common product, the values of the specific rate constants must be evaluated from the overall rate of reaction which is first-order in one reagent but of nonintegral order in the other.

$$B \xrightarrow[\text{slow}]{k_1} P' \xrightarrow[\text{fast}]{+\,C} P \quad \text{first-order}$$

$$B + C \xrightarrow{k_2} P \quad \text{second-order}$$

If the concentration of B, C, or P can be followed it is possible to obtain values of k_1 and k_2 from the expression

$$-d[B]/dt = d[P]/dt = k_1[B] + k_2[B][C]$$

If the appearance of P or disappearance of B can be measured when C is large and therefore constant.

$$\ln ([B]_t/[B]) = k_1 + k_2[C] \tag{92}$$

Values of k_1 and k_2 can be obtained by a series of experiments at different concentrations of C. Alternatively, it may be possible to choose conditions so that only the first-order or second-order process occurs. The hydrolysis of butenyl chlorides (BCl) follows this kinetic path (66). In this case it was not convenient to follow the reaction

$$BCl \xrightarrow[\text{slow}]{k_1} B^+ + Cl^- \xrightarrow[H_2O,\ OH^-]{\text{fast}} BOH$$

$$BCl + OH^- \xrightarrow{k_2} BOH + Cl^-$$

at high and constant concentrations of OH^- or to isolate the first- and second-order reactions. A plot of [RCl] versus time was prepared and from slopes of tangents at appropriate times, values of $-d[BCl]/dt$ obtained and $(-d[BCl]/dt)/[BCl]$ calculated. Since one hydroxide ion is consumed in both the first-order and second-order steps:

$$[OH^-] = [OH^-]_t - \Delta BCl = [OH^-]_t - [BCl]_t - [BCl] \tag{93}$$

from Equation (93):

$$(-d[BCl]/dt)/[BCl] = k_1 + k_2([OH^-]_t - [BCl]_t - [BCl]) \tag{94}$$

From the plot of the two variables k_2 was obtained as a slope and k_1 as the intercept.

Most reactions involving consecutive reactions also involve competition

for some reaction intermediate. The evaluation of the individual rate constants or the ratio of k_3/k_2 for the simplest example of this type of process:

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_3} C$$

can usually be achieved only if the concentration of intermediate B can be estimated. The system:

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$$

$$B + C \xrightarrow{k_3} D$$

can in certain cases be treated to yield the ratio of rate constants for the competing first-order and second-order reactions, k_2/k_3, without knowledge of the concentration of B. A similar system has been investigated by Hammond and Moore (67) using photochemical techniques. It was found that in the photolysis of benzophenone (B) in the presence of benzhydrol (BH_2) to produce benzpinacol (BHBH):

$$(C_6H_5)_2C{=}O + (C_6H_5)_2CHOH \xrightarrow{h\nu} (C_6H_5)_2C(OH)\text{—}C(OH)(C_6H_5)_2$$

a plot of the reciprocal of the quantum yield (molecules of benzpinacol per quanta of light absorbed) versus the reciprocal of benzhydrol concentration gave a straight line with an intercept of unity. Such an observation is consistent with a mechanism involving:

$$B + h\nu \longrightarrow B' \text{ (singlet)} \longrightarrow B^3 \text{ (triplet)}$$

$$B^3 \xrightarrow{k_d} \text{deactivation}$$

$$B^3 + BH_2 \xrightarrow{k_r} 2BH\cdot \longrightarrow BHBH$$

Here the quantum yield would be:

$$\Phi = k_r[B^3][BH_2]/(k_d[B^3] + k_r[B^3][BH_2]) = k_r[BH_2]/(k_d + k_r[BH_2]) \quad (95)$$

or:

$$1/\Phi = 1 + \{k_d/(k_r[BH_2])\} \quad (96)$$

From the value of k_d/k_r of 0.050, k_d can be estimated as certainly less than 5×10^7 sec.$^{-1}$ while it can be argued that the singlet state must be either deactivated (nonradiative quenching) or converted to the triplet state with a rate constant of about 1×10^{10} sec.$^{-1}$. Therefore, the active intermediate with a k_d of less than 5×10^7 sec.$^{-1}$ is not the singlet state but must be the triplet state as formulated in the mechanism shown.

A rather common kinetic situation involves the following circumstances:

$$A \rightleftharpoons B + C$$

$$B \longrightarrow D$$

or

$$B + E \longrightarrow F$$

For example, in unimolecular nucleophilic displacement reactions (S_N1) a number of kinetic analyses of reactions of the type:

$$RCl \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^+ + Cl^-$$

$$R^+ + Z^- \text{ (or ZH)} \xrightarrow{k_3} RZ \text{ (or RZ + H}^+\text{)}$$

have been performed. A specific example of this type of process is the hydrolysis of 3°-alkyl chloride where a common ion effect is observed (68) or in the reaction of tetra-*n*-butylammonium azide with triphenylmethyl chloride in benzene solution (69). If the concentration of R^+ is small so that at any time:

$$-d[RCl]/dt = d[RZ]/dt$$

it follows that:

$$-d[RCl]/dt = k_1[RCl]\{k_3[Z^-][R^+]/(k_2[R^+][Cl^-] + k_3[Z^-][R^+])\} \quad (97)$$

or:

$$-d[RCl]/dt = k_1k_3[RCl][Z^-]/(k_2[Cl^-] + k_3[Z^-]) \quad (98)$$

If $v_3 \gg v_2$ (v = velocity of step 2, 3, etc.) only the value of k_1 can be obtained while if $v_3 \ll v_2$ only the value of k_1k_3/k_2 can be evaluated. When v_3 and v_2 are similar, values of k_1 and k_2/k_3 can be obtained. If $[Cl^-]_t = 0$, integration of Equation (98) with $a = [RCl]_t$, $b = [Z^-]_t$, and $x = [RCl]_t - [RCl] = [RZ] = [Cl^-]$ yields

$$k_1t = \left(1 - \frac{ak_2/k_3}{a - b}\right) \ln \frac{a}{a - b} + \left(\frac{bk_2/k_3}{a - b}\right) \ln \frac{b}{b - x} \quad (99)$$

For every experimental point a series of values of k_1 consistent with assumed values of k_2/k_3 can be calculated and the best values of k_1 and k_2/k_3 evaluated from the intersection of plots of k_1 versus k_2/k_3. A preferable method of evaluating k_1 is to calculate values of $k_1^{(x)}$ according to the first-order rate law $k_1^{(x)}t = \ln \{a/(a - x)\}$. Values of $k_1^{(x)}$ will decrease as x increases due to the reversal of the ionization step but can be extrapolated to give the true value of k_1 at $x = 0$. Experimentally a smooth plot of

$a - x$ versus time can be prepared and $k_1^{(x)}$ then calculated at appropriate time intervals. Knowing k_1 the ratio k_2/k_3 can be obtained by solving Equation (99) at various values of x and t but as might be expected the value of the right hand side of the equation is not very sensitive to changes in the ratio of k_2/k_3.

In the event HZ represents solvent whose concentration is therefore large and constant the integrated rate expression for $[Cl^-]_t = 0$ is

$$-k_1 t = (k_2/k_3)\{[RCl]_t \ln ([RCl]/[RCl]_t) + [RCl]_t - [RCl]\} + \ln ([RCl]/[RCl]_t)$$

Again, k_1 can be solved by the extrapolation of the "apparent first-order rate constant" to $x = 0$. Alternately the initial rate of reaction, $v_0 = -d[RCl]/dt$, can be measured by some graphical method and k_1 thereby evaluated. When $[Cl^-]_t \neq 0$ values of the "apparent first-order rate constant" at $x = 0$ would be equal to $k_1k_3/(k_2 + k_3[Cl^-]_t)$. Thus, as $x \rightarrow 0$

$$1/k_{\text{apparent}} = \{(k_2/k_3)[Cl^-]_t + 1\}/k_1 \qquad (100)$$

and values of k_2/k_3 and k_1 can be obtained from a plot of $1/k_{\text{apparent}}$ versus $[Cl^-]_t$ as observed in a number of experiments at different values of $[Cl^-]_t$. If $[Cl^-]_t$ is very large and thus independent of x, $k_1^{(x)}$ will be independent of the values of x. In this case k_1 and k_2/k_3 can still be determined from Equation (100).

A unique kinetic analysis wherein both a rate constant and an equilibrium constant were evaluated from kinetic data has been reported by Duke and Yamamoto for a system that can be generalized:

$$A \rightleftharpoons B + 2C$$

$$B \longrightarrow 2D$$

where B has an appreciable concentration (70). In a study of acid-base reactions it was found that pyrosulfate ion reacts with nitrate ion (potassium nitrate–sodium nitrate solvent) to produce nitrogen dioxide, oxygen and sulfate ion. The kinetics were consistent with the mechanism

$$S_2O_7^{2-} + NO_3^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} NO_2^+ + 2SO_4^{2-} \text{ (fast)}$$

$$NO_3^- + NO_2^+ \xrightarrow{k_3} 2NO_2 + O \text{ (slow)}$$

The reaction was followed by titration of aliquots for total acidity (T_A):

$$S_2O_7^{2-} + H_2O \longrightarrow 2SO_4^{2-} + 2H^+$$

$$NO_3^+ + H_2O \longrightarrow NO_3^- + 2H^+$$

Hence:

$$T_A = [S_2O_7^{2-}] + [NO_2^+]$$

and:

$$-dT_A/dt = k_3[NO_2^+][NO_3^-]$$

Since:

$$K_e = k_1/k_2 = ([NO_2^+][SO_4^{2-}]^2)/([NO_3^-][S_2O_7^{2-}])$$

it follows that:

$$NO_2^+ = T_A/\{([SO_4^{2-}]^2/K_e[NO_3^-]) + 1\}$$

and:

$$-d(T_A)/dt = k_3[NO_3^-]T_A/\{1 + ([SO_4^{2-}]^2/K_e[NO_3^-])\}$$

When $[NO_3^-]$ and $[SO_4^{2-}]^2$ are large and constant:

$$\ln \{(T_A)_t/(T_A)\} = \left\{k_3[NO_3^-]\Big/\left(1 + \frac{[SO_4^{2-}]^2}{K_e[NO_3^-]}\right)\right\} t = k't \quad (101)$$

The reciprocal of Equation (101) is:

$$[NO_3^-]/k' = (1/k_3) + \{[SO_4^{2-}]^2/(K_e k_3[NO_3^-])\} \quad (102)$$

Plots of $1/k'$ versus $[SO_4^{2-}]^2$ at constant $[NO_3^-]$ and a variety of constant $[SO_4^{2-}]$ yields an intercept from which k_3 can be calculated and a slope from which K_e can be calculated once k_3 is known.

Kinetics of enzyme reactions invariably involve competing and consecutive processes. The simplest such reaction is:

$$E + S \rightleftharpoons X \longrightarrow E + P$$

where E is the enzyme, S the substrate, X a complex, and P the product. An excellent discussion of the kinetic aspects of this reaction sequence wherein the second step is also considered to be reversible has been given by Alberty (71).

Acid- and base-catalyzed reactions in aqueous solution involve competitive reactions, particularly if general acid or base catalysis is observed (72). For example, consider the situation:

$$SH + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} H_2O + S^-$$

$$SH + B \underset{k^b_{-1}}{\overset{k_1^b}{\rightleftharpoons}} BH + S^-$$

$$S^- \xrightarrow{k_2} \text{product}$$

If:

$$k_1[SH][OH^-] + k_1^b[SH][B] \ll k_{-1}[H_2O][S^-] + k^b_{-1}[BH][S^-] \quad (102)$$

The value of $[S^-]$ can be calculated from a steady state assumption to be:

$$[S^-] = (k_1[SH][OH^-] + k_1^b[SH][B])/(k_{-1}[H_2O] + k^b_{-1}[BH] + k_2) \quad (103)$$

Thus:

$$-d[SH]/dt = \{(k_1[OH^-] + k_1^b[B])\, k_2[SH]\}/(k_{-1}[H_2O] + k^b_{-1}[BH] + k_2) \quad (104)$$

and:

$$-[SH]/\text{rate} = \{1/(k_1[OH^-] + k_1^b[B])\} + K_w/(k_2K_{SH}[OH^-]) \quad (105)$$

The reaction is catalyzed by both B and OH^- (general base-catalysis) but the rate is not a linear function of catalyst concentrations. If, in addition to the restrictions set forth in Equation (102):

$$k_2[S^-] \gg k_{-1}[H_2O][S^-] + k^b_{-1}[BH][S^-] \quad (106)$$

Equation (104) reduces to:

$$-\text{rate}/[SH] = k_1[OH^-] + k_1^b[B] \quad (107)$$

The rate is now a linear function of catalyst concentrations, the rate of the general base-catalysis being determined by the rate of the competing proton transfer from SH to OH^- and B. The values of k_1 and k_1^b may be determined experimentally.

If, however:

$$k_2[S^-] \ll k_{-1}[H_2O][S^-] + k^b_{-1}[BH][S^-]$$

Equation (104) reduces to:

$$-[SH]/\text{rate} = K_w/k_2[OH^-]K_{SH}$$

and the reaction shows only specific catalysis by hydroxide ions. Proton transfers still occur *via* attack of both B and OH^- upon SH but since the ionization stage of the reaction is at equilibrium only $[OH^-]$ is important in determining $[S^-]$. Similar equations can be derived for acid catalysis involving competing reactions between the hydronium ion and unionized acids for a base.

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CHAPTER IX

KINETIC ISOTOPE EFFECTS

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I. THEORY OF ISOTOPE EFFECTS

The following discussion will attempt to outline the present state of the theory of isotope effects in a manner comprehensible to the organic chemist. The inevitably mathematical approach is not intended to be thorough or rigorous, and qualitative aspects of the theory will be emphasized. More complete treatments are available elsewhere (1).

There is general agreement that the major factor in kinetic isotope effects is the difference in zero-point vibrational energy between bonds to different isotopes. The vibrational energy levels of a diatomic molecule A—B will be given by Equation (1), where h is Planck's constant, ν the frequency of the A—B stretching vibration, and n the vibrational quantum

$$E = h(n + {}^1/_2)\nu \tag{1}$$

number. At ordinary temperatures most A—B molecules will be in their lowest vibrational energy level ($n = 0$) and will have the *zero point energy* of ${}^1/_2h\nu$ (so called because the molecule will still have this energy at absolute zero). If A—B behaves as a simple harmonic oscillator, its frequency is given by Equation (2). Here k is the "force constant" (a measure of the

$$\nu = (1/2\pi)(k/\mu)^{1/2} \tag{2}$$

stiffness of the bond) and μ is the reduced mass of A—B, equal to $m_A m_B/(m_A + m_B)$.

From the foregoing, one can conclude that the replacement of B by a heavier isotopic B* will *increase* μ and *decrease* ν (k should be unaffected by isotope substitution, since it depends only on the nature of the A—B bond). Thus the vibrational energy levels of A—B* will be shifted downward relative to those of A—B. Now dissociation of both A—B and A—B* will lead to atoms having only translational energy and under identical conditions the translational energies of A + B and A + B* must be identical. Since A—B* starts from a lower energy level, complete dissociation of A—B* will require more energy than will complete dissociation of A—B.

The preceding ignores many factors which should be considered in a complete discussion of the theory of isotope effects. In polyatomic molecules frequencies other than the stretching frequency of the bond being broken may be affected by isotopic substitution. If bond breaking is incomplete in the transition state, the assumption of identical energies for the two isotopic transition states is unjustified. In addition, the effect of mass on velocity of passage over the energy barrier and the possibility of nonclassical penetration of the energy barrier ("tunnel" effect) should be included in any complete theory.

At this point, a more rigorous approach to isotope-effect theory will be presented. While this approach meets, in principle, most of the objections raised above, practical application often involves drastic simplification. Indeed, under appropriate conditions it reduces to the same result predicted in the opening paragraphs. The derivation given is due mainly to Bigeleisen (1,2). No attempt will be made to present the mathematics in detail, but important assumptions will be indicated.

The basis of the Bigeleisen approach lies in the transition-state theory of reaction rates. Let two reactants A_1 and A_2 (which differ only isotopically) react according to Equations (3) and (4), where C_1 and C_2 represent the two transition states (also called activated complexes). The rate constants, k_1 and k_2, of the two reactions are given by Equations (5)

$$A_1 + B + \ldots \rightleftharpoons [C_1] \longrightarrow \text{products} \tag{3}$$

$$A_2 + B + \ldots \rightleftharpoons [C_2] \longrightarrow \text{products} \tag{4}$$

and (6).

$$k_1 = \kappa_1 (kT/h) K_1^{\ddagger} \tag{5}$$

$$k_2 = \kappa_2 (kT/h) K_2^{\ddagger} \tag{6}$$

Here the κ's are transmission coefficients, k is Boltzmann's constant, T the absolute temperature, and h Planck's constant. The factor $K^{\ddagger}$ is an equilibrium constant for the equilibrium between reactants and activated complex. The isotope effect is simply the ratio of k_1 to k_2 (Equation 7). The equilibrium constants may be expressed in terms of partition-function

$$k_1/k_2 = (\kappa_1/\kappa_2)\ (K_1^{\ddagger}/K_2^{\ddagger}) \tag{7}$$

ratios and one usually assumes that $\kappa_1 = \kappa_2$ (though this may or may not be valid). The result is Equation (8). It is important to remember

$$k_1/k_2 = (Q_{A_2}/Q_{A_1})\ (Q_1^{\ddagger}/Q_2^{\ddagger}) \tag{8}$$

that the $Q^{\ddagger}$'s differ from normal Q's in that one vibrational degree of freedom, that corresponding to motion along the reaction coordinate, is missing. The partition-function ratio for two isotopic molecules is given by Equation (9).

$$\frac{Q_2}{Q_1} = \frac{S_1}{S_2}\left(\frac{I_{X_2}I_{Y_2}I_{Z_2}}{I_{X_1}I_{Y_1}I_{Z_1}}\right)^{1/2}\left(\frac{M_2}{M_1}\right)^{3/2}\prod_i^{3n-6}\exp(\Delta u_i/2)\,\frac{1-\exp(-u_{1i})}{1-\exp(-u_{2i})} \tag{9}$$

Here S is the symmetry number, I_X, I_Y, and I_Z are the principle moments of inertia, M is the molecular weight and $u = h\nu/kT$ ($\Delta u = h(\nu_1 - \nu_2)/kT$), where the ν's are the normal vibrational frequencies of the molecule. Application of the Teller-Redlich product rule converts Equation (9) to Equation (10). The m's are the masses of the constituent atoms of the

$$\frac{S_2}{S_1}f = \prod_j^n\left(\frac{m_{1j}}{m_{2j}}\right)^{3/2}\frac{S_2}{S_1}\times\frac{Q_2}{Q_1} = \prod_i^{3n-6}\frac{u_{2i}}{u_{1i}}\exp(\Delta u_i/2)\,\frac{1-\exp(-u_{1i})}{1-\exp(-u_{2i})} \tag{10}$$

molecules. The corresponding expression for $Q_2^{\ddagger}/Q_1^{\ddagger}$ (Equation 11) differs somewhat because of the missing vibrational degree of freedom. The

$$\frac{\nu_{1L}^{\ddagger}}{\nu_{2L}^{\ddagger}}\times\frac{S_2^{\ddagger}}{S_1^{\ddagger}}\times f^{\ddagger} = \prod_j^n\left(\frac{m_{1j}}{m_{2j}}\right)^{3/2}\frac{S_2^{\ddagger}Q_2^{\ddagger}}{S_1^{\ddagger}Q_1^{\ddagger}}$$

$$= \frac{\nu_{1L}^{\ddagger}}{\nu_{2L}^{\ddagger}}\prod_i^{3n-7}\frac{u_{2i}^{\ddagger}}{u_{1i}^{\ddagger}}\exp(\Delta u_i^{\ddagger}/2)\,\frac{1-\exp(-u_{1i}^{\ddagger})}{1-\exp(-u_{2i}^{\ddagger})} \tag{11}$$

ratio of rate constants then becomes Equation (12). The frequencies

$$k_1/k_2 = (\nu_{1L}^{\ddagger}/\nu_{2L}^{\ddagger})\ (f_A f_B \ldots/f^{\ddagger}) \tag{12}$$

$\nu_L^{\ddagger}$ correspond to motion along the reaction coordinate and the ratio can also be expressed as $(m_2^{\ddagger}/m_1^{\ddagger})^{1/2}$, where $m^{\ddagger}$ is the "effective mass along the reaction coordinate." More will be said on this later.

For elements other than hydrogen a more convenient expression for the isotope effect can be derived after some fairly lengthy algebra, and is given

in Equation (13). The function $G(u)$ can be obtained quite simply from

$$(k_1/k_2)(S_2S_1^{\ddagger}/S_1S_2^{\ddagger}) = (m_2^{\ddagger}/m_1^{\ddagger})^{1/2}\left[1 + \sum_i^{3n-6} G(u)\Delta u_i - \sum_i^{3n-7} G(u_i^{\ddagger})\Delta u_i^{\ddagger}\right] \tag{13}$$

Equation (14) or from tables provided by Bigeleisen and Mayer (3). Recently Johnston, Bonner, and Wilson (4) have noted that the approxima-

$$G(u) = 1/2 - 1/u + 1/[\exp(u) - 1] \tag{14}$$

tion used in obtaining Equations (13) and (14), namely, $\exp(\Delta u/2) = 1 + \Delta u/2$, is not always justified even with relatively heavy elements such as carbon.

Neither Equation (12) nor Equation (13) includes a correction for the tunnel effect, but the correction can be made if the relevant data are available (1,5). Strict application of either equation involves knowledge of all fundamental vibrational modes of reactants and transition states. The frequencies for reactants may be available from spectroscopic data; those for the transition state must be guessed or calculated from an appropriate model (4). Usually all vibrations except those involving motion of the isotopically-substituted atom will be the same in both isotopic species. A frequently-made (and not always justified) assumption is that the stretching frequency of the bond being broken goes to zero in the transition state and that all other frequencies remain unchanged. The desired frequency can usually be estimated from spectroscopic data. If the harmonic oscillator approximation (Equation 2) holds, the stretching frequency for the other isotopic species is given by Equation (15) where μ is the reduced mass

$$\nu_1/\nu_2 = (\mu_2/\mu_1)^{1/2} \tag{15}$$

of a hypothetical molecule made up of the two atoms forming the bond. Implicit in this treatment is the assumption that the stretching vibration of a particular bond is a normal mode of the molecule and that elongation of this bond is a true representation of the motion along the reaction coordinate.

Evaluation of the ratio $(m_2^{\ddagger}/m_1^{\ddagger})^{1/2}$, or $\nu_{1L}^{\ddagger}/\nu_{2L}^{\ddagger}$, can be approached through a complete vibrational analysis of the system under investigation (4). Such computations become very laborious for systems of the complexity normally encountered in organic chemistry, so simplified models are usually employed. For dissociation of a simple diatomic molecule, the ratio $(\mu_2/\mu_1)^{1/2}$ of Equation (15) can be used. Where simple bond-breaking in a complex molecule occurs, Bigeleisen (6) has suggested that the reduced masses be calculated from the masses of the entire molecular fragments on each side of the bond. For three-center reactions

(A + BC → AB + C), an expression has been derived which takes into account the relevant masses and the ratio of the extent of bond-breaking to the extent of bond-making (7).

The foregoing should make it apparent that isotope effects calculated from highly simplified models may be misleading. Indeed, the two- and three-center models are really useful only in evaluating maximum effects. Where the bond (or bonds) to the isotopic species is incompletely ruptured in the transition state, the reaction coordinate can no longer correspond to a simple elongation of that bond and only a detailed vibrational analysis will give a true picture. In such cases, the isotope effect may not vary in a simple manner with the strength of the bonds to the isotopic atom in the transition state.

Equation (13) cannot be applied to deuterium or tritium isotope effects, but there are several useful alternate simplifications of Equation (12). For a two-center system R—H, only a single stretching vibration need be considered. This leaves only one term in the product of Equation (10). The remaining $3n$-7 vibrations are assumed to be unchanged in the transition state and thus cancel the $3n$-7 terms of Equation (11) (the C—H stretch corresponding to the reaction coordinate is already missing from Equation 11). Equation (12) thus becomes Equation (16). Now both

$$\frac{k_H}{k_D} = \frac{S_H S_D^{\ddagger}}{S_H^{\ddagger} S_D} \times \frac{\nu_H^{\ddagger}}{\nu_D^{\ddagger}} \times \frac{u_D}{u_H} \times \exp\left[\frac{u_H - u_D}{2}\right] \times \frac{1 - \exp(-u_H)}{1 - \exp(-u_D)} \quad (16)$$

u_D/u_H and $\nu_H^{\ddagger}/\nu_D^{\ddagger}$ can be written as ratios of reduced masses of R—H and R—D and thus will cancel. Also, the $\exp(-u)$ terms are negligible at ordinary temperatures because most bonds to hydrogen have vibrational frequencies > 1,000 cm.$^{-1}$ (A common exception is restricted or free internal rotation, but this contribution will usually be small enough to neglect.) We thus get the very simple Equation (17), which predicts k_H/k_D to be

$$\frac{k_H}{k_D} = \left(\frac{S_H S_D^{\ddagger}}{S_H^{\ddagger} S_D}\right) \exp\left[\frac{u_H - u_D}{2}\right] \quad (17)$$

around 7 at room temperature (8).

Perhaps more realistic would be the three-center model X + H—Y → X—H + Y, since this brings in the reagent which always must be present to abstract the hydrogen. Here the $\nu_H^{\ddagger}/\nu_D^{\ddagger}$ term is given by the Bigeleisen-Wolfsberg expression (7), but for m_X and $m_Y \gg m_H$ or m_D this reduces to $(m_D/m_H)^{1/2}$ which again cancels u_D/u_H. Thus the stretching contribution remains the same and Equation (17) need only be altered by a term allowing for the additional vibrational frequencies of the three-center system. The symmetric stretching mode of X—H—Y does not involve

appreciable motion of hydrogen and will be almost unaffected by isotopic substitution. The transition state will have two bending modes (in-plane and out-of-plane "plucking") that do involve motion of the hydrogen. These will usually be similar to the two C—H bending frequencies of H—Y (assuming that H—Y is an organic molecule; if H—Y is a diatomic molecule it will, of course, have no bending frequencies). To allow for changes in these bending modes between ground state and transition state, we multiply Equation (17) by $(k_H/k_D)_b$, defined in Equation (18) (unless X and Y are single atoms, there will be other bending modes to the transition state, but these involve little motion of hydrogen).

$$\left(\frac{k_H}{k_D}\right)_b = \prod_i^2 \frac{u_{Di}}{u_{Hi}} \exp\left[\frac{u_{Hi} - u_{Di}}{2}\right] \frac{1 - \exp(-u_{Hi})}{1 - \exp(-u_{Di})} \div \prod_i^2 \frac{u_{Di}^{\ddagger}}{u_{Hi}^{\ddagger}} \exp\left[\frac{u_{Hi}^{\ddagger} - u_{Di}^{\ddagger}}{2}\right] \frac{1 - \exp(-u_{Hi}^{\ddagger})}{1 - \exp(-u_{Di}^{\ddagger})} \quad (18)$$

For the unlikely case of the two bending modes going to zero in the transition state, a grand maximum deuterium isotope effect of around 20 is predicted. No deuterium isotope effects this large have been observed, but slight loosening of the bending modes in the transition state could easily cause the effect to exceed by a substantial margin the value from Equation (17)(8). A factor which might increase the effect somewhat further is the "tunnel" effect, which is more probable for hydrogen than deuterium (5,9).

A common belief concerning three-center reactions, such as X + H—Y → X—H + Y, is that the isotope effect from H—Y cleavage will be diminished or even cancelled by an inverse isotope effect in the formation of the H—X bond. Actually one must consider the vibrational modes of the transition state as a whole rather than the vibrations of individual bonds. Even when H is connected by half-strength bonds equally to X and Y, an isotope effect corresponding to nearly complete H—Y rupture may result (10). The H—Y stretching frequency becomes in the transition state the asymmetric stretch

$$\vec{X}—\overleftarrow{H}—\vec{Y}$$

This corresponds to motion along the reaction coordinate and is already missing from the transition-state "f" function (Equation 11). The symmetric stretch

$$\overleftarrow{X}—H—\vec{Y}$$

will be of low frequency and, as noted above, will usually be little affected by the substitution of D for H. Equation (17), then, still satisfactorily describes the contribution to the isotope effect from the H—Y stretching frequency even when bond formation is extensive in the transition state.

So far we have assumed that the atoms involved in the reaction coordinate lie in a straight line. This assumption seems reasonable for abstraction of a proton or of a hydrogen atom. Hydride-ion transfers and intramolecular hydride shifts probably proceed *via* triangular transition states. Here the reaction coordinate can be crudely approximated as a C—H bending mode and the deuterium isotope effect calculated from Equation (17) is *ca.* 2.5 (see Section II.7).

The assumptions employed in deriving Equations (17) and (18) should be kept in mind and the equations not used where they are unsuited. They would not, for example, apply to the reaction $H_2 + Cl \rightarrow HCl + H$. Here there are no bending modes in the reactants to correspond to those of the transition state and the symmetric stretching frequency of H—H—Cl *will* be seriously affected by isotopic substitution (because the requirement that m_X and $m_Y \gg m_H$ is no longer fulfilled). Most of the hydrogen transfers found in organic reactions, however, can be treated by Equations (17) and (18). Suitable expressions for other situations can often be derived from Equation (12).

Some alternate simplifications of Equation (12) will be considered briefly. At high temperatures the u's become small and the f's reduce to ratios of symmetry numbers, giving Equation (19). For a simple bond

$$k_H/k_D = (S_D^{\ddagger}S_H/S_H^{\ddagger}S_D)\ (\nu_H^{\ddagger}/\nu_D^{\ddagger}) \tag{19}$$

rupture the deuterium isotope effect should approach $(m_D/m_H)^{1/2}$ or $2^{1/2}$ as the temperature increases.

Secondary deuterium isotope effects can also be treated by Equation (12). This situation has been considered by Streitwieser (11). The term $\nu_H^{\ddagger}/\nu_D^{\ddagger}$ will be nearly unity, since the main contribution to the reaction coordinate is elongation of an R—X bond and this will be little affected by deuterium substitution in R. Similarly, the term in f corresponding to the R—X stretching vibration will also be near unity. Thus only stretching and bending modes involving the isotopically-substituted hydrogens need by considered. We can again neglect the exp $(-u)$ terms and thus arrive at Equation (20). Streitwieser (11) obtains the equivalent Equation (21), in which constant terms have been given their numerical values.

$$k_H/k_D = \Pi_i \exp\ [(u_{Hi} - u_{Di})/2]/\Pi_i \exp[(u_{Hi}^{\ddagger} - \mu_{Di}^{\ddagger})/2] \tag{20}$$

$$k_H/k_D = \Pi_i \exp\ [(0.187/T)\ (\nu_{Hi} - \nu_{Hi}^{\ddagger})] \tag{21}$$

A comment on the value of one of these constant terms is in order. For an R—H vibration, $\nu_H/\nu_D = 2^{1/2}$ by Equation (15) if R is heavy compared to H. Since R is not infinitely heavy, and since the vibration does not

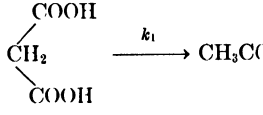
obey Equation (15) exactly, because of anharmonicity, actual observed values run *ca.* 1.35–1.40. The figure 1.35 was used by Streitwieser (11). Effects predicted by this equation are of the order of magnitude of those observed (11).

One can derive the relationship between isotope effects to be expected with different isotopes of the same element such as C^{13} versus C^{14} or D versus T. Comparison of C^{13} and C^{14} isotope effects played an important role in early studies aimed at verification of Bigeleisen's equations (Section III.1). A general relation between deuterium and tritium isotope effects has been derived (Equation 22) (13). This equation should be applicable

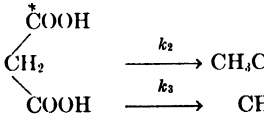
$$k_H/k_T = (k_H/k_D)^{1.442} \tag{22}$$

in the normal temperature range (around 0–100°C.). The reader is referred to the original article for the derivation.

A distinction which has not always been made clear in the literature is that between intermolecular and intramolecular isotope effects. Consider the decarboxylation of normal malonic acid versus malonic acid labeled with C^{13} in one carboxyl. Three reactions are possible (Equations 23–25). The *intramolecular* effect is given by k_3/k_2. There are two possible



$$\xrightarrow{k_1} CH_3COOH + CO_2 \tag{23}$$



$$\xrightarrow{k_2} CH_3COOH + {}^{*}CO_2 \tag{24}$$

$$\xrightarrow{k_3} CH_3{}^{*}COOH + CO_2 \tag{25}$$

intermolecular effects: $k_1/2k_2$ (the 2 is a statistical factor) or $k_1/(k_2 + k_3)$. All three of these ratios can be computed from appropriate experimental data (14). Another example in which a multiplicity of effects is possible is radical attack on toluene versus toluene-α-*d*.

These distinctions should be kept in mind in comparing isotope effects. The intermolecular effect usually arises primarily from differences in zero-point energies of the ground states of the two isotopic species. The intramolecular effect has the same ground state for each of the two processes and hence the difference between the two transition states will be the only factor. Secondary isotope effects (of possible importance mainly with hydrogen isotopes) may make different contributions to inter- and intramolecular effects. Obviously, indiscriminate comparisons of isotope effects from different sources can be misleading. Often inter- and intramolecular

effects will be of quite similar magnitude, but this cannot safely be assumed in advance.

The preceding pages were intended to carry the lesson that theoretical calculations of isotope effects should be approached with caution and with due consideration for the special characteristics of individual cases. There was no intention to discourage intelligent comparison of theory and experiment, for relatively crude applications of theory can be informative and suggestive provided they are not taken as immutable laws. Even when predictions are complex or ambiguous, much benefit can be derived from analogy to similar reactions of known mechanism and known isotope effect. Numerous examples of such reasoning will be found in subsequent sections.

II. DEUTERIUM AND TRITIUM ISOTOPE EFFECTS

1. Some Simple Proton Transfers

The most straightforward use of hydrogen isotope effects is in deciding whether a bond to a given hydrogen is cleaved in the rate-determining step. Here one is concerned mainly with the presence or absence of an effect and only incidentally with its magnitude. A few of the many studies of this type will be mentioned by way of illustration.

The rate of bromination of acetone in aqueous solution was known to be independent of bromine concentration. The rate-determining step was therefore assumed to be enolization of the acetone (15). This enolization involves removal of a proton from carbon and should show an isotope effect. Confirmation of this conclusion was provided by some of the early studies of deuterium isotope effects (16). The values of k_H/k_D were around 7 at room temperature, a reasonable figure (see Section I). Bromination of nitromethane (17) behaved similarly. The isotope effect was shown to vary with the catalyzing base (k_H/k_D = 6.53 for acetate ion and 4.28 for chloroacetate ion at 25°C.), a phenomenon which will be considered in more detail later.

A few other reactions in which substantial deuterium isotope effects were expected and obtained are worthy of mention. The E2 elimination appears to be a one-stage process and should thus show an isotope effect. Shiner (18) found that replacement by deuterium of the methyl hydrogens

$$(CH_3)_2CHBr + OEt^- \begin{cases} \xrightarrow{E_2} CH_3CH{=}CH_2 + EtOH + Br^- \\ \xrightarrow{S_N2} (CH_3)_2CHOEt + Br^- \end{cases} \qquad (26)$$

of isopropyl bromide slowed the E2 reaction by a factor of 6.7 at 25°C. The accompanying S_N2 displacement was substantially unaffected by the presence of deuterium.

Another obvious case for hydrogen isotope effects is the oxidation of an alcohol. Westheimer studied the reaction of 2-propanol and of 2-propanol-2-*d* with chromic acid to produce acetone. The k_H/k_D of 6.7 gave unequivocal evidence that the C—H bond on the carbinol carbon was breaking in the rate-determining step (19).

2. Electrophilic Aromatic Substitution

Results so far considered are all positive. We turn now to a case where some of the results are negative, but still instructive.

The steps directly involving the aromatic hydrocarbon in an electrophilic substitution are attack by the substituting agent (Equation 27) and loss of a proton (Equation (28), where B is solvent or a base). Rate control by

$$\text{Ar—H} + \text{X}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\text{Ar}\begin{matrix}\text{H}\\\diagdown\\\text{X}\end{matrix}\right]^+ \tag{27}$$

$$\left[\text{Ar}\begin{matrix}\text{H}\\\diagdown\\\text{X}\end{matrix}\right]^+ + \text{B} \xrightarrow{k_2} \text{ArX} + \text{BH}^+ \tag{28}$$

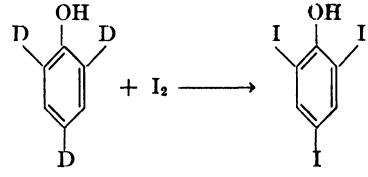
the first step should give at most a small secondary effect; rate control by the second step *might* give a substantial effect. The word *might* is used advisedly, since Hammond (20) has pointed out that Equation (28) could be rate-determining and still give a very small effect if the C—H bond is only slightly stretched between the ground state and the transition state. This situation is likely if the intermediate is of rather high energy and the proton loss involves only a small activation energy. A one-step mechanism in which C—H bond stretching has progressed only slightly would also fit a small isotope effect.

It may seem to some readers that this consideration robs the results of the experiments of much of their value. In fact, one still obtains unequivocal information on the nature of the C—H bond in the transition state. The uncertainty lies in the fact that this knowledge may or may not allow us to assign an overall rate-determining step. This limitation on deducing the behavior of the whole molecule from the behavior of a particular bond is common to all isotope-effect studies and should be kept firmly in mind.

Melander's (21) classic study of tritium isotope effects in aromatic substitution provided the first experimental evidence. Nitration and bromination of ring-tritiated toluene showed no appreciable isotope effect. Sulfonation, on the other hand, showed a k_H/k_T of 2.5. The intermediate

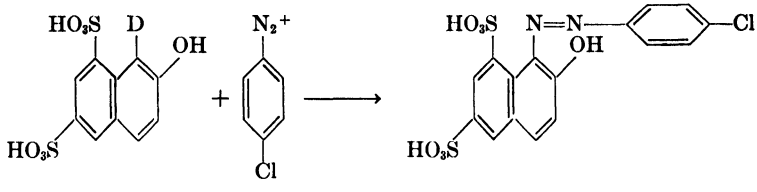
formed by attack of SO_3 on an aromatic would be a zwitterion and might be expected to be more stable than the positively-charged intermediates of nitration or bromination. The second step (Equation 28) would thus be much slower for sulfonation and might become partially or entirely rate-determining. The relatively small effect suggests that Equation (28) may not have attained complete control.

The conclusion that factors which make the intermediate more stable should increase the isotope effect has been confirmed by a number of subsequent investigations. The iodination of phenol-2,4,6-d_3 in an acetate buffer (Equation 29) shows an isotope effect of 4.0 (22). The diazo coupling reaction (Equation 30) is even more interesting (23). The value of



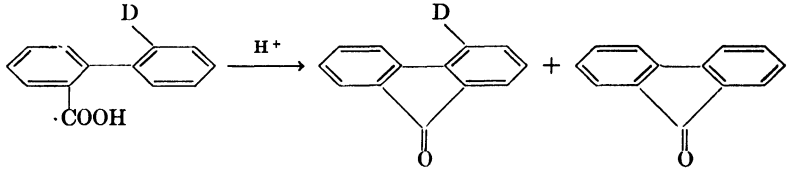
(29)

k_H/k_D is as high as 6.5 under some conditions and the reaction is base-catalyzed. Here Equation (28) seems capable of assuming firm control of the rate. The value of k_H/k_D for the overall reaction varied considerably, but k_2^H/k_2^D remained constant at 6.4 ± 0.3. Zollinger has recently given an excellent review of his work (24).



(30)

An intramolecular electrophilic substitution has been studied by Denney (25). The cyclization of deuterated *o*-carboxybiphenyl (Equation 31) gives relatively small isotope effects when catalyzed by sulfuric or poly-



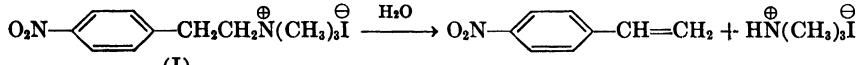
(31)

phosphoric acids (k_H/k_D = 1.13 to 1.46), but a rather large effect when catalyzed by HF (k_H/k_D = 3.0). Since no data on isotope effects in ordinary noncyclizing acylations are available at this writing, one cannot

say whether an isotope effect is likely to be observed generally in cyclizations.

3. Bimolecular Eliminations

One example of an E2 elimination has already been cited in Section II.1. The observed effect was near the predicted "maximum" effect, so that C—H bond cleavage must occur in the rate-determining step. Here the reaction rate was known to be proportional to both base and alkyl halide concentrations. When the solvent is the only potential base, one cannot determine directly the dependence on base concentration. Such a problem is faced with 2-(*p*-nitrophenylethyl)trimethylammonium iodide (I),



(I)

(32)

which reacts with water at 100°C. according to Equation (32). This could be either a solvolytic reaction, or (more probably) an E2 reaction with water functioning as base. Hodnett and Flynn (26) studied the rate of reaction with water of (I) labeled in the 2-position with tritium and found a substantial isotope effect, thereby providing evidence that the E2 mechanism prevailed.

Another possible use of deuterium isotope effects is to determine the extent of C—H bond breaking in the transition state. One must, of course, make reasonably precise measurements so that differences between k_H/k_D ratios will be significant. One should also restrict the investigation to a series of related reactions in which it is probable that the same vibrational frequencies are being altered in about the same manner. Comparison of a hydride ion transfer with a proton transfer, for example, is unwise.

A study of isotope effects in E2 eliminations from 2-phenylethyl derivatives has recently been completed (27). The results are summarized in Table I. A number of conclusions are apparent. The change in isotope effect with the leaving group X is in the order —Br > —OTs > —$SMe_2^{\oplus}$ > —$NMe_3^{\oplus}$. This is the order of ease of displacement of these groups. Stretching of the C—X bond thus appears to provide some driving force for the concomitant stretching of the C—H bond. This point had been in some doubt, at least in the 2-phenylethyl system, as a result of other work (28).

Other conclusions from the study were comparatively straightforward. *tert*-Butoxide is a stronger base than ethoxide and should give the larger isotope effect observed. Base strength is evidently not the only factor in changing solvent. The change from ethanol to water has no clear-cut

TABLE I
Isotope Effects in Elimination Reactions of $C_6H_5Cl)_2CH_2X$ with RO^- in ROH

Leaving group, X	Solvent, ROH	Temp., °C.	k_H/k_D
Br	EtOH	30	7.1
Br	*t*-BuOH	30	7.9
OTs	EtOH	30	5.7
OTs	*t*-BuOH	30	8.0
SMe_2Br	EtOH	30	5.0
SMe_2Br	H_2O	60	4.7
SMe_2Br	H_2O	30	5.9[a]
NMe_3Br	EtOH	50	3.0
NMe_3Br	[b]	50	3 0

[a] Extrapolated from data at 60, 70, and 80°C.
[b] Solvent in this run was 50% EtOH–H_2O.

influence on the isotope effect, even though hydroxide is less basic than ethoxide.

The only other comparison of deuterium isotope effects within a series of elimination reactions has been made by Shiner and Smith (29). They studied the Hofmann reaction of ethyl-2,2,2-d_3-trimethylammonium hydroxide in ethylene glycol at 137°C. The result (k_H/k_D = 3.9) was compared with that for 2-phenyl-1-bromopropane-2-*d* in ethanol with ethoxide ion (k_H/k_D = 2.8, extrapolated from lower temperatures). The order with respect to leaving group differs from that of the other study (27), but the change in solvent and alkyl group may account for the difference. Incidentally, comparison of isotope effects measured at different temperatures should be made only if the temperature dependence of at least one effect has been determined. In several eliminations the isotope effect was shown to arise from differences in both energies and entropies of activation (27,29).

A few miscellaneous instances of isotope effects in eliminations will be mentioned. Roberts (30) provided telling evidence for an elimination-addition ("benzyne") mechanism for the reaction of aryl halides with amide ion in liquid ammonia by showing that bromobenzene-2-*d* lost hydrogen 5.5 times faster than deuterium during its conversion to aniline. Curtin and Kellom (31) noted isotope effects in pyrolytic eliminations from esters of 1,2-diphenylethanol-2-*d*.

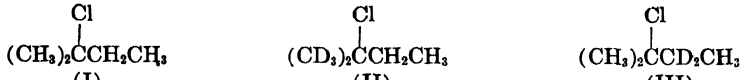
4. Secondary Isotope Effects

A C—H bond need not be broken in the rate-determining step of a reaction for an isotope effect to be observed. The only requirement is that a stretching or bending frequency of the C—H bond must change appreciably

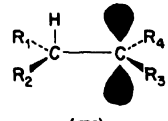
between the ground state and the transition state. One is thereby provided with a means of observing changes in bond strength which directly or indirectly may give a very precise picture of the transition state. In principle similar considerations apply to isotope effects involving heavier elements, but here the magnitude of a secondary effect may be too small for reliable measurement.

Hyperconjugation has for some time been regarded as a possible mode of electron release by alkyl groups, but the difficulty of obtaining convincing evidence has kept it a subject of lively controversy. Even the isotope-effect studies described below have not quieted this controversy, but at least they provide evidence for a phenomenon possessing most of the characteristics usually ascribed to hyperconjugation.

Substitution of deuterium for hydrogen on the β-carbon atoms of alkyl halides and related compounds was found to slow the rates of S_N1-type reactions by about 10–30% per deuterium atom (32,33). For example, in ethanolysis (I) was 1.78 times faster than (II) and 1.41 times faster than (III). Evidently the rate determining step involves not only ionization of the C—Cl bond, but also appreciable loosening of the β C—H bonds.



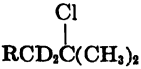
A priori, this might result from either hyperconjugative or inductive electron release. A means of making the distinction follows. Hyperconjugation involves overlap of the σ-electrons of the C—H bond with the vacant p-orbital of the carbonium ion and should be at a maximum when the C—H bond is parallel to the p-orbital as in (IV). (This argument



(IV)

makes the reasonable assumption that the transition state for ionization resembles the carbonium ion.)

The first evidence for steric influence on the β-deuterium isotope effect came from the work of Shiner (34), who studied the solvolysis in 80% ethanol of (V) (R = Me or *t*-Bu) and the corresponding undeuterated com-



(V)

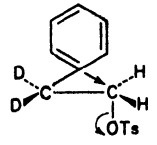
pounds. For R = Me, k_H/k_D = 1.40 but for R = *t*-Bu, k_H/k_D = 1.08.

The most reasonable explanation is that the bulky *t*-Bu group forces the molecule into a conformation unfavorable to the overlap of the C—D bonds and the *p*-orbital.

A second piece of evidence is found in the formolysis of 2-phenylethyl-2,2-d_2 *p*-toluenesulfonate (VI). The ionization is aided by phenyl participation (35) and this places the β-deuterium atoms in a very unfavorable position for overlap (VII). There is, in fact, no detectable isotope effect (36).

$C_6H_5CD_2CH_2OTs$

(VI)



(VII)

Evidence which at first sight appears to contradict these studies was obtained by Streitwieser (37). Acetolysis of *cis*- and *trans*-cyclopentyl-2-*d* *p*-toluenesulfonates gave similar isotope effects. Actually neither C—D bond is in position for maximum overlap with the *p*-orbital. If the two lobes of the orbital are symmetric in the transition state, the same extent of overlap is expected with either a *cis* or *trans* C—D bond in the 2-position.

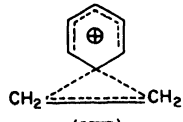
More recently, secondary isotope effects have been observed in the solvolysis of compounds containing deuterium in the α-position (37). The explanation advanced by Streitwieser appears to fit most of the facts so far available. He points out that the hybridization of the α-carbon changes from sp^3 to sp^2 on going from a tetrahedral to a trigonal (carbonium ion) state. If the aldehydic C—H is taken as a model for the trigonal carbon, spectroscopic evidence shows that the out-of-plane bending frequency is markedly lower than the corresponding frequency of a C—H bond to a tetrahedral carbon. The predicted effect is somewhat larger than that observed. Interestingly, the C—H stretching frequency and the in-plane bending frequency are little affected by changes in hybridization.

Various other workers have also observed α-deuterium isotope effects (38,39,40). The effect varies considerably in magnitude and actually becomes a small *inverse* effect in some S_N2 reactions (40). Evidently the leaving and displacing groups are close enough to hinder markedly the out-of-plane C—H vibration in an S_N2 transition state.

Halevi (38) has suggested that electron distribution in C—H and C—D bonds may differ sufficiently to give appreciable isotope effects. The influence of deuterium on acid and base strength is such that the C—D bond appears to be *more* electron-releasing than the C—H bond, so this obviously is not the dominant factor in the kinetic isotope effects. Halevi also points out that the frequency shifts when aromatics are complexed

with chloranil appear to be in the wrong direction to explain the isotope effect on the equilibrium constant. The generality and significance of this interesting observation cannot be easily judged at present. It does show that the origins of secondary deuterium isotope effects are not yet entirely understood.

One final use of secondary deuterium isotope effects may be mentioned. Formolysis of 2-phenylethyl-1,1-d_2 *p*-toluenesulfonate gave a 17% isotope effect, while there was no isotope effect with the 2,2-d_2 isomer (36). This reaction also results in phenyl migration (41), which suggests that a phenonium ion intermediate (VIII) may be involved. The α and β hydrogens in a *symmetrical* intermediate such as (VIII) are equivalent, but the dis-



(VIII)

parate isotope effects show that this cannot be the case in the transition state for ionization. The transition state for ionization therefore must have the phenyl group considerably closer to the β-carbon than to the α-carbon.

5. Solvent Isotope Effect and Acid-Base Catalysis

A change of solvent from H_2O to D_2O may influence a reaction in several ways. The most obvious of these is by a change in the solvating power of the medium, but often more specific effects are involved as well. The solvent may be a reactant or catalyst and will then exert an effect which depends on how it functions. Finally, a change in solvent changes the strengths of acids and bases and thereby will influence acid- or base-catalyzed reactions.

Recent studies by Swain and Bader (42) have made important contributions to our knowledge of solvent isotope effects. Their work employed the methods of statistical thermodynamics to calculate the properties of H_2O versus D_2O and of ionic solutions in these two solvents. Their main assumptions and results will be described briefly.

The individual molecules in liquid water are held together in a rather definite structure by hydrogen bonding. The structural unit appears to be a water molecule surrounded tetrahedrally by four other water molecules (43). Within this structure the molecules experience a considerable hindrance to free rotation. The term "libration" has been applied to this hindered rotation. Pitzer and Gwinn (44) have shown that hindered rotors can be treated as harmonic oscillators provided the barrier to free rotation

is large enough. A band due to the librations is observable in the infrared. Frequencies of internal vibrations will also differ from H_2O to D_2O, but these frequencies are well known. It is thus possible to calculate the ratio of partition functions for H_2O versus D_2O and from this ratio the relative thermodynamic properties (45) of the two liquids.

For solutions of ionic substances the assumption is made that the ions become tetrahedrally solvated by water molecules. New librational bands for the coordinated water molecules appear in the infrared spectra. Except at very high concentrations, only the immediate solvation shell is affected, and the librational frequency is practically independent of concentration. Thus the only important contribution to the ratio of partition functions for solution in H_2O versus solution in D_2O is from the librations of the water molecules coordinated with the ions. Calculations of various thermodynamic quantities for transfer of halides from H_2O to D_2O give good agreement with experiment. The only exception is iodide ion, which requires a coordination sphere of six water molecules to give agreement. All of the salts except lithium fluoride are more soluble in H_2O than in D_2O, a fact predicted by the calculations.

Application of these ideas to kinetic solvent isotope effects is of particular interest. The details of such applications are not unequivocal, but the arguments of Swain and Bader (42) provide a plausible and convenient starting point. A reaction in which charge is created in the transition state should break up the water structure and hence proceed more rapidly in light water. A reaction in which charge is destroyed or dispersed should return structure to the water and hence proceed slower in light water.

Evidence available so far is not entirely in agreement with these predictions, but is at least in the proper order. Various alkyl halides solvolyze 20–30% slower in heavy water (46,47). The effect is smaller with alkyl sulfonates, sulfates, and nitrates, around 10–15%. All of these solvolyses create charge. As would be expected, the substances producing the larger anions with more diffuse charge give smaller effects. Somewhat surprisingly, the nature of the alkyl group has little effect. One would offhand expect the extent of charge separation in the transition state to be quite different for methyl chloride and *tert*-butyl chloride. Finally, the solvolysis of *tert*-butyldimethylsulfonium ion, which involves charge dispersal, does not proceed slower in light water, but slightly faster (*ca.* 5%).

Solvent isotope effects have proved very useful in the study of acid- and base-catalyzed reactions. When a proton transfer from solvent to substrate occurs in the rate-determining step one can predict unequivocally that the reaction will be slower in D_2O. Prominent among the numerous examples of this behavior are the mutarotation of glucose (48) and the

decomposition of diphenyldiazomethane (49,50). Reactions of this type are examples of general acid catalysis.

In many reactions the proton transfer is not in the rate-determining step but in a pre-equilibrium (Equations 33 and 34).

$$S + H_3O^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} SH^+ + H_2O \tag{33}$$

$$SH^+ \xrightarrow[\text{slow}]{k_3} \text{products} \tag{34}$$

Here the rate depends upon the concentration of SH^+, which in turn depends upon the hydrogen ion activity. Since D_3O^+ in D_2O is a stronger acid than H_3O^+ in H_2O (51), these hydronium-ion catalyzed reactions should proceed faster in D_2O than in H_2O. Likewise, deuteroxide ion in D_2O is a stronger base than hydroxide ion in H_2O, so hydroxide-ion catalyzed reactions should show similar behavior. Among reactions which proceed faster in D_2O are the acid hydrolysis of epoxides (52) and the reaction of nitroalkanes with base (53).

Unfortunately, the failure of a reaction to go faster in D_2O cannot be taken as evidence against specific hydronium-ion catalysis. The rate-determining step (Equation 34) may, for example, involve a normal isotope effect which counteracts the more favorable pre-equilibrium (Equation 33). A more reliable distinction can be made between the types of acid catalysis by studying the reaction in various mixtures of H_2O and D_2O. Butler (54) pointed out that the isotope effect should depend in a predictable manner on the mole fraction of D_2O if one knew the rates in the pure solvents and the proton and deuteron activities in the mixtures. The derivation which follows is based on essentially the same assumptions as Butler's, but omits his rather complex treatment involving an empirical "activity function." It has been given in quite similar terms in two recent articles (55,42).

One assumes the mechanism of Equations (33) and (34) and also that the rate ratio k_H/k_D and the activity coefficient ratio $(f_{H^+} f_S/f^*)$ are independent of solvent composition. In H_2O and in D_2O, Equations (35) and (36) respectively, define the overall rate constants. Here K_H and K_D are equilibrium constants for the reaction of Equation (33) in H_2O and D_2O,

$$k_H = r_H K_H (a_{H^+})_H (f_S/f^*) \tag{35}$$

$$k_D = r_D K_D (a_{D^+})_D (f_S/f^*) \tag{36}$$

r_H and r_D are rate constants for the rate-determining step (Equation 34), $(a_{H^+})_H$ is the proton activity in H_2O and $(a_{D^+})_D$ is the deuteron activity in

D_2O. For a mixed solvent containing a mole fraction n of deuterium, the rate constant is given by Equation (37).

$$k_n = r_H K_H (a_{H^+})_n (f_S/f^*) + r_D K_D (a_{D^+})_n (f_S/f^*) \quad (37)$$

Division of Equation (37) by Equation (35) yields Equation (38). If the

$$k_n/k_H = (a_{H^+})_n/(a_{H^+})_H + r_D K_D (a_{D^+})_n \, (f_S/f^*)/$$
$$r_H K_H (a_{H^+})_H \, (f_S/f^*) \quad (38)$$

definitions of k_H and k_D (Equations 35 and 36) are now substituted into Equation (38), Equation (39) results. Thus we can predict the variation of

$$k_n/k_H = (a_{H^+})_n/(a_{H^+})_H + (k_D/k_H) \, [(a_{D^+})_n/(a_{D^+})_D] \quad (39)$$

k_n with solvent composition if we know k_H, k_D, and the proton and deuteron activities in the pure and mixed solvents. Butler's data have been used satisfactorily in various investigations, but more recent calculations by Swain and Bader (42) give values obtained by the methods of statistical thermodynamics. This approach eliminates some assumptions which Butler had to make and the results should give better agreement with experiment.

Several recent articles (56) deserve mention. Purlee has recalculated Butler's activity function using newer experimental date and obtains numerical predictions agreeing well with those of Swain and Bader. Gold has derived an expression for the dependence of a rate-determining proton transfer on mole fraction of deuterium in the solvent. This dependence is not linear, as had previously been assumed, and Gold shows that it is indistinguishable from the predictions of Equation (39) (or Butler's equivalent equation) under certain conditions. Experimental tests of Gold's equation are obviously needed. More recently, Halevi, Long, and Paul[56] have also cast doubt on the usefulness of Butler's theory, though on different grounds from Gold.

The approach of Butler also may be used on base-catalyzed reactions, although here little has been done. Recent applications to cases of acid catalysis include the hydrolysis of epoxides (52) and the hydration of olefins (55).

6. Abstraction of Hydrogen by Free Radicals

This field provides a number of investigations which illustrate admirably the mechanistic utility of isotope effects. It also illustrates the need for care, since more than the usual amount is called for in obtaining and interpreting data because of the frequent occurrence of side reactions in radical processes.

An example of the latter point is shown in the reaction of toluene and

other alkylbenzenes with the free radicals derived from peroxides. This reaction produces dimeric products according to the scheme of Equations (40) and (41), where M· is CH_3· from acetyl peroxide. This reaction

$$C_6H_5CH_3 + M\cdot \longrightarrow MH + C_6H_5CH_2\cdot \quad (40)$$

$$2C_6H_5CH_2\cdot \longrightarrow C_6H_5CH_2CH_2C_6H_5 \quad (41)$$

was studied by Urry (57) using toluene-α-*d* as starting material. The isotope effect was computed from the deuterium content of the methane (MH in Equation 40). The isotope effect had the rather high value of 9.9. A reinvestigation of this reaction showed that some of the hydrogen in the methane came from the ring rather than from the methyl group of the toluene (58). This, of course, means more undeuterated methane and hence a larger apparent isotope effect. The isotope effect calculated from the deuterium content of the dimer was substantially less. The isotope-effect error did serve the useful purpose of calling attention to the competing reaction of alkyl radicals with the aromatic ring (59).

Another interesting use of isotope effects was in a demonstration of the unimportance of the "identity reaction" (reaction of a molecule RX with

$$R\cdot + R{-}X \longrightarrow R{-}X + R\cdot \quad (42)$$

the radical R· as in Equation 42) of benzyl radicals with toluene (60). The formation of benzyl radicals from $C_6H_5CH_2D$ should, of course, involve a substantial isotope effect, but if reaction (42) is fast compared to dimerization the deuterium will be statistically distributed in the dimer. A statistical distribution corresponds to no *apparent* isotope effect, contrary to fact.

The autoxidation of alkylbenzenes has been studied recently by Russell (61). The mechanism of the reaction, as elucidated by kinetic studies, is given in Equations (43–46). The autoxidation of cumene-α-*d* showed

$$\text{Initiator} \rightarrow 2R\cdot \quad (43)$$

$$R\cdot + O_2 \rightarrow ROO\cdot \quad (44)$$

$$ROO\cdot + RH \rightarrow ROOH + R\cdot \quad (45)$$

$$2ROO\cdot \rightarrow \text{nonradical products} + O_2 \quad (46)$$

an isotope effect for the chain-propagation step (Equation 45) of 5.5. The data on the autoxidation of ethylbenzene-α-*d* were such that either the chain-propagation step must have a very low isotope effect or the chain termination must have an isotope effect as well ($k_H/k_D = 1.7$ fits the data if $k_H/k_D = 5.5$. is assumed for chain propagation). The latter assumption

is much more reasonable and we thus have evidence that chain-termination involves a hydrogen transfer.

A thorough and careful study of side-chain halogenations of toluene-α-d has been made by Wiberg and Slaugh (62). Some of the data are given in Table II and represent the relative rates of replacement of hydrogen and deuterium of toluene-α-d by halogen (i.e., the *intramolecular* isotope effect was measured).

TABLE II
Isotope Effects in the Side-Chain Halogenation of Toluene in Carbon Tetrachloride at 77°C.

Reagent	Toluene-d_1	p-Chlorotoluene-d_1
N-bromosuccinimide	4.86 ± 0.03	5.08 ± 0.14
Bromine	4.59 ± 0.03	5.22 ± 0.17
Chlorine	1.30 ± 0.02	1.44 ± 0.08
Sulfuryl chloride	1 42 ± 0.02	——

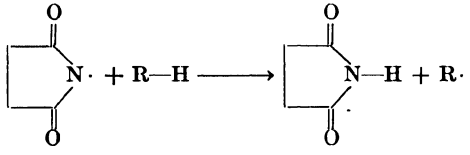
The magnitudes of the isotope effects vary considerably and the higher isotope effects are noted with the reactions of higher activation energies, in support of an earlier suggestion by Wiberg (8). This parallelism appears to be quite general for radical abstractions of hydrogen and might be expected to hold in any reaction where stretching of a C—H bond is the only important process occurring between the ground state and the transition state. Where other bonds in the molecule are involved as well, the relation may break down, as it does for some E2 eliminations (27) and ketone enolizations (13). A particularly interesting result of the halogenation work was a demonstration that the isotope effect is useful in identifying the attacking species in the hydrogen abstraction. Data for halogenation with a number of reagents are given in Table III.

TABLE III
Halogenation of Toluene-d_1 at 110°C.

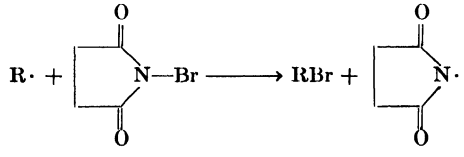
Reagent	k_H/k_D
N-bromosuccinimide	3.59 ± 0.05
N-chlorosuccinimide	1.59 ± 0.05
Chlorine	1.47 ± 0.02
Sulfuryl chloride	1.73 ± 0.05

Available evidence strongly supports Equations (47) and (48) as the mechanism of allylic bromination of N-bromosuccinimide. Clearly the chlorination by N-chlorosuccinimide cannot involve a rate-determining

hydrogen abstraction by succinimidyl radical for if it did it should show the same isotope effect as bromination. Probably attack by a chlorine atom occurs, since this is the mechanism of chlorination by elemental chlorine and the two effects are similar. The isotope effect in the sulfuryl chloride reaction appears to be significantly larger than that for elemental chlorine, suggesting that $SO_2Cl\cdot$ rather than $Cl\cdot$ is the attacking species.



(47)



(48)

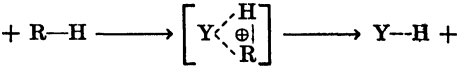
7. The Mechanism of Hydrogen Transfer in Some Redox Reactions

Most redox reactions of organic compounds involve rupture or formation of a C—H bond and, if this occurs in the rate-determining step, an isotope effect is to be expected. The previously-cited chromate oxidation of 2-propanol-2-*d* (19) gives $k_H/k_D = 6.7$ at 25°C. The concurrent oxidation and cleavage of phenyl *tert*-butyl carbinol also shows a large effect (63). In these oxidations, a proton transfer from the α-carbon of a chromate ester appears to be the rate-determining step. Hydrogen atom transfer in radical reactions is also a redox process and frequently involves sizable isotope effects (Section II. 6).

Obviously isotope-effect studies aid in identifying the rate-determining step in a redox process. One is also interested in whether the hydrogen is transferred as a proton, a hydrogen atom, or a hydride ion. Present indications are that the isotope effects may vary predictably with the nature of the hydrogen-transfer process. Much of the discussion that follows is based on Hawthorne and Lewis (64).

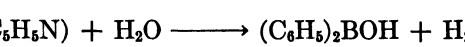
Analogy with the $H + H_2$ reaction (65) suggests that hydrogen-atom transfer occurs *via* a transition state in which hydrogen donor, hydrogen atom, and hydrogen acceptor are in a straight line. A proton transfer involves nucleophilic attack on hydrogen and such attack should occur away from the electron-rich C—H bond. Hence a linear transition state is to be expected here as well. Transfer of a proton or a hydrogen atom thus should involve alteration of the same stretching and bending vibrations

in about the same fashion so that similar isotope effects seem indicated. A hydride transfer, in contrast, involves electrophilic attack on hydrogen and should occur at the electrons of the R—H bond. This process should go through a triangular transition state, as shown schematically in Equation (49). The R—H stretching vibration should be relatively little affected with perhaps more important alterations in the bending vibrations. Such qualitative considerations suggest a smaller isotope effect for hydride transfer than for proton or hydrogen-atom transfer (see Section I).



(49)

Available evidence is in agreement with this prediction. The hydrolysis of pyridine diphenylborane (Equation 50) shows, when the borane hydrogen



(50)

is replaced by deuterium, an isotope effect of only 1.5. The effect calculated for complete loss of the B—H stretching vibration is 4.2 (from Equation 17). Several other reactions which are almost certainly hydride transfers likewise show small effects. These include the hydrolysis of triphenylsilane (66) and the reaction of triphenylcarbonium ion with 2-propanol-2-*d* (67).

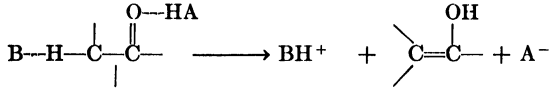
This generalization promises to be quite useful provided that future evidence continues to support it. One apparent exception has been noted by Dauben (64b), who obtained a large isotope effect in the hydride transfer between tris-(*p*-anisyl)methane and trityl carbonium ion. Here the triangular transition state is probably prohibited on steric grounds, so our generalization is not necessarily invalidated. Another limitation should be kept in mind; while a hydride transfer should almost always occur with a small isotope effect the inverse is not true, for proton and hydrogen atom transfers may also show small isotope effects. Thus the k_H/k_D of 1.8 for the Cannizzaro reaction (68) is consistent with a hydride transfer but does not prove it. On the other hand, the large isotope effects observed in the reduction of diazonium salts with ethanol-1-*t* (69) militate against a hydride-transfer mechanism. Later results (70) do point to a free-radical mechanism for this reduction.

A side issue is worth brief mention. Small secondary isotope effects ascribable to hyperconjugation have already been discussed (Section II.4). As hyperconjugation shades over into actual hydrogen migration, k_H/k_D goes up to around 2–3 (71,72). The transition state for hydrogen migration should resemble the triangular one for hydride transfer (Equation 1). An isotope effect of the observed magnitude is consistent with this conclusion (see Section I).

8. Isotope Effects and the Detailed Mechanism of Enolization

Recently a number of investigations aimed at obtaining a very detailed mechanistic picture of ketone enolization have been reported. The information sought in these studies is of a type that isotope effects are almost uniquely capable of providing. Such subtle uses of isotope-effect data will undoubtedly become increasingly important, so a discussion of these studies seems an appropriate way to end our discussion of hydrogen isotope effects.

The enolization of a ketone requires the abstraction of a proton from carbon by a base and the donation of a proton to oxygen by an acid (Equation 51). The process in fact is catalyzed by a variety of acids and bases. For any given catalyst, the nature of the attacking species may or may not



(51)

be obvious. When the catalyst is hydronium ion, the acid can be only H_3O^+ and the base only H_2O. When the catalyst is acetic acid, however, there are two possibilities. These are either HA = AcOH and B = H_2O, or HA = H_3O^+ and B = AcO^-. Similarly, hydroxide-ion catalysis must involve OH^- as base, but acetate-ion catalysis may involve either HA= H_2O and B = AcO^-, or HA = AcOH and B = OH^-.

A solution to these ambiguities was sought by Swain (13) in a study of tritium isotope effects in the racemization of α-phenylisocaprophenone. The isotope effects associated with catalysis by various substances were determined and are recorded in Table IV.

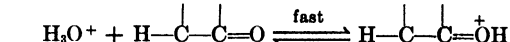
TABLE IV
Tritium Isotope Effects in Enolization of α-Phenylisocaprophenone in Aqueous Dioxane at 98°C.

Catalyst	k_H/k_T	HA	B
H_3O^+	9.7	H_3O^+	H_2O
AcOH	11.4	H_3O^+	AcO^-
AcO^-	10.2	H_2O	AcO^-
HO^-	12.9	H_2O	HO^-

The conclusions given in the last two columns of the table were arrived at with the aid of the assumption that the stronger the acid, the larger the isotope effect. Since the reaction catalyzed by acetic acid shows a *larger* isotope effect than the reaction catalyzed by hydronium ion, acetic-acid catalysis must involve H_3O^+ and AcO^-. With HA the same as in catalv-

sis by H_3O^+, the acetic-acid catalysis shows a larger effect because AcO^- is a stronger base than water. Catalysis by acetate must involve H_2O and AcO^- rather than AcOH and OH^- because k_H/k_T is less than for hydroxide catalysis, where HA must be H_2O, the weakest of the acids.

Another question of interest is whether the proton abstraction from carbon and the proton donation to oxygen are simultaneous or stepwise.



(52)

(53)

In acetic-acid catalysis, for example, the stepwise process of Equations (52,53) might operate and would predict the same kinetic behavior as for the concerted process (Equation 51). The isotope effect for reaction by (52,53) can be predicted approximately from the relationships of Equations (54–62).

$$\text{Rate} = k_O(R_2CO) + k_{H^+}(H^\oplus)(R_2CO) + k_{AcOH}(AcOH)(R_2CO) \quad (54)$$

$$= k_O(R_2CO) + k(R_2COH^\oplus) + k'(AcO^-)(R_2COH^\oplus) \quad (55)$$

$$K_{AcOH} = (H^+)(AcO^-)/(AcOH) \quad (56)$$

$$K_{HS} = (H^+)(R_2CO)/R_2COH^+) \quad (57)$$

$$k_{H^+} = k/K_{HS} \quad (58)$$

$$k_{AcOH} = k' K_{AcOH}/K_{HS} \quad (59)$$

$$k_{H^+}/k_{D^+} = K_{DS}/K_{HS} \quad (60)$$

$$k_{AcOH}/k_{AcOD} = K_{DS}K_{AcOH}/K_{HS}K_{AcOD} \quad (61)$$

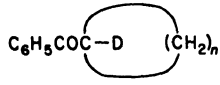
$$= k_{H^+}K_{AcOH}/k_{D^+}K_{AcOD} \quad (62)$$

The constants k and k' are assumed to be the same in light as in heavy water. The ratio k_{H^+}/k_{D^+} is usually around 0.50–0.35 at room temperature for specific hydronium-ion catalysis (Section II.5), while K_{AcOH}/K_{AcOD} is 3.3 at 25°C. (73). The value of k_{AcOH}/k_{AcOD} should thus run around 1.6–1.1 at 25°C., and probably closer to unity at 100°C. A one-step process (Equation 51) involves a proton transfer in the rate-determining step and should show a substantial isotope effect, probably about 3–4.

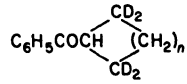
The above reasoning was followed by Swain (74) in interpreting a study of the acetic acid catalyzed enolization of α-phenylisocaprophenone in dioxane-H_2O versus dioxane-D_2O. The observed k_{AcOH}/k_{AcOD} at 100°C.

was 1.1. This figure agrees with the prediction for a stepwise process, but is unlikely for a concerted process.

Evidence of a somewhat different type on the nature of the transition state in enolizations has been presented by Emmons and Hawthorne (75). Both primary and secondary isotope effects in the bromination of phenyl cycloalkyl ketones I–IV were determined. The results are given in Table V.



I, $n = 4$
II, $n = 5$



III, $n = 2$
IV, $n = 3$

TABLE V
Isotope Effects in the Enolization of Phenyl Cycloalkyl Ketones in Aqueous Acetic Acid at 36.70°C.

R in C_6H_5COR	Catalyst	k_H/k_D (primary)	k_H/k_D (secondary)
Cyclopentyl	NaOAc	6.17	1.24
Cyclopentyl	HCl	3.96	1.21
Cyclohexyl	HCl	6.72	1.41

The substantial secondary isotope effects are interpreted as evidence that the transition state resembles enol and thus would be stabilized by hyperconjugation with the β-hydrogens. This is, of course, consistent with Swain's evidence on the acid-catalyzed reaction. Emmons and Hawthorne argue that the acetate-catalyzed reaction cannot involve rate-determining formation of an enolate anion because such a species could scarcely be stabilized by hyperconjugation. They accordingly favor a concerted rather than a stepwise mechanism for the enolization. Whether this evidence against a transition state resembling an enolate ion can be generalized is problematical, since anionic species should be considerably more stable in the less acidic media often used for enolizations.

III. ISOTOPE EFFECTS WITH THE HEAVIER ELEMENTS

1. Carbon

The decarboxylation of malonic acid has been the most thoroughly studied of all reactions with respect to carbon isotope effects. Since these

studies have brought out some points of general interest, it will be instructive to consider this reaction first.

Both inter- and intramolecular isotope effects (see Section I for definitions) have been determined for C^{13} and C^{14}. Theory (76) predicts that the C^{14} effect should be about twice the C^{13} effect. The earliest studies (77,78), however, gave considerably larger ratios. Later work improved the situation somewhat, but still left much to be desired. Most of the C^{13} effects were just under 3% (79,80,81), but the agreement was much poorer for the C^{14} effects (82,83). Eventually, careful work (84), in which both C^{13} and C^{14} effects were determined using the same analytical procedure (mass spectrometry), gave satisfactory agreement with theory; 2.85 $\pm$ 0.09% for the C^{13} effect and 5.45 $\pm$ 0.46% for the C^{14} effect.

Measurement of isotopic ratios in the mass spectrometer can be done with considerably greater precision than measurement of radioactivity. Even this is insufficient to account for all of the variation in the C^{14} effects. A more fundamental source of error lies in the differing effects of impurities. (The argument that follows was brought to my attention by Bourns (85).) In determination of radioactivity, 1–2% of an inactive impurity will cause a 1–2% error. C^{13} effects are usually studied with material of natural C^{13}/C^{12} ratio and the reactants and products differ by only a few percent in this ratio. Any impurity would also have a near-to-natural abundance of C^{13} and would consequently cause a negligible error unless present in gross amounts.

The above is not meant to imply that C^{14} effects are always unreliable. With appropriate care in purification and frequent checking of the counting device against a standard, excellent precision can be obtained. Use of C^{14} is often more convenient since a degradation is not required to isolate the particular carbon atom involved in the effect as with C^{13}.

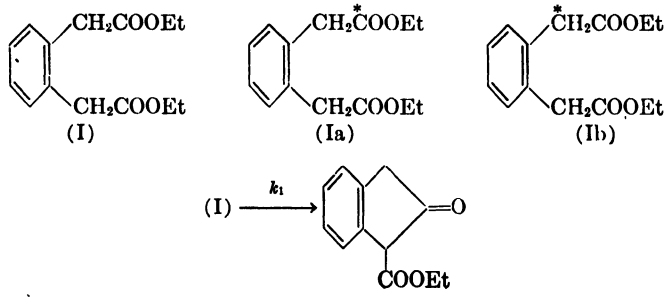
Carbon isotope effects have now been determined for a good many reactions besides simple decarboxylations. A number of specific mechanistic applications will be mentioned later, but first factors that can cause the isotope effect to vary in magnitude will be discussed.

A change in the extent of bond rupture in the transition state will, of course, change the effect. Generally an increase in activation energy in a given type of reaction results in an increase in the isotope effect (see, however, Section II.6). This is true of the reaction of chlorine and bromine with formic acid (86), the hydrolysis of substituted ethyl benzoates (with one exception) (87), and a number of displacement reactions (88). An increase in temperature reduces the isotope effect for a bond-breaking reaction (87). (See Section III.2 for the effect of temperature on a bond-forming reaction.) Comparisons of isotope effects consequently should be made at a common temperature.

Recent studies of C^{14} isotope effects in S_N1 and S_N2 reactions illustrate some difficulties which may be encountered in predicting and interpreting relative magnitudes of isotope effects. Intuitively, one might expect the S_N1 reaction to involve more bond rupture and hence a larger effect. Unfortunately this simple prediction does not agree with the facts and does not follow from a closer examination of the theory.

The reactions of methyl-C^{14} iodide with triethylamine, pyridine, hydroxide ion, and silver ion give k_{12}/k_{14} values of 1.10, 1.14, 1.09, and 1.09, respectively (90). The magnitude of the effect obviously does not correlate with the degree of S_N1 or limiting character (which should be greatest for the silver-ion reaction). The hydrolysis of 2-chloro-2-methylpropane-2-C^{14}, certainly a *bona fide* S_N1 reaction, gives the low value of 1.03 for k_{12}/k_{14} (91). Empirically, then, one can so far draw no reliable conclusions about carbon isotope effects in S_N1 versus S_N2 reactions.

A theoretical approach to the question also fails to give a clear-cut picture. For a three-center reaction A + B—C → A—B + C, the mass factor in the Bigeleisen equation (Equation 13) can be represented by a rather complex quantity which involves the masses of A, B, and C, and the ratio of the extent of bond-making to bond-breaking in the transition state (7). Surprisingly, the variation of this ratio between 1 (S_N2 reaction) and 0 (S_N1 reaction) has little influence on the magnitude of the mass factor. For evaluation of the $G(u)$ factors the assumption was made that the carbon-halogen bond is completely ruptured in the transition state and that no other bonds are altered. The overall calculated effects were mostly in reasonable agreement with the experimental values. One might argue that the $G(u)$ factors should be different for S_N1 and S_N2 reactions, or that the assumption of complete bond rupture is unjustified. Unfortunately, any quantitative evaluation of these possibilities would be quite uncertain. At present, then, neither theory nor experiment seems to provide any usable generalizations. Further work to establish the factors influencing isotope effects in replacement reactions is obviously in order.



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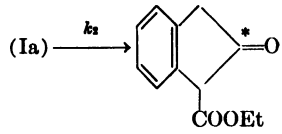

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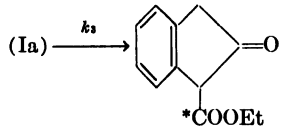

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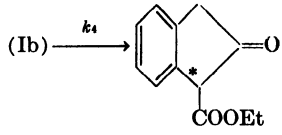

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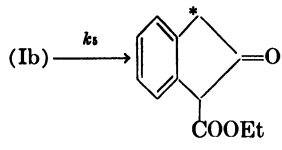
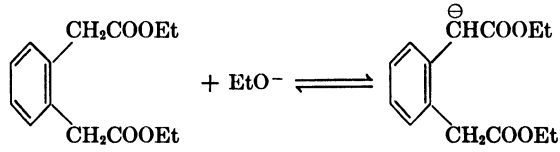


(67)

A thorough study of C^{14} isotope effects in the Dieckmann condensation of diethyl phenylenediacetate (I) has been made by Carrick and Fry (92). They used samples labeled with C^{14} in the carboxyl carbon (Ia) and in the methylene carbon (Ib). The reactions of Equations (63–67) were thus possible. With sodium ethoxide in ethanol as catalyst the intramolecular effect, k_3/k_2, was 1.056 and the intermolecular effect, $k_1/2k_4$, was 1.085.

These results show clearly that bonds to both the carbonyl and methylene carbons must be involved in the rate-determining step. From this the authors suggest that Equation (69) represents the rate-determining step, since no other step in the sequence (68–70) involves both carbons. They dismiss the possibility that Equations (69) and (70) are coalesced



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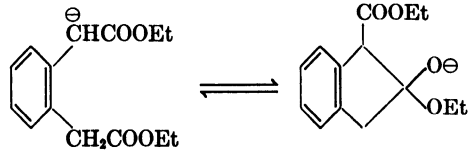

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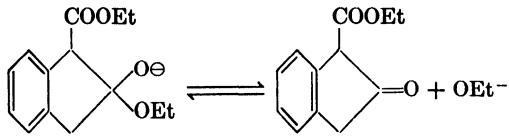
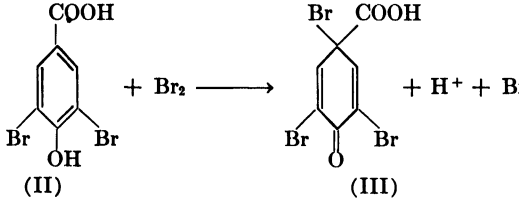


(70)

into a single step, since they feel such a concerted displacement reaction should lead to little or no isotope effect. This assumption is not supported by the recent studies of Bender (see above). As the authors point out, the observed effects are rather larger than expected for simple bond-formation reactions. The situation is further complicated by changes in bond hybridization and resonance effects, however, so a simple calculation might not represent the actual reaction very well.

In some reactions the rate-determining step may change with changing reaction conditions. Such a change was demonstrated by an isotope-effect study of the bromodecarboxylation of 3,5-dibromo-4-hydroxy benzoic acid (II) (93). In the proposed mechanism either (II) or its monoanion reacts with bromine to give an intermediate (III) which subsequently loses CO_2 (several proton-transfer equilibria are omitted in this discussion for simplicity). The authors consider the bromination (Equation 71) to be rate-determining and find confirmation of this assumption in the lack of a C^{13} isotope effect on CO_2 loss. When the solvent is made



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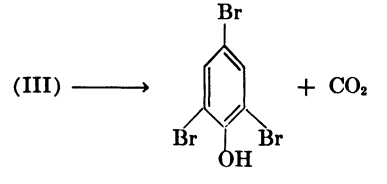


(72)

0.3M in HBr, however, k_{12}/k_{13} becomes 1.045. Obviously the bromination has become a pre-equilibrium and the loss of CO_2 (Equation 72) is now the rate-determining step.

A number of other investigations deserve brief mention. The decarbonylation of benzoylformic acid in sulfuric acid appears to involve carbon–oxygen rather than carbon–carbon bond cleavage in the rate-determining step (94). A large isotope effect is observed with C^{14} in the carboxyl, but the effect is small or negligible when the C^{14} is in the α-carbon. The

observation of an isotope effect from both ends of a bond, as exemplified by this work and the work of Carrick and Fry (92), is a technique which promises to be very effective in mechanisms studies.

The decomposition of some substituted ureas in propionic acid was found to give C^{13} isotope effects which varied considerably with the structure of the urea (95). This variation paralleled the activation energies, but again the picture is complicated by resonance effects and changes in bond hybridization. An isotope effect on a pre-equilibrium has been suggested to explain the small C^{14} isotope effect found in the cyclization of *o*-benzoylbenzoic acid to anthraquinone (96). A qualitative search for C^{14} isotope effects in addition reactions found effects in some carbonyl-addition reactions but not in the addition of bromine to olefins or in the Diels-Alder reaction (97).

2. Sulfur, Nitrogen, and Oxygen

Studies on the heavier elements other than carbon have been relatively few. Indeed, with oxygen no results of direct interest to organic chemists have been reported at the time of this writing. Fractionation of O^{18} has been noted in some biochemical processes (98,99) and in a few inorganic reactions. Among the latter is the study of the reactions of hydrogen peroxide with various oxidizing and reducing agents (100). Undoubtedly O^{18} isotope effects will prove useful in organic chemistry, since many organic reactions involve the cleavage of carbon–oxygen or oxygen–oxygen bonds.

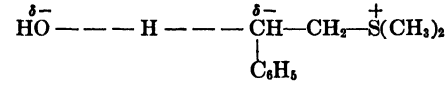
A number of interesting studies of S^{32}/S^{34} isotope effects have been performed. The equilibrium between an aldehyde or ketone and its bisulfite addition compound (Equation 73) concentrates the heavier isotope in

$$R_2C{=}O + HSO_3^- \rightleftharpoons R_2C(OH)SO_3^- \qquad (73)$$

the free bisulfite to the extent of 1–2%, depending on the particular ketone or aldehyde (101). Such fractionation is to be expected only if the bonding to sulfur is different in the bisulfite ion and the addition product. The fractionation thus provides striking evidence for the presence of a C—S bond in the addition product. Examination of the isotope effect on rates of formation of bisulfite addition compounds gave k_{32}/k_{34} values close to unity (102). This result is consistent with rate-determining formation of a C—S bond, since the mass-ratio and zero-point-energy terms of the Bigeleisen equation (Equation 13) work in opposition for a bond-forming reaction and in the present case should approximately cancel.

Elimination reactions of sulfonium salts have been examined for S^{32}/S^{34} isotope effects (103). The first reaction studied was the decomposition of

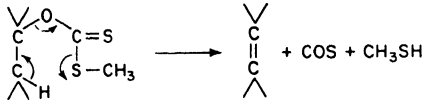
tert-butyldimethylsulfonium iodide in water. This is known to be an S_N1 reaction and therefore must involve carbon–sulfur bond cleavage in the rate-determining step. An isotope effect of 1.8% was in fact found, a figure in reasonable agreement with that calculated (1.5–1.6%) for the complete rupture of the hypothetical C—S molecule. In contrast, the E2 reaction of 2-phenylethyldimethylsulfonium bromide with sodium hydroxide in water gave an isotope effect of 0.15%. Evidently here the C—S bond is only slightly stretched in the transition state. A carbanion-like



(I)

transition state (I) is the most reasonable interpretation, but there cannot be a carbanion *intermediate* of appreciable stability, since no exchange of the β-hydrogens occurs under the reaction conditions (27).

A particularly elegant application of both carbon and sulfur isotope effects was made by Bourns (104) in his study of the Tschugaev Reaction. This thermal elimination from xanthate esters has for some time been considered to proceed *via* a cyclic transition state in which a sulfur atom abstracts the β-hydrogen. *A priori*, either the thiol sulfur (105) (Equation



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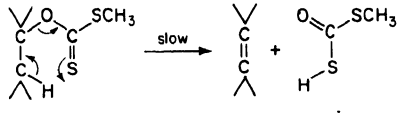
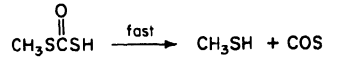


(75)



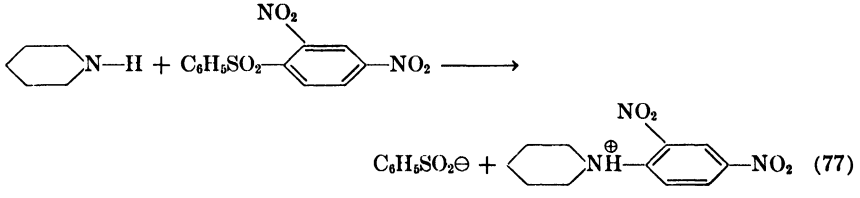
(76)

74) or the thion sulfur (106) (Equations 75 and 76) could function in this manner.

The reaction was examined for isotope fractionation in both the thiol and thion sulfur atoms, and in the carbonyl carbon. The compound employed was *trans*-2-methyl-1-indanyl xanthate. For the thiol sulfur a carbon–sulfur bond is broken and a sulfur–hydrogen bond formed in Equation (74) (predicted effect using the three-center model (7), 1.3%), but in Equation (75) the bonding to this sulfur is undisturbed. Experimentally, the S^{32}/S^{34} effect was 0.21 ± 0.06%. For the thion sulfur, no effect is

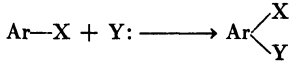
predicted from Equation (74) but the carbon–sulfur bond changes from double to single in Equation (75). The change from C=S to C—S should give an effect of around 0.7%. The observed effect was 0.86 ± 0.12%. Finally, Equation (74) predicts a C^{13}/C^{12} isotope effect of about 3.5% (rupture of a single bond to carbon) while Equation (75) predicts little or no C^{13}/C^{12} effect. There was in fact no isotopic fractionation in the carbonyl carbon. These three observations are consistent only with the mechanism of Equations (75) and (76).

Sulfur isotope effects have also been studied in the reaction of piperidine with phenyl 2,4-dinitrophenyl sulfone (107) Equation (77). This is a typical nucleophilic aromatic substitution and undoubtedly proceeds *via* a mechanism such as that of Equations (78) and (79). The sulfur isotope effect was strikingly solvent dependent. Values of 1.27 ± 0.10% in benzene,



(77)

1.57 ± 0.16% in acetonitrile and 0.56 ± 0.07% in methanol were observed. Evidently Equation (79) represents the rate-determining step for reaction in the first two solvents. The considerably lower effect for the reaction in methanol suggests that the rates of reactions (78) and (79) are of similar



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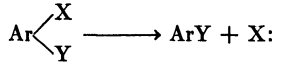
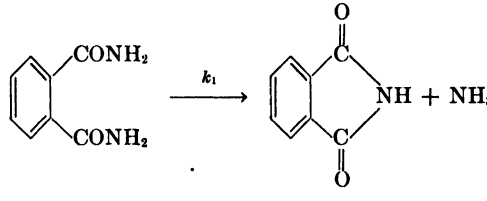


(79)

magnitude in this solvent. This conclusion is reasonable, since methanol should aid reaction (79) by solvation of the departing phenylsulfinate ion.

Nitrogen isotope effects (N^{15}/N^{14}) have been determined for a few reactions. The decomposition of phthalamide to phthalimide (108) (Equations 80–82) shows an intramolecular effect of $k_2/k_3 = 1.012$ and an intermolecular effect of $k_1/2k_3 = 1.006$.



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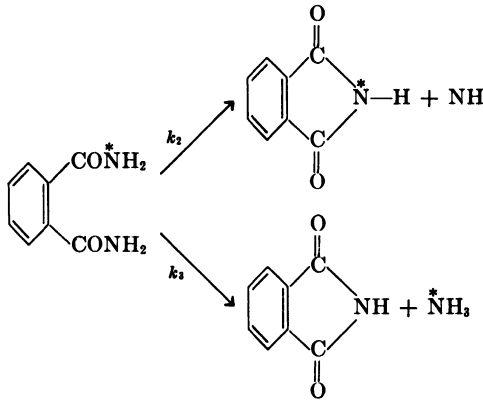

(81)

(82)

A qualitative test of the Bigeleisen equation has been made in a study of the formation of carbon–nitrogen bonds. The reaction chosen was that of tertiary amines with alkyl halides (107). Since carbon–nitrogen bonding is tighter in the transition state than in the ground state, the zero-point energy term should be *less* than unity. However this term approaches unity as the temperature is raised, so the isotope effect for a bond-forming reaction should *increase* with increasing temperature. The observed changes of isotope effect with temperature were small but appeared from statistical tests definitely to confirm the prediction.

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CHAPTER X

HOMOGENEOUS GAS PHASE REACTIONS

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I. INTRODUCTION

The study of homogeneous gas phase reactions is of importance for two reasons; first because they occur by the interaction of a small number of molecules (usually one, two, or three) and are thus more amenable to theoretical study, and secondly because of their increasing importance in industrial processes. The material in this chapter will deal with the type of apparatus that has been used for studying gas phase reactions, the experimental techniques used for establishing the stoichiometry of a reaction,

and the measurement of its rate. The remainder of the chapter will be concerned with the methods of determining the kinetics of the reaction from rate measurements and finally with the assignment of a mechanism to the reaction. It is intended to deal primarily with reactions that follow simple mechanistic schemes, since it is from the study of these types of reactions that an understanding of the more intimate details of kinetic processes will emerge. Of recent years, great progress has been made by the study and isolation of individual, elementary reactions which may occur in a complex chain reaction, rather than by the attempt to identify the elementary reactions by studying the overall chemical process. As in the first edition, examples will in the main be chosen from the field of organic reactions such as thermal decompositions and isomerizations. Oxidation will not be discussed, as this is a highly specialized field, nor will photochemistry, since this has already been treated in an earlier volume (1).

II. APPARATUS*

The choice of apparatus will be largely decided by the nature of the reaction to be investigated, which will determine whether chemical or physical methods are employed (see Section IV). However, common to all methods are (*a*) a thermostat to ensure that the reaction is studied under isothermal conditions, (*b*) a reaction vessel, and (*c*) a vacuum line for the introduction of the reactant into, and the removal of the products from, the reaction vessel. In addition, since the most widely applicable physical method for meausring rates of chemcal change involves the measurement of pressure, a subsection will be devoted to this technique.

1. The Thermostat

Since most gas phase reactions of interest occur at elevated temperature, some method must be devised for maintaining the reaction vessel at a high, uniform, and constant temperature.

The constancy of temperature is important, since the rate of a gas phase reaction increases by 5–10%/1°C. rise in temperature. Uniformity is also of importance, since if appreciable temperature gradients exist in the reaction vessel, rate data will be of dubious validity. It is not difficult, at elevated temperatures, to achieve a temperature gradient throughout the reaction vessel of less than 0.5°C., and variations of temperature with time of the order of 0.25°C.

The most widely used methods employ (*a*) an electrically heated metal block (2); (*b*) a bath of molten salts (3); (*c*) a vapor bath (4), consisting of a

* Additional references to experimental techniques will be found in the Appendix.

refluxing liquid, the pressure over which can be maintained constant; and (*d*) an air bath (5). Of these, (*a*) is probably the most convenient and satisfactory, provided a metal with a high thermal conductivity is used. For temperatures up to 500°C. a block of aluminum or copper may be used, while up to 700°C. aluminum bronze (90% Cu–10% Al) is satisfactory. A reaction vessel of 2 in. diameter and 6 in. length, which can be fitted in a cylindrical block 12 in. long and 6–8 in. in diameter, has been found satisfactory. The block has a $2^1/_8$ in. hole, drilled centrally, to hold the reaction vessel. The lower end of the vessel well is closed by a closely fitting cylin-

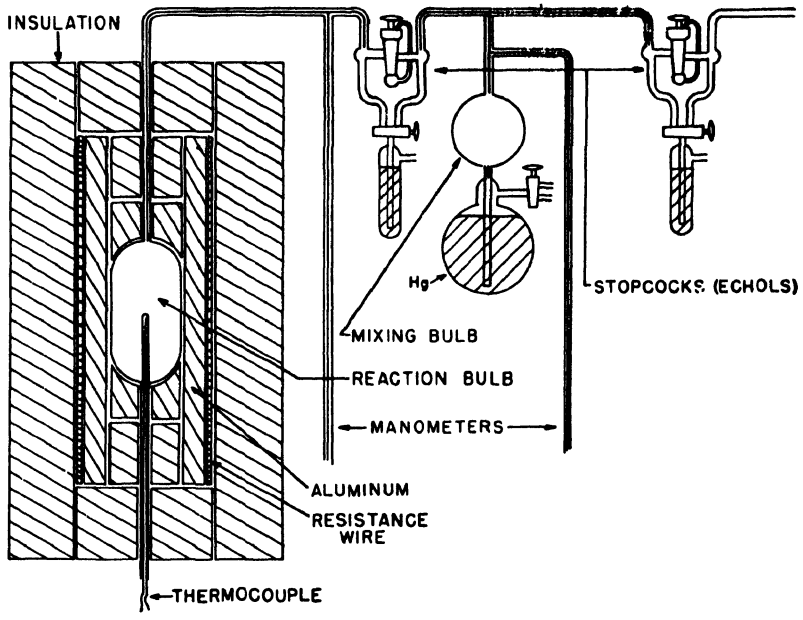


Fig. 1. Apparatus for the study of thermal decompositions (2). A second thermocouple for temperature control is not shown. The Echols-type stopcocks are lubricated with graphite and sealed with mercury.

der with a hemispherical top, and the upper end is closed by a similar cylinder, split along its axis as shown in Figure 1. These cylinders tend to promote an even temperature within the block and reaction zone.

The outer surface of the aluminum block is covered with several layers of asbestos paper and wound with resistance wire, making the spacing between the turns greater at the center than at the ends. The spacing required to give an even temperature is best determined by trial. The wire can be fixed in position with the aid of heat-resisting cement. The windings are then covered with layers of asbestos board, moistened so that it

can be wrapped around the block. The ends can be insulated by circles of asbestos board. To reduce heat losses further, the outer surface may be covered with thin aluminum. The block may be mounted either vertically or horizontally. Before use, the temperature in various regions of the reaction vessel should be checked to ensure that no serious temperature gradients exist. A typical vapor-thermostat is shown in Figure 2.

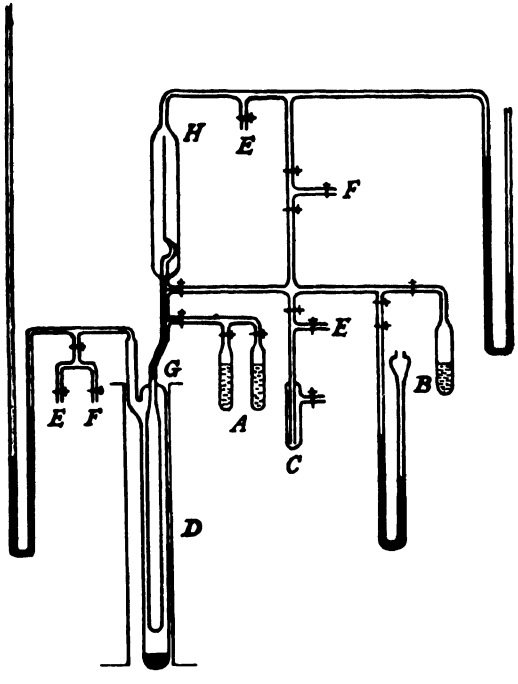


Fig. 2. Apparatus for the study of thermal decompositions (4). *D* is a vapor reservoir, and *H* a spoon gauge used for measuring the rate of pressure change.

For the control of temperature (6), a large number of methods have been devised. However, there are now available commercially several devices which have been found satisfactory. The simplest of them is essentially a mercury in glass thermometer, with an adjustable wire contact. Another involves a bimetallic element, while a third involves a platinum resistance element, the response from which alters the open to close ratio of an electronic relay. This latter device can be set over a wide range of temperatures and is remarkably stable. In each case it is best to include a resistance in series with the furnace winding. This is adjusted so that the temperature of the thermostat is a few degrees less than the required tempera-

ture. The control device may then be used to short-circuit the resistance when the temperature of the thermostat falls. Some care is needed in the adjustment of the steady and booster currents of such a system.

For the measurement of temperature (7) a mercury thermometer, thermocouple, or platinum resistance thermometer may be used. The most widely used of these is the thermocouple. Care must be taken in the calibration of this instrument, and probably the best procedure is to have a master thermocouple which has been calibrated by the National Physical Laboratory, National Bureau of Standards, or equivalent organization. The working thermocouples can then be calibrated against the master when necessary.

2. The Reaction Vessel

In the static method of measuring reaction velocity in the gaseous phase, cylindrical or spherical vessels of 200–1,000 ml. have been most widely used, though larger vessels have been used for the collection of reaction products or for reactions at very low pressure (8). For flow experiments, either a straight tube or a coil of tubing may be used. The material from which the reaction vessel is made will be determined by the nature of the reaction to be investigated. The reaction vessel must be capable of withstanding the temperatures and pressures of the investigation, be immune to attack by the reactants or products, and, further, it must not exert a catalytic influence upon the reaction. If it is desired to follow the reaction by light absorption, then it must be transparent to light of the chosen wavelength. For temperatures up to 550°C. and pressures up to about one atmosphere, Pyrex glass is satisfactory. Jena glass can be used to slightly higher temperatures (~625°C.). For higher temperatures, silica vessels have proven satisfactory, and these have the advantage of transmitting ultraviolet light. Vycor glass, having a temperature limit of about 900°C. has the additional advantage of transmitting appreciably the 2,537 Å. mercury line. For very high temperatures and pressures, metal vessels such as stainless steel (9) or platinum (10) may be used.

It is a reasonable assumption that most reactions may be caused to proceed on the surface of a reaction vessel. It is therefore generally too much to hope for that a given reaction will proceed homogeneously in vessels with different surfaces. The problem is rather to find a surface which has no appreciable effect upon the rate of reaction. Of recent years, a widely used technique in preparing reaction vessels for use consists of seasoning them with the products of decomposition of either the substance to be investigated or of some other substance. This technique was evolved when it was found that starting with a clean reaction vessel, measured rates

fell with successive runs until finally a limiting rate was achieved (4,11). A method which has proven successful in the study of unimolecular elimination from halides (12) and from esters (13) is to allow allyl bromide to pyrolyse in the vessel. One of the products of decomposition is a carbonaceous film, which effectively prevents wall catalysis by the glass of the vessel. Care must be taken not to alter the temperature of such a seasoned vessel too abruptly, or the film may develop cracks; also, oxygen must be rigorously excluded from the vessel after seasoning, as it tends to destroy the coating. It should be noted, however, that while the method of seasoning described above is very effective in affording reproducible kinetic behavior in the case of unimolecular reactions, it may give rise to irreproducibility in the case of chain reactions, possibly due to the adsorption on the surface of inhibitors or initiators.

In order to test the homogeneity of the reactions studied, the surface-to-volume ratio of the reaction vessel should be altered. A small variation may be made by changing the diameter; in the case of a cylinder $S/V = 2/r$, while for a sphere $S/V = 3/r$. Where possible, however, it is better to pack the vessel with glass or silica tubing that has fire polished ends. The increase in S/V is then readily calculable, which is not the case if glass wool or powdered silica is used. On the basis of the simple equation

$$k = k' + k'' S$$

where k is the overall rate, k' the homogeneous rate and k'' the heterogeneous rate, an increase in k by 10% with S increased by a factor of 5 implies the reaction is about 97% homogeneous.

A novel method of testing for homogeneity is the method of differential calorimetry, developed by Koval'skii and described by Semenov (14). The method involves the use of two thermocouples, one mounted in the center of the reaction vessel, the other on the wall. The temperature difference (ΔT) is proportional to the heat of reaction and thus provides a measure of the reaction rate. Different expressions are obtained for ΔT in the case of a homogeneous and a heterogeneous reaction. If the rate of reaction is measured independently and if the heat of reaction is known, it is possible to predict ΔT for both cases. Comparison of the actual behavior with that predicted enables a determination to be made of the type of reaction.

3. Components of the Vacuum Line

A. VALVES, STOPCOCKS, AND LUBRICANTS

The most widely used device for isolating the reaction vessel from the remainder of the system, and for gas handling in general is a stopcock lubricated with grease. The chosen lubricant should withstand the required

temperature, have a low vapor pressure, and should neither affect the rate of reaction nor dissolve either the reactants or products appreciably. Many types of grease are available commercially; for relatively low temperature, hydrocarbon greases are satisfactory, for higher temperatures (100–150°C.) silicon greases have been used. Other substances which have been used are polyisobutylene greases (15), greases containing cellulose acetate (16), fluorinated oils (17), glycerol containing silica (18), and phosphoric acid (19). Silica (18) has been used to prolong the life of greases. Fluorocarbon and chlorofluorocarbons have been used as lubricants in the presence of corrosive gases (20,21).

Another useful valve in dealing with corrosive gases is the Bodenstein glass valve (22) with a fused silver chloride seat. Other designs of greaseless valves have been published (23). In the case of gases which are unaffected by high temperatures a valve with a glass capillary which can be sealed and opened can be used (24). Now available commercially are metal valves with polythene seatings.

When mercury vapor has no effect on the reaction being studied, a number of other devices can be employed as valves. For handling organic vapors which dissolve readily in ordinary lubricants, mercury-sealed and graphite-lubricated stopcocks, as well as other valves employing mercury may be used. In particular a mercury cut-off involving a sintered glass disc has been described (25). Another method sometimes used is to fill the tubing adjacent to the tap with mercury (26); this both obviates the necessity for heating the tap and also reduces the contact between the gases in the vessel and the lubricant. For vacuum systems operating at pressures above atmospheric, spring-loaded stopcocks are available.

B. MANOMETERS AND PRESSURE GAUGES

The method of measuring pressure depends upon the pressure range to be investigated. For pressures from 20 mm. upwards, manometers are the most satisfactory. For the higher pressure ranges, the manometer may be filled with mercury, for the lower ranges, with a liquid such as silicone oil, sulfuric acid, α-bromonaphthalene, or a dialkyl phthalate. If the reactants and products do not react with the manometer fluid, the manometer may be connected directly to the reaction vessel; if this is not the case, an all glass system must be employed. Where the manometer is directly connected to the reaction system, care must be taken to keep the volume between the reaction vessel and the manometer—the dead space—as small as possible. The volume of the dead space should not exceed 1–2% of the reaction volume. To prevent the condensation of higher boiling reactants or products, the space between the reaction vessel and the manom-

eter is usually heated. For rate studies at lower pressures, McLeod gauges of small volume may be employed.

In the case of corrosive gases, or substances which react with the manometric fluid, three types of pressure gauges may be used. The most widely known of these is the Bourdon or spoon gauge (4,27). The pointer may be observed directly with a microscope, it may be used in conjunction with an optical lever, or it can be made to record the pressure (28). The second is the Bodenstein spiral manometer (5,29). Both these gauges can be made with wide ranges of sensitivity, but the higher the sensitivity, the smaller the pressure difference they will withstand. Both can be used either as null gauges, or to give direct readings of pressures after calibration. Vaughan (30) has published detailed instructions for making quartz spiral manometers, while a machine for producing glass spirals has been described by Yorke (31).

Glass diaphragm gauges have been used successfully as instruments (11,32). Movements of the diaphragm may be detected orally, optically, or electrically, the last method being the most convenient. The sensitivity can be made better than 0.2 mm., with a diaphragm capable of withstanding a pressure difference of 1 atmosphere. Kabesh and Nyholm (33) have described a gauge designed so that the zero setting does not depend upon the temperature of the gauge. An all metal system employing metal diaphragms has also been described (34), as was a system involving a metal bellows (35).

C. VACUUM PUMPS

For many reactions, a two stage rotary oil pump ($\sim 10^{-4}$ mm.) suffices for exhausting the vacuum line; when this is not sufficient an oil or mercury diffusion pump may be used in conjunction with a rotary backing pump. For testing the vacuum, a Pirani gauge may be build into the vacuum line near the reaction vessel, or alternatively a Tesla coil may be used. Vacuum pumps and vacuum techniques are thoroughly discussed in a number of reference books (36).

4. Typical Systems and Their Operation

In this sub-section two types of apparatus are described, one a static and the other a flow system. In a static system, the range of reaction half-lives that may be investigated lies between 3 minutes and 12 hours, although the latter value may be extended depending on the patience of the observer. In the flow system, the range is much greater and the absolute value much smaller, from a fraction of a second upwards. One advantage of the flow method is that experiments can be carried out at

very low conversions, thus decreasing the possibility of subsequent reactions of the products. A brief discussion of the potentialities and limitations of the flow method has been given by Long (37).

A. A STATIC SYSTEM

This is shown in Figure 3 (12) and involves an all-glass apparatus, using a diaphragm gauge as a null instrument. The gauge B is joined to the reaction vessel A which has a side-arm C connected to it by capillary tubing to minimize dead space. The side-arm and connecting tubing are wound with resistance wire through which a current is passed in order to prevent condensation of the reactants and products. The reaction system

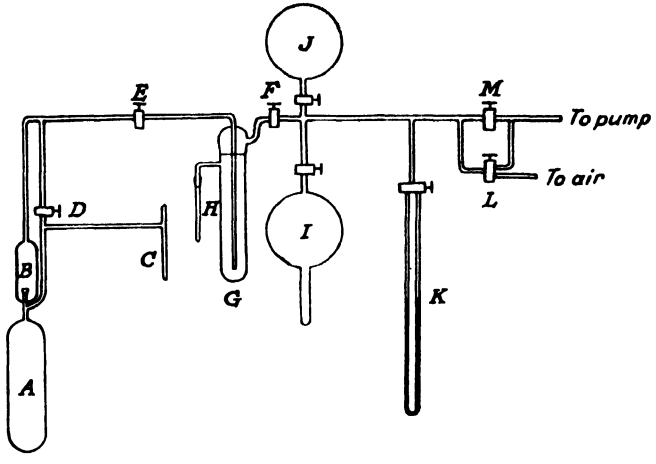


Fig. 3. A static system for measuring the rate of pyrolysis (12). The glass diaphragm gauge B is used as a null instrument.

is isolated from the remainder of the system by the tap D. A trap, G, which can be isolated from the rest of the system by means of taps E and F can be used for condensing out the products at the end of a run. The removable side-arm H enables the products to be removed from the system. Two large flasks I, and J, are attached to the vacuum line which can be used for gas storage. A large bore tap, M, permits rapid evacuation of the system, while for pressure adjustments the two-way capillary tap L could be used. Pressures are read on the manometer K.

To commence a run a small vial filled with previously degassed reactant is introduced into the side-arm C, which is then cooled with liquid air and the top sealed off. The system is then exhausted, and the reaction vessel isolated by closing tap D. The gauge zero is then determined by allowing

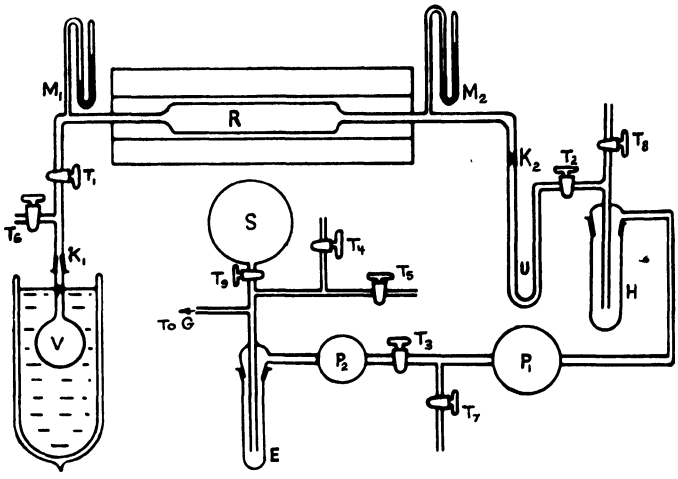


Fig. 4. A flow system for measuring rates of pyrolysis (38).

air or nitrogen to enter through tap L until the contact at the diaphragm gauge just breaks. The pressure necessary to do this is then subtracted from all subsequent pressure readings. Air or nitrogen is then admitted through tap L, to give a pressure approximately equal to the expected initial pressure, and then tube C is heated to vaporize the reactant, and the stopwatch is started. The pressure in the reaction vessel is then measured as a function of time. At the end of the run, provided the products are completely or nearly completely condensible, a liquid air trap can be placed around C and the system evacuated. Closing tap F, placing a liquid air flask around G, and opening tap C, transfers the products to G, from which they may be removed.

An alternative method of introducing the reagent is shown in Figure 2 and involves a vapor reservoir. This is probably the most convenient method with reasonably volatile substances. In the case of a reaction involving two reactants or if a reaction is to be done in the presence of added substances, the nonreactive component may be introduced first and its pressure measured. It is then condensed out in C. Then the reactive component is introduced and its pressure may be determined by difference, knowing the total pressure. If the first component is very volatile and if the vial method is used, a small indentation about $^1/_2$ in. from the bottom of C will prevent its evaporation when the vial is dropped in.

B. A FLOW SYSTEM

This is shown in Figure 4 (38). The reactant is stored in vessel V which can be kept at a given temperature in order to maintain a constant

vapor pressure. V can be weighed before and after each experiment, in order to determine the weight of reactant used in a run. By opening tap T_1, the vapor of the reactant can be admitted to the reaction vessel R, manometers M_1 and M_2 giving the pressures before and after R. The vapor leaving R passes through a heated tube and a small trap, U, cooled in an appropriate cooling mixture. A further trap, H, cooled in liquid air serves to remove the remaining condensible species. Trap H is followed by two diffusion pumps, P_1 and P_2, capable of pumping all the gases into the storage vessel S. By changing the capillaries K_1 and K_2, and varying the temperature of the bath around V, contact times and the pressure of reagent in R could be varied. When two reactants were involved, the apparatus can be modified to include a further storage vessel (39).

III. INVESTIGATION OF THE STOICHIOMETRY OF A REACTION

Before embarking on a kinetic study of a given reaction, it is necessary to have detailed knowledge of the chemistry involved. This enables the investigator to select the most suitable method for following the progress of the reaction, and also the conditions under which it is best studied. Three questions arise: (*a*) What is the major reaction involved? (*b*) Are there any side reactions? (*c*) Do the products themselves react under the conditions of the investigation? A valuable source of information on the thermal reactions of organic compounds is the book by Hurd (40).

Where the reaction products are stable under the given conditions, it will suffice to allow the reaction to proceed to completion, and then carry out a complete analysis of the products. It is important to investigate the material balance for each atomic species, to ensure that none of the products has escaped detection. When the products of the primary reaction react further, the composition of the products may be investigated at various percentages of reaction, and an extrapolation made to zero parent reaction.

In general, unless a very large static system is used, the quantities of products obtained are very small. So it is often convenient to use a flow technique in order to acquire sufficiently large samples of products for conventional chemical separation and analysis. As the methods for doing this depend so much on the reaction to be investigated, no further discussion will be given of them.

Two very powerful techniques that have recently been applied to gas-kinetic investigations are those of mass spectrometry and of vapor phase chromatography. In addition, these two techniques used in conjunction provide a very useful means of studying the nature of reaction products.

Low resolution mass spectrometry has been used, for example, by Stubbs *et al.* (41) in an investigation of the pyrolysis products of hydrocarbons. Further, the development of high resolution mass spectrometry, which depends upon mass defect differences, has added further power to this method (42). Vapor phase chromatography has also proved invaluable in investigating the stoichiometry of a reaction (43). It has the advantage of being much more generally accessible than mass spectrometry, added to the fact that separated samples are available for further study. Isomers are often readily detected by this technique (44). However, much can be done by combining the two former techniques, by means of which vapor phase chromatography is used to separate the products, and mass spectrometry to identify them (45).

The techniques of infrared and ultraviolet spectroscopy (46) are too well known to warrant more than mention.

IV. MEASUREMENT OF RATE OF REACTION

1. General Considerations

Having established the stoichiometry of a reaction, measurements of rate may be made by either following the rate of disappearance of one or more of the reactants or the rate of appearance of one or more of the products, or a combination of both. If the reaction obeys a simple kinetic scheme

$$A \longrightarrow P$$

$$A + B \longrightarrow P + Q$$

then measurement of either

$$-dA/dt = dP/dt \text{ or } -dA/dt = -dB/dt = dP/dt = dQ/dt$$

will give the required rate. However, if the reaction involves more than one step, and the rates are comparable, then the above equalities may no longer hold and it may be necessary to measure more than one of the individual rates.

Preliminary investigation will indicate the most favorable conditions for following the reaction, and also the method (chemical or physical) best suited to the purpose. If a clean glass vessel is used, the products of reaction should be left in contact with it for a prolonged period in order to see whether there is any wall catalysis. This can also be checked by packing the reaction vessel as previously described (Section II.2) with glass

tubing. If the walls are found to have pronounced effect, seasoning (Section II.2) may be employed to decrease the heterogeneous component of the reaction. Reproducibility of rates, and lack of dependence of the rate upon surface–volume ratio is strongly indicative of a homogeneous reaction. Since heterogeneous reactions usually have a lower activation energy than homogeneous ones, working at higher temperatures will often favor homogeneous processes. This technique is not so useful in the case of first-order reactions, as the rate may become too large for convenient measurement. For higher order reactions, the concentration of reactants may be reduced in order to lower the rate. It is sometimes advantageous to concentrate upon the initial stages of a reaction, as the products may inhibit or accelerate the reaction.

When possible it is desirable to use a physical method of following the rate of reaction, as this is usually simpler than using chemical methods. However it must first be established that the physical technique chosen does in fact give a faithful measure of the rate of reaction. Thus in the case of olefin elimination from alkyl halides or from esters (4,12,13) measurement of the rate of total pressure increase gives a measure of the rate of reaction, which can be justified by analyzing for acid, after a given time and comparing the percentage decomposition with that obtained from the total pressure.

Great care must be taken as regards the purity of the reagents, for small amounts of impurities may have fantastic effects upon the rate of reaction. A common source of trouble is the effect of oxygen (47), which can be minimized by careful degassing of the reagents under vacuum and by only admitting oxygen free nitrogen into the reaction system. Where possible the reagents should be made or purified by different methods, and then shown to give the same rate of reaction. In addition to oxygen, any substances capable of producing free radicals may stimulate chain reactions in the reacting substrate. Similarly, small amounts of nitric oxide or olefins (48) may inhibit a chain reaction under investigation. Care should be taken to eliminate substances such as ethers or olefins, which readily form peroxides. It is sometimes advisable to store the reactants at low temperature and in the dark.

Mention should be made of an indirect method of measuring the rate of a one step reversible reaction by measuring the rate of the reverse reaction together with the equilibrium constant (49). Thus, suppose k_1 and K are known for

$$AB \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A + B$$

Then

$$k_2 = k_1/K$$

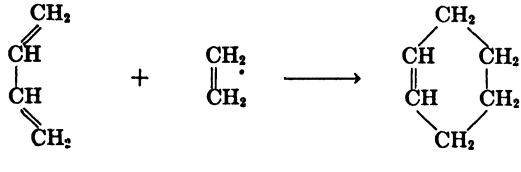
This method is of particular value if the reverse reaction is heterogeneous or if the equilibrium is unfavorable in the temperature range concerned.

Measurement of a rate of reaction resolves itself into two operations; (*a*) the measurement of the extent of reaction and (*b*) the measurement of the time of reaction.

2. Measurement of Extent of Reaction

A. STATIC METHODS

In this method of following reaction rates the reactants are introduced into the reaction vessel and the required concentrations either measured continuously or after a lapsed period of time. The former method, which usually involves a physical technique of measurement, is to be preferred, since the concentrations are obtained as a function of time from a single run, whereas in the latter method, only one point is obtained from each run. In the case of a single component, this can be admitted to the heated reaction vessel in the manner described in Section II.4.A. This technique is preferable, as the heating up time at ordinary pressures is not more than 30 seconds If the reaction vessel and reactant are placed in the thermostat, the time to reach thermal equilibrium is much longer, up to 5 minutes, although this may be somewhat reduced by temporarily raising the temperature of the thermostat by 1–2°C. before admitting the vessel. Where more than one reactant is involved, and both are stable at the reaction temperature, preheating is possible. Alternatively, premixing may be employed. In the interests of accuracy it is obviously desirable to reduce the time of introduction and removal of the reactants to a minimum.

Reaction	P_f/p_0
$\mathrm{R{-}X \longrightarrow O + HX}$ X = Cl, Br, R CO_2; O = olefin	2
$\mathrm{CH_2{-}CH_2 \longrightarrow 2CH_2{=}CH_2}$ $\mathrm{CH_2{-}CH_2}$	2
$\mathrm{R{-}I \longrightarrow {}^1/_2RH + {}^1/_2O + I_2}$	1.5
$\mathrm{2NO + O_2 \longrightarrow 2NO_2}$	1 5
	0.5

Continuous Methods. These will depend either upon the measurement of some physical property of either the reactants or the products, or upon the withdrawing of small samples at specified time intervals for either physical or chemical analysis.

Pressure Measurements. Many gas phase reactions occur at constant volume with an increase or decrease in pressure. Some examples are given below, together with the theoretical ratio of final (P_f) to initial (p_0) pressure.

Provided the stoichiometry is established, measurement of the rate of pressure increase will suffice to measure the velocity of the reaction.

For a reaction involving one reactant, if the stoichiometry is such that

$$\mathrm{A} \longrightarrow n\mathrm{Q}_1 + n_2\mathrm{Q}_2 + n_r\mathrm{Q}_r \qquad n = \sum_r n_r$$

then if p_0 is the initial pressure of A, and p is the pressure of A decomposed at time t, then the total pressure P_t is given by

$$P_t = p_0 - p + np = p_0 + (n - 1)p$$

Thus the pressure of A at time t will be

$$p_0 - p = (np_0 - P_t)/n - 1$$

and is readily determinable from the total pressure. A typical pressure–time curve for the case of n equal to 2 is shown in Figure 5.

For the reaction

$$n_\mathrm{A}\mathrm{A} + b_\mathrm{B}\mathrm{B} = n_\mathrm{Q}\mathrm{Q} + n_\mathrm{R}\mathrm{R}$$

the total pressure is given by

$$P_t = p_\mathrm{A}^0 + p_\mathrm{B}^0 + (n_\mathrm{Q} + n_\mathrm{R} - n_\mathrm{A} - n_\mathrm{B})p$$

from which the pressure of A and B at time t, ($p_\mathrm{A}^0 - n_\mathrm{A}p$) and ($p_\mathrm{B}^0 - n_\mathrm{B}p$) may be obtained. It cannot be overemphasized, however, that it is essential in using this method, to show that the stoichiometry is indeed represented by the equation used; that is, that side and consecutive reactions play only a negligible role. It is obvious that a knowledge of the initial pressures is of vital importance in this method. These may often be determined by an extrapolation of the pressure–time curve to zero time. In the case of first-order reactions, an alternative method has been devised by Swinbourne (50) for graphical extrapolation. A check on the stoichiometric equation may be obtained from the determination of P_f/p_0 values. Some workers in the field of gas phase decompositions have preferred to use a p_0 derived from P_f/n. This is all right if the stoichiometry is well established and extrapolation may be used to determine the initial time (51). Others have used P_f in place of np_0, which in effect

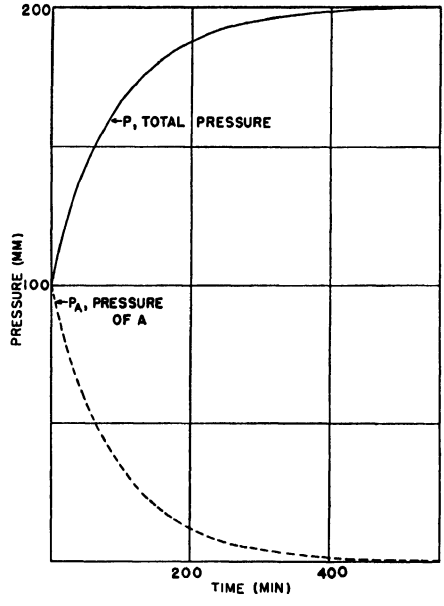


Fig. 5. Pressure–time curve for a first-order reaction:

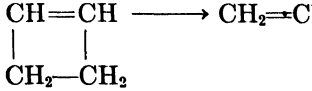
$$A \rightarrow B + C$$

$$dP/dt = -dP_A/dt = kP_A$$

makes n nonintegral (52). There seems little theoretical justification for this. It should be noted that dead-space in the apparatus will tend to lower the ratio of P_f/p_0. Allen has shown how to correct for this factor (53).

If weighed amounts of reactants are admitted to the reaction vessel, then by use of the gas laws, initial pressures may be calculated. An appreciable discrepancy between the extrapolated and the calculated initial pressures can sometimes be explained as due to a very rapid reaction during the starting and warming up period.

Optical Methods. A number of interesting reactions occur at constant volume without change in pressure. These include, among other reactions, the very important class of isomerization. Some typical reactions are shown below.



$$\begin{array}{l} CH{=}CH \\ | \quad | \\ CH_2{-}CH_2 \end{array} \longrightarrow CH_2{=}CH{-}CH{=}CH_2 \qquad (1)$$

$$CH_2{=}CHOCH_2CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2CH_2CHO \qquad (2)$$

$$RI + HI \longrightarrow RH + I_2 \qquad (3)$$

$$Br_2 + RH \longrightarrow RBr + HBr \qquad (4)$$

In these cases, if it is desired to follow the reaction by a physical method, one based on optical extinction coefficients is often suitable. In such a case it is desirable that either one of the reactants or one of the products should have an absorption band in an accessible region where no other absorption occurs. Thus for reaction (1), the isomerization of cyclobutene, Cooper and Walters (54) have used the absorption of butadiene at 2,100 A. For reaction (2), the isomerization of allyl vinyl ether, the absorption of allyl acetaldehyde at 3,130 A. has been used (55) while for reactions (3) and (4) the absorption of iodine (56) and of bromine (57) in the visible was

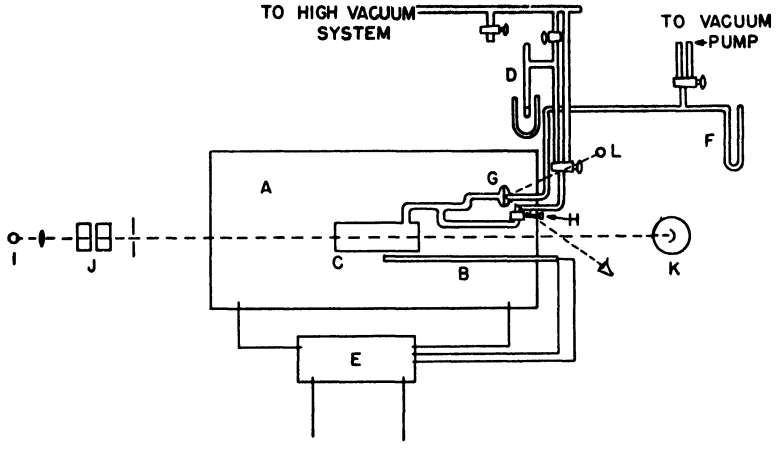


Fig. 6. Apparatus (55) for following gaseous rearrangements photometrically: *A*, oven; *B*, resistance element for temperature control; *C*, reaction cell; *D*, sample holder; *E*, electronic temperature control; *F*, manometer; *G*, diaphragm gauge; *H*, Hoke bellows valve; *I*, H-4 mercury lamp; *J*, filter solutions; *K*, photomultiplier tube; *L*, light for reflection from diaphragm.

employed. A typical apparatus is shown in Figure 6. Continuous infrared absorption has been used for the study of the pyrolysis of ethylene oxide (58). Both absorption and emission were used to give continuous measurements of the reactants and products. This technique revealed the presence of ketene among the products, which had not previously been suspected. A fast-scanning infrared spectrometer (59) capable of recording up to twenty spectra per second has been described. This has been used for the study of a number of moderately fast reactions (60). Care must be taken, however, when using this method because of the danger of pressure broadening rendering the analysis unreliable (61).

One difficulty which underlies the use of optical methods relates to the

possibility of absorbing films being deposited on the windows of the vessel, which would invalidate measurements of concentration. And of course, the method is not suited for those reactions that are only reproducible in seasoned vessels, if the film absorbs the effective radiation.

Mass Spectrometric Methods. Since the amount of vapor needed for mass spectroscopic analysis is so small, provided samples can be removed after various elapsed times, this instrument can be used for following a reaction continuously. Thus Leifer and Urey (62) followed the pyrolyses of dimethyl ether and acetaldehyde by withdrawing samples from a reaction vessel at a rate of 0.01–0.05 ml. per hour and making mass spectrometric measurements every 3 minutes. Again Bragg, McCarty, and Norton have followed the thermal decomposition of diborane by a similar technique (63). The applications of mass spectrometry to the identification of free radicals and the measurement of the rates of free radical reactions will be discussed later.

Vapor Phase Chromatographic Methods. Since the quantity of vapor required for this technique is relatively small, the withdrawal of small samples from a large vessel at given intervals and their analysis by vapor phase chromatography provides another useful physical method for following gas phase reactions.

Discontinuous Methods. Reaction rates may be measured by allowing a reaction to proceed for a given length of time and then rapidly quenching the reaction mixture and analysing by appropriate chemical or physical methods. The measurement of any physical property which is a function (preferably a linear one) of not more than two of the species present can be used for analysis. Again, if two properties are measured, analysis for three species may be carried through. Thus the range of techniques available for studying quenched samples is much wider than that which can be used for the continuous determination of rates. In addition to the methods mentioned in Section IV.2, methods have been used depending on (*a*) the vapor pressures of the various components, (*b*) melting point, (*c*) thermal conductivity, (*d*) radioactivity, (*e*) refractive index.

As has been previously mentioned, chemical methods of analysis are often arduous, but despite this they often have the advantage of specificity and accuracy. Of particular importance in gas kinetic studies are methods of gas analysis. Since the chemical methods of analysis are dependent upon the nature of the reaction being studied, no further discussion will be given here.

As regards the technique of quenching, this is usually done by removal of the contents of the reaction vessel to a cold zone by expansion, condensation, or pumping. Where only a portion of the reaction mixture is used for analysis, care must be taken to see that it is a representative sample.

B. FLOW METHODS

A typical apparatus for measurements by the flow technique, which is capable of handling a one or two component reaction system, has been described in Section II.4. The method of achieving the flow through the reaction vessel depends upon the nature of the reactants. In the case of a substance which is normally gaseous, the displacement from a storage container by a liquid, or from a cylinder by expansion may be employed. If necessary, suction may be applied on the exit side of the reaction vessel. The rate of flow may be controlled by reducing valves or by capillaries, and measured by flow or displacement meters. By reducing the pressure or elevating the temperature, a liquid reactant may be introduced as a vapor into the reaction tube. If the reaction is being studied in the presence of a carrier gas, or if one of the reactants is a gas, this may be passed through a saturator containing the liquid reagent at the appropriate temperature, to give the required partial pressure. When both are liquid, maintaining them at the appropriate temperature and drawing off through capillaries will suffice (39). Other alternatives are (*a*) adding the liquid reagent or reagents at a constant rate by flowing them through capillaries under a constant head and at a constant temperature, or (*b*) injection of the liquid or liquids with a motor driven syringe (64). A method has also been devised for the introduction of a solid reagent (65).

One difficulty in the case of reactions carried out at elevated temperatures by this technique arises from longitudinal temperature gradients in the reaction vessel. This arises from the fact that the gases are not instantaneously heated and cooled on entry into and exit from the reaction vessel. This effect may be minimized by preheating the reagents and by chilling the exit gases quickly. If one of the reactants is unstable, reactions in the preheater may be corrected for by taking a sample just before entry into the reaction vessel.

The amount of reaction may be determined from a knowledge of the composition of the gas stream before and after entering the reaction zone. It is usual to run the apparatus for a known length of time at a given flow rate and collect the products for subsequent analysis, the extent of reaction being determined by product analysis, together with the weights of reactants used. However, instantaneous physical methods of analysis have been used in the investigation of the pyrolysis of hydrogen peroxide by the flow method, by photometrically determining the peroxide concentration before entering and after leaving the reaction vessel (66). As in the static method, it is desirable that the amount of reaction calculated from the reactants used should equal the amount of reaction calculated from the products formed.

3. The Measurement of Time

Stop watches and stop clocks are in general sufficiently precise for the study of most reactions. Their calibration is readily carried out, and should be done periodically. In the case of the flow method, the reaction time is not directly measurable. However, it may be calculated from a knowledge of the flow rate and the volume of the reaction vessel. If there is no change in the number of molecules in the reaction, then the reaction time or time of contact is the ratio of reactor volume to rate of flow at the entrance to the reaction vessel, measured at the temperature and pressure of the reaction. Where a volume change occurs in the reaction at constant pressure, and hence the flow rate depends upon the amount of reaction, this may be allowed for in calculating the reaction time (Section V.3). Alternatively the reaction may only be allowed to proceed to a small extent, or may be carried out in the presence of a large excess of carrier gas; in either case the volume change can be rendered negligible.

The reaction time may then be altered either by changing the rate of flow or the reaction volume. Butler and Polanyi (67) have employed a single vessel such that by heating only a portion of the vessel, the constant time could be cut by a factor of ten, without altering the flow rate.

V. DETERMINATION OF THE KINETICS FROM RATE MEASUREMENTS

1. General Considerations

Having determined the stoichiometry of a reaction, and measured the rate of disappearance or appearance of the reactants or products, the next step is to determine the order of the reaction and the rate constant. In the early stages of an investigation, it is often desirable, since the products of reaction may influence the rate, to consider only the initial phase of the reaction. If the reaction appears to be obviously of a given order, then the following methods are available, the first three based on the integrated equation, the last on the differential rate equation. (*a*) Constancy of the rate constant k, calculated from time to time during a run. (*b*) Graphical test of the constancy of k. (*c*) The use of fractional times. (*d*) Graphical investigation of the rate of reaction as a function of concentrations. Of these methods, (*b*) is in general to be preferred on the grounds of simplicity. The first method (*a*) has the advantage of showing up any trends in the rate constant as the reaction proceeds. Method (*d*), while extremely useful in certain cases, suffers from the fact that it is difficult to derive an accurate value of the tangent to the concentration-

time curve (which gives the rate). It is important that whatever method is employed, the rate constant derived from the experimental results should be independent of the initial concentrations of reagents over a wide range of initial concentrations. This is probably the best justification of a given kinetic equation.

Having shown, at one temperature, the lack of dependence of the rate constant upon initial concentration of reactants, the temperature variation of the rate constant may then be investigated. This should be done over as wide a range of temperatures as possible. In the case of a first-order reaction this may be achieved by a combination of static and flow measurements. For a second-order reaction, followed by a static method, variation of the initial concentrations should suffice to enable a sufficiently wide range of temperatures to be covered.

2. Arithmetical Methods

In the case of a first-order reaction, the rate constant is given by

$$k_1 = [2.303/(t'' - t')] \log p_A'/p_A''$$

where p_A' and p_A'' are the partial pressures of the reactant times t' and t'', respectively. By substituting for these quantities, the value of k may be obtained. This method has its widest application when a discontinuous method is used to follow the rate. Thus in their study of the isomerization of *cis*- and *trans*-methyl cinnamate Kistiakowsky and Smith (68) used this method to establish the first-order character of the reaction. Some of the results are given in Table I.

TABLE I
Rate of Isomerization of *cis*-Methyl Cinnamate

T., °K.	P., mm.	Time, sec.	*trans*-compd., %	$k \times 10^4$ sec.$^{-1}$
637 5	570	7,410	80.6	2 22
635.0	565	3,660	59.6	2.48
635 5	290	7,200	79.2	2.18
637 0	72	4,170	60 4	2.22
635.5[a]	71	3,798	59.4	2.38
635.5	6.8	5,730	66.2	1.89
599 5	73	12,975	23.0	0.202
599 5	69	19,200	34.3	0.219
599 0	71	21,840	35.2	0.199
598.0	71	43,530	56.6	0.192

[a] In a packed flask with six times the surface.

Three conclusions follow from these results, namely that the rate constant is (*a*) independent of reaction time, (*b*) independent of initial pressure over nearly a 100-fold range, (*c*) unaffected by packing the reaction vessel. It was therefore concluded that the reaction is of the first order. This method is extremely sensitive, and can be used within a given run to see whether the velocity coefficient changes as the reaction proceeds.

Corresponding integrated equations exist for higher order reactions. Thus for reaction of order 1.5

$$k_{1.5} = [2/(t'' - t')]\,[1/(p_A'')^{1/2} - 1/(p_A')^{1/2}]$$

while for reactions of order 2

$$k_2 = [2.303/(p_A^\circ - p_B^\circ)(t'' - t')]\,\log p_A'' p_B'/p_A' p_B''$$

For a second-order reaction involving a single reactant

$$k_2 = [1/(t'' - t')]\,[1/p_A'' - 1/p_A']$$

Other integrated equations may be used for more complicated kinetic equations. This method has not been used by many workers, it being more usual to employ the graphical methods described in the next section.

3. Graphical Methods

The first-order rate equation shows that a plot of log p_A or log p_A°/p_A against t will yield a straight line of slope $-k_1/2$ .303 or $+k_1/2.303$. Such a plot is shown in Figure 7, for the isomerization of isopropenyl allyl ether, which has been studied photometrically by Stein and Murphy (69). This demonstrates the first-order character of the reaction and serves to determine the rate constant. This method has been used extensively in the case of elimination reactions of alkyl halides and of esters. While the chlorides (4) usually give good first order plots up to 80–90% decomposition, with the bromides the rate often tends to fall after some 40–50% decomposition (12). This has been interpreted as due to the incursion of a reverse reaction.

An alternative procedure for first-order reactions has been given by Guggenheim (70). It has the advantage that it is not necessary to assume any particular stoichiometry for the reaction. For suppose that

$$A \longrightarrow nQ$$

then

$$P_A = (np_0 - P_t)/(n - 1)$$

Suppose a series of total pressures are taken at times t_1, t_2, t_3... and a second set at times $t_1 + \tau$, $t_2 + \tau$, $t_3 + \tau$..., where τ is preferably two or

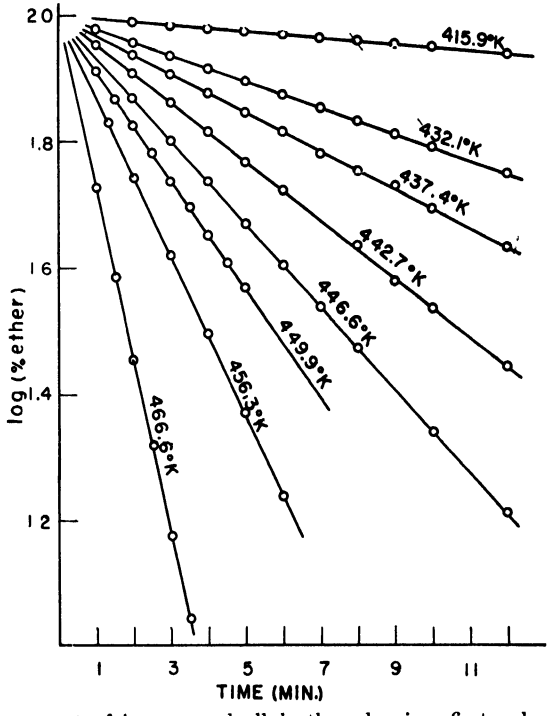


Fig. 7. Rearrangement of isopropenyl allyl ether showing first-order behavior (69).

three half-lives. Then

$$P_A{}^{+}/P_A{}^{\circ} = (np_0 - P_t)/(n - 1)p_0 = \exp(-k_1 t)$$

Also,

$$P_A{}^{t+\tau}/P_A{}^{\circ} = (np_0 - P_t')/(n - 1)p_0 = \exp[-k_1(t + \tau)]$$

where $P_t' = P_{t+\tau}$.
By subtraction

$$P_t' - P_t = p_0(n - 1)\{\exp(-k_1 t) - \exp[-k_1(t + \tau)]\}$$

$$= p_0(n -)\exp(-k_1 t)[1 - \exp(-k_1 \tau)]$$

and 2.303 log $(P_t' - P_t)$ = constant $-k_1 t$. Hence a plot of log $(P_t' - P_t)$ against t will yield a straight line of slope $-k_1/2.303$. It will be noted that n does not appear in the slope. This method has been applied by a number of authors to studies of thermal decompositions (32e,71).

In the case of a reaction of order 1.5,

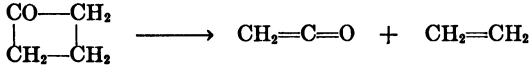
$$k_{1.5} = (2/t)[1/(p_A{}^t)^{1/2} - 1/(p_A{}^0)^{1/2}]$$

and hence a plot of $(p_A{}^t)^{-1/2}$ against t will give a straight line of slope $k_{1.5}/2$. This method has been used in the analysis of the results for the dehydrobromination of *n*-propyl bromide (72). For a reaction of order 2, the corresponding plot is of log $(p_A{}^t/p_B{}^t)$ against t, the slope in this case being equal to $k_2/2.303(p_A{}^0 - p_B{}^0)$. This method has been applied to the second-order reaction between fluorine and iodine pentafluoride (73).

If necessary, a "least-squares" method can be used to devise the best value of k from the experimental results (74).

4. Use of Fractional Times

For a first-order reaction, the time for a given amount of reaction is independent of initial pressures. This may be used to establish reaction order, and has indeed been used by Walters *et al.* in their study of the decomposition of cyclobutanone (75).



Some results are shown in Table II.

TABLE II
Quarter-life Independence of Initial Pressure

p_0, mm.	29.5	15.3	10.3	9.5
$t_{1/4}$, min.	7.0	7.0	6.7	7.1

Another method often used is to show that the ratios $t_{1/2}/t_{1/4}$ or $t_{3/4}/t_{1/2}$ are independent of initial pressures, and have the values 2.41 and 2.00 respectively, as shown in Tables III and IV in the case of the thermal decomposition of *tert*-butyl propionate (76) and *tert*-butyl chloride (77) respectively.

TABLE III
Thermal Decomposition of *tert*-Butyl Propionate at 250°C.

p_0, mm.	18	45	75	90	120
$t_{3/4}/t_{1/2}$	2.08	1.95	2.10	2.02	2.00

TABLE IV
Thermal Decomposition of *tert*-Butyl Chloride at 320°C.

p_0, mm.	133	172	189	194	204	229	353
$t_{1/2}/t_{1/4}$	2.44	2.40	2.43	2.46	2.44	2.42	2.41

For reactions of order other than unity, the fractional-lives become dependent upon initial concentration. Thus in the pyrolysis of diethyl ether, Newitt and Vernon (78) have shown that in the initial pressure range 3–14 atmospheres, $t_{1/2}P_0^{1/2}$ is approximately constant, indicating a reaction of order 1.5. Similarly in his study of the pyrolysis of formaldehyde, Fletcher (79) showed that for initial pressures between 30 and 380 mm., a plot of $(t^1/_2)^{-1}$ against P_0 was linear, pointing to a second-order rate law. The fractional-life ratios may also be used in these cases. The velocity constants may be obtained from the half-lives by means of the following:

$$\text{Order 1: } k_1 = 0.691/t_{1/2} \qquad \text{Order 1.5: } k_{1.5} = 0.828/p_0^{1/2}t_{1/2}$$

$$\text{Order 2: } k_2 = 1/p_0t_{1/2}$$

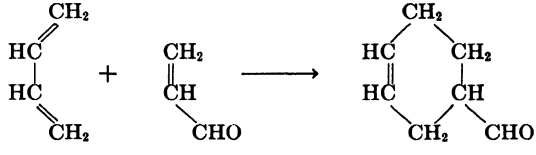
in the cases where only one reactant is involved or where reactants of equal concentration are involved. More general relationships may be derived where necessary.

Chang (80) has described a method, involving fractional lives, for deriving the reaction order and the rate constant from the experimental results.

If the differential rate equation may be written

$$-dP_A/dt = k_nP_A^n$$

then a plot of log (dP_A/dt) against log P_A will give a straight line of slope n. This method has been used by Letort (81) in the case of the pyrolysis of acetaldehyde, where he has shown that for a given run, $n = 2$. The method may also be applied by plotting log $(dP_A/dt)_0$ against log P_A^0 for a range of initial pressures; when this is done for acetaldehyde, n is found to be 1.5 The curves for different temperatures are shown in Figure 8. In their study of the kinetics of the gas phase Diels-Alder reaction



Kistiakowsky and Lacher (82) have used the second-order differential rate equation to calculate the velocity constants. This method has also been employed by Fletcher (79) in his study of the decomposition of formaldehyde and by Vaughan (83a) in the case of the polymerization of 1,3-butadiene.

This method is of great utility in the case where a reaction follows a complex rate equation. Thus for the decomposition of ethylene iodide, Arnold and Kistiakowsky (84) have shown that

$$-d[C_2H_4I_2]/dt = k_1[C_2H_4I_2] + k_{1.5}[C_2H_4I_2][I_2]^{1/2}$$

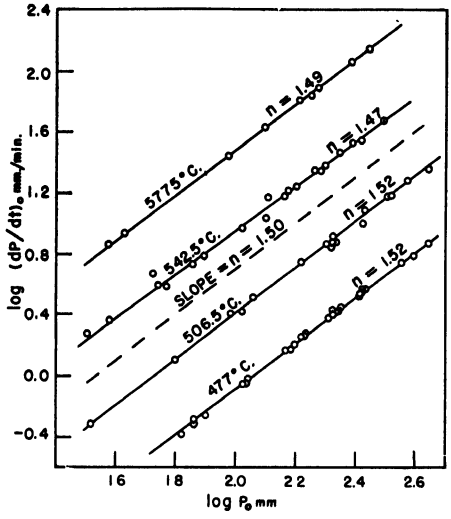


Fig. 8. Thermal decomposition of acetaldehyde (81).

A plot of $[C_2H_4I_2]^{-1}\, d[C_2H_4I_2]/dt$ against $[I_2]^{1/2}$ then gave a straight line of slope $k_{1.5}$ and intercept k_1.

It may happen that, because of side reactions, further reaction of the products or an equilibrium between reactants and products, the rate constant derived by one of the methods previously described, varies throughout the course of the reaction. In such a case it may happen that the reaction is of simple order in its initial stages, and a plot of k against percentage reaction will enable an extrapolation to zero reaction. This method has been used by Schultz and Kistiakowsky (85) in their investigation of the pyrolysis of *tert*-butyl and *tert*-amyl alcohols.

Pasfield and Waring (86) have described a method for analyzing pressure-time curves based upon the expansion of the total pressure as a power series in the time,

$$P_t = a_0 + a_1 t + a_2 t^2 + \ldots$$

If it is assumed that

$$P_0 - P_A = \alpha(P_t - P_0)$$

and that

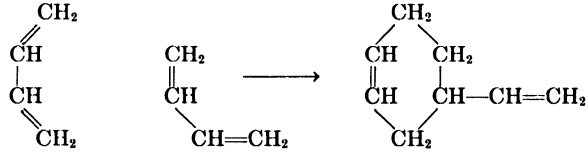
$$dP_t/dt = k_r P_A{}^n$$

then it is shown how α, n, and k_n may be determined from the experimental results.

5. The Flow Method

Flow experiments are usually done under conditions of constant pressure, rather than of constant volume as obtains in static experiments. This gives rise to two additional factors: (*a*) the change in volume during reaction and (*b*) the effect of diffusion. The latter effect will depend upon the relative effects of diffusion and flow and two extreme cases have been discussed; the first is the case of diffusion being negligible, the second when it is so large as to give complete mixing.

In the first case, where diffusion is small compared with the linear velocity, if there is no change in the number of molecules during reaction, the expressions for calculating the rate are the same as for static experiments. The contact time (time of reaction) is calculated by dividing the volume of the reactor by the volume of reactant gases entering the reaction vessel per unit time (at the reaction temperature and pressure). If the reaction involves a change in the number of molecules, then the use of a carrier gas or the keeping of the percentage reaction at a low level will suffice to enable the "no volume change" equation to be used for calculating the rate constant. This approach has been used by Rowley and Steiner (83b) in their investigation of the dimerization of butadiene to form vinylcyclohexene.



The equation used for calculating the rate constants was

$$-\Delta a/\Delta t = k_2(a - \Delta a/2)^2$$

where a is the concentration of butadiene, and Δa is the decrease in concentration during the time of contact Δt.

Where the volume changes during reaction, the time of contact is a function of the extent of reaction. For a first-order reaction of the type

$$\mathrm{A} \longrightarrow \nu\mathrm{Q}$$

the rate constant may be calculated by means of Benton's equation (87),

$$k = (V'/V_R)[\nu \ln 1/(1 - F) - (\nu - 1)F]$$

where V' is the volume of entering gas per second (at the temperature and

pressure of the reactor), V_R is the volume of the reaction space and F is the fraction of A which has reacted. This equation has been employed in analyzing the results of the pyrolysis of methane (88) and of acetic acid (89). In the case of the second-order reaction A + B = νQ, Harris (90) has given for the case $N_A = N_B$

$$k_2 = \frac{V^2}{V_R}\left[\frac{(\nu-2)^2}{N_A{}^2}\left(\frac{N_Q}{\nu}\right) + \frac{N_Q}{N_A(N_A - N_Q/\nu)} + \frac{2\nu\,(\nu-2)}{N_A}\ln\frac{(N_A - N_Q/\nu)}{N_A}\right]$$

where N_A and N_B are the number of moles of A and B entering the reactor per second, and N_C the number of moles of C leaving the reactor per second. Equations for cases other than this have also been derived (91).

Where diffusion is large compared with the linear velocity, that is in the case of complete mixing, Bodenstein and Wolgast (92) have given the following equation for the case of no volume change.

Reaction: A = Q

$$k_1 = (V/V_R)[N_Q/(N_A - N_Q)]$$

Reaction: A + B = 2C ($N_A = N_B$)

$$k_2 = (V^2/V_R)[N_Q/(N_A - {}^1/_2N_Q)^2]$$

Harris has given the equations for both first- and second-order reactions, with and without volume change.

As in the case of the static method, the velocity constant should be shown to be independent of the initial pressures of the reactants, and of the extent of reaction.

Janz and Waite (93) have shown that the rate constant is proportional to the space-time yield, that is the amount of products produced per unit volume per unit time, under those conditions where the conversion is a measure of the initial rate. Application of this idea would enable the relative rates of these reactions to be determined as the ratios of the space-time yields of the respective products.

6. The Arrhenius Equation

Where the velocity constant of a reaction has been investigated as a function of temperature it is usual to report the results in the form of the equation first suggested by Arrhenius, namely

$$k = A \exp(-E/RT) \qquad (1)$$

or

$$\ln k = \ln A - E/RT$$

Thus a plot of log k against T^{-1} yields a straight line of slope $-E/2.303R$ and intercept of log A. The parameter E is the energy of activation, while A is the pre-exponential term. An obvious interpretation of A is that it equals the rate constant at infinite temperature. The Arrhenius equation (1) has been widely used in kinetic studies, and usually good straight lines are obtained for those reactions proceeding by a single mechanism. Modifications to (1) have been suggested. Thus, in the case of bimolecular reactions, the collision theory (see Chapter II) implies a relationship of the form

$$k = BT^{1/2} \exp(-E/RT) \tag{2}$$

and in this case a plot of (log k − $^1/_2$log T) against T^{-1} would yield a straight line. The rate data for the thermal polymerization of isoprene has been treated in this fashion (94). Again, the thermodynamic theory of reaction rates (95) gives the expression

$$k = (kT/h) \exp \Delta S^{\ddagger}/R \exp(-\Delta H^{\ddagger}/RT) \tag{3}$$

where $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ are the entropy and enthalpy of activation. This would suggest the use of an equation of the form

$$k = B'T \exp(-E/RT) \tag{4}$$

which has indeed been used by Brokaw and Pease (96) in their studies of the first-order dissociation of aluminum borohydride. It should be pointed out, however, that in principle both $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ are dependent upon temperature. A further modification of Equation (1) has sometimes been used (97)for unimolecular reactions, based on the Hinshelwood-Lindemann theory (98). It is

$$k = [B''/(n-1)!](E/RT)^{n-1} \exp(-E'/RT) \tag{5}$$

The parameter n is equal to the number of internal degrees of freedom in the molecule involved in the activation process. Equations (2) and (5) would all imply that a plot of log k against T^{-1} should not be strictly linear. However the departure from linearity due to this cause is small, and very careful experimental work over a large temperature range would be required to detect it. This may occur when the methods for studying fast reactions in the gas phase (99) become further developed.

A much more likely cause of curvature in the Arrhenius plot is the incursion at low temperatures of a heterogeneous reaction. Such reactions often have a low A and low E, and so may predominate at the lower end of the temperature range. The case of nitric oxide (100) is illustrated in Figure 9. If this is the correct explanation, then packing the reaction vessel should make the curvation more pronounced. From the slopes of the

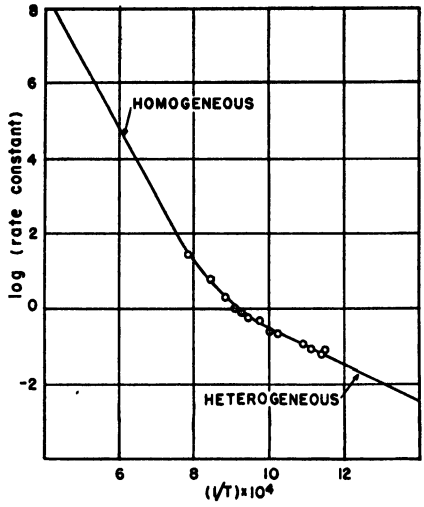


Fig. 9. Thermal decomposition of nitric oxide (100). Circles, experimental values; solid line ($k_1 + k_2$) calculated on the basis of a heterogeneous reaction ($k_1 = 1.4 \times 10^4 \exp(-21{,}400/RT)$) plus a homogeneous reaction ($k_2 = 3.1 \times 10^{15} \exp(-82{,}000/RT)$).

intersecting straight lines shown in Figure 9, the Arrhenius parameters for the homogeneous and heterogeneous reactions may be obtained.

While E may vary over a wide range for different reactions, the pre-exponential term A has well established values for the so-called "normal" reactions of simple mechanism. Thus for unimolecular reaction $A \approx 10^{13}$ sec.$^{-1}$ (however, see Section VI.2). In the case of bimolecular reactions,

$$A = PZ \tag{6}$$

where

$$Z = \sigma_{AB}^2(8\pi RT/M)^{1/2} \tag{7}$$

where P is the steric factor, σ_{AB} the collision diameter, and M the molecular weight. For the case of P equal to unity, A will be of the order of magnitude of 10^{15} cc. mole^{-1} sec.$^{-1}$.

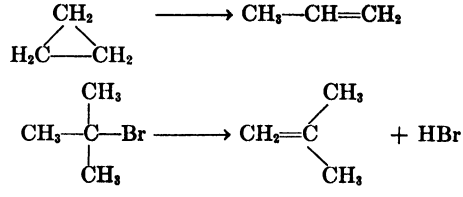
Benson (101) has discussed the effects of temperature gradients in reaction systems upon the Arrhenius parameters. Neglecting convection, it is shown that the average temperature differences between the walls and the reacting gas can be of the order of magnitude of 2°C. or higher, depending upon the conditions. Such a temperature difference could have a significant effect upon the rate constant and the Arrhenius parameters. However, it is not at all clear to what extent convection would tend to offset the effect of conduction.

VI. THE ASSIGNMENT OF A MECHANISM TO A REACTION

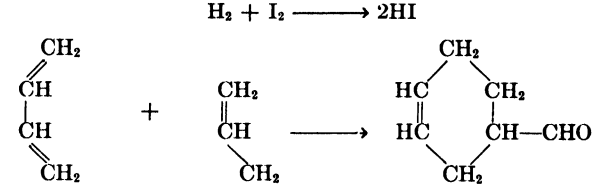
1. General Considerations

It will be assumed that the stoichiometry of the reaction, the reaction order and the variation of the rate constant with temperature have been determined. The next question relates to the mechanism by which the reaction proceeds. The simplest type of mechanism involves only one reaction step:

Unimolecular



Bimolecular



Termolecular

$$I + I + M \longrightarrow I_2 + M$$

$$2NO + O_2 \longrightarrow 2NO_2$$

The molecularity is defined for the gas phase as the number of molecules involved in the transition state of the reaction. Over a wide range of initial conditions, the order of a one-step gas phase reaction will be integral and numerically equal to its molecularity. However as Rice and Herzfeld (102) were the first to show, an integral order does not necessarily imply a one step reaction. These authors showed that radical chain reactions involving a number of individual steps can lead to a simple overall rate equation. Thus consider the following scheme:

$$M_1 \xrightarrow{k_1} R_1 + R_2 \qquad \text{Initiation} \qquad (1)$$

$$R_1 + R_1 \longrightarrow M_2$$

$$R_2 + M_1 \xrightarrow{k_2} M_3 + R_3 \qquad (2)$$

$$R_3 \xrightarrow{k_3} M_4 + R_2 \qquad (3)$$

Propagation

$$R_2 + R_3 \xrightarrow{k_4} \text{end of chain} \quad \text{Termination} \tag{4}$$

If assumption is now made that the concentrations of radicals R_2 and R_3 do not change over the period under consideration, then

$$-d/dt[M_1] = (k_1k_2k_3/2k_4)^{1/2}[M_1]$$

if it is assumed that step (1) makes a negligible contribution to the overall reaction compared with steps (2) and (3). The activation energy is given by

$$E = {}^1/_2(E_1 + E_2 + E_3 - E_4)$$

and the A factor by

$$A = (A_1\, A_2\, A_3/2A_4)^{1/2}$$

Since reactions (1) and (3) are unimolecular, while (2) and (4) are bimolecular, A will be of the order of magnitude to be expected for a unimolecular reaction. Thus a reaction proceeding by the above mechanism could well be mistaken for a single step unimolecular reaction, unless further investigation were made to show the presence of reaction chains. The chain length for such a scheme is given by

$$\begin{aligned}\text{Chain length} &= \text{rate of reaction/rate of initiation} \\ &= (k_1k_2k_3/2k_4)^{1/2}[M]/k_1[M] \\ &= (k_2k_3/2k_1k_4)^{1/2}\end{aligned}$$

Since $E_1 + E_4$ is usually greater than $E_2 + E_3$, the chain length will usually decrease as the temperature is raised.

The order is dependent upon the nature of the initiation and termination steps (1) and (4). Thus Goldfinger, Letort, and Niclause (103) have considered a number of cases and have shown that half integral values of the order from zero to two may be obtained. They distinguished between a β radical which carries the chain without decomposing (R_2) and a μ radical which decomposes (R_3). Initiation may be bimolecular and termination may involve a third body M. The results are shown in Table V. This table may be usefully employed to work out the order pertaining to a given scheme without the necessity of detailed working. It must be borne in mind, however, that the data of Table V are based upon the type of reaction scheme given on page 457. If additional reaction steps are included, the order has to be worked out anew.

Chain reactions can also give rise to complex kinetic equations. Thus in the bromination of R—H (104) the rate equation is given by

$$-d/dt[Br_2] = k[Br_2]^{1/2}[RH]/(1 + k'[HBr]/[Br_2])$$

TABLE V
The Effect of Initiation and Termination upon the Order of a Chain Reaction

	Unimolecular initiation		Bimolecular initiation	
Order	Simple collision term.	Triple collision term.	Simple collision term.	Triple collision term.
2			$\beta\beta$	
1.5	$\beta\beta$		$\beta\mu$	$\beta\beta$(M)
1.0	$\beta\mu$	$\beta\beta$(M)	$\mu\mu$	$\beta\mu$(M)
0.5	$\mu\mu$	$\beta\mu$(M)		$\mu\mu$(M)
0		$\mu\mu$(M)		

If the reaction is homogeneous, a complex rate equation is a reliable indication of a complex mechanism.

It may be that while a reaction proceeds mainly by a chain mechanism, there is also an underlying molecular change. Use of inhibitors may reveal the rate of the molecular process. In the case of the primary aliphatic bromides, the rate constant for chain initiation (breaking of the C—Br bond) is given approximately by

$$k_i \approx 10^{13} \exp(-67{,}000/RT) \text{ sec.}^{-1}$$

whereas the rate constant for unimolecular elimination is

$$k_u \approx 10^{13} \exp(-50{,}000/RT) \text{ sec.}^{-1}$$

This means that chains will only contribute to the overall rate if the chain length is long, and that the unimolecular reaction may be investigated if some means of removing bromine atoms from the system can be devised. This has been done by the use of cyclohexene (105) or toluene (106) as inhibitors.

The overall study of a reaction proceeding by a chain mechanism may lead to the postulation of a scheme of elementary reactions, but such a scheme will merely be plausible and not conclusive. It is for this reason that a great deal of attention in recent years has been focused upon elementary reaction steps, rather than upon overall chain reactions. On the basis of the scheme given on page 457, this will involve a study of initiation reactions (bond dissociation energies), propagation reactions, often hydrogen abstraction by radicals and radical dissociation reactions, and finally termination reactions, radical or atom recombinations. Methods have been devised for investigating all of these types of elementary reactions. Once the rates of the elementary reactions are known these may be inserted in the expression for the overall rate in order to verify the proposed mechanism.

2. Molecular Reactions

A great deal of interest has been shown in recent years in those gas phase processes which occur without the intervention of atoms or radicals. Some examples of such processes have been given in Section VI.1. Investigation of molecular processes may be dealt with at two different levels, which may be described as the physical and the chemical level. In the former, attention is focused upon the process of producing activated molecules; in the latter a series of related molecules is studied in order to see the effect of variations in structure upon the rate of reaction. Both of these aspects will be dealt with in the present section, reactions being classified according to their molecularity.

A. UNIMOLECULAR REACTIONS

The problem as to the manner in which collisions could be responsible for activation and yet the overall rate proportional to the first power of the concentration was considered by Lindemann in 1921 and subsequently developed by Hinshelwood. The essential idea of the Lindemann mechanism is that a time lag exists between activation and reaction, during which the most probable fate of the activated molecule is deactivation. In its simplest form the mechanism can be represented by:

$$A + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A^* + A$$

$$A^* \xrightarrow{k_3} B + C$$

Assuming a stationary concentration of active molecules gives

$$[A^*] = k_1[A]^2/(k_2[A] + k_3)$$

and thus

$$-d/dt[A] = k_3[A^*] = k_1k_3[A]^2/(k_2[A] + k_3)$$

At high pressures, $k_2[A] \gg k_3$ and

$$-d/dt[A] = (k_1k_3/k_2)[A]$$

the reaction being of the first order. On the other hand if the pressure is low and $k_2[A] \ll k_3$

$$-d/dt[A] = k_2[A]^2$$

and the reaction is of the second order. At intermediate pressure

$$k = k_1k_3[A]/(k_2[A] + k_3)$$

and the first-order rate coefficient will decrease as the pressure is lowered.

Also if k is plotted against $[A]^{-1}$ a straight line should result. In this simplest form of the theory the assumption is made that all activated molecules react at the same rate, independent of the energy they possess. This restriction was removed by Rice and Ramsperger (107) and by Kassel (108) and in more recent years by Slater (109). Since nonchemically active gases may also contribute to the activation process, the rate of a unimolecular reaction in the intermediate or low pressure region should be capable of being restored to its high pressure value by the addition of an inert gas. From studies of this effect the relative efficiencies of different added gases may be determined. The above two criteria, namely the fall in the first-order rate constant as the pressure is lowered, and its restoration to the high pressure value in the presence of sufficient inert gas constitute an important verification of the unimolecular character of a first-order gas reaction.

Perhaps the best example of unimolecular behavior is afforded by the isomerization of cyclopropane, which has been studied by a number of workers (110). Thus from 84 to 0.067 mm., Trotman-Dickenson *et al.* (110) have shown that the rate constant falls from 3.15×10^{-4} sec.$^{-1}$ to 3.19×10^{-5} sec.$^{-1}$. In addition added gases have been shown to be effective in maintaining the equilibrium concentration of activated molecules, and the efficiencies of a number of different molecules in this respect have been determined. Finally, Slater (109b) has applied his theory in detail to this decomposition, the agreement with experiment being reasonably good.

Slater (109a) has predicted that only molecules with six or more atoms should show unimolecular rates of decomposition, approaching the limiting high pressure rate at pressures as low as two atmospheres. Goodall and Howlett (111) have reported that trichloroethylene decomposes in part by a unimolecular process, the order of the reaction being 2 at pressures around 50 mm. Similarly in the case of the 1,2-dichloroethylenes the residual reaction at maximal inhibition has been shown to have an order between the first and the second (112). An interesting case from the field of inorganic chemistry is the pyrolysis of nitryl chloride (113), for which at low pressures, the reaction is first order with respect to nitryl chloride in a given run, but the rate constants themselves are first order in initial concentration.

The criteria that are usually accepted for a homogeneous reaction proceeding by a unimolecular mechanism are; (*a*) the reaction follows a first-order law, at least at high pressures; (*b*) the rate of the reaction is independent of the presence of inhibitors such as propene, cyclohexene, toluene, or nitric oxide; (*c*) the absence of induction periods; (*d*) the exclusion of a radical non-chain mechanism on the basis of energy considerations or otherwise. Of these only (*d*) needs further explanation. In considering various possible modes of decomposition of ethyl bromide, Daniels and Veltman (114) considered the possibility of the following scheme

TABLE VI. Arrhenius Parameters for Some Unimolecular Elimination Halides

	log A[a]	E	Ref.	log A[a]	E	Ref.
Alkyl radical						
		Bromides			*Chlorides*	
Ethyl	13 45	53.9	115	14.60	60.8	4,129
	12 86	52.3	105			
n-Propyl	12.90	50.7	105	13.45	55.0	130
	13.00	50.7	106			
n-Butyl	13.18	50.9	105	14.00	57.0	130
n-Pentyl	13.09	50.5	116			
n-Hexyl	13.13	50.5	116			
Isobutyl	13.06	50.4	117	14.02	56.9	131
sec-Propyl	13.62	47.8	12b	13.40	50.5	129
	13.60	47.7	105			
	12.74	47.0	118			
sec-Butyl	12.63	43.8	119	13.75	50.1	132
	13.54	46.5	120			
	13.04	45.5	121			
Cyclopentyl	12.84	43.7	122	13.39	48.1	133
	12.11	41.6	123			
Cyclohexyl	13.51	46.1	124	13.17	50.0	134
tert-Butyl	14 00	42 2	125	12.40	41 4	135
	13.30	40.5	126	13 90	45.0	136
	13.23	41.0	121	13.73	45.0	51
tert-Amyl	13.60	40.5	127	13.82	44 2	51
2-Halogeno-2,3-dimethylbutane	13 54	39.0	128	13.38	42.3	51
		Formates			*Acetates*	
Ethyl	11.33	44 1	137	12.49	47 8	137
sec-Propyl	12.33	44.2	137	13.00	45.0	137
	12.58	44.0	137	13.26	45.9	139
sec-Butyl				13 15	45.7	139
tert-Butyl	11.10	34.6	140	13 34	40.5	76
				13.29	40 4	139
tert-Amyl				13.35	40.1	139
		Propionate			*Benzoate*	
tert-Butyl	12.80	39.2	141			
Menthyl				11.00	38.1	142
		Vinyl Alkyl Ethers				
Ethyl	11.43	43.6	143			
sec-Propyl	12.58	43.6	144			
Molecule						
		Hydrocarbons				
Cyclobutane	15.60	62.5	145			
Ethyl cyclobutane	15.56	62.0	146			
Cyclohexene	13.0	57.5	147			
		Ketones				
Cyclobutanone	14.56	52.0	75			
Methyl cyclobutyl ketone	14.53	54.5	148			

[a] A and E are given in sec.$^{-1}$ and kcal./mole, respectively.

$$C_2H_5Br \longrightarrow C_2H_5 + Br$$

$$Br + C_2H_5Br \longrightarrow HBr + C_2H_4Br$$

$$C_2H_5 + C_2H_4Br \longrightarrow C_2H_4 + C_2H_5Br$$

for which the activation energy would be equal to $D(C_2H_5—Br)$. Since $D(C_2H_5—Br) \approx 65$ kcal./mole and the activation energy ≈ 54 kcal./mole, this scheme can be ruled out. Such a radical non-chain mechanism has however been suggested for the pyrolysis of allyl bromide (12).

The Arrhenius parameters for a number of unimolecular elimination reactions are shown in Table VI.

By the criteria discussed earlier in this section, all the reactions listed are unambiguously unimolecular.

A further class of reactions which are unimolecular includes certain isomerizations. The Arrhenius parameters for some of them are shown in Table VII.

TABLE VII
The Arrhenius Parameters of Some Isomerizations

Reactant	Product	log A	E	Ref.
Cyclopropane	Propene	15.7	65.0	110
Cyclobutene	Butadiene	13 08	32.5	54
cis-2-Butene	*trans*-2-Butene	11.0	52.0	149
Allyl vinyl ether	Allyl acetaldehyde	11.7	30.6	159
Isopropenyl allyl ether	Hex-5-ene-2-one	11.7	29.3	69
trans-Dideuteroethylene	*cis*-Dideuteroethylene	13.0	65	151
trans-Dichloroethylene	*cis*-Dichloroethylene	12.5	61.3	152

The values of the A factors shown above all lie within the range normally associated with unimolecular reactions. The recent study of the rate of isomerization of *cis*-2-butene (149) casts some doubt on the classification of cis-trans isomerizations into those with a "normal" A and high E, and those with a low A and low E (95). For reactions in the latter class, it is possible that the mechanism is not unimolecular.

By considering the rates of pyrolysis of a series of related alkyl halides, it has been suggested that an analogy exists between the gas-phase elimination reaction and the S_N1 or E1 reactions of these compounds in a polar solvent (153). In particular, the technique of substituting such groups as CH_3, $CH_2=CH$, C_6H_5, CH_3O, Cl, or Br at or near the seat of reactions has been used to establish the analogy. The effects of α- and β-methylation are shown in Table VIII. The temperatures have been chosen so that in the α-methylated series, the rate of decomposition of the *iso*-Pr compound is 10^{-4} sec.$^{-1}$ and in the β-methylated series that of the ethyl compound is

10^{-4} sec.$^{-1}$ The evidence for the analogy has been fully presented elsewhere (153).

TABLE VIII
The Effect of α- and β-Methylation upon the Relative Rate of Dehydrohalogenation

At 320°C.	
EtBr	1
iso-PrBr	280
tert-BuBr	78,000
At 361°C.	
EtCl	1
iso-PrCl	223
tert-BuCl	41,000
At 404°C.	
EtBr	1
n-PrBr	3.3
iso-BuBr	5.9
At 457°C.	
EtCl	1
n-PrCl	3.9
iso-BuCl	3.9

In the case of the esters, the trends are the same, but on a somewhat reduced scale. The results of a calculation of the effect of α-methylation on the relative rates are as follows:

At 305°C.	
EtOAc	1
sec-PrOAc	47
tert-BuOAc	4,050

On the basis of this, and other evidence, it has been suggested that the factors which are responsible for substituent effects in the E2 reaction in a polar solvent are also responsible for substituent effects in dehydrocarboxylation in the gas phase (154).

This raises the question as to whether there is not a whole class of gas-phase reactions, for which the effects of structural alterations are best discussed in terms of the theoretical concepts well recognized in the case of heterolytic reactions in polar solvents. It has been suggested that such a class of reactions, as illustrated by the gas-phase olefin eliminations from alkyl halides and from esters, should be called quasiheterolytic (153b). A further interesting reaction which appears to fall into this category is the homogeneous catalysis by hydrogen halides of elimination from alcohols (155).

B. BIMOLECULAR REACTIONS

The most widely investigated bimolecular gas-phase reaction involving organic molecules is the Diels-Alder Reaction. Reactions with butadiene as the common species which have been analyzed kinetically are set out in Table IX.

TABLE IX
The Arrhenius Parameters of Some Diels-Alder Reactions

Dienophile	log A*	E	Ref.
Butadiene	9.96	23.7	156
	11.15	26 8	82b
Acrolein	9 96	19 7	81
Crotonaldehyde	8 95	22.0	157
Ethylene	17.48	27.5	82b
Cyanogen	12 20	31.6	158
Trifluoroacetonitrile	9.32	21 5	158

* In Tables IX and X, A is in cc. mole^{-1} sec.$^{-1}$

It is possible that for this class of reactions, discussion of the effects of polar substituents may be made in terms of the theories used in the discussion of heterolytic reactions in a polar solvent (159).

A further class of somewhat related bimolecular reactions is the dimerization of substituted ethylenes. The results of some investigations are given in Table X. For all these reactions, discussion has been given of the magnitude of the A factors in the Arrhenius equations.

TABLE X
The Arrhenius Parameters for Some Dimerization Reactions

Molecule	log A	E	Ref.
Tetrafluoroethylene	11 22	26 3	160
	8 01	25 4	161
Trifluorochloroethylene	10.54	26 3	160
$C_2F_4 + C_2F_3Cl$	10.93	26.3	160

3. Free Radical Reactions

A. DETECTION OF FREE RADICALS

Reactions with Mirrors. A method that has often been used for the detection and identification of free radicals is the Paneth mirror-removal technique (162). Paneth and his co-workers identified methyl, ethyl, and benzyl radicals in a fast flowing, low pressure, gas stream from the reaction

zone to a mirror of a metal such as lead, antimony, zinc, mercury, or bismuth, which could be removed by the radicals. Removal of the mirror served to detect the radicals; the identification was achieved by examination of the products of mirror-removal.

Rice and his associates (163), by a modification of this technique were able to detect radicals, mainly methyl, in the pyrolyses of a number of types of organic compounds in the temperature range 500–1,000°C. The reaction of the radicals with mercury and the subsequent conversion of the mercury alkyls into mercury alkyl halides, was found to be a useful means of identification. The ethyl radical has been identified in the pyrolysis of propionaldehyde at 850–950°C. (164). Pearson and his collaborators (165) have used mirror methods to demonstrate the existence of propyl and *tert*-butyl radicals in certain photochemical reactions.

Tellurium has also been used as a mirror (166,167). In addition to visual methods of observation, methods involving photoelectric cells (168), radioactivity (169,170,171), electrical conductivity (172), microanalysis (173), and direct weighing (171) have been used for measuring the rate at which mirrors are attacked by free radicals. By measuring the rate of mirror removal at different temperatures, Rice and Johnston (174) were able to determine the activation energies for the dissociation of molecules into free radicals.

In many of the studies for the detection of free radicals by the mirror method in pyrolytic reactions, the temperatures involved have been higher than those usually employed in kinetic experiments. However, Burton, Ricci, and Davis (169) have shown that it is possible by using the radioactive technique to detect free radicals in the thermal decomposition of acetaldehyde in the region of 500°C.

Reactions with Other Substances. Besides metallic mirrors, a number of other substances have been used for the detection of free radicals and atoms. A film containing triphenylmethyl radicals in solution has been used to capture hydrogen atoms or methyl radicals from the gas phase, to form triphenylmethane or 1,1,1-triphenylethane respectively (175). Melville and Robb (176) have devised a method for the determination of hydrogen atoms or alkyl radicals by the use of the color change of molybdenum oxide (from light yellow to blue) produced by the fragments. Szwarc and his co-workers have used extensively the toluene flow technique for the detection and determination of the number of free radicals (see p. 476). Mercury vapor has been found useful for the detection of phenyl and benzyl radicals (177). Iodine vapor (178) has been used extensively for the detection and identification of radicals, particularly in photochemical processes; radioactive iodine has also been employed (179).

A further technique has involved the conversion of *para*-hydrogen to the

normal mixture (~3 ortho:1 para, at temperatures above room temperature). This reaction is accelerated by hydrogen atoms according to

$$H + H_2\,(p) = H_2\,(n) + H$$

in which three-quarters of the *para*-hydrogen is converted into *ortho*-hydrogen. From a knowledge of the rate constant for this reaction and the rate of conversion, the hydrogen atom concentration in the mixture may be determined. If alkyl radicals (R) are present in a mixture containing hydrogen and an organic compound (R'H), the following reaction occurs

$$R + H_2 \longrightarrow RH + H \quad k_1$$

$$H + R'H \longrightarrow H_2 + R' \quad k_2$$

when the concentration of hydrogen atoms is stationary

$$[R] = [H]k_2[R'H]/k_1[H_2]$$

and so if k_1, k_2, [R'H], and [H_2] are known, and if [H] is measured by means of the para-ortho conversion, [R] may be calculated. By this means Patat and Sachsse (180) have found that free radicals are present during the pyrolyses of many organic compounds. However, radical concentrations calculated on the basis of Rice-Herzfeld schemes were many times larger than those calculated by Patat and Sachsse from their experiments. In view of the uncertainties in the rate constants of the elementary reactions, at that time, the disagreement is not surprising. In the case of acetaldehyde, Letort and also von Müffling and Maess (181) have concluded that within the limits of the uncertainties involved, the agreement is satisfactory. Anderson, Davison, and Burton (182) have recalculated the para-ortho hydrogen data with a different activation energy for k_1 and obtained better agreement with the Rice-Herzfeld mechanisms. Now that the rate constants of elementary reactions are becoming more accurately determined, the para-ortho hydrogen method should afford an increasingly useful method for determining radical concentrations.

Mass Spectrometric Methods. This method was first developed by Eltenton (183) and depends upon the fact that the potential required to ionize a radical is smaller than that required to produce the same radical ion from a molecule

$$R + e \longrightarrow R^+ + 2e, \qquad I_z(R)$$

$$RH + e \longrightarrow R^+ + H + 2e, \quad I_z(R) + D(R—H)$$

By the selection of the appropriate electron bombardment energy, the positive ion current of a given mass can be used to give a measure of the concentration of the corresponding free radical. Eltenton designed a very

elegant apparatus for this technique. A diaphragm with a pinhole was used for introducing a sample of the pyrolyzing mixture into the ionization chamber of a mass spectrometer. While the pressure in the pyrolysis tube was ~100 mm., that in the chamber was 10^{-3} mm.; thus very rapid pumping from the latter was necessary. This technique has been further developed by Lossing and his co-workers (184) and by Robertson (185). Thus Lossing and Ingold have described a furnace which can be moved towards and away from the pinhole, so that radicals can be examined at various stages of their history. In one study, the concentration of methyl radicals was found to be smaller and that of ethane greater, the further the furnace was from the pinhole (186). The rate of recombination of methyl radicals could then be determined. An apparatus has also been designed by Lossing *et al.* (187) for dealing with photosensitized decompositions, and in particular in the Hg photosensitized decomposition of acetone, methyl, and acetyl radicals and their dimerization products, ethane and diacetyl have been detected.

The Use of Isotopic Tracers. The decomposition of a substrate in the presence of an indicator (one or the other of the two being deuterated) provides a powerful method of studying elementary reactions. Thus Morris (188) analyzed the products from the decomposition of a mixture of CH_3CHO and CD_3CDO and found with hydroquinone-treated acetaldehyde, only CH_4 and CD_4. He concluded that the decomposition was intramolecular. Untreated acetaldehydes gave CH_2D_2 and other deuterated methanes. On the basis of a Rice-Herzfeld mechanism CD_3H and CH_3D would be expected from the reactions

$$CH_3 + CD_3CDO \longrightarrow CH_3D + CH_3CO$$

$$CD_3 + CH_3CHO \longrightarrow CD_3H + CH_3CO$$

Zemany and Burton (189) found CD_3H as well as CD_4 present in the decomposition products of a mixture of deuteroacetaldehyde and acetaldehyde at 465 and 510°C., and concluded that a free radical mechanism accounts for 75 and 85% of the decomposition at these temperatures. Subsequently, Rice and Varnarin (190) showed that in an equimolar mixture of CH_3CHO–C_2D_6 or CD_3CDO–C_2H_6, the amount of isotopic mixing as given by CH_3D/CH_4 or CD_3H/CD_4 is proportional to the amount of acetaldehyde decomposed. These authors concluded that the pyrolysis of both CH_3CHO and CD_3CDO proceeded by a chain mechanism, confirming the observations of Wall and Moore (191).

These latter authors have also applied the isotopic tracer method to the decomposition of ethane (191), the products from the decomposition of a mixture of C_2H_6 and C_2D_6 being examined. The presence of HD and mixed

methanes in the products was taken to imply the participation of free radicals and atoms in the decompositions. This reaction has also been the object of study by Rice and Varnarin (192) and by Danby, Spall, Stubbs, and Hinshelwood (193). In both the cases of acetaldehyde and ethane, Rice and Varnarin showed that in the presence of NO, inhibition occurred, but that for a given fractional decomposition the ratio CH_3D/CH_4 was independent of the nitric oxide concentration. This would seem to give reasonable proof of the chain nature of the reaction even under conditions of maximal inhibition. The possibility of secondary exchange reactions between CH_4 and CD_4 has to be considered, though the work of Morris (188) and Wall and Moore (191) seems to indicate that the exchange reaction is too slow to affect the results appreciably. The occurrence of exchange reaction between C_2D_6 and C_2H_6 or CH_4 in the presence of nitric oxide is discussed by Danby *et al.* (193) together with their own observation that CH_3D from mixtures of *n*-butane and deuterium is not affected by the pressure of nitric oxide. They conclude that the CH_3D may be formed after the formation of 1-butene, and that exchange reactions do not necessarily imply the participation of radical reactions. Deutero compounds containing a single deuterium atom per molecule have also been used to study the decomposition of butane and of propylene (194). It was concluded that some of the butane remaining after partial pyrolysis was not the original butane, but butane formed from butyl radicals, particularly *n*-butyl radicals. Moore and Wall (191) also examined the pyrolysis of acetone and suggested that the mechanism of this reaction might be largely intramolecular. However, McNesby, Davis, and Gordon (195) repeated and have extended the work and shown the decomposition to be consistent with a Rice-Herzfeld mechanism.

Other Methods. Many other physical methods have been employed to detect and examine the properties of atoms and free radicals. Moseley and Robb (197) developed a diaphragm manometer of high sensitivity and fast response, which they have used to study the stationary state in photoinitiated gas reactions. In the case of acetone, they obtained a rate constant for methyl radical recombination, in good agreement with that of earlier workers.

Modern spectroscopic techniques lend themselves to the study of species of short life, particularly the technique of flash photolysis (198) introduced by Norrish and Porter. Essentially, a high intensity light flash is used to produce a high concentration of radicals, the spectra of which can be measured at short time intervals after the flash. Recently Callomon and Ramsay (199) have described a microsecond flash photolysis apparatus. Flash spectroscopy has also been used to detect radicals in the wake of a shock wave (200).

The shock tube, in which the passage of a shock wave causes rapid adiabatic heating of the gas through which it passes, can also be usefully employed to study atoms and free radicals (201).

B. THE SENSITIZATION OF FREE RADICAL REACTIONS

In a number of investigations, information concerning the possibility of a substance decomposing by a chain mechanism has been obtained by observing whether reaction can be induced or accelerated by the addition of free radicals. The radicals which may be produced either photochemically or thermally, e.g.,

$$(CH_3)_2CO \xrightarrow{h\nu} CH_3 + CH_3CO$$

or

$$(CH_3)_3COOC(CH_3)_3 \longrightarrow 2(CH_3)_3CO$$

followed by

$$(CH_3)_3CO \longrightarrow (CH_3)_2CO + CH_3$$

are usually generated in the presence of a substrate at a temperature at which it is thermally stable. Some of the substances which have been used for the thermal production of sensitizing radicals, together with the temperature ranges within which they have been used are (202): azomethane (245–330°C.), metal alkyls (275–525°C.), ethylene oxide (425–470°C.), and *tert*-butyl peroxide (150–220°C.). In the thermal method, the sensitizer is often added in a relatively small amount and so the occurrence or otherwise of a chain reaction is readily determined. However, the calculation of a chain length in terms of the rate of production of radicals is not always straight forward because of the uncertainty of the rate measurement. The advantage of the photochemical method lies in the fact that a high temperature is not necessary, thus giving the method a wider range of application.

Some of the reactions which have been sensitized markedly by the addition of atoms or free radicals are: the decomposition of dimethyl ether, methyl ethyl ether, diethyl ether, divinyl ether, acetaldehyde, acrolein, acetone, propane, butane, ethyl alcohol, and dioxalane; the polymerization of ethylene and propylene and the hydrogenation of ethylene (203).

Care has to be taken regarding the interpretation of sensitization experiments. If sensitization is observed, it means that the substrate is capable of sustaining chains at the temperature of the experiment and not necessarily that its normal mode of decomposition is a chain one. On the other hand, if the rate of decomposition of a substrate is unaffected by the sensitizer at a given temperature, this only implies that at that temperature the substrate cannot support a chain reaction; at higher temperatures radical decompositions may occur. Thus acetone does not undergo chain decom-

position when methyl radicals are added at 400°C., while at temperatures above 500°C., such a reaction is possible (204). There is also the possibility that if a source of free radicals is used which decomposes at a temperature much lower than that to be investigated, by the time the substrate has been raised to the reaction temperature, all the radicals will have been produced and destroyed.

The ability of a decomposing substance to sensitize another reaction has often been taken as an indication that atoms or free radicals are present during the decomposition of the substance. Thus diethyl ether (205), ethyl bromide (206), vinylethyl ether (207), and ethylene oxide (208) accelerate the decomposition of acetaldehyde.

C. THE INHIBITION OF FREE RADICAL REACTIONS

If a reaction is proceeded by an atom or a free radical chain mechanism, and some substances can be added which will remove the atoms or radicals, then the reaction rate will either be that of the initiation step, or will be that of an underlying molecular process. Such substances are nitric oxide (209), propylene (210), toluene (38,39,106), and cyclohexene (105). Small quantities of nitric oxide (0.01–1%) have been found to inhibit markedly many decompositions (209) as well as polymerizations (211,212). If the nitric oxide is present in large amounts it may accelerate the decomposition (209,213). In studies of inhibition by nitric oxide, it has been found convenient to express the amount of inhibition by the ratio of the initial rate of decomposition of the substrate to the slowest initial rate observed in the presence of inhibitor ($\rho_{\infty 2}$, maximal inhibition). The values of ρ_0/ρ_∞ have been called the mean chain length by Hinshelwood and his collaborators, on the assumption that nitric oxide completely suppresses the chains. Nitric oxide inhibition has been used by these workers (214) in the case of the pyrolyses of a number of straight and branched chain hydrocarbons, to isolate and study the decomposition at maximal inhibition. The identification of these residual reactions with molecular processes is doubtful in view of the results of the experiments with isotopically labelled species (192,193) described on page 468. In support of this, Steacie and Folkins (215) have shown that nitric oxide does not stop all the chains in the ethylene oxide sensitized decomposition of *n*-butane. These authors conclude that in the case of *n*-butane the residual reaction involves short chains of the same type as occur in the uninhibited reaction. Inhibition by nitric oxide certainly indicates a chain mechanism, even though the nature of the residual reaction at maximal inhibition remains in doubt.

The nature of the inhibition step has been investigated in a number of

instances. According to Taylor and Bender (216) the reaction with methyl radicals is

$$CH_3 + NO \longrightarrow CH_3NO \longrightarrow CH_2{=}NOH$$

formaldoxime being the final product. This view receives some support from the work of Chilton and Gowenlock (217) who showed that in the case of isopropyl radicals the primary products are 2-nitro-isopropane and acetone oxime. In the study of the reactions of methyl radicals from di-*tert*-butyl peroxide (218) with nitric oxide, a product has been isolated and identified as formaldoxime. The kinetics of the reaction have also been investigated (219) and collision yields of 1.5×10^{-4} at 25°C., 3.9×10^{-4} at 480°C., and 3.4×10^{-4} at 900°C. reported. Further, Hinshelwood *et al.* (219) have suggested that the steric factor for the combination of a methyl radical with nitric oxide is about 7×10^{-5} that for the association of two methyl radicals to form ethane. These values would suggest that the activation energy for the reaction is small.

It has also been suggested that the inhibition observed at low concentrations and the acceleration at higher concentrations may be due to an equilibrium of the type (220–222)

$$CH_3NO \rightleftharpoons CH_3 + NO$$

the dissociation of the nitrosomethane feeding back methyl radicals to the system. This has however, been shown to be untenable (223) though it is possible that some such equilibrium does occur (223).

Propylene has been widely used as an inhibitor of chain reactions, its efficiency being ascribed (210) to its susceptibility to attack by an alkyl radical and to the stability of the allyl radical formed.

$$R + CH_3CH{=}CH_2 \longrightarrow RH + CH_2\overset{\frown}{\text{—}}CH\overset{\frown}{\text{—}}CH_2$$

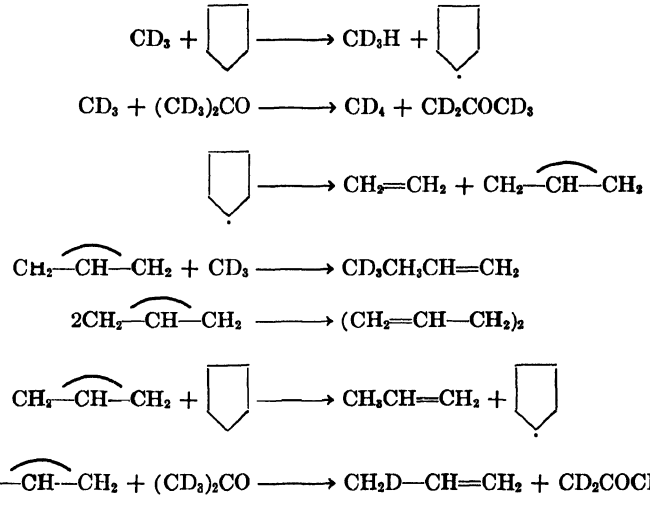
However, its efficiency is much less than that of nitric oxide, relatively large amounts being required to bring about maximal inhibition. However, it has been found effective in inhibiting the pyrolyses of certain compounds (210,224) containing acetyl groups, such as acetaldehyde and acetone (210,224) for which compounds nitric oxide does not appear to be very efficient (224–227). Because of the large amounts of propylene required to give maximal inhibition, care must be taken in following the reaction by pressure change. Although good agreement has been obtained in a number of instances (224,226) between total pressure change and chemical analysis, the latter is probably to be recommended (228).

Other olefinic inhibitors have been used. These usually contain at least one α-methyl group attached to the double bond (229), although ethylene has been reported as being effective in inhibiting the decompositions of

diethyl ether and ethane (230), but ineffective in the case of butane (220) and acetaldehyde (231). Toluene has been widely used for inhibiting chain decompositions, both for investigating the initiation step of a chain reaction (see p. 476) and for isolating a molecular process underlying a chain decomposition (106,143).

Hinshelwood (232,224) and his co-workers have used the dependence of the rate of a reaction upon the inhibitor : substrate ratio as a means of identifying some of the elementary reactions in the chain mechanism.

Light has recently been thrown on the nature of propylene inhibition by Gordon and his associates (233). These authors photolyzed $(CD_3)_2CO$ in the presence of cyclopentane and accounted for their results by the following scheme:



At 381°C. the propylene:ethylene ratio is small, the ratio increasing at 453°C. By 500°C. the ratio is near unity. This implies that allyl radicals can abstract hydrogen with some facility at temperatures around 500°C., although the specific rate is less than that of the analogous process with methyl radicals.

In the case of some pyrolyses, propylene has been reported as increasing the rate of decomposition (234).

D. OTHER FACTORS INFLUENCING THE RATES OF RADICAL REACTIONS

Although this chapter is primarily concerned with homogeneous gas phase reactions, it is of value to consider briefly the effect of the vessel walls, and the effect of added inert gases upon the rates of chain reactions.

If the reaction rate is increased by increasing the surface/volume ratio, it may be that the initial step occurs on the walls of the vessel, propagation and termination occurring by homogeneous processes. If, on the other hand, the rate is decreased, it may be that initiation and propagation occur homogeneously while termination occurs on the walls. On the other hand, if the rate of reaction is independent of surface/volume ratio, it may be that both initiation and termination occur at the walls (235) rather than the reaction taking place entirely in the gas phase. Changing the nature of the wall surface may afford a means of differentiating between these two possibilities (236).

Many studies of gas reactions have included investigations of the effect of added inert gases, such as helium, hydrogen, nitrogen, and carbon dioxide. The ability of an inert gas to maintain the Maxwell-Boltzmann distribution of activated molecules has been discussed on page 461. Other possible functions of an inert gas include (*a*) acting as a third body in atom or radical recombination; (*b*) participation in some bi- or trimolecular process in a chain reaction; (*c*) hindering the diffusion of atoms or radicals to or from the walls; and (*d*) altering the character of the active surface of the walls. In addition there is always the possibility, from an experimental standpoint, of the inert gas reacting with the substrate or containing impurities which may accelerate or inhibit the reaction.

Thus, in the case of acetaldehyde, hydrogen and carbon dioxide (237) have been found to decrease the rate, in contrast to the observations of earlier workers. It was suggested that this was due to traces of oxygen in the inert gases. The inhibition observed was taken to confirm the chain nature of the acetaldehyde decomposition (237). In the thermal decomposition of ethylene oxide the decrease in rate observed on the addition of an inert gas has been attributed to an increase in the number of chain ending triple collisions (238). A similar effect has been reported for the decomposition of divinyl ether with added nitrogen (239). Waring and Spector (240) have used the fact that while propylene reduces the rate of decomposition of methyl ethyl ketone, nitrogen does not, to show that propylene acts by removing radicals.

An effect of type (*c*) would be expected to show itself in those cases where chain initiation starts on the walls and terminates in the gas phase or vice versa. In the former case, the added gas would probably inhibit the reaction, in the latter accelerate it. Increasing surface/volume ratio would have the opposite effect.

It may happen that the rate of a reaction is almost immeasurably slow at the start, or that the rate increases with time during the initial stages and attains a maximum value at some later time; the reaction is then said to possess an induction period. This period may be only a few

seconds or it may last for hours. The existence of a real induction period, as distinct from an effect caused by the apparatus or the experimental technique, provides evidence that the reaction is not a simple one-step process. Induction periods can arise from (*a*) slow attainment of the steady state radical concentrations (241), (*b*) autocatalysis by an intermediate or final product (234,242), or (*c*) initial inhibition by an impurity which is removed as the reaction proceeds. Induction periods in the dehydrochlorination of 1,2-dichloroethane are shown in Figure 10 (4).

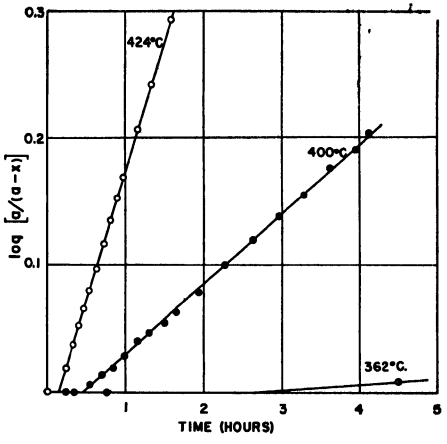


Fig. 10. Induction period in the dehydrochlorination of 1,2-dichloroethane: *a*, initial concentration; *x*, concentration reacted (4).

Induction periods may appear if the rate of reaction is determined by the appearance of the final products rather than the disappearance of the reactants in the case of some consecutive reaction (228, 243). This may also be the cause if the decomposition is followed by total pressure measurements and there are simultaneous pressure increasing and pressure decreasing processes (244).

Semenov (245) has discussed a number of thermal decompositions exhibiting induction periods.

E. THE INVESTIGATION OF ELEMENTARY REACTIONS

Initiation. The initiation step of a chain reaction will involve bond ruptures to form a pair of atoms, an atom and a radical or a pair of radicals. Examples of such process are

$$Br_2 + M \longrightarrow 2Br + M$$

$$CH_3Br \longrightarrow CH_3 + Br$$

$$CH_3CHO \longrightarrow CH_3 + CHO$$

$$(CH_3)_2CO \longrightarrow CH_3 + CH_3CO$$

$$\{(CH_3)_3CO\}_2 \longrightarrow 2(CH_3)_3CO \longrightarrow 2(CH_3)_2CO + 2CH_3$$

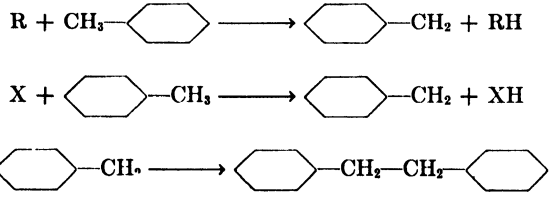
The heat of reaction for these processes is known as the bond dissociation energy, $D(A - B)$. Thus measurements of bond dissociation energies in recent years have led to an increasing knowledge of the rate of initiation reactions. Methods that have been used for measuring bond dissociation energies include (*a*) pyrolysis, (*b*) toluene carrier techniques, (*c*) photobromination, and (*d*) mass spectrometry.

The pyrolysis method (246) was used by Polanyi and his co-workers (247) to study the bond dissociation energies in a series of alkyl iodides. The assumption was made that the initial step is

$$RI \longrightarrow R + I$$

but the results were in some cases difficult to interpret because of the production of hydrogen iodide (248). The flow method that was used with low pressures and short contact times minimized the subsequent reactions of stable products, but could have no effect upon the secondary reactions of the free radicals produced. Szwarc modified the flow method by using toluene (38,39) as a carrier gas, which effectively removed any free radicals produced, by the following scheme

$$RX \longrightarrow R + X$$



Thus for each molecule of RX that decomposes, one molecule each of RH, XH, and bibenzyl are produced. This method has been extensively applied (249). Steacie and co-workers (250) have re-investigated the pyrolysis of toluene and have shown the reaction to be more complex than it was at first thought. However, this is not thought to invalidate the general applicability of the toluene flow method. Szwarc and Taylor (251) have discussed critically the applicability of the toluene flow technique and conclude that for pyrolyses that involve methyl radicals, the method will give reliable results provided the methyl radical concentration is not very high. Results are also claimed to be reliable if a large radical which splits

into a stable molecule and a smaller radical is formed in the initial step, the stable product being used to follow the reaction. Some of the values of bond dissociation energies obtained in this way are shown in Table XI.

TABLE XI
Bond Energies from Pyrolyses

Molecule	Bond dissociation energy, kcal./mole	Ref.
$CH_2{=}CH{-}CH_2{-}H$	77	252
$C_6H_5CH_2{-}H$	77.5	38
$CH_2Cl{-}Br$	61.0	249
$C_6H_5{-}CH_2{-}Br$	50 5	39
$CH_3{-}CO{-}CH_3$	72	251
$\{(CH_3)_3CO\}_2$	37	253

For a more extensive list of bond dissociation energies see References 196 and 246.

In the photobromination method (104), the following scheme applies:

$$Br_2 \xrightarrow{h\nu} 2Br \quad (1)$$

$$Br + RH \longrightarrow HBr + R \quad (2)$$

$$R + Br_2 \longrightarrow RBr + Br \quad (3)$$

$$R + HBr \longrightarrow RH + Br \quad (4)$$

$$Br + Br + M \longrightarrow Br_2 + M \quad (5)$$

leading to the kinetic equation given in the introduction to this section. Reaction (2) is the slow, rate-determining stage, and so the observed activation energy may be equated to E_2. The heat of reaction for (2) is $E_2 - E_4$; E_4 is estimated to be 1.5 and E_2 is 17.8 kcal./mole in the case of methane, hence $E_2 - E_4$ is 16.3 kcal./mole. Adding this to the heat of dissociation of hydrogen bromide (85.8 kcal./mole) gives D (CH_3—H) as 102 kcal./mole.

By measuring the appearance potentials of ions from hydrocarbon molecules in a mass-spectrometer, Stevenson (254) has obtained a number of values of D (R—H), from which by thermochemical arguments, D (R—X) may be obtained. The appearance potential measures the energy of the process

$$RH \longrightarrow R^+ + H + e$$

and if the radical ionization potential, that is the energy of the process

$$R \longrightarrow R^+ + e$$

is known, D (R—H) may be calculated. A number of bond dissociation energies have been obtained by this method (255).

Propagation. Two important propagation steps in a free radical mechanism are the attack of a radical on a substrate molecule

$$R + R'H \longrightarrow RH + R' \qquad (1)$$

and the breakdown of a radical to form a stable molecule and an atom or radical

$$R' \longrightarrow M + R \qquad (2)$$

where M represents the molecule. Hydrogen abstraction reactions have been very widely investigated. The metathetical reaction (1) has been extensively investigated, using both thermal and photochemical sources of radicals. Of these two, the latter is the more usual, since the rate of production of radicals can be more readily controlled. The method depends upon the following scheme, in the case of methyl radicals produced in the photolysis of acetone (256).

$$CH_3 + CH_3 \longrightarrow C_2H_6 \qquad (3)$$

$$CH_3 + CH_3COCH_3 \longrightarrow CH_4 + CH_2COCH_3 \qquad (4)$$

Now the rate of production of ethane and of methane are given by

$$R_{C_2H_6} = k_3[CH_3]^2 \qquad R_{CH_4} = k_4[CH_3]\,[CH_3COCH_3]$$

and so

$$R_{CH_4}/R_{C_2H_6}^{1/2} = k_4/k_3^{1/2}\,[CH_3COCH_3]$$

Hence if the rates of formation of methane and ethane are known, $k_4/k_3^{1/2}$ may be determined, and hence $E_4 - {}^1/_2E_3$ and $A_4/A_3^{1/2}$, if the temperature variation is studied. If now acetone and another hydrogen containing compound are photolyzed, the reaction

$$CH_3 + RH \longrightarrow CH_4 + R \qquad (5)$$

will also occur. In this case

$$R_{CH_4}/R_{C_2H_6} = (k_4/k_3^{1/2})\,[CH_3COCH_3] + (k_5/k_2^{1/2})\,[RH]$$

and so $E_5 - {}^1/_2E_3$ and $A_5/A_3^{1/2}$ may be determined. The vital investigation of k_3 and hence E_3 and A_3 will be discussed in the next section.

An alternative procedure is to use a fully deuterated acetone as a radical

source, in which case (3) and (4) and (5) become replaced by

$$CD_3 + CD_3 \longrightarrow C_2D_6 \qquad (3')$$

$$CD_3 + CD_3COCD_3 \longrightarrow CD_4 + CD_2COCD_3 \qquad (4')$$

$$CD_3 + RH \longrightarrow CD_3H + R \qquad (5')$$

and

$$k_5'/k_4' = (R_{CD_3H}/R_{CD_4})/[CD_3COCD_3]/[RH]$$

The ratio of the rates is readily determined by mass spectrometry and hence k_5'/k_4'. Thus if k_4' is known, k_5' may be determined. Also the ratio k_5/k_5' may be obtained from other experiments and hence k_5 can be calculated. In these methods, a knowledge of the absolute rates of (3) or (4') is a prerequisite for the measurement of the absolute rates of other hydrogen abstraction reactions. The measurement of the absolute rate of (3) is discussed in the next section. Some recent values of $E_4 - {}^1/_2E_3$ and $A_4/A_3^{1/2}$ are given in Table XII. Trotman-Dickenson (262) has tabulated values of the rate constant at 182°C., E and A, the latter calculated on the basis of $E_3 = 0$, $A_3 = 4.5 \times 10^{13}$ cc. moles^{-1} sec.$^{-1}$. For more extended tables and discussions, reference should be made to Steacie (196).

TABLE XII
The Arrhenius Parameters for Some Metathetical Reactions

Radical	Molecule	$E_4 - {}^1/_2E_3$, kcal./mole	$A_4/A_3^{1/2}$, (cc. mole^{-1} sec.$^{-1}$)$^{1/2}$	Ref.
CH_3	H_2	10.2	—	257
CH_3	D_2	11.9	—	258
CH_3	D_2	12.1 ± 0.6	13 9 × 10^4	259
CH_3	$(CH_3)_2CO$	9.8 ± 0.4	8 5 × 10^4	259
CD_3	$(CD_3)_2CO$	11.2 ± 0.3	—	260
CF_3	D_2	9.7	5 8 × 10^4	261
CF_3	H_2	8 8	8 4 × 10^4	261

One of the simplest propagation steps involving the breakdown of a radical to yield a stable molecule and an atom or radical is

$$C_2H_5 \longrightarrow C_2H_4 + H \qquad (6)$$

which was postulated by Rice and Herzfeld (102) as occurring in the pyrolysis of ethane. These authors assigned an activation energy of 49 kcal./mole to this reaction. Since the reaction is endothermic, a lower limit for the activation energy may be obtained if the heat of formation of the ethyl radical is known (263). This leads to $E_6 \approx 38$ kcal./mole. By-

water and Steacie (264) investigated the mercury photosensitized decomposition of ethane at high temperatures, and with certain assumptions obtained a value of 39.5 kcal./mole for E_6.

Termination. Two possible modes of chain ending are by combination or disproportionation, e.g.,

$$R_1 + R_2 \longrightarrow R_1R_2 \tag{7}$$

$$R_1 + R_2 \longrightarrow O + P \tag{8}$$

where O and P represent an olefin and a paraffin respectively. The importance of a knowledge of the rate of (7) has already been stressed in the last section. The difficulty inherent in the investigation of reaction (7) lies in the determination of the concentration of methyl radicals. Two methods have been used, the first employing a rotating sector photolytic technique, the second depending upon a comparison of the rate of methyl radical recombination and the rate of another process involving methyl radicals.

In the photolysis experiments the rate of production of radicals is known, and the lifetime can be obtained by the use of intermittent light (265). Hence the radical concentration and the rate of recombination. Gomer and Kistiakowsky (266) used this method and were able to show that recombination occurred at about every collision. Kistiakowsky and Roberts (267) extended this work and found a decrease in the rate constant with decreasing pressure, indicating that the second-order recombination moved over towards the third order at low pressures. The form of the pressure dependence, which sets in at about 10 mm. acetone (the source of methyl radicals) pressure was in agreement with the predictions of the theory of third-body stabilization. More recently Shepp (268) has given a new analysis of the rotating sector technique and applied this to the results of the earlier work. Trideuteromethyl (267), trifluoromethyl (269), and *n*-propyl (270) radical recombination have also been investigated. The results obtained for the rate of methyl radical recombination are shown in Table XIII.

Marcus and Steacie (271) compared the rate of reaction (7) with that of reaction (9) the rate of (9) being known from an investigation by the Paneth

$$CH_3 + NO \longrightarrow \text{products} \tag{9}$$

method (see Section VI.A.). They concluded that the collision efficiency of (7) was $\sim 5 \times 10^{-3}$. However, using the more accurate value of k_9, the collision efficiency comes out to be ~ 0.6 (Steacie, Ref. 196). Later work by Durham and Steacie (219) gives the collision efficiency as 0.01. Mass spectrometric measurements by Ingold and Lossing (272) indicate that the reac-

TABLE XIII
The Rates of Recombination of Methyl Radicals

Method	Temp., °C.	$10^{13}k$, cc. mole^{-1} sec.$^{-1}$	Ref.
Photolysis $(CH_3)_2CO$	125	4 5	266
	175	4.2	266
Photolysis $(CH_3)_2Hg$	175	4 6	266
	220	6 7	266
Photolysis $(CH_3)_2CO$, $(CD_3)_2CO$	105	3 7	267
Photolysis (recalculation)	125–175	2:2	268
Mass Spectrometric	850–975	0.51	184,186
Mass Spectrometric	160	1.3	186
Diaphragm Manometer	25	3.8	197

tion has a negative temperature coefficient. Within the limitations of experimental error, and in view of the temperature and pressure dependence of the rate constant for reaction (7), it may reasonably be concluded that methyl radicals combine on every collision. For reactions between methyl radicals and oxygen, Ingold and Bryce (273) have suggested a steric factor of 10^{-3} to 10^{-4}.

For radicals larger than methyl, disproportionation becomes a possible chain ending step,

$$C_2H_5 + C_2H_5 = C_2H_4 + C_2H_6 \qquad (10)$$

Using a rotating sector technique, Irvin and Steacie (274) showed that assuming a zero activation energy for Equation (11)

$$C_2H_5 + C_2H_5 = C_4H_{10} \qquad (11)$$

$E_{10} = 0.8$ kcal./mole, $A_{10} = 1.65 \times 10^{13}$ and $A_{11} = 1.57 \times 10^{13}$ cc. mole^{-1} sec.$^{-1}$, corresponding to a collision efficiency of the order of 0.1. Bradley, Melville, and Robb (275) have studied the collision efficiency of these reactions at room temperature by allowing them to compete with the destruction of the ethyl radicals on a molybdenum oxide surface. The collision efficiency was found to be 0.15 ± 0.03, in good agreement with the result of Irvin and Steacie (274). Later work by Brinton and Steacie (276) gave $k_{10}/k_{11} = 0.12$, close to the value 0.15 selected by Smith *et al.* (277) as the best estimate from the results of a number of investigations. Shepp and Kutschke (278) have estimated E_{11} to be 2 ± 1 kcal. by the rotating sector technique. For *n*-propyl and *sec*-butyl radicals values of the ratios of the rate constants for disproportionation to those for recombination of 0.125 (270) and 1.67 (279) have been reported. For the former radical, a value of 0.6 has also been obtained (280).

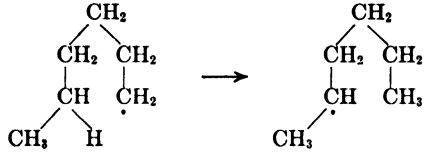
In the case of the reaction between methyl and ethyl radicals a recombination rate constant of $4.2 \pm 0.5 \times 10^{13}$ cc. mole^{-1} sec.$^{-1}$ and a ratio of the rate constant for disproportionation to that for recombination of 0.06 have been reported (281).

Other Reactions of Radicals. A further possibility of reaction for the larger alkyl radicals is a decomposition into an olefin and a smaller radical. Thus in the case of primary and secondary *n*-butyl radicals it has been shown (282) that hydrogen atoms cannot rearrange in the butyl free radicals and that the main decompositions are as follows:

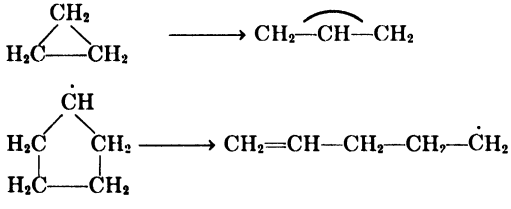
$$CH_3—CH—CH_2—CH_3 \longrightarrow CH_3—CH=CH_2 + CH_3$$

$$CH_2—CH_2—CH_2—CH_3 \longrightarrow CH_2=CH_2 + C_2H_5$$

However, such rearrangements have been postulated for a number of free radicals such as (283):



In the case of the thermal dissociation of the higher hydrocarbons, the products predicted on the basis of free radical chain mechanisms involving isomerizations of free radicals analogous to the one shown above are in better agreement with those observed than are the products predicted on a scheme without isomerization (283,284). An isomerization has also been suggested in the case of cyclic radicals, such as cyclopropyl and cyclopentyl (285),



in order to explain the reactions of deuteromethyl radicals with the parent hydrocarbons.

Skeleton-breaking reactions of the types

$$CH_3 + CH_3CH_2CH_2CH_3 \longrightarrow CH_3CH_2CH_3 + C_2H_5$$

$$CH_3 + CH_3CHO \longrightarrow C_2H_6 + CHO$$

$$CH_3 + CH_3OC_2H_5 \longrightarrow CH_3OCH_3 + C_2H_5$$

have been regarded as less important than hydrogen abstraction reactions on both experimental (286) and theoretical grounds (287). However the reaction

$$CH_3 + CH_3COCOCH_3 \longrightarrow CH_3COCH_3 + CH_3CO$$

has been reported in the photolysis of biacetyl (288).

Reactions that may have to be taken account of in a chain mechanism are the addition of alkyl radicals to unsaturated molecules. Mandelcorn and Steacie (289) have given the activation energies of the addition of methyl radicals to ethylene, propylene, acetylene, and butadiene as 7.0, 6.0, 5.5, and 2.5 kcal./mole respectively, the P factors being of the order of 10^{-4}. Such reactions have been observed by Gordon *et al.* in their investigation of the reactions of deuteromethyl radicals with the butenes (282). To account for the production of light methanes, the authors postulate the following reaction scheme

$$CD_3 + CH_2{=}CHCH_2CH_3 \longrightarrow CD_3\dot{C}H_2CHCH_2CH_3$$

$$CD_3CH_2\dot{C}HCH_2CH_3 \longrightarrow CD_3CH_2CH{=}CH_2 + CH_3$$

the methyl radical abstracting either hydrogen or deuterium to give CH_4 or CH_3D.

F. THE OVERALL REACTION KINETICS PREDICTED FROM A KNOWLEDGE OF THE ELEMENTARY REACTIONS

As an illustration of the way in which a knowledge of the elementary reactions involved may be used to predict the overall rate constant of a chain reaction, the case of acetaldehyde will be considered. The experimental evidence and a discussion of the possible modes of decomposition have been given by Niclause (290). The salient features of the decomposition are as follows:

1. The products of the homogeneous reaction are methane and carbon monoxide in approximately equimolar amounts (291,292).
2. The order of reaction is 1.5 with respect to initial concentration (292).
3. The activation energy is 46–48 kcal./mole (292,293).
4. Free radicals have been detected in the pyrolysis above 740°C. (174) and at 500°C. (169); also, the para-ortho hydrogen technique has demonstrated the existence of radicals in the reaction mixture (180). Further, acetaldehyde and its deutero analog have been used as sources of free radicals (294).
5. The pyrolysis is inhibited by propylene (210,224).

6. The chain decomposition can be induced by the addition of free radicals (293,295,296).

7. The pyrolysis is similar to the photolysis, for which a high quantum yield has been reported (297).

8. Mixed methanes have been reported in the pyrolysis of mixtures of CD_3CHO and CH_3CHO (189,191).

Most of these observations can best be interpreted on the basis of the mechanism proposed by Rice and Herzfeld (102).

$$CH_3CHO \longrightarrow CH_3 + HCO \quad (1)$$

$$HCO \longrightarrow H + CO \quad (2)$$

$$H + CH_3CHO \longrightarrow H_2 + CH_3CO \quad (3)$$

$$CH_3 + CH_3CHO \longrightarrow CH_4 + CH_3CO \quad (4)$$

$$CH_3CO \longrightarrow CH_3 + CO \quad (5)$$

$$CH_3 + CH_3 \longrightarrow C_2H_6 \quad (6)$$

Making the usual assumptions, namely that the concentrations of radicals are stationary yields

$$-d\,[CH_3CHO]/dt = k_4\,(k_1/k_6)^{1/2}\,[CH_3CHO]^{3/2}$$

assuming also that the chains are long. On this scheme the reaction follows kinetics of order 1.5 and

$$k_{1.5} = k_4(k_1/k_6)^{1/2} \qquad E = E_4 + {}^1/_2\,(E_1 - E_6)$$

and $A = A_4\,(A_1/A_6)^{1/2}$. Thus to predict the rate of the overall reaction, the absolute rates of reactions (1), (4), and (6) need to be known. For reaction (1), Rice and Johnston (174) have given a value of 96.4 kcal./mole, while Grahame (298) has derived a value of 75 ± 2 kcal./mole, a value obtained by combining the results of the photolysis and pyrolysis of acetaldehyde. From a study of the pyrolysis of acetone by the toluene flow technique, Szwarc and Taylor (299) have obtained the heat of formation of the acetyl radical, namely −10.8 kcal./mole. In conjunction with the data of Roberts and Skinner (300) this yields a value of 81 kcal./mole for $D(CH_3—CHO)$. As the value of A for the acetone decomposition is 2.4×10^{14} sec.$^{-1}$, the value for acetaldehyde will be taken as 10^{14} sec.$^{-1}$.

Reaction (4) has been the object of study by many workers. Of them, the value obtained by Dodd (301), will be taken as representing a value somewhere in the middle of the published range. This gives E_4 as 8 kcal./

mole and A as $6.3 \times 10^{10}\, T^{1/2}$ cc. mole^{-1} sec.$^{-1}$. For reaction (6), E_6 will be taken as zero, and $A_6 = 4 \times 10^{13}$ cc. mole^{-1} sec.$^{-1}$.

From these values

$$E = 8 + {}^1/_2\,(81 - 0) = 48.5$$

and

$$A = 6.3 \times 10^{10}\,[10^{14}/(4 \times 10^{13})]^{1/2}\, T^{1/2} = 10^{11}\, T^{1/2}$$

and so at 800°K., $A = 2.8 \times 10^{12}$ cc.$^{1/2}$ mole$^{-1/2}$ sec.$^{-1}$ Thus the calculating value of the rate constant is

$$k_{1.5} = 2.8 \times 10^{12} \exp\,(-48{,}500/RT) \text{ cc.}^{1/2} \text{ mole}^{-1/2} \text{ sec.}^{-1}$$

which is to be compared with the experimental value of

$$k_{1.5} = 4 \times 10^{12} \exp\,(-48{,}000/RT) \text{ cc.}^{1/2} \text{ mole}^{-1/2} \text{ sec.}^{-1}$$

as given by Niclause for the temperature range 700–900°K. The agreement is reasonable, in view of the uncertainties in the elementary rate constants. This gives some idea of the way in which overall rate constants for a complex chain mechanism can be calculated from a knowledge of those of the elementary reactions which participate.

The sensitized experiments can also be interpreted in terms of the replacement of step (1) by

$$CH_3COCOCH_3 \longrightarrow 2CH_3CO \tag{7}$$

$$\{(CH_3)_3CO\}_2 \longrightarrow 2(CH_3)_3CO \tag{8}$$

$$CH_3N_2CH_3 \longrightarrow CH_3N_2 + CH_3 \tag{9}$$

respectively. The rate equation found in these cases is

$$-d[CH_3CHO]/dt = k_{1.5}[S]^{1/2}[CH_3CHO]$$

the overall activation energies and frequency factors being shown in Table XIV.

TABLE XIV
The Arrhenius Parameters of Some Stimulated Acetaldehyde Decompositions

Stimulant	$10^{12}A$, cc.$^{1/2}$ mole$^{-1/2}$ sec.$^{-1}$	E, kcal./mole	Ref.
—	4 0	48 0	290
Azomethane	0.18	39 4	302
Biacetyl	5.3×10^3	51 5	293
tert-Butyl peroxide	1.3	26 0	293

It will be seen that the activation energies lie roughly in the order of ease of bond breaking in the initial step.

A recent study by Hinshelwood *et al.* (303) of the pyrolysis of acetaldehyde in the presence of nitric oxide, suggests in opposition to the view advanced by Niclause, that there may be a molecular mechanism underlying the chain decomposition of acetaldehyde, the rate of which can be approached by studying propylene inhibition.

In conclusion, it may be emphasized as indeed it was in the introduction, that current emphasis in the field of gas phase reactions is upon the investigation of simple one stage reactions, be they molecular or elementary reactions involving atoms or radicals. For it is by a more detailed investigation of these reactions that it will eventually become possible to give a more complete account of the more complex processes in the decomposition of many organic molecules.

APPENDIX

Sources of Information Concerning Apparatus and Methods Useful in Gaseous Kinetics

Subject	Page references				
	Weissberger[a]	Farkas-Melville[b]	Reilly-Rae[c]	Drucker, Ostwald-Luther[d]	Sanderson[e]
Reaction vessels		266–278		158–159	
Vapor thermostats	Egly, Vol. III, 42–43			121–125	
Molten baths	Egly, Vol. III, 74–75	133–134			
Electric furnaces	Egly, Vol. III, 56–61	127–129		148–158	
Temperature measurement	Sturtevant, Vol. I, Pt. I, 1–27; Egly, Vol. III, 25–30	103–126	Vol. I, 359–389	698–716	
Temperature control	Sturtevant, Vol. I, Pt. I, 29–48	130–132			
Stopcock lubricants		67–68		258–259	9–12
Greaseless valves		62–65			63
Manometers and gages	Thomson, Vol. I, Pt. I, 143–170	82–87	Vol. I, 559–572	195–216	
Vacuum pumps	Hecker, Vol. IV, 563–586	42–60	Vol. I, 237–265; Burrows, Vol. III, 457–476		30–42
Flow technique	Komarewsky and Riesz, Vol. II, 24–29	102, 300–307			
Gas analysis		174–201 279–288	Vol. II, 25–37: Vol. III, 493–514		
Low-temperature baths	Egly, Vol. III, 87	135–140			48–56
Low-temperature distillation of gases	Rose and Rose, Vol. IV, 389–461				89–93

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CHAPTER XI

KINETICS IN SOLUTION
Principle and Practice

B. KATHLEEN MORSE

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INTRODUCTION

In this chapter the importance of kinetic studies in the determination of the mechanism of organic reaction in solution is discussed from the experimentalist's point of view. The author has attempted to take into consideration the two major limiting factors that ultimately decide the value of any scientific study—the limit of precision and accuracy with which a phenomenon is observed and the investigator's ability to perceive and interpret the phenomenon.

In a branch of science which hovers between empiricism and law and whose direction is an ever-closer approach to the microscopic detail of the molecular model, the experimentalist must take into account the applicable laws and molecular theories, as well as the grosser physical aspects of the kinetic problem, in order to design critical experiments. Therefore the molecular theories derived from statistical considerations have been emphasized.

In the examples chosen to illustrate various specific techniques applicable to the study of kinetics in solution, the attempt has been made to choose those with a uniformity of effort in laboratory technique, mathematical analysis of the data, and thermodynamic and extrathermodynamic (molecular) interpretation. The subject matter covered in most cases includes the principle and assumptions upon which the method is based, the apparatus required, the type of measurement and calibration, the limits of accuracy and precision, the range of reactions to which the method has been applied, and one or two examples cited in detail with the interrelation of kinetic and nonkinetic data. References throughout may act as keys to the periodical literature; recent references have been included to breach any gap.

It is hoped that this form of presentation will be useful to the experimentalist. The chapter may be of value in the teaching of theoretical organic chemistry where students can easily lose sight of the fact that the material they are learning was once contested experimental evidence.

I. MECHANISMS FROM KINETIC STUDIES

1. The Problem of the Mechanism of a Reaction

The mechanism of a reaction is a description on a molecular scale of the transformation of the reactants into the products. Organic chemistry is one of the precise natural sciences from the point of view that thousands of chemical reactions are known; given quantities of reactants A and B always yield under certain environmental conditions a quantity of isolable products, C and D. Each of the entities, A, B, C, and D, to which names and symbols are assigned, possesses identifiable properties described by physical measurement. The transformation of A and B into C and D is possible in a given environment by the repetition of a description of a skill. When the question arises of how this transformation occurs, one is immediately in the realm of molecular theories, the product of human imagination, arrived at inductively from the facts of observation. The success of such theories, measured by the diversity and number of specific cases described, is therefore dependent upon the fineness of experimental detail and imagination. A model that fulfills the response to a particular measurement is imagined. As the type of measurement is made more exacting revisions are made in the model. From the quantitative study of experiments of the static type, centering about equilibria, stoichiometry, side reactions, and dependence upon structure, a great deal may be learned about the requirements of the reaction which permit the reaction to be envisioned on a molecular scale. The rate of the reaction, however, is one of the quantitative measurements with the desired molecular scale.

2. Kinetics as a Solution to the Mechanism Problem

The measurement of the kinetics of the reaction provides the quantitative criterion of the exactness of the model. A mechanism inferred from static experiments must satisfy the mathematical conditions of kinetic studies in order to be valid. Kinetic studies as a criterion may, however, be carried out at various levels of exactitude depending upon the theory employed. The evolution of the theories of reaction rate from the first concepts of rate as a part of an equilibrium through the concepts of equilibria via an activated complex, the transition state, and the collision theory to the statistical treatment by the theory of absolute reaction rates, is easily traced (1). Since the experimentalist's aim has progressed so far beyond the tangible, full cognizance must be taken of the current theories and their implications. The mechanism or theory of an organic reaction cannot be divorced from the theory of the rate which is used as a quantitative criterion. For in-

stance, the interpretation of rate measurements solely as the description of the activated complex neglects the fact that the rate is a measure of the difference between two states. A great many of the problems in the formulation of a mechanism are not those of describing the makeup of the activated complex, but those of describing the state of the dissolved reactant.

3. The Kinetic Problem

The measurement of the rate of a reaction is an involved technique, depending equally upon the chemical techniques (synthesis, purification, and analysis), time-concentration measurements by either chemical or instrumental methods, and their mathematical analysis. The interpretation of these data to formulate a mechanism depends upon the use of thermodynamic and extrathermodynamic theories, and upon ingenuity. The validity of the interpretation is no greater than that of the assumptions made in any of these categories. The application of the chemical techniques is straightforward. The type of time-concentration measurement chosen often precludes some thermodynamic assumption which is often ignored, e.g., that a partial molar quantity is constant throughout the measurement. The assumptions in connection with the actual measurements of rates are examined in Sections IX.1–7 on the specific techniques. The application of various theories with rigorous detail is of interest at this point.

The theory by which the actual rate measurements are interpreted should influence the design of the experiments. It would appear from a survey of the literature that the transition-state theory, particularly as embodied in the Bronsted-Bjerrum equation, is used exclusively in the interpretation of results and the devising of mechanisms; the theory of absolute reaction rates is used in the calculation of the theromodynamic energy functions and in the interpretation of the temperature coefficient of the reaction. The thermodynamic requirements of the transition-state theory are loosely defined; the interpretation of the temperature coefficient of a reaction by this theory is nebulous. The extrathermodynamic theory of absolute reaction rates, which also embodies the concepts of equilibrium and the activated complex, makes these thermodynamic requirements abundantly clear—even for work in solution. These requirements are discussed in detail in Sections IV–VIII. The theory of absolute reaction rates has not as yet had a rigorous application or an honest test in solution. The author has been able to demonstrate that the strict thermodynamic translation of this theory to dilute solution, along with other results of statistical mechanics, makes possible a general rate-environment correlation and criterion of mechanism, for which experimental verification exists in the

literature to the extent that some data approach the thermodynamic requirements quite closely.

II. Preliminary Experimental Assessment of the Kinetic Problem

There are a number of experimental aspects of a kinetic problem to be considered at the outset. Let us assume that one is interested in a reaction,

$$X + Z \longrightarrow P_1 + P_2 \qquad (1)$$

which was reported to give a high yield of P_1 in solvent S after 24 hours at the reflux temperature of the solvent.

1. The Stoichiometry

A. THE MAIN REACTION

The first preliminary work should be conducted on the stoichiometry of the reaction under the conditions of complete reaction. The number of moles of Z required to react with X must be determined as well as the amount and the nature of the products formed. This can be achieved by careful isolation and weighing of unreacted starting materials and of the products. In some cases where one of the products or the reactants is an acid or a base, as in an alkyl halide solvolysis or an ester hydrolysis, the whole solution may be treated by volumetric analysis; then the remaining product of the reaction may be isolated by the more arduous procedures for weighing. The accuracy required should be the same as that for the analytical method used in the rate determination, i.e., about 1% or better, if possible. Perhaps for more complex reactions this is an ideal that cannot be attained. The statement may be qualified to this extent: the critical measurement, the one relating the two reactants (if measuring a rate of disappearance of a reactant), or the one relating the loss of a reactant to the appearance of a product (if following a rate of formation), must be determined within the smallest tolerance and becomes one of the limiting factors in the rate constant to be determined.

B. SIDE OR COMPETITIVE REACTIONS

It is essential to know the extent to which the reaction of interest is accompanied by side reactions so that their effect upon the stoichiometry of the main reaction may be taken into account. The origin of these reactions is also of importance; they may be secondary reactions of the reagents, individually or in unison, possibly through the same activated complex, or they may arise from a decomposition of a primary product. The

source of these reactions may most simply be established by a process of elimination. Empirically the stability of the products or the reactants, singly, may be determined by heating under the specified experimental conditions (solvent, temperature, pressure) for ten half-lives. In this way lack of interference or the extent of by-product formation may be established. In the same vein the products formed must neither react with the reactants nor decrease their effective concentration by complex formation. If this is not the case then the situation must be remedied by sufficient preliminary quantitative work in order to permit corrective calculations to be made, or must be eliminated by an alternative choice of reagents or concentrations.

2. Solvent

For the hypothetical reaction the choice of solvent depends upon the nature of the reaction, the extent of the inquiry into its mechanism, the temperature, and the analytical method. In temperature ranges between 15 and 100°C. there are ample data on aqueous and nonaqueous solvent systems, such as the aliphatic acids, alcohols, ketones, ethers, and various aromatic and aliphatic hydrocarbons or halocarbons. For work below 0 and above 100°C. one is almost limited to chloroform, carbon tetrachloride, and petroleum ethers, on the one hand, and to high molecular weight hydrocarbons or perhaloaliphatics on the other. In general the choice of a solvent, whether it is polar or nonpolar, should be based upon the following criteria: a wide workable range between its boiling and freezing points, good solubility characteristics for both the reactants and the products, compatibility with the analytical procedure, stability in the temperature range being used (between the reaction temperature and the quenching temperature), and availability in a high degree of purity with easy reproducibility. For these reasons the alcohols, water, ethers, esters, ketones, aliphatic and aromatic hydrocarbons, and aliphatic acids are excellent solvents if one is fortunate enough to be working in the 25 to 70°C. temperature range.

The theoretical aspects of ideal solute behavior in a nonideal solvent are discussed in detail in Sections III.5 and IV; theoretical aspects of the effect of the solvent as environment, in Sections VII and VIII. For specific examples of solvent effect, the reader is referred to the above sections.

3. Limits of Precision and Accuracy

A. THE PYRAMIDING ERROR

The consideration of errors is a valuable aid in the planning of experimental work so that the exactness of measurement may be commensurate

with the experimentalist's goal. The estimate must be made in the light of the dependence of a rate constant or energy of activation upon the measurements of concentration, time, and temperature, at constant pressure. In the hypothetical reaction let us assume that the reaction has been established as being first order in both X and Z, and that Z has been related to X so that the extent of the reaction can be measured by the analysis for X. One would then apply the following equation for the calculation of the rate constant, k, in a bimolecular reaction in which the initial concentrations of X and Z were equal.

$$(1/\mathrm{X}) - (1/\mathrm{X}_0) = kt \tag{2}$$

The parameter, k, may be considered a function of the variables, X and t, in order to use the differential of the function to approximate the error in k due to small errors in the observation of X and t. The equation

$$dk = (\partial k/\partial \mathrm{X})d\mathrm{X} + (\partial k/\partial t)dt$$

in which $\partial k/\partial \mathrm{X} = -1/t\mathrm{X}^2$ and $\partial k/\partial t = [(1/\mathrm{X}) - (1/\mathrm{X}_0)](-1/t^2)$ may be easily transformed to Equation (3). This expression

$$dk/k = [1/(1 - \mathrm{X}/\mathrm{X}_0)](d\mathrm{X}/\mathrm{X}) - dt/t \tag{3}$$

indicates that an error of 1% in X is propagated by the factor $\mathrm{X}_0/(\mathrm{X}_0 - \mathrm{X})$, and the error in t, by unity. The error in k at 30% completion of the reaction due to a 1% error in the concentration would be 3.3%; at 10% completion a 1% error in X would give a rate constant uncertain by 10%.

If the hypothetical reaction were a rapid one with $k = 5.5 \times 10^{-4}$ moles/liter/second, a 30 second error in the time would make k uncertain by 0.17% at the time of half-reaction; at 10% completion the error in k would be 1.5%. A 30 second error in time is rather large, since one can usually reduce a sampling technique to an uncertainty of 10 seconds.

A guide to the influence of small temperature fluctuations upon the rate constant may be similarly obtained from the Arrhenius equation:

$$dk/k = (E^{\ddagger}/RT)(dT/T) \tag{4}$$

For a reaction conducted at 27°C. with an $E^{\ddagger}$ of the order of 30 kcal./mole, a 1° temperature fluctuation affects the rate constant by 16%.

The integrated Arrhenius equation may be used for the consideration of the effect of errors in k and T upon $E^{\ddagger}$. By differentiating the logarithmic form of

$$E^{\ddagger} = [RT_1T_2/(T_2 - T_1)] \ln (k_2/k_1)$$

the following expression may be obtained

$$d \ln E^{\ddagger} = (1/\ln K)(dK/K) - (dT_2 - dT_1)/(T_2 - T_1) + d \ln T_2 + d \ln T_1$$

in which $K = k_2/k_1$. If the absolute errors in the temperature observation are alike in magnitude and sign, the second term to the right of the equal sign vanishes; the equation then reduces to

$$d \ln E^{\ddagger} = (1/\ln K)(dK/K) + d \ln T_2 + d \ln T_1 \qquad (5)$$

For illustration, if the thermostat temperatures were accurate to 0.3° at 27 and 37°C., and the ratio of the rate constants were approximately 2, the 0.1% error in the temperature measurements makes the energy of activation uncertain by 0.2%. An error in the ratio of the rate constants of 4% within a 10° temperature range is propagated by a factor of 1.44; the energy of activation would be uncertain by 6%. The danger inherent in the evaluation of an energy of activation over a mere 10° temperature range has been pointed out by Taft *et al.* (2).

The dependence of $\Delta H^{\ddagger}$, $\Delta F^{\ddagger}$, and $\Delta S^{\ddagger}$, thermodynamic values of greater theoretical interest than the empirical $E^{\ddagger}$, upon the measured $E^{\ddagger}$, k (assumed to be a thermodynamic k for these purposes), and T in the following relationships,

$$k = (kT/h) \exp(-\Delta F^{\ddagger}/RT)$$
$$\Delta F^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$
$$\Delta H^{\ddagger} = E^{\ddagger} - RT \text{ (no expansion work)}$$

permits the coefficients of propagation of errors to be evaluated as before.

$$\begin{aligned} d(\Delta F^{\ddagger}) &= (\Delta F^{\ddagger} + RT)\, d \ln T - RT\, d \ln k \\ d(\Delta H^{\ddagger}) &= dE^{\ddagger} - RdT \\ d(\Delta S^{\ddagger}) &= (1/T)d(\Delta H^{\ddagger}) - (1/T)d(\Delta F^{\ddagger}) \end{aligned} \qquad (6)$$

Therefore, a relative error of 5% in the measurement of the rate constant at $T = 300$°C. gives an absolute error of 30 cal./mole in $\Delta F^{\ddagger}$. An error of 6% in $E^{\ddagger}$ (for an $E^{\ddagger} = 30$ kcal./mole) or an absolute error of 1,800 cal. makes $\Delta H^{\ddagger}$ uncertain by the same amount. An entropy of activation, $\Delta S^{\ddagger}$, based upon a $\Delta H^{\ddagger}$ and $\Delta F^{\ddagger}$ uncertain by 1,800 and 30 cal., respectively, at 300°C. is uncertain by 5.9 e.u.

The foregoing is a simple device to show the interdependence of the calculated parameters and the measured variables. The accumulative nature of the errors is a factor to be reckoned with in the planning of experiments. An error of as little as 1% can make k uncertain by 5% and $\Delta S^{\ddagger}$ uncertain by 5 e.u.

B. THE MINIMIZATION OF ERRORS: THE MATHEMATICAL ANALYSIS

Two methods of mathematical analysis of kinetic data are very convenient to use. Both are algebraic in origin.

The Method of Guggenheim (3). This method, which requires that concentration determinations be made at equal time intervals, prevents the overemphasis of the initial concentration at zero time in the calculations, as would be the case if the data were used in the integrated form of a rate equation between the zero time and each subsequent concentration-time value. This method has been of value particularly in the determination of the rate constant from calorimetric measurements (Section IX.4.A) where initial and final values of the temperature readings (equivalent to concentration or the progress of the reaction) are not reliable.

The Method of Least Squares. The method of least squares is fundamentally an algebraic method of calculation of the parameters (in this case the slope and intercept for linear, nonvertical relationship of two variables) by the solution of n simultaneous equations for n pairs of values of the measured variables such that the calculated parameters represent the best fit of the data through the minimization of the square of the differences (measured vertically) between the points and the line. The rigorous statistical interpretation of this treatment depends upon a knowledge of the frequency functions of the variables.

In application to kinetic data the problem is the determination of two types of linear regression lines. The first is dependent upon the measurements of time and concentration (the regression of the concentration function on time), and the second upon the rate constant and the temperature. From the first set of data, pairs of values of concentration as the logarithm or reciprocal, etc., y, and of time, t, and from the second set, of the rate constants and the reciprocal of the absolute temperature, estimates of the regression coefficients, the rate constant and the Arrhenius activation energy (actually containing a constant, $R = 2.303$, etc.), respectively, may be obtained. From the normal equations of the least squares method, the variance (equal to the square of the standard deviation) of the function of the concentration, y, may be estimated. The variance of the regression coefficient, which is the rate constant in the first instance, may be estimated only if one has a knowledge of the distribution (frequency functions) of the y's (4).

The usual practice, based upon the assumption that indeterminate errors possess a normal (Gaussian) distribution (5) seems to be an evasion of the problem. In measurements of temperature or heights of columns of liquid the error is probably uniformly distributed. The measurement to a degree of accuracy brought about by rounding off is usually considered to give rise to the rectangular (or uniform) distribution in which the true value lies within an interval and the error in measurement is uniformly distributed within that interval. A rigorous mathematical treatment of kinetic data should take into consideration the distributions of the measurements for

the determination of the variance of the calculated parameters. In the case of the evaluation of energy parameters it would be of value to be able to determine the confidence limits of these estimates with respect to a theoretical true parameter. This too is impossible without a knowledge of the distribution function of the y's.

4. The Measurement of the Extent of a Reaction

A. GENERAL REQUIREMENTS

The methods employed for determining the extent of a reaction will of course, along with the solvent-system used, be determined by the reaction being studied. The method may be based upon chemical analysis or upon a combination of physical and chemical measurements. Because of the uniqueness of individual chemical systems for kinetic studies, only some of the general minimum requirements may be set forth.

Accuracy: the Primary Standard. Both chemical and physical methods depend upon a primary standardization or calibration against a known substance. The standard should give reliable values in response to whatever analytical technique is employed, whether it is the calibration of a melting point block, a standardization with benzoic acid, or the establishing of a graph of optical densities. Data relative to a nonreproducible value are quite meaningless. The same criteria of chemical purity should also apply to the solutes and solvent of the kinetic determination.

Precision. The method chosen should be as precise as possible for maximum accuracy. A concentration determination (or the equivalent physical measurement) good to 1% gives a rate constant uncertain to 3–10% in the initial phase of the reaction up to 30% completion. Since this is the thermodynamically important stage of the reaction (see Section IV) for the establishment of a mechanism, a greater precision than 1% would be advantageous. The measurement of time then becomes more important also, and should be made with commensurate precision.

Quenching the Reaction. For methods of noncontinuous analysis which require removal of a sample from a reaction mixture, quenching is important. This is most easily accomplished by decreasing the temperature (if the temperature coefficient of the reaction is large), by dilution of the sample, or by chemical removal of a reactant.

Ease. The method should be both rapid and simple. For reactions followed on the calorimetric or spectrophotometric principle set up for automatic recording, the great burden of the mechanics of the kinetic determination is removed from the investigator. For other methods it is well to keep the intricacies of a chemical analysis or manipulations of in-

strument reading at a minimum, so that the operations may be made rapidly.

B. CHEMICAL AND PHYSICAL METHODS

The common techniques of chemical analysis—volumetric, gravimetric, and spectrophotometric procedures, for systems in which a reactant or product possesses a reactive functional group—are always applicable. These methods are also essential in establishing the accuracy and precision of a physical method of measuring the extent of a reaction. These methods have not been discussed in detail.

The physical properties of the solutes or of the reaction itself, which may be utilized for the determination of the extent of a reaction are: density by volume measurements (Section IX.5); light absorption (Section IX.3.C); the heat evolved or absorbed (Section IX.4); the conductivity, etc., of ionic solution (Section IX.3.A); the evolution or absorption of gases (Section IX.7); or the optical rotation (Section IX.3.B). A number of the methods based upon these properties impose the requirement of ideal solute behavior in addition to the general kinetic requirement of ideality. These specific details are discussed in the respective parts of Section IX indicated above.

III. THE THEORY OF ABSOLUTE REACTION RATES IN DILUTE SOLUTION

1. The Statistical Theory and Its Postulates

The theory of reaction rates which holds the greatest interest, both quantitatively and qualitatively, for the organic chemist is the theory of absolute reaction rates (6) incorporating the concept of the activated complex or transition state. It is well to review it briefly to keep in mind the scope of its application to reactions occurring in solution. The theory applies to those reactions possessing an activation energy and for which diffusion is not a rate-determining step. The theory is based upon the concept of the activated complex whose formation coincides with the top of the energy barrier in the minimum energy reaction path of continuous change from the initial to final states as described on a potential energy surface for a reaction. It was postulated that the activated complex, which was shown to have the thermodynamic properties of a normal molecule with the exception of having one less degree of vibrational freedom, was in equilibrium with the initial reactants at all times. This postulate made possible a statistical treatment in which the net rate of reaction was determined by

the average velocity at which the complexes traversed the barrier. The rate of a reaction could then be expressed in terms of a thermodynamic equilibrium constant for the activation process,

$$k = \kappa(kT/h)K^{\ddagger} \tag{7}$$

in which κ was the transmission coefficient which allowed for the possibility of the activated complex returning to the initial state and $K^{\ddagger}$ was expressed in terms of concentration for substances which behaved ideally. For reactions in the gaseous phase where the equilibrium constant, $^{c}K^{\ddagger}$, expressed in terms of partition functions per unit volume may be calculated from spectroscopic data, the success of the theory in predicting the rate of reaction has been extraordinary.

2. Thermodynamic Statements of the Theory: the Differential Equations

The ideality of the solution must be considered in application of the equation to reactions in the liquid phase. Difficulties are encountered in correlating the results of a molecular theory with changes in a medium which is characterized by observation of its macro properties.

A. IN IDEAL SOLUTION

An ideal solution by classical thermodynamics is one in which all components obey Raoult's law over the entire composition range at all temperatures and pressures and whose vapors may be treated as perfect gases. The state is postulated from the observation of the limiting laws of real solutions. For such a solution the chemical potential or partial molar free energy of a constituent at a given temperature and pressure is a function of the mole fraction of the constituent, and the thermodynamic equilibrium constant, K_x, in terms of mole fractions, is a function of temperature and pressure only (7). It is only in *dilute* ideal solution that a thermodynamic equilibrium constant, dependent only upon the temperature and pressure, may be defined in terms of the molarity or molality. The rate of the reaction, $XY + Z \rightarrow P$, is given by Equation (8), for any ideal solution in which the concentrations and $K^{\ddagger}$ are expressed in mole fractions and for any *dilute* ideal solution in which they are expressed in molarities or molalities.

$$dP/dt = k_{obs}(XY)(Z) = \kappa(kT/h)K^{\ddagger}(XY)(Z) \tag{8}$$

B. IN NON-IDEAL SOLUTION

In real solutions the concept of relative fugacity or activity is employed to define the partial molar free energy (chemical potential) of the constit-

uents in solution. The thermodynamic equilibrium constant of activation, $K_0^{\ddagger}$, for a *dilute*, real solution is defined in terms of the activities of the reactants, a_i, of the activated complex, $a^{\ddagger}$, and of any other products formed in the transition state, a_j, and in terms of molalities and activity coefficients of the respective species by Equation (9).

$$K_0^{\ddagger} = a^{\ddagger}\Pi a_j/\Pi a_i = (m^{\ddagger}\Pi m_j/\Pi m_i)(\gamma^{\ddagger}\Pi\gamma_j/\Pi\gamma_i) \qquad (9)$$
$$= K^{\ddagger}(\gamma^{\ddagger}\Pi\gamma_j/\Pi\gamma_i)$$

The symbol for the activity coefficients, γ, is used in the sense that it is a practical coefficient based upon molality, which will be the only concentration term used henceforward for convenience. The activity coefficients need not be defined so that their value is unity when the solute behaves ideally, although this definition gives the most convenient form. The standard states and the values of the corresponding coefficients will be discussed in a following section. There is no dilution requirement on Equation (9) if the concentration unit, activity coefficient, etc., is expressed in mole fraction.

Substitution of the value of the equilibrium constant in terms of concentration, $K^{\ddagger}$, of Equation (9) into Equation (8) gives the general form of the rate of reaction in terms of molalities.

$$dm_p/dt = \kappa(\boldsymbol{kT/h})\ K_0^{\ddagger}(\Pi\gamma_i/\gamma^{\ddagger}\Pi\gamma_j)(m_{xy})(m_z) \qquad (10)$$

In this equation $\kappa(\boldsymbol{kT/h})K_0^{\ddagger}$ may be represented by k_0 to give the general expression for a non-ideal, *dilute* solution in terms of molal concentrations.

$$dm_p/dt = k_0(\Pi\gamma_i/\gamma^{\ddagger}\Pi\gamma_j)(m_{xy})(m_z) \qquad (11)$$

The k_0 may be considered to be the specific rate constant in the hypothetical standard state where XY, Z, and the activated complex behave ideally. This derivation of Equation (11) for dilute solution has been made with the reservation that, because of the complexity of organic reactions, the comparison of the rate of reaction in solution with that of a real reaction in the gaseous phase through activity coefficients defined in concentrated solution (in terms of mole fractions) is extremely limited.

3. The Transmission Coefficient

The constancy of the transmission coefficient, κ, has been assumed for the reaction in the standard and in the actual solution in Equation (11). This assumption does not appear to be serious for isolated cases but is serious for the comparison of rates and energy values in homologous series, in which one is interested in only the more subtle variations of the structure on the rate as measured by differences in the energy values within the series.

Variations in structure may well affect the potential energy surface and the transmission coefficient. For a full discussion of the transmission coefficient and reactions for which it may be assumed to be unity the reader is referred to the texts of Laidler (8a) and Glasstone, Laidler, and Eyring (8b).

4. Activity Coefficients and the Standard State

Equation (11) is not the familiar form of the rate equation; it has been presented in this fashion to emphasize the need for consideration of the solution's approach to the postulated state of ideality. The activity coefficient is a function of concentration as well as of temperature and pressure. The differential equation, (11), may be considered an exact thermodynamic statement of the theoretical treatment in contrast to the empirical approach, without the activity coefficient factor.

A. THE LIMITING LAW OF THE SOLUTE IN DILUTE SOLUTION

The importance of the experimental solution's approach to ideality may be most easily illustrated by consideration of a solution of a volatile nonelectrolyte whose vapor pressure is sufficiently low so that the solute in the gaseous phase may be treated as a perfect gas. If the partial pressure, equal to the fugacity, f, of the solute were plotted as a function of the molal concentration of the solute in solution, only in the dilute concentration range would the fugacity be a linear function of the molality, m.

$$f = lm \tag{12}$$

Outside this limiting concentration range the fugacity is a more complicated function of the molality, $f = g(m)$, which would need to be described mathematically in several parameters (9). There is, of course, in the graph of a binary system of fugacity versus mole fraction of the solute, another linear range, corresponding to Raoult's law in the vicinity of the pure (liquid) solute. The limiting law of the concentrated solution, Raoult's, is of interest primarily in the consideration of a direct comparison of a rate in solution to that of a real reaction occurring in the gaseous phase, and is not of concern here. The limiting law of the dilute solution for a nonelectrolyte is equivalent to Henry's law.

B. THE ACTIVITY COEFFICIENT AS A FUNCTION OF CONCENTRATION

The activity of the solute is defined as the relative fugacity, $a = f/f^0$. The customary standard state chosen to define f^0 is the hypothetical solution of one molal concentration, obeying the limiting law corresponding to Henry's law. The fugacity in the standard state, f^0, is therefore numerically equal to the value of the limiting-law constant, l, for the system.

The activity of the solute at any concentration m is equal to its fugacity at m divided by l, $a = g(m)/l$. At this molality the activity coefficient, $\gamma = a/m$, would be

$$\gamma = g(m)/lm \tag{13}$$

It is apparent that as the concentration decreases the activity coefficient approaches a constant value determined by the approach to the region where the fugacity is linearly related to the molality, neglecting for the present the fact that the loss of the constituent occurs through a reaction and that product formation affects the partial molar free energy of the reacting solute. In this concentration range of adherence to Equation (12), $g(m)$ is replaced by lm in Equation (13), and the activity coefficient becomes unity. Outside of the concentration range of the limiting law the activity coefficient would have to be determined as a function of m (Equation 13).

C. THE STANDARD STATE

The standard state, above, is the one usually chosen for the practical activity coefficient—an activity coefficient which approaches unity as the solute concentration approaches zero. This standard state is not an infinitely dilute solution, but a hypothetical solution which conforms to the limiting law of the infinitely dilute solution at a concentration of one molal. Other reference states for the solute may be chosen based upon the same limiting law (Equation 12). For example, one such state is the gaseous phase in which the pressure of the solute is one atmosphere and which is in equilibrium with the hypothetical solution of concentration $1/l$. Within the limiting law range the activity coefficient is constant with the value of l. Another possibility would be the gaseous mixture (in equilibrium with the hypothetical solution) in which the number of moles of the solute in the gaseous phase per volume is unity; in this case the standard fugacity, f^0, is equal to RT and the activity coefficient in solution in the limiting-law concentration range is equal to l/RT. The most convenient standard state is the first one. The others illustrate the danger of the statement that in dilute solution activity coefficients are equal to unity; the truth of the statement depends upon the choice of standard states.

5. Thermodynamic Requirements of the Integrated Rate Equation

A. THE SOLUTE'S ADHERENCE TO ITS LIMITING LAW

Outside of the actual range of conformity to the limiting law the activity coefficient is a function of concentration, the temperature and pressure

(on the solution) being held constant. The integration of Equation (11) depends upon the determination of the activity coefficients as a function of concentration.

Within the range of conformity to the limiting law of the solute (for strong electrolytes the limiting law takes the form $f = lm^n$, where n is the total number of ions formed, positive and negative) the observed specific rate constant from the empirical equation may be equated to the theoretical rate constant:

$$k_{obs} = k_0(\Pi\gamma_i/\gamma^{\ddagger}\Pi\gamma_j) \tag{14}$$

If no stable molecules are produced in the transition state along with the activated complex, Equation (14) becomes the same as the more familiar expression derived by Bronsted and Bjerrum which has been of such value in the studies of kinetics in ionic media, i.e.,

$$k_{obs} = k_0(\Pi\gamma_i/\gamma^{\ddagger}) = k_0\Gamma \tag{15}$$

B. THE CONSTANCY OF THE MEDIUM

The attendant limitation in Equations (14), (15), or (11) is that the medium remains constant. One desires a measure of the free energy change of the reaction uncomplicated by changes of the free energy due to composition changes; the partial molar free energy of each constituent is an intensive property dependent upon the composition of a particular solution. The equivalent of Equation (15) in terms of the equilibrium constant must be imagined in an infinite copy of the solution, such that the ratios of the constituents do not change. The presence of the product of the reaction in the solution alters the partial molar free energy of the reactants. The direction of the change for each constituent is unpredictable by classical thermodynamics, but the change for all the constituents must satisfy the Gibbs-Duhem equation, $\sum n_i d\bar{F}_i = 0$.

The ideal behavior of a solute in a non-ideal solvent system is discussed in Section VIII.

IV. THE PRACTICAL APPROACH TO IDEALITY

1. The Measurement of Activity Coefficients

Equation (15) shows the influence of the environment on the specific rate constant. Since this influence is measured by the activity coefficient factor, the conformity of the solute's behavior to the limiting law must be considered to insure that the activity coefficient factor is constant within

the experimental concentration range with respect to the reactants, the activated complex, and the products. The activity coefficient of the activated complex is not directly measurable. Since it partakes of the character of both the reactants and the products, although it might favor one more strongly than the other, a knowledge of the activity coefficients in the given solvent of both the reactants and products would serve to set the limits. The lack of the necessary information in the literature often places the entire burden on the kineticist. The situation may be circumvented by a literal translation of the theory for dilute solution to the initial rates of reaction.

2. The Initial Rate of Reaction

The concentration range for which the activity coefficient factor of equation (15) is constant may be established by the use of Equation (11) for initial rates. Substitution of $v = \Delta m/\Delta t$ for the differential of Equation (11) transforms the equation to the following form.

$$v_{\text{initial}} = k_0(m_{xy})(m_z)(\Gamma) \tag{16}$$

An upper limit, M_n, to the practical concentration range in which Γ remains constant may be delineated by the measurement of the initial rates over a range of concentrations $M_1, M_2, \ldots M_n$, where $m_{xy} + m_z = M$ and the ratio, m_{xy}/m_z, is kept constant and equal to r.

$$v_{\text{initial}} = [k_0 r/(r + 1)^2]M^2(\Gamma) \tag{17}$$

For a given r the constancy of the ratios, $v_1/M_1^2, v_2/M_2^2, \ldots v_n/M_n^2$, within experimental error would serve to set the upper limit of the solute's adherence to its limiting law. This approach is equivalent to ascribing experimental orders of reactions other than integers or rational fractions to the variation of the solute activity with composition changes. In conjunction with the establishment of the order of the reaction, either by the customary procedures (10) or the more precise one of Bateman and Hughes (11), the region of the solute's conformity to the limiting law may be described. The interpretation with respect to unimolecular reactions is obvious.

Of great interest is the measurement of v/M^2, at a given r, in the presence of the reaction product. This measurement would be equivalent to establishing whether a drift in the observed rate constant toward the completion of the reaction was attributable to a change in the activity of the reactants due to the presence of the products, or to a secondary reaction. Inherent in the approximations to the practical experimental region of the solute's conformity to the limiting law of dilute solution, and to the constancy of the solute's partial molar free energy with respect to product

formation, is that the constancy of the initial velocities lies within experimental error. This requirement is similar to that describing the reproducibility of a state (12) except that one is comparing a fugacity with respect to a standard fugacity.

3. Reaction Rates in Ideal Solutions

An indication of the solution's approach to ideality is important either by direct measurement (Section IV.1) or by estimation from the initial rates (Section IV. 2). For it is only in the region of the solute's adherence to the limiting law that activity coefficients are constant. Within this region, if the standard state is chosen such that the coefficients are unity, the observed rate constant becomes an exact measure of the difference in the free energy of the reactants and the activated complex, Equation (15). The ideality of the solution is essential for some experimental methods of determining the rate constant, e.g., the dilatometric or calorimetric methods depend upon observations in solutions in which the partial molar volumes or heat capacities are constant.

V. THE MECHANISM OF ORGANIC REACTIONS

1. The Aims

The goal of mechanistic studies in the condensed phase is the complete description of the interaction of a molecule with its environment and of the transformations brought about by mutual interaction and reaction which lead to the formation of another molecule. In this task present symbolism, both graphical and mathematical, is a limitation in that structural formulas at present do not reflect our concepts of steric hindrance or electronic interaction of atoms without a glossary and mathematically we tend to think in terms of planes instead of spaces and of discrete reaction steps rather than continuous functions. For the system composed of the compound XY, with the reagent Z, in the solvent HS, one seeks to know the effect of Z and HS on XY that leads to a moiety which through a series of changes leads to the activated complex and the products of the reaction. By analogy to the potential energy diagrams of reactions occurring in the gaseous phase a criterion has been established for reactions in the liquid phase. But the serious limitation is the lack of information on the microscopic change in state in solutions.

2. The Role of Kinetics

The application of the theory of absolute reaction rate to solutions provides the means of evaluating the energy difference between the reactants

and the activated complex, with the experimental limitations imposed by the activity concept. The nature of the reacting moieties in the rate determining step (or steps) is unknown, however. It is only through the systematic manipulation of the variables, X and Y in XY, Z, and HS, that the fundamental questions may be answered. The measurement of the reaction rates provides a quantitative key to the measurement of the microscopic change in state from the reactants to the activated complex as a function of these variables. Our inadequate knowledge of solutions is reflected in the investigation of reaction mechanisms. Often more is discovered about the various equilibria in solution than is learned qualitatively about the nature of the activated complex.

3. The Systematic Control of the Variables

The studies of nucleophilic aliphatic substitution by Hughes and Ingold and their co-workers provide a classic example of the establishment of a mechanism through the systematic variation of the structure of the reactants and the solvent and through the effects of this upon the products. Between 1933 and 1940 their studies (13) of the effect of structural changes of the alkyl halide and of varying basicity of the substituting agent upon the rate differentiated between two mechanisms, the bimolecular, one-step substitution and the unimolecular ionization. Further studies on the stereochemical course of the reaction and the effect of solvent changes on the rate and products permitted the kinetic form of the reactions and the effect of salts on the unimolecular ionization to be considered quantitatively. The accompanying development of the qualitative theory of the effect of solvent on the rate, based upon electrostatic interactions between solvent, reactants, transition complex and products, the extension to elimination reactions, and the studies of ionizations in aprotic solvents are exemplary. Other examples, equally important, are to be found in the researches of Winstein and Grunwald *et al.* (14) on the effect of beta substituents on the ionization reaction, and those of Brown *et al.* (15) on the steric effect in organic reactions.

In general the kinetic investigation of the mechanism of reactions consists of three parts: (1) survey kinetics, qualitative with respect to the mechanism, including a systematic variation of reactants and environment with respect to a reference reaction, directed towards postulation of the rate determining step; (2) structural alterations, electronic, isotopic or configurational, of reactants and/or environment to demonstrate control over the rate-determining step and directed toward the postulation of the structural formula of the activated complex; (3) kinetics, quantitative with respect to the mechanism, to demonstrate compatibility with a model of the postulated transition complex.

4. The Test of Ingenuity

The determination of the mechanism is the correlation of a measured rate of reaction, which by the present statistical theory is proportional to the exponential of the free energy of activation, with the molecular species in solution which represent that particular change in state. The test of ingenuity is the identification of these molecular species responsible for the observed rate of reaction. In this sense the mechanism of a reaction is, itself, an extrathermodynamic relationship.

VI. REACTION RATE AND THE STRUCTURE OF THE PRINCIPAL ORGANIC REAGENT

The variation of the structure of XY and its effect upon the rate is discussed in detail elsewhere in this volume. The subject is mentioned briefly at this point to place it in perspective with respect to the whole kinetics-mechanism problem, and to note, in passing, the quantitative correlations that have resulted. These are the linear free energy relationships between rate and equilibrium constants, such as the Bronsted relationship and the Hammett "rho-sigma" treatment (16) which has been broadened by the efforts of Taft (17) to include not only polar effects, but also resonance and steric effects of a substituent on a reaction center transmitted through a benzene ring, relative to the unsubstituted benzene derivative. The linear free energy relationship for discrete changes in the substituent behaves as a continuous mathematical function, and describes the change in reactivity with the change in structure, or an internal effect upon the rate of reaction.

VII. REACTION RATE AND ENVIRONMENT

1. The Environment

As the environment it is well to consider all other substances in solution with respect to the principal organic reagent, XY, and to assess, if possible, their effect upon its structure in solution, its molecularity in the reaction, and the effect upon the equilibrium with the activated complex. It is proper to consider the effect of the secondary reactant or a nonparticipating additive, Z, an electrolyte (acid, base, or salt) or an electrically neutral molecule, and the effect of the solvent, HS, single or mixed, upon the partial molar free energy of the primary reactant and the activated complex. This is a difficult task. The environmental influence on reaction rate has been

considered mainly from two points of view, that of the effect of solvent and that of the effect of salts, the effect of electrically neutral secondary reactants having received little attention.

2. Solvent

The qualitative theory of the effect of solvent which has been the mainstay of the organic chemist is that which evolved in the course of Hughes' and Ingold's early work on nucleophilic substitutions in 1935 (18). Discussions of the theory may be found in various texts (19). On the basis of electrostatic interactions it states that the reaction rate increases upon the change to a more polar solvent if the activated complex is more polar than the initial reactants. Refinements were possible by consideration of assumptions based upon the ability of the solvent to solvate as a function of dipole moment and shielding of the dipole charge of the solvent, and the magnitude and dispersal of the charge on the moiety to be solvated.

A quantitative, though empirical, correlation between rate and solvent may be found in the studies of Grunwald and Winstein (20). The "mY" treatment relates the rate of solvolysis, k, of XY in a particular solvent to that, k_0, in 80 volume per cent ethanol through the following relationship, in which Y is equal to $\log(k/k_0)$ for *tert*-butyl chloride in the given solvent and in 80% ethanol:

$$\log(k/k_0) = mY \tag{18}$$

The correlation as originally proposed envisioned m as a constant characteristic of the reaction. This approach of using the rate of solvolysis of a standard substance in a reference solvent as a measure of gross solvent effects has great merit. The relationship, Equation (18), has been studied intensively through the temperature coefficients of the reactions (21). These studies have resulted in an ABC-group classification of numerous binary solvents.

3. Salts

The presence of a salt has a pronounced effect on polar reactions. For solvents of high dielectric the effect may be exercised either as participation in an equilibrium with the reactant or activated complex, termed a "mass-law" effect, or simply as an alteration of the polar character of the solvent, termed the "ionic strength" effect (19a). The former may not be divorced from the latter. The "ionic strength" effect might be described more precisely as the effect on the partial molar free energies of the reactant and the activated complex in a particular solvent containing the electro-

lyte. It is purely an environmental effect. If the ions of the electrolyte participate in an equilibrium with either or both the reactants and the activated complex, then in addition to the effect of the ionic environment on $\bar{F}_r$ and $\bar{F}^{\ddagger}$, there is imposed an alteration in the specific rate due to the equilibrium. The colligative properties of electrolytes in dilute solution of high dielectric may be utilized for reactions in which one of the reactants is an electrolyte by buffering the solution ionically with added salts to eliminate the effect of the change in the total ionic strength on the observed rate. By variation of the nature of the added salt with common and uncommon ions the existence of an actual equilibrium may be detected and its importance with respect to the reactants or activated complex assessed. The nature of the ion aggregates of the electrolytes in solvents other than water must also be taken into account. The traditional example may be found in the work of Bateman, Hughes, and Ingold (22) in which, particularly through the work on *tert*-butyl bromide in aqueous acetone, the kinetic salt effect was established as a criterion of the ionization reaction. The same approach has been recently employed by Winstein and Fainberg (23) in their studies of salt effects upon ion-pairs, the initial criterion being here that the rates of racemization and ionization for neophyl *p*-toluenesulfonate were not the same. The mathematical analysis consists of plotting instantaneous integrated rate constants versus the per cent completion of the reaction; in this way retardation may be shown by a common ion whose concentration is increasing with the progress of the reaction. This effect has to be sorted out, however, from the ionic strength effect.

4. The Bronsted-Bjerrum Equation

A. IONIC STRENGTH AND THE DIELECTRIC OF THE MEDIUM

One of the most valuable relationships for the correlation of rates is that of Bronsted-Bjerrum, Equation (15), which relates the rate in a given medium to that in the standard state through the activity coefficients. It has been used mainly in the study of polar reactions in dilute ionic media where the activity coefficients may be evaluated by the Debye-Hückel theory on the basis of their charge. In very dilute solution the activity coefficient of an ion may be evaluated from the expression $\ln \gamma_i = -Az^2\mu^{1/2}$ (limiting law) in which A is a constant dependent upon the solvent (dielectric constant) and the temperature, z the charge of the ion, and μ the ionic strength. The application of this correlation of the rate and the ionic strength is discussed in various texts (6,8a). Recently, the equation was used in the studies of the reaction of trimethylsilylmethyl benzoate and hydroxyl ions in water and aqueous methanol (24). The more complex treatments, based upon the Bronsted-Bjerrum equation and the Debye-Hückel theory,

by Scatchard and by Laidler and Eyring (25) depend upon spheroid or double-spheroid models of the activated complex and reduce to the limiting law form of the equation above in the infinitely dilute solution. The rate may be correlated with either the ionic strength or the dielectric constant of the medium, one variable being held constant. The limitations or inadequacies of the purely electrostatic theory have been discussed by a number of authors (8a,26). An example of the difficulty may be found in the kinetics of the acid-catalyzed hydrolysis of γ-butyrolactone in various salt solutions (27). Sodium chloride had a slight positive salt effect; sodium perchlorate, in contrast, had a slight negative salt effect on the rate.

The Bronsted-Bjerrum equation has also been employed in conjunction with Kirkwood's equation for the activity coefficient of a strong dipole in a medium of dielectric D. A comparison of this equation and the "mY" rate-solvent correlation has been made by Winstein and Fainberg (28). An example of an application is presented in Section IX.6.A.

B. THE ACIDITY AND OTHER FUNCTIONS

Of great significance is the acidity-rate correlation of Hammett (29) made possible by his acidity function in conjunction with the Bronsted-Bjerrum equation and the Zucker-Hammett hypothesis of mechanism. The acidity function H_0 is defined by the equation

$$H_0 = -\log (a_{H^+} f_B/f_{BH^+}) = -\log h_0 = -\log (m_{H^+} f_{H^+} f_B/f_{BH^+}) \quad (19)$$

and is dependent upon the hydrogen ion activity and the activity coefficients, f, of the base, B, and its conjugate acid, BH^+. For an acid-catalyzed reaction, occurring by protonation of the substrate, the Bronsted-Bjerrum equation takes the form, $k = k_0(a_{H^+} f_X/f_X^{\ddagger})$. Substitution of the value of the proton activity in terms of h_0 gives the following relationship:

$$\log k = \log k_0 + \log h_0 + \log (f_X f_{BH^+}/f_X^{\ddagger} f_B) \quad (20)$$

The last member of the Equation (20), the activity coefficient factor, has been shown in the case of comparisons of basic indicators not differing radically from each other in structure to be constant in a wide range of acidic solvents, including aqueous acid solutions where the f's are unity. It was concluded that the activity coefficient factor was unity in all cases and the logarithm, zero. Zucker and Hammett proposed that the activity coefficient factor of Equation (20) also was unity; the rate would be proportional to the acidity function (as h_0, which is a more convenient form). For an acid-catalyzed reaction in which a water molecule is involved in the transition state, the rate, in contrast, would be dependent upon the stoichiometric acid concentration. In this case the Bronsted-Bjerrum equation

would have the logarithmic form

$$\log k = \log k_0 + \log (H_3O^+) + \log (f_X f_{H_3O^+}/f_X^{\ddagger}) \qquad (21)$$

where a direct correlation of rate and the stoichiometric acid concentration depends upon the constancy of the activity coefficient factor also.

The success of the diagnostic use of the acidity function, i.e., unit slopes of log k versus log h_0, has been striking. The acidity function and its diagnostic use are discussed in Section VIII.5.C and D. An application to the hydration of olefins is presented in Section IX.7.C; other uses of the Zucker-Hammett hypothesis have been made on the hydrolysis of γ-butyrolactone (27a), and trimethylene oxide (30), the racemization of *sec*-butanol (31), the denitration of nitroguanidines (32), and the hydrolysis of thioacetamide (33).

The exactness of the Zucker-Hammett proposal as a criterion of mechanism depends upon the activity coefficient factors of Equations (20) and (21) being unity and their logarithms zero (34). Since the ratio, $f_X/f_X^{\ddagger}$, varies as much as several powers of ten (35), the factor may achieve unity where it varies in the same way with the medium as f_B/f_{BH^+}; therefore this may be the case if $f_X \approx f_B$ and $f_X^{\ddagger} \approx f_{BH^+}$ (30). Other functions, the J_0 of Gold and Hawes (36) and the C_0 of Deno *et al.* (37), have been defined for the measure of the equilibria between alcohols and carbonium ions in conjunction with the acidity function. These too depend upon an activity coefficient factor's being unity.

VIII. A THEORY OF REACTION RATE-ENVIRONMENT CORRELATION

1. The General Equation

It is enlightening to consider the various equilibria present in solution formally. Those of interest are the equilibria between the reactant and the activated complex in solution and their respective vapor phases. The compound XY, represented simply for the present by X, is assumed to possess a measurable vapor pressure in solution, its vapor pressure being sufficiently low that its partial vapor pressure, p_s, may be used in place of its fugacity. The unimolecular reaction, X $\rightarrow$ products, at a given temperature T and at constant pressure P on the solution, composed of X at molality m in solvent s within the concentration range of the solute's adherence to the limiting law corresponding to Henry's law ($f = lm$), will be considered. The chemical potentials, μ, and the standard states for X and the activated complex, $X^{\ddagger}$, are shown beneath the equilibria in Equation (22).

The standard states are the hypothetical one molal solutions of X and $X^{\ddagger}$ in solvent s above which the vapor pressures of the solutes are l_s and $l_s^{\ddagger}$, respectively. (T and P remain constant).

$$\begin{array}{lcl} X_{solution} & \rightleftharpoons & X^{\ddagger}_{solution} \\ \mu_s = f_s + RT \ln (m\gamma) & & \mu_s^{\ddagger} = f_s^{\ddagger} + RT \ln (m^{\ddagger}\gamma^{\ddagger}) \\ \mu_s^{ss} = f_s & & \mu_s^{\ddagger ss} = f_s^{\ddagger} \\ \Big\| & & \Big\| \\ X_{vapor} & \rightleftharpoons & X^{\ddagger}_{vapor} \\ \mu_v = f_v + RT \ln p_s & & \mu_v^{\ddagger} = f_v^{\ddagger} + RT \ln p_s^{\ddagger} \\ \mu_v^{ss} = f_v + RT \ln l_s & & \mu_v^{\ddagger ss} = f_v^{\ddagger} + RT \ln l_s^{\ddagger} \end{array} \qquad (22)$$

The chemical constants, f_v and $f_v^{\ddagger}$, for X and $X^{\ddagger}$, respectively, are dependent only upon the temperature and the nature of the solute molecules in the gaseous phase. The symbol, f, with a subscript denoting the phase, has been used for compatibility with F, the free energy, rather than Sommerfeld's (38) notation of g in conjunction with the equivalent Gibbs function or the free enthalpy; the conventional notation of k (39) has not been used to emphasize the statistical interpretation by the third law of thermodynamics placed on this integration constant. The quantities f_s and $f_s^{\ddagger}$ however are functions of both temperature and pressure. The activity coefficients have the property, $\gamma \to 1$ as $m \to 0$, by the choice of standard states. Within the concentration range of the solute's adherence to the limiting law, γ for X is always unity. Since the concentration of the activated complex, $m^{\ddagger}$, is always microscopic compared to m, $\gamma^{\ddagger}$ is also unity.

The condition of equilibrium for an infinitesimal unit of reaction is that $\mu_v = \mu_s = \mu_s^{\ddagger} = \mu_v^{\ddagger}$. From these equalities the following relationships may be derived from Equation (22).

$$f_s - f_v = RT \ln (p_s/m) = RT \ln l_s \qquad (23a)$$

$$f_s - f_s^{\ddagger} = RT \ln (m^{\ddagger}/m) = RT \ln K_m^{\ddagger} \quad \text{(no expansion work)} \qquad (23b)$$

$$f_s^{\ddagger} - f_v^{\ddagger} = RT \ln (p_s^{\ddagger}/m^{\ddagger}) = RT \ln l_s^{\ddagger} \qquad (23c)$$

$$f_v - f_v^{\ddagger} = RT \ln (p_s^{\ddagger}/p_s) \qquad (23d)$$

It is noted that Equation (23b) is the definition of a thermodynamic equilibrium constant which, since activity coefficients are unity, is equal to the concentration equilibrium constant. The statement of the theory of absolute reaction rates, $k_s = \kappa_s(kT/h)K_m^{\ddagger} = \lambda_s K_m^{\ddagger}$ (Equation 7), allows Equation (23b) to be identified with the rate of the reaction in solvent s, $f_s - f_s^{\ddagger} = RT \ln K_m^{\ddagger} = RT \ln (k_s/\lambda_s)$. Elimination of the solution constants, f_s and $f_s^{\ddagger}$, in Equations (23a, b, and c) gives the fowolling relation-

ship between the rate and the ratio of the limiting law constants.

$$f_v - f_v^{\ddagger} = RT \ln (k_s l_s^{\ddagger}/\aleph_s l_s) = RT \ln (p_s^{\ddagger}/p_s) = RT \ln (k_v/\aleph_v) \quad (24)$$

The hypothetical rate of the reaction at unit fugacity is denoted by k_v, it being dependent only on the temperature and the nature of X and $X^{\ddagger}$ in the gaseous phase. In any solvent, $a, b, \ldots, s, \ldots$, the rate of reaction and the ratios of the limiting law constants, $l_s^{\ddagger}/l_s = L_s$, for each solvent, must satisfy the general expression,

$$k_v/\kappa_v = k_a L_a/\kappa_a = \ldots = k_s L_s/\kappa_s \quad (T \text{ and } P \text{ are constant}) \quad (25)$$

in which κ_s is the transmission coefficient for the reaction in solvent s from the notation $\aleph_s$ above. In the event that X were a slightly soluble solid, the standard state to choose would be that state and the limiting law constants, l, would be replaced by solubility data, i.e., the distribution constants between the solid and the dissolved state rather than between the solution and the vapor state.

To pursue the problem of reaction rate-environment correlations further a set of equations analogous to (25) may be derived for the unimolecular reaction of the compound X', X' → product, in the same set of solvents, $a, b, \ldots, s, \ldots$, and T at unit pressure on the solution, in the concentration range of the solute's (X') adherence to the limiting law.

$$k_v'/\kappa_v' = k_a' L_a'/\kappa_a' = \ldots = k_s' L_s'/\kappa_s' = \ldots \quad (25a)$$

Equation (25a) divided by (25) gives

$$(k_v'/k_v)(\kappa_v/\kappa_v') = (k_a'/k_a)(\kappa_a/\kappa_a')(L_a'/L_a) = \ldots = (k_s'/k_s)(\kappa_s/\kappa_s')(L_s'/L_s) \quad (26)$$

which by rearrangement of the right-hand members gives a general equation for the unimolecular reaction rate-environment correlation.

$$k_s'/k_a' = (k_s/k_a)(L_a' L_s/L_a L_s')(\kappa_a \kappa_s'/\kappa_a' \kappa_s) \quad (27)$$

Equation (27) states that the ratio of the equilibrium constants ($k = \aleph K^{\ddagger}$ in general) between the reactant X' and its activated complex in solvents s and a is proportional to that of compound X in the same solvents. The proportionality constants, the πL- and the $\pi\kappa$-factors, depending upon the equilibrium distributions (T, P) of the solutes, X, $X^{\ddagger}$, X', and $X'^{\ddagger}$, between the solution and the vapor phase and the transmission coefficients for the reactions of X and X' in solvents s and a, respectively.

A. THE TRANSMISSION COEFFICIENT

The value of the $\pi\kappa$-factor of Equation (27) may not be summarily assumed to be unity (40). The transmission coefficient of each reaction de-

pends upon the reflection probabilities of the initial and final states. If these probabilities, which are dependent upon the shape of the potential energy surface, are small compared to unity, the transmission coefficient itself is close to unity (41). For some reactions in the gaseous phase, the combination of atoms or some unimolecular reactions, κ is very small where the interchange or dissipation of energy is critical. In solution, the assumption of unity for its value in the case of an individual reaction does not appear to be serious. It is believed that an error of less than 10% would be introduced in so doing (42). If the four transmission coefficients of the $\pi\kappa$-factor were assumed to be unity within 10%, the error in the factor would be of the order of 20%. It is expected that the error introduced might well be less. In the study of the rate of a particular substrate, X, as a function of environment, the potential energy surface may be altered by the environmental change brought about by a change of solvent, e.g., $\kappa_a \neq \kappa_s$. If similar substrates, X and X′, are considered it does not seem inconceivable that their transmission coefficients might be similarly affected by the change from solvent a to s and that κ_a/κ_s is about equal to κ_a'/κ_s'. To the extent that this may be anticipated the $\pi\kappa$-factor might be expected to be closer to unity than 20% or than the individual transmission coefficients.

B. SOLUTE-SOLVENT INTERACTION MEASURED BY THE SOLVENT: A POSTULATE

The nature of the πL-factor may be appraised from the recent work of Hill (43) on the theory of solutions. The theory is a formally exact derivation of the thermodynamic functions of solutions from the postulates and methods of statistical mechanics. The presentation is particularly valuable since it accommodates molecular interpretation. With the partition function Γ, the limiting law constant, equivalent to Henry's law, for a solute in binary solution (T, P) was expressible as a function of exp $(-\mu_v^0/kT)$, μ_v^0 being the chemical potential *of the solute* in the vapor phase *at unit fugacity* ($\mu_v^0 = \mathrm{f}_v$, the chemical constant), and a *ratio of the intensive properties of the solvent*, the isothermal-isobaric partition functions of the pure solvent and the solvent containing small sets of solute molecules. The concept of the formal theory that the effect of the *solute in solution* in the limiting law range is measured by *two states of the solvent* permits an evasion of the dilemma posed by the Gibbs-Duhem equation in ternary or multicomponent solutions. The thermodynamics of the kinetic problem is difficult, for even in the simplest case, that of a binary solution, the solution is no longer binary shortly after mixing and reaction occurs. The chemical potentials of the solvent cannot be used to assess solute-solvent interactions. The Gibbs-Duhem equation gives the overall energy restriction for changes in composition, but the magnitude and direction of the change of the

chemical potentials of the components of the solution are predictable only in the case of a binary solution.

Translation of the concept by postulate to complex solution is expressed as:

$$l_s^{\mathrm{x}} = (I_s/I_s^{\mathrm{x}}) \exp(-\mathrm{f}_v^{\mathrm{x}}/RT) \tag{28}$$

for the solute X in solvent s, at T and P, where I_s and I_s^{x} are constants, dependent upon the temperature and pressure on the solution, for the solvent without solute and the solvent in the hypothetical solution one molal in solute X. The limiting law constant has the dimensions of reciprocal concentration, since the pressure units of partial vapor pressure per unit pressure on the system cancel. The ratio I_s/I_s^{x} should be considered a measure of the change of the energy distribution of the solvent due to the presence of the solute, X. The factor I_s^{x} should be considered dependent upon the effect of the constitutive properties of the solute, X, on the solvent; generally the similar substrates, i and j, are expected to have the same effect upon the same solvent, $I_s^i = I_s^j$.

2. The Reduced Equation

In the present problem substitution of the appropriate forms of Equation (28) for X and X′ in the definition of $L = l^{\ddagger}/l$ gives

$$L_s = (I_s^{\mathrm{x}}/I_s^{\mathrm{x}\ddagger}) \exp[(\mathrm{f}_v^{\mathrm{x}} - \mathrm{f}_v^{\mathrm{x}\ddagger})/RT] \tag{29}$$

For simplicity in the determination of the value of the πL-factor of Equation (27) through the use of Equations (28) and (29), the substrates, X, $\mathrm{X}^{\ddagger}$, X′, and $\mathrm{X}'^{\ddagger}$, are designated in detail by superscript only on the individual I-factors and the exponentials. The values of L_a, L_s' and L_a' for the substrates X and X′ and their respective activated complexes in solvent s and a are analogous to Equation (29). Substitution of these values in the πL-factor shows that it becomes dependent only upon the ratios of the changes in the solvent energy distributions due to the presence of the various solvent-solute combinations,

$$\pi L\text{-factor} = L_a'L_s/L_aL_s' = I_a^{\mathrm{x}'}I_s^{\mathrm{x}}I_a^{\mathrm{x}\ddagger}I_s^{\mathrm{x}'\ddagger}/I_a^{\mathrm{x}'\ddagger}I_s^{\mathrm{x}\ddagger}I_a^{\mathrm{x}}I_s^{\mathrm{x}'} \tag{30}$$

since the exponential factors cancel. A comparison is being made between two unimolecular reactions of X and X′ whose constitutive properties are similar, and $I_s^{\mathrm{x}} = I_s^{\mathrm{x}'}$. If, likewise, the two reactions proceed through similar activated complexes, their factors are identical, $I_s^{\mathrm{x}\ddagger} = I_s^{\mathrm{x}'\ddagger}$. These relations would also hold for the solvent a. Under these conditions the πL-

factor becomes unity. Equation (27) assumes the simple form of Equation (31) since the $\pi\kappa$-factor also becomes unity. For the comparison of the

$$k_s'/k_a' = k_s/k_a \qquad (T, P \text{ constant}) \tag{31}$$

unimolecular reactions of solutes X and X′ within the limiting law range of concentration for each, if both the solutes and their respective activated complexes are similar in constitutive properties, i.e., if the substrates, X and X′, $X^{\ddagger}$ and $X'^{\ddagger}$, are similar to each other in charge distribution, dipole moment, and type of bonding, and affect the solvent in similar manners, the rate constants are related by Equation (31).

A. THE LIMITING LAW RESTRICTION

The restriction on the observation of the rates within the limiting law range of concentration is equivalent to the use of a solution in which the solute behaves ideally in a non-ideal solvent. The non-ideality of the solvent is not important since the solvent in solution is always compared to the solvent without solute and since these ratios are observed for pairs of substrates. This formulation also allows for the preferential solvation of the substrate by one of the solvent components as might be expected, for instance, when ions are involved in an aqueous solvent. As long as similar ionic substrates are compared the degree of preferential solvation by water might be expected to be identical.

B. THE SIMILAR SUBSTRATE RESTRICTION: A CRITERION OF MECHANISM

The restriction on the similarity of the substrates should not be defined more specifically than it has been at present. The πL-factor is a mathematical expression of a molecular theory of solute-solvent interaction dependent upon the nature of the substrate and its solvent environment. The appraisal of these interactions is inexact at the present time, except through the work of Hammett (29), Long (27,30), and Deno (37), and their respective co-workers. The quantitative description of solute-solvent interaction can be based only upon the study of reactions for which accurate details of the substrates, dissolved reactants and their activated complexes, are known. In the case of polar reactions a great amount of material is available which will be discussed presently. For the reactions involving radicals there is not a great deal of data. The near equality of the rates of dissociation of bis-isobutyronitrile in hydrocarbon and halohydrocarbon solvents (44) suggests that the individual L_s of Equation (29) for any solvent does not vary a great deal; there is no information on the rates of dissociation to form radicals in a wide variety of solvents, and therefore little can be surmised at present. It might be expected that in general,

$I_s^{\text{neutral}} \neq I_s^{\text{ionic}} \neq I_s^{\text{radical}}$, but the extent to which substrates may be categorized should be left to the future when more is known about the intervening spectra of the extremes designated above. Where confidence may be placed in an assessment of the form of the substrate of a reaction, that reaction and its variation with environment may be used to assess the mechanism of another reaction with Equation (31) as a criterion of mechanism. The evolution of this theory depends upon reciprocity of the measurement of solvent-solute interaction based alternately upon substrate knowledge applied to solvents, and solvent information applied to other substrates.

C. TEMPERATURE DEPENDENCE

It may be noted that if the comparison of reactions occurring at different temperatures, X at T and X′ at T', is made, the effect on the πL-factor depends only upon the temperature coefficients of the I-factors. Equation (30) under such circumstances would have the value

$$\pi L\text{-factor} = I_a^{x'}(T')I_s^{x}(T)I_a^{\ddagger x}(T)I_s^{\ddagger x'}(T') \div I_a^{\ddagger x}(T')I_s^{\ddagger x'}(T)I_a^{x}(T)I_s^{x'}(T') \quad (32)$$

where the temperature dependence of the I-factor is shown in parentheses. For solvent a there are two ratios, one for X′ and X dependent upon T'/T, and one for $X^{\ddagger}$ and $X'^{\ddagger}$ dependent upon T/T′. Since these ratios appear in pairs and in a reciprocal relationship for solvents a and s the πL-factor may be regarded as largely insensitive to temperature.

3. Verification of the Theory of Absolute Reaction Rate in Solution

It must be pointed out that Equations (25) through (27) are statements of the theory of absolute reaction rate in dilute solution. This theory is dependent upon two points: the statistical derivations of the universal frequency factor, kT/h, and of the nature of the activated complex and κ, and the postulate of equilibrium between the reactants and the activated complex. Strict translation of the equilibrium postulate by the first and second laws of thermodynamics to dilute solution gives these equations and defines the area of validation of the theory in dilute solution. Within the limits of the formulation and acceptance of the author's πL-factor postulate, a proof of the theory of absolute reaction rate in dilute solution may be demonstrated by Equation (31).

Evidence may be found in the data gathered for the "mY" correlation (Section VII.2) for the rates of solvolysis (k_s') of the substrates X′, α-phenylethyl chloride and bromide (45a) and *tert*-butyl bromide (45b) compared to those (k_s and k_a) of substrate X, *tert*-butyl chloride, in a number of sol-

vents, s, compared to solvent a. The solvent series s comprised aqueous mixtures (*ca.* 20–90%) of ethanol, methanol, acetic acid, dioxane, and acetone and acetic–formic acid mixtures; solvent a was 80% ethanol. The use of extremely dilute solution, less than 0.04M, makes it highly probable that the rates of solvolysis for *tert*-butyl chloride (X) were observed in the region of ideal solute behavior; the data for the Henry's law constant for *tert*-butyl chloride in acetic acid versus concentration (20) indicate that the upper limit of the concentration range of adherence to the limiting law is a little less than 0.04M. For the substrates, X′, the concentration range of 0.01 to 0.04M used for the rate studies is sufficiently dilute that it may well have been within the limiting law range also, though data are lacking. α-Phenylethyl and *tert*-butyl halides appear to meet the similar substrate restriction since the reactants are dipolar molecules possessing a carbon-halogen bond and their activated complexes are of the same type, an ion pair (46). In 26 to 35 different solvents, s, enumerated above, for each substrate X′, integrated rate constants (k_s') gave slopes of 1.056, 1.031, and 0.924, respectively, at 25°C., and 0.974, 1.123, and 1.001 at 0 or 50°C. for the least squares treatment of Equation (31), $\ln k_s' = \ln (k_s/k_a) + \ln k'_a$. The probable error of the least squares fit, 16 to 32% (45), though large, is remarkable. Rate constants integrated over a range up to 50 or 80% completion of the reaction were used rather than those integrated over a moderate initial range (10–30%) to insure noninterference by the products of the reaction. The fact that some constants were extrapolated to initial rates (45b) (from near completion) probably attests to some difficulty in the interference of the products on the constancy of the medium (Section III.5.B). It would seem improbable that the deviation could be attributed solely to the transmission coefficient factors. It might be added that of the X′-compounds in unimolecular reactions treated by the "mY" correlation (20), about half likely to meet the similar substrate restriction at least, have unit slopes within 30%. The remaining compounds possess slopes between 0.2 and 0.7. It is not profitable in this initial presentation however, to delve into these data further, since many do not come as close as those enumerated above to meeting the thermodynamic requirements of Equation (31).

4. The Comparison of Reaction Rates of Dissimilar Mechanism

The extension of these concepts as a criterion of mechanism to bimolecular restrictions is of interest. For the bimolecular reaction, $X'' + Z \rightarrow$ products, an equation analogous to Equation (25a) may be derived.

$$k_s''/\kappa_s'' = (k_a''/\kappa_a'')(l_a''^{\ddagger}/l_a''l_a^z) = \ldots = (k_s''/\kappa_s'')(l_s''^{\ddagger}/l_s''l_s^z) = \ldots \quad (33)$$

If this reaction is compared to the unimolecular reaction of Equation (25), the πL-factor again is dependent only upon the I-factors.

$$\pi L\text{-factor} = I_s^{x} I_a^{x} \overset{\ddagger}{I}_a^{x''} I_a^{z} I_s^{x''} \overset{\ddagger}{I}_s \div I_s^{x} \overset{\ddagger}{I}_a^{x} I_a^{x''} \overset{\ddagger}{I}_a I_s^{x''} I_s^{z} \tag{34}$$

The value of the πL-factor would depend upon the type of substrates involved. Let it be assumed that the substrates, X and $X^{\ddagger}$, are an electrically neutral molecule (but dipolar) and an ion pair, respectively, and that X'', Z, and the activated complex$(X''Z)^{\ddagger}$, designated simply by $X''^{\ddagger}$ are all electrically neutral. Allowing that X and X'' are similar in their effect on the solvent and that conceivably the activated complex, $X''^{\ddagger}$, has an effect on the solvent similar to that of Z, one obtains for the value of the πL-factor for each solvent pair $I_a^{x} \overset{\ddagger}{I}_s / I_a I_s^{z} \overset{\ddagger}{}$, which for reactions conducted at the same temperature is equal to $l_s^{\ddagger}/l_a^{\ddagger}$. The rate correlation would take the form.

$$k_s''/k_a'' = (k_s/k_a)(l_s^{\ddagger}/l_a^{\ddagger}) \tag{35}$$

where the $\pi\kappa$-factor, equal to $\kappa_a\kappa_s''/\kappa_s\kappa_a''$, would be equal to unity within the limitation of Section VIII.1.A. This particular example was chosen for speculation concerning the bimolecular participation by one of the solvent components, for instance, water (Z) in the solvolysis of an alkyl halide in aqueous solvents. The observed pseudo unimolecular rate, of course, would be related to the thermodynamic rate constant by the equation, k_s'' (expt.) $= k_s''\, a_{H_2O}$, where as before the concentration of the solute X'' would lie within the limiting law concentration range.

As a criterion of bimolecular mechanism it would appear that individual reference reactions of pairs of types of substrates might prove to be useful. Comparisons of an unknown reaction by relatively simple kinetic methods to those whose mechanisms had been established kinetically and independently, through the equivalent of Equation (31) for bimolecular reactions, $k_s''/k_a'' = k_s'''/k_a'''$, would appear to be of advantage. It is noted, however, that *positive correlations of unit slope only are meaningful*, since a non-unit slope or nonlinearity for data treated by Equation (31) or its equivalent may indicate lack of adherence to either the thermodynamic requirement or to the substrate restriction or both, as well as the occurrence of different molecularities.

5. Rates and Equilibria in Ionic Media

The extension of these concepts to cover reactions involving ions requires careful consideration of the form of the limiting law for these solutes in solution. The rate-environment correlation developed so far depends upon the limiting law of the substrate, the standard state, and for the neutral

molecule a phase equilibrium which permits the reaction rate in dilute solution to be related to its hypothetical counterpart in the gaseous phase where it is dependent only upon the temperature.

A. CONSIDERATION OF THE LIMITING LAW FOR IONS

For a uni-univalent salt in solution a variety of species may exist; simple ions, ion pairs, triple ions, quadrapoles, for instance, have been in evidence (47). The existence of multiple species is particularly important in solvents of low dielectric. A recent example may be found in the work of Hughes, Ingold, *et al.*, on the conductance studies of quaternary ammonium salts in benzene (48), where conductance data interpreted by the Bjerrum and Fuoss and Kraus electrostatic theory showed that at low concentration (10^{-4}–$10^{-5}M$) the conductance went through a minimum in which most of the salt existed as neutral ion-pairs. At this concentration the current was carried entirely by small concentrations of single ions or triple ions. From these data the dissociation constants for the ion-pair or the triple ions could be evaluated. Uncertainty over the type of ionic species in solution makes the elucidation of the mechanism difficult since this depends ultimately upon the identification of the form of the reactant and the activated complex present in the solution. Further, as implied in the statement of the theory of absolute reaction rate and its dependence upon the thermodynamic equilibrium constant, it is mandatory that one finally consider the chemical potentials defined for the individual ionic species for the reactions occurring by such a route.

In general the limiting law of a salt has the form, $f = lm^n$, where n is the sum of the ionic charges. The activities of the ionic species may be defined by the equation, $\mu_i = \mu_i^0 + \nu_i RT \ln a_i$, where ν_i is the charge of the species. The postulate of Section VIII.1.B for complex solutions, that the state of the solute in solution within the range of adherence to its limiting law is determined by two states of the solvent, solvent without and with solute (in small numbers), may be broadened to include ionic substrates in a very simple fashion.

B. THE LIMITING LAW FOR IONS BY THE POSTULATE OF VIII.1.B

As a consequence of Hill's (43) definition of activity in terms of isothermal-isobaric partition functions of the solvent for a dilute binary solution, the f_s of Equations (22) and (23) is equal—by the present postulation for complex solutions—to $RT \ln (I_s/I_s^i)$. For a uni-univalent salt, the chemical potentials of the cation, anion, and ion pair in terms of the I-factors are expressed as follows:

$$\mu_+ = RT \ln (I_s/I_s^+) + RT \ln a_s^+ \qquad (36)$$

$$\mu_{-} = RT \ln (I_s/I_s^{-}) + RT \ln o_s^{-} \quad (37)$$

$$\mu_{ip} = RT \ln (I_s/I_s^{ip}) + RT \ln a_s^{ip} \quad (38)$$

The chemical potential of the dissociated salt in solution is the sum of those of its ions. The ion-pair of Equation (38) distinguished from the many types of pairs of ions differing in contiguity present in a solution, is defined as the one possessing a vapor pressure. The limiting law for this ion-pair in solution then becomes

$$l_s^{ip} = p_s^{ip}/a^{+}a^{-} = f_s^{ip}/a^{+}a^{-} = (I_s^2/I_s^{+}I_s^{-}) \exp(-\mu_{ip}^0/RT) \quad (39)$$

where $\mu_s^{ip} = f_s + RT \ln p_s^{ip}$, f_s^{ip} is the fugacity, and f_s is the chemical constant of the ion pair. In solvents of low dielectric more complicated equilibria to form quadrapoles or triple ion would have to be considered. For the present the ions–ion-pair equilibria only will be regarded to show compatibility of the theory with the acidity function and its applications.

C. ACID-BASE EQUILIBRIA: THE ACIDITY FUNCTION

The acidity function (49) depends upon activity coefficients which are largely undefined as in the equation of the earlier section, VII.4.B except that the standard chemical potential was considered independent of the medium (50). As a consequence an equilibrium constant based upon a reference state of the hypothetical unit molal solution obeying the laws of the infinitely dilute solution was regarded as a constant independent of the medium. By the theory developed in this section, this reference state is considered to be solvent-dependent, and an equilibrium constant referred to this state would be measured by solvent-dependent partition functions. In addition it has been postulated that for similar substrates in a given solvent the solvent-dependent I-ratios would be alike. Thus in demonstrating the uniformity of the theory both with respect to the reactions of neutral molecules and ionic substrates connected with the acidity function, the author shall adhere strictly to the principles of the Hammett-Deyrup derivation, but will alter the symbolism to suit what is believed to be a more clearly defined physical picture of the equilibria.

Let us consider a series of solvents composed of sulfuric acid and water in the range in which the water predominates, such that the mechanism of proton transfer may be represented by the equilibrium

$$BH^{+} + S \longrightarrow B + SH^{+} \quad (40)$$

upon the addition of a small amount of base, B, to the solution. The activities of the base, its conjugate acid, BH^{+}, and the oxonium ion, H_3O^{+} (SH^{+}), in solvent s of the series are defined with respect to the hypothetical

solution of unit concentration obeying the laws of the infinitely dilute solution. The activity coefficients, as defined before, approach unity as the concentration of the substrate approaches zero. The concentration of B and BH^+ as indicators always being minute, their respective activity coefficients are unity. From the definition of the thermodynamic equilibrium constant one obtains for the equilibrium of Equation (40) in solvent s

$$K_s = a_B a_{SH^+}/a_{BH^+}a_S = (m_B/m_{BH^+})(a_{HS^+}/a_S) \tag{41}$$

With the limiting law of dilute solution for each constituent, e.g., $l_s^B = p_s^B/a_s^B$ (equivalent to Henry's law for the base), $l_s^{BHZ} = p_s^{BHZ}/a_s^{BH^+}a_s^{Z^-}$ where Z^- is the anion of the solution, and $l_s^{SHZ} = p_s^{SHZ}/a_s^{HS^+}a_s^{Z^-}$ (for the ion-pair charges have been omitted for simplicity), the equilibrium constant may be referred to the vapor phase for all constituents but the solvent, and Equation (41) may be transformed as follows:

$$K_s = p_s^B p_s^{HSZ} l_s^{BHZ}/p_s^{BHZ} l_s^B l_s^{HSZ} a_s = K_v l_s^{BHZ}/l_s^B l_s^{HSZ} a_s \tag{42}$$

Therefore for a series of solvents of variable composition, $a, \ldots, s, \ldots$

$$K_v = K_a a_a\,(\Pi l_a) = K_b a_b\,(\Pi l_b) = \ldots = K_s a_s\,(\Pi l_s) \tag{43}$$

where Πl_s, in general, is equal to $l_s^B l_s^{SHZ}/l_s^{BHZ}$, and K_v is the value of the ratio, $p^B p^{HSZ}/p^{BHZ}$, at unit fugacity at temperature T. By dividing Equation (43) by Πl_a where the solvent a is defined as an extremely dilute aqueous acid solution, and by substituting for each K_s its value from Equation (41), allowing the ratio of m_B/m_{BH^+} to be represented by $1/r_{B,s}$, Equation (44) is obtained relating a series of aqueous acid solutions of increasing acid content to an extremely dilute one. In Equation (44) the

$$K_v/\Pi l_a = (a_{H^+a}/r_{B,a}) = (a_{H^+b}/r_{B,b})(\Pi l_b/\Pi l_a) = \ldots = (a_{H^+s}/r_{B,s})(\Pi l_s/\Pi l_a) \tag{44}$$

second member of the series in solvent a, the dilute aqueous acid solution, is simply equal to the molarity of the acid, since the reference state of each individual solution is its hypothetical $1M$ solution obeying the limiting law. The ratios, $r_{B,s}$, are those determined experimentally for each solvent system; for the evaluation of a_{H^+s} in solvent s it remains only to assess the value of the Πl-ratio in solvents s and a.

Equation (44) may be put into the form of the acidity function, $-H_0 = \log K_B + \log r_B = \log h_0$, if the thermodynamic constant K_v as $K_v/\pi l_a$ is identified with "K_B." The more convenient h_0 may be obtained for the reference solvent a and solvent s.

$$h_0 = (K_v/\Pi l_a) r_{B,a} = a_{H^+a} \qquad \text{(for the reference)} \tag{45}$$

$$h_0 = a_{H^+a} r_{B,s}/r_{B,a} = a_{H^+s}(\Pi l_s/\Pi l_a) \qquad \text{(for solvent } s\text{)}$$

Substitution of the appropriate forms of Equation (39) for the ionic substrates and of Equation (28), for the neutral molecule, allows the acidity function to be expressed in terms of I-factors.

$$h_0 = a_{H^+a}(I_s I_s^{BH^+}/I_s^{B} I_s^{H^+s})(I_a^{B} I_a^{H^+a}/I_a I_a^{BH^+}) \tag{46}$$

It would appear that in solutions of ions, particularly the case of relatively concentrated aqueous acids as predominately ionic solvents, that the electrostatic effects of solute-solvent interaction, rather than the more subtle forms of solute-solvent perturbation, are the more important. If on the basis of the success of the Debye-Hückel treatment, which is purely electrostatic, the masking of the subtle perturbations may be taken for granted; the charge of an ion-substrate may be the more important factor in determining the I-ratio. In highly ionic solvents $I_s^{BH^+}$ may equal $I_s^{H^+s}$, etc. In that event Equation (46) might reduce to the simple form.

$$h_0 = a_{H^+s}(I_s I_a^{B}/I_s^{B} I_a) \tag{47}$$

This problem will be considered again in the presentation.

It is of interest to examine the formation of the acidity function scale in solvents of decreasing water content. Experimentally an indicator, B′, is chosen whose range overlaps that of the indicator B. For indicator B′ in a series of solvents, $m \ldots w$, an equation analogous to Equation (43) or (44) may be obtained. Comparison of Equations (44) and (48) in the solvent of

$$K_v' = a_{H^+m}/r_{B',m}(\Pi l_m) = \ldots = a_{H^+s}/r_{B',s}(\Pi l_s) = \ldots \tag{48}$$

composition s gives

$$a_{H^+s} = K_v r_{B,s}/\Pi l_s^{B} = K_s' r_{B',s}/\Pi l_s^{B'}$$

from which a "$K_v^{B'}$" may be calculated since "K_B" $= K_v^{B}/\Pi l_a^{B}$. The quantity, $K_v^{B'}\Pi l_s^{B}/\Pi l_a^{B}\Pi l_s^{B'}$, in which the I_s^{i}-factors and the exponential factors dependent upon B, BHZ, and H_3OZ (HsZ or HaZ) cancel is essentially equal to $K_v'/\Pi l_a^{B'}$ because the substrates are of similar structure as well as charge. By this calculation the acidity scale is extended to the solvent range in which a "$K'_{B'}$" for the indicator B′ may not be evaluated directly.

D. THE RATE IN IONIC MEDIA

The diagnostic use of the acidity function proposed by Zucker and Hammett (16) predicted a one-to-one correlation of the logarithms of the rate and acidity function for reactions whose activation step depended upon a

protonated substrate.

$$X + H^{+}{}_{s} \underset{}{\overset{K_s}{\rightleftharpoons}} XH^{+} + s \tag{49}$$

$$XH^{+} \overset{K_s^{\ddagger}}{\rightleftharpoons} (XH^{+})^{\ddagger}$$

In solvent s the equilibrium constants, suitable forms from Equation (39), for the two stages are

$$K_s = K_M(\gamma_{H^+X}/\gamma_X\gamma_{H^+s})a_s = (I_s^{X^+H}I_s/I_s^{X}I_s^{H^+s})a_s \tag{50}$$

$$K_s^{\ddagger} = K_M^{\ddagger}(\gamma^{\ddagger}/\gamma_{X^+H}) = (I_s^{\ddagger}/I_s^{X^+H}) \tag{51}$$

As defined before, the activity coefficients approach unity as M_i approaches zero; the standard state is the hypothetical solution obeying the limiting law for each substrate in solvent s at unit molarity; K_M and $K_M^{\ddagger}$ are the concentration equilibrium constants. The rate of the second step is $k_s = \varkappa_s K_M^{\ddagger} = \varkappa_s K_s^{\ddagger}(\gamma_{X^+H}/\gamma^{\ddagger})$ which becomes upon substitution of the value of γ_{X^+H} from Equation (50).

$$k_s = \varkappa_s(K_s^{\ddagger}K_s/K_M a_s)(\gamma_X\gamma_{H^+s}/\gamma^{\ddagger}), \tag{52}$$

and the observed rate is k_s'

$$k_s' = k_s K_M M_{H^+s} = (\varkappa_s K_s^{\ddagger}K_s/a_s)(\gamma_X/\gamma^{\ddagger})a_{H^+s} \tag{53}$$

by substitution of $\gamma_{H^+s} = a_{H^+s}/M_{H^+s}$. Substitution of the values of $K_s^{\ddagger}$ and K_s from Equations (50) and (51) and that for the activity of the proton in solvent s in terms of the acidity function, Equation (46), indicates the extent of solvent-substrate dependency. The concentration of the reactant, X, is assumed to be sufficiently low that its activity coefficient is unity; that of the activated complex is unity due to the probability of the state.

$$k_s' = \varkappa_s h_0^s(I_s^{B}I_s^{\ddagger}/I_s^{B^+H}I_s^{X})(\Pi I_a^{B}) \tag{54}$$

E. THE SUBSTRATE RESTRICTION IN PREDOMINATELY IONIC MEDIA

Equation (54) shows that the correlation of the rate and acidity function depends upon the variation of the transmission coefficient in $\varkappa_s$ with the solvent as well as the ratio of the I-factors of the substrates involved; the factor πI_a^{B} is constant throughout. In a rate-equilibrium correlation the transmission coefficient for the rate in solvent s is not compared to that for the same substrates in solvent a; therefore one can only assume that it may be close to unity (5–10%). The I'_s-factors are another matter. It would appear, however, that in a solvent containing a high ionic background such as the aqueous mineral acid solvents, the solvent-solute interaction of importance would be the electrostatic influence and would outweigh the con-

sideration of the more subtle solvent-solute perturbations. If this assessment of the interaction is correct the effect of the activated complex, $(XH^+)^\ddagger$, may be compared with that of the conjugate acid of the basic indicator, B^+H, even though they differ greatly in structure, bonding, and dispersal of the charge. Similarly the substrates X and B, both being electrically neutral, may have similar effects on the predominately ionic solvent. This similarity of the activity coefficients (solubility data) of neutral molecules in sulfuric acid solutions has been reported by Deno *et al.* in 1957 (37). The correlation of Equation (54) then may be written as

$$k_s' = \lambda_s h_0^s (\pi l_a^B) \tag{55}$$

Experimentally, correlations of reactions fitting the gross restrictions have slopes in the log-log graph of the data of unity within 15 to 30% (34). Whether this variation is attributable to the non-proportionality of the I-factors, the variation of the transmission coefficients, or the use of kinetic data outside of the range of ideal solute behavior, is problematical.

Objectively, in the use of these equations or theory it might be pointed out that a parallelism is demanded between the substrates of the rate and those of the equilibrium which is being used, for a one-to-one correlation. The mechanism of proton transfer in the acid-base equilibrium must be considered; a one-to-one correspondence of rate and equilibrium constants or rate and rate constants means primarily that the substrates have similar effects on the solvent in the range of the limiting law; the exact nature of the participating substrates, reactants and activated complexes, and reactants and products (equilibrium) must be inferred. This is the essence of the problem of determining a mechanism.

In the course of the preparation of this section as many new questions have arisen as the author originally sought to answer. The further consideration of the mechanism-rate-environment relationship or of the temperature coefficients of reactions is not possible at this time.

IX. SPECIFIC TECHNIQUES AND ILLUSTRATIONS

1. Open Systems

One of the simplest methods used for rate measurements is that based upon the techniques of volumetric analysis. The reaction solution is maintained in a thermostated, stoppered flask from which samples may be withdrawn periodically by pipet for analysis. This arrangement lends itself unusually well to work being conducted near room temperature. In this case a large volume of solvent may be handled without too great a time

delay in reaching the thermostat temperature. The method is reliable if there is no loss of volatile solvent or solute and no interference by atmospheric oxygen, carbon dioxide, or water with the reaction being studied. Usually where this technique can be used one cannot quench the reaction for analysis by lowering the temperature, but must stop it by either diluting in a large volume of solvent or by the removal of one of the reaction components by delivering the aliquot into a suitable reagent. The technique is excellent for studies in aqueous systems which must be analyzed chemically. Precision work may be accomplished. For systems with volatile components the technique is apropos only as a preliminary survey for orientation.

For fast reactions multi-compartment vessels are useful to facilitate the mixing of the thermostated solutions of the reagents. An H-shaped flask was used for the studies of the chlorination of *p*-anisic acid with hypochlorous acid (51). For the studies of the oxidation of phenanthrenediols with lead tetraacetate, a three-compartment vessel, Criegee's "dreischenkelrohr," was needed in order to hold an iodide solution to stop the reaction (52).

For survey purposes above room temperature a flask fitted with a reflux condenser, which will accommodate a pipet for the withdrawal of samples, may be used for the study of a reaction at the temperature of the refluxing solution. In this case one allows for the effective concentration of the solute by obtaining an initial value after thermal equilibrium has been established. Other variations are possible, such as suspending the reaction mixture in an out-size test tube through one neck of a multineck flash which contains a solvent of the desired boiling point and which bears a reflux condenser and thermometer. Actually a thermostat formed by a refluxing solvent (53) gives a flexible bath of wide temperature range and close temperature control when provided with a pressure regulator. It is desirable for use with small volumes of reaction solutions with as large a surface area as possible exposed to the refluxing liquid.

2. Closed Systems

A. AN INERT ATMOSPHERE

In some chemical systems it is not necessary to use a sealed reaction vessel, but the reaction system must be protected to a certain extent from the atmosphere. In such cases a stream of nitrogen or inert gas across the surface of the liquid suffices (54). The decomposition of *tert*-butyl hydroperoxide in dodecane (55) is an example of a reaction which needed protection from two sources of contamination by oxygen. Both a primary decomposition of the hydroperoxide to give off oxygen and a secondary reac-

tion involving the formation of alkyl radicals which could absorb either the atmospheric or internal oxygen were established. By using a flask having a capillary inlet (nitrogen), an arm to hold a specially designed pipet for the removal of samples under a stream of oxygen-free nitrogen, and a vapor barrier (at 20°C.) to prevent entrainment of the solute, the system could be flushed for the study of the primary decomposition at 98°C.

B. SEALED AMPOULES

The technique involving sealed ampoules is by far the most widely used for experiments whose vessels are not dictated by the analytical method employed. It is necessary where the solute and/or the solvent losses might be great due to the duration of the measurements of the reaction or to an unfavorable differential in the temperature of the reaction study and the boiling points of the components of the solution. It is a versatile method for reactions whose rates are not appreciable at room temperature or below, and whose solutions may be exposed briefly to the atmosphere so that ampoules may be filled with ease. Hygroscopic solutions as well as those sensitive to oxygen at room temperature must be transferred and sealed by a vacuum line technique. Briefly the ordinary procedure consists of the following steps: test tubes which have been previously washed, rinsed, and dried or baked are drawn out in an oxygen flame to make a constricted neck of about 3 mm. diameter. Care should be taken to allow the wall of the tube to collapse partly and thus to thicken before being drawn out, otherwise the wall at the seal may be dangerously thin. A test tube of about twice the size of the sample is convenient so that there is ample length for making the constriction. The position of constriction should allow a minimum space for vapor above the intended sample, yet permit the constriction to be sealed without endangering the solution. The tubes may be flushed with an inert gas before and after filling. The filling of the tubes may most easily be accomplished by using a large pipet containing a half or so of the master solution. During the sealing it is often advantageous to work with the samples immersed in an ice bath. It is a convenience to have a number of baskets of coarse mesh which can be labelled with the run number, etc., for holding the set in the thermostat. The ampoules may then be broken at suitable time intervals for analysis.

The reaction solution may be prepared volumetrically, but calibration and temperature corrections tend to become cumbersome unless one is working in the 15 to 30°C. range. It is far simpler to make solutions on a weight basis. The ampoules may be filled with the approximate amount of the solution, and an aliquot removed when the seal is broken. During the course of the investigation an aliquot may be weighed, before analysis. Usually this is done at the beginning and at the end of the experiment.

The employment of approximate volumes in the ampoules as opposed to measured amounts eliminates the necessity of rinsing a measured volume into a container for analysis.

For the study of the hydrolysis of methylene dichloride in aqueous potassium hydroxide (56) in the absence of a vapor phase, a nickel reaction vessel sealed with a mercury piston was used.

3. Special Analytical Methods

For kinetic studies the applications of polarography, polarimetry, and spectrophotometry are essentially the use of the respective instruments for the quantitative analysis of one or more constituents of the reaction solution. As analytical problems which are best reviewed in the treatises on the use of the instruments only a few brief points need to be mentioned here.

A. POLAROGRAPHY

This method (57,58,59) is applicable specifically to compounds or ions which may be reduced at a dropping mercury electrode as cathode, or oxidized if the dropping mercury electrode is made the anode, within the theoretical voltage range of the dropping mercury electrode of +0.6 v. and −2.8 v. In customary analysis both the potential and the current are measured automatically and recorded as the electomotive force is being increased. From the graph of the current versus the voltage both the concentration and the nature of the species present may be determined since the half-wave potentials are characteristic and need to differ by only 0.2 v. For kinetic studies conducted in the cell a suitable fixed voltage for the species is chosen and the change in current is observed with time. The method has been of value in the studies of the equilibria (60) and kinetics (61) of formation of complexes of cupric (60) and chromic ions (61) with the anions of various organic acids in aqueous solution. In kinetic studies of the pinacol-pinacone rearrangement of 2-methylpropane-1,2-diol and its dimethyl ether (62) to form isobutyroaldehyde, polarographic determination of the aldehyde (in suitably diluted aliquots of the reaction mixture) was found more reliable than methods depending upon oxime or hydrazone formation. In nonaqueous solution dimethylformamide with either tetraethyl ammonium iodide or lithium chloride as supporting electrolytes was used for the determination of the half-wave potentials of anthraquinone and its hydroxy derivatives, various aromatic aldehydes and ketones, and polycyclic aromatic hydrocarbons (63). Measurements have also been made in dioxane–water mixtures (63,64), acetonitrile (63,65), and 2-methoxyethanol (63).

B. POLARIMETRY

Some Aspects of Instrumentation. The polarimeter most often used in organic laboratories is the Lippich double-field (or half-shadow) type with Nicol prisms for the measurement of the change in the direction of vibration of linearly polarized light in the visible range upon passing through an optically active substance either as a pure liquid or in solution. This type of instrument and its use have been described briefly in several texts (66,67). A detailed treatise on the broader aspects of the instrumentation of polarimetry for all three types of polarized light in the visible, ultraviolet, and infrared appeared as part of this series of volumes (68). The monochromatic light source usually used is the yellow sodium-D line; however Heller (68) recommended the use of the green mercury arc since the eye was more sensitive to it than the yellow sodium line. The solution of the optically active constituent with either must be colorless since the rotation of a compound at a wavelength at which it absorbs may be anomalous (the Cotton effect) or the extinction too great. For compounds whose rotatory dispersion curves (rotation versus wavelength) are available a shorter wavelength may be found where a larger rotation than ordinarily possible with a sodium source would be advantageous for more precise work.

Calibration. Besides the wavelength of the light source, the rotation of a substance is a function of the concentration, temperature, length of the sample path, the nature of the solvent, and the degree of dissociation. For analytical purposes in kinetic problems temperature, solvent, wavelength, and path distance are held constant in order that the concentration change may be observed as a function of the rotation and time. That the rotation is a linear function of the concentration of the optically active species in the solution is usually tacitly assumed. This assumption based upon the constancy of the specific (or molecular) rotation in dilute solution should be demonstrated. The molecular rotation of 1-menthyl esters of substituted benzoic acids, for instance, is not constant (69). If an optically active salt or acid or base were present its degree of dissociation would have to be considered (67). For sufficiently slow reactions the kinetic studies near room temperature are most conveniently conducted in a thermostated polarimeter tube. At higher temperatures or with rapid reactions the polarimetric analysis is conducted on quenched samples.

Application. The racemization of substituted *N*-benzoyldiphenylamine-2-carboxylic acids in which the optical activity is due to restricted rotation has been studied in a fixed chloroform–ethanol mixture at 20°C. with the mercury arc source (70). The pseudo first-order racemization of benzyl-α-*d* bromide by lithium bromide was determined in ethylene glycol diacetate at 34°C. (71). The solvolysis of α,γ-dimethylallyl acid phthalate in aqueous acetone was studied in sealed ampoules in the tem-

perature range of 70 to 100°C. (72). The difference between the polarimetric and titrimetric rates indicated that the greater rate of loss of optical activity was due to a partial racemization of the ester by an isomeric intramolecular allylic rearrangement before solvolysis. The mechanism consistent with the kinetic data for the racemization and solvolysis depended upon an equilibrium between the ester and the symmetrical ion-pair intermediate and the irreversible formation of the solvolysis products from the ion-pair intermediate.

A study in which the optically active center was not affected but served as a measure of the extent of the reaction was the methoxide catalyzed methanolysis of 1-methyl esters (73). In this case the correlation of the rate and the concentration depended upon the difference (and the constancy) in the specific rotation of the ester and the 1-menthol.

C. SPECTROPHOTOMETRY

The measurement of the absorption spectra of compounds in the ultraviolet, visible, or infrared range, either for the characterization or the quantitative analysis of a constituent, has become such a familiar process that amplification is unnecessary. The greater availability of spectrophotometers and photometers (used with a filter or filters to give a narrow spectral band), based upon a null principle or double beam, has made this method of analysis very attractive for the measurement of rate constants, especially for studies in the ultraviolet or visible at temperatures between 15 and 30°C. where thermostated cells may be used. For discussions of instrumentation the reader is referred to the manuals accompanying specific instruments, or to the articles of West (74), Brode (75a), and Nielsen and Otejen (75b).

The Analytical Principle in Complex Solutions. The guiding principles are the laws of Lambert and Beer which may be expressed in the following form,

$$A = \log (I_0/I) = -\log (I/I_0) = \log (1/T) = \epsilon M \mathrm{d}$$

in which A is the molar absorbance (synonymous with optical density), T the transmittance, I_0 the intensity of the incident monochromatic beam (through the solvent), I the intensity of the transmitted beam (through solvent and solute), ϵ the molar extinction coefficient, M the concentration in moles per liter, and d the thickness of the cell in cm. For a mixture of components all of which possess an absorption maximum in a particular spectral region, the absorbance of the mixture at a particular wavelength is considered to be a linear combination of the absorbances of the constituents at that wavelength.

$$A = \mathrm{d}\sum \epsilon_i M_i \qquad (56)$$

For the absolute determination of M_i for each component in an n component system, the absorbance of the mixture is determined at n wavelengths, and the extinction coefficients for each component are determined at each of the n chosen wavelengths to give the n^2 parameters for the n equations in n unknowns. That each species in the mixture obeys the Lambert-Beer law, that A_i is a linear function of M_i passing through the origin and possessing a slope of $\epsilon_i d$, is established experimentally for each component at each wavelength. The instrument should also be calibrated with a solution for which the extinction coefficients are accurately known: potassium nitrate or chromate may be used for the ultraviolet (74,75a). In the determination of the extinction coefficients one weighing and series of dilutions constitutes one point. At least three master solutions should be prepared for precise work; the extinction coefficient should be evaluated by a least squares procedure. In kinetic studies the absolute values of the concentrations need not always be determined, but the conformity to the Lambert-Beer law should be checked.

Unimolecular Reactions at One Wavelength. The spectrophotometric method is most easily applied to unimolecular reactions which in some cases may be followed at one wavelength only. For the reaction, $A \rightarrow B + C$, in which $-dM_A/dt = dM_B/dt = dM_C/dt = kM_A$, the molar absorbance of the solution at a particular wavelength at any time may be expressed by Equation (57) if the three components obey the Lambert-Beer relationship. Differentiation of equation (57) with respect to time and substitution

$$A = d(\epsilon_A M_A + \epsilon_B M_B + \epsilon_C M_C) \tag{57}$$

of the differentials above gives the following expression for the change in absorbance of the solution with time.

$$-dA/dt = d(\epsilon_A - \epsilon_B - \epsilon_C)\,(-dM_A/dt)$$
$$= d(\Delta\epsilon)\,(-dM_A/dt) = d(\Delta\epsilon)kM_A \tag{58}$$

From the consideration of the stoichiometry of the reaction, $M_B = M_C = M_A^\circ - M_A$, and the absorbance at the end of the reaction, $A_\infty = d(\epsilon_B - \epsilon_C)M_A^\circ$, M_A, M_B, and M_C may be eliminated in Equations (57) and (58) to give the following expression for the rate of change in the absorbance.

$$dA/dt = k(A - A_\infty) \text{ or } \ln (A - A_\infty) = kt + \ln (A_0 - A_\infty) \tag{59}$$

For a system of components for which the $\Delta\epsilon$ of Equation (58) is large at a particular wavelength, the rate constant may be determined easily by the percentage change in the absorbance at that wavelength.

Each application is unique for a particular set of components; therefore only a few keys to the literature are cited to illustrate the general analytical approach to the problem. A reaction to which this type of analysis was

applicable in the ultraviolet was the study of the rearrangement of 1-phenylallyl *p*-nitrobenzoate and other esters in chlorobenzene (100–130°C.) (76). The first order reaction was accompanied by formation of small amounts of *p*-nitrobenzoic acid giving a constant dependent upon the acid concentration. Other reactions for which catalytic constants were determined by Equation (59) were the dehydration of 4-(X-phenyl)-4-hydroxy-2-butanones in aqueous acids (estimate of precision: 3%) (77) and the hydrolysis of diacetylamine and succinimide in aqueous alkali (78). A Guggenheim treatment of the data of the imidazole-catalyzed hydrolysis of *p*-nitrophenyl acetate in a solvent composed of dioxane and water gave catalytic rate constants for which the precision of the fit of the data was in some cases less than 1%, the worst being 3 to 5% (79). The imidazole-catalyzed hydrolysis of *p*-substituted-phenyl acetates was also studied in ethanol–water solution; concentrations were calculated in this study from calibration curves (80). If ϵ_B and ϵ_C are negligible with respect to ϵ_A in Equation (57), or if any two coefficients are negligible with respect to the third, the solution of Equation (58) is trivial. Recent examples of this more simple case were the hydrolyses of thioacetamide (Guggenheim treatment of the data) (81) and xanthate (82).

Unimolecular Reactions at Several Wavelengths. In the event that the absorption curves for the reactants and products are coincident such that there is no wavelength at which $\Delta\epsilon$ is sufficiently large, the kinetics would have to be studied at a number of wavelengths determined by the number of concentrations to be determined. Such was the case for the hydrolysis of diethylaminoethyl acetylsalicylate hydrochloride in various buffers (83a); the hydrolysis of methyl pyrrolidylacetylsalicylate hydrochloride was followed in contrast by Equation (59) (83b). In the case of uncertain stoichiometry due to simultaneous reactions, such as A → B and A → C, or the occurrence of a side reaction, the study would have to be followed at three wavelengths, the three extinction coefficients having been determined at each of three wavelengths to give the nine parameters for three equations in three unknowns. The kinetics of the *o*-semidine rearrangement of *p*-hydrazotoluene, accompanied by disproportionation, required analysis of four components (16 parameters); the precisions of the determinations was estimated at 5% (84). The kinetics of the rearrangement and oxidation of hydrazobenzene were determined by complete resolution of the observed absorption spectra (85).

Bimolecular Reactions. The study of second order reactions, A + B → C, is somewhat more complicated. Only in the case of equal initial concentrations of reactants and a large difference between the molar extinction coefficients of the reactants and products may an expression similar to Equation (59) be derived—for the reciprocal of $A_\infty - A$ versus t.

If the initial reactant concentrations are not equal, and the absorption of the reactants and products differs, the following expression may be derived for the change in absorbance at a particular wavelength.

$$\ln (A_\infty - A) - \ln (A'_\infty - A) = (A_0 - A_\infty)rki - \ln (r + 1)$$

in which $r = (M_A^\circ - M_B^\circ)/M_B^\circ$, $A_0 - A_\infty = d(\Delta\epsilon)M_B^\circ$, $A'_\infty = (r + 1) A_\infty - rA_0$, and $(\Delta\epsilon)(M_A^\circ - M_B^\circ) \neq 0$. It has been found more convenient to reduce the kinetics to pseudo first order by keeping one reactant in large excess. From the initial rates and the concentration of the reactant in excess the second-order constant may be estimated. This solution was used for the study of the following reactions; (*1*) chloral hydrate and *p*-nitrophenyl acetate to give *p*-nitrophenol in buffer solution (86), (*2*) the alkylation of mesitylene and anisole by diphenylmethanol in acetic–sulfuric acid mixtures (87), (*3*) the nucleophilic substitution of piperidine and 1-X-2,4-dinitrobenzenes in methanol (88), and (*4*) the acid-catalyzed formation of *N-tert*-butylacrylamide from acrylonitrile and *tert*-butyl alcohol (89). In the condensation of phenylhydroxylamine and nitrosobenzene to form azoxybenzene the concentrations of all three components were determined by the use of a triangular composition diagram based upon the measurement of the absorbance of the pure components at a fixed concentration at four wavelengths (90).

In the Visible. Absorption techniques in the visible range were used for the determination of manganic ion; initial rates of oxidation of aldehydes and ketones by manganic pyrophosphate indicated that the oxidation occurred after enolization (91). The rates of the condensation of various heterocycles (92) have been studied by the colorimetric determination of the unreacted diazonium salt with β-naphthol in a borax buffer (93,94). In these cases the absorption of the coupled heterocycle was slight; a small correction was applied. In the study of the nitrite-catalyzed solvolysis of acetic anhydride in 50% aqueous acetone the catalytic effect of nitrite ion was believed to produce an intermediate, acetyl nitrite (95). Rate measurements conducted in the presence of α-naphthylamine in which 4-amino-1,1′-azonaphthalene was measured confirmed the assumption.

4. Measurements of the Heat of Reaction

A. CALORIMETRY

The Principle and Assumptions. The calorimetric method of determining the rate of a reaction is based upon the measurement of the heat evolved or absorbed with time. If the heat capacity of the solution remains constant throughout the course of a reaction and no external work is per-

formed, the energy released (for an exothermic reaction) in unit time is proportional to the amount of reaction which occurs. The data in the form of temperature measurements of the contents of the calorimeter describe the course of the reaction with time.

The methods were developed in conjunction with the study of the heats of slow reactions. Barry (96) was the first to employ calorimetric measurements for the determination of both the rate and the heat of the reaction in studies of the inversion of sucrose in hydrochloric acid solution. Sturtevant (97,98) refined and enlarged the technique through his studies of both first- and second-order reactions.

The Apparatus. For rate studies which are necessarily conducted in dilute solution in order that the heat capacity of the solution may be assumed constant, a sensitive all-metal calorimeter of low heat capacity is desirable. Temperature measurements are usually made with resistance thermometers or thermocouples of low lag which necessitate the use of a sensitive potentiometer and galvanometer. The technique of using twin calorimeters where the heat necessary to duplicate the reaction is measured is probably the more precise method (97). Sturtevant (97) described in detail an unstirred adiabatic calorimeter whose design was kept as simple as possible, yet consistent with a sensitivity of 1 to 2%, for the study of the inversion of sucrose (exothermic) and the decomposition of diacetone alcohol (endothermic). The assembly consisted of a heated platinum calorimeter, an electrically heated adiabatic jacket composed of concentric chromium plated copper cylinders within a Dewar flask which in turn was placed in a submarine can of copper and submerged in a thermostat (25°C.). Temperature measurements were made in this case against a reference calorimeter by multijunction thermocouples (thermels). The intricacies of calorimetry are beyond the scope of this paper. An excellent presentation of the subject is available in this series (99) and should be consulted for calorimeter design, temperature measurement and control, the design of thermels, calibration techniques, circuitry, and the corrections for thermal leakage and the heats of stirring.

The Measurements. Temperature measurements (or the equivalent) are made from the inception of the reaction up to about 75% completion beyond which point the correction for thermal leakage and stirring, if used, may become as great as the heat effect of the reaction. Due to the heats of mixing or solution, depending upon how the reaction is initiated, and the calorimetric difficulties at the end of the reaction, initial and final temperatures are obtained by an extrapolation procedure. From the temperature readings taken at equal intervals of time, the initial and final temperatures may be calculated by a method based upon the Guggenheim treatment of data (100,101). At the end of the reaction the heat capacity

of the calorimeter and its contents may be determined. The calculated values of the initial and final temperatures along with the heat capacity of the solution permit the calculation of the heat of the reaction with the same accuracy as the velocity. If the temperature change for the reaction is large, as would be the case for reactions with high energies of activation, the calculations are more detailed in order to arrive at the value of the isothermal reaction rate constant. The method outlined was applied (97) to reactions with half-lives of 15 minutes to 3 hours with an accuracy of about 2%. It would appear that very precise values could be obtained by this method for compounds whose analysis is otherwise difficult. There would be a limitation imposed by calorimetric difficulties for extremely slow reactions. An advantage of the method is its adaptation for automatic control and temperature recording.

The Mechanism of Nitration: the Nitronium Ion (Nonadiabatic Calorimeter). The exigencies of war-time research led Westheimer and Kharasch (102) to use the less accurate nonadiabatic calorimeter to investigate the nitration of nitrobenzene in sulfuric acid. The calorimeter for these studies consisted of a 500 ml. Dewar flask supported on a cork in a can which was sealed with an oil-resistant gasket and lid. The lid of the can accommodated a Beckman thermometer, a stirrer, and the introduction of materials. The calorimeter, charged with a solution of nitrobenzene in sulfuric acid, was submerged in an oil thermostat at 25°C. to a depth of 1 cm. After thermal equilibrium was established a solution of nitric acid in sulfuric acid was added. Temperature readings, taken at equal intervals, were corrected for thermal leakage and the heat of stirring. Calculations were made by the method of Roseveare (100) using successive approximations. This type of calorimeter could be used successfully for these experiments where large differences in rates were being measured and where the temperature change in the course of the reaction was large.

The rate studies of dilute solutions of nitrobenzene and nitric acid (0.02*M*) in moderately concentrated (85–95.6%) sulfuric acid as the solvent gave second-order kinetics, first order in nitrobenzene and first order in nitric acid. The velocity of nitration reached a maximum in 90% sulfuric acid. Addition of bisulfate ion increased the rate only in solutions which were more than 90% sulfuric acid and decreased the rate in those in which the solvent was less than 90%. These data indicated that the maximum rate of nitration was a function of a definite acidity, not of the dehydrating power or the concentration of the sulfuric acid solvent. The addition of bisulfate, lowering the acidity of the solvent if added at concentrations of less than 90%, would decrease the rate. If the bisulfate were added at acid concentrations of greater than 90%, it would decrease the acidity to the optimum and thereby increase the rate. Other nitroaromatics were

surveyed to ascertain the effect of structure upon the position of the maximum rate. The acidity–rate curves proved to be alike. In order to decide which of the possible ionizations of nitric acid in sulfuric acid was the more likely, two indicators which ionized in 80 to 90% sulfuric acid were chosen as a measure of the acidity. These were anthraquinone, whose ionization would be similar to that of nitric acid if it ionized as $HNO_3 + H_2SO_4 \rightarrow H_2ONO_2^+ + HSO_4^-$, and tri-*p*-nitrophenyl carbinol, whose ionization would be similar to that of nitric acid should the latter ionize as $HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$. Colorimetric measurements of the fraction of the colored, ionized form were made as a function of the concentration of sulfuric acid. The similarity of the curves of the logarithm of the rate of nitration and the logarithm of the fraction of carbonium ion from the carbinol, respectively, versus the percentage of sulfuric acid indicated that both reactions depended upon the same type of ionization. The fraction of ionized anthraquinone versus the composition of the sulfuric acid solvent bore no resemblance to the other curves. In this fashion evidence was accrued for the identification of the species of nitrating agent, NO_2^+, in sulfuric acid solution.

B. DIFFERENTIAL THERMAL ANALYSIS

A method of great flexibility, dependent upon the measurement of the heat effects, is the application of differential thermal analysis (103) to the kinetics of simple reactions. The method depended upon the measurement of the temperature difference between the reactant solution and a reference solution, and the measurement of the temperature of the reactant solution, both as a function of time, as the two solutions were heated simultaneously in a bath. The reference solution may be the pure solvent or a solution lacking one of the reactants. The temperature of the cells must be uniform. It was assumed that heat was transferred to the solutions only by conduction. The apparatus consisted of a pair of matched Pyrex tubes, each stirred, a bath with a heating element controlled with a Variac (heating did not need to be a linear function with time), and a calibrated thermometer for the determination of the temperature of the reactant solution. The temperature difference between the two cells was measured by a differential thermocouple whose signal was amplified and recorded automatically on fine-scale chart paper. This apparatus was found to be suitable for the quantitative measurement of reactions accompanied by a heat transfer of 5 kcal./mole.

The reaction was begun at a temperature sufficiently low to ensure that the rate was inappreciable. Measurement was continued until the reaction had gone essentially to completion. The resulting curve of the temperature difference, ΔT, versus time was normal in shape, beginning and

ending with a ΔT equal to zero. It was analyzed in terms of the total area under the curve, A, the fractional area under the curve from zero to time t, a, the value of ΔT at t, and the slope $d\Delta T/dt$ at t. For a first-order reaction the expression for the rate constant at any particular temperature was

$$k = [C_p(d\Delta T/dt) + K\Delta T]/[K(A-a) - C_p\Delta T]$$

where in addition to the values described above, all that was needed was the value of K and C_p. Form the equation, $\Delta H = KA$, the proportionality constant, K, characteristic of the apparatus, was evaluated by dissipating a known quantity of heat in the cell. The heat of dilution of sulfuric acid was used. The total heat capacity, C_p, of the reactant solution or the reference solution was approximated by using the value of the pure solvent. It was assumed that the heat capacity was constant throughout and that those of the two cells were equal. These assumptions required the use of dilute solutions and equal volumes in each cell.

From the single curve the specific rate constant could be calculated at any number of temperatures in the range studied, upon the assumption of a definite order for the reaction. If it were assumed that the energy of activation was constant over the temperature range, the rate constants would be a linear function of $1/T$ only if the correct assumption as to the order of the reaction were made. In addition to the assumptions of the constancy of ΔH, C_p, and K and of the proportionality of an element of reaction to an element of enthalpy, it was assumed that the reaction could be described by a single rate constant. The method was applied to the first order decomposition of benzene diazonium chloride between 21 and 67°C. and to the pseudo first-order reaction of ethyl iodide and dimethylaniline, as the solvent, to form the quaternary salt in the temperature range 25 to 150°C. The advantages of this method appear to be many. For simple reactions the energy of activation may be evaluated from one experiment, as well as the heat of the reaction, both these data being necessary for the calculation of the activation energy of the reverse process.

5. Dilatometry: Measurements of the Volume Change

A. THE PRINCIPLE

An extensive property of a system which has been used during the past sixty years to determine the rate of reaction is the volume. Volume measurements may be used whenever there is a difference between the densities of the reactants and those of the products, and the volume change is directly proportional to the change in the concentration. The application therefore depends upon the use of sufficiently dilute solutions in which

the partial molar volumes of the solutes are constant. If the total volume of the solution, V, consisting of both the reactants and the products, is a linear function of their molar concentrations at constant temperature and pressure the relationship is expressed by equation (60),

$$V = \sum v_i M_i + v \tag{60}$$

where v_i and M_i are the constant and the molar concentration for the ith constituent respectively. For the reaction, A + B → C + D, the decrease in volume (for a reaction accompanied by a contraction) at time t may be expressed in terms of the extent of the reaction; x = molar concentration of C or D at t.

$$V_0 - V = (v_A + v_B - v_C - v_D)x = (\Delta v)x \tag{61}$$

If A is the constituent in lesser amount, at the completion of the reaction the total volume change is shown in Equation (62). Elimination of the factor, Δv, in Equations (61) and (62) gives the following expression:

$$V_0 - V_\infty = M_A^\circ(\Delta v) \tag{62}$$

$$(V_0 - V)/(V_0 - V_\infty) = x/M_A^\circ \tag{63}$$

The general rate equation may then be obtained in terms of the volume change.

$$-dV/dt = [kM_A^\circ/(V_0 - V_\infty)]\,(V - V_\infty)^2$$

The validity of the application of this method depends upon establishing the linearity of the volume-molarity function either directly by Equation (60) or indirectly by Equations (61) and (63). The coefficients, v_i, of Equation (60) could be determined empirically. However, the linearity is usually demonstrated by showing the constancy of $\Delta v = (V_0 - V_\infty)/M_A^\circ$ for various values of M_A° which are checked by chemical or spectrophotographic means.

B. THE APPARATUS, THE CALIBRATION, AND THE SOURCES OF ERROR

A dilatometer is used for the measurement of the change in volume. In general this consists of a bulb to which is sealed a capillary for the observation of small changes in the volume. In design there are many variations necessitated by the requirements of particular experimental conditions, but in general dilatometers fall into two classes; those whose bulbs are filled by a large bore inlet controlled by a stopcock and those filled through the capillary. An example of the dilatometer with a tap may be found in the work of Bronsted and Guggenheim (104) on the effect of acidic and basic catalysis on the mutarotation of glucose (18°). The

dilatometer for these experiments consisted of an 165 ml. cylindrical bulb with a graduated capillary. The bulb was connected through a U of glass tubing, regulated by a stopcock, to a mixing chamber which accommodated a stirrer, thermometer, and heater. The whole apparatus with the exception of the capillary was thermostated. The solvent for the study was heated one degree above the thermostat temperature to compensate for the absorption of heat upon dissolving the glucose. For reactions accompanied by small changes in volume it was found advantageous to provide a mercury seal between the bottom of the dilatometer bulb and the stopcock. This was provided by the addition of a T-seal to a mercury reservoir. After reaction solution was transferred to the dilatometer from the mixing chamber by suction, mercury was admitted to the system to the designated section of tubing to eliminate errors due to leakage about the stopcock.

The tapless dilatometers developed by Benford and Ingold (105) offer a number of advantages. Not only were the difficulties of greasing and maintaining a leakless stopcock eliminated, but a greater range of application was possible also, since the system was not restricted to compatibility with the mercury seal. For the studies of Hughes, Ingold, *et al.* (106) of the mechanism of nitration of aromatics in nitromethane and acetic and nitric acids three designs were used. The dilatometers were U-shaped, the bulb being placed on the vertical or semi-vertical to avoid entrapping bubbles, the two arms being capillaries. The dilatometer was filled by applying a vacuum to one arm while the other was submerged beneath the surface of the reaction mixture. If needed, the reaction mixture could be stirred by the incorporation of a glass-sealed magnetic bar in the bulb for use with a magnetic stirrer which could be mounted adjacent to the bulb in the thermostat. It was found that the height of the liquid needed to be measured only in one arm of the dilatometer. For the nitration of sulfonic acids in aqueous nitric acid, however, it was necessary to use the dilatometer with a tap in order to avoid erratic surges of the meniscus.

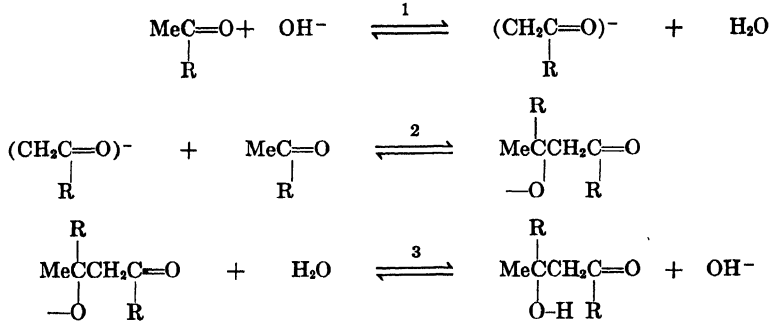
For dilatometric measurements a device for observing the height of the column of solution in the limb of the dilatometer and a precise thermostat are needed. The height may be measured by simply affixing a scale (in mm.) to the capillary (105); with a graduated capillary the meniscus may be viewed by a magnifying glass through a short length of tube to avoid parallax (104). For more precise measurements a cathetometer is advisable (105). Since the volume is a function of temperature very careful thermostating is necessary. It is desirable to use a sensitive regulator; toluene or mercury sealed under hydrogen. Benford and Ingold described two such thermostats, one for use between 25 and 80°C. accurate

to 0.001°C., and the other suitable for work between 15 and −10°C. accurate to 0.002°C. From the densities of the solvent at different temperatures or the coefficient of expansion (107) of the solvent, the cross sectional area of the capillary, and the volume of the dilatometer, the fluctuation in temperature allowable for a minimal fluctuation of the meniscus may be estimated.

Two of the errors to which this technique is subject have been pointed out; (*1*) leakage, if a dilatometer with a stopcock is used; and (*2*) excessive fluctuation of the column of liquid due to inadequate temperature control. Since the rate constant is dependent upon the difference in readings, the height of the solution in the capillary need not be related to the total volume. The uniformity of the capillary bore, however, is important. Bronsted and Guggenheim (104) calibrated their apparatus by observing the apparent length of a weighed thread of mercury. The tapless dilatometers of Benford and Ingold (105) were calibrated by observing the thermal expansion of conductivity water in an adjustable precision thermostat; a Beckman thermometer was used for the determination of the temperature differences. The dilatometer constant so determined had the dimensions of the fractional change in volume per centimeter; the coefficient of expansion of glass was negligible in the calculations for the dilatometer constant. The initial heat effect (heat of solution or dilution) is important with respect to the first readings. The heat of reaction is assumed to be compensated for by the thermostatic bath. An expression for the change in the level of the meniscus with the heat effects, heat capacity of the solution, and the rate of reaction was applied, however, to the hydrolysis of acetal (108). The initial heat effect may be compensated for by preheating or chilling the solvent before the reactant is added (104). In the exothermic nitration of benzene (105) readings were taken upon filling the dilatometer (2 or 3 minutes after mixing), and the initial reading was obtained by extrapolation. In the event that the reaction does not go to completion, the contents of the dilatometer at the end of the period of measurement must be analyzed by other means in order to determine the extent of reaction so that the extrapolation may be made. Another precaution that should be emphasized for either type of dilatometer is cleanliness of the apparatus. Any interference with drainage will introduce an error. Benford and Ingold (105) also mentioned, in conjunction with the use of the tapless dilatometer, that a droplet remaining in the capillary tip after filling interferred with the hydrostatic pressure. This difficulty was largely eliminated by the use of a removable bent tip used only for the filling of the dilatometer.

C. ADOLIZATION AND DEALDOLIZATION: THE RATE OF AN INACCESSIBLE REACTION FROM EQUILIBRIUM AND KINETIC DATA

Applications of the dilatometric technique of considerable interest are the studies of aldolization and dealdolization. These reactions are related by the following equilibria:



The magnitude of k_1 and k_{-1} compared to k_2 was established by tracer studies and kinetic work conducted by the dilatometric method.

The forward reaction, aldolization, was studied in the case of acetaldehyde (R=H) by Bell (109). The dilatometric method was used for these studies because the reaction was too fast to give accurate rate constants by analysis for the aldehyde with bisulfate to form the addition compound. Density measurements showed that in dilute solution the condensation was accompanied by a contraction of 50 cc./g. The chemical analysis was used to establish that the acetaldehyde concentration did indeed drop to one-half of its original value. The aldolization in aqueous solution (0.0005-0.03*M*) was first order in acetaldehyde and nearly so in hydroxyl ion. Step 1 was considered to be rate-determining since the tracer studies of Bonhoeffer and Walters (110) showed that the aldol formed in the presence of heavy water was free of carbon-bound deuterium. For the reaction of acetaldehyde k_2 was very much larger than k_{-1}. In the case of acetone (R=Me) the aldolization proceeded to an equilibrium mixture of only a few percent of the condensation product in dilute solution and was not accessible by direct kinetic study.

The reverse of the sequence of reactions above, the dealdolization of diacetone alcohol, has been the subject of many investigations—the earliest of which was made in 1900 by Koelichen (111). He used a dilatometer (with tap) and facilitated the filling by use of a mercury leveling bulb. The decomposition to form acetone, catalyzed by hydroxyl ion, was first order with respect to diacetone alcohol. Subsequent dilatometric rate studies were made by Akerlof(112), French (113), Murphy (114), J. Miller

and Kilpatrick (115), and LaMer and M. Miller (116) on the salt effects, the basic catalysis, and the temperature coefficient of the reaction. The reaction was considered to be specifically catalyzed by hydroxyl ion. Westheimer and Cohen (117), while verifying the work of Miller and Kilpatrick with primary and secondary amines, were forced on the basis of their work with tertiary amines and the work of French with phenolate buffers to conclude that the basic catalysis was not general. Therefore in the dealdolization of diacetone alcohol it appeared that the reverse of step 2 was rate-determining and was preceded by the rapidly established equilibrium between the alcohol and the alcoholate ion (117). Bonhoeffer and Walters also studied the exchange between acetone and deuterium oxide in the presence of OD^- to show that the enolate form of acetone reacted faster with water than with another molecule of acetone. Thus step 2 would be rate-determining in the case of the aldolization of acetone in contrast to the aldolization of acetaldehyde.

Of particular interest is the estimation of the rate of aldolization of acetone from the rate of dealdolization and the equilibrium constant. Koelichen's primary interest was the determination of the equilibrium constant for the reaction, 2 acetone $\rightleftharpoons$ diacetone alcohol, which is the overall reaction of steps 1 to 3 above. In solution containing only 4 to 40% water and 0.2 to 0.05M sodium or potassium hydroxide (other bases were also used), the equilibrium lay between 90 and 87% acetone. The equilibrium constant was obtained by an extrapolation calculation from dilatometric measurements of the approach to the equilibrium position from both sides of it, i.e., by measurement of contraction and expansion. The expression for the equilibrium constant, $K = k_a/k_d$, was obtained from the rate of aldolization, k_a (acetone)^2 (OH^-), and the rate of dealdolization, k_d (diacetone alcohol) (OH^-), the two rates being equal at equilibrium. From Koelichen's data on K and k_d, k_a was estimated (110). The value of k_a was an approximation due to the high concentration of the solutions used in the equilibrium studies. On the basis of steps 1 to 3 the equilibrium constant, K, was equated to $K_1K_2K_3$. Similarly the observed rate constant for the dealdolization, k_d, was equated to $k_{-2}K_3$. It was assumed that the equilibrium between the diacetone alcohol and alcoholate ion, involving proton removal from an oxygen atom, was rapidly established and that in the expression for the steady state concentration of the enol that k_{-1} was much greater than k_2. The rate of aldolization, k_a, was equated to k_2K_1. In the aldolization k_2 is rate determining and is preceded by the rapidly established carbonyl-enol equilibrium. The magnitude of the ratio of k_2/k_{-1} was also estimated since the rate of enolization of acetone, k_1, was known from other experiments.

D. THE MECHANISM OF NITRATION: THE ALTERATION OF THE RATE-DETERMINING STEP

An example of the application of the dilatometric technique is to be found in the work of Hughes, Ingold, *et al.* (106) on the mechanism of aromatic nitration. Just a fraction of the work, that which supports the evidence for nitronium ion as the nitrating agent in acidic media, is presented for illustration of the technique. As pointed out previously, tapless dilatometers were usually used for the experiments conducted in nitric acid, acetic acid, and nitromethane as solvents. Such dilatometers did not require solvent or reagent compatibility with mercury and allowed the studies to be carried out over the wide temperature range of −14 to 80°C. It should be noted that each dilatometric experiment was confirmed by one or more chemical methods. In every case the nitroaromatic present in the solution at the conclusion of the dilatometric measurements was estimated by titration with titanous chloride (accurate to 0.2%) to insure that only mononitration had occurred. In a few cases the nitration product was isolated for microanalysis for carbon, hydrogen, nitrogen, etc. In the case of the observation of reactions of mixed order, the mononitration product of the aromatic compound under surveillance was checked to see that it did not undergo further reaction in order to insure that the mixed order observed was not attributable to consecutive reactions. Rapid reactions, of which only the last part could be followed dilatometrically, were observed entirely by a colorimetric method based upon the color intensity of the molecular compound formed by the nitroaromatic with dimethyl aniline. The colorimetric method served as a rough check on the dilatometric measurements which were possible.

The rate studies in nitric and acetic acids and nitromethane on the variation of the order of the reaction with the nature of the solvent and the aromatic compound underscore the kinetic method of providing independent evidence for the nitronium ion. That the nitration in sulfuric acid was second order, first order in nitric acid, and first order in the aromatic substrate, was known for many years. That the nitration in nitric acid was first order at high constant nitric acid concentration was to be expected. The first order dependence of nitric acid in sulfuric acid was indicative of the nitrating agent's being a nitric acid molecule or a species derived therefrom in constant proportion to the nitric acid concentration throughout the reaction. In acetic acid and nitromethane, solvents which provided a slower rate of nitration compared to sulfuric or nitric acids, zero-order kinetics were obtained at high constant nitric acid concentrations. Zero-order kinetics were observed for all the active hydrocarbons susceptible to an easy nitration such as benzene, ethylbenzene, toluene, and mesitylene. There rates were equal. For aromatic substrates of low or intermediate

activity first order or an order between zero and first was observed. The observation of zero-order kinetics indicated that the rate of formation of the nitrating agent was being measured. In multistep reactions the rate measured is the slowest. If the rate of nitration was not only independent of the concentration of the nitric acid but also of the concentration and the nature of the hydrocarbon, the rate-determining step under these conditions was considered to be the rate of production of the nitrating agent since a change in the solvent was unlikely. The rate-determining transformation in the nitric acid was not attributed to the shift of a proton since these transfers occur rapidly and would not be attended by an activation process. On the basis of the classification of the nitration reaction as electrophilic, the reorientation of the nitric acid was considered to involve an activation step, a bond-breaking step, with the formation of an electrophilic agent. The likely reaction was the formation of nitronium ion which could occur in nitric acid or the nitromethane solvent as follows:

$$HNO_3 + HNO_3 \rightleftharpoons H_2ONO_2^+ + NO_3^-$$

$$H_2ONO_2^+ \longrightarrow NO_2^+ + H_2O \,.$$

The effect of sulfuric acid, nitrate ion, and water upon the kinetics of the nitration in nitric acid and nitromethane was studied to establish the dependency of the observed rate constant upon the concentration of the additive. None of these additives changed the order of the observed kinetics (either zero or first order). Sulfuric acid accelerated, and both nitrate ion and water retarded the rate of nitration. In nitric acid as the solvent the effects of all were weak; in nitromethane the accelerative effect of sulfuric acid and the decelerative effect of nitrate ion were strong, but the retardation by water was a weak effect. The accelerative effect of sulfuric acid showed that proton transfer was necessary for nitronium ion formation; retardation by nitrate ion indicated that nitronium ion formation depended upon a reaction in which nitrate was eliminated reversibly. In the zero-order nitration in nitromethane which nitrate retarded sharply without affecting the order, the production of nitronium ion was considered to occur in two steps, the reversible formation of nitrate ion and the irreversible formation of nitronium ion. The small effect produced by the addition of water, even in the nitromethane solutions, was consistent with the view that water was formed in the irreversible step. However, since the rate was depressed with water, a second process of the destruction of $H_2NO_3^+$ was indicated.

$$HNO_3 + H_3O^+ \rightleftharpoons H_2NO_3^+ + H_2O$$

$$H_2NO_3^+ \longrightarrow NO_2^+ + H_2O$$

The nitration of the aromatic was shown to occur via nitronium ion production in a slow step which in nitromethane was made more rapid than the formation of nitronium ions. Due to the absence of isotope effects the completing steps in the mechanism of nitration were presented as follows:

$$NO_2^+ + ArH \longrightarrow O_2N{-}{-}Ar^+{-}{-}H$$

$$O_2N{-}Ar^+H \longrightarrow O_2NAr + H^+$$

Throughout the studies the amount of nitrous acid, which exists mainly as dinitrogentetroxide in nitric acid, present in the solution was carefully controlled. The negligibility of its effect was established since it is a powerful anticatalyst. Its influence on the reaction rate was attributed to the nitrate ion formed in the equilibrium, $N_2O_4 \rightleftharpoons NO_3^- + NO^+$.

E. OTHER APPLICATIONS

The dilatometric technique has been applied to a wide variety of reactions. The scope of the method may be realized by the following studies: the ortho-Claisen rearrangement in diphenyl ether at 190°C. (118), the cleavage of diphenyl mercury (119), the amine-catalyzed addition of mercaptans to phenylisocyanate (120), the hydrolysis of cyanamide (121), the addition of hydrogen halides to propylene (122) and isobutylene (122), the hydration of ethylene oxides (123) and isobutene (124), the hydrolysis of dialkyl carbonates (125), *p*-methoxydiphenyl acetate (126), and alkyl borates catalyzed by tertiary amines and phenols (127), the dimerization of diphenyl ethylene in benzene with stannic chloride (sealed dilatometer with vacuum transfer technique) (128), the iodine catalyzed dimerization of olefins (129), and ionic polymerization (130).

6. The Electrical Properties of Solutions

A. CONDUCTOMETRY

The Principle. Another indirect evaluation of the extent of the reaction is dependent upon the measurement of the change in conductivity of a reaction solution. The method is applicable to polar reactions in which at least one reactant or product is an electrolyte with the limitation that none of the solutes undergoes preferential absorption or catalytic decomposition at the electrodes. The specific resistance of the solution, ρ, the reciprocal of the specific conductance, κ, is measured as a function of time in a cell with electrodes of fixed dimension and position by the familiar principle of the Wheatstone bridge.

The specific conductance of an electrolyte is not a simple function of the concentration; it depends not only on the number of ions but also on their mobility. The equivalent conductance, $\Lambda = \kappa 10^3/N$, where N is the normality, increases usually with decreasing concentration to give the extrapolated value, Λ_0, at infinite dilution. The conductance-concentration relationship is best established empirically by the measurement of the conductance of known concentrations of the ionic species involved in the reaction at the experimental temperature and pressure of the kinetic study. In concentration ranges where the equivalent conductances of the ionic species were constant, the specific conductance of the solution was treated as an additive function of the specific conductances of the electrolytes in the solution (131).

$$1/\rho = \kappa = \sum c_i N_i$$

The extent to which a reaction has progressed, x in the number of equivalents per liter, may be expressed in terms of the observed specific resistance.

$$1/\rho_0 - 1/\rho = x(\Delta c_i)$$

The proportionality constant, Δc_i, may be eliminated in a number of ways, by using three consecutive pairs of data or by the measurement of the total change where the total number of equivalents, x_0, is known from the initial concentration or is determined at the conclusion of the reaction.

$$1/\rho_0 - 1/\rho_\infty = x_0(\Delta c_i)$$

If the linearity persists throughout the concentration range, the extent of the reaction at any time is given by the expression,

$$x/x_0 = (\rho_\infty/\rho)(\rho - \rho_0)/(\rho_\infty - \rho_0)$$

This treatment is applicable to reactions whose change in conductivity depends upon the replacement of an ionic species by another whose mobility is greatly different. For reaction solutions in which the growth or loss of a single strong electrolyte is being followed the linearity of the conductance of the solution with concentration could be expected only in a limited concentration range. If measurements were required of the formation of a weak acid or base, or the salt of either, the calibration of the system would be necessary since the degree of ionization varies with the concentration.

The Apparatus and the Calibration. The circuitry for various conductance bridges, the cells, and the preparation of electrodes were discussed in detail in Volume I of this series (132). It suffices here to mention only the general needs.

The apparatus consists of a cell, conductance bridge with its a.c. power source, and a detecting device. The cell may be designed in a number of

ways to accommodate the mixing of the reaction solution. In general it should be composed of a highly insoluble glass and have the electrodes so mounted that through usage their geometry remains unchanged. The design most often used is that of Jones and Bollinger (132) in which the stray currents, resulting from poor positioning of the filling-tubes with respect to the electrodes, are eliminated. Archer and Hudson (133) designed an elaborate cell, based upon the design of the Washburn cell, for the study of the hydrolysis of acid chlorides. This cell permitted the addition of the reactive material to the solvent in a thermostated, mercury-sealed system. The electrodes usually used for conductivity work are platinum coated with platinum black. This surface has proven excellent for the elimination of errors due to polarization, but it offers difficulties for use with organic compounds which may be absorbed and decomposed, e.g., α,γ-dimethylallyl chloride (134). The difficulty may be reduced by heating the coated electrodes to redness until the deposit turns gray (132). Archer and Hudson (133) used platinum-iridium alloy electrodes etched with aqua regia. Bright platinum electrodes were used for the alkaline hydrolysis of ethyl nitro-1-naphthoates (135). Polarization effects which occur with smooth electrodes necessitate measurements at several frequencies and the use of an extrapolated value (132).

The calculation of the specific conductance of a solution from resistance measurements, R, depends upon the determination of the cell constant which is determined by the geometry of the cell. The specific resistance (ohms/cm.) of a solution is defined as the resistance of a sample 1 sq. cm. in area and 1 cm. in length. These quantities are related by the equation, $\kappa = 1/\rho = l/aR$, in which l is the distance between the electrodes in cm., a is the area of the electrode in sq. cm., and l/a is the cell constant. These dimensions could be measured directly to evaluate the constant. It is more convenient, however, to obtain the cell constant by the measurement of the resistance of a solution of potassium chloride whose specific conductance has been determined accurately at a number of concentrations (136).

For conductance measurements alternating current is used to eliminate the effects of polarization of the electrodes. Direct current may be used with electrolytes for which nonpolarizable electrodes are known; a number of systems were described by Shedlovsky (132). The Wheatstone bridge is usually used to balance the resistance of the cell against that of a standard resistance by means of a calibrated slide-wire resistance. However, more precise measurements may be obtained in modified circuits, incorporating the Wagner ground, in which the bridge has fixed arms and the current is controlled by adjusting the impedances. Such circuits, e.g., the Jones-Joseph bridge (137), give direct readings of the cell resistance and eliminate or minimize the errors due to current leakage. A vacuum tube oscillator is

usually used as the a.c. power source. For the detecting device a telephone receiver to which the signal may be amplified for greater sensitivity is customary. An oscilloscope for visual detection has proven convenient (138). For less precise work an a.c. galvanometer suffices. To decrease current leakage an oil bath is preferred to one of water. Closer thermostatic control then becomes necessary because of the high temperature coefficient of the resistance and the low heat capacity of the oil.

The Neutralization of Nitromethane. The kinetics of the neutralization of nitromethane and nitroethane with hydroxyl ion (131) and with ammonia and amines (138) were studied as a function of the change in conductance. In these investigations the conductance was treated as a linear function of the concentration by assuming the constancy of the equivalent conductances. Bell and Norris (139), whose studies of the same reaction were over a wide temperature range, −32 to 20°C., calibrated their cell at each reaction temperature with a known solution of sodium hydroxide and the sodium salt of the nitroparaffin. Their calculations depended upon the assumption that the equivalent conductivity of a salt in a mixed solution was the same as that in a pure solution of the same ionic strength.

The experiments of Maron and LaMer (131) were conducted with quite simple apparatus, consisting of two variable 10,000 ohm standard resistance boxes and a student slide-wire, a 1,000 cycle microphone hummer, and tuned Brown headphones. Pearson (138) used a modified Jones-Joseph bridge and a visual detector. Maron and LaMer used three types of cell, one of which was suitable for measurements on 2 to 3 ml. of solution. Platinized electrodes were found to be without catalytic effect.

The Hydrolysis of Benzoyl Chloride: the Rate versus the Dielectric of the Solvent. An elaborate study of the kinetics of the hydrolysis of benzoyl chloride as a function of the water content of aqueous acetone solutions was conducted by Archer and Hudson. The reaction was investigated between 0 and 35°C. by conductivity methods or potentiometric methods for the faster reactions. Their conductivity measurements were made with a bridge with a Wagner ground; its sensitivity was estimated at 0.002%. The cell of the Washburn design with the modifications, mentioned earlier, was stirred. The cell constant was determined by the measurement of the resistance of a 0.001*M* potassium chloride solution at 25°C. This solution was prepared from twice recrystallized potassium chloride and conductivity water. The cell was calibrated by the observation of the resistance (averages of six readings) of a portion of a solution of hydrochloric and benzoic acids which was formed by the complete hydrolysis of a known amount of benzoyl chloride in aqueous acetone. The remainder of the master solution was analyzed for chloride ion gravimetrically. The portion of the solution in the cell was allowed to warm to room

temperature so that an aliquot could be withdrawn for dilution and subsequent resistance measurements. By the repetition of this sequence six or seven points were determined for each solvent mixture and temperature. In an experiment the solvent was thermostated; a portion of the acetone was placed in a separate vessel connected to the main cell by a siphoning device. To this adjunct vessel the benzoyl chloride was added just before the initiation of the reaction. The bridge was set to the highest resistance expected, and the reaction was started by forcing the benzoyl chloride–acetone solution into the cell under pressure. Readings were taken every 20 seconds to 2 or 3 minutes in the slower reactions; about fifty or sixty were made in all. An infinity point was determined after twenty half-lives. The data were treated by a modification of the Guggenheim method.

The first-order rate constants, divided by the concentration of the water in the solvent, were found to be linear with the concentration of water. The authors pointed out that this relationship was indicative of the participation of water in the formation of the transition state and was compatible with the general rate expression in ionizing solvents,

$$d(\mathrm{HCl})/dt = k'(\mathrm{RCl})(\mathrm{H_2O})(S)^m + k''\,(\mathrm{RCl})(\mathrm{H_2O})^n \text{ or}$$
$$k(\text{obs.})/(\mathrm{H_2O}) = k'(S)^m + k''(\mathrm{H_2O})^{n-1}$$

where S is the concentration of the inert solvent. Since the linear relationship found depended upon the concentration of water to the first degree, n was equal to 2. The linear relationship was obeyed accurately in the 0 to 30% water range of composition at 25 and 35°C.

Another approach to the problem of solvent participation in the transition state was made by the comparison of the variation of the rate of reaction with the dielectric of the medium (140). The relationship, $\ln k = \ln k^0 - (1/kT)[(\mathrm{D} - 1)/(2\mathrm{D} + 1)]\sum\mu^2/r^3$, was based upon the Kirkwood expression for the transfer of a strong dipole, μ, from a vacuum to a medium of dielectric constant D and the Bronsted-Bjerrum activity relationship; nonelectrostatic forces were neglected, and r is the molecular radius. The slope of the linear graph of $\ln k$ versus $(\mathrm{D} - 1)/(2\mathrm{D} + 1)$ for the data in 0 to 30% water concentration range at 25 and 35°C. indicated that there was a considerable increase in polarity in the transition state. The transition state was believed to resemble the product more closely than the reactants. In solvents of water composition greater than 30% the activation energy increased, and the rate was found to be dependent upon a much higher power (7.5) of the water composition. These correlations substantiated the authors' (140) earlier view that the hydrolysis proceeded with dual mechanisms, SN1 and SN2, the ionization being predominate at higher water concentrations and the bimolecular mechanism being present at low water con-

centrations (0 to 30% water) where the termolecular kinetics were observed as described above.

The ethanolysis of substituted benzoyl and acyl chlorides was studied also by the conductometric method in ether–alcohol solution (141).

The Solvolysis of Arylmethyl Chlorides: the Correlation of the Rate with the Pi-Energy in the Transition State. Dewar and Sampson (142) used a conductance bridge similar to that of Archer and Hudson in their studies of the solvolyses of arylmethyl chlorides at 25°C. in very dilute solutions in moist formic acid. Their cell had electrodes of bright platinum. Calibration curves of the conductance-concentration relationship were obtained by the measurement of solution prepared by bubbling dry hydrogen chloride into the appropriate solvent to give a concentration of about $0.05N$ which was established by a volumetric chloride analysis. By dilution, curves were obtained in the concentration range of 0 to $5 \times 10^{-3}M$ in hydrochloric acid. The reaction in the case of the more reactive halides was followed to equilibrium, $ArCH_2Cl \rightleftharpoons ArCH_2OH + HCl$. The magnitude of the rate constant for the forward reaction, calculated by the usual expression for the approach to an equilibrium, was checked by a study of the reverse reaction, the two constants being related linearly. The equilibrium constant was calculated from the equilibrium concentrations of the species. The rates of the forward and reverse reactions of the less reactive compounds were measured by initial rates of formation or removal of acid. The equilibrium constant for these compounds was calculated on the principle of microscopic reversibility which also served as a check on the equilibrium constants of the more reactive compounds. These values were reported to be in "reasonable" agreement.

Dewar and Sampson compared their experimental rates in moist formic acid (0.38 and $1.2M$ in water) and those of Fierens *et al.* (143) in ternary mixtures of water, formic acid, and dioxane with the values predicted by a simple molecular orbital treatment. The activation energy of the solvolysis was assumed to depend upon the energy difference between $ArCH_2Cl$ and a transition state composed of an ion pair, $ArCH_2^+Cl^-$, in which there was insignificant covalent bonding between the ions and in which $ArCH_2^+$ possessed a definite configuration. The energy of activation was considered to be the sum of three contributing energy changes, the breaking of the carbon–chlorine bond, the difference in solvation energy, and the change in the pi-energy upon conjugation of the extracyclic carbon atom with the aromatic ring. The contribution of the change in the pi-energy was calculated for the system, $Ar \rightarrow ArCH_2^+$, in terms of a single parameter, β, by application of perturbation theory. The energy contributions from bond-breaking and solvation and the entropy of activation were assumed, as a first approximation, to be independent of the structure of the aromatic resi-

due and to be constant. Substitution of the predicted energy of activation into the transition state theory equation relating the rate constant, the energy of activation, and the entropy of activation gave the equation, $\log k_1 = -2\beta\alpha_{0r}/2.3RT + D$, in which k_1 was the experimental rate, α_{0r} the coefficient of the nonbonding molecular orbital in Ar at the juncture atom, β was the resonance integral between the two juncture atoms, and D a constant. The equation predicted a linear relationship between ln k_1 and the calculated values of $2\alpha_{nr}$. The data so graphed fell into two groups: the "benzene-type" in which the Ar-groups were phenyl, 2- and 3-phenanthryl and 2-naphthyl, and the "1-naphthalene-type" in which the Ar-groups were 1- and 9-phenanthryl and 1-naphthyl. The slopes for each were the same, but the "1-naphthalene-type" showed retardation which was attributed to steric strain arising from interference of the peri-hydrogen atom and a side-chain hydrogen in achieving coplanarity. The values of β for these data and the estimates of steric strain were discussed in the paper. The second order rate constants for the exchange of arylmethyl chlorides with iodide ion in anhydrous acetone were also treated in a similar fashion. In this case there was no distinction between the "naphthalene" and "benzene" types; all the points fell on a single line with one exception. The lower value of β for the SN2 reaction was in agreement with the idea that in the exchange reaction there was only a partial conjugation of the side chain with the aromatic ring since the iodine and chlorine atoms were covalently bound. Of interest was the proposal of the diagnostic use of the parameter in that it would be higher the more nearly the transition state achieved formation of an ion, $ArCH_2^+$, and conjugation. With studies of a reaction series in different environments the nucleophilic character of the environment could be correlated with β. The authors further tested their theory by the extension to solvolyses of tertiary halides in 80% ethanol with an appropriate change in the parameter. Qualitative agreement only was obtained, in that the more reactive of the compounds solvolyzed more rapidly than predicted. This observation suggested to the authors that the less reactive compounds were more susceptible to nucleophilic assistance.

Other Applications. Other systems studied by conductometric methods were the hydrogen chloride production in the solvolysis of chloromethyl aryl sulfides in 80% aqueous dioxane (144) and of alkylbenzhydryl chlorides in aqueous ethanol or acetone (145), the alkaline hydrolysis of *tert*-butyl esters (146), of ethyl nitronaphthoates (135), and the neutral hydrolysis of *n*-alkyl esters of perfluoro acids in aqueous acetone (147), and the displacement reaction of sodium guaiacoxide and alkyl iodides in ethanol (148).

B. THE CONCENTRATION CELL

Another method depending upon the electrical properties of the solution is that of the concentration cell. Swain and Ross (149) applied this to the study of the solvolysis of *tert*-butyl chloride in aqueous acetone in which the concentration of water was so high that an extremely rapid analysis was necessary. In this method twin cells, each with an electrode and connected by a salt bridge, were used. In one cell the reaction solution was placed; the other contained a duplicate solution lacking only one reactant. The two electrodes were connected through a galvanometer. As the reaction progressed liberating an ion to which the electrodes were sensitive, the galvanometer was thrown out of balance. By the addition of a known volume of solution of the ion being measured to the duplicate cell, the galvanometer was returned to the zero position. The concentration of the solution being added did not need to be known. If the reaction went to completion the total volume was equivalent to 100% reaction. For the measurement of chloride ion Swain and Ross used electrodes of silver wire; for the measurement of hydrogen ion quinhydrone electrodes were used. They pointed out that one disadvantage was the high inert salt concentration necessary in the cells in order to minimize the potential between the salt bridge and the solutions. This method was also applied to the kinetics of the amidation and the hydrolysis of ethyl chloroformate in sterically hindered phenolic buffers (150).

For the measurement of the hydrolysis of *cis*-dichloro-bis-(ethylenediamine)-chromium(III) ion in acidic solution the principle of the concentration cell was employed because the reaction was too fast to follow by titration techniques (151). The rate of chloride production was determined by measuring the change in the cell potential against a standard chloride solution. In these experiments a salt bridge was not used, but the two solutions, reaction and standard, were allowed to come into contact in a middle chamber. A guarantee that no chloride ion transfer occurred was obtained by testing the cell with two standard chloride solutions of differing concentration. Over the normal period of a kinetic run no change in the cell potential was observed.

7. The Measurement of a Gaseous Component

The progress of a reaction which is accompanied by either the evolution or absorption of a gas may be conveniently determined by the measurement of the amount of the gas appearing or disappearing above the solution. Reactions falling into this category are the decarboxylation of acids, the decomposition of diazocompounds, of azides, and of Grignard reagents, the

autoxidation of hydrocarbons, and the hydration of low molecular weight olefins.

A. VOLUME MEASUREMENTS AT CONSTANT PRESSURE

A simple procedure is the measurement of the volume of a gas at constant temperature and pressure. This may be illustrated by some of the work on the deamination of amines (152), the decomposition of benzene diazonium salts (153–155), the homolytic fission of azo-compounds (156,157), and the rearrangement of benzazides (158,159) (the Curtius rearrangement) and arylalkyl azides (160,161) (Schmidt rearrangement), all of which proceed by the evolution of nitrogen. For the volume measurement at atmospheric pressure the apparatus need consist only of a reaction flask connected to a gas buret, both suitably thermostated. Since nitrogen easily forms a supersaturated solution, agitation of the solution is desirable by vigorous shaking or stirring. With the use of a shaker a jacketed reaction vessel through which thermostated water may be circulated is an aid. An apparatus with a specially designed stirrer was described by Taylor and Feltis (155) for precision measurements of the benzene diazonium decomposition. Whether the reactant is added to the thermostated solvent before the system is closed or after depends upon the speed of the reaction being studied and the necessity of obtaining a reliable initial point. The automatic addition of a reactant to the closed system was accomplished by the magnetic release of a vial (158) or a siphoning device (155). The apparatus for the measurement of the volume of gas may be a buret and leveling bulb. It is advantageous for the rapid response of the system to have the tubing connecting the reaction flask and the gas buret of as small a volume as possible. For greater sensitivity the fluid in the buret should be butyl phthalate, a light oil, etc., rather than mercury. Should the solvent have an excessive vapor pressure at elevated temperatures, a condenser may be inserted between the reaction flask and the gas-measuring system. A differential manometer, filled with a light oil or glycol and open to the room pressure, may be used as an aid in adjusting the leveling bulb of the gas buret. A differential manometer between the system and a standard pressure, such as a thermostated flask containing just the solvent, was found useful by Newman *et al.* (158). The level of the gas buret could be set at a constant pressure, and the necessary corrections for the vagaries of the barometric pressure were eliminated. The readings so obtained needed to be corrected only for the vapor pressure of the solvent and brought to standard conditions.

B. PRESSURE MEASUREMENTS AT CONSTANT VOLUME

Equally simple is the measurement of the change in pressure at constant volume where the reaction flask is connected to a mercury manometer in a

closed system. The volume of the system may be determined by calibration with water or mercury. In the strictest sense the volume is not constant in that the change in the position of the manometer fluid with the pressure affects the volume. Corrections may be applied however. The extent of the decomposition of azo-bis-isobutyronitriles (162) and triaryl methyl azides (163) was determined in this fashion by the measurement of the increase in pressure.

In solutions of sufficient acidity where the evolution of carbon dioxide may be considered complete, the decarboxylation of variously substituted benzoic or cinnamic acids (164–166) and the Dakin-West reaction (166) were studied by measuring the volume at constant pressure by the methods of Section IX.7.A. The decarboxylation of α,α-dimethylacetoacetic acid in amine buffer solutions, of *N*-carboxyamino anhydrides, and of β-isovalerolactone was followed by the determination of the carbon dioxide pressure above the solution (167). The decarboxylation of the substituted sodium acetates, in contrast, was conducted in sealed tubes whose contents were analyzed by the measurement of the volume of carbon dioxide liberated upon acidification (168). In the studies of the decomposition of diacylperoxide in solution Szwarc *et al.* (169), in order to establish the nature of the formation of ethane within the "cage" of solvent molecules, analyzed the gases methane, ethane, and carbon dioxide by distillation and fractionation with the absorption of the carbon dioxide on Ascarite.

Of greater precision than the simple assemblies described previously is an apparatus of glass which may be shaken and completely thermostated in order to eliminate errors due to leakage of the glass-to-rubber (or tygon) seals and to the variation in pressure resulting from temperature changes in the system between the two thermostated vessels. One design on a semimicro scale for the measurement of the evolution of a gas by pressure increase was described by LaMer *et al.* (170). The apparatus consisted of a 25 ml. flask with a long neck bearing a side arm which was connected to a U-shaped manometer through a glass spring of thin-walled capillary tubing. A spring of four turns permitted a stretch up to 2 cm. for use with an off-center shaking device. The flask was indented at the neck to prevent the reaction solution's splashing into the side arm and capillary spring and thereby interferring with the pressure measurements. The manometer was of the pancake design having a flat bulb of large cross-section in the arm connected to the system. The bulb provided a section in which there was a negligible change in the mercury level with respect to the pressure change. The volume of the system was rendered constant to this degree. A very successful modification of the apparatus was made to accommodate the studies of the hydration of gaseous olefins in aqueous nitric acid (171). The adaptation required the addition of a gas inlet system regulated by a pre-

cision stopcock to the spiral so that the manometer-U was connected in a T-seal. In addition to the indented neck of the flask which acted as a baffle for the solution, the side arm of the flask was enlarged and angled. The spiral spring was not constructed of capillary tubing. The graduated mercury manometer, 30 cm. in length, read to 0.01 cm., was sealed off under a pressure of about 0.2 mm. One of the procedures used in gathering data was the following: The flask was charged through the neck of the flask with a known volume of acid, and the neck was sealed. The olefin was admitted to the system after the customary freezing-melting-degassing procedure. The whole system was then frozen, evacuated, and sealed with the removal of the gas inlet system. The total volume of the experimental system, flask, spiral, and section of the manometer up to the pancake, was determined by weighing the apparatus in sections filled with water or mercury. The whole was divided into the portions where there was capillary tubing so that the reassembly would be accomplished without the introduction of error. Where the apparatus was customarily sealed in the preparation for an experiment, at the flask neck and the gas inlet capillary, the calibration was made to a reference point to which a small correction in volume could be added by linear measurement, the volume per centimeter of tubing being known. LaMer *et al.* (170) calibrated their apparatus by measuring the hydrogen evolved from a weighed amount of zinc in hydrochloric acid. Corrections for the change in volume during the course of the reaction due to the change in pressure were made by applying the conversion factor, volume per centimeter of capillary tubing, to the difference in manometer readings.

C. THE HYDRATION OF OLEFINS: RATES AT UNIT FUGACITY AND IN SOLUTION, AND THE CORRELATION WITH THE ACIDITY FUNCTION; THE EQUILIBRIUM BETWEEN A PI-COMPLEX AND A CLASSICAL CARBONIUM ION

The apparatus for the measurement of the decrease in vapor pressure, outlined briefly above, was developed for the studies of the kinetics of the hydration of isobutene and 1-methylcyclopentene-1 in aqueous nitric acid (171). For the hydration measurements the apparatus, charged as described above, was placed in a thermostat in a shaking device. Readings were taken as soon as thermal equilibrium was reached; in the event of the occurrence of a substantial reverse reaction, the apparatus was allowed to warm to room temperature before thermostatic control was exercised. It was assumed that the extent of the reaction occurring during the warming process without shaking was negligible. Manometer readings were taken after ten half-lives to establish the value of the equilibrium pressure. All readings were corrected for the partial pressure of the solvent. The

logarithm of the difference in pressure at time t, and at the equilibrium point was a linear function of the time with a slope, s. On the assumptions that (*1*) the rate of formation of the alcohol in solution was proportional to the difference in the velocity at which the dissolved olefin was hydrated and that at which the alcohol was dehydrated, (*2*) there was equilibrium at all times in the distribution of the olefin between the gaseous and liquid phases, and (*3*) the vapor could be treated as a perfect gas, the slope was related to a function of the specific rate constant (unit pressure), k_p, the distribution constant for the olefin between the two phases, h, the ratio of the volume of the gaseous phase to the liquid phase, r, and the specific rate constant for the conversion of the alcohol to the olefin in solution, k_{-1}.

$$s = -(\mathrm{P} - \mathrm{P}^e)^{-1}dP/dt = k_p(h + r/RT)^{-1} + k_{-1}$$

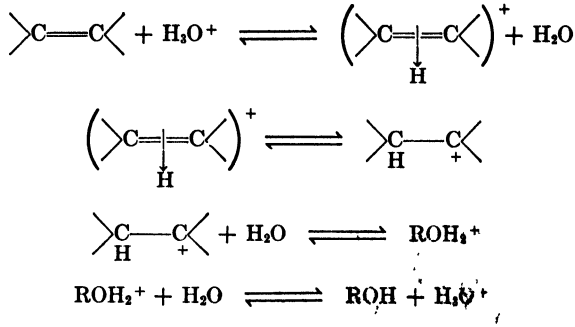
Since P^0, P^e, and s were determined experimentally, the value of k_{-1} was computed with sufficient accuracy from the relationship, $k_{-1} = sP^e/P^0$, which arose in the same derivation above. Each experiment at a given value of r gave an s-value. The parameters k_p and h were obtained graphically from the equation above by plotting $RT/r(s - k_{-1})$ versus RT/r to give the slope, h/k_p, and the intercept, $1/kp$. This form was chosen to give the maximum precision to the value of k_p; the probable error was estimated at 1% or less. By this treatment of the data h could not be determined with as great certainty. The specific rate constant at unit concentration, $k_c = k_p/h$, could only be estimated. Because of the low pressures used (less than 30 cm.) k_p was considered the specific rate constant at unit fugacity.

The distribution constants, h, were determined experimentally by the measurement of the decrease in the vapor pressure in a modification of the apparatus used for the kinetic study. Due to the velocity of the hydration reaction above 25°C., an extrapolation procedure was employed for the calculation of the distribution constants. With an independently determined value of h, a value of k_p was obtained from each experiment, k^{-1} being computed as before. In addition to the initial studies on isobutene and 1-methylcyclopentene-1 in dilute nitric acid (0.1–1M) at three temperatures between 15 and 25°C. (171), Taft *et al.* extended the work on isobutene to 45° (1M HNO_3) (173) and also studied the hydration of trimethylene, methylenecyclobutane, and triptene (*asym*-methyl-*tert*-butylethylene) in 1 to 5 M acid (173). This thoroughness was prompted by anomalies observed in the dependence of the rate upon acidity and in the variation of the enthalpies of activation with the structure of the substrate. The extension of the temperature range in which isobutene and trimethylethylene were studied (1M HNO_3) permitted the evaluation of the enthalpy and entropy of activation with greater precision. By a least squares treatment of

the graph of log k_p versus $1/T$, from which the quantities above were derived, the activation energy was found to be linear with a median deviation of less than 1% (173). The enthalpies of activation for the gaseous reactants were therefore independent of the temperature within experimental error. The enthalpies of activation for the hydration of the dissolved olefin at 25°C., obtained from that for the gaseous olefin by subtracting the respective enthalpy of solution, were temperature dependent and differed for the two olefins by 1.1 kcal. The evaluation of the mean values of the enthalpy of solution for each olefin was made from the measurement of the distribution constants (172) in the temperature range.

The dependency of the first-order rate of the hydration reaction upon the acidity was considered in the concentration range of 1 to 5M acid (173,174). It was found that log k_p was linear with the acidity function, H_0, with slopes varying from 1.20 to 1.30. The values of log k_c were linear with the acidity function, the slope being close to unity. The values of k_c were obtained from the equation, $\log k_c = \log (k_p/h^\circ) + \log f^\circ$, where h° was the distribution constant in 0.1M nitric acid and f^0 the activity coefficient of the dissolved olefin. The equation was derived from a consideration of the Bronsted equation and the equation relating the two rates by the distribution constant. The activity coefficients for the dissolved olefin at various dilute acid concentrations were likewise computed from the $k_p/(H_3O^+)$ and $k_c/(H_3O^+)$ ratios based upon the Bronsted equations. The activity coefficients, so calculated, for acid concentrations up to 1M appeared to fit the empirical Setschenow equation, which states that the logarithm of the activity coefficient is directly proportional to the molar concentration. For the calculation of k_c in solutions up to 5M the Setschenow equation was assumed to hold.

The diagnostic use of the dependence of the rate constant for the dissolved olefin upon the acidity function led to the conclusion that the transition state was made up of the substrate and a proton, but that it was without a water molecule. The Zucker-Hammett hypothesis is discussed in Sections VII.4.B and VIII.5.C and D. The results of earlier work established that in the hydration of isobutene, *tert*-butyl nitrate was not an intermediate (175). Hammett *et al.* (176) further demonstrate that the reaction did not occur through rapid equilibria between the olefin, alcohol, and a classical carbonium ion since no isomerization was detected in the reactions of two olefins which would give the same carbonium ion when the reaction was stopped at 50% completion. On the basis of this experimental work Taft *et al.* proposed that the rate determining step in the hydration reaction was the equilibrium between a pi-complex of the olefin and a classical carbonium (174,173).



By experiments in deuterium oxide-water mixtures (177) confirmation of the conclusion that the rate-determining step was preceded by a reversible proton transfer was obtained. Since the formation of a carbonium ion was inadmissable on other evidence the formation of the pi-complex was implied. These studies were recently extended to include the hydration of small ring compounds (178); the consideration of reactivity and structure led to the conclusion that the pi-complex was the more appropriate model for the transition state than the classical carbonium ion.

The application of a simpler apparatus, flask and gas buret, to the investigation of the reactions of the gaseous olefins, cyclopropane and propene, with aqueous acids in a Friedel-Crafts alkylation was made recently (179).

D. THE AUTOXIDATION OF HYDROCARBONS: THE ANALYSIS OF A SIX STEP REACTION

Studies on the autoxidation of hydrocarbons provide an illustration of an area of research in which kinetics have played a definitive role. In general the oxidation mechanism depends upon initiation, propagation, and termination reactions. The carriers in these steps are alkyl and alkyl peroxy radicals; in some cases alkoxy radicals were considered (180). For free radical chain reactions, the isolation of intermediates or the identification of products does not always give discriminative evidence for one or another possible reaction route. Kinetic studies give a mathematical criterion for the selection of steps whose overall rate must be compatible with that observed experimentally.

The low-temperature (25–45°C.) oxidation of liquid, nonconjugated olefins with molecular oxygen was studied by the measurement of the rate of absorption of oxygen at various pressures of oxygen. The absorption of oxygen with the formation of hydroperoxides was shown to depend upon the following chain reaction (181), in which step 1 was the initiation, steps 2 and 3 comprised the propagation reaction, and steps 4, 5, and 6 the termination.

$$\text{initiator} \xrightarrow{1} \text{R}\cdot, \text{ or } \text{RO}_2\cdot \text{ radicals at rate } r_i$$

$$\text{R}\cdot + \text{O}_2 \xrightarrow{2} \text{RO}_2\cdot$$

$$\text{RO}_2\cdot + \text{RH} \xrightarrow{3} \text{ROOH} + \text{R}\cdot$$

$$\left.\begin{aligned} 2\text{R}\cdot &\xrightarrow{4} \\ \text{R}\cdot + \text{RO}_2\cdot &\xrightarrow{5} \\ 2\text{RO}_2\cdot &\xrightarrow{6} \end{aligned}\right\} \text{noninitiating products}$$

In these equations RH was the olefin and R·, the radical derived from the olefin by the removal of an alpha hydrogen atom.

The oxidations were conducted in an apparatus in which the decrease in the volume of oxygen was measured at a constant predetermined pressure. The apparatus consisted of a long-necked flask with a glass ring below the neck as a baffle and with a side arm connected through a glass spiral spring (182) to a manifold which held the gas measuring system (183). In some experiments the flask was simply coupled to the manifold by a flexible rubber joint (182,183). The gas measuring system consisted of a differential manometer, U-shaped gas buret, an automatic pressure equalizing device (184), and a regulator. The pressure regulator was a U-shaped, make-or-break, one limb of which was set at the desired pressure and which controlled an electrolytic cell. The electrolytic cell, connected to the free limb of the gas buret, regulated the upward movement of the mercury in the gas buret by its evolution of gas. The manometer, whose free limb was also set at the desired pressure, functioned only as a device to insure that the readings of the volume were taken when the pressures were equal. The volume measurements were made with a cathetometer trained on one limb of the buret. The advantages to the apparatus with the glass spring were that the whole could be thermostated and a shaking rate as high as 1,000 per minute could be employed. The temperature of the thermostat was maintained within 0.005°C. In the earlier studies (181) benzoyl peroxide was used as an initiator; later bis-azoisobutyronitrile (182) was found more suitable. The pressures were corrected for the dilution by the nitrogen evolved by the azoisobutyronitrile, and its rate of initiation, r_i, was determined independently in ethyl linoleate *in vacuo*.

With the assumption that the chain length was long giving the equation, $k_2(\text{R}\cdot)(\text{O}_2) = k_3(\text{RH})(\text{RO}_2\cdot)$, and the usual steady state approximations, the generalized kinetic expression for the rate of oxidation, r, was obtained,

$$r = r_\infty[1 + 2\phi A^{-1}B(\text{RH})(\text{O}_2)^{-1} + A^{-2}B^{+2}(\text{RH})^2(\text{O}_2)^{-2}]^{-1/2}$$

where r_∞ was the limiting rate at sufficiently high oxygen pressures and the

constants, A, B, and ϕ, were related to the specific rate constants of the steps by the following equations:

$$A = k_2k_4^{-1/2} \qquad B = k_3k_6^{-1/2} \qquad \phi = k_4^{-1/2}k_5k_6^{-1/2} \qquad r_\infty = B(\mathrm{RH})r_i^{1/2}$$

If ϕ were assumed to be unity, the rate of oxygen absorption was simplified to

$$r = r_\infty[1 + A^{-1}B(\mathrm{RH})(\mathrm{O_2})^{-1}]^{-1}$$

At high pressures where $B(\mathrm{RH})$ was negligible compared to $A(\mathrm{O_2})$, the rate of oxidation was independent of the oxygen concentration,

$$r = r_i^{1/2}k_2k_6^{-1/2}(\mathrm{RH})$$

and the termination occurred by step 6, the combination of two alkyl peroxy radicals. At low oxygen pressures the reaction was terminated by step 4 at the rate,

$$r = r_i^{1/2}k_2k_4^{-1/2}(\mathrm{O_2})$$

The assumption that $\phi = 1$ was an oversimplification which made the value of A uncertain (182), but it serves presently to illustrate the dependence of the observed kinetics upon the termination step.

Experimentally the concentration of oxygen in the liquid, $(\mathrm{O_2})$, was related to the pressure, p, by the equation, $(\mathrm{O_2}) = \beta p - rk^{-1}$, in which β was the solubility of the oxygen in the olefin and k was a shaking constant. The correctness of the general rate equation, above, was confirmed by the linearity of the graph of $[(r_\infty/r)^2 - 1](\mathrm{O_2})$ versus $(\mathrm{O_2})^{-1}$ from which the slope and intercept were equated to $A^{-2}B^2(\mathrm{RH})^2$ and $2\phi A^{-1}B(\mathrm{RH})$, respectively. The value of ϕ was also determined graphically by plotting r_∞/r versus $(\mathrm{O_2})^{-1}$ to obtain the value of r_∞/r at $(\mathrm{O_2})^{-1} = 0$. Evaluation of the ratios of k_2/k_4 and k_3/k_6 was possible through photochemical-oxidation studies based upon an intermittent illumination technique (182). With these values and those from the graphical analysis, sufficient data (5 equations in 5 unknowns) were available for the estimation of the individual rate constants of the six step reaction.

E. THE INHIBITION OF THE OXIDATION OF HYDROCARBONS: THE IMPORTANCE OF THE TERMINATION REACTION

Of equal interest to the problem of the mechanism of oxidation of hydrocarbons (185) is the mechanism of the inhibition of oxidation by phenols or aromatic amines. Bickel and Kooyman (186) used an apparatus consisting of a cylindrical Pyrex-glass vessel fitted with a mercury-sealed Vibromixer, a capillary for the oxygen addition, and a system for the support and the

crushing of an ampoule. The oxygen supply was regulated by a manometer (octyl phthalate as the fluid) and a gas buret with leveling bulb. The apparatus, charged with the solvent, bromobenzene 9,10-dihydroanthracene (RH), a phenol or amine (AH), and an ampoule filled with the solid initiator, 2,2,3,3-tetraphenylbutane (R_2), was thermostated and connected to the oxygen supply. After thermal equilibrium was established the reaction was started by breaking the ampoule. The initial rates of oxidation, determined graphically as the volume of oxygen versus time and expressed as $-d(O_2)/2(R_2)dt$ sec.$^{-1}$, were reproducible within 2 to 3%.

The hydrocarbon chosen, dihydroanthracene (RH), had the advantages of being stable toward oxygen up to 100°C. in the absence of an initiator, yet of reacting rapidly with alkyl peroxy radicals. The stability of the hydroperoxides from the initiator and from the hydrocarbon at 60°C. was demonstrated by their respective preparations and isolations in good yield at 80°C. Either hydroperoxide was not considered capable of initiation of any additional chains. The initiator, tetraphenylbutane, dissociated unimolecularly at a convenient rate in solution to give two diphenolethyl radicals. These radicals were similar in structure to the hydrocarbon substrate. The initiation and propagation steps were those of the oxidation.

$$R_2 \xrightarrow{1} 2R\cdot$$

$$R\cdot + O_2 \xrightarrow{2} ROO\cdot$$

$$ROO\cdot + RH \xrightarrow{3} ROOH + R\cdot$$

The inhibitory action of the alkylphenols was considered to function in the following capacities

$$ROO\cdot + AH \xrightarrow{4} ROOH + A\cdot$$

$$ROO\cdot + A\cdot \xrightarrow{5} ROOA$$

$$2A\cdot \xrightarrow{6} A_2$$

The measurements of the initial rates of oxidation with varying relative ratios of R_2:AH:RH indicated that the trialkyl phenols (AH) studied fell into three categories. The first group showed a linear relationship between the initial rate and (RH)/(AH). The second went through a minimum before entering into a linear relationship between the initial rate and $(AH)^{1/2}$. The third group possessed linear relationships between the initial rates and both (RH) and 1/(AH). There were three possible routes of termination which met the conditions of the first group: termination *a* by steps 4 and 6, termination *b* by steps 4 and 5, and simultaneous termination

by a and b. Terminations a, b, and a and b, gave values of $-d(O_2)/2(R_4)dt$ of $k_1[1 + k_3(RH)/k_4(AH)]$, $k_1[1 + k_3(RH)/2k_4(AH)]$, and $k_1[1 + k_3(RH)/(3k_4)(AH)]$, respectively. The distinction between these three different courses was possible by the study of the products of the oxidation of the trialkyl phenols in six different oxidation systems (187) since those phenols with benzyl-type radicals (A·) led to the dimer, A_2, in termination a, and those of the phenoxy-type radicals let to the peroxide, ROOA Antioxidant efficiencies, based on the prevailing mechanism, were calculable from the slopes of the graphs and were expressed as the ratio of the specific rate constants of the termination step to the rate of the propagation step, k_3. The more complicated kinetics of the phenols of groups two and three were considered the result of the participation of the radical, derived from the phenol by hydrogen-abstraction, in a chain-transfer reaction with the hydrocarbon, $A\cdot + RH \longrightarrow AH + R\cdot$. Termination by peroxide formation (course b) gave rise to the kinetics observed for group two; termination by dimerization (course a) gave the kinetics observed for the third group. The antioxidant activity of the strongly sterically hindered phenols (group 1) was attributed to the absence of the chain-transfer reaction by A with the substrate rather than to a particular affinity for peroxy radicals. The study of amines as inhibitors was also conducted by these methods (188). The detail of the energy of activation of the reaction was discussed recently (189).

Kinetic studies by the oxygen absorption technique were conducted by Hammond *et al.* (190). These were based upon the measurement of the inhibition periods (phenols and amines) of the oxidation of cumene in benzene and chlorobenzene initiated by azo-bis-isobutyronitrile. The mechanism of the inhibition of oxidation by phenols. or amines is somewhat controversial. A great deal of work, both qualitative and quantitative, has been carried out by several groups (191) over the past ten years.

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CHAPTER XII

HOMOGENEOUS SOLUTION CATALYSIS

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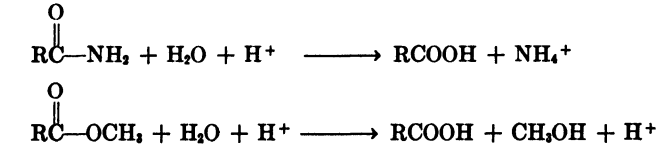
I. INTRODUCTION

In this chapter, the role of catalyst in homogeneous solution will be considered for some well-investigated reactions, with emphasis on common mechanistic pathways. A definition of the word "catalyst" satisfactory to all critical readers presents a major challenge to the author. Usually definitions of a "catalyst" in some way involve the notion of a lack of correspondence between the number of catalyst molecules involved in the stoichiometric equation for the overall reaction and that involved in the catalytic reaction-rate expression. Consider the hydrolysis of esters and amides in acid solution;



Although the two reactants are similar and the detailed catalytic mechanism of hydrolysis may be the same, the stoichiometry of the two reactions is different in respect to hydrogen ion. Definitions of catalysts as materials which alter the velocity of reaction, i.e., enter the velocity equation *without exhibiting a corresponding function in the stoichiometric reaction equation*, would exclude the acid hydrolysis of amides (above) as an example of hydrogen ion catalysis. If it is our purpose to correlate chemical reactions in terms of common catalytic pathways, definitions of the above type are of little value. Perhaps the only reasonable definition of a "catalyst" for these purposes is "a substance which alters the rate of a chemical reaction." If it does not appear in the stoichiometric reaction equation, a catalyst cannot alter the position of equilibrium of the reactions which it catalyzes; if it does appear, it can only alter the position of equilibrium to the extent predicted from its activity, according to the stoichiometric equation.

Our purpose in applying reaction kinetics methodology to organic reactions is two-fold: first, to attempt to deduce the mechanism of catalysis in particular reactions and then to combine the conclusions regarding these mechanisms so as to make predictions of catalytic action in new situations. The approach in this chapter will be to consider the methods for elucidating catalytic mechanisms, and to examine some common mechanisms of catalytic action particularly as they bear on the relationship between catalyst and reactant.

II. CONSIDERATIONS IN THE ELUCIDATION OF CATALYTIC MECHANISMS IN HOMOGENOUS SOLUTION

1. Complex Formation in Solution Catalysis

A. THE PATHWAY IN CATALYZED REACTIONS

Every chemical reaction must involve the interaction of atoms separated by one chemical bond length during some critical phase of the reaction process. In order to affect the overall rate of a chemical reaction, a catalyst must either provide an altered environment for the chemically interacting atoms (for example, by altering the effective dielectric constant or by restricting free rotation of nearby atoms in the molecule), or else

it must provide a new chemical pathway by which the transformation from reactants to products is accomplished. The smaller the molecular dimensions of the catalyst, the more likely will this latter pathway of catalysis be. Thus, it is likely that protons or hydroxyl ions would in some way alter the chemical pathway from reactant to product whereas in some specific enzymic reactions in homogeneous solution, the enzyme catalyst may provide the proper environment for the realization of a particular reaction pathway which would occur in the uncatalyzed homogeneous solution reaction as well, but at a much slower rate. Even with catalysts of small molecular dimensions, however, the rate of a chemical reaction may be accelerated due to a change in the nature of the environment rather than by altering the chemical pathway to products.

B. PHYSICAL FORCES BETWEEN ORGANIC MOLECULES IN SOLUTION

In solution, complexes may form between molecules without the concomitant formation of new chemical bonds (i.e., without an energy of activation). The physical forces by which such complexing is affected are as follows:

Dispersion Forces. The interaction between any two atoms from the mutually induced electric dipoles (due to the instantaneous localization of electrons into orbitals) was first investigated from quantum mechanical considerations by F. London (1). London developed an *approximate* equation relating this *stabilizing* energy of interaction (W) to the distance of separation between the two atoms (r_{AB})

$$W = -(3/2)(\alpha_A\alpha_B/r_{AB}^6)\{I_AI_B/(I_A + I_B)\} \quad (1)$$

where I_A and I_B are the average energies between ground and first ionized states and α is the electronic polarizability. It should be noted that the total energy of interaction contains a repulsion energy term arising from the repulsion between electrons at small distances, and is highly sensitive to the separation of the two atoms ($W_{\text{repulsion}} \propto r^{-12}$). The separation at which the stabilizing interaction energy ($W_{\text{attract}} - W_{\text{rep.}}$) is at a maximum is usually referred to as the Van der Waals' contact distance. Pauling and Pressman (2) have argued that the ionization potentials in Equation (1) are nearly the same for all first and second row atoms (with which we are particularly concerned in this chapter), and can be replaced by a constant term. From examination of the interaction energies in crystals, these authors argue further that the above mentioned repulsive energy term is a constant fraction of the total energy at the Van der Waals' contact distance. They derived the following expression for the interaction energy between any two first or second row atoms, making use of the

experimentally determined Van der Waals' contacts radii (from X-ray and electron diffraction data)

$$W(\text{cal./mole}) = -(23{,}000/r_{AB}^6)[R_A][R_B] \quad (2)$$

the polarizability "α" of Equation (1) having been replaced by the experimentally ascertainable "mole refraction" $[R]$.

$$[R] = (4/3\pi)N\alpha$$

In considering interactions arising from the London dispersion forces between two atoms in solution, one must in reality account for the quantitative difference between the energy of interaction of the two atoms and the interaction energy of each atom with the solvent. This difference in energy is given by Equation (3), where n is the number of solvent molecules replaced as a result of the interaction and $[R_s]$ is the mole refraction of the solvent.

$$W = -23{,}000\{([R_B] - n[R_s])[R_A]\}/r_{AB}^6 \quad (3)$$

In aqueous solution, the interaction of a second row atom with an organic molecule such as an amide, results in a stabilization of about three to five hundred small calories per mole due to dispersion forces alone. If the stereochemistry allows for the interaction of a number of atoms between the two molecules (with minimum replacement of solvent), this interaction energy becomes appreciable and is likely to play a major role in complex formation in organic solutions (especially in the absence of charge). The extent to which complex formation occurs in organic solutions therefore depends considerably on the size and shape of the interacting molecules.

Charge-Charge and Dipolar Interactions. The energy of interaction between two widely separated charged particles is given by Coulomb's law (Equation 4)

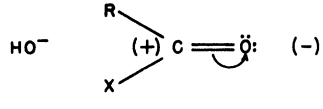
$$W = Z_A Z_B \epsilon^2 / D r_{AB} \quad (4)$$

where Z is the charge number and ϵ is the charge of an electron. D is the dielectric constant of the medium; qualitatively, D is a measure of the static polarizability of the solvent itself. Highly polarizable solvents (such as water, formamide, etc.) will effectively screen the interaction between the two charged particles and result in small values of W. As the charged particles come closer and closer together, the "medium" surrounding these interacting particles becomes less and less like that of the solvent as a whole, due to the strong orienting influence exerted by the charged particles on the polarizable solvent molecules in their immediate vicinity. The net result is a smaller "effective dielectric constant" (a less polarizable solvent medium) as the two charged species approach each other. It is

in the region where the "effective dielectric constant" of the medium surrounding the two interacting charges begins to differ significantly from the dielectric constant of the solvent, that charge-charge interactions begin to contribute appreciably to complex formation. A number of empirical and theoretical approaches to the determination of the "effective dielectric constant" (or more to the point, the interaction energy between charges at short distances) have been developed. Schwarzenbach (3) empirically developed an equation relating W to r_{AB} based on the first ionization constants of the di-positive n-alkyl diammonium ions. Kirkwood and Westheimer (4) have developed a theory for the ionization constants of dicarboxylic acids which leads to quantitative predictions of the "effective dielectric constant" as a function of the distance between, and the arrangement, of the charges. The general conclusion of both of the above studies is that the interaction energy between charged particles increases more rapidly than predicted by the relationship between W and r_{AB} given by Coulomb's law, in the region below about 8 A. in aqueous solvents.

The interaction between dipolar molecules may be quite important in specific instances although the dipole-dipole interaction energy is apt to be of secondary importance where other physical forces (described above and below) are operative.

At very short distances, even in aqueous solution, the interaction energy between charged species is apt to become very large due to the low "effective dielectric constant." This is true as well for an ion dipole interaction (4), as for example:



The ion-dipole interaction energy has been treated in detail by Kirkwood and Westheimer (4). The energy is dependent on the closeness of approach of the ion to the complementary dipolar position (governed by the Van der Waals' contact radii of the atoms and the geometry of the organic molecule) and the effectiveness with which the solvent molecules can sterically and electronically shield the interacting atoms, and is of the form of Equation (5), where μ is the dipole moment of the non-ionic species.

$$W = \epsilon\mu \cos\theta / D_E R_{AB}^2 \tag{5}$$

The ion-induced dipole interaction energy is given by Equation (6) and is generally small. For $[R] = 40$, where $[R_B]$ is the mole refraction of the dipole (an average value), $W = -200$ cal./mole.

$$W = \epsilon^2 [R_B] / 4\pi N D r^4 \tag{6}$$

Similar considerations apply to ion-induced dipole and "dipole-induced dipole" interactions (Equation 7). The absolute energies of such interactions are small, and contribute significantly to the total energy of complex formation only when the interacting molecules are small or the possibility of multiple interactions per molecular pair exist.

$$W_{\text{ind.}} = (-8\mu_A^2)/(3\pi N[R_B]r_{AB}^6) \quad (7)$$

Hydrogen Bonding. These "low energy bonds" (relative to covalent bonds) can play an important role in complex formation in solution when the hydrogen bond energies between interacting molecules are greater than the sum of the hydrogen bond energies between each type of molecule and the solvent. Hydrogen bonds between molecules contribute to complex formation particularly when the solvent is neither a good hydrogen bond donor nor a good hydrogen bond acceptor.

The above mentioned forces of interaction can all contribute to the formation of a complex of reactant with catalyst. It is via such interactions that catalysis (acceleration of reaction velocity) may occur without a major change in the chemical pathway.

Entropy of Complex Formation. In addition to the energy considerations listed above, entropy factors in complex formation must be taken into account. Although it is often assumed that the entropy factor in complex formation is negative (i.e., that complex formation is unfavorable entropically), this is not a general situation in homogeneous solutions due to the role of the solvent molecules. In an ionic interaction, for example, the association of charged species may free the highly polarized solvent molecules surrounding each of the charged ions, with a resultant increase in the entropy of the system. Similarly, if hydrogen bond formation between molecules is involved in complex formation, the potential release of hydrogen bonded solvent molecules during formation of the complex may again lead to a positive entropy change for the process. During complex formation, restrictions are imposed on the internal degrees of freedom of both reactant and catalyst. For this reason, two different catalyst molecules, with common chemical catalytic centers, will differ in their catalytic efficiency depending on the degree to which motions of the entire molecule are restricted in complex formation (5). Thus, the catalyst molecule with greater internal degrees of freedom in the uncomplexed state will stand to lose more entropy in formation of the complex and hence will have a lower catalytic efficiency relative to a more rigid catalyst. It is likely that this is an important factor in the prevalence of small molecule catalysts. As the size of an organic catalyst molecule increases, the entropy lost in complex formation increases, and hence the free energy of complex formation becomes more positive. When the catalyst molecule grows to sufficiently

large size, internal interactions between parts of the organic framework may again limit the entropy loss on formation of reactant–catalyst complex. There may exist an intermediate-sized structure in which catalytic efficiency is at a minimum. It may be noted that most catalysts for organic reactions are either very small or very large.

C. CATALYSIS VIA CHEMICALLY BONDED CATALYST–REACTANT

The nature of interactions between catalyst and reactant which accelerate an otherwise slow spontaneous reaction *without change of reaction path*, have thus far been considered. Formally, this situation can be visualized

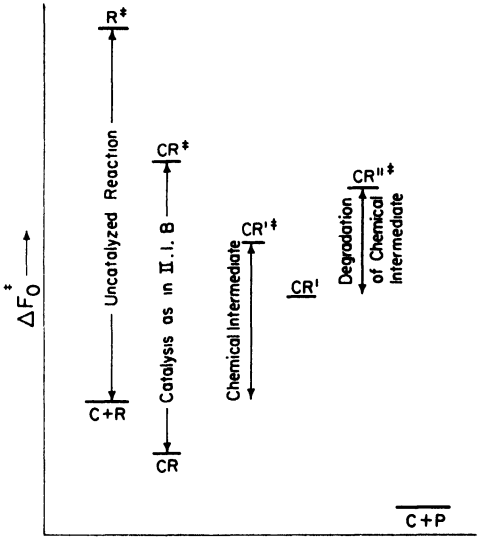


Fig. 1. Free energy of activation in catalysis.

with the aid of Figure 1. Catalysts function by lowering the free energy difference between reactant and activated complex. From the discussion thus far, this could only be accomplished by lowering the free energy of the activated state at the top of the barrier $CR^{\ddagger}$ in Figure 1 to a greater extent than the corresponding free energy decrease (if any) of the reactant in the ground state CR. One must consider however, the large number of cases of catalysis in which the catalyst functions by entering into the chemical reaction pathway. In order for a catalyst to radically affect the path of a chemical reaction, it must itself enter into chemical bond formation during some intermediate stages in this reaction path. Formation of such a catalyst–reactant intermediate, and its subsequent decomposition to prod-

ucts and regenerated catalyst, must each be faster than an alternate pathway for the spontaneous reaction in the absence of catalyst. The distinction between "catalyst–reactant chemical compound intermediate" and "catalyst–reactant dissociable complex" can be defined operationally by the presence or absence of a positive activation energy for complex formation. A characteristic of chemical bond formation is the high activation energy required for the approach of two atoms from the distance of separation given by the sum of their Van der Waals' contact radii, to the much smaller distance between atoms in a chemical bond. If this activation energy is too great, the formation of chemical intermediates cannot be achieved. If the disruption of the chemical intermediate itself requires an activation energy which is large, the intermediate becomes a metastable product and catalysis cannot be effected. Ideally, catalysis, via the formation of a chemical intermediate involving the catalyst, requires that the intermediate be both readily formed (low activation free energy) and readily degraded into the final product via another low activation free energy process. In Figure 1 catalysis via the formation of chemical intermediate is schematized on the right side of the figure. Catalysis may be effected either by raising the free energy of a reactant–catalyst species (compensated energetically by the chemical reaction) or by the formation of an alternate activated state of lower free energy than the activated state of the spontaneous reaction.

Although the "reactant–catalyst complex" and the "reactant–catalyst intermediate compound" have been treated as alternate routes in catalysis, it is quite likely that a combination of both types of catalysis exists in many instances, particularly with enzymes and other large molecule catalysts.

2. The Detection of Intermediates

The complete understanding of a catalytic reaction implies a knowledge of all the transient reactant–catalyst complexes and their sequence in the reaction pathway. In the past, the usual approach toward solution of the problem involved two steps: inference of particular intermediates from the stoichiometry demanded by kinetic studies, and inference of the chemical composition and stereochemical configuration by molecular or structural chemical intuition. This latter step has been aided appreciably by the use of isotopic tracers (see Chapters IX and XXVI). Recently, with the advent of both rapid reaction techniques (Chapters XIV–XIX) and more precise techniques of microanalysis, particularly by means of spectroscopy, it has been possible to either identify directly, or infer more specifically, some of the intermediates involved in homogeneous catalytic

mechanisms. Methods for the direct identification of intermediates are considered in detail in Chapters XX and XXV. However, since techniques for the direct identification of intermediates are not generally available (for reasons to be considered below) the formal chemical-kinetic approach coupled with chemical experience (intuition) still remains a common pathway toward the understanding of solution catalysis.

A. FORMAL REACTION KINETICS INVOLVING DISSOCIABLE COMPLEXES

In considering the formal reaction kinetics of catalysis in homogeneous solution, it is again useful to differentiate between catalysis effected by altering the environment of a chemical reaction, and catalysis effected by an alternate chemical pathway for a reaction (i.e., catalysis involving the catalyst as an intermediate reactant with the formation of intermediate products). Where the catalyst functions as a new medium in which a bimolecular reaction takes place, the reversible association-dissociation of

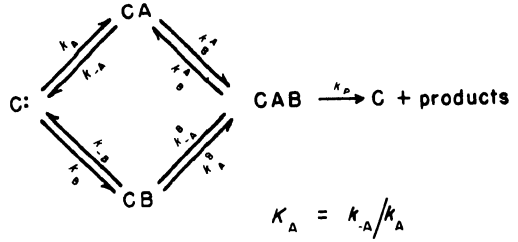


Fig. 2

reactant between catalyst and solvent phases must be taken into account in addition to the chemical reaction in the "catalyst phase."

If the catalyst does not take part in chemical bond formation the scheme shown in Figure 2 can serve as a general model of catalysis. No useful solution to the time dependence of product formation exists for this scheme without the assumption of the *stationary state* for all catalytic species, namely

$$d[C_i]/dt = 0$$

The general applicability of the stationary state approximation in such kinetics schemes has been considered in very great detail elsewhere (6,7). Suffice it to say that the approximation is reasonable in the present discussion, if the distribution between solvent and catalyst "phases" is determined by weak physical forces alone (not by the formation of strong chemical bonds). In other words, the rate of formation and dissociation of reversible complexes must be rapid in order for the stationary state approx-

imation to be valid for all intermediates. With this assumption a complete solution to the model shown in Figure 2 exists if the concentrations of reactants are both very much larger than the concentration of catalyst (C_0). In the stationary state, the velocity of product formation is given by Equation (8)

$$v = k_p C_0 / \{1 + (K_A^B/[A]) + (K_B^A/[B]) + (K_A K_B^A/[A][B]) + k_p Q_{A,B}\} \quad (8)$$

where

$$Q_{A,B} = \{(\mu_A \mu_B K_A K_B^A/[A][B]) + (\mu_A k_{-A} K_B^A/[B]) + (\mu_B k_{-B} K_A^B/[A])\} \div (k^B{}_{-A}\, k_{-B} \mu_B + k^A{}_{-B} k_{-A} \mu_A)$$

$$\mu_A = k_{-B} + k_A^B[A]$$

$$\mu_B = k_{-A} + k_B^A[B]$$

Equation (8), although intractable as it stands, simplifies under specific limiting conditions into the following useful relationships.

Equilibration between "Phases." If, as has been implied in the model of Figure 2, the catalyst is not itself an intermediate reactant in the chemical process, then dissociation of catalyst-bound reactant should be a rapid process impeded only by the physical forces of interaction described above. These physical forces generally contribute not more than a few kilocalories per mole (see Table I). On the other hand, the dissociation of reactants from the triple complex (Fig. 2) into products will involve a chemical activation energy which will usually be considerably greater. It is therefore likely in this type of catalysis, that the reactants distribute themselves between solvent and catalyst phase in a manner predictable from equilibrium thermodynamic considerations. Since the rates of adsorption are more rapid than the rate of reaction under such conditions, the ratios k_p/k_{-A}^B and k_p/k_{-B}^A become vanishingly small and Equation (8) reduces to Equation (9) (the quasi-equilibrium expression, Ref. 8).

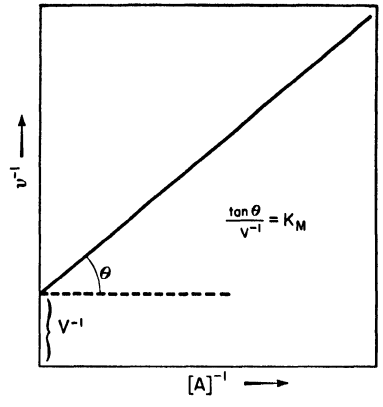
$$v = k_p C_0 / (1 + K_A^B/[A] + K_B^A/[B] + K_A K_B^A/[A][B]) \quad (9)$$

Under conditions in which there is equilibration of intermediates, and maintained concentration of one reactant, a plot of the inverse concentration of the variable reactant (A in this example) versus the inverse of the initial velocity is linear (9) as shown in Figure 3a. The slope of such a plot is equal to

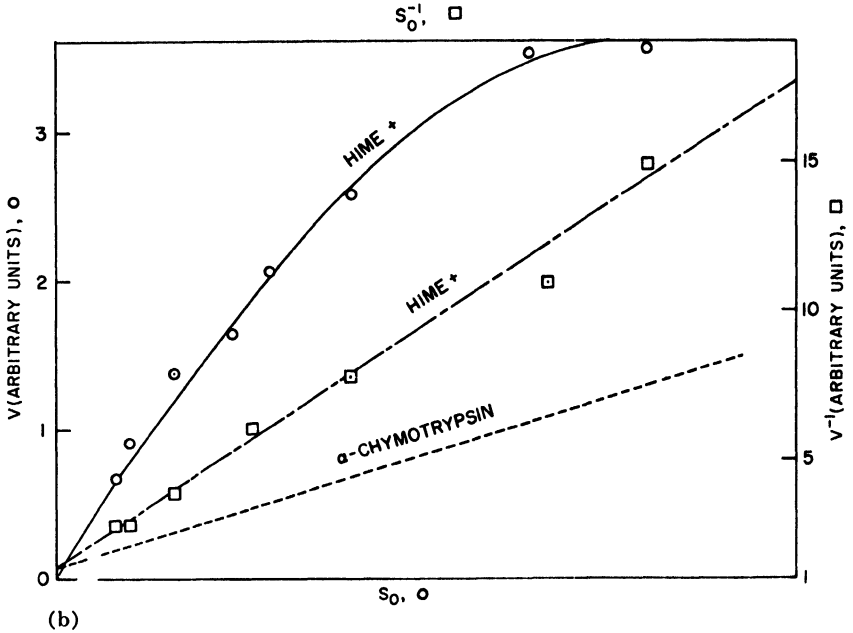
$$K_A^B(1 + K_B/[B])/k_p C_0$$

and the intercept with the ordinate is equal to

$$(1 + K_B^A/[B])/k_p C_0$$



(a)



(b)

Fig. 3. (a) Plot of Equation (9). (b) Illustrative examples in the hydrolysis of *p*-nitrophenyl acetate: ⊙ velocity–rate plot for histidine methyl ester catalysis, ⊡ same data plotted following Equation (9) (Fig. 3(a) right ordinate, upper abscissa), (– – –) α-chymotrypsin catalyzed reaction plotted as in Fig. 3(a).

Even in the absence of equilibrium conditions, the plot of $1/v$ versus $1/[A]$ as shown in Figure 3(a) will intercept the ordinate at a finite value of $1/v$, *if intermediate complex is formed.*

A finite value of $1/v$, at $1/[A]$ equal to zero, is clear cut evidence for intermediate complex formation. Conversely, the plot of $1/v$ versus the inverse concentration of the other reactant (maintaining the concentration of the first reactant) leads under quasi-equilibrium conditions to a slope of

$$K_B^A(1 + K_A/[A])/k_pC_0$$

and a Y intercept of

$$(1 + K_A^B/[A])/k_pC_0$$

A systematic study of concentration-velocity dependence of this sort, in which the limiting values of velocity at saturation of reactants to catalyst can be approached experimentally, yields useful information regarding the interaction of each reactant with the catalyst, as well as the interaction of the two reactants at the catalytic site. The possibility of interaction of the catalyst with a preformed double-reactant complex can be investigated by this approach as well.

Independent Binding of Reactants. If the binding of one reactant to a catalyst does not affect the stability of the complex formed between the catalyst and another reactant, the above quasi-equilibrium expression simplifies considerably to yield the expression

$$v = k_pC_0/\{(1 + K_A/[A])(1 + K_B/[B])\} \tag{10}$$

This situation is detectable under quasi-equilibrium conditions since the ratio of the slope to the intercept with the ordinate (from the plot shown in Figure 3(a)) is not dependent on the maintained concentration of the other reactant.

Very Low Affinity of Catalyst for One of the Two Reactants. If, under all experimental conditions the complexing (binding) of one of the two reactants to the catalyst is a very unlikely event, the concentration of all catalyst-bound intermediates containing this reactant will be trivially small in comparison to those catalyst species which do not contain this reactant. The rate of chemical reaction under such conditions (which may frequently be encountered in catalyses involving one very small reactant) becomes limited by formation of the ternary catalyst–reactant–reactant complex (10) of Figure 2. Equation (8) then reduces to Equation (11).

$$v = k_pC_0/\{(K_B/[B])(1 + K_A/[A] + k_p/k_1[A])\} \tag{11}$$

In the quasi-equilibrium case (Equation 10), the velocity is first order in the concentration of this low affinity reactant throughout the experimental

concentration range. If equilibration of intermediates does not occur, however, concentration dependencies in the nonequilibrium terms of Equation (8) can result in a complicated dependence of velocity on the concentration of this reactant. The low affinity of catalyst for reactant may be due either to a steric strain inhibiting complex formation between two bulky molecules, or to a lack of complementary forces of interaction to prevent the rapid dissociation of a once formed complex. In the case of small molecule reactants, the latter situation most probably obtains. In the event that neither reactant will complex with the catalyst to a stoichiometrically significant extent, the reaction velocity becomes first order in each reactant (for a simple bimolecular reaction path) irrespective of the quasi-equilibrium considerations. Most homogeneous solution catalyzed reactions appear to fall into this latter category of simple reactions in which complex formation is not observed. This is probably due to a number of conditions, most notably, that small molecule catalysts are generally employed, that the concentration of reactants cannot be studied over a sufficiently wide range, and that the dependence of velocity on the concentration of one reactant, over a variety of fixed concentrations of the other reactant is rarely followed.

B. FORMAL REACTION KINETICS INVOLVING REACTIVE CHEMICAL INTERMEDIATES

If a set of chemical transformations, involving the catalyst as well as the reactants, are all of sufficiently low activation free energy, the reversibility shown in the model of Figure 2 may apply to chemically bonded catalyst–reactant complexes as well. However, when irreversible (high activation energy) steps are introduced in the intermediate stages of the catalyzed reaction process, the formal kinetic scheme can become extremely complex due to the potential invalidity of the stationary state approximation (11). Under such circumstances, the direct approach of chemical or physical identification of the intermediates (transients) in the chemical process becomes the only feasible method for elucidation of the pathway. A number of cases of reactions involving chemically bonded catalyst intermediates which can be treated by formal chemical kinetic methods deserve special mention here.

Sequential Catalytic Reactions. A common mechanism of chemical catalysis is a sequence of bimolecular reactions in which the catalyst first "activates" one reactant and then this activated catalyst–reactant complex subsequently reacts with a second reactant.

$$A + C \longrightarrow X$$

$$X + B \longrightarrow \text{products} + C$$

The *exact* solution to the differential equation for the time dependence of product formation, according to this model, is sufficiently complex to be of little value in experimental analysis. For this rather common mechanism of homogeneous catalysis we have the condition

$$\dot{X} = \dot{B} - \dot{A}$$

The condition for the stationary state assumption to be valid is $\dot{X} = 0$. This latter condition is satisfied only when both rates ($\dot{A}$ and $\dot{B}$) are limited by a common rate controlling step, namely the first step in the above model. With v_2 fast and v_1 slow (the simplest condition for stationarity), however, the concentration of the reactive intermediate X becomes vanishingly small and the chances of its detection decrease correspondingly. Conversely, in systems of this type, if an intermediate can be postulated to accumulate in significant amounts then the stationary state hypothesis cannot be invoked unless particular restrictions are made on the concentrations of A, B, and C (see below). In order to extract the pertinent rate constants from this system, limiting conditions of concentration of A, B, and C must be taken advantage of. If A_o and B_o (original concentrations) are both very large it becomes possible to attain a stationary state in X, by virtue of the regeneration of catalyst in the second step, under conditions where the total concentration of A and B have not changed appreciably. Whenever in sequential catalyzed reactions of this sort, there is a bimolecular step in which both reactants are consumed to considerable extent, the solution of the resulting differential equation becomes unwieldy and one must resort either to simplification of experimental conditions or to approximate solutions which are obtainable either from electronic computer techniques or from limiting assumptions on the relative values of the specific rate constants. The kinetic analysis of all such sequential systems is facilitated considerably if a detectable product occurs in an intermediate step, namely

$$\begin{aligned} A + C &\longrightarrow X + P_1 \\ X + B &\longrightarrow P_2 + C \end{aligned} \qquad (12)$$

In this situation the concentration of A is given directly from the appearance of P_1. For the special case where the catalyst concentration can greatly exceed the concentration of A and the reaction still be measurable, at high concentrations of B, the equations reduce to consecutive pseudo first-order reactions, viz.

$$X = \{k_1C_oA_o/(k_2 - k_1C_o)\}\{\exp(-k_1C_ot) - \exp(-k_2[B_o]t)\} \qquad (13)$$

To investigate more complex catalytic reactions involving chemical intermediates, it is usually necessary to either maintain experimental condi-

tions favorable to the simplest solution of the differential equations, or else to introduce the approximation of the stationary state. The second alternative is usually taken. Unfortunately, it is often the case that the conditions for which the stationary state assumption is valid are those which make it most difficult to investigate the transients (the invariant, and often low concentration of transient in the stationary state limits methods based on measurement of the physical properties of the transients).

Reversible and Sequential Reactions. An interesting catalytic situation which has been described in detail (12,13) by Gutfreund is the reversible version of the above sequential model.

$$\mathrm{C} + \mathrm{A} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{CA} \xrightarrow{k_2} \mathrm{X} + \mathrm{P}_1$$

$$\mathrm{X} + \mathrm{B} \xrightarrow{k_3} \mathrm{C} + \mathrm{P}_2 \qquad (14)$$

The introduction of reversibility into the scheme makes the stationary state approximation more likely, particularly since the concentration of complex CA may be less sensitive to the concentration of C than is the first step in the reaction. As has been postulated by Gutfreund, the early phase of this reaction (prior to the establishment of the stationary state) can, under special conditions of concentration, yield the parameter k_1 in this scheme (Equation 14). At low C_o and high B_o, on the other hand, stationary state kinetics can readily yield the parameters k_o and K_M (14)

$$k_o = k_2 k_3 B_o/(k_2 + k_3 B_o)$$

$$K_M = \{k_3 B_o/(k_2 + k_3 B_o)\}\{(k_{-1} + k_2)/k_1\} \qquad (15)$$

Thus a combination of approximate methods and special conditions in non-stationary state kinetics, coupled with the measurement of the same reaction in the stationary state, can yield a number of parameters useful in describing a catalyzed reaction. It is interesting to note that equilibration of CA ($K_M = K_{eq.}$) can only occur by the double condition, $k_{-1} \gg k_2$ and $k_3[B] \gg k_2$, i.e., at negligible concentrations of X.

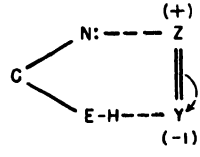
The use of analog computers in formally fitting the experimental description of reactions involving chemically detectable catalyst intermediates (by spectral analysis) has received much attention by Chance and co-workers and is described in detail elsewhere in this volume.

Any experimental device by which the concentration of reactants and/or catalysts and intermediates can be maintained at fixed levels (either high or low concentrations) will aid enormously toward the formal kinetic description of a catalyzed sequential reaction. A common device for maintaining concentrations is the "continuous flow stirred reactor" (15–17) (described in Chapter XIV, Part 6), by which any reactant or

transient can be maintained at a fixed stationary state concentration by adjusting the rate of flow into a fixed volume reactor. A device often used for maintaining constant hydrogen or hydroxyl ion concentration in acid and base catalyses, the "pH-stat," functions by adding titrant to a solution whenever the potential of a glass–calomel electrode system falls below or above a preset value (18,19). With the aid of suitable electrodes and the use of other titrants this method can be adapted to a host of chemical reactions in solution (e.g., oxidation-reduction reactions).

C. FORMAL REACTION KINETICS OF CHEMICAL SYSTEMS OF GREATER COMPLEXITY

Thus far only systems in which all reaction steps were bimolecular or unimolecular have been discussed. Many examples of bimolecular reactions are in reality either trimolecular or complex, with the solvent participating in intermediate steps of the chemical reaction. Although true trimolecular reactions in solution have been observed (20,21), the solvent can usually function as one of the catalysts. Many highly efficient and specific catalysts may function by replacement of two independent molecular catalyst participants in a trimolecular reaction with a single bifunctional molecule which has the participating groups properly oriented for attack on the reactant (21).



Other catalytic reaction pathways such as the transfer of an activated reactant from one catalytic species to another, or the chemical interaction of catalyst with a sequence of intermediary products of reaction, will not be discussed in this chapter.

D. INHIBITION OF CATALYZED REACTIONS

The phenomena of inhibition of catalyzed reactions can often be used to good advantage in the detection, and physical and chemical description, of intermediates. The mechanisms of inhibition of catalyzed reactions are numerous. A feature common to all of the inhibitory mechanisms (described below) is the ability of the inhibitor to interact with the catalyst in one or more of the ways normally restricted to interactions of either catalyst with reactant, or to interactions of catalyst-containing intermediates with subsequent reactants. The inhibitor must differ from a reactant in that the conversion of the inhibitor to a reaction product with regeneration of

catalyst, if it occurs at all, cannot be a rapid process. Although the inhibition situations described below do not include all of the possible mechanisms, they are representative of a majority of the reported examples of inhibition of catalyzed reactions.

Competitive Inhibition. When an inhibitor interacts reversibly with a catalyst in such a way that interactions between reactant and catalyst molecule are completely excluded by formation of this catalyst–inhibitor complex, then the reaction is said to be "competitively inhibited," that is, the only complexes allowed are the bimolecular complexes CI and CA:

$$C + I \rightleftharpoons CI$$

$$C + A \rightleftharpoons CA \longrightarrow C + \text{products}$$

The undetected presence of such an inhibitor will result in an apparent lower affinity of reactant for catalyst without any formal change in the kinetics (the concentration-velocity dependence will be of the same mathematical form as in the absence of inhibitor). If a homologous series of competitive inhibitors are available much can be learned of the nature of some of the reversible interactions between reactant and catalyst (22–28).

Catalyst–Reactant Complex Formation in the Presence of Catalyst–Inhibitor Complex. The inhibitor may function by modifying the interaction between catalyst and reactant without actually completely blocking this interaction. The formal kinetic consequences in this case are quite complex. Attempts to treat such interactions for the scheme shown in Figure 2, modified by the introduction of reversible inhibitor, have been made by Botts and Morales (29,30). The results are unwieldy except when all rates of chemical reaction are slow compared to all rates of desorption (the quasi-equilibrium condition). A very special example of this type is "noncompetitive inhibition." Here the interaction of catalyst with reactant, or catalyst with inhibitor, is unimpaired by the presence of the other, namely:

$$K_A = K_A^I$$

$$K_B = K_B^I$$

As has been shown by Botts and Morales (29), Laidler (31), and others, a simple kinetic solution for the stationary state situation can only result when the rates of reaction are slow relative to all rates of desorption involved. When this "quasi-equilibrium condition" exists, the velocity of reaction is given by

$$v = k_p C_0 / \{1 + K_A^B/[A] + K_B^A/[B] + (K_A K_B^A/[A][B])(1 + [I]/K_I)\} \quad (16)$$

This so-called equation of noncompetitive inhibition is valid only for the special case of quasi-equilibrium. It has sometimes been mistakenly assumed that the above Equation (16) is valid for any stationary state situation. An error implicit in this assumption is that equilibrium can be maintained in one part of a reversible cycle but not in another.

Chemical Inhibition of the Active Catalytic Group. In some instances it is possible to chemically inactivate part of the catalyst molecule so that catalyst may still interact with reactant but no longer lead to chemical reaction. If methods exist for the detection of this chemical interaction, this information, coupled with the chemical information on the reactivity of the catalyst, may shed much light on the mechanism of catalysis. This type of "irreversible inhibition" is most interesting in the situation where a catalyst–reactant intermediate can be blocked from proceeding further in the direction of catalysis. Chemically reactive inhibitors may thus be used in the detection of intermediates.

Complex between Inhibitor and Reactant. Inhibition sometimes occurs either by complex formation or chemical reaction between the inhibitor and a reactant, rather than between the inhibitor and the catalyst or the catalyst–reactant complex. Such inhibition is readily distinguished from other types in that the inhibitor must be present in the high concentrations characteristic of reactants, rather than in the usual trace amounts characteristic of catalysts. The velocity-concentration dependence will change in mathematical form if the inhibitor complexes with the reactant rather than with catalyst-containing species.

What has been stated above regarding inhibitors, with the exception of the competitive-type inhibitory effect, can of course be valid for any *modifier*, whether it accelerates or decelerates the chemical reaction.

III. SPECIFIC EXAMPLES OF MONOFUNCTIONAL CATALYSIS IN HOMOGENEOUS SOLUTION

A majority of the reactions presently under investigation take place in homogeneous solution. Most of these are catalyzed reactions. To select from this nearly endless variety of catalyzed reactions, a representative few as illustrative examples requires a nearly arbitrary and biased decision. This chapter presents a biased and highly provincial selection, restricted to one representative type of organic compound undergoing catalyzed reactions. The *reactions*, and particularly the *hydrolysis, of esters* have been selected. This choice is based primarily on the experience of the author, and in part on the diversity of information pertaining to the catalysis of these reactions. The catalyzed hydrolysis of esters has probably re-

ceived as much attention as any other organic reaction in homogeneous solution. Studies of this reaction have dealt with the nature of the catalyst (acids, bases, solvents, enzymes, metal ions, and heterogeneous catalysts) and the effect of structure of the carboxyl and alcohol ends of the reactant molecule on the catalysis. The effect of solvent composition, temperature, ionic strength, and pH have been studied extensively. An attempt will be made to illustrate all, or almost all, of the principles considered above with emphasis on both the common, and the diverse mechanisms of catalysis. It is felt to be more appropriate to the title of this chapter to emphasize the effect of catalyst and medium on the reaction rate, than to point out the role of the reactant in determining the reaction mechanism.

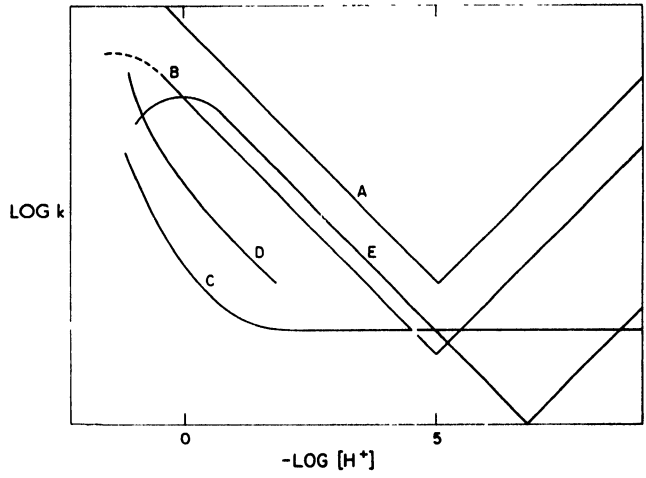


Fig. 4. Acid-catalyzed hydrolysis of various esters and related compounds, k is in relative units varying with each curve. (A) ethyl acetate, ν-butyrolactone; (B) methyl benzoate; (C) β-propiolactone; (D) methyl mesitoate; (E) acetamide.

1. Hydrogen-Ion Catalysis

Virtually all esters are hydrolyzed in aqueous solvents in the presence of strong acid. This does not imply a common mechanism of catalysis in every case. From the hydrogen-ion concentration–velocity relationship in Figure 4 it is evident that a number of different mechanisms must be responsible for the various catalyses. Attention should be drawn to the sharpness of the inflection in these various curves. A very sharp inflection, as exists with ethyl acetate, is indicative of two clearly defined catalyzed reactions; in this case, hydrogen-ion catalysis and hydroxyl-ion catalysis. A broad minimum in the velocity–$[H^+]$ profile as in curve C of Figure 4

is indicative of another reaction in the neutral pH range, in this case the "spontaneous H_2O reaction." In the region pH 1, all of the curves show a linear hydrogen-ion concentration–velocity relationship. At higher and at lower hydrogen-ion concentrations, however, the curves deviate widely one from the other. A nonlinearity in the above relationship has been found to be the result of a variety of mechanisms. These are considered in the sections below.

A. THE h_0 FUNCTION AND ACID CATALYSIS

In more concentrated acidic solutions it is useful to define the quantity h_0 (32,33)

$$h_0 = a_{H^+}(f_B/f_{BH^+}) \tag{17}$$

where f is the activity coefficient of a molecular species in a particular solvent and a_{H^+} is the activity of protons in this solvent. This quantity (h_0) expresses the tendency of a solution to transfer a proton to a neutral base. Thus, if a protonated complex were involved as an intermediate in an acid-catalyzed ester reaction, the quantity h_0 would measure the tendency of a particular acidic solvent to transfer a proton to the basic (uncharged) ester molecule. The value of h_0 depends both on the activity of hydrogen ion in the concentrated acid solution, and on the ratio of the activity coefficients of a neutral base to its conjugate acid. There is evidence, both experimental and theoretical, to suppose that the ratio of activity coefficients of neutral base to conjugate acid is a constant for any particular solvent, independent of the nature of the molecule B. This assumption is not valid if the charge of the molecule B is different from that shown. For ionizations of the type

$$HA \rightleftharpoons H^+ + A^-$$

the ratio of activity coefficients

$$f_{A^-}/f_{HA}$$

will not be the same as

$$f_B/f_{BH^+}$$

although once again the ratio may, to a good approximation be independent of the nature of the molecule A^-. The quantity h_0 is readily determined (34,35). By substituting $f = a/c$, where c is the concentration, one obtains for h_0

$$h_0 = (a_{H^+}a_B/a_{BH^+})(C_{BH^+}/C_B)$$

Substituting K_{BH^+} for the dissociation constant of BH^+, we have

$$h_o = K_{BH^+}(C_{BH^+}/C_B) \tag{18}$$

If, as has been postulated, f_B/f_{BH^+} is a constant for a particular solvent, h_o can be determined by measuring in this solvent, the ratio of C_{BH^+}/C_B for any indicator for which K_{BH^+} is known and is of convenient magnitude to experimentally identify both species. By analogy with the definition of pH, the quantity H_o can be defined as:

$$H_o = -\log h_o = pK_A - \log (C_{BH^+}/C_B)$$

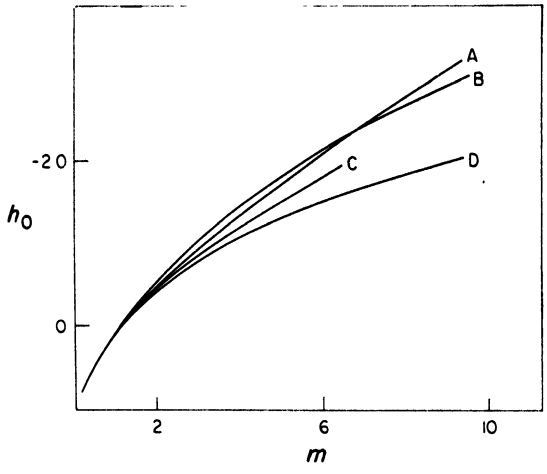


Fig. 5. H_0 as a function of molality of acids in aqueous solution (taken from Ref. 33). (A) $HClO_4$, (B) H_2SO_4, (C) HCl, (D) HNO_3.

For dilute aqueous solutions where the activity coefficients are essentially equal to unity, h_o becomes equalto the hydrogen ion concentration ($H_o \approx$ pH). At higher acid concentrations (and in other solvent media) the two quantities diverge due to the inequality between concentration and activity. In Figure 5 the relationship between h_o and m for a series of moderately concentrated aqueous acid solutions is plotted. It can be seen that in this range of concentration the quantity h_o increases very much more rapidly than does the hydrogen-ion concentration.

B. THE BRONSTAD RATE EQUATION AND CATALYSIS

If the velocity of an acid-catalyzed reaction is dependent on the concentration of a protonated form of the reactant, the velocity as given by the Brønsted rate equation (36), is

$$v = k(\mathrm{RH}^+)(f_{\mathrm{RH}^+}/f_{x^+}) \tag{19}$$

where f_x is the activity coefficient of the corresponding protonated transition state. The concentration of protonated reactant (RH^+), under the reasonable assumption that proton equilibration between reactant and solvent is rapid (i.e., that it is not a rate-limiting step in the reaction), is given by

$$c_{\mathrm{RH}^+} = \frac{\mathrm{R_o} a_{\mathrm{H}^+} f_{\mathrm{R}}/f_{\mathrm{RH}^+}}{K_{\mathrm{A}} + a_{\mathrm{H}^+}(f_{\mathrm{R}}/f_{\mathrm{RH}^+})}$$

The velocity of reaction is hence:

$$v = \frac{k\mathrm{R_o} a_{\mathrm{H}^+} f_{\mathrm{R}}/f_{x^+}}{K_{\mathrm{A}} + h_{\mathrm{o}}} \tag{20}$$

where $K_{\mathrm{A}} = a_{\mathrm{R}} a_{\mathrm{H}^+}/a_{\mathrm{RH}^+}$ and $\mathrm{R_o} = c_{\mathrm{R}} + c_{\mathrm{RH}^+}$. If the quantity f_{R}/f_{x^+} is equal to $f_{\mathrm{R}}/f_{\mathrm{RH}^+}$, which seems reasonable since it implies that the activity coefficient of the transition state is affected by the medium in the same way as is the activity coefficient of any other conjugate acid, Equation (20) may be expressed as

$$v = K\mathrm{R_o} h_{\mathrm{o}}/(h_{\mathrm{o}} + K_{\mathrm{A}}) \tag{21}$$

Hence, if the rate of a chemical reaction can be expressed in terms of the rate of decomposition of a protonated reactant alone, this rate should be proportional to h_{o}, in moderately concentrated acid solution if the complexing affinity is low ($K_{\mathrm{A}} > h_{\mathrm{o}}$) and should approach a constant maximum velocity at very large values of h_{o} ($h_{\mathrm{o}} \gg K_{\mathrm{A}}$). The hydrolysis of β-propiolactone (curve C of Fig. 4) is a classic example of a hydrolysis dependent on the quantity h_{o} in concentrated acid solutions (37). The rate of hydrolysis of methyl mesitoate (38) is also linearly dependent on h_{o}.

The equality, or even the constancy, of the ratio

$$f_{\mathrm{R}} f_{\mathrm{SH}^+}/f_{x^+} f_{\mathrm{S}}$$

(where S is the solvent) has been considered in great detail recently. Long and Paul (39) have reviewed evidence both for and against the constancy of $f_{\mathrm{R}}/f_{\mathrm{RH}^+}$ in dissociation equilibria and conclude that constancy depends on close similarity of structure and absence of steric constraints in the set of acids under consideration. There is some indication that the constancy of the above ratio depends on the nature of the solvent as well. In this regard, the strong mineral acids which have been employed as solvents in most catalytic studies appear to give reasonably constant h_{o} values.

It is important in investigations of the mechanism of reaction to examine as much of the concentration range as possible. An interesting case in

point is the acid-catalyzed hydrolysis of amides (40–42). In moderately concentrated acid, the concentration–velocity profile is that which would be predicted from a first-order dependence of velocity on $[H_3O^+]$ rather than on h_o. The protonation of the reactant can actually be detected by the leveling to a maximum velocity at higher $[H_3O^+]$. However, for still higher values of $[H_3O^+]$ the rate of reaction decreases rather than remaining constant (as would have been anticipated in a reaction dependent on $[RH^+]$). The explanation for this phenomena must lie in the role of water in the rate determining process. At lower acid concentration the concentration of water is either constant or sufficiently high so that the reaction step in which it is involved is not rate limiting. At higher hydrogen-ion concentration, however, the overall reaction velocity becomes limited to some extent by a step involving the water molecule.

For much weaker bases such as ordinary aliphatic esters, the complex between reactant and proton may be an unlikely event even in very concentrated solutions of acid. *If the protonated reactant (RH^+) were the only species entering the rate equation*, the concentration of RH^+ in this case ($K_A > h_o$) would be given by:

$$[RH^+] = R_o h_o / K_A$$

and hence the reaction velocity is given by

$$v = k_2 R_o h_o / K_A$$

However, for ethyl acetate and related alkyl aliphatic esters the rate of reaction has been found to be proportional to the hydrogen ion concentration (rather than h_o) up to very high concentrations of acid. Clearly, the mechanism of hydrolysis of these esters cannot be one involving only a protonated reactant in the rate equation.

Consider the case where reaction is limited by the species of RH^+ and H_2O. The rate of this reaction is given by

$$v = k'(RH^+)(H_2O)(f_{RH^+}/f_{z^+})$$

and substituting in the value of RH^+ we have

$$v = \frac{k' R_o (H_2O) a_H f_R / f_{z^+}}{K_A + h_o} = \frac{k' R_o K' W (H_3O^+)}{K_A + h_o} \frac{f_{H_2O} f_R}{f_{H_3O} f_{z^+}} \qquad (22)$$

The acid-catalyzed hydrolysis of both aliphatic esters and amides can be interpreted in terms of Equation (22) (43,44). At relatively low concentrations of mineral acid K_a is greater than h_o in both cases, and the velocity of hydrolysis is proportional to the concentration of mineral acid. At higher concentration of mineral acid, however, the stronger base (the amide) becomes significantly protonated ($K_a \approx h_o$) and the increase in

velocity due to increase in H_3O^+ is offset by the now significant increase in h_o. Finally, since the value of h_o increases more rapidly than the concentration of H_3O^+ in concentrated solutions of strong mineral acids, the velocity reaches a maximum and then decreases at still higher concentrations of H_3O^+ (Fig. 4). With very weak bases (esters), the situation $h_o > K_a$ is never achieved, hence for all experimentally investigated values of H_3O^+ (and h_o) the velocity is directly proportional to the concentration of H_3O^+ (45). It is interesting to note that in spite of the much greater tendency toward complex formation in the case of the amide, the ester is still much more rapidly hydrolyzed in acid solutions. If the mechanism of hydrolysis of protonated intermediates is the same for both derivatives, the ratio of rate of hydrolysis of the protonated ester to that of the protonated amide must be still greater than the ratio of specific hydrolysis rates. The difference between the behavior of β-propiolactone and methyl mesitoate which are dependent on h_o in strong acid (curves C and D, Fig. 4) as compared with ethyl acetate and acetamide (curves A and E, Fig. 4) has been used repeatedly as a test for the presence (Equation 22) or absence (Equation 21) of water in the rate-limiting step. This test is based on a suggestion originally proposed by Zucker and Hammett (46). The Zucker-Hammett suggestion of h_o dependence as a general test for solvent participation in the transition state has been severely criticized (47) because of both the demonstrated inconstancy of activity coefficients of the type f_R/f_{RH^+} with variation in R in particular instances, and the possibility of alternative mechanisms leading to similar functional relationships (48,49).

An interesting example of catalysis apparently, not dependent on h_o (38), is the acid catalyzed hydrolysis of methyl benzoate in which the condition $h_o > K_A$ is realized in concentrated sulfuric acid solutions (50–52). The velocity of this reaction becomes independent of water concentration at very high mineral acid concentration.

2. General Acid Catalysis

In addition to catalysis via direct (equilibrium) proton transfer between solvent and reactant, catalysis may be effected by the transfer of a proton from a molecular acid to a basic reactant without intermediate protonic dissociation of the molecular acid. Consider the reaction

$$A + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B + RH^+$$

$$RH^+ \xrightarrow{k_2} \text{products} \qquad (23)$$

The resultant velocity expressions have been summarized by Bell (53)

TABLE I
Kinetic Consequences of Equation (23) at Fixed Reactant Concentration

Initial condition (k_{-1} relative to k_1)	k_{-1} relative to k_2	k_{apparent} $v = k[R]$	Type of catalysis
$k_{-1}[B] \gg k_1[A]$	$k_2 \gg k_{-1}[B]$	$k_1[A]$	General acid catalysis
	$k_2 \ll k_{-1}[B]$	$k_2([H^+]/K_{RH^+})$	Specific oxonium-ion catalysis
	$k_2 \quad k_{-1}[B]$	$k_2[H^+]k_1[A]/(K_{RH^+}k_1[A] + k_2[H^+])$	Mixed catalysis, both types observable in principle
$k_{-1}[B] \approx k_1[A]$	$k_2 \gg k_{-1}[B]$	$k_1[A]$	General acid catalysis
	$k_2 \ll k_{-1}[B]$	$k_2[H^+]/(K_{SH^+} + [H^+])$	$1/v$ proportional to $1/[H^+]$ oxonium-ion catalysis only
	$k_2 \approx k_{-1}[B]$	Complex kinetics not first order	Mixed catalysis, but difficult to analyze

and are listed in Table I. From Table I it is evident that catalysis by molecular acids (other than the protonated solvent) will be experimentally observed only when the rate of decomposition of the protonated reactant (RH^+) is significant relative to the bimolecular rate of reversion of RH^+ and B to reactant and protonated base. In order for this rate ($k_{-1}[B]$) to be slow, it must follow that the interaction between R and the molecular acid is partially chemical in nature, rather than purely physical. If the dissociation rate ($k_{-1}[B]$) is rapid relative to k_2, the rate of reaction will always be dependent on hydrogen ion (solvated proton) only, and will not exhibit catalysis by molecular acids. Thus, although catalysis by molecular acid may in actuality exist, if the equilibrium

$$A + R \rightleftharpoons B + RH^+$$

can be established (by virtue of a small value of k_2) the concentration of RH^+ will be that predicted by the direct effect of the protonic equilibrium,

$$H^+ + R \rightleftharpoons RH^+$$

and hence the catalysis will be kinetically indistinguishable from direct hydrogen-ion catalysis. Catalysis by molecular acids (other than the protonated solvent) is referred to as "general acid catalysis." It is a situation which can arise only via the "chemical" transfer of proton from molecular acids to an activated form of the reactant for which the reverse reaction (k_{-1} in Equation 23) has a high activation energy (relative to kT).

For simplicity in discussion, consider the special case $k_2 \gg k_{-1}[B]$.

Rate-Limiting Proton Transfer and the Bronsted Catalysis Relation. In the special case $k_2 \gg k_{-1}[B]$, if k_{-1} is less than or of the order of magnitude of k_1, the concentration of the intermediate RH^+ will be small, and the condition for the steady state will be maintained. In this situation, the rate of product formation $\dot{X}$ is equal to $k_1[A][R]$. The ratio of forward to reverse specific rate constant (k_1/k_{-1}) is given by

$$k_1/k_{-1} = v_1[B][RH^+]/v_{-1}[A][R] = K_A/K_{RH^+}$$

For a given reactant (R), the equilibrium constant (k_1/k_{-1}) will be directly proportional to the acid strength of the acid catalyst (K_A). As the acidity of the catalyst increases (increasing K_A), the forward rate will increase, whereas the reverse rate will decrease since the conjugate base is now a weaker base. Since the ratio k_1/k_{-1} must be proportional to K_A it follows necessarily that k_1 increases less rapidly than K_A while k_2 decreases less rapidly than $1/K_A$ (54), which may be expressed as

$$d \log k_1 = \alpha d \log K_1$$

$$-d \log k_2 = (1 - \alpha) d \log K_2$$

where $1 \geqq \alpha \geqq 0$. The right-hand side of the equation, at constant temperature and medium, is proportional to the free energy of dissociation of the acid. *If α is a constant over a range of acids of different strengths,* the equations may be integrated to

$$k_1 = g_R K_A^{\alpha}$$

$$k_{-1} = g_{RH^+} K_A^{(\alpha-1)} \tag{24}$$

where g_{RH} and g_R are characteristic of a given reactant at a given temperature and in a given solvent. It is well to point out that the above derivation does not depend on R and RH^+ maintaining their equilibrium ratio during the course of the reaction. Equation (24) is known as the Bronsted Relation (55). Under fixed conditions of reactant, solvent, and temperature it predicts a linear relationship between the logarithm of the rate constant for catalysis and the standard free energy of dissociation. The relationship depends on the constancy of the quantity α (i.e., on α being dependent on reactant but not on catalyst). This is likely to be true for a group of catalysts of varying acid strength as long as the structures of the various catalysts are similar (56), i.e., the same type of chemical proton transfer reaction is possible for all catalysts. For the example under consideration here, $k_2 \gg k_{-1}[B]$, the specific first-order rate constant for the reaction is $k = g_R K_A^{\alpha}[A]$. The ability of molecular acids to act as general acid catalysts depends on the value of the exponent α. Thus for reactions involving high values of α (α approximately equal to 1) only acids with

large values of K_A will function as effective catalysts. For the case of $\alpha \ll 1$, if general acid catalysis is observed with one acid it will be experimentally observable with many others. It should be pointed out that general acid catalysis of ester hydrolysis has been observed only with especially reactive esters (such as ethyl chloroformate). Such catalysis is due either to the ease of proton transfer to these esters, or to the unusual instability of the protonated intermediate (such that k_2 becomes very large). The latter possibility seems the more likely. General acid catalysis has been observed in the esterification reaction of acetic acid and methanol (57). It has been presented as a likely explanation of a number of intramolecular hydrolysis reactions (via intramolecular hydrogen bond transfer) (43).

3. Medium Effects on Acid Catalysis

Since most reactions of esters involve catalysis of the type

$$R^0 + Z^a \rightleftharpoons RZ^a \xrightarrow{H_2O} \text{products}$$

where "a" can be greater than, less than, or equal to zero. Little effect of the solvent medium on the reaction rate is to be expected since there is no difference in the charge of the species on either side of the equation. Thus, for example, a maximum of only a few percent change in rate can be achieved by change of medium from distilled water to $0.1M$ univalent salt (58). Medium effects may be expressed as the variation in the ratio of activity coefficients of reactants (f_A, f_B) to transition state (fx), with variation in solvent. (See Equation 19.)

$$v = kf_A f/fx \tag{25}$$

As has been shown (see h_0 function above), under limiting conditions these medium effects can become quite large. If an ester carries a formal charge the interaction of this charged reactant with charged proton will be highly sensitive to medium, the reaction becoming more rapid in solutions of high dielectric constant if the charges are the same and less rapid if the charges are opposite. Similarly, increase of foreign salt concentration will increase the rate of reaction between like charges and decrease the rate of reaction between unlike charges. Direct effects of the electrolytic medium on reactants or catalysts, as described above, are known as "primary salt effects." In chemical reactions involving more than one ion the effect of dilute electrolyte on the reaction rate has been treated assuming the Debye-Hückel theory (59,60). The lesser effect of added electrolyte on reactions involving one ion has been summarized by Bell (58). In addition, the

rate of reaction may be dependent upon the ionization of a weak acid, namely

$$HA \rightleftharpoons H^+ + A^-$$

The concentration of hydrogen ions will depend on the ionization constant of the weak acids in the medium. For acids of the type

$$HA^0 \rightleftharpoons H^+ + A^-$$

increasing salt and increasing dielectric constant should increase the hydrogen ion concentration and hence increase the rate. For ionizations of the type

$$BH^+ \rightleftharpoons H^+ + B^0$$

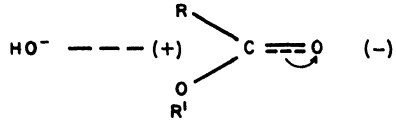
however, changes in dielectric constant or in salt concentration should have little effect on the concentration of hydrogen ions. The effect of the medium on chemical reaction has been treated in detail by Bjerrum (60). The velocity of a reaction limited in the k_2 step (Equation 23) is given by Equation (26)

$$v = k_2 K c_A c_B (f_A f_B / f x) \tag{26}$$

where K is the thermodynamic equilibrium constant for the system A + B $\rightleftharpoons$ X. Effects of the medium can then be interpreted in terms of the relative effect on the activity coefficients of reactants and transition state (X), it being assumed that the solution properties of the transition state are like that of a complex AB, and that the effect of medium will be manifested only in the ratio of activity coefficients of reactants to activated complex (k_2 and K are assumed to be dependent on temperature alone).

4. Hydroxyl-Ion Reactions

The saponification of esters are in reality examples of nucleophilic reactions (see below) rather than of specific hydroxyl-ion catalysis. Nevertheless, the wide extent of studies with this particular nucleophile merits its separate discussion. As was shown in Figure 2, the pH at the inflection point in the hydrolysis rate–pH curve occurs considerably below pH 7 with many esters in aqueous solution. In general, this is an indication of the more rapid rate of reaction of hydroxyl ion with esters relative to the rate of acid catalyzed hydrolysis. The rapid reaction must be due to a strong interaction between hydroxyl ion and carbonyl carbon.



Esters are usually susceptible to saponification by hydroxyl ion. The saponification reactions have been found to be first order in hydroxyl ion in all instances.

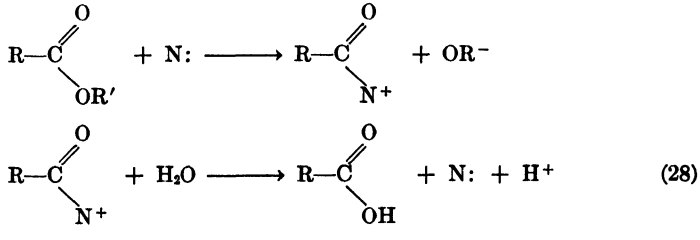
An interesting example, related to saponification of esters, is the "hydrolysis" of imides. Imides are susceptible to nucleophilic attack by hydroxyl ion. The dependence of rate on $[OH^-]$ is not linear however, but sigmoid. The results can be explained on the basis that the only reaction which occurs at a significant rate is that of uncharged imide with OH^-. The rate of reaction according to this mechanism is given by Equation (27).

$$v = k[\mathrm{HI}][OH^-] = \frac{kI_0[OH^-]}{(K_A/K_W)[OH^-] + 1} \tag{27}$$

where K_A is the ionization of the imide and I_0 is the total concentration of imide. Thus at higher $[OH^-]$, the rate of reaction becomes independent of $[OH^-]$. This situation is to be contrasted with the rate of hydrolysis of substituted imides, thus in the hydrolysis of *N*-carbobenzoxyaspartyl-*n*-methylimide the rate of reaction is always proportional to $[OH^-]$ since there is no possibility of ionization to the imidate ion in this case. The hydrolysis of imides represents a striking example of the importance of the charge of the interacting species in influencing the rate of a reaction.

5. Nucleophilic Catalysis

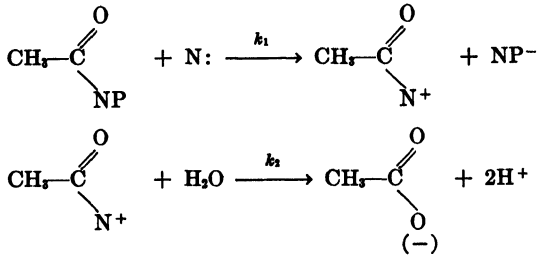
There are many examples of nucleophilic reactions involving esters. In some instances the nucleophile is regenerated in a succeeding step; for example,



(28)

In such cases the nucleophile serves as a true "chemical" catalyst. It is to this type of nucleophilic reaction that discussion is restricted in this section. It is probable that more detailed chemical information concerning the nature of the intermediates in catalysis has come from studies of nucleophilic catalysis than from any other type of reaction. One of the most thoroughly studied examples of nucleophilic catalysis is the hydrolysis of *para*-nitrophenyl acetate (NPA). The reaction has been investigated

in great detail by Bender, Bruice, Jencks, and their collaborators and has been reviewed by Bender (43). The reaction has been postulated to proceed via the mechanism



(29)

The intermediate nucleophile–reactant complex has been detected in a number of instances (61–63). The spectral changes accompanying the hydrolysis of *para*-nitrophenyl acetate in the presence of imidazole have been investigated by Bender. The intermediate in this case has been postulated to be acetylimidazole ion to correspond with the observed spectral absorption peak at 245 mμ (61,62). A curve similar to that obtained by Bender is shown in Figure 6(a). From this figure it can be seen that the appearance of nitrophenolate ion (curve A, λ_{max} = 410 mμ) is a first-order rate process not dependent upon the concentration changes corresponding to the time-dependent spectra at 245 mμ (curve B). From the precise data of Figure 6(a), it can be shown that the kinetics of this system are entirely described by the two steps in the equation given above (Equation 29). The solid line in Figure 6(a), curve B, is the calculated curve for the two-parameter (k_1 and k_2) equation governing the acetylimidazole ion concentration. k_1 is the first-order specific rate of formation of nitrophenolate ([imidazole] $\gg$ [NPA]), and k_2 may be obtained by successive approximations (for the best value) from the time (t_M) at which the maximum adsorption at 245 mμ is reached. At this time,

$$d[\text{acetylimidazole}]/dt = 0 \text{ and}$$

$$k_2[\text{acetylimidazole}] = k_1[\text{imidazole}]\,[\text{NPA}]_0 \exp -k_1[\text{imidazole}]t_M$$

$$= k'[\text{NPA}]_0 \exp (-k't_M)$$

where $[\text{NPA}]_0$ is the initial reactant concentration. Under the conditions for obtaining Figure 6(a), the concentration of intermediate corresponding to the 245 mμ maximum turns out to be nearly equal to $[\text{NPA}]_0$. Whereas a still higher concentration of imidazole (relative to this [NPA]) would only increase the positive slope of the early phase of the reaction, a decrease

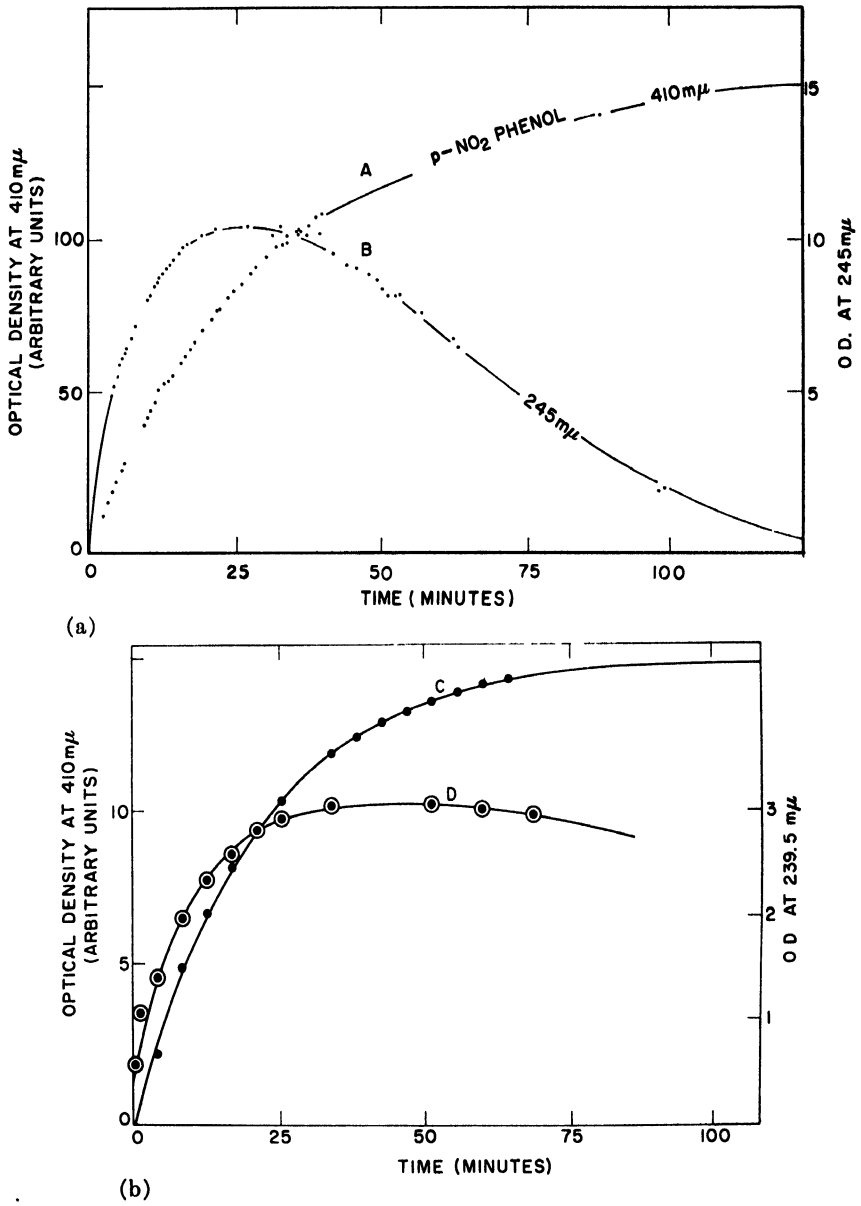


Fig. 6. Appearance of intermediates and products in the nucleophilic catalysis of *p*-nitrophenyl acetate. (a) The catalyst is imidazole (pH 7.0) in curves A (410 mμ) and B (245 mμ). (b) The catalyst is histidine methyl ester (pH 7.5) in curves C (410 mμ) and D (239.5 mμ).

in the concentration of imidazole would change the entire time–adsorption profile considerably by both decreasing the slope of the early phase and lowering the adsorption maximum due to the now more comparable rates of the two steps in the reaction. An interesting comparative case of nucleophilic catalysis is observed in the hydrolysis of NPA by histidine methyl ester (64). Curves C and D of Figure 6(b) illustrate the data. The spectrum at 240 mμ shows an even more stable intermediate with adsorption maximum shifted to lower wavelength than in the corresponding case of imidazole catalysis. The maximum is quite broad, the initial phase of reaction faster, and the later phase of reaction much slower than with imidazole. It is interesting to note that the appearance of nitrophenolate is again a first-order reaction. Due to the wide discrepancy in relative rate constants for formation and decomposition of intermediate in this instance, a first-order rate of intermediate formation at 240 mμ can also be measured. Contrary to expectations, the first-order specific rate of formation of intermediate is not the same as the specific rate constant obtained for the appearance of nitrophenolate, but rather, is three times faster. This result is found over a wide range of histidine methyl ester (HIME) concentration provided that [HIME] $\gg$ [NPA]. The simplest explanation compatible with the data is that a *stable complex* between HIME and NPA forms *prior* to the release of nitrophenolate ion. This complex must perturb the imidazole spectrum sufficiently such that this complex and the trigonal complex postulated in Equation (29) have similar adsorption spectra. These two apparently similar nucleophilic catalyses serve to point out the pitfalls in the qualitative interpretation of kinetic data. The two examples (imidazole and HIME catalysis) could very easily have been interpreted as being representative of the same catalytic intermediate by qualitative inspection of the curves. The data are also indicative (in the case of HIME catalysis) of the formation of tetrahedral intermediates during nucleophilic catalysis. In the case of HIME the α-amino group must somehow participate in the formation of a more stable tetrahedral intermediate. It is interesting to note that in spite of this effect the second-order rate constant for liberation of nitrophenolate ion is not significantly larger in the case of HIME catalysis than it is for imidazole catalysis. Nucleophilic catalysis by imidazole and derivative has been investigated in great detail by Bruice and coworkers (65–67). Some of their results are plotted in Figure 7. For a number of imidazole derivatives, the rate of reaction is related to the base strength of the imidazole as predicted by the Bronsted relationship. Some derivatives however, do not fit the general Bronsted relationship (selected examples are discussed below). In a further examination of the relationship between base strength and nucleophilicity in the release of nitrophenolate ion from NPA, Jencks

and co-workers (68) have investigated the reaction of NPA with a large number of nucleophiles. The results are summarized in Figure 8. Since the effectiveness of a nucleophilic catalyst will depend on its ability to bind (complex) with an electrophilic center of the reactant, the strength of this complex should, to a first approximation, be related to the strength with which a nucleophile can bind a proton. If the two processes (complex formation between the nucleophile and reactant or proton) are

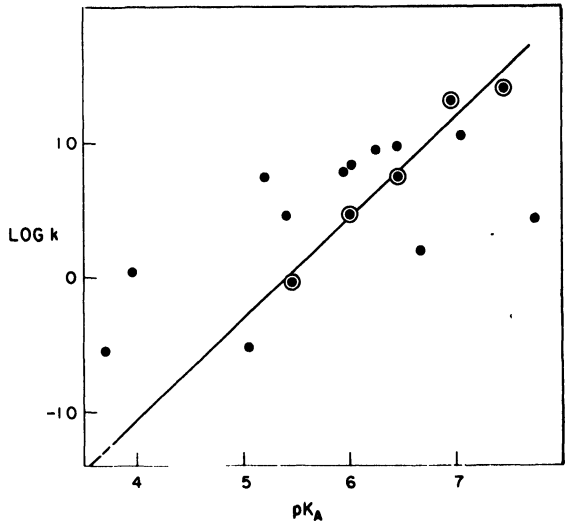


Fig. 7. Bronsted plot for catalysis of *p*-nitrophenyl acetate hydrolysis by imidazole derivatives (Ref. 67). The best straight line has been drawn through the points (circled) where steric effects should be minimal and where catalysis only occurs via the uncharged base.

analogous, the *difference* between these two interactions should be essentially independent of the nature of the R group, i.e.,

$$R{-}N{:} + X \rightleftharpoons R{-}N^{(+)}{-}(X^{-})$$

$$R{-}N{:} + H^{(+)} \rightleftharpoons R{-}N^{(+)}{-}H$$

and hence a constant energy term should represent this difference. If the rates of a reaction catalyzed by nucleophiles were dependent on the rate-limiting formation of such a complex, the logarithm of these rates should be linearly related to the pK_A's of the respective nucleophiles. As is seen in Figure 8 the actual nucleophiles examined scatter significantly about this linear prediction. The divergence from the linear relationship between basicity and reactivity in nucleophilic reactions has been considered in terms of factors which play a large role in the catalytic reaction without

exerting a complementary influence on the ionization (68). Most important among these factors are: (*1*) polarizability of both the nucleophile and the reactant, in which a greater effect would be exerted in the interaction between a large and a small molecule relative to the interaction between two small molecules (nucleophile and proton); (*2*) hydrogen bonding and proton transfer in the reactant–nucleophile complex leading

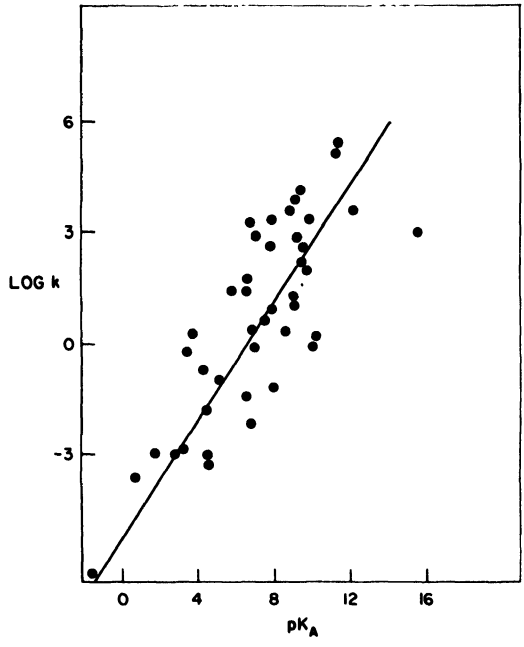


Fig. 8. Attempted Bronsted plot for 43 nucleophilic reactions of *p*-nitrophenyl acetate (Ref. 68).

to acceleration of reaction; (*3*) electrostatic effects when the reactants are charged; and (*4*) a difference in solvation for the two processes (complex formation and ionization). Finally, and obviously, the steric restraints on the formation of complex between nucleophile and reactant may be completely different from the rather low steric specificity usually associated with the binding of a proton. In spite of all of these considerations limiting the applicability of the Bronsted relation in nucleophilic reactions, the qualitative behavior of nucleophiles are clearly related to their base strengths.

6. General Base Catalysis

In addition to nucleophilic catalysis "general base catalysis" of some ester hydrolyses has been observed. "General base catalysis" may be defined in the same way as general acid catalysis (Section III.2) with the roles of catalyst and the reactant reversed, i.e., catalyst is the proton acceptor and the rate-controlling step is the slow chemical proton transfer from reactant to catalyst. Since in ester hydrolysis the reactant itself has no proton to lose, general base catalysis is, in fact, an indication of the participation of water (or other proton donor molecules) in the reaction. The rate-limiting step must involve the deprotonization of a water-reactant type of complex

$$R \cdot OH_2 + B \rightleftharpoons ROH^- + A$$

An interesting example of general base catalysis occurs in the hydrolysis of β-lactones. These compounds exhibit both nucleophilic catalysis and general base catalysis (69–71), the nucleophilic reactions taking place at the β-carbon atom with alkyl-oxygen cleavage, whereas general base catalysis involves acyl-oxygen cleavage. These results are of particular interest since the "uncatalyzed" nucleophilic attack of water (the water reaction) which predominates between pH 1 and pH 7 (see Fig. 4, curve C) involves alkyl-oxygen cleavage (72) (nucleophilic attack at the β-carbon atom).

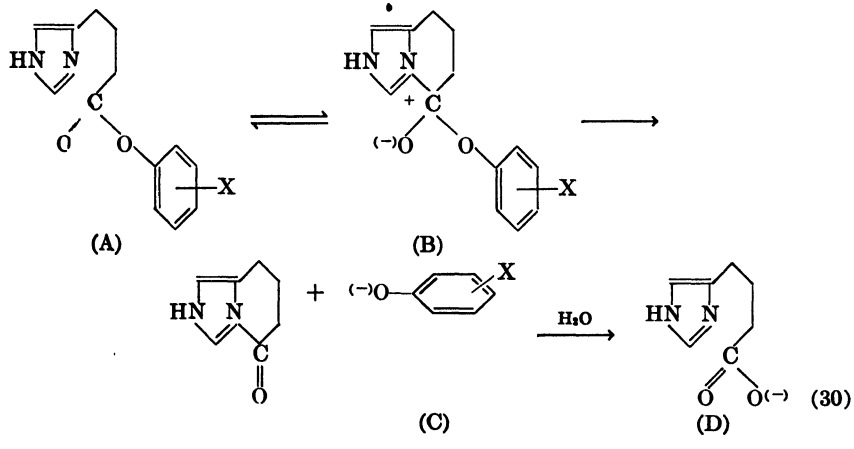
The aminolysis and ammonolysis of esters have been controversial examples of general base catalyzed reactions (73,74). Recently clearcut evidence for general base catalysis has been presented for the reaction of ethyl formate with *n*-butylamine (75) and the aminolysis and ammonolysis of phenyl acetate by a large variety of NH-containing bases (76). The aminolysis of phenyl acetate exhibits specific hydroxide ion catalysis as well as general base catalysis. The mechanism of the general base catalyzed aminolysis reactions have been discussed in detail by Bender (43) and by Bunnett and Davis (75). A number of alternate mechanisms have been proposed which are kinetically indistinguishable; the general principle in all the mechanisms being the slow transfer of a proton donated by the nucleophile (NH-containing compounds) from the nucleophile–reactant complex to the general base catalyst in the rate-controlling phase of the reaction process.

7. Intramolecular Nucleophilic Catalysis

The unfavorable entropic factor (Section II.1.B) makes complex formation between small molecules a very unlikely event when only weak physical or chemical forces are involved. It is for this reason that catalysis via

relatively weakly interacting pairs of molecules (such as esters and molecular acids and bases) is rarely observed, except where the reaction involves a very labile bond (such as the nitrophenyl ester bond in NPA discussed above); for example, general base, nucleophilic, and general acid catalysis have not been observed in the hydrolysis of more stable esters (aliphatic esters) at room temperature. If the entropic factors can be drastically reduced, considerable change in the catalytic situation may result. A common way in which diminution of this unfavorable entropic factor may be accomplished is by combining the reactant group and the catalytic group on the same rigid molecule, namely, "freezing" the reactant in the vicinity of the catalyst. If intramolecular catalysis occurs via the interaction of two groups which are rigidly fixed in proximity, the reaction may become much more highly probable if complex formation is restricted to that favorable for the chemical bond leading to catalytic reaction. It is not surprising therefore, that many of the examples of intramolecular catalysis involve nucleophilic reactions, i.e., chemical bond formation between catalytic center and reactant center, and that these two centers are so separated chemically that formation of a chemical bond results in the formation of either a 5- or 6-membered ring. A series of such intramolecular catalyses involving carboxylate ion as catalyst have been summarized by Bender (43). The leaving (alcohol group) is usually a stabilized ion, as in the hydrolysis of carboxylate-substituted phenyl esters, although there is circumstantial evidence for nucleophilic carboxylate catalysis in the hydrolysis of monomethyl phthalate at neutral pH.

The catalytic group may be one of many nucleophiles. Much attention has been given to the intramolecular imidazole-catalyzed hydrolysis of esters by Bruice and co-workers. An interesting example is the hydrolysis of *p*-X-phenyl γ-(4-imidazolyl) butyrate (77), Equation (30) A. The pH



(30)

dependence of the imidazole catalyzed reaction is a function of the particular substituent X of the carbophenoxy group although the pK_A of the imidazolium residue remains essentially invariant. The rapid elimination of the phenol has been shown spectrophotometrically to the result of rapid lactam formation (78,79), Equation (30) C. A mechanism consistent with all of the data would hence have to involve the formation of a reversible complex containing the carbobenzoxy group, Equation (30) B, prior to lactam formation.

A. SPECIFIC HYDROXYL CATALYSIS IN INTRAMOLECULAR REACTIONS

An interesting example of intramolecular catalysis in the cleavage of "usually stable" ester bonds occurs in the hydrolysis of β-esters of aspartyl

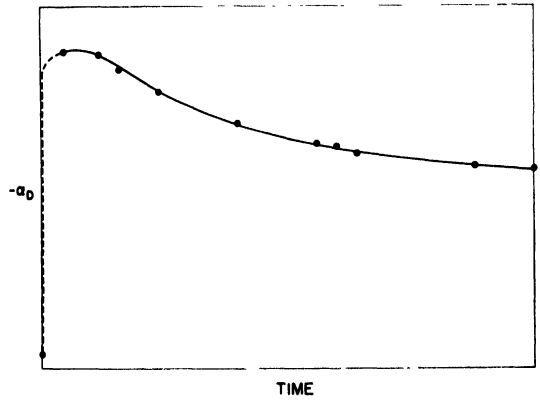


Fig. 9. Change in optical rotation at the sodium D-line during the hydrolysis of *N*-carbobenzyloxy-*N*-methyl-β-benzyl isoasparaginate in 50 vol. % aqueous dioxane.

amides and peptides (80,81). *N*-Carbobenzyloxyaspartylamide β-benzyl ester (BENCAA) is relatively rapidly degraded to benzyl alcohol and *N*-carbobenzyloxyaspartylimide (80). The reaction rate is greater than 10^2 times the rate of hydrolysis of *N*-carbobenzyloxy-β-alanine benzyl ester, and is probably dependent on ionization of the amide nitrogen (a reaction similar to the formation of lactam in the case of the imidazole derivative mentioned above). The low acidity of the amide nitrogen requires a catalyst of base strength comparable to hydroxide ion to effect catalysis. As in the case of succinimide, the resulting cyclic structure is relatively unreactive towards hydroxyl-ion catalysis because of the repulsion between the negative charges of the hydroxide ion and the imidate ion. The imide in the carbobenzyloxyaspartic derivative is a considerably stronger acid than is succinimide. The ester (BENCAA) therefore, does not meet the

requirements for rapid intramolecular catalyzed *hydrolysis*. If imidate ion formation (ionization) is prevented in the intermediate, as for example, by starting with the corresponding *N*-methylamide, hydrolysis of the intermediate occurs via hydroxide-ion catalysis, the rate-limiting hydrolysis of the imide being approximately 10^3 as fast as the rate of hydrolysis of an unsubstituted benzyl ester. The optical rotation versus time curve is shown in Figure 9. An intermediate, which is more rapidly formed than degraded, occurs in the reaction. The molar rotation difference between reactant and intermediate is the same as the molar rotation difference between BENCAA and *N*-carbobenzyloxyaspartylimide. The time-optical rotation profile of the intermediate can be fitted by a two parameter equation (in buffered solution) involving the first-order formation and decomposition of intermediate. The rate of proton liberation at

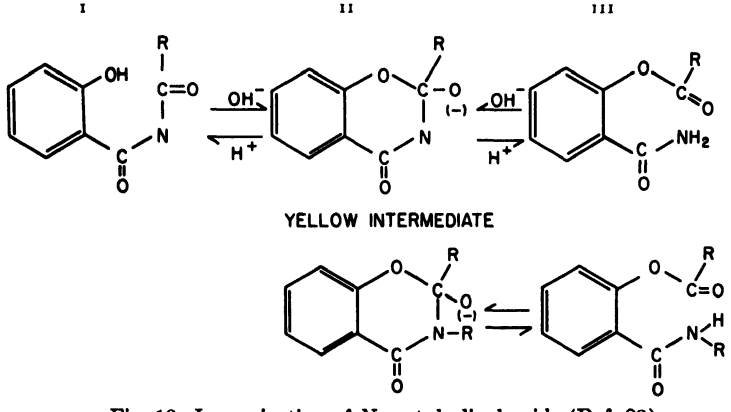
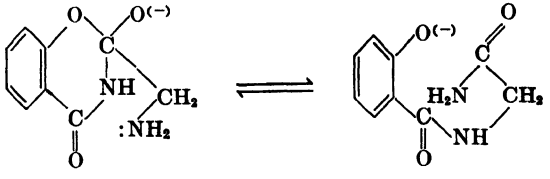


Fig. 10. Isomerization of *N*-acetylsalicylamide (Ref. 83).

fixed pH is virtually equal to the rate of decomposition of the intermediate. This is the predicted result for a reaction sequence involving a rapid first and slow second step. A similar type reaction has been observed by Brenner (82) in the isomerization of acetylsalicylamide (I in Fig. 10) (83). The isomerization in Figure 10 is base catalyzed in either direction, the pH–rate profile being sigmoid in shape with an apparent pK_A' for isomerization equal to 6.1 (84). Isomerization in either direction is accompanied by the appearance of a yellow intermediate, the pH–rate profile for yellow intermediate being the same as that for isomerization. The tetrahedral intermediate (II) has been postulated as the yellow intermediate in the reaction. Ring opening in II takes place spontaneously with the formation of either the imide (III) or acetylsalicylamide. That the yellow intermediate is the compound postulated above is strongly indicated by

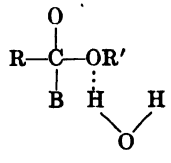
the fact that the corresponding *N*-methylacetylsalicylamide (IV) forms a yellow compound as well, although it does not isomerize. The pH dependence of formation of the yellow compound is the same as that in the unsubstituted amide. An interesting variant of this reaction is the *postulated* two-step nucleophilic intramolecular reaction of glycylsalicylamide (85) via two cyclization steps, the first step being essentially the same as that postulated above and the second involving attack of amine on the carbonyl carbon. Subsequent ring opening results in the formation of the inverted isomer *N*-glycylsalicyl amide as shown in Equation (31).



(31)

IV. MULTIFUNCTIONAL CATALYSIS

Up to this point, catalysis in solution has been treated as if a single molecular species were responsible for the catalysis of a chemical reaction. This is often not the case. Nevertheless, much of solution catalysis *can* be treated as if a single group were responsible for the catalysis due to the predominance of this particular group in determining the velocity of the reaction. Many reactions involving both acid and base catalysis have one of these functions performed by solvent molecules (usually the function which is less specific, or has a smaller value of the exponent α of Equation (24)). For example,



A classic example of the requirement of both acid and base catalysis is the mutarotation of tetramethyl glucose. This reaction, which in inert solvents is catalyzed by both pyridine and phenol (20), is very much more effectively catalyzed when the two functional groups (the nitrogen base and the phenolic OH) are on the same molecule and in suitable position for acting as proton donor and acceptor (21). Although no quite so effective bifunctional catalyst has yet been found in ester hydrolysis, a good deal of evidence has been accumulated bearing on the participation of more than one group in the chemical catalysis. An interesting example bearing on a

previous discussion (Section III.4) is the hydrolysis of *N*-carbobenzyloxy-(β-benzyl)aspartyl *N*-methyl amide. The hydrolysis of this compound, to yield the isomeric asparagine and isoasparagine compounds, proceeds via the formation of the cyclic imide (86). Hydrolysis of this intermediate proceeds by the direct attack of hydroxyl ion on the imide, presumably to form the tetrahedral addition compound. Catalysis, in this instance, involves both the α-peptide (ionized) and hydroxyl ion. An even more effective multifunctional catalysis is achieved, when the above hydroxyl ion is replaced by a covalently linked alkoxyl ion in the proper stereochemical configuration. The extreme rate of ester hydrolysis of *N*-carbobenzyloxy-(β-benzyl)-aspartylserylamide has been postulated to be the result of a concerted nucleophilic and proton transfer reaction process (80) (Fig. 11). The hydrolysis of *N,O*-diacetylserineamide has been shown to be much more rapid than the *corresponding O*-monoacetylserineamide, and exhibits general base catalysis (89).

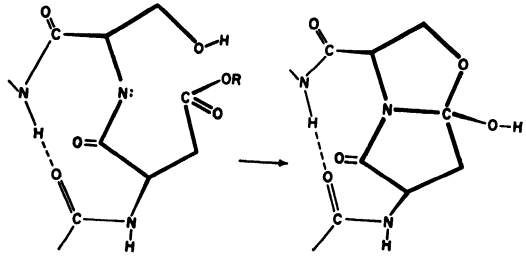
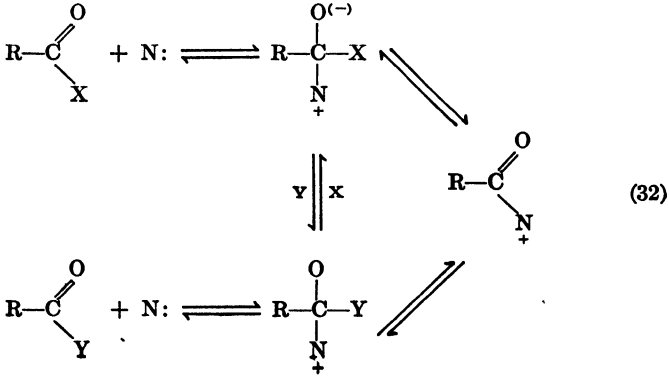


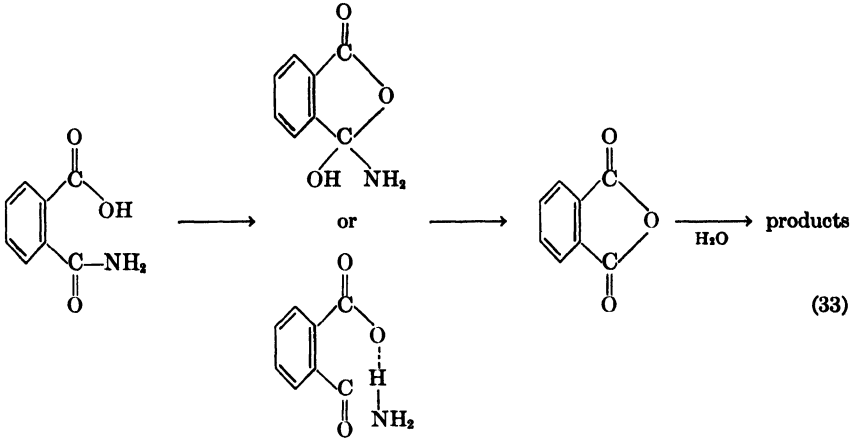
Fig. 11. Proposed intermediate in the hydrolysis of *N*-carbobenzyloxy-(β-benzyl)-L-aspartyl-L-serylamide (Ref. 82).

From the frequency of nucleophilic-catalysis mechanisms, an effective catalytic pathway appears to be nucleophilic attack to form tetrahedral intermediate, followed by decomposition of tetrahedral intermediate to trigonal product, namely Equation (32)



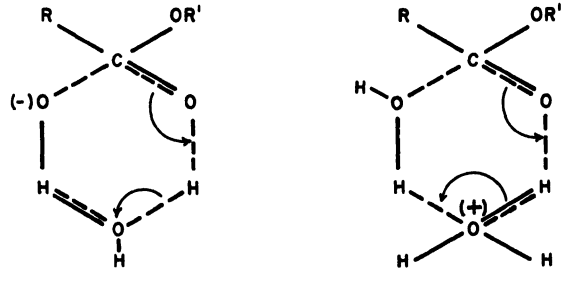
(32)

The demonstrated formation of trigonal intermediates such as acylimidazole may actually impede the otherwise rapid catalysis via tetrahedral intermediates. The hydrolysis of phthalamic acid (Equation 33) has been postulated to involve both electrophilic (general acid) catalysis and nucleophilic catalysis mediated by the OH of carboxylic acid. The course of reaction has been postulated to be as shown in Equation (33) (87,88,43).



(33)

Discussion of multifunctional catalysis should not be ended without mention of the stereochemically attractive postulate of Syrkin (90–92), that simple monofunctional catalysis is effected by structurally defined solvent–catalyst–reagent cyclic complexes involving minimal entropic change. Such complexes yield products by rearrangement of the chemical bonds with virtually no change in atomic positions. Two noteworthy models are the simple oxonium- and hydroxyl-ion reactions with esters.

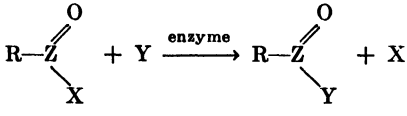


The above mechanisms are attractive from the viewpoint of the stereochemistry, the involvement of tetrahedral intermediates throughout, and the detailed role assigned to solvent molecules. At present, however, there

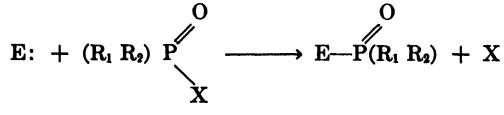
are no experimental details which differentiate between these cyclic transition states and some of the more usual mechanisms.

V. ENZYME CATALYSIS

The kinetics of enzyme catalyzed reactions and the mechanisms of enzyme catalyzed reactions have been under intensive study for many years. A voluminous literature has accumulated relating to the formal kinetics, the substrate specificity and the mechanism of substrate decomposition (reaction). Nevertheless, little is known of the chemical nature of the particular molecular catalytic groups responsible for enzymic catalysis except in a few specific instances. This is doubly unfortunate, both from the biological point of view and from the view of investigation of the relative importance of various factors in multifunctional catalysis. Of the enzymes for which there is some information on the chemical nature of the active sites, nearly all are involved in reactions of acyl or phosphoryl transfer, namely

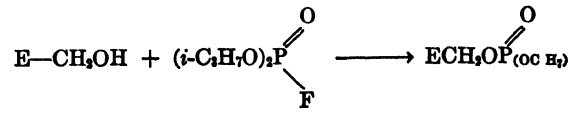


These enzymes fall into two groups chemically (8); those which react with organic phosphate esters irreversibly



and those which are highly sensitive to oxidizing agents and heavy metals. In the first class are the proteolytic enzymes (chymotrypsin, trypsin, subtilisin, thrombin, and elastase), the esterases (cholinesterase and various liver esterases), and the phosphomutases (phosphoglucomutase and phosphofructomutase). In the second group are the sulfhydryl-containing enzymes, papain and ficin. Both groups of enzymes show no requirements for specific metal ion or other coenzyme. *Among* the amino acid residues in the sequence defining the reactive sites of the first group (above) are the common sequences of either glycyl–aspartyl–seryl–glycyl or glycyl–glutamyl–seryl–alanyl (93). This common tetrapeptide sequence is not only unusual as a statistical event, but the serine residue in this tetrapeptide is unusual in respect to all other known serine-containing peptides and proteins in its extreme reactivity toward acylating agents (94) and organo-

phosphate esters, such as di-isopropylfluorophosphate (DFP) (95).



The properties of this particular alcoholic hydroxyl are sufficiently different to consider the possibility that it is chemically modified in reactive enzymes (80). It reacts much more rapidly with acetic anhydride, for example than do any of the free NH_2 groups in α-chymotrypsin (94). The unusual behavior of this serine residue coupled with the observation of a sigmoid pH–activity curve with mid point of pH at about 7 for these enzymes has suggested a number of related mechanisms involving this alcoholic hydroxyl and an imidazole residue from histidine (96–98). These postulated mechanisms all involve concerted nucleophilic-electrophilic catalysis, but differ one from the other as to which catalytic group is the nucleophile. Experimentally, a stable product (acyl or phosphoryl serine) is observed only under conditions such that the site can no longer carry out its normal catalytic function. It has been argued, that these observations have been made following a transfer of acyl (or phosphoryl) group from a more reactive to a less reactive position (99). More direct evidence for the intermediate steps in the chemical mechanism of catalysis is still to be obtained. All deductions as to catalytic mechanisms are based on the circumstantial evidence presented below.

1. The "R Group" Specificity and the Catalytic Efficiency

To a large extent, with some of the proteolytic enzymes and esterases, the binding of substrates to the enzyme site (the reversible complex) is determined by rather simple considerations of charge, non-polar surface, and overall dimensional complementarity (100). Thus for example, a number of ester substrates of the enzyme acetylcholinesterase do not differ more widely in first-order enzymic hydrolysis rate, once the enzyme has been saturated with substrate, than they do in hydroxyl-ion catalysis (101). This appears to be the case in the reactions of esterified derivatives of acetylated amino acids catalyzed by proteolytic enzymes as well (8). Acetyl tyrosine, acetyl tryptophan, acetyl phenylalanine, and acetyl leucine ethyl esters are hydrolyzed at comparable rates in the presence of α-chymotrypsin when the enzyme site is saturated with substrate. Saturation of the site occurs however, at very different concentrations with different substrates (102,103), depending on the extent of complementary forces between enzyme and substrate molecules. Due to the somewhat

unspecific nature of the physical interactions, especially between smaller molecules and the enzyme site, very large differences in rates of reaction may be observed between specific substrates and smaller less-specific substrates, if the less-specific substrates can complex to the active site with significant strength in a configuration which does not lead to reaction

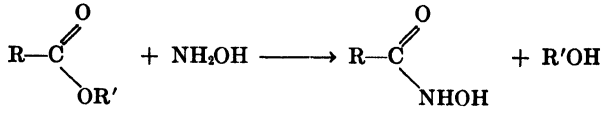
TABLE II
Effects of Dispersion Forces, Electrostatic Interactions, and Chemical Bonding on the Binding Constants of Substrate to Enzyme

Enzyme	Substrate or competitive inhibitor	Binding constant	
		Type	Value ($M \times 10^3$)
Acetylcholinesterase	$(CH_3)_2\overset{+}{N}HCH_2CH_2OCOCH_3$	K_M	8.0
	$(CH_3)_2CHCH_2CH_2OCOCH_3$	K_M	1.0
	$CH_3CH_2CH_2OCOCH_3$	K_M	500
	$(CH_3)_3\overset{+}{N}H$	K_I	1.4
	$(CH_3)_2\overset{+}{N}H_2$	K_I	11
	$CH_3\overset{+}{N}H_3$	K_I	63
	Nicotinamide	K_I	4
	Ethyl nicotinate	K_I	.06
	β-Acetyl pyridine	K_I	.10
	n-Acetyl trimethylanilinium$^+$	K_I	5×10^{-5}
α-Chymotrypsin	Acetyl-L-tyrosinamide	K_M	32
	Acetyl-L-tyrosine ethyl ester	K_M	0.7
	Acetyl-L-leucine ethyl ester	K_M	~70
	Acetyl-D-tyrosinamide	K_I	16
	Acetyl-D-tyrosine ethyl ester	K_I	3
Trypsin	Benzoyl-L-arginine ethyl ester	K_M	0.01
Ficin	Benzoyl-L-arginine ethyl ester	K_M	15
Trypsin	Benzoyl-L-arginine amide	K_M	3.3
Ficin	Benzoyl-L-arginine amide	K_M	~15

(8). Thus small substrates which may bind to the enzyme site preferentially in an unreactive configuration, and larger molecules which cannot bind at all due to steric restraints may exhibit no catalyzed reaction. Some examples of dispersion forces, electrostatic interactions, and chemical bonding in enzyme substrate complexes are illustrated in Table II.

2. Formal Enzyme Kinetics and the Mechanism of Enzyme Reaction

Although the kinetics of many proteolytic and esteratic enzyme-substrate reactions have been studied, these studies have been designed, on the whole, for the determination of the reaction specificity and the binding characteristics of particular enzymes, rather than for the elucidation of their chemical mechanisms of action. An important issue in the mechanism of enzyme catalysis is that of metastable versus unstable intermediates. This problem is amenable to investigations by the formal methods of both transient and steady state kinetics. The formation of metastable intermediates in the hydrolysis of nitrophenyl esters catalyzed by α-chymotrypsin has been demonstrated by Gutfreund (96,104,105) from the formal analysis of the transient kinetic data according to Equation (14). The reaction



catalyzed by α-chymotrypsin can be measured under conditions of variable hydroxylamine concentration (106). The metastable intermediate model of Equation (14) would predict a variation of K_M with hydroxylamine such that

$$\{V_{[S]\to\infty}\}\{d(1/v)/d(1/[S])\} = K_M = \{k_3[NH_2OH]/(k_2 + k_3[NH_2OH])\}\{(k_{-1} + k_2)\}/k_1\}$$

Under the condition that the observed rate is a function of $[NH_2OH]$, K_M is invariant to hydroxylamine concentration throughout the measurable concentration range when the substrate is either methyl hippurate or acetyl-L-tyrosine ethyl ester. Under these same conditions (where the rate is dependent on hydroxylamine concentration) the reversible intermediate model of Figure 2 would lead to the result (from Equations 1, 10, and 15)

$$K_M = K_s = k_{-s}/k_s$$

if the binding of hydroxylamine and substrate to the enzyme are independent phenomena. For both acetyl L-tyrosine ethyl ester and methyl hippurate, the binding of hydroxylamine to the enzyme *is independent of the binding of substrate*, indicative of the formation of a ternary complex ESN in which the alkoxyl group of the substrate molecule is still in ester linkage, prior to any chemical reaction (i.e., there is no chemical intermediate). The apparent anomaly in the mechanism, as deduced from two different substrates, can be explained on the basis of the breakdown of a tetrahedral

complex of nitrophenyl ester with enzyme prior to final product formation, as described in Section IV, resulting in a trigonal metastable product. This reaction may not occur when the leaving group is not as stabilized it is in the nitrophenolate ion.

A. INHIBITION STUDIES

The inhibition of catalysis by protons is common to all of the enzymes described above. Wherever this inhibition is reversible, it can be described by a sigmoid curve relating activity to pH. It should be pointed out that this sigmoid curve does not always have the exact profile predicted for a reaction catalyzed by the conjugate base of a single acidic group in the catalyst, although with particular substrates and enzymes the resemblance is striking. Since the substrates themselves do not ionize, the effect of protons must be at the enzyme site. The binding of methyl hippurate (106) to α-chymotrypsin and of benzoyl-L-arginine ethyl ester (107,108) to ficin have been found to be independent of the hydrogen-ion concentration over ranges of pH where the effect of pH on the enzymatic activity resulted in changes of rate of at least a factor of ten. If the rate of decomposition of active enzyme–substrate complex (k_p) were to affect the steady state constant (K_M), this steady state binding constant of substrate to enzyme could not be independent of the hydrogen-ion concentration in this range. Since the binding constant of protons to enzyme is independent of the substrate concentration and K_M is independent of pH in both the above enzyme–substrate systems, both these binding constants must be equilibrium constants.

Competitive inhibitors of the catalysis of L-amino acid derivative substrates are found with proteolytic enzymes. Thus with chymotrypsin the D-isomers of substrates are generally strong competitive inhibitors indicating that the spatial requirements for binding substrate to the enzyme site are in general far less stringent than are the requirements for catalytic action (again contributing circumstantial evidence for multifunctional participation in enzyme catalysis). Inhibition of a rapid, specific enzymic reaction by introduction of another substrate which forms a more slowly degraded metastable intermediate with the enzyme can be used as a technique for following the kinetics of decomposition of these metastable intermediates to regenerate active enzyme (99). In this way it has been shown that the metastable acyl–enzyme intermediate produced by the reaction of chymotrypsin with nitrophenyl acetate is a different species at pH 5 than it is at pH 8. The conversion of pH 5 species to pH 8 species being a kinetically observable phenomena.

3. Catalytic Activity and Electrophilicity of the Substrates

With the first group of enzymes described above there is a striking correlation between the electrophilicity of substrates and inhibitors, and both the binding constants (K_M or K_I) and the specific rate. Both the rate of hydrolysis and the strength of binding increase monotonically in the series carboxylate, amide, hydroximate, ester (8). Although many molecular factors must enter into the catalytic activity of the enzyme it would appear that nucleophilic attack by enzyme must be a major factor. In contrast, consider ficin, an enzyme of the second type. Here the hydrolysis of benzoyl arginine ethyl ester and benzoyl arginine amide have the same specific rate constant (108), whereas, with trypsin the rates differ by a factor of more than 1,000 (109). Although the binding constant of ester and amide to ficin differ slightly, this factor is small. The mechanism of ficin catalysis clearly excludes a rate-limiting nucleophilic attack on the intact substrate.

4. Metastable versus Unstable Intermediates in Enzyme Catalysis

As discussed in Sections II.2.A and II.2.B, catalysis may proceed by either the formation of new chemical compounds as intermediates in the reaction or catalysis and *total* product formation may proceed in a single concerted process;

$$E + S + N \rightleftharpoons ESN \longrightarrow E + \text{products}$$

as is shown in Figure 12. It has been pointed out that stepwise catalysis

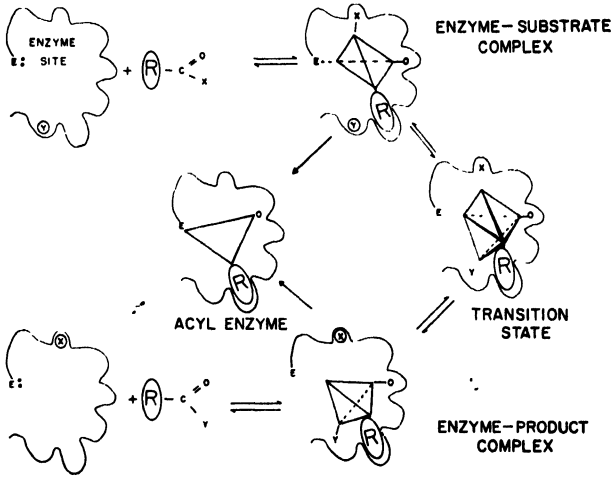


Fig. 12. Tetrahedral and trigonal intermediates in enzyme catalysis as a function of substrate.

is more frequently observed when one of the products of reaction, formed in an intermediate step, is stabilized by the cleavage (43). Thus Equation (14) has been experimentally verified with nitrophenyl esters of substrates of α-chymotrypsin where a product found in an intermediate step (nitrophenolate$^-$) is stabilized. As yet no experimental evidence has been furnished for the involvement of more stable aliphatic alcohol esters in this stepwise mechanism of catalysis. As has been shown from studies of nucleophilic catalysis by small molecules, the formation of trigonal intermediates of the type of acyl imidazole are usually restricted to the more reactive esters; alkyl esters and amides do not exhibit this type of nucleophilic catalysis (with some interesting exceptions as pointed out in Section IV). Circumstantial evidence, both for and against a concerted catalysis via tetrahedral intermediates in the hydrolysis of esters by chymotrypsin, has been presented (8). Whether one or the other path (Fig. 12) is the route for catalysis of specific ester and peptide hydrolysis by these enzymes, has not yet been established. It is of course possible that both routes may occur depending on the nature of the specific substrate, the temperature, or the solvent medium. Whichever the path of specific enzymic catalysis, the mechanism must explain the enormous velocity of such reactions relative to any rate which has as yet been observed in other homogeneous solution catalyzed reactions of esters. Attempts at explanation of these rate phenomena have to a large extent resulted in the experimental findings discussed in Sections III.C and IV. Whatever the mechanism of enzymic catalysis, it is clear that further investigations in this area will lead to still more illuminating discoveries regarding the mechanism of catalysis in homogeneous solution.

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CHAPTER XIII

HETEROGENEOUS REACTIONS AND CATALYSIS*

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I. INTRODUCTION

The kinetic study of chemical reactions is not only interesting from a scientific viewpoint but is also very important for the rational design and operation of chemical processes in the laboratory as well as in the plant. The identification and calculation of the parameters which control the evolution of the system with time furnish data indispensible for the determination of the reactor which will guarantee the maximum hourly yield at the least cost.

When the desired reaction is accompanied by parasitic side processes, a kinetic study reveals the conditions under which the main reaction will be favored so the selectivity of the process can be maximized. Moreover, kinetic analysis is a working tool that can point the way to new paths of chemical synthesis. In effect, it defines criteria which determine whether a given apparently simple transformation is actually simple or whether it is complex. Then the intermediate products can be identified and perhaps recovered by means of a kinetic analysis. As examples, one might cite

* Translated from the French by M. Boudart, Princeton University.

kinetic control of the synthesis of certain complex peroxides or their derivatives in the autoxidation of hydrocarbons.

The kinetic analysis elucidates in detail the mode of activation of chemical systems and establishes the intimate mechanism of the fundamental chemical act. Thus it provides the basic information required to imagine new reactions. Without it, this must be left to chance or to laborious experimentation.

The object of chemical kinetics is to analyze the reaction scheme as well as the intimate mechanism of the component reaction steps and to determine the factors affecting the overall rate and the relative rate of the desired reaction. The reaction rate is affected by many factors. Bond rearrangement can take place only as a result of the intimate contact of reaction partners, so that the rate of reaction depends on the frequency, duration, and energy of collisions of reactive forms. These conditions will be different from case to case: the reaction can occur in a homogeneous phase of uniform composition or the reactants may be present in different phases or in different regions of the same phase.

In a homogeneous phase of uniform composition, molecules collide as a result of thermal agitation at a frequency which depends on their concentration. In heterogeneous processes, the contact between reactants is made by diffusion and may therefore depend on the extent of the interface. On the other hand, the structure of reactive molecules may be such that they interact with other molecules of the same species or of a different kind and such interactions can alter the frequency and success of reactive collisions. The rate of reaction can thus be affected by the physical properties of the medium, especially its electrical characteristics, as well as by the chemical properties of the various substances that are present.

At first glance, kinetic study of a chemical reaction appears to be very complex since, as the reaction proceeds, concentrations vary together with the properties of the medium which affect the reactivity of the system. The approach to this problem consists of modifying the parameters one at a time, so as to be able to recognize more easily and clearly the influence of each one on the reaction. By keeping the other variables constant, the variance of the reaction system is reduced artificially and the complex kinetics degenerates in certain cases, to simpler kinetics. It is understandable that the first attempts in the intimate analysis of chemical changes were carried out with homogeneous gas phase reactions, because in this case the interactions between reacting molecules are not appreciably affected by the presence of neighbouring molecules. While there is still no single theory to account for all the facts related to gas phase kinetics, the collision theory and the activated complex theory present a picture of the chemical reaction which includes the principal characteristics.

In a homogeneous liquid phase the transformation of molecules, by the way of ions or dipoles, is affected by various factors. The approach to this problem is to study dilute solutions which fulfill the requirements for an ideal solution. The study can then be related to that of gas phase reactions with this profound difference: in solutions the space which exists between the reacting particles is occupied by solvent molecules which affect their interaction. By using a binary solvent the proportions of its constituents can be gradually modified, thereby varying the dielectric constant of the medium. Thus the effect of the dielectric constant on the reaction rate can be determined. By adding foreign salts to the medium in small enough quantities so that its properties are not changed, the effect of ions on the reaction can be studied. In certain cases, the effect of the dielectric constant and the salt effect have been explained successfully for reactions carried out in dilute solutions of known composition.

It is established, however, that when two different solutions have the same dielectric constant but are made of two different pairs of solvents, the reaction rate is not the same in both cases. This is not surprising since the various types of associations between like and unlike molecules must affect the reactivity of the system in different ways.

The effect of a solvent due to its chemical action can exceed by far the effect it can exert as a result of its physical properties. For instance, certain catalysts sharply activate a reaction while they can not notably modify the physical properties of the medium because of their very small concentration. The solvent may also exhibit catalytic properties and it is then difficult to separate its chemical effect from its physical action. In concentrated solutions, the analysis of the phenomenon is even more complex. Most syntheses in the laboratory and in industry are actually carried out in concentrated solutions for obvious reasons such as economy of solvent and equipment. In this case, reactant substances affect the reaction differently not only because of their concentration, but because they exert various influences on their own transformation which can manifest a different solvent. Therefore, by modifying only the composition of the system, several factors are simultaneously varied and it is extremely hard to identify them and to determine their individual effects.

Heterogeneous reactions present even more formidable problems. Besides the factors important in homogeneous reactions, there are other specific difficulties involved. In heterogeneous systems, it is difficult to make direct measurements of the effective concentrations at the locus of reaction. The extent of the contact surface is hard to determine. All parts of that surface, if solids intervene, will not be equally active. Finally, mass transfer between phases may be slow and diffusion can become the rate-de-

termining step. These problems constitute the subject matter of the first part of this chapter.

In the case of heterogeneous catalysis, the kinetic study is still incomplete because the mechanism of the phenomenon taking place at the surface has not been elucidated and the nature of the catalyst itself is poorly known. Nevertheless, there is at least one great simplification: the extent of interface stays constant. If catalyst samples are taken from the same batch of catalyst, the characteristics of these will be a constant factor in a series of experiments. It is then possible to determine the influence of each of the fluid reactants on the rate of the reaction, to find the laws governing their interaction with the catalyst, and to formulate practical rules to guide a systematic experimentation for process research and development. These topics will be treated in the second part of this chapter.

II. HETEROGENEOUS REACTIONS

As in the case of chemical equilibria, reactions are called heterogeneous when reactants, catalysts, or products belong to several phases. Nevertheless, the concept of kinetic heterogeneity is broader than that of thermodynamic heterogeneity. Indeed, in a one-phase system, the differences in composition may be such that the various parts of the system may be considered as different phases from a kinetic viewpoint. Thus reactions between separated gaseous reactants, such as diffusion flames, must be considered as heterogeneous. Even the combustion of pre-mixed gases is heterogeneous in the sense that reactants and products are separated by a flame front.

Certain reactions are heterogeneous with respect to only one of their component steps. For instance, in certain chain reactions, initiation and termination occur at the wall while propagation of the chain takes place in the bulk of the fluid phase. When products form a new phase, they may not affect the kinetics. Thus in a liquid phase reacting system, they may appear as a solid or a gas without altering the homogeneous character of the reaction. On the contrary, if the new phase localizes the chemical transformation, the kinetics will exhibit special features as in the case where reactants are in different phases.

If reactants are soluble in two phases, the reaction is effectively homogeneous in each phase as long as composition equilibria can be realized and maintained. When, however, mass transfer is too slow for the needs of the reaction, a concentration gradient will be set up, leading eventually to a steep discontinuity, i.e., to a reaction interface. The reaction is then heterogeneous in the strict sense of the word. The various possibilities relative

to only elementary cases are represented in Figure 1 where some of the possible combinations are illustrated by examples. It must be noted that in some heterogeneous reactions, reactants may be present in more than two phases. Thus, in certain leaching processes and in the catalytic hydrogenation of organic compounds, three phases are involved: solid, liquid, and gas.

The study of heterogeneous reactions can therefore be broken down in a large variety of cases depending on the nature and number of intervening phases, the degree of uniformity of the phases during reaction, and the variety of important kinetic factors. A few examples will serve to illustrate the diversity of cases and methods required for their study: (*1*) the attack of metallic salts by gaseous reactants as in the roasting of pyrites and the preparation of certain metallic catalysts; (*2*) the combustion in a flame

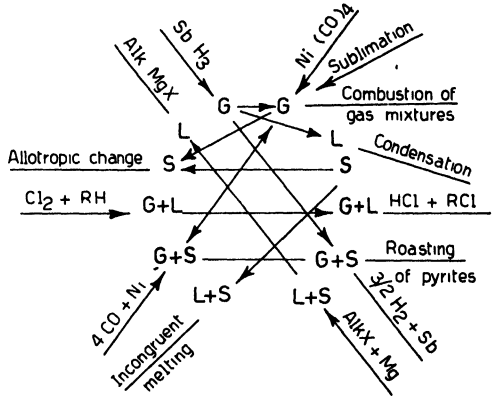

Fig. 1

front of gaseous fuels and solid explosives; (*3*) suspension or emulsion polymerization; (*4*) the attack of a metal or its salts as in leaching processes and, in particular, the preparation of certain organo–metallic compounds; (*5*) the development of the photographic emulsion; and (*6*) reactions taking place at electrodes in electrochemical processes.

Certain processes, such as the purification of nickel by the successive formation and decomposition of nickel carbonyl in the Mond process, actually consist of cycles involving two different heterogeneous reactions. When the reaction takes place homogeneously in one of the phases of the heterogeneous system, as in the autoxidation of hydrocarbons, the determination of driving concentrations is already more difficult than in the case of a single phase of uniform concentration. But when partition equilibrium is not reached and diffusion is important kinetically, the analysis becomes

even more complicated. As the reaction rate becomes much larger than the rate of diffusion, reaction will be limited to a narrow zone, i.e., the reaction interface. Under such conditions, it will frequently be difficult to characterize the chemical phenomenon itself.

When the reaction is very fast, as in the combustion of powders or in flames in general, the problem will be worse yet because, besides the concentration gradient, there will be a temperature gradient along which the reaction rate will vary. The study of these phenomena, e.g., the combustion of gaseous mixtures, necessitates additional measurements such as the velocity of the reaction interface and the maximum temperature of the flame.

Since the kinetics of homogeneous reactions in concentrated media are still incompletely understood, it is hardly surprising that the data available on the various types of heterogeneous reactions are inadequate, that no general formulation of their laws can be given, and that it is hard to give rules to guide research in this field. Consequently, all that will be attempted in this section is a survey of several types of simple reactions in order to unravel some of the important parameters, and to provide some qualitative rules as to how these processes must be carried out.

The study of heterogeneous reactions is more difficult, both theoretically and experimentally, if one or more solid phases are involved. If there are only fluid phases, it is usually relatively easy to reproduce exactly the reacting system in a series of experiments. On the contrary, with solids, samples are not easily reproducible Their behavior will be largely determined by the structure, texture, and imperfections of their crystal lattices; properties that are sensitive to the conditions in which they are formed.

The study of heterogeneous reactions between fluids and solids as well as the study of reactions of solids in general are thus within the province of solid state research. Much is known about the nature of solids of various types. But the complete description of a given sample remains, even in the most favorable cases, a laborious undertaking. What needs to be done in the future is the simultaneous study of the solid together with a complete kinetic analysis of its reactions.

1. Systems with Only Fluid Phases

In a system with two partially miscible phases of uniform composition, the kinetics of homogeneous reactions will apply if the reaction takes place in one, or even in both, of the phases. The experiment must determine the kinetic constants in each phase and, in particular, the driving concentrations. To simplify the problem, it will be sometimes best to study each phase separately.

As an example of kinetics of reaction between fluid reactants, consider the simple case of a gas phase, g, in equilibrium with a liquid phase, l, where the reaction takes place. If both phases are in equilibrium with respect to composition, concentrations are related by the partition coefficient β. For instance, consider reactant A distributed between a gas phase and a liquid phase where it is transformed into B. The reaction scheme is:

$$A_g \rightleftharpoons A_l \longrightarrow B_l$$

The concentrations of A in both phases are related by the expression:

$$[A]_g = \beta[A]_l$$

The reaction, of order n in the liquid phase, takes place at a rate:

$$v = d[B]_l/dt = k_l[A]_l^n = (k_l/\beta^n)[A]_g^n = k_g'[A]_g^n$$

If the gas phase concentrations $[A]_g$ are used, the rate constant contains the coefficient β. The activation energy will then also contain a term expressing the variation with temperature of the partition coefficient.

If on the other hand, the reaction is so fast that partition equilibrium cannot be maintained, the rate will be limited by diffusion of the reactant from the phase where it does not react to the phase where it reacts. The rate of diffusion which controls the reaction is given by Fick's Law: the amount of material crossing a surface per unit time is proportional to the area of the interface, S, to the diffusion coefficient, D, and to the concentration gradient:

$$v = DS(dc/dx)$$

If the bulk of each phase is of homogeneous composition, the concentration gradient is established in a film of thickness δ. The rate is then given by:

$$v = DS\{(c_e - c)/\delta\}$$

where c_e is the equilibrium concentration in the gas and c is the concentration in the liquid. The film thickness and the area S depend on the technique used to bring about mass transfer and to insure uniformity of concentration. The equilibrium concentration, c_e, will be a constant if the gas phase composition remains constant.

The concentration in the phase where reaction takes place may remain small because the solubility of reactants is limited or because of the rapidity of the reaction. Then the absolute rate of transfer between phases is equal to the rate of reaction for the entire volume V_l of the phase where reaction occurs:

$$-V_g d[A]_g/dt = +V_l d[B]_l/dt$$

or

$$DS\{(c_0 - c)/\delta\} = V_1 k_1 [A]_l^n$$

where $k_1 c^n$ is the rate of reaction per unit volume in the liquid phase. When diffusion is the rate determining step, the rate depends on the efficiency of the stirring technique. In this case the apparent activation energy of the reaction is very small ($E_{apparent} \leq 5$ kcal.) and corresponds to the thermal increment in the diffusion coefficient.

If the concentration in the phase where the reaction takes place is not negligibly small, the steady state condition is not fulfilled and it is necessary to consider the differential equations for mass transfer between phases:

$$-V_g(d[A]_g/dt) = DS\{(\beta[A]_g - [A]_l)/\delta\}$$

and

$$V_l(d[A]_l/dt) = DS\{(\beta[A]_g - [A]_l)/\delta\} - V_l k_1 [A]_l^n$$

These equations may be of practical value only if the quantities therein can be related to experimentally measurable variables. All of the preceding considerations remain valid whatever the nature of the fluid phases in contact.

It is seen, however, that the application of the formulas is made difficult by the nature of the techniques required to insure mutual dispersion of the phases and uniformity of composition in each phase. Another complication is that reactants, primary or secondary products or surface-active additives used to improve the dispersion, may be adsorbed preferentially at the interface and affect the rate of mass transfer or the rate of reaction. This effect may be used to promote the reaction.

In the laboratory, efforts are generally made to obtain information on the chemical phenomenon itself. Techniques are used to reach a perfect dispersion of the phases in order to reach a large enough rate of mass transfer to eliminate diffusion as the rate determining step. It is also preferable, but not necessary, to determine the driving concentrations in the phase where reaction takes place. In this fashion, the results do not depend on the partition coefficient, which may depend on the composition of the reacting mixture.

Examples of reactions in a heterogeneous system that could be reduced to a homogeneous reaction are: the autoxidation of liquid hydrocarbons (1), the absorption of ethylene in sulfuric acid of suitable concentration (2), and certain basic rearrangements where radicals are captured by gaseous reactants (O_2, NO, etc.) (3).

2. Systems with One or More Solid Phases

In reactions involving solid reactants or products interphase mass transfer, as well as the chemical reaction itself, will usually be localized at the external surface of the solid phase or phases. Such phenomena are therefore heterogeneous in the restricted sense of the word. Nevertheless the surface taking part in the reaction may not be the apparent surface and the first stage in the reaction may be the formation of a reactive interface with its subsequent growth and propagation in the solid or fluid phases, as the case may be. These two stages are easily visualized in an allotropic transformation where the new phase, as in the rest of tin, starts at a few centers in the solid, and then propagates throughout the entire mass. The two stages are even more sharply differentiated in the formation of the photographic image where the nuclei are the result of a photochemical process while their growth is due to a subsequent chemical reaction starting from the nuclei.

In reactions involving solids, it is therefore necessary to treat separately the formation of the reaction interface, and its propagation which is directly related to the speed of the chemical change.

A. FORMATION OF THE REACTION INTERFACE

In certain cases, as in the condensation of a vapor or the vaporization of a liquid, it is observed that a larger free energy difference is required at the start, before the new phase can appear. But frequently, the formation of an interface between fluid phases does not necessitate particular experimental precautions and good reproducibility is easily obtained. The situation is quite different in reactions involving solids. When the formation of the reaction interface requires a larger activation than its propagation, a long induction period may be necessary before the process can start. A few examples will serve to illustrate this point.

It is known that certain hydrated salts may be kept intact indefinitely under conditions such that they should lose their water of crystallization, in whole or in part. Yet, when one of the crystal faces is damaged by means of a scratch, a reaction interface is formed and it is propagated throughout the mass which causes the water of crystallization to be lost. Also, notably in the preparation of certain metal catalysts by reduction of their oxides (e.g., nickel and copper), if the reaction is triggered at high temperature, it may then proceed at a lower temperature at which it would not have started in the first place.

Failure to understand these basic observations may lead to erroneous conclusions. Thus, because organic salts of thorium require a higher temperature for their decomposition than the decarboxylation of fatty acids on

thoria, it was concluded that the catalytic process could not involve a salt as intermediate. But it can be shown that if the decomposition of thorium acetate is triggered at a higher temperature, it can then proceed at a lower temperature corresponding to that of the catalytic decarboxylation, at a rate comparable to that of the catalytic process (4).

The general trend of nucleation phenomena is illustrated by the curves of Figure 2 showing, respectively, the extent and the rate of reaction as a function of time. The curves show that, once the reaction is triggered, it accelerates till the reaction interface reaches its maximum size, and then slows

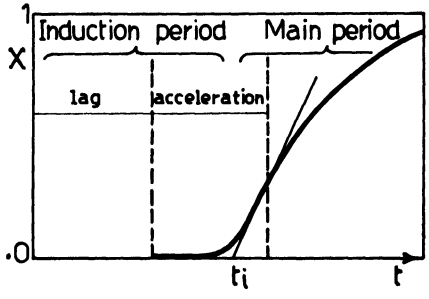

Fig. 2A

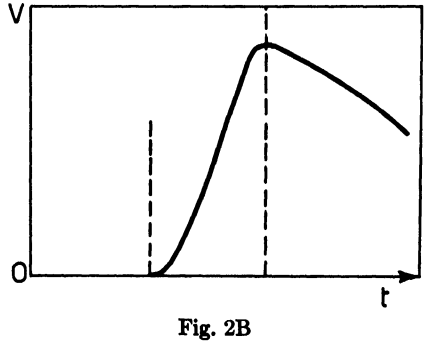

Fig. 2B

down as the reaction interface shrinks and the original phase disappears. A more refined analysis reveals that the induction period can be broken down into a pre-nucleation period and a period of acceleration.

How can the pre-nucleation period be explained? It has already been pointed out that the appearance of a new phase is thermodynamically more difficult than its growth. For dust-free water vapor, pressure at 0°C. must be four times the vapor pressure before condensation takes place. The vapor pressure of a droplet is inversely proportional to its radius. Because of the fluctuations within the vapor phase, clusters of molecules are

formed, but it is only when they reach a critical size corresponding to experimental conditions that they can survive and grow. The growth will then proceed under less difficult conditions than those required for the appearance of the new phase. It is also known that ions and dust particles exert a beneficial action on the formation of the nuclei. Wilson's chambers are based on this principle.

Nucleation also determines the appearance of a new solid phase. A preliminary process, which is less easy than the subsequent events, consists in the formation of an adsorbed mobile layer at the surface of the solid. When the adsorbed molecules reach a critical concentration, they form clusters which are the nuclei of the new phase. The nucleation time-lag corresponds to the time required to form the first nucleus. Imperfections at the surface of the crystal lattice play the role of dust in condensation: they constitute potential nuclei.

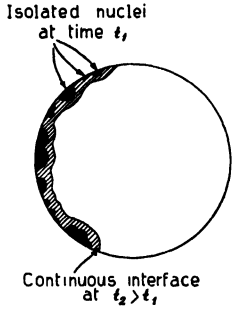

Fig. 3A

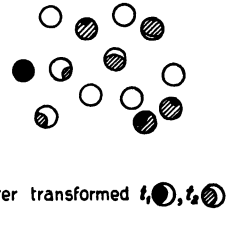

Fig. 3B

The acceleratory period corresponds to the formation and growth of the nuclei, i.e., to the formation and development of the reaction interface. The general trend of the phenomenon during this period depends on the surface concentration of potential nuclei, on the law of nucleation, and on the size and shape of the solid particles on which nuclei appear. For large spherical particles with a high density of potential nuclei, the development of the latter may rapidly lead to formation of a continuous envelope surrounding the reacting grain. The phenomenon is then controlled only by the progression of the reaction interface (Fig. 3A).

In the case of very small particles, the phenomenon exhibits a different behavior: since the number of nuclei per particle is small and since their formation is a relatively improbable event, whenever a nucleus appears at the surface of a particle it will transform the latter at a rate which is higher than the rate of nucleation on the same or any other particle. The rate of

reaction is then controlled by the rate of nucleation. These two extreme cases are illustrated by the schematic pictures A and B of Figure 3.

The activation energies will naturally have a different meaning in both cases. The examples demonstrate clearly that, for a given sample, the kinetics of nucleation and of propagation of the reaction interface generally overlap in a manner determined by the nature of the particles, their shape and size distribution. In the following section, the effect of the propagation of the reaction interface on the character of the reaction will be examined.

B. GROWTH AND PROPAGATION OF THE REACTION INTERFACE

Since nucleation involves only very small amounts of reactant, the reaction rate, measured by the amount of substance transformed per unit time, is directly proportional to the rate of development and propagation of the reaction interface. The reaction rate also depends on the nature and composition of the fluid phase, as expressed by a function $f(c,c', \ldots)$; it is proportional to the area of the reaction interface, S:

$$v = kSf(c,c', \ldots)$$

This law has been verified in a number of cases. Examples are the combustion of explosives, and the attack of metals by acids. It can be checked by changing the geometry of the sample which may be a flat plate, a cylinder, a sphere, etc. For a flat plate, if end effects are neglected, the rate will remain constant and the reaction will be of zero order with respect to the amount of solid material. With a cylinder, again if end effects are neglected, the area is proportional to the radius of the cylinder, and since the mass M is proportional to the square of the radius, the reaction order will be one half:

$$v = -dM/dt = kS = k'r = k''M^{1/2}$$

For a sphere of area $4\pi r^2$ and mass proportional to $(4/3)\pi r^3$, the order of reaction is $2/3$:

$$v = -dM/dt = kS = k'r^2 = k'' \, M^{2/3}$$

These formulas are valid for both the growth ($+ dM/dt$) and the disappearance ($- dM/dt$) of the solid phase.

The dependence of the rate on the fluid phase is different when the phenomenon is controlled by diffusion or by the reaction itself. In the first case, the rate is given by:

$$v = DS\{(c_e - c)/\delta\}$$

where c is the concentration in the fluid phase and c_e is the concentration at

the interface. When the chemical reaction itself is rate controlling, the rate equation is:

$$v = kSf(c,c', \ldots)$$

where k is now a true rate constant.

Then $f(c,c', \ldots)$ may be such that there exists a definite order with respect to the fluid reactants, or it may be a complex expression. In the first case, for a single gaseous reactant, we have:

$$v = kSp^n$$

When the attack of the solid involves the formation of an intermediate complex, the process can be represented schematically as follows:

$$n\,\mathrm{G} + \mathrm{S} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} (\mathrm{SG}_n) \xrightarrow{k_r} \text{products}$$

Let σ be the fraction of the surface engaged, at any given time, in the formation of the complex. Then the fraction of the surface free to react is $(1 - \sigma)$ and the rate of formation of the complex is:

$$v_f = k_f(1 - \sigma)\, p^n$$

where p represents the pressure or concentration of the fluid reactant.

The decomposition of the complex occurs in two ways: dissociation into its elements, $k_d\sigma$, and transformation into products, $k_r\sigma$. At the steady state, the rates of formation and disappearance of the complex are equal:

$$k_f(1 - \sigma)\, p^n = (k_d + k_r)\, \sigma$$

Solving for the surface coverage σ, we get:

$$\sigma = k_f p^n/(k_d + k_r + k_f p^n)$$

The rate of formation of products per unit surface is $k_r\sigma$. The total rate is then:

$$v = k_r S\sigma = k_r S\, \{k_f p^n/(k_d + k_r + k_f p^n)\}$$

When pressure is sufficiently high, the rate of complex formation is high ($k_f p^n \gg k_d + k_r$) and the rate determining step is the transformation of the complex:

$$v = k_r S = \text{constant}$$

At low pressures ($k_f p^n \ll k_d + k_r$), the rate of complex formation determines the kinetic behavior:

$$v = k_r S\{k_f p^n/(k_d + k_r)\} = k' S p^n$$

Complex formation may involve one or two molecules per element of surface and the rate equations are, respectively:

$$v = k_1'p \qquad \text{or} \qquad v = k_2'p^2$$

The first case occurs in the oxidation of metallic sulfides. The general rate expression is also applicable when the reaction involves only one half molecule of reactant per element of surface, provided that adsorption equilibrium is established instantaneously. Such a case is the oxidation of uranyl uranate, U_3O_8.

These considerations indicate that it is relatively easy to determine the kinetic role of fluid reactants, if the surface is kept constant. Although the surface changes progressively during reaction, this change can be kept small if only small amounts of fluid reactant are used for a large quantity of solid.

Thanks to this method, it has been possible to obtain rate equations corresponding to the theoretical ones. An example is the reduction of silver chloride by gaseous hydrogen (5,6) where the following relation was found:

$$v = k\{[H_2]/(\text{const.} + k'[H_2] + k''\,[HCl])\}$$

Such expressions are familiar in the study of heterogeneous catalysis. In this case, the reaction has a reaction interface which stays strictly constant since the decomposition of the reaction complex gives back the surface site unchanged.

If now the concentrations are kept constant, it should be possible to determine the kinetic role played by the surface. In fact, the problem is quite complex because the rate varies not only with the surface area but also, in a very sensitive way, with the nature of the surface. It is known that in the sublimation or melting of crystals, the various surface elements do not all take part in the transformation on an equal basis. First, all crystalline faces are not equivalent in this respect. Moreover, all elements of a given face are not equally active. The deposition or removal of a structural unit on or from a perfectly ordered surface layer is as unlikely, from a thermodynamic standpoint, as nucleation. Indeed, it corresponds to the nucleation of a new layer (Fig. 4A). Therefore, mass transfer between phases will occur at crystal defects, e.g., dislocations. Figure 4B illustrates crystal growth at a screw dislocation. Consequently, mass transfer between phases may depend on the concentration of defects. A strong supersaturation favors rapid condensation but crystals are very small and imperfect. Conversely, the dissolution of such solids is easier and faster. It can be seen that impurities that favor condensation will also favor vaporization and all the processes involving the solid. It is as if the solid remembered the conditions under which it was formed.

The behavior of a solid is also influenced by its later history. In particular, when crystals (metals, anhydrous salts) are heated, annealing will largely destroy lattice defects. The reaction can also be affected by other factors. In an exothermic process, e.g., the condensation of a vapor into a solid, condensation brings about an elevation of temperature that opposes further condensation. For the process to occur, heat must be removed as condensation proceeds. This is easier if the process is slow. The shape of snow crystals is determined by such factors: their surface will be large and their shape will be dendritic if they are formed suddenly.

These considerations are also valid in processes involving a solid reactant which produces a new solid phase. Here, elastic stresses may occur as a result of a misfit of crystal lattices (lack of epitaxy) and these may affect the rate of reaction.

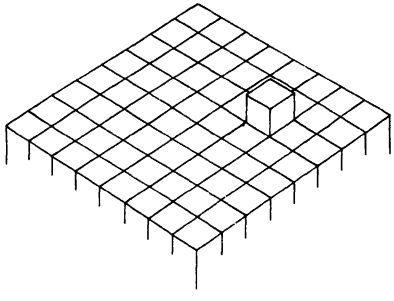

Fig. 4A

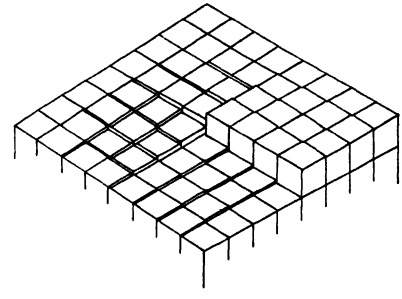

Fig. 4B

When the reaction interface is situated between two solid phases, diffusion can play a predominant kinetic role. Indeed, it is well known that bulk oxidation of metals may be difficult despite a very easy surface attack. When the attack requires penetration through a homogeneous film of growing thickness, the reaction rate is controlled by diffusion and slows down very sharply. Letting dm be the amount of fluid reactant diffusing per unit surface during the time dt, to form the amount dM of solid product; the reaction rate is then given by the expression:

$$dM/dt = kD\{(P_e - P_0)/\delta)\}$$

where P_0 may be considered as zero in the bulk of the solid reactant. Since δ is proportional to the amount M formed at time t, this relation becomes:

$$dM = kD(P_e/k'M)dt$$

Integration gives:

$$M^2 = 2k''DP_e t$$

This is the parabolic law of Tammann and Wagner. It shows that, under the assumed conditions, the amount formed by reaction is proportional to the square root of the time of reaction. If the layer of products contains cracks, the access of fluid reactant to fresh solid is made easier and the diffusion obeys another law.

In general, these reactions will be slow and their kinetics complicated. They can be modified if the attack by the reactant is combined with a dissolution of the product so that the reaction becomes one where a solid reactant is transformed into a fluid product. This happens in the synthesis of organomagnesium compounds by reaction of alkyl halides with magnesium in the presence of ether. A similar process is involved in certain leaching reactions that have attracted much attention recently. In these reactions, a gas reacts with a solid suspended in a solution which dissolves the product formed. Such processes have been used in the metallurgy of copper, nickel, and cobalt where the oxidation product of sulfides is dissolved in ammonia or amine solutions. A similar process is used in the treatment of pitchblende.

This ore consists chiefly of uranyl uranate or green uranium oxide, U_3O_8. This oxide is transformed into soluble salts by the combined action of oxygen and alkali carbonates:

$$U_3O_8 + {}^1/_2O_2 + 3CO_3^{2-} + 6HCO_3^- \longrightarrow 3UO_2(CO_3)_3^{4-} + 3H_2O$$

The kinetic analysis indicates that uranyl uranate is oxidized to the trioxide:

$$U_3O_8 + {}^1/_2O_2 \longrightarrow 3UO_3$$

which is then attacked by the alkaline solutions.

At low oxygen pressures, the rate of reaction is proportional to the square root of the oxygen pressure, all other factors being kept constant:

$$v_1 = k_1 S_1 P^{1/2}$$

As the pressure is raised, the rate increases and reaches a limiting value at a given temperature and for a given composition of the solution. This experimental result can be understood if two consecutive reactions are assumed: the oxidation of reactant followed by dissolution of product. The latter can be represented by the relation:

$$v_2 = k_2 S_2 f(c,c', \ldots)$$

At the steady state, the rate of leaching is equal to the rate of each step:

$$v = v_1 = v_2$$

Whence:

$$k_1 S_1 P^{1/2} = k_2 S_2 f(c,c', \ldots)$$

Since, however, the total surface is the sum of the fresh (S_1) and oxidized (S_2) surfaces:

$$S = S_1 + S_2$$

we get:

$$v = k_1 k_2 S P^{1/2} f(c,c', \ldots) / \{k_1 P^{1/2} + k_2 f(c,c', \ldots)\}$$

It can be seen that when the rate of dissolution becomes small, $k_2 f(c,c', \ldots) \longrightarrow 0$, and the overall rate must tend to the limit:

$$v = k_2 S f(c,c', \ldots)$$

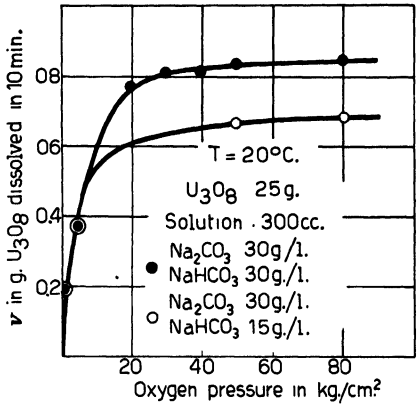

Fig. 5

At constant total surface, this limit must vary with the composition of the solution. This prediction could be verified experimentally, as shown by the data of Figure 5 (7).

Figure 6 shows analogous results obtained for the oxidizing dissolution of copper in an aqueous ammonia solution (8). In this case, the rate of oxidation at low pressure is first order with respect to the oxygen pressure. It is seen that the limiting rates become higher as the ammonia concentration in the solution increases.

C. OVER-ALL EVOLUTION OF THE PHENOMENON

As has just been shown, it is possible in certain cases to understand part of the phenomenon by simplifying the over-all kinetics into simpler limiting

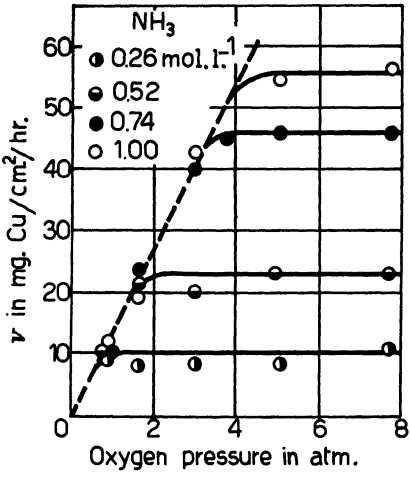

Fig. 6

cases. Thus, first the effect of the composition of the fluid phase must be studied with samples drawn from a given batch of reactant. Then, the composition of the fluid phase being kept constant, the effect of the extent of reaction can be examined. If, however, different samples are investigated and if the phenomenon is studied in all its complexity, the kinetic measurements will be much more laborious and their interpretation quite

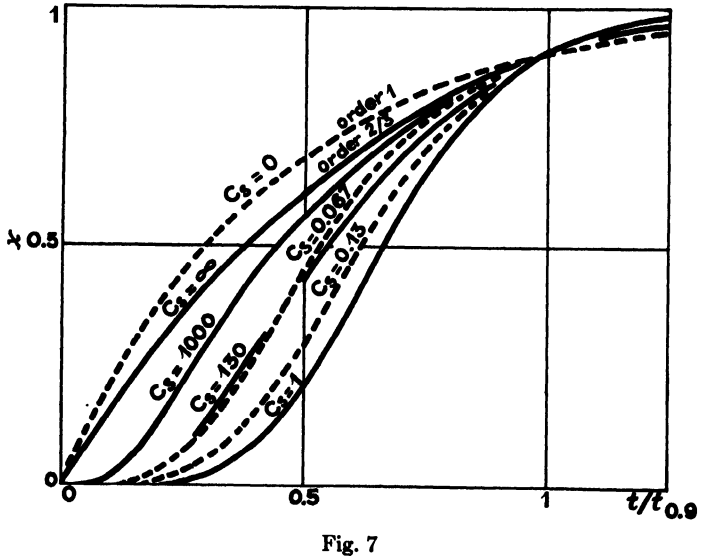

Fig. 7

intricate. Complexities arise from the combined effects of nucleation, propagation of the reaction interface, diffusion, variations in the nature, structure, and texture of the solid, and the shape and size distributions of its particles. Then kinetic data alone cannot elucidate the phenomenon.

Indeed, fundamentally different processes can lead to very similar kinetic curves (9). To illustrate this point, let us examine Figures 7 and 8. In order to facilitate comparison of the curves, the extent of reaction is plotted against dimensionless time, namely, the time of reaction divided by the time required to transform 90% of reactants.

Figure 7 represents the case schematized in Figures 3A and B: the attack of a solid made of identical spherical particles where nucleation is zero

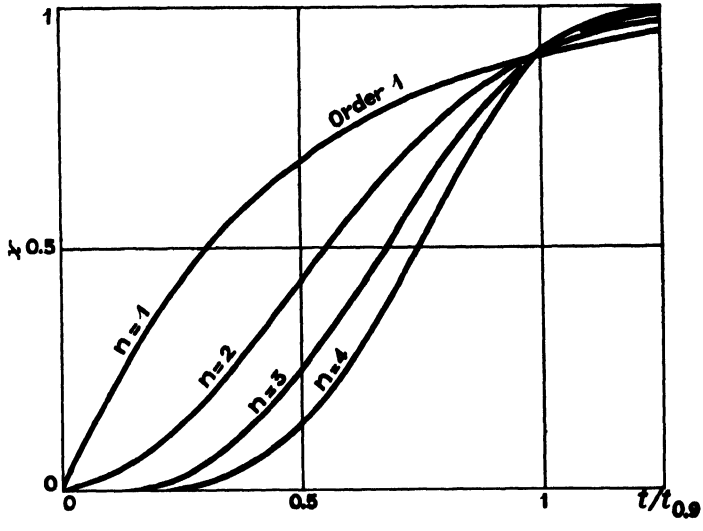

Fig. 8

order with respect to the fresh surface and growth occurs in three dimensions. For small grains ($C_s = 0$) nucleation is the rate-determining process and the order of reaction is unity. The other extreme case ($C_s = \infty$) concerns large spheres on which the reaction interface is formed relatively rapidly. Then the propagation of the interface is practically rate determining and at the limit, the order of reaction is $^2/_3$. In intermediate cases, the phenomenon depends both on nucleation and growth. The curves are then characterized by their S-shape (see Fig. 2).

Figure 8 represents a reaction starting with a nucleation in the bulk of the crystal and of zero order with respect to unreacted material. The kinetic curves are expressed by the relation:

$$-\ln(1-x) = \text{const.} \times t^n$$

With $n = 1$, the curve represents reaction of a finely divided sample where only nucleation is rate limiting. The curve with $n = 4$ represents the kinetic behavior of a compact sample where both nucleation and growth overlap. The curve with $n = 2$ can represent either a zero order nucleation followed by a one-dimensional growth of the nuclei, or a very fast nucleation followed by a two-dimensional growth. The curve with $n = 3$ is interpreted either as due to a zero-order nucleation with two-dimensional growth or a very fast nucleation with three-dimensional growth.

As can be seen, despite the distinctly different assumptions used in each case, the curves are so similar that an interpretation is very ambiguous. In fact, all the cases considered are not mutually exclusive. They constitute simple limiting cases which may overlap, and with the possible intervention of other factors the experimental results will be very complex. Thus, in the study of solids, recourse must be made to numerous auxiliary methods to define a sample and follow the course of its transformation (surface area measurements, x-rays, electron microscopy, etc.).

III. HETEROGENEOUS CATALYSIS

Reactions between fluid reactants catalyzed by solids are characterized by a fixed reaction interface. The chemical act occurs at the interface between the fluid and solid phases. The analysis of the phenomenon is made simpler by the fact that, in the ideal case, the reaction interface remains invariant in shape, area, and activity. It is then a constant in a given experiment or in a series of experiments with a given sample. It is then easier than in the case of reactions with moving reaction interface, to determine the behavior of reactants on a given catalyst. Nevertheless, in order to secure information on the catalyst itself, it is necessary to change the latter, i.e., its quantity and quality, while all other experimental conditions are kept the same. Then the same difficulties attending the study of fluid–solid reactions are met again, and ultimately the study of the solid must be made.

It is seen that the problem of heterogeneous catalysis is two-fold in nature. On the one hand, it comprises the kinetic study of the behavior of reactants at the solid surface. On the other hand, it involves a study of the catalyst itself. The activity of the catalyst is best determined by the rate of reaction, which is the proper quantity to relate to the various properties of the solid.

The very large number of investigations designed to interpret the catalytic action of solids has not yielded, thus far, any indication on the basis of

which it would be possible to select a catalyst for a given reaction. Nor have they revealed, once this selection has been made, what must be done to secure the maximum activity. There are no general theories. No special rules are available either. It is therefore still necessary to proceed in an empirical way in order to select the proper catalyst, and trial and error will lead to a catalyst of suitable activity. Nevertheless, it is sometimes possible to use the results of previous investigations as a guide in the choice of a catalyst for a proposed reaction. The reasoning here generally follows the lines of chemical analogy. This subject will not be treated here, and the reader is referred to another chapter in this series (V. I. Komarewsky, C. H. Riesz, and F. L. Morritz, "Catalytic Reactions," in *Technique of Organic Chemistry*, Vol. II, Interscience, New York, 1956). The classical books may also be consulted, e.g., the fundamental work of P. Sabatier (10). This reference material provides indications on the choice of a catalyst.

Before a study of there action itself can be undertaken, it must be isolated, i.e., a single reaction path for the desired reaction must be found. Then the rate equation can be found, i.e., the relation between rate and the various parameters on which it depends, particularly the temperature and the concentrations of reactants and products. The data thus obtained, as well as information on the composition of the system during reaction and on eventual intermediate products will establish the reaction scheme, i.e., the sequence of elementary steps reproducing the over-all chemical change. Finally, the mechanism of each step should be elucidated and the nature of the interactions between the various species and the catalyst should be established. But this again concerns the catalyst itself and it is seen therefore that a kinetic analysis provides information not only on the chemical reaction but also on the catalyst on which it takes place.

1. Catalytic Action

Even though a given reaction is thermodynamically feasible, the corresponding system will often stay indefinitely in a state of metastable equilibrium. The chemical system must be activated before the transformation can occur. The most obvious procedure is to increase the temperature. But this method presents definite limitations. First of all, a higher temperature susceptible of activating the reaction will also affect the position of chemical equilibrium; in particular, if the reaction is exothermic, the equilibrium will shift in the undesired direction. Examples are the syntheses of ammonia and methanol. Consequently the mode of activation of the reaction must be such as to permit a satisfactory degree of conversion. It may also happen, when the molecules are more complex, that various

parallel reactions take place simultaneously. Then a raise in temperature will activate all these reactions in a more or less pronounced fashion. In particular, parasitic reactions may become more important at higher temperatures. Consequently, the mode of activation must orient the system selectively toward the desired path.

Among the possible modes of activation, catalysts are particularly important. In the laboratory or industrially, they achieve an infinite variety of syntheses. *In vivo*, they are the enzymes. It is now well established that a catalyst, whatever its nature, takes part in the reaction just like reactants do. The difference is that it is recovered unchanged as a reaction product. Since the elementary steps of a process have in general a low molecularity with respect to reactants or products, the catalytic cycle will usually involve a large number of steps. A simple reaction of the type:

$$A + B \longrightarrow C + D$$

which could happen in a single step, will necessitate a sequence of steps in the catalytic cycle:

(I) Catalytic Reaction

$$A + K \longrightarrow AK$$

$$AK + B \longrightarrow AKB$$

$$AKB \xrightarrow{\text{reaction}} CKD$$

$$CKD \longrightarrow CK + D$$

$$CK \longrightarrow C + K$$

(II) Complex Reaction

$$A + B \longrightarrow C + D$$

Since the catalyst can in principle repeat the reaction cycle indefinitely, only a limited amount of catalyst is required to transform an unlimited amount of material. But this is an extreme case. Generally, the catalyst presents a certain affinity for the product. An increasing amount of catalyst will be neutralized as the product accumulates so that the reaction may even stop before completion. The other extreme case is when the reagent is neutralized quantitatively by the product. A stoichiometric amount of reagent is required to complete the reaction.

The possible cases are illustrated by the action of aluminum chloride in Friedel-Crafts reactions. In the attack of aromatic hydrocarbons by alkyl halogenides, only a small quantity of aluminum salt is required to transform a large quantity of reactants (scheme I). On the contrary, in the action of acyl chlorides on the aromatic ring, the ketone forms complexes

with the aluminum chloride and the complex is so stable that a stoichiometric amount of chloride is required (scheme II).

In principle, a large quantity of reagent may be used at the start and small amounts of reactants are then added progressively. The activating effect of solvents is used in this fashion but they do not deserve the name of catalyst, which refers to substances that are active in small concentrations or quantities. This restriction is justified by the fact that a solvent in large quantities alters the physical and chemical properties of the system in such a way that not only reaction rates but chemical equilibria may be affected by its presence. By contrast, a catalyst in small quantities is unable to alter significantly the physico-chemical properties of the system or the free energy of the final state.

According to this restrictive definition, so-called autocatalytic reactions are not catalytic processes. Such would be the case only in diluted systems where the product that activates the reaction cannot affect the thermodynamics of the system. The definition implies that a catalyst accelerates the evolution of a system toward equilibrium without altering the latter. Since chemical equilibrium is the result of the opposition of forward and backward reactions, it follows that a catalyst, if it changes the rate of the forward process, must also and to the same extent change the rate of the backward process. This requirement, a consequence of the second law of thermodynamics, is strictly valid only in the vicinity of equilibrium. Yet, generally, a catalyst activates in a comparable way the evolution of both systems toward their common equilibrium.

This conclusion is of considerable practical interest in experimental work. Indeed some reactions may be limited by an unfavorable equilibrium and are not easily investigated by conventional techniques. Yet, some useful information which may often be sufficient can be accrued from the study of the reverse reaction which, going practically to completion under the same conditions, will lend itself to much simpler experimental techniques.

These considerations are valid whatever the nature of the activating agent: acids, bases, or salts in homogeneous catalysis; enzymes in biochemical processes; solids in contact catalysis. According to the preceding definition, initiators of polymerization may be regarded as catalysts because they are used in small quantities, are able to transform a large amount of material, and do not alter the properties of the final system. These substances provide free radicals much more readily than the reactants themselves and these radicals, by successive addition of monomer molecules, build up the macromolecules. Activating agents of this sort affect only the first link of the chain: what follows depends on the reactants themselves. Different initiators exert similar effects.

In catalytic processes, the activating agent plays a part at every cycle of the process and can therefore directly influence the reaction path. Thus various catalysts will orient a reaction toward different thermodynamically feasible states. In fact, catalysts are used not only to enhance the rate of reaction but also to achieve a selective chemical change.

2. Experimental Methods

In the study of catalytic reactions, it will be necessary to observe all rules directing experimentation in the case of homogeneous reactions. Additional precautions are needed because of the heterogeneity of the reaction system and the lack of stability of solid catalysts.

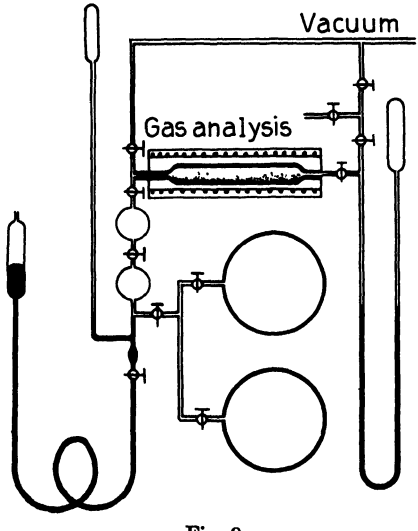

Fig. 9

A. PRINCIPLES OF EXPERIMENTAL SYSTEMS

There are three main types of systems used in quantitative work: closed systems, open systems, and systems with partial or total flow. With homogeneous reactions, a phase where the reaction takes place is said to be closed when it does not exchange matter (reactants or products) with its surroundings. With heterogeneous reactions involving more than one phase by definition, it is more convenient to consider the system as a whole within the walls of the reaction vessel.

Closed Systems (Batch Reactors). In the static method using a closed system, reactants are introduced in the reactor at the start and products

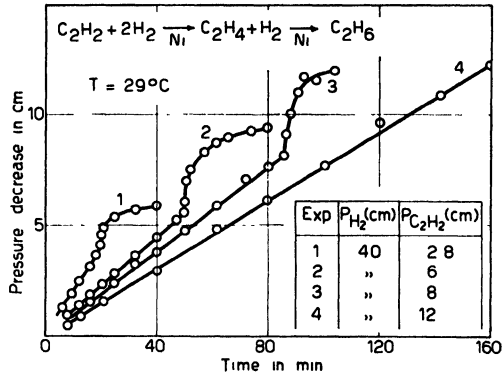

Fig. 10

are withdrawn when the experiment is completed. The evolution of the system is determined by measurements of physical or chemical properties of the system related to the values of the concentrations. These measurements are performed on the system itself or on samples.

This closed system technique, whenever applicable, is best suited to a kinetic analysis. Indeed, the reaction then takes place at constant volume in gaseous systems. With liquid phase operation, the change in volume can generally be neglected. In addition, the data give directly the variation of the concentrations or even sometime of the rate itself as functions of time, which are the data best suited to mathematical analysis.

Figure 9 shows a type of apparatus used frequently in the study of reactions between gaseous reactants. Some of the details represented are the

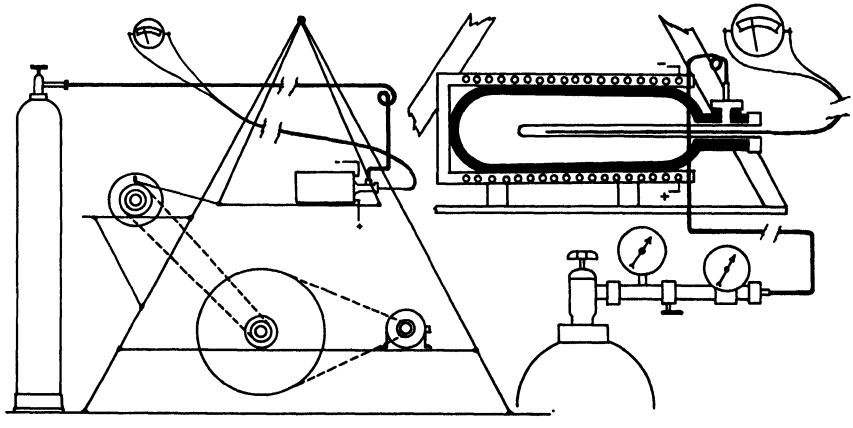

Fig. 11

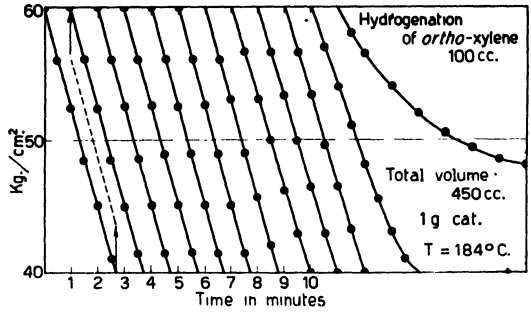

Fig. 12

storage bulbs, the filling system and the reactor. As an illustration, some of the data obtained in an apparatus of this kind are shown in Figure 10. The reaction was the hydrogenation of acetylene on nickel (11).

An apparatus used for the hydrogenation under pressure of organic compounds is shown in Figure 11. On the right hand side are the autoclave with its oven, the hydrogen inlet, the pressure gages, and the thermocouple for temperature control. The left hand side shows the mechanical set-up required to agitate the reacting system. Figure 12 shows data obtained in the hydrogenation of *ortho*-xylene, the hydrogen being admitted in successive batches (12).

It is necessary that the rate, as measured directly or indirectly, represent the chemical phenomenon exclusively. In particular, the rate must not be affected by the transport of reactants or products to or away from the catalyst surface. Thus no significant concentration gradient may be tolerated between the immediate vicinity of the catalyst surface and the bulk of

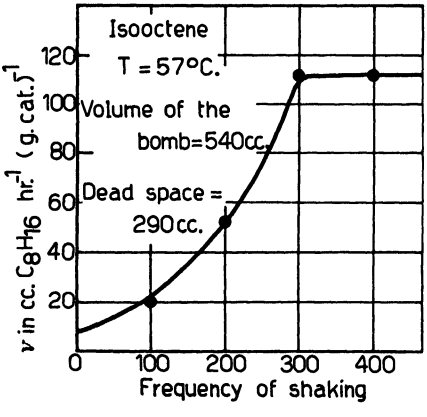

Fig. 13

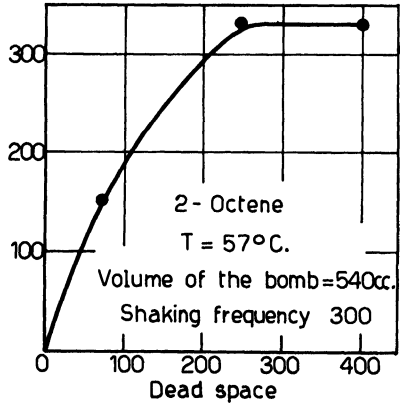

Fig. 14

the fluid phase. The composition of the reacting system must remain uniform. This requirement can be satisfied relatively easily in laboratory equipment if all reactants are gaseous. On the contrary, if the catalyst is suspended in a liquid, suitable agitation of the system is necessary to insure a perfect homogenization. It must be noted here that most types of reactors now commercially available may well be suited to laboratory syntheses, but their use in kinetic work is warranted only if it can be shown that the rate is determined exclusively by the chemical process.

Figures 13 and 14 illustrate the effect of agitation frequency for an autoclave filled to the amount indicated in the hydrogenation of isooctene and 2-octene on nickel under identical conditions. Only the maximum value of the rate has kinetic significance. As temperature increases, a degree of agitation which was adequate at lower temperatures may become insufficient because of the increase of reaction rate with temperature. This

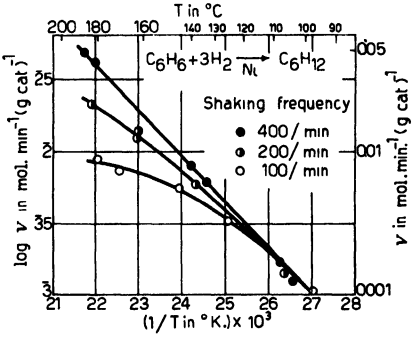

Fig. 15

is shown by the data of Figure 15. In the hydrogenation of benzene on nickel the agitation must be more violent at higher temperatures in order to avoid the controlling effect of diffusion (14).

Open Systems (Semibatch Reactors). It is not always possible nor desirable to carry out the reaction in a closed system. This is particularly true when one of the reactants or products is a gas. It is then easier to introduce the reactant into the reactor as it is consumed, or to remove the volatile product as it is formed.

This technique is illustrated by Figure 16 showing an apparatus used in the dehydrogenation of secondary alcohols on nickel. The reactor contains catalyst and reactant. The ketone is removed by the fractionating column. The hydrogen is received and measured in a gas buret which it reaches through a mercury valve of controlled height so that the boiling temperature of the alcohol can be regulated. Since it exchanges matter

with its surroundings, the reaction phase may undergo important variations of volume if the main reactant is initially in the pure state or in concentrated solution. Then more complex formulas taking into account the change of volume must be used in the kinetic analysis. In order to obtain meaningful results, it is necessary as before to avoid any concentration gradient in the homogeneous phase.

If variations of pressure can be measured, it is also possible to admit the gaseous reactant in successive batches and to follow the rate of disappearance of each one. Since the concentration of liquid reactant changes very little from batch to batch, the order of reaction with respect to gaseous reactant can be determined. Also, the progressive change in the rate of re-

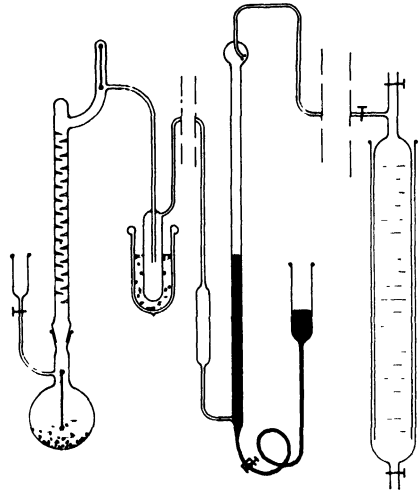

Fig. 16

action of successive batches indicates how the rate changes as the concentration of liquid reactant decreases (Fig. 12). This method is often called the "saw-tooth method" because of the shape of the kinetic curves. It combines the principles of closed and open systems and provides in a single experiment, results which would necessitate a series of runs in either closed or open systems.

Flow Systems (Flow Reactors). In the preceding methods it is assumed that reactants or products can stay in contact with the catalyst during an entire run. Frequently, secondary reactions take place which transform the first reaction product or deactivate the catalyst. It is then necessary to use flow systems in which the reacting mixture resides in the reactor only during the required time. Flow methods can also be used when a reaction is

limited by an unfavorable equilibrium or inhibition by products so that only a small degree of conversion can be reached. Then it is necessary to eliminate products from the reaction mixture.

Flow may be partial or total. With total flow, the catalyst must also circulate through the reactor. This method is used successfully in industrial practice with catalysts requiring frequent regeneration. However, the kinetic interpretation of results is difficult. Even in the case of experiments with a fixed bed of catalyst, experiments are laborious and the interpretation of data is relatively difficult. Actually, in laboratory experiments, the usual flow technique consists in feeding reactants at a given rate. Once the steady state is reached, samples are taken. In order to get a single curve of time versus concentration or time versus rate, a new feed rate must be used for each point. Similar results may be obtained in a single run in a static system.

The flow technique thus necessitates a great deal of work. Reproducibility is doubtful since all conditions must be kept constant. Besides, the deactivation of the catalyst must be taken into account. Also, if rates themselves are measured, they are only average rates corresponding to the contact time whereas instantaneous rates are best suited to a kinetic analysis. If the reaction involves a volume change, this added complication makes the interpretation even more cumbersome.

In a flow system, each mass element as it progresses through the reactor undergoes the same change as in a static system, as a function of time. Thus a concentration gradient is set up in the reactor and this must not be perturbed. Otherwise results would again be more difficult to interpret. To avoid this, a tubular reactor should have a large ratio of length to diameter. This reduces the importance of back-mixing. By contrast, the radial composition of the mixture must be as uniform as possible.

It must be noted in particular that the practice consisting of packing the catalyst in a short bed is acceptable only in experiments with a small conversion, designed to measure the initial rate. Under such conditions, the variation of composition throughout the contact mass is small and, in first approximation, the reaction may be considered as taking place at constant concentration.

Instead of keeping a concentration gradient, the other alternative is to maintain a uniform composition throughout the reactor. At a given feed rate, the reactant concentration is then constant at every point. This concentration decreases as the feed rate goes up and a steady state is established. Steady state flow systems with complete mixing can be used in reactions with a liquid reactant, product, or solvent.

Several types of apparatus must sometimes be used in order to secure all the necessary kinetic information in the case of a single reaction. But it

would be ill-advised, in order to save time, to build the experimental system for fundamental work following the presumed design of the industrial plant. To obtain a viable process, it is faster and safer to start the experimentation with batch or semi-batch systems if the reaction lends itself to such systems. Only later will flow systems be used for the development of a continuous process.

B. THE CATALYST

The kinetic analysis designed to determine the nature and effect of the reaction variables is based on the assumption that the catalyst is kept constant in amount and activity during a given experiment or in a series of runs. Here then is a case of simplification of the general kinetic situation.

The exact duplication of samples is already quite difficult in the case of solids in a thermodynamically stable form. It is even more difficult in the preparation of catalysts that can be obtained in a variety of metastable states. Of course, a standard technique of preparation will help in reproducing samples of comparable activity. However, this method is too laborious in the research phase of the work and fluctuations in activity may still occur which make it difficult, if not impossible, to determine quantitatively the effect of the various reaction variables.

The best way to minimize or even eliminate the variations in catalyst samples is to obtain these samples from a single batch of catalyst prepared in sufficient quantity to satisfy the needs of a series of runs. If samples are taken with sufficient care, results can be obtained that are reproducible with a few percent. When runs are carried out with samples from a given batch of catalyst, it is necessary to control the constancy of the catalyst activity with time. By means of control runs, it is possible to correct results of other runs carried out with catalysts of reduced activity.

In heterogeneous catalysis, it is not advisable to change monotonously the variable under study. A simultaneous change in catalyst activity could then change all results in a nondetectable way. It is preferable to operate alternatively under widely different conditions so that results obtained within a given interval will reveal an eventual modification in catalyst activity. It is then sometimes possible to correct for such changes. This experimental design is sometimes called the "sandwich method."

In the determination of kinetic constants, useful and very precise results can be obtained, even with a catalyst of changing activity, if two competing reactants which react simultaneously on the catalyst are used. In this method of competitive reactions, results do not depend on the amount of catalyst used. Nor do they depend, to a large extent, on variations of catalyst activity. According to this method, one reaction is measured relative to another. Thus, only relative kinetic constants are obtained.

Yet the data are very valuable to compare the reactivity of the various members of a given chemical family or of different families. In particular, such data indicate the selectivity of the attack of a given component of a mixture. On the other hand, since the transformation of two reactants must be determined, this method is more difficult from an analytical viewpoint than the study of each reaction taken separately.

C. MEASUREMENTS

All methods used to follow the change of a system in homogeneous kinetics can be used in heterogeneous catalysis. But especially when reactants are diluted or when the amount of catalyst is important, it is necessary to check whether the concentration of the reactants in the fluid phase corresponds to the calculated composition of the mixture. Indeed, if the reactant, the product, or an inhibitor are present in relatively small concentration, adsorption on the catalyst may well deplete its bulk concentration by a relatively important quantity. Since the concentrations, measured directly or indirectly, are those of the homogeneous phase, while the active concentrations are the concentrations at the catalyst surface, an error of this kind would falsify the interpretation of data.

3. Interpretation of Results

Fundamental studies carried out in the past fifty years have established that kinetics is generally complex even for reactions of simple stoichiometry. The only hope of obtaining results suitable for elucidating the scheme and the mechanism of the reaction rests on a systematic way of carrying out experiments and of interpreting kinetic data.

A. METHODS OF INVESTIGATION

In the study of a new chemical system, the first experiments do not generally yield information that can be treated mathematically. Their aim is rather to delineate the conditions under which results can be obtained which can be interpreted theoretically and treated mathematically.

Since a chemical system of some complexity can follow several competing reaction paths (this is generally the case in organic systems), a catalyst of suitable activity and selectivity must first be found. Then one of the reaction paths must be isolated by a suitable choice of conditions such as temperature and concentration. The desired reaction can then proceed preferentially or even exclusively. This isolated reaction can still consist of a sequence of steps. The scheme may even be more complex. When it is certain that the isolated reaction is stoichiometrically simple, the rate of re-

action can be studied as a function of concentration or total pressure, composition of the reacting mixture, and temperature. Since all substances implied: reactants, products, or solvents can exert an effect on the kinetics, a systematic experimental design is necessary in order to obtain interpretable results.

After determining the effect of reactants used in different ratios and at different concentration levels, mixtures containing only one of the reaction products must be studied systematically. Initial rates are measured and the data obtained must describe the evolution of the system over the entire range of conversion if the reaction scheme is complete. When it is known or strongly suspected that the process takes place via a sequence of reactions, the first identified or suspected product can be studied separately. The various steps of the reaction are studied in this fashion and the overall scheme is progressively established. Conversely, the first product can be eliminated from the reacting system. This is the capture method for which flow systems are particularly suitable.

The role of a given compound in the reaction scheme can sometimes be determined by the substitution method. The compound is replaced by an isomeric or homologous compound having a high degree of chemical similarity but which does not take part in the same reactions. For example, in the dehydration of ethanol on alumina, ether and ethylene are observed simultaneously as reaction products. On the other hand, methanol cannot yield an olefin and its only reaction product is dimethyl ether. Since it is legitimate to assume that the formation of dimethyl ether is analogous to that of diethyl ether, a kinetic study of the behavior of methanol is pertinent to a kinetic study of ethanol (15).

B. PRINCIPLES

Kinetic studies of elementary reactions and their satisfactory interpretation reveal that a chemical act, in the gaseous phase, rarely involves more than two molecular species. Therefore, if a reaction possesses a complex stoichiometry, it cannot take place in one step but necessitates the intervention of successive elementary steps of low molecularity. This situation corresponds to the principle of least structural change or the principle of least motion. The probability of a multiple collision decreases as the number of colliding partners increases. The probability of reaction is even further reduced because of the steric requirements of the collision. Therefore, complex molecules are built by means of a sequence of processes of low molecularity, which are more probable and not so restricted sterically.

In the hydrogenation of nitrobenzene on nickel, the only product found in older work was aniline and its reaction products. Yet, the principle of least motion dictates that the reaction is not likely to proceed in one step

involving one molecule of nitrobenzene and three molecules of hydrogen:

$$C_6H_5NO_2 + 3H_2 \longrightarrow C_6H_5NH_2 + 2H_2O$$

But then, if the process occurs through a sequence of hydrogenation steps, intermediate compounds must be formed and it is entirely possible that some of these intermediates have a relatively long lifetime. In fact, under suitable conditions, it is possible to obtain phenylhydroxylamine as an intermediate product and the yield may reach 80% of theoretical value (16). Although nitrosobenzene has not been found in the reacting mixture, its kinetic characteristics indicate that it may intervene as a shortlived intermediate product.

Whereas it is unlikely that several molecules join up in a single act to give a complex product, it is just as unlikely that the latter, once formed, will dissociate into more than two fragments under conditions favoring its decomposition. This would necessitate the simultaneous rupture of several linkages. However, the law of distribution of energy in molecular species indicates that the probability of accumulating enough energy in more than a bond at a time is negligibly small. A possible exception to this rule might be found among strongly endothermic molecules, e.g., explosive compounds.

In the dehydration of ethanol, a formerly accepted reaction scheme assumed that ether formed by partial dehydration would decompose into two molecules of ethylene and one molecule of water:

$$\begin{array}{l} 2C_2H_5OH \longrightarrow (CH_3CH_2)_2O + H_2O \\ \qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\quad 2C_2H_4 + H_2O \end{array}$$

But experiments carried out with ether alone (isolation method) show that it dissociates into only two molecules, ethylene and alcohol, with the latter returning to the reaction cycle (15):

$$(C_2H_5)_2O \longrightarrow C_2H_4 + C_2H_5OH$$

It is concluded that if a reaction is impossible in one direction because it involves the collision of too many molecules, it will also be ruled out in the reverse direction because it would require a prohibitively high accumulation of energy. As a consequence, if the build-up of a complex molecule follows a sequence of steps of low molecularity, it can also decompose in successive steps, each one requiring a small amount of energy. This conclusion finds its expression in the principle of microscopic reversibility according to which the direct and inverse reactions follow the same path of elementary processes.

If the overall reaction is limited by equilibrium, when this state is reached,

each of the elementary steps will also be in a position of equilibrium. This conclusion is expressed by the principle of entire equilibrium or detailed balancing. This principle may be considered as the thermodynamic expression of the principle of microscopic reversibility.

These principles are valuable in the analysis of reaction schemes because they provide information concerning the reverse of a reaction if the mechanism of the direct process is known. This is particularly useful when the study of a reaction in a given direction can not be done easily. It must be understood that these rules provide only qualitative indications and care must be used in their application.

4. Quantitative Treatment of the Data

The results obtained in the exploratory phase of the work and analyzed with the help of the general principles can be used to clarify the reaction scheme initially. They indicate how to isolate the component steps which must be submitted one by one to a quantitative study. The kinetic information can then lead to an overall kinetic expression characterizing the phenomenon as a whole. This goal can be attained only in the case of relatively simple reaction schemes, since the difficulties of a detailed analysis are even more formidable in heterogeneous catalysis than in homogeneous kinetics. A quantitative treatment of the data requires a proper mathematical formulation. The latter must be based on a correct theory in order to obtain self-consistent results which can yield meaningful information on the chemistry involved.

In the various types of catalysis, it is postulated that one or several of the reactants must first form a reactive complex with the catalyst. The complex then reacts and this constitutes the reaction itself. Products which are still bound to the catalyst must finally escape so that the catalyst can start a new cycle of transformations. In the simplest case of an isomerization, the catalytic cycle can be represented schematically as follows:

$$R + K \overset{\text{adsorption}}{\rightleftharpoons} RK \overset{\text{reaction}}{\longrightarrow} PK \overset{\text{desorption}}{\rightleftharpoons} P + K$$

Almost always, one of these steps is significantly slower than the others and determines the rate of the overall process. If the reaction of the complex RK and subsequent steps are fast, the rate determining step is the formation of the complex which is called a van't Hoff complex. If on the other hand the reaction itself is slow, a thermodynamic equilibrium is established between the reactant or reactants and the complex, which is then an Arrhenius complex.

In the overwhelming majority of cases studied thus far, it has been found that the kinetic results agree with the assumption of an Arrhenius complex.

This will also be the assumption made in what follows, but it must be kept in mind that there may be exceptional cases where the assumption of an Arrhenius complex does not hold.

Following the reaction scheme considered here, the driving force of the reaction itself is determined by the concentrations of reactants on the catalyst. These concentrations usually cannot be measured directly but must be expressed in terms of the concentrations in the homogeneous phase. The latter are determined by means of the usual techniques. Since the reactive complex is in equilibrium with reactants, the concentration of reactive complex can be expressed in terms of the concentrations of reactants by the equilibrium relation:

$$x_{RK} = b_R(c_R - x_{RK})\ (c_K - x_{RK})$$

In this expression c denotes total concentrations and $c - x_{RK}$ denotes concentrations of free species. The equilibrium constant is represented by b.

Since the amount of catalyst is small as compared to the amount of reactants, the concentration of catalyst complex itself can be neglected as compared to the concentration of reactants. The preceding equation then becomes:

$$x_{RK} = b_R c_R(c_K - x_{RK})$$

or:

$$x_{RK} = c_K\{b_R c_R/(1 + b_R c_R)\}$$

The reaction rate is then

$$v = kx_{RK}^n = kc_K^n\{b_R c_R/(1 + b_R c_R)\}^n$$

where n is the order of reaction with respect to the complex.

In homogeneous catalysis, the catalyst concentration stays constant during the course of an experiment and can be included in the apparent rate constant which is determined:

$$k_{app.} = kc_K^n$$

In a series of experiments, the catalyst concentration may be varied and the true rate constant can be found.

In heterogeneous catalysis, the active centers which form the catalyst complexes are fixed at the surface of the solid. Their surface concentration σ depends on the nature and activity of the catalyst. This concentration stays constant during a given experiment and also in separate experiments if the catalyst comes from the same batch. Consequently, the concentration of active centers cannot be modified although their number can be changed by changing the mass, m, of the catalyst.

Making surface concentrations proportional to one gram of catalyst, the equation defining x_{RK} becomes:

$$x_{RK} = m\sigma_{RK} = b_R c_R(m\sigma_K - m\sigma_{RK})$$

Whence:

$$\sigma_{RK} = \sigma_K\{b_R c_R/(1 + b_R c_R)\}$$

The rate is now given by:

$$v = mk(\sigma_{RK})^n = mk\sigma_K^n\{b_R c_R/(1 + b_R c_R)\}^n$$
$$= mk'\{b_R c_R/(1 + b_R c_R)\}^n$$

With $k' = k\sigma_K^n$. It must be noted that this expression is obeyed in a large number of cases in homogeneous catalysis and is identical to the expression first derived by Michaelis and Menten to describe the inversion of sucrose catalyzed by enzymes. For the sake of simplicity, no distinction will be made hereafter between true and apparent rate constants.

Until now it has been assumed that only reactants cover the surface of the catalyst. If the product P or a foreign substance S also compete for the surface, this must be taken into account. The concentration of reactive complex becomes then:

$$\sigma_{RK} = \sigma_K\{b_R c_R/(1 + b_R c_R + b_P c_P + b_S c_S)\}$$

The rate, with $n = 1$, is now:

$$v = k\{b_R c_R/(1 + b_R c_R + b_P c_P + b_S c_S)\}$$

When the catalyst surface is completely saturated ($1 \ll \Sigma b_i c_i$), the rate expression becomes:

$$v = k\{b_R c_R/(b_R c_R + b_P c_P + b_S c_S)\}$$

It is seen that, for a given amount of catalyst, the rate of reaction is determined by the mole fraction of reactant in the adsorbed phase.

When the reaction takes place between two reactants adsorbed at the surface of the catalyst, the rate expression is:

$$v = k\{(b_A c_A \times b_B c_B)/(1 + \Sigma b_i c_i)^2\}$$

All these forms of the rate equation correspond to particular cases which will be treated further below.

The catalytic reaction, even with the simplest scheme conceivable, is nevertheless a complex phenomenon. In the case considered here (Arrhenius complexes), besides the reaction itself, there is an adsorption equilibrium between the catalyst and the substances taking part in the reaction. The

effect of temperature on the rate of reaction is therefore complex since temperature affects the various steps of the process. The effect of temperature on the reaction itself is given by the law of Arrhenius

$$k = k_0 \exp(-E/RT) \tag{1}$$

where E is the activation energy.

The effect of temperature on chemical equilibria depends on the type of reaction. Since adsorption corresponds to a decrease of entropy, it must be exothermic to be feasible at all. According to the principle of Le Châtelier, an increase of temperature must decrease the amount adsorbed. If λ represents the heat of adsorption, the adsorption coefficient will obey the law of van't Hoff:

$$b = b_0 \exp(\lambda/RT) \tag{2}$$

These expressions are those of the theory of Langmuir and Hinshelwood. These authors derived similar relations following parallel though not identical paths of reasoning.

There exist other theories which have been advanced to explain heterogeneous catalysis. It has been suggested in particular that each reactant could be adsorbed on separate surface sites. With this type of noncompetitive adsorption, the rate expression would be:

$$v = k\{b_A c_A/(1 + b_A c_A)\}\ \{b_B c_B/(1 + b_B c_B)\}$$

It should also be noted that all surface sites forming reactive complexes may not be identical from an energetic standpoint, there exists on the surface a gradation in active centers. Also, molecules adsorbed on the surface may interact with each other. These interactions have not been taken into account in the theory presented here. Nevertheless, in the majority of the cases studied so far, the formulas of the theory of Langmuir and Hinshelwood account satisfactorily for the observed facts.

Finally, the adsorption coefficient related to the partition coefficient between homogeneous and adsorbed phases depends on the nature of these phases. The solvent may, for instance, affect the solute molecules so that they are attracted differently by the catalyst. Similarly, if a film of foreign material is found at the surface of the catalyst, this film may also change the partition coefficient of the reactant between the two phases. These interactions may be different for reactants and products and modify the rate and kinetics of the reaction. This is more likely to happen when reactants are pure liquids. Then, the nature of the liquid phase changes as the reaction proceeds, and consequently the adsorption coefficients may well change also.

First the case where adsorption coefficients do not change in a given ex-

periment or in a series of experiments will be considered. This situation will be referred to as ideal. In a subsequent paragraph, the non-ideal cases will be treated and it will be shown how the effects of solvent and adsorbed film may be used to enhance the selective action of the catalyst toward a single component of a complex mixture.

A. IDEAL SYSTEMS

In this section, simple and complex reactions will be considered in turn. Simple reactions, according to this classification, are those for which no intermediate products can be detected by usual analytical means. The rate equation also indicates whether a reaction is simple in this sense. Of course even reactions which appear simple in their kinetic behavior will take place in a number of steps, but only one of these steps determines the evolution of the system during the entire course of the reaction. For example, the catalytic reaction between carbon dioxide and hydrogen to give methane is of second order although the reaction scheme must be quite complex as indicated immediately by the stoichiometry of the reaction together with the principle of least change of structure.

Among complex reactions, we will consider equilibrated, parallel, and consecutive reactions. These cases can be combined in schemes of higher complexity which will not be treated systematically, although some examples will be mentioned in the last section, which is devoted to applications.

Simple Reactions. Even in simple cases, catalytic reactions are determined by a relatively large number of parameters. The rate of reaction depends not only on the absolute values of the concentrations of reactants but also on the composition of the reacting mixture. The first factor determines the degree of saturation of the catalyst, the second decides how the catalyst sites will be distributed among the chemical species. A third factor is the temperature, and its effect is also complex since it changes both the rate constant and the concentrations in the adsorbed phase. Therefore, in order to determine all the constants of a catalytic reaction, it is necessary to carry out more experiments under more varied conditions than is necessary for reactions with a definite order.

Generally, it is advisable to first study the kinetics as a function of initial concentrations. To do this, a preliminary series of runs is carried out with reactants at different concentrations and in different ratios and only initial rates are retained in order to avoid the effect of products. In another series of runs, the effect of each product on the reaction is studied. The kinetic constants determined in this way can then be used to define the kinetics as the concentrations change with time and the reaction is pushed to completion.

Among simple reactions, it is necessary to consider only reactions of order one or two on the catalyst. No definite indication of higher orders has been obtained so far.

First-Order Reactions on the Catalyst. With competitive adsorption of the various components of the system, the general rate law of these reactions can be written as:

$$v = k\{b_R c_R/(1 + b_R c_R + b_P c_P + b_S c_S)\} \tag{3}$$

When several products are formed, the corresponding adsorption coefficient will be the average of individual coefficients. The general expression will have different forms according to the absolute and relative values of the concentrations and of the adsorption coefficients which measure the affinity of the various chemical species for the catalyst.

Consider first the case where only the reactant is adsorbed on the catalyst. This happens when the other species have a very small affinity for the catalyst ($b_x = 0$; $b_x c_x = 0$). The rate equation then reduces to:

$$v = k\{b_R c_R/(1 + b_R c_R)\} \tag{4}$$

The only variable is the concentration of reactant, and measurements of the evolution of the system with time will determine the kinetic constants, i.e., the rate constant and the adsorption coefficient. Even if the other species possess a nonvanishing affinity toward the catalyst, Equation (4) can still be used at zero time when $c_P = 0$ in a series of runs where the reactant concentration is varied.

The simplified equation can itself be reduced to particular forms. When the reactant is weakly adsorbed, the term $b_R c_R$ can be neglected in the denominator and the equation becomes:

$$v = k b_R c_R = k' c_R \tag{5}$$

The reaction appears to be first order with respect to reactant. The apparent rate constant is the product of the true rate constant and the adsorption coefficient.

When the reactant is strongly adsorbed because its concentration is large or its affinity for the catalyst is high, unity can be neglected in the denominator and the expression becomes:

$$v = k \tag{6}$$

The reaction order is now zero and the true rate constant is measured. This constant characterizes the system reactant-catalyst and varies with the nature and quality of catalyst. This last type of kinetics is realized at sufficiently high pressure or when the reactant is liquid or in a concentrated

solution. Examples of these various cases have been documented in the chemical literature.

By comparing rate constants kb when the reaction is first order and k when it is zero order, it is possible in principle to determine the adsorption coefficient. In practice, experimental techniques are not usually adequate to follow the reaction in a sufficiently wide interval of pressures or concentrations.

Results obtained in the intermediate range of concentrations are in themselves sufficient to determine the constants of Equation (4) which can be linearized as follows:

$$k/v = (1/b_R c_R) + 1 \tag{7}$$

or

$$1/v = (1/kb_R c_R) + 1/k \tag{8}$$

In these expressions, v represents the actual rate and k the rate when the catalyst is completely saturated.

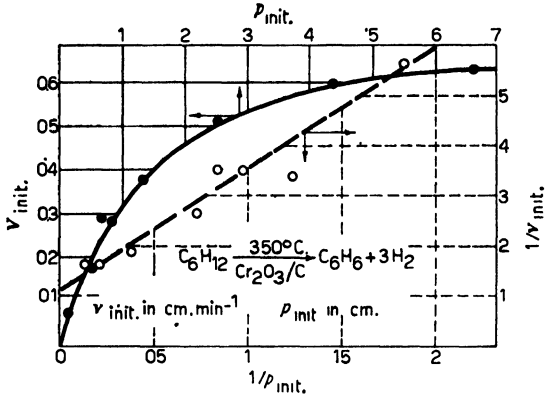

Fig. 17

If the true catalytic constant k can be found separately, Equation (7) can be used to determine the adsorption coefficient. Otherwise, Equation (8) is used. This case is illustrated by Figure 17 which shows the data for the dehydrogenation of cyclohexane on chromium oxide (17). The curve shows the initial rate as a function of initial pressure (initial kinetics). The straight line expresses the same data by means of Equation (8). The rate constant is given by the inverse of the intercept on the ordinate axis. The adsorption coefficient can be calculated from the inverse of the slope. This quantity is the product kb_R. In this example, the intercept is 1.1 and the rate constant in arbitrary units is 0.85. Since the slope is equal to 2.3,

the adsorption coefficient is 0.85/2.3 = 0.37. Since the concentration is measured by the pressure in cm. Hg, the adsorption coefficient is expressed in (cm.Hg).$^{-1}$

When the adsorption coefficients of products cannot be neglected, the kinetic data obtained during the course of the reaction must be interpreted by means of the equation:

$$v = k\{b_R c_R/(1 + b_R c_R + b_P c_P)\} \tag{9}$$

In this expression, $b_P c_P$ stands for a sum of terms if there are several products. Equation (9) can be simplified when the catalyst is completely saturated, as happens in the liquid phase, and becomes

$$v = k\{b_R c_R/(b_R c_R + b_P c_P)\} \tag{10}$$

The linearized form of Equation (10) is:

$$k/v = (b_R - b_P)/b_R + (b_P/b_R)\{(c_P + c_R)/c_R\} \tag{11}$$

or

$$1/v = 1/k + (1/k)(b_P c_P/b_R c_R) \tag{12}$$

Equation (11) can be used if k is already known. Otherwise, Equation (12) is the one to use. It must be noted that in this case corresponding to complete saturation of the catalyst, only the ratio of adsorption coefficients can be determined, i.e., the partition coefficient of the catalyst between the two substances involved.

An example is the dehydrogenation of secondary alcohols on nickel (18)

$$\text{RCHOHR}' \xrightarrow[\text{Ni}]{-\text{H}_2} \text{RCOR}'$$

TABLE I

Catalytic Dehydrogenation of 2-Butanol on Nickel

R = 2-butanol P = butanone

$(c_R)_{init.}$ = 10.90 mol. l.$^{-1}$ T = 98.8°C.

k = 28.4 cc. H_2 min.$^{-1}$ g.$^{-1}$ $x_{max.}$ = 6.6%

v	k/v	c_R	c_P	c_R/c_P	b_R/b_P
10.12	2.8	10.714	0.186	57.6	104
7.66	3.7	10.616	0.284	37.4	101
6.42	4.4	10.529	0.371	28.4	97
5.40	5.3	10.464	0.436	24.2	104
5.06	5.7	10.408	0.502	20.9	98
4.54	6.3	10.365	0.535	19.3	102
4.02	7.1	10.310	0.590	17.5	107
3.84	7.4	10.268	0.632	16.2	104
3.49	7.8	10.235	0.665	15.2	105

In the apparatus represented schematically in Figure 16, hydrogen is removed from the system and the ketone may then be regarded as the sole reaction product. The calculation is illustrated for the case of 2-butanol in Table I. At 100°C., butanone is 100 times more strongly adsorbed than the corresponding alcohol. These results, together with others for various alcohols are shown in Figure 18 where the data are plotted following Equation (11).

It can be seen that ketones possess a much higher adsorption coefficient than the corresponding alcohol. At the limit, the rate equation would be:

$$v = k(b_R c_R / b_P c_P)$$

so that the rate would become order one with respect to the reactant and minus one with respect to the product.

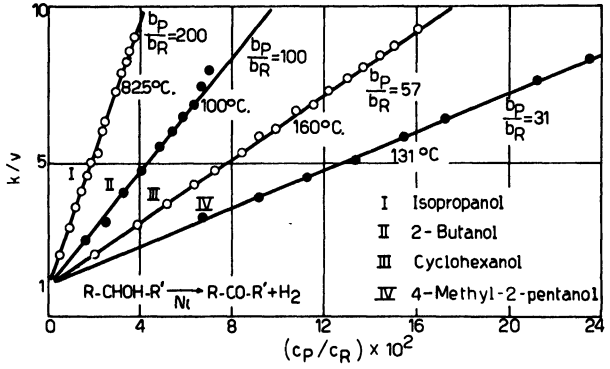

Fig. 18

In this example only one product, namely, the ketone, must be considered since as a result of the experimental technique, hydrogen is eliminated as it is formed. When there are several products, the calculation gives an overall adsorption coefficient for the products formed in stoichiometric ratio. Individual adsorption coefficients can be obtained in experiments where each product is added initially to the reacting system.

The effects of foreign substances, such as solvents, can also be analyzed in this way except that the term $b_S c_S$ stays constant during the course of an experiment. Such measurements are very useful practically since they reveal solvents which are catalytically inert.

Second-Order Reactions on the Catalyst. The general rate equation for these reactions is:

$$v = k\{(b_A c_A \times b_B c_B)/(1 + b_A c_A + b_B c_B + b_P c_P)^2\} \qquad (13)$$

In this form, it is far too complicated for a meaningful analysis of data and recourse must be made to cases of kinetic degeneration which simplify the rate of expression and facilitate the progressive determination of the parameters. With pure reactants on a saturated catalyst, Equation (13) reduces to:

$$v = k\{(b_A c_A \times b_B c_B)/(b_A c_A + b_B c_B)^2\} \tag{14}$$

Thus the rate is zero when each reactant is used alone and reaches a maximum when the reactants on the catalyst are in stoichiometric ratio:

$$b_A c_A = b_B c_B$$

The ratio of concentrations in the homogeneous phase is then inversely proportional to the ratio of corresponding adsorption coefficients. This ratio determines how both reactants share the total surface of the saturated catalyst. This case may be illustrated by the esterification of organic acids on thoria (19) as shown on Figure 19.

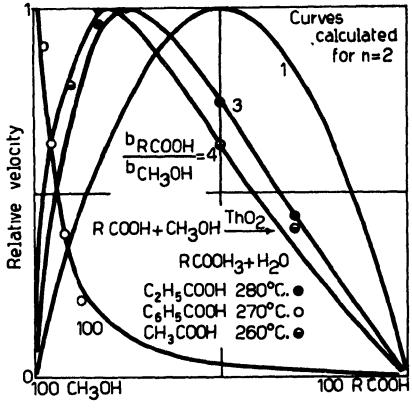

Fig. 19

When one of the reactants occupies almost exclusively the entire surface of the catalyst, Equation (14) becomes:

$$v = k(b_A c_A / b_B c_B)$$

The order of reaction is plus one with respect to the weakly adsorbed substance and minus one with respect to the strongly bound reactant.

When the catalyst is not completely saturated, the equation for initial rates is:

$$v = k\{(b_A c_A \times b_B c_B)/(1 + b_A c_A + b_B c_B)^2\}$$

This can be written in the form:

$$(c_A/v)^{1/2} = (1 + b_B c_B)/(k b_A b_B c_B)^{1/2} + \{b_A/(k b_B c_B)^{1/2}\} c_A$$

In a series of runs at constant c_B but variable c_A, the data should obey the relation:

$$(c_A/v)^{1/2} = C + M\, c_A$$

The constants C and M can again be measured in another series of runs with a new constant value of c_B and variable values of c_A. This can be repeated till the absolute values of the adsorption coefficients can be determined. An example is the hydrogenation of acetylene on nickel (20).

In order to determine the adsorption coefficients of the products, an easy technique is to use a stoichiometric mixture of reactants and study, during the initial kinetics, the effect of the various products. With a saturated catalyst, the rate equation is then:

$$v = k\{(b_A c_A \times b_B c_B)/(b_A c_A + b_B c_B + b_P c_P)^2\}$$

A good illustration is the dehydration of phenols on thoria. Since $b_A c_A = b_B c_B = b_R c_R$, the preceding relation becomes:

$$v = k\{b_R c_R/(b_R c_R + b_P c_P)\}^2 \qquad (15)$$

The square root of this expression has a form identical to the rate equation for first-order reactions.

Table II shows the details of the calculation for the dehydration of *p*-cresol in the presence of di-*p*-cresyl ether. It is seen that the ratio of ad-

TABLE II

Dehydration of *p*-Cresol on Thoria in the Presence of Di-*p*-Cresyl Ether

R = *p*-cresol
P = di-*p*-cresyl ether
$[R]_0$ and $[P]_0$ = initial concentrations
Concentrations in mol. $l.^{-1}$
k = 2.3 mol. $min.^{-1}$ (g. cat.)$^{-1} \times 10^{-1}$
Data of column 4 are averages between actual and initial values.

$[R]_0$	$[P]_0$	$[\bar{R}]$	$10 \times [\bar{P}]/[\bar{R}]$	$v \times 10^{-5}$	$'_P/b_R$	
					$n = 1$	$n = 2$
8.18	0 735	7 56	1.14	0.815	16	5 9
7.30	1 19	6.94	1.80	0 475	22 5	6 6
7.19	1.25	6 84	1.90	0 46	21	6 4
6.82	1.94	6.58	2.99	0.32	19	5 7
5.88	2.00	5.64	3.55	0.25	29	5.7
5.18	2.29	5.04	4.55	0.18	25	5.6
5.13	2.36	5.00	4 72	0.17	26	5 6
4.95	2.67	4 85	5.50	0.13	30	5.8

sorption coefficients exhibits less variations if the reaction is assumed to be of order two. With first-order kinetics, this ratio varies as shown in column 6. This reaction is in fact limited by equilibrium. Yet, if the extent of reaction is kept small enough, the effect of the back reaction can be neglected so that the forward process may be treated like a simple reaction.

Effect of Temperature. The effect of temperature on a catalytic reaction is complex since temperature changes not only the rate of reaction of adsorbed molecules but also the adsorption coefficients which determine the relative concentrations on the catalyst. Furthermore, temperature has a different effect on each adsorption coefficient.

To illustrate the various effects, let us consider a few cases in order of increasing kinetic complexity. When the reaction is of zero order in the entire range investigated, the catalyst remains saturated and the temperature

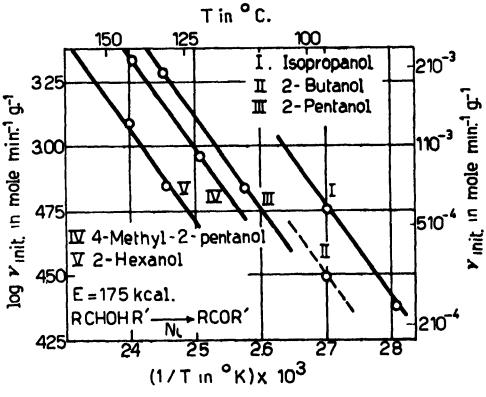

Fig. 20

acts only to activate the adsorbed molecules without altering their concentration. The relation is then:

$$v = k = k_0 \exp(-E/RT)$$

The reaction obeys the Arrhenius Law. This can be verified by plotting the decimal logarithm of the rate versus the inverse of absolute temperature. On this Arrhenius diagram the data give a straight line, the slope of which after multiplication by 4.57 gives the true activation energy of the reaction. This calculation is illustrated in Figure 20 for the dehydrogenation of secondary alcohols (22). The zero order is here due to the fact that the reaction products are removed continuously as they are formed.

When the order of reaction is unity, the effect of temperature is not only to activate the reaction but also to depopulate the catalyst surface. The

appropriate relation is then:

$$v = kbc = k_0 \exp(-E/RT) \times b_0 \exp(\lambda/RT) \times c$$

The apparent activation energy is given by:

$$E_{app.} = E - \lambda$$

It is equal to the difference between the true activation energy and the heat of adsorption. This result means that the rate of reaction increases less rapidly with temperature than for a zero-order reaction. In order to get the maximum benefit from a rise in temperature, it is necessary to oppose the depopulation of the catalyst by an adequate increase in pressure. At

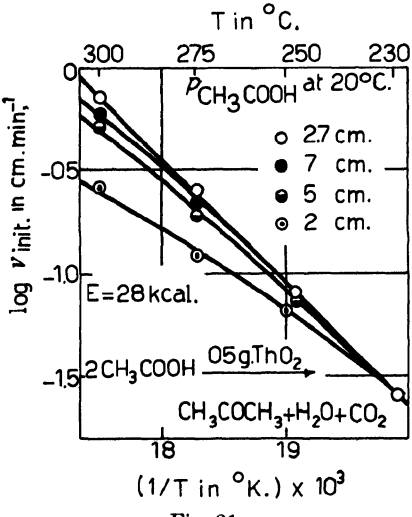

Fig. 21

constant concentration, there would be a transition from zero order to first order as temperature goes up and on an Arrhenius diagram, the line passing through the data would become flatter at higher temperatures. The decarboxylation of fatty acids on thoria (19) is of second order but can be used anyway to illustrate this effect (Fig. 21).

For a second-order reaction involving two reactants, the apparent activation energy is the difference between the true activation energy and the sum of the heats of adsorption of the reactants:

$$E_{app.} = E - \lambda_A - \lambda_B$$

When the order of reaction is negative with respect to a reactant or a strongly adsorbed product, the apparent activation energy is increased by

the heat of adsorption of the inhibitor:

$$E_{app.} = E - \lambda_R + \lambda_P$$

Now, the rate increases faster with temperature than in the preceding case. This is because a rise in temperature liberates a part of the surface from the inhibitor and more surface becomes available to the reactant.

By means of the kinetic analysis, it is possible to determine separately the rate constant and the absolute or relative values of adsorption coefficients. Therefore, the true activation energy can also be calculated together with the heat of adsorption or the difference between heats of adsorption as the case may be. As shown in Figure 22, the adsorption coefficients on nickel of secondary alcohols and corresponding ketones

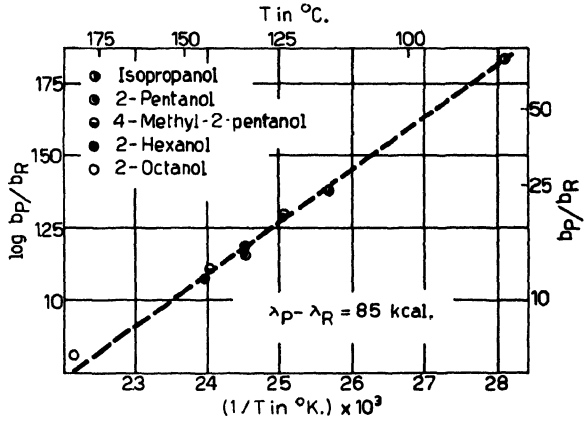

Fig. 22

change with temperature. The difference λ(ketone) − λ(alcohol) is equal to 8.5 kcal. for the four systems investigated (22). This means that the heat of adsorption of ketones is higher than that of corresponding alcohols. It follows that higher temperatures will modify the relative concentrations on the catalyst in favor of the alcohol.

It must be kept in mind that the various kinetic constants characterize both the reacting system and the catalyst. They change with the nature and activity of the catalyst. Let us also note that it is extremely laborious to determine all these constants for a given reacting system. To do this would necessitate several types of apparatus operating between wide ranges of temperature and concentration. Such an undertaking is already vast enough in favorable cases but the results will become very inaccurate if the activity level of the catalyst is not rigorously stable. Another limitation

is the assumption made in this theory concerning the uniformity of the catalyst. In fact, in different ranges of concentration and temperature, different active centers may come into play and it may be difficult to compare data obtained under widely different conditions.

B. COMPLEX REACTIONS

The complexity of reaction schemes is one of the prime reasons for the frequently low space time yields of chemical processes. Opposed, parallel or consecutive reactions will either slow down the rate or decrease the yield of desired product. The kinetic analysis of complex changes reveals the conditions under which the desired reaction may be favored while the parasitic processes are repressed.

Equilibrated Reactions. In a system of equilibrated reactions the net rate of reaction, v, is the difference between forward rate $\overrightarrow{v}$ and backward rate $\overleftarrow{v}$:

$$v = \overrightarrow{v} - \overleftarrow{v}$$

Each one of the opposed rates can be expressed by means of one of the rate equations considered in our study of simple reactions. Yet if one of them is known, the choice for the other is not arbitrary since together they must be consistent with the equilibrium relation.

Instead of enumerating all possible cases of equilibrated reactions, the general ideas will be presented by means of an example which will also serve to illustrate the general plan of experiments. The example is the dehydration of phenol to give diphenyl ether on thoria (21). This type of reaction is quite general. The same kind of kinetics is observed for the dehydration of alcohols (23) and the dehydrosulfurization of mercaptans (24) on alumina. But the reaction scheme is more complicated for these two types of processes because of the further decomposition of ethers and thioethers.

In order to undertake a kinetic analysis of the phenomenon, one of the opposed reactions must be studied independently. This can be done if the extent of reaction is kept low so that the products are maintained in low concentration and cannot speed up the reverse reaction. To do this, the flow method can be used.

Although the direction of the chosen reaction is immaterial, the decomposition of phenol will be selected rather than the reverse reaction for reasons of simplicity. First, it must be verified whether the catalyst is completely saturated, since this eventuality simplifies the equations. The data of Table III show that a reduction of the partial pressure of phenol by addition of benzene does not significantly alter the reaction rate (column 3).

TABLE III

Dehydration of Phenol on Thoria

(Effect of dilution on rates)

Pure phenol: 11.42 mol. l.$^{-1}$ Diluent: benzene

Total flow: 0.43 cc. min.$^{-1}$ T: 414°C.

v in mol. min.$^{-1}$ (g. cat.)$^{-1}$ Extent of reaction in %

c_R	x	$10^5\, v$ (measured)	$10^5\, v$ (corrected)
11.42	7	4.52	5.20
8.00	9.5	4.34	5.25
6.86	11	4.25	5.25
5.72	12.5	4.08	5.20
3.90	17	3.72	5.15

If the data are corrected by means of other data presented later (see Fig. 24), the correction taking into account the change in extent of reaction, the initial rates are indeed indentical. Thus, under these conditions, the catalyst is completely saturated. The reaction rate per gram of catalyst gives the value of the rate constant k:

$$k = 5.2 \text{ mol. phenol (g. catalyst)}^{-1} \text{ min.}^{-1} \times 10^{-5}$$

Subsequent experiments gave the value of 4.6 which will be adopted in what follows. To determine the order of reaction on the catalyst, another component must be added to the reactant so as to modify its concentration in the adsorbed phase. To this end, a foreign substance or one of the products may be used since without both products the reverse reaction cannot take place. The equation that must be verified is:

$$v = k\{b_R c_R/(b_R c_R + b_P c_P)\}^n$$

The results obtained with diphenyl ether are shown in Table IV. They are

TABLE IV

Dehydration of Phenol on Thoria in the Presence of Diphenyl Ether

R = phenol Concentrations in mol. l.$^{-1}$

P = diphenyl ether k = 4.6 mol. min.$^{-1}$ (g. cat.)$^{-1}$

$[R]_0$ and $[P]_0$ = initial concentrations Data in column 4 are averages between initial and actual values.

$[R]_0$	$[P]_0$	$[R]$	$10 \times [\bar{P}]/[\bar{R}]$	$v \times 10^5$	b_P/b_R
10 10	0.82	8.6	0.91	2 56	3.7
9.05	1 29	7.9	1.73	1.98	3.1
8 50	1.54	7.6	2.15	1.54	3.4
7.87	1.94	7.07	2.73	1.37	3.1
7.15	2.34	6.6	3.53	0.93	3.4

also shown in Figure 23 together with data obtained for water. First it is found that a satisfactory fit of the data is obtained for second-order kinetics. Then the relative adsorption coefficients are:

$$b(\text{diphenyl ether})/b(\text{phenol}) = 3.3 \qquad b(\text{water})/b(\text{phenol}) = 0.64$$

In the experiments with water, it is necessary to correct for the back-reaction and the relative adsorption coefficient of water becomes 0.42.

Since now the rate constant is known together with the relative adsorption coefficients of both products, it is possible to calculate the rate at which the forward reaction would proceed if it could be studied independently. This rate is represented by curve 1 of Figure 24.

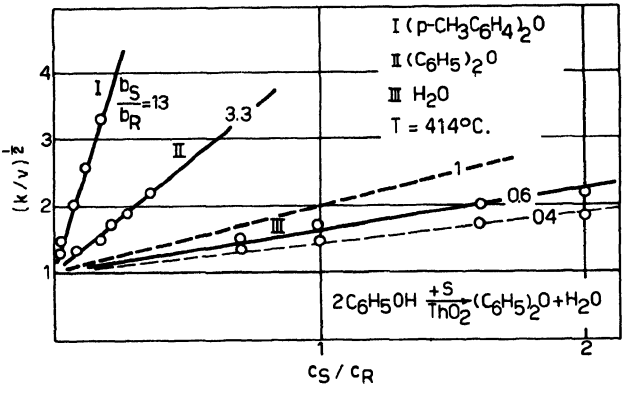

Fig. 23

Since the kinetics of forward and backward reactions must be consistent with the equilibrium relation, we can conclude from previous results that the rate of the reverse reaction should be expressed by the equation:

$$\overleftarrow{v} = \overleftarrow{k} \quad \{(b_P c_P \times b_Q c_Q)/(b_R c_R + b_P c_P + b_Q c_Q)^2\}$$

In order to verify this point, first the pure products will be used without the reactant that they regenerate. The rate will be a maximum when both products are adsorbed on the catalyst in stoichiometric proportion.

Results for initial rates (Fig. 25) indicate that the maximum rate is found in mixtures deficient in diphenyl ether. The data, while lacking the precision of those shown in Figure 23, are located in the vicinity of a curve calculated with a ratio of adsorption coefficients equal to seven This is indeed the experimental value found earlier: 3.3/0.42 = 7.8. Since the experiments also give the rate constant for the reverse reaction and since the relative adsorption coefficients of all components taking part in the re-

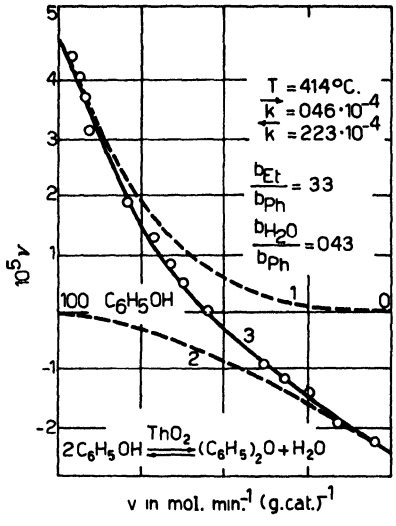

Fig. 24

action are known, the rate at which the reverse reaction would proceed if it could be studied separately can be calculated. The result of this calculation is curve 2 of Figure 24. Finally, the difference between forward and backward rates gives the net rate of dehydration of phenol as a function of the extent of reaction. The theoretical curve is curve 3 of Figure 24. The points on this curve are experimental data and the agreement between calculated and measured values illustrates the self-consistency of the kinetic constants. From this curve, the composition of the equilibrium mixture can also be calculated: it is given by the intersection of curve 3 with the

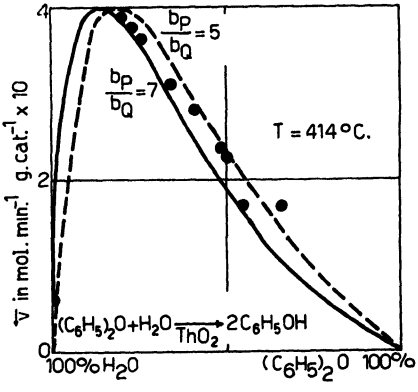

Fig. 25

horizontal axis, since at that point the net rate becomes equal to zero. The calculated value is 55% phenol in the equilibrium mixture. The experimental value is 57%.

The mode of action of the catalyst can be clarified if the equilibrium constant is expressed in terms of the rate constants of the purely thermal processes and also in terms of the catalyst constants. The equilibrium constant K is related in a general way to the rate constants of the thermal processes:

$$K = (\vec{k}/\overleftarrow{k})^{n}_{\text{thermal}}$$

on the other hand, the kinetic expressions of the forward and backward catalytic reaction lead to

$$K = (\vec{k}/\overleftarrow{k})_{\text{cat.}}\,(b_{\text{R}}^{2}/b_{\text{P}}b_{\text{Q}})$$

If then the ratio of the thermal constants is different from the catalytic constants, the adsorption coefficients which also depend on the nature of the catalyst will adjust themselves in such a way that the thermodynamic requirements be satisfied.

The effect of temperature on the equilibrium constant is determined by the heat of reaction, a quantity characterizing the reaction under study. The activation energies of the opposed reactions and the heats of adsorption of the various components must be such that they also reproduce the heat of reaction when properly combined.

Parallel Reactions. There exist several types of parallel reactions. First, a single reactant or several reactants may react on the catalyst following different paths. Secondly, several independent reactants or groups of reactants may compete for reactive sites on the catalyst. Thirdly, several independent reactants compete for the catalyst and for a common reactant. These cases, if only two product components are considered, can be represented schematically as follows:

$$\text{R} + \text{K}\begin{matrix}\nearrow \text{P} \\ \searrow \text{Q}\end{matrix} \qquad \begin{matrix}\text{R} \\ \text{T}\end{matrix} + \text{K}\begin{matrix}\nearrow \text{P} \\ \searrow \text{Q}\end{matrix} \qquad \begin{matrix}\text{R} \\ \text{T}\end{matrix} + \text{K} + \text{X}\begin{matrix}\nearrow \text{P} \\ \searrow \text{Q}\end{matrix}$$

The most general kinetic expression corresponds to the last alternative. If the reactions are all of first order with respect to each reactant, the rate of formation of each product is given by:

$$d[\text{P}]/dt = k_{\text{R}}\{(b_{\text{R}}c_{\text{R}} \times b_{\text{X}}c_{\text{X}})/(1 + \Sigma b_i c_i)^2\}$$

and

$$d[\text{Q}]/dt = k_{\text{T}}\{(b_{\text{T}}c_{\text{T}} \times b_{\text{X}}c_{\text{X}})/(1 + \Sigma b_i c_i)^2\}$$

This type of transformation raises two kinetic problems: the measurements of the total rate at which the system changes with time, and the determination of the relative rate at which the competing reactants are consumed. This second problem usually comes first in the kinetic analysis and it will be treated before the other.

When the competing reactants are of the same order with respect to both the catalyst and the common reactant, the ratio of reaction rates is given by:

$$d[P]/d[Q] = k_R b_R c_R / k_T b_T c_T$$

According to this expression, a determination of the relative reactivity of the competing substances would require a measurement of the instantaneous rates of reaction of these two substances. This cannot usually be done and, in general, the problem is solved by the analysis of samples taken at time t. Then the preceding expression must be integrated:

$$S = k_R b_R / k_T b_T = (\log [R]_0 - \log [R]_t)/(\log [T]_0 - \log [T]_t)$$

TABLE V

Competitive Dehydrogenation of Alcohols on Nickel

R = isopropanol P = acetone

T = 4-methyl-2-pentanol Q = 4-methyl-2-pentanone

[P]	[Q]	log $[R]_0/[R]_t$	log $[T]_0/[T]_t$	$k_R b_R / k_T b_T$
	$[R]_0$ = 7.15 mol. l.$^{-1}$; $[T]_0$ = 3.58 mol. l.$^{-1}$; T = 90°C.			
0.29	0 059	0 01787	0.00647	2.77
0.37	0 070	0.02284	0.00860	2.65
0 50	0.113	0 03141	0.01321	2.38
0.70	0.140	0.04571	0.01703	2.69
0.86	0.180	0.05614	0.02243	2.52
	$[R]_0$ = 3.04 mol. l.$^{-1}$; $(T)_0$ = 6.08 mol. l.$^{-1}$; T = 104°C.			
0.34	0.235	0.05077	0.01745	2.91
0.40	0.350	0 06145	0.02612	2.36
0.58	0.480	0 09307	0 03543	2.63
0 68	0 670	0 11092	0 05024	2.22
0.92	0.740	0.15655	0.05614	2.78
1.01	0.930	0.17522	0.07188	2.45
1 20	1.190	0 21458	0.09412	2.30
	$[R]_0$ = 1.73 mol. l.$^{-1}$; $[T]_0$ = 6.85 mol. l.$^{-1}$; T = 110°C.			
0 33	0.47	0.09272	0.03100	2.96
0 42	0 62	0 12090	0.04100	2.94
0 46	0.87	0.13001	0.05680	2.30
0 61	1.07	0.19089	0.07262	2.63
0.76	1.20	0.23930	0.08350	2.85
0.95	1.90	0.35050	0.13194	2.65

In this equation, S is a measure of the selectivity of the catalyst and subscripts 0 and t refer to zero time and time t, respectively.

As an example, let us consider the dehydrogenation of secondary alcohols (25). Table V shows the data relating to the pair isopropanol and 4-methyl-2-pentanol. These data are summarized in Table VI which also gives results for the pairs: 4-methyl-2-pentanol/2-butanol and isopropanol/2-butanol. It is seen in Table V that the ratio of reactivities of the two alcohols stays constant during the reaction as predicted by theory. Also, in the case of aliphatic alcohols, the relative reactivities do not change with temperature.

From the data of Table VI, it can be checked that the relative reactivity of two alcohols obtained by direct observation agrees with that calculated if each alcohol is compared in turn to a third one: (4.60/1.70) = 2.70.

TABLE VI

Relative Adsorption Coefficient and Reactivities of Secondary Alcohols on Nickel

x = extent of reaction in %

T = reaction temperature in °C.

Concentration in mol. $l.^{-1}$

$[R]_0$	$[T]_0$	T	x	$k_R b_R / k_T b_T$
	R = isopropanol	T = 4-methyl-2-pentanol		
1.73	6.85	110	32	2.72
3.04	6.08	104	26	2.52
7.15	3.58	90	10	2.62
	R = 4-methyl-2-pentanol	T = 2-butanol		
6.50	3.25	100	18	1.70
	R = isopropanol	T = 2-butanol		
8.20	4 10	85	9	4.56
9.33	3 11	83	7	4.62
3.85	7.70	88	9	4.62

The total rate of reaction is equal to the sum of competing reactions. These are not the rates that would be measured separately but rates in the complex mixture. Generally, the total rate is given by the equation:

$$v = v_R + v_T = \{(k_R b_R c_R + k_T b_T c_T)\, b_X c_X\}/(1 + \Sigma b_i c_i)^2 \qquad (17)$$

Since the total rate is determined not only by the rate constants but by the adsorption coefficients, several cases may occur. The most interesting corresponds to the case where the less reactive substance is also the more strongly adsorbed. Then, as it is consumed, it makes room on the surface for the reactant with the larger rate constant. If products are weakly

adsorbed, the reaction rate increases as the transformation proceeds. This phenomenon is particularly interesting since usually the rate decreases with time either because reactants are consumed by the reaction or because of the accumulation of products, or as a result of catalyst deactivation.

In order to observe this phenomenon, a number of favorable circumstances are required. They are realized in the liquid phase hydrogenation of aromatic hydrocarbons on nickel, in particular in the competitive hydrogenation of tetralin and *p*-xylene (26). In the liquid phase, the catalyst is completely saturated and the naphthenes exert no inhibiting effect ($b_P c_P = 0$) as indicated by the fact that the order of reaction remains zero with respect to a pure aromatic compound (Fig. 12).

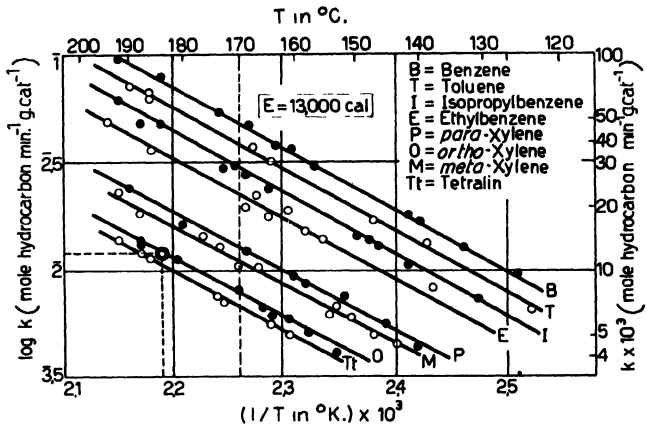

Fig. 26

It will also be noted that the reaction is of zero order with respect to hydrogen. This fact common to all aromatic hydrocarbons is difficult to reconcile with the theory of simultaneous adsorption. Nevertheless, it brings about a fortunate simplification since the reactions may be treated as first order reaction on the catalyst.

The over-all rate can now be written in the form:

$$v = \frac{k_R(b_R/b_T)\{c_R/(c_R + c_T)\} + k_T\{c_T/(c_R + c_T)\}}{(b_R/b_T)\{c_R/(c_R + c_T)\} + c_T/(c_R + c_T)}$$

The reactant concentrations are determined analytically so that the rate constants and the ratio of adsorption coefficients must be measured separately. The rate constant k can be obtained easily for each hydrocarbon since the kinetics are particularly simple: it is equal to the rate proportional to one gram of catalyst. At 170°C., the following data can be derived from

Figure 26: k_T = 12.9 moles hydrocarbon min.$^{-1}$ (g. cat.)$^{-1}$ × 10^{-3} for *p*-xylene, and k_R = 6.7 in the same units for tetralin.

The kinetic analysis of the data obtained in the competitive hydrogenation is shown in the first six columns of Table VII. The ratio of reactivities

TABLE VII

Competitive Hydrogenation of Tetralin and *p*-Xylene on Nickel

R = tetralin
T = *p*-xylene
k_R = 6.7
k_T = 12.9

Concentration in g. l.$^{-1}$
x = extent of reaction in %
v and k in moles of hydrocarbon min.$^{-1}$ (g. cat.)$^{-1}$ × 10^{-3}

[R]	[T]	x	$\log [R]_0/[R]_t$	$\log [T]_0/[T]_t$	$\frac{k_R b_R}{k_T b_T}$	$v_{calc.}$	$v_{exp.}$
280	610					8 5	8 5
235	566	10	0.069	0.025	2.76	8 9	8.8
139	462	32	0.280	0.098	2 86	9 4	9 4
57	334	56	0 650	0.221	2 94	10.4	10 4
10	159	81	1.390	0.525	2.65	11 4	11 3

is 2.8 in favor of tetralin. It must be noted that in the present case the reaction is accompanied by a slight volume increase so that the number of molecules rather than the concentrations must be considered here. Since the rate constants are known, the ratio of adsorption coefficients can be calculated. It is 5.4 in favor of tetralin. Thus this substance is more reactive, although its rate constant is smaller because it is more strongly adsorbed. All the unknowns are now available and the results of the calculation of the total rate are given in column 7 of Table VII; the predicted rate of hydrogenation indeed goes up as the reaction proceeds. This prediction can be checked experimentally by measuring the amount of hydrogen absorbed at various stages of the conversion of the mixture. The agreement between calculated and experimental values is excellent.

Consecutive Reactions. The study of processes which exhibit different kinetics in their successive steps is very complicated and only the case of competitive consecutive reactions of indentical order will be considered in the next paragraph.

Consider the reaction scheme:

$$A \xrightarrow{+X} B \xrightarrow{+X} C$$

where the primary reactant and its first product react on the catalyst with a common reactant X. The rate of change of A is given by:

$$v_A = -dc_A/dt = k_A\{(b_A c_A \times b_X c_X)/(1 + \Sigma b_i c_i)^2\} \qquad (18)$$

The rate of appearance of the final product C is:

$$dc_C/dt = k_B\{(b_B c_B \times b_X c_X)/(1 + \Sigma b_i c_i)^2\} \quad (19)$$

The rate of accumulation of the first product B is the difference between its rate of formation from A and its rate of transformation into C:

$$dc_B/dt = -dc_A/dt - dc_C/dt = \{(k_A b_A c_A - k_B b_B c_B)\, b_X c_X\}/(1 + \Sigma b_i c_i)^2 \quad (20)$$

The study of this phenomenon raises two problems: the determination of the total rate of disappearance of the common reactant and the determination of the relative rates of reaction of the competing substances. As in the case of parallel reactions, it is the second problem which offers the most interest for the kinetic analysis of the phenomenon. It is also this aspect of the phenomenon which will be illustrated in more detailed fashion.

The change in concentration of the first product with respect to that of the primary reactant is obtained by way of Equations (18) and (20):

$$dc_B/dc_A = -1 + k_B b_B c_B/k_A b_A c_A = -1 + K(c_B/c_A) \quad (21)$$

where K is defined as:

$$K = k_B b_B/k_A b_A$$

This quantity effectively measures the relative reactivity of the substances involved. If only A is present initially ($c_B = 0$), the solution of Equation (21) is:

$$c_B = \{1/(K - 1)\}(c_A - c_A^K)$$

This relation is represented graphically on Figure 27 which shows a number of curves calculated for several values of the parameter K. These curves present a maximum: at that point, the rate of accumulation of B becomes equal to zero and from Equation (20) it follows that:

$$k_A b_A c_A = k_B b_B c_B$$

or

$$k_A b_A/k_B b_B = c_B/c_A$$

At the maximum, the ratio of the concentrations of intermediate product and primary reactant is equal to the inverse of their reactivities. When the first product exhibits a small reactivity ($K \longrightarrow 0$), the maximum occurs when the primary reactant is practically totally consumed. Then the intermediate product appears as a stable product. When the first product exhibits a large reactivity ($K \longrightarrow \infty$), the maximum becomes smaller and is shifted toward the origin. The case illustrates the conditions

postulated by the hypothesis of the steady state used in kinetics to establish the schemes of reaction.

The representation illustrated in Figure 27 has been very fruitful in the kinetic analysis of consecutive reactions. If the analytical values of the concentrations of remaining reactant are plotted versus those pertaining to the first product, a curve is obtained which gives immediately the value of the parameter K. When the system of reactions obeys the proposed kinetics, it is not necessary to establish the whole curve experimentally. All that is necessary is to define a significant portion of the curve. The maximum is then determined by the intersection of the curve with the locus of maxima shown by the dashed curve in Figure 27.

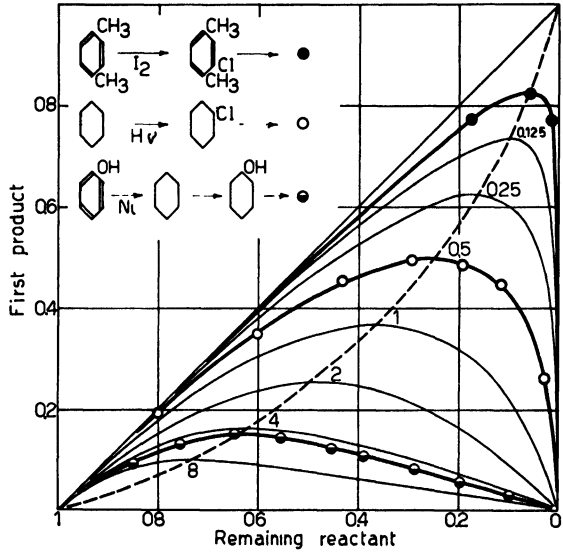

Fig. 27

The data obtained in the hydrogenation, on nickel, of phenol into cyclohexanol via cyclohexanone as an intermediate (27) are represented on Figure 27. In order to show the generality of the method, the results obtained in a photochemical reaction (28) are also shown together with those relative to a homogeneous catalytic reaction (29).

For a more complete analysis of the phenomenon, it is necessary to determine the absolute values of the rate constants or their ratio. This problem is similar to the problem of parallel reactions solved in the preceding paragraph and there is no need to repeat the reasoning here. Let us note only that the first product must be isolated in order to determine the

rate constant of the second step. In order to determine the rate constant relative to the primary reactant, it is required to operate in the range of initial kinetics so as to avoid interference by the first product. It will thus be necessary to limit the degree of conversion and this limitation is more severe the more reactive is the first product.

For consecutive reactions, as was the case for parallel reactions, the total rate equal to the rate of disappearance of the common reactant is the sum of the rates of individual steps:

$$v = \{(k_A b_A c_A + k_B b_B c_B) b_X c_X\}/(1 + \Sigma b_i c_i)^2$$

If the data provide not the rates but the concentrations as a function of time, the integrated expressions which must be used for their interpretation will be very complex. Indeed, in consecutive reactions, the concentration of intermediate product depends on that of primary reactant. For a simple case, namely two first-order reactions on a saturated catalyst, the integrated equation is:

$$t = \frac{1}{k}\left\{-\frac{b_C}{b_A}\ln c_A + \left(1 + \frac{b_B - Kb_C}{(K-1)b_A}\right)(1 - c_A) - \frac{b_B - b_C}{K(K-1)b_A}(1 - c_A^K)\right\}$$

Such an expression is much too complex to be useful in the kinetic analysis of experimental data. Yet, if the constants that it contains are known, it gives a representation of the process as a function of time. Figure 28 refers to one of the experiments shown in Figure 27, the agreement between calculated and experimental values is excellent.

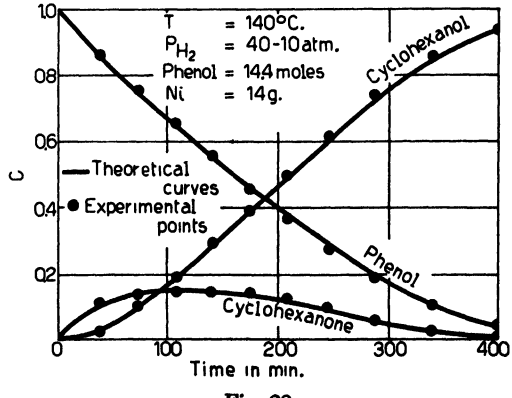

Fig. 28

C. NONIDEAL SYSTEMS

So far the possible effect of the nature of the homogeneous phase on the adsorption coefficient has not been considered in our treatment of adsorption on the catalyst. In the liquid phase, the adsorption coefficient can be regarded as the partition coefficient of the solute between the solvent and the catalyst surface. If the solvent has an affinity for the solute, the attraction between the latter and the surface will be reduced. On the contrary if the solution tends to show phase separation, the attraction between solute and surface may be enhanced. Since the solvent modifies the thermodynamic equilibrium for adsorption, the adsorption coefficients will be valid only for a given solvent-catalyst pair.

It could thus be expected that solvents might have an effect on catalytic changes. In fact, a solvent presenting a high affinity for a strongly adsorbed product of reaction would counteract the inhibiting effect of the latter on the catalytic process. Yet the effect could not be observed at first in the quantitative studies reported in the previous section This can be explained by the close resemblance between reactants and products such as, aromatic hydrocarbons and naphthenes, secondary alcohols and ketones, aromatic and naphthenic amines, etc. When however, reactants of a very different nature were studied, the effect appeared very clearly (30). This will be illustrated in this section.

Another expected phenomenon concerns the effect of a substance that would be strongly adsorbed physically and form a film at the catalyst surface. This film could act as a filter. It would let through a reactant for which it presents some affinity but would repel from the surface reactants of a different nature. This effect has also been observed. Substances acting in this manner will be called modifiers.

Effect of Solvent. To study the effect of the solvent, the method of competitive reaction has been used. Reactants of a different nature would then exhibit clearly any differential effect. Acetone (A) and cyclohexene (B) were selected as typical reactants in catalytic hydrogenation. They react at room temperature, low pressures, and at comparable rates ($k_A = 0.4k_B$). Moreover their mixtures can be analyzed readily.

The choice of solvents was as wide as possible among substances which do not react with reactants, products, or catalyst. Relatively large amounts of solvent (60 cc. versus 10 cc. of reactants) were used so that the nature of the medium would not change appreciably during the course of the reaction. Table VIII shows the experimental conditions and data. The latter were analyzed as shown above in the paragraph on parallel reactions It is seen that, with each solvent, the ratio of reactivities stays quite constant till one of the reactants is exhausted. But as the solvent is changed, the ratio of reactivities changes very much, by more than an order

TABLE VIII

Effect of Solvents on Catalytic Selectivity

R = acetone, 10 cc. Amount solvent used: 60 cc.
T = cyclohexene, 10 cc. T = 25°C.
Concentrations in g. $l.^{-1}$

[R]	[T]	$\log [R]_0/[R]_t$	$\log [T]_0/[T]_t$	$k_T b_T/k_R b_R$
		Solvent: cyclohexane		
91.5	95			
84.0	84	0.032	0.054	1.69
76.5	70	0.078	0.153	1.70
69.5	59	0.120	0.207	1.72
63.8	49	0.157	0.288	1.83
52.7	36	0.240	0.422	1.76
42.8	27	0.330	0.580	1.76
36.5	17	0.399	0.748	1.87
27.8	10	0.517	0.950	1.83
11 0	2	0.920	1.680	1.83
		Solvent: dioxane		
103	106			
102 5	82	0.006	0.112	18.5
99 5	59	0.015	0.255	17.0
97	37	0.026	0.457	17.5
93	14	0 045	0 879	19.5
88.5	5	0 066	1.326	20.0
		Solvent: benzene		
103	106			
100.5	86	0.011	0.091	8.3
98	65	0.022	0.213	9.7
94	42	0.040	0.402	10.0
83.5	18	0.091	0.770	9.0
69.5	3	0.171	1.584	9.3
		Solvent: dimethylaniline		
95	100			
83.5	84	0.057	0.076	1.32
71	69	0.126	0.162	1.28
59.5	53	0.204	0.276	1.36
45	42	0.325	0.377	1.16

of magnitude for the solvents used. At first glance, this effect is susceptible to several interpretations. The role of the solvent might be due, as expected, to a modification of adsorption coefficients but it might also be caused by a change of rate constants or a simultaneous variation of both parameters.

In order to examine the effect of solvents, both reactants were studied

separately. Table IX shows the rates observed with pure cyclohexene or with cyclohexene in three different solvents. It is seen that the rates are identical except with isopropanol for which the rate is slightly higher. This difference is probably due to the presence in hydrocarbons of small amounts of water which exerts a modifying effect on the rate as shown later. Table IX also shows the results obtained in the hydrogenation of acetone dissolved in benzene and isopropanol. Again rates are almost identical in spite of the very different nature of both solvents. Consequently, the effect of the solvents consists of altering the adsorption coefficients and it is because of these changes that reactivities and the catalytic selectivity are modified.

TABLE IX

Rate Constants in Different Solvents

R = acetone k in mol. min.$^{-1}$ (g. cat.)$^{-1}$ $\times 10^{-3}$
T = cyclohexene T = 25°C.

	Cyclohexene	Cyclohexane	Benzene	Isopropanol
k_T	4.3	4.3	4.4	4.6
k_R		1.7		1.7

These facts agree with what is known about the relative affinities of solvents and solutes. In cyclohexane, acetone shows a tendency to phase separation and this is indicated by the vapor pressures of these solutions. On the contrary, cyclohexane and cyclohexene form ideal solutions. As a result of this difference in affinities, acetone is repelled to the catalyst surface while cyclohexene is kept in solution. Also, the total rate of reaction in this system is smaller (2.8 mol. min.$^{-1}$ g.$^{-1}$ $\times 10^{-3}$), approaching that of acetone (1.7). In isopropyl alcohol the situation is reversed, and cyclohexene is repelled toward the catalyst surface. Then the total rate is relatively higher (3.5), approaching that of cyclohexene taken separately (4.6).

Effect of Modifiers. It can also be expected that the adsorbed layer will play a role in catalysis by changing the relative reactivity of competing reactants. This effect has indeed been observed as indicated by the results in Table X. It is known that the additives are strongly adsorbed because the concentrations of modifiers in the homogeneous phase are markedly reduced by the presence of the catalyst. Also, the initial rate of reaction in the mixture ($v_{init.}$) is always substantially smaller than that of pure cyclohexene ($k_B/v_{init.}$) > 1.

It can also be seen that the additives investigated have a much larger

TABLE X

Effect of Modifiers on Catalytic Selectivity

R = acetone, 10 cc. T = cyclohexene, 10 cc.

Amount solvent used: 60 cc. Concentration in g. $l.^{-1}$

[R]	[T]	log $[R]_0/[R]_t$	log $[T]_0/[T]_t$	$\frac{k_T b_T}{k_R b_R}$
	Modifier: pyridine, 0.078 mol. $l.^{-1}$			
	Solvent: cyclohexane	$k_T/v_{init.} = 30$		
94 5	101.5			
77.2	96.7	0.087	0.021	0.24
54.0	90	0.293	0.052	0.21
31.4	80.4	0.473	0.103	0.22
19 5	74	0.686	0.139	0.21
	Modifier: piperidine carbonate, 0.043 mol. $l.^{-1}$			
	Solvent: cyclohexane	$k_T/v_{init.} = 5$		
86.4	96			
70 8	94.8	0.085	0.005	0.059
55.6	93.1	0.191	0.013	0.068
40	90 8	0.335	0.024	0.071
27 8	88	0.502	0.036	0.077
11	84	0 895	0.058	0.065
	Modifier: stearic acid, 0.044 mol. $l.^{-1}$			
	Solvent: cyclohexane	$k_T/v_{init.} = 8$		
80.5	93			
73.6	54	0 039	0.261	6.7
67.2	30	0.079	0.491	6.2
54.5	6	0.170	1.190	7.0
40	0			
	Modifier: stearic acid, 0.090 mol. $l.^{-1}$			
	Solvent: dioxane	$k_T/v_{init.} = 16$		
87	87			
86	48	0 005	0.258	52
84.6	21	0.012	0.617	51
81.2	26	0.030	1.160	40

effect than solvents on the relative reactivity. The selectivity is such that in certain cases, the second reactant participates noticeably in the reaction only after the first reactant is practically entirely consumed. The effect favors one or the other reactant. These results may be explained qualitatively. Pyridine, and especially piperidine carbonate because of its salt character, repel cyclohexene but let the more polar acetone through. On the contrary, stearic, acid, with the very pronounced character of a hydrocarbon, acts in the opposite direction. It is then natural to try to combine

the solvent effect and the effect of modifiers: in the presence of both dioxane and stearic acid, cyclohexene is transformed with a very high selectivity. Thus, by a suitable combination of both effects (solvent and modifier), the ratio of reactivities, i.e., the catalytic selectivity has been changed three thousand-fold. This is the limit of our experimental technique but even wider differences are conceivable.

So far we have considered only separate actions but it is clear that a given substance can act both as a solvent and as a modifier. This is, for instance, the case of dimethylaniline. It can be checked that this substance is effectively adsorbed. Thus, in the dehydrogenation of isopropyl alcohol, the first fractions of dimethylaniline which are adsorbed on the catalyst considerably reduce the rate of reaction whereas subsequent fractions have a progressively lower effect. Consequently, dimethylaniline can be used as a solvent in this reaction although it will decrease the reaction rate.

IV. APPLICATIONS

In its first phase, the kinetic analysis of catalytic reactions is a tool that gives information on the reaction scheme of the process under study and on the eventual appearance of intermediates that can be isolated. In its second quantitative phase, the kinetic study isolates the pertinent reaction or system of reactions excluding parasitic reactions in order to determine the best conditions of operation which maximize energetic, product, and hourly yields.

In the laboratory, this study will not generally be exhaustive and the solution will keep an approximate character. Indeed, the weeks or months of work required to elucidate the kinetics of a catalytic reaction can hardly be justified to achieve an improvement in the yield of an occasional laboratory synthesis. On the contrary, in the case of an industrial operation involving a large daily production over a long period of time, the expenditure appropriated for an exhaustive study is amply rewarded by the savings in the plant due to a higher yield or a simplification in the various operations required. It must be emphasized that a 95% yield on a weight basis means more than a 5% loss in raw material. Indeed, such a yield usually necessitates a purification of the product by separations that often are costly and may even be prohibitive. If this loss is shown to be unavoidable by the kinetic research, it may indicate that the process is competitive since similar limitations would be encountered by an eventual competitor.

The kinetic analysis in fundamental investigation will now be illustrated by examples which show its application to industrial practice.

1. Hydrogenation of Olefins (31)

The hydrogenation of cyclohexene on nickel at low temperature (<70°C.) so that disproportionation into benzene and cyclohexane can be avoided, is a zero-order reaction with respect to cyclohexene. A saw-toothed diagram similar to that of Figure 12 is obtained. By contrast, in the hydrogenation of 1-octene, a sharp decrease in rate occurs during the reaction as shown in Figure 29A. This phenomenon can be interpreted in several ways. For instance, it could be due to the presence of various isomers at the start of reaction since it is difficult to obtain pure 1-octene. In fact, infrared spectra (Figure 29B) show that reactants contain 98% 1-octene. Therefore it is during the reaction that one or several isomers may have ap-

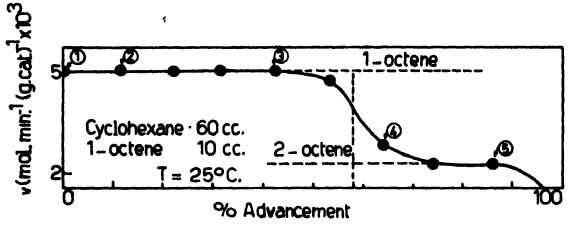

Fig. 29A

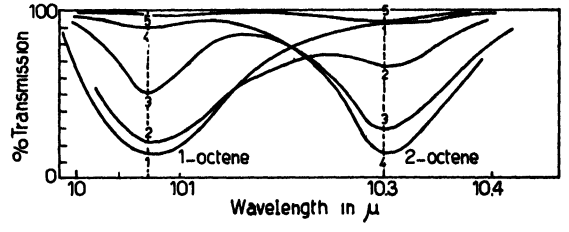

Fig. 29B

peared. This is revealed by the infrared spectra of samples taken during the transformation. In particular, the fourth sample corresponding to an overall conversion of 63% shows only traces of 1-octene. Consequently, in parallel with the hydrogenation of 1-octene, isomerization into 2-octene or other isomers must take place and these isomers must, in turn, be hydrogenated to form octane.

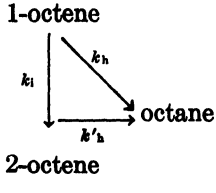

Figure 29A shows that the first step is characterized by a rate equal to 5.1 mol. min.$^{-1}$ (g. cat.)$^{-1}$ corresponding to the first plateau. The second plateau, related to the hydrogenation of the isomer, shows a rate equal to 2.3 in the same units. This last figure can be checked by studying the rate of hydrogenation of the particular isomer alone. To do this, 1-octene is placed with relatively large amounts of catalyst. After filtration, reaction is allowed to take place under the usual conditions. These experiments give the expected figure for the rate of hydrogenation, 2.2 mol. min.$^{-1}$ (g. cat.).$^{-1}$

These details on the isomerizing activity of nickel are obviously of great interest to the study of the hydrogenation of olefinic bonds. This has been studied extensively in the case of ethylene, and the facts presented here may throw more light on the intimate mechanism of the reaction.

2. Hydrogenation of Nitrobenzene

Another example of application of kinetic analysis is provided by the hydrogenation of nitrobenzene on metallic catalysts (32). Several studies have been devoted to the hydrogenation of nitrobenzene to give aniline. Nevertheless, according to the principle of least structural change, it is clear that the reaction cannot take place in a single step but must involve intermediates probably identical to those obtained by electrochemical hydrogenation and by the action of nascent hydrogen. That these intermediates have not been isolated or even detected in ther eaction on nickel can be explained by the fact that nitrobenzene exerts an inhibiting effect on the catalyst which is already active at room temperature. This inhibition must then be counteracted by a rise in temperature (T' = 200°C.). As a result, the intermediates become so much more reactive that aniline and its hydrogenation products become the only detectable products. As the temperature of reaction is progressively lowered, chemical analysis reveals a more complex reaction scheme. At first, the analysis was directed only toward the remaining nitrobenzene and the aniline formed. The data show that the material balance is incomplete and necessitates the presence of intermediates or secondary products.

The results are represented graphically on Figure 30 following the method used in the treatment of consecutive reactions (Fig. 27). It is seen at once that the curves expressing the lack of stoichiometric material balance present a maximum as would correspond to the formation of an intermediate product. Yet, the data cannot be fitted to the network of curves calculated for a system of first-order consecutive reactions. The reactions may therefore not be a simple succession of consecutive steps or their order might be different from unity.

The discrepancy can be explained if the behavior at the end of reaction is examined more carefully. The final product cannot be aniline exclusively, as seen on the right ordinate axis where it appears that another product exists at the end of the reaction. The identification of the species accounting for the incomplete material balance reveals that phenylhydroxylamine was formed in quantities up to 70% of theoretical yield under certain conditions. Moreover, the product remaining at the end of reaction besides aniline was found to be hydrazobenzene. These facts indicate that there must be two parallel paths of reaction: one through phenylhydroxylamine and one through hydrazobenzene.

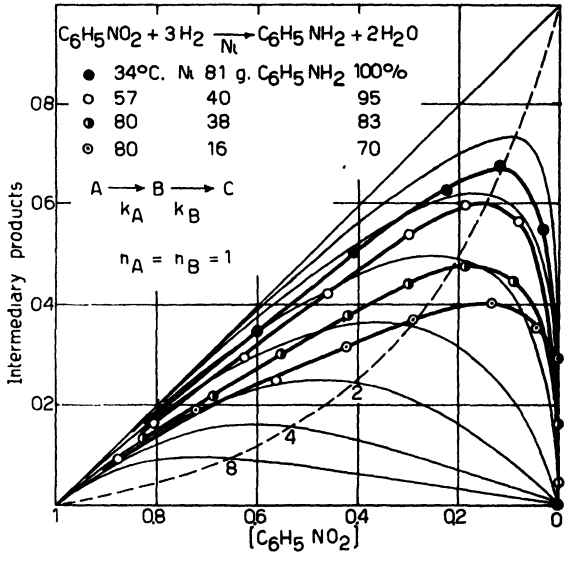

Fig. 30

The direct path itself must involve more intermediates as can be guessed from the participation of three molecules in the reduction of nitrobenzene to aniline:

$$C_6H_5NO_2 \xrightarrow{+H_2} ? \xrightarrow{+H_2} C_6H_5NHOH \xrightarrow{+H_2} C_6H_5NH_2$$

The measurements performed on the mixture catalyzed by nickel did not succeed in revealing the expected nitrosobenzene. This failure may be due to the very large reactivity of this compound under these conditions. That this explanation is correct is proved by the fact that in a mixture of nitrobenzene and nitrosobenzene, the latter reacts completely before the former starts reacting appreciably. The kinetic behavior of nitrosobenzene

agrees therefore with the observations made in the sequence of reactions. Another argument in favor of the proposed scheme is that, on platinum, the green color of nitrosobenzene can be observed for a while during the hydrogenation of nitrobenzene.

The series of compounds with two nitrogen atoms could find its origin in the noncatalytic reaction between nitrosobenzene and phenylhydroxylamine. The latter would then be hydrogenated into azobenzene and hydrazobenzene. Although the two compounds preceding this last one have not been found directly, their kinetic behavior is compatible with their postulated intervention in the chain of processes.

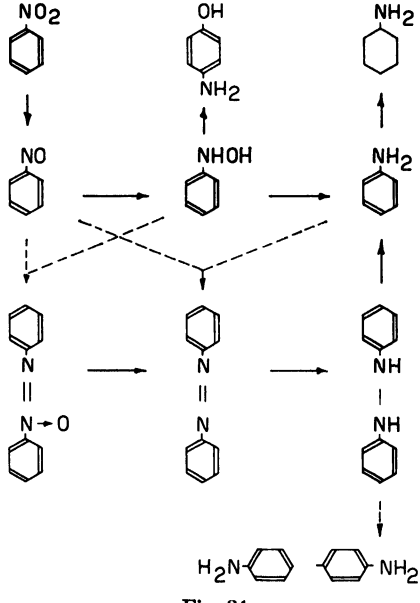

Fig. 31

A summary of the steps just discussed and a few of the possible reactions are shown in Figure 31. The results are sufficient to determine the conditions required to produce phenylhydroxylamine industrially with good yields. Moreover, they give indications on what should be done to obtain some other compounds. In fact it is known that the reaction between nitrosobenzene and phenylhydroxylamine is particularly rapid in basic media. Under such conditions then, the hydrogenation of nitrobenzene could be directed to the formation of hydrazobenzene, the intermediate required to obtain benzidine. Experiments based on this idea have been quite successful. They were carried out on platinum with which the re-

action scheme is similar to that just described, although reactivities are somewhat different (33). Conversely, in an acid medium, the reaction leading to phenylhydroxylamine could be favored. Nevertheless, this compound isomerizes to aminophenol in an acid medium so that the formation of aniline could then be prevented. Since nickel loses its activity in acid solutions it cannot be used in this case, but with platinum the expected results could be obtained successfully (33).

3. Dehydrogenation of Secondary Alcohols (34)

The various results presented in this chapter at several places can be used to design a new process to produce ketones industrially by dehydrogenation of secondary alcohols. Until recently, this reaction was carried out exclusively at high temperatures, i.e., 400 to 450°C. This mode of operation seemed compelling since at low temperatures, the equilibrium favors the hydrogenation of ketones. Yet, following the rule of Berthollet, it is possible to drive an equilibrated reaction to completion by elimination of one or several products from the system. By keeping the reaction mixture at its boiling point, it is easy to eliminate hydrogen. Table I for butanol and Figure 18 show that the reaction does take place but it slows down rapidly because of the preferential adsorption of the ketone on the catalyst. If both the ketone and the hydrogen are eliminated, the complete dehydrogenation of the alcohol can take place at relatively low temperature. Under these conditions, the boiling temperature which determines the rate of reaction is practically that of the pure alcohol.

Nevertheless, it is important to raise the temperature in order to increase the rate constant (E = 17.5 kcal., Fig. 20) and also to reduce the inhibition by the ketone ($\lambda_P - \lambda_R$ = 8.5 kcal., Fig. 22). This goal could be achieved by operating at higher pressures but this solution presents technical difficulties. It is simpler to use a solvent that is inert both chemically and catalytically. For isopropanol, decalin was chosen and the boiling point was thus raised from 82.5 to 150°C., a temperature which can be reached by economical steam heating.

The method of kinetic analysis presented in this chapter was used to determine all the kinetic constants required for the design and operation of the process.

The large scale reactor is based on the same principle as the laboratory apparatus (Fig. 16). Since it must remain in continuous operation, the alcohol feed rate must be equal to the rate of production of acetone. A steady state concentration of acetone is then set up in the reactor. It is determined by the rate of reaction and the efficiency of the column which removes it from the reactor. At the steady state, the reactor is fed at a

rate D and its product is a gaseous mixture with a mole fraction Y_P in acetone, calculated on the basis of the isopropanol–acetone mixture, the solvent being disregarded. The exit flow rate of acetone, i.e., the rate of reaction, is then DY_P. For a quantity m of catalyst, Equation (11) can be written as:

$$mk/DY_P = (b_R - b_P)/b_P + (b_P/b_R) \times (1/X_R)$$

where X_R is the mole fraction of alcohol in the liquid phase, based on the alcohol–acetone mixture.

Curve 1 in Figure 32A shows how, for a given amount of catalyst, the rate of reaction decreases as the acetone concentration in the mixture increases. Curve 2 shows how the amount of catalyst required to counteract the inhibition due to acetone must be raised to maintain a given hourly yield. From a purely kinetic standpoint, the steady state concentration of acetone should be kept as small as possible. But the cost of acetone separa-

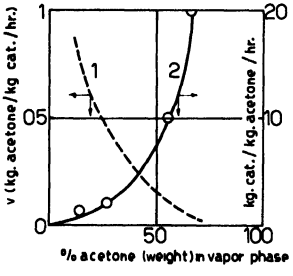

Fig. 32A

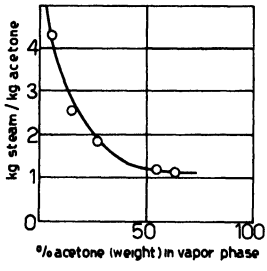

Fig. 32B

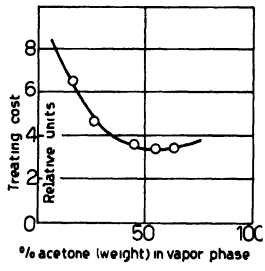

Fig. 32C

tion increases as the acetone concentration is reduced. The energy required is obtained by a classical column calculation. The result, expressed in kg. of steam is shown in Figure 32B. If now the costs of catalyst and steam are taken into account, the corresponding curves (Fig. 32B, Fig. 32A, curve 2) can be combined to form a single curve (Fig. 32C) giving the cost of the process for various acetone concentrations. The minimum of this curve determines the most economical operating conditions.

Naturally there are other technical and economical factors which will determine the economic balance of the process and will decide its ultimate design. The preceding considerations simply emphasize the capital role played by the kinetic data in a rational design. The rate of production was 0.05 kg./day in the laboratory. The pilot plant produced 50 kg./day. This was scaled up to 3,000 kg./day in the plant. The unit is represented schematically in Figure 33 showing the reactor, fractionating tower, hydrogen scrubber, and rectifying tower for acetone.

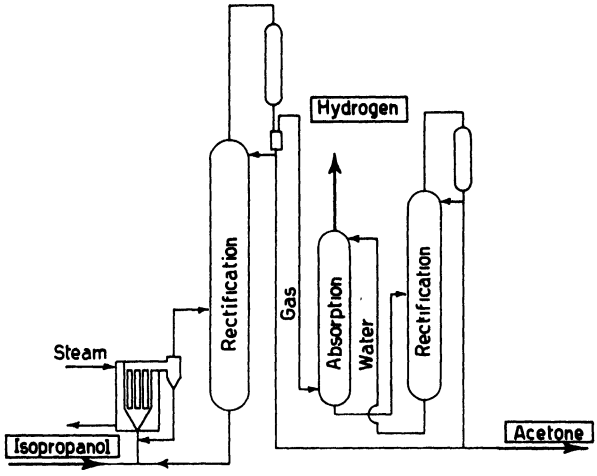

Fig. 33

This unit was started in 1954 and has been in operation since that time without any particular trouble in start-up or operation. This example illustrates the safeguards obtained by properly obtained fundamental kinetic data in the rational design of industrial processes.

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