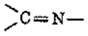
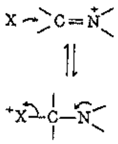
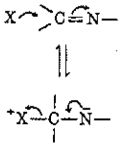
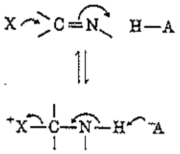
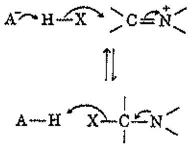
2. 	*Carbonyl derivatives*	*Acyl derivatives*
"Uncatalyzed" ($\alpha = 1$ for free imine)		
	Alkoxide and hydroxide	Alkoxide expulsion in the reaction of imido esters with basic amines Amine attack–imidates Hydroxide attack–imidates
Uncatalyzed		
	Imines and BH_4^- (probably) OH^- + benzylidene anilines, oximes (?)	
GAC-GBC		
	Thiosemicarbazones	
GBC-GAC		
	ROH Amines(?)	Alcohol expulsion in the reaction of imido esters with weakly basic amines ROH–amidinium ions ROH–imidates

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part four

11

Practical Kinetics

Kinetics may be approached either as a discipline unto itself or as a tool for the elucidation of reaction mechanism. The purpose of this chapter is to describe some elementary kinetic techniques and interpretations which are useful in the diagnosis of reaction mechanism. The author shares the healthy distrust of many students for proofs of reaction mechanism based on complicated kinetic equations which are difficult to understand in a concrete manner as a reflection of the observed behavior of a reaction. In fact, he has followed a rule of not finally accepting kinetic evidence for a proposed reaction mechanism unless he (1) can clearly see the relationship of the experimental observations to their kinetic description and presentation and (2) can understand the mechanistic significance of a particular type of kinetic behavior or equation in an intuitive, nonmathematical way. The consequences of this philosophy over a period of years have been that a few significant kinetic demonstrations of reaction mechanisms have not been accepted as soon as they deserved, but a far larger number, which later turned out to be incorrect, have been rightfully regarded with distrust because they failed to meet these criteria.

It is impossible to emphasize too strongly to the beginning experimentalist in this field the importance of obtaining and plotting data in such a way that the experimental manifestation of a particular kinetic observation is obvious and is of maximum size. For this reason, it is desirable to plot experimental results in a form as close to the raw data as possible in order to demonstrate a particular point. All too often, the use of mathematical functions of the observed rate constants, which are some distance removed from the experimental data, has led to incorrect conclusions based, perhaps, on some small systematic error which would have been obvious if the raw data had been plotted directly. In general, if one wishes to demonstrate the existence of a particular kinetic term in a reaction, it is desirable to choose experimental conditions such that at least a 50% change in observed rate is brought about by the variable which is being examined. The most convincing way to plot and present kinetic data is often in the form of uncorrected, experimental rate constants, with theoretical lines showing the calculated rate constants which would be expected in the presence and absence of this particular variable. Other types of linear plots are usually used to obtain numerical values of the rate constants, but even with these plots it is important to attempt to visualize the relationship of the experimental observations to the derived quantity which is being plotted.

For the application of kinetic techniques to the elucidation of reaction mechanism it is generally more useful to obtain five rate constants with an accuracy of ±5% than one point with an accuracy of ±1%. Experimental data obtained over a wide range of reaction conditions permit a clear-cut demonstration of the effect of a variable on the reaction rate and often reveal some unexpected result which leads to a more important conclusion than that which the experiment was originally intended to demonstrate.

The material in this chapter is elementary for any professional kineticist (which the author is not), but should provide enough background to understand and even to apply kinetic techniques for the elucidation of the mechanisms of a large number of reactions which take place in aqueous solution. The reader is referred elsewhere for more advanced experimental and theoretical treatments of reaction kinetics.[1]

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[1] A. A. Frost and R.G. Pearson, "Kinetics and Mechanism," 2d ed., John Wiley & Sons, Inc., New York, 1961; L. P. Hammett, "Physical Organic Chemistry," chap. 4, p. 96, McGraw-Hill Book Company, New York, 1940; S. L. Friess, E. S. Lewis, and A. Weissberger (eds.), "Technique of Organic Chemistry," 2d ed., vol. VIII, parts I and II, Interscience Publishers, Inc., New York, 1963; K.B. Wiberg, "Physical Organic Chemistry," part 3, p. 305, John Wiley & Sons, Inc., New York, 1964; I. Amdur and G. G. Hammes, "Chemical Kinetics: Principles and Selected Topics," McGraw-Hill Book Company, New York, 1966; E. L. King's short book on "How Chemical Reactions Occur" (W. A. Benjamin, Inc., New York, 1964) is an excellent and readable introduction for those with no previous experience with the subject.

A. RATES, RATE CONSTANTS, AND REACTION ORDER

In the simplest case the rate of reaction of two molecules A and B to form a product P in solution (equation 1) is proportional to the number of collisions of the two molecules with each other and is, therefore, proportional to the concentration of each of the reactants. This relationship is described in equation 2, in which the second-order rate constant k describes the proportionality of the rate to the concentrations of the two reacting molecules. If the concentrations of the reactants are expressed on the molar scale, the units of this rate constant are M^{-1} time^{-1}. The rate of a first-order reaction (equation 3) is proportional to the concentration of a single species and is described by a first-order rate constant with the dimensions of reciprocal time, such as sec^{-1} or min^{-1} (equation 4). Thus, the order of a reaction describes the number of molecules to which the reaction rate is proportional, as in equation 2 or 4, but it does not necessarily indicate the number of molecules involved in the reaction, because some molecules can react without affecting the rate (equations 5 and 6). A reaction is said to be zero order with respect to such a reactant.

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{P} \tag{1}$$

$$\text{Rate} = v = -\frac{d\mathrm{A}}{dt} = -\frac{d\mathrm{B}}{dt} = \frac{d\mathrm{P}}{dt} = k[\mathrm{A}][\mathrm{B}] \tag{2}$$

$$\mathrm{A} \longrightarrow \mathrm{P} \tag{3}$$

$$v = k[\mathrm{A}] \tag{4}$$

$$\mathrm{A} \xrightarrow[\text{slow}]{} \mathrm{A}^* \xrightarrow[\text{fast}]{+\mathrm{X}+\mathrm{Y}} \mathrm{P} \tag{5}$$

$$v = k[\mathrm{A}] \tag{6}$$

1. FIRST-ORDER REACTIONS

Equation 4 for a first-order reaction may be integrated from t_0 to the time of an experimental measurement according to equations 7 to 10, in which A_0 is the concentration of A at zero time. The

$$\int_{A_0}^{A} -\frac{d[A]}{[A]} = k \int_{t_0}^{t} dt \tag{7}$$

$$-\ln [A] + \ln A_0 = kt \tag{8}$$

$$\ln \frac{A_0}{[A]} = kt \tag{9}$$

$$[A] = A_0 e^{-kt} \tag{10}$$

variables in these equations are [A] and t, so that the concentration of A decreases exponentially and a plot of log [A] against t is linear with a slope of $-k/2.303$ (Fig. 1). The half-time of the reaction is the time at which the concentration of A has decreased to half its initial value, $0.5A_0$. Substitution in equation 9 gives equation 11 and shows that the half-time of a first-order reaction is

$$\ln \frac{A_0}{0.5A_0} = kt_{1/2} = \ln 2 = 0.693 \tag{11}$$

directly related to the first-order rate constant as shown in equation 12.

$$k = \frac{0.693}{t_{1/2}} \tag{12}$$

In practice, it is convenient to plot [A], or some experimental quantity which is directly proportional to [A], on semilogarithmic graph paper as a function of time. The half-time can then be read directly off the plot by noting the amount of time required for the

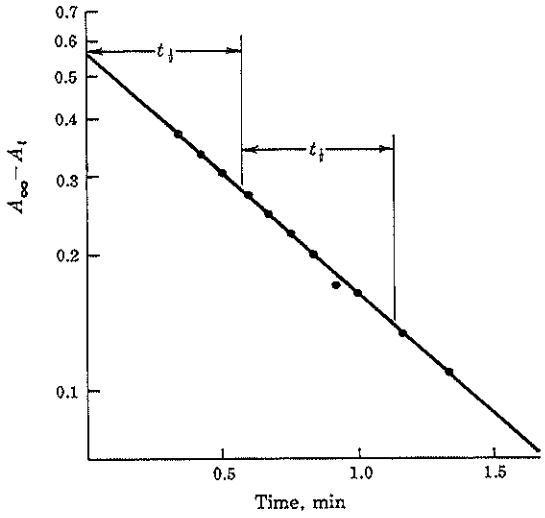
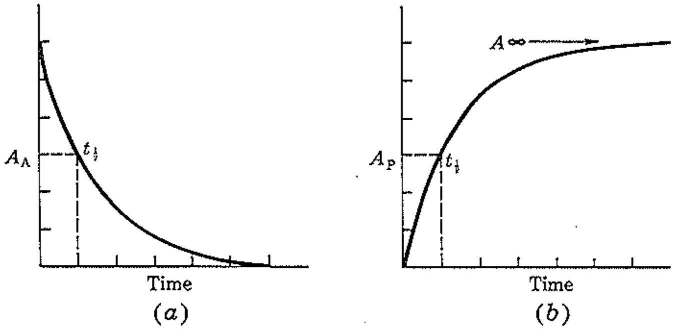


Fig 1. Semilogarithmic plot of the change in absorbance at 270 mμ caused by the release of phenol and phenolate ion in the reaction of 5×10^{-4} *M* phenyl acetate with 0.6 *M* ethylamine buffer, 40% free base, ionic strength maintained at 1.0*M* with potassium chloride, at 5°. The reaction follows (pseudo) first-order kinetics with a half-time which is independent of the amount of reaction.

concentration of A to decrease to half its initial value. The first-order rate constant is then obtained from equation 12. Since the half-time (or any other fractional reaction time) is independent of the concentration of A, it can be read from any part of the plot, and in order to avoid errors it is important to check the half-time over at least one additional time period (Fig. 1).

One of the greatest practical advantages of first-order rate constants arises from the fact that the kinetic behavior of a first-order reaction is independent of the concentration of the reactant, so that the rate constant may be obtained from the half-time for the observed appearance or disappearance of a product or reactant without knowing its absolute concentration. Thus, instead of plotting log [A] against time, it is possible to plot the results of any experimental measurement which changes with the concentration of A (or P) in such a way that the concentration of A (or P) and the change in the experimental measurement have the same half-time. This is obvious if one plots the absorbance of A or of the product P which is formed from A in the absence of interfering absorbance from other species (Figs. 2*a* and 2*b*). It is less obvious, but equally true, if the absorbances due to both A and P are changing at the wavelength at which measurements are being carried out (Fig. 3). That the half-time for such a change in absorbance, $0.5\,\Delta A$, is the same as for the disappearance of A or the appearance of P is apparent from the fact that the observed absorbance at the half-time



(*a*) (*b*)

Fig 2. The change in the absorbance of a reactant A_A or a product A_P, with time in a first-order reaction when only the reactant or product gives absorbance at the wavelength of the experimental measurements.

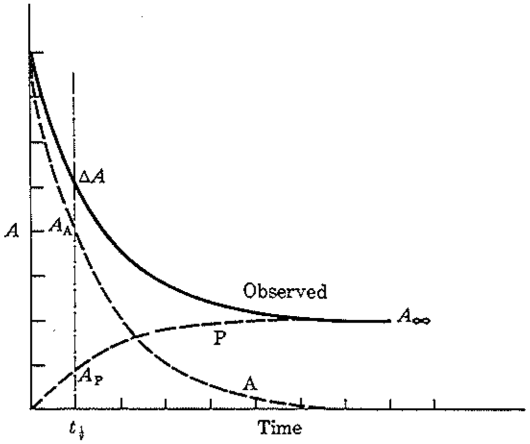


Fig 3. The observed change in absorbance and the changes in absorbance of the starting material and product when both of these species absorb, showing that the half-times for all absorbance changes are the same.

is that of half of the original concentration of A, $0.5A_0$, plus that of half the final concentration of P, $0.5\,P_\infty$, as shown in equation 13, in

$$0.5\,\Delta A_{\text{tot}} = A_0\epsilon_A - 0.5A_0\epsilon_A + 0.5P_\infty\epsilon_P = 0.5A_0\epsilon_A + 0.5P_\infty\epsilon_P \qquad (13)$$

which ϵ_A and ϵ_P refer to the molar extinction coefficients of A and P, respectively. Thus, the course of a first-order reaction may be followed by measurements of the half-time for changes in visible, ultraviolet, infrared, nuclear magnetic resonance, or infrared absorbance as well as changes in volume, conductivity, release of heat, optical rotation, refractive index, and hydrogen ion concentration, so long as the half-times for the changes in these quantities are the same as for the changes in the concentrations of A and P. This will be the case if the measured quantity is linearly related to the concentration of A, P, or A and P.

In practice, if the absorbance (or other quantity being measured) increases during an experiment, the quantity $A_\infty - A_t$ is plotted against time on semilogarithmic graph paper. If the absorbance is decreasing, the quantity $A_t - A_\infty$ is plotted. It is important to be certain that changes in absorbance caused by factors other than the reaction under consideration are not taking place during the experiment.

2. THE ENDPOINT

By far the most important experimental quantity which is required for the determination of first-order rate constants is the value of the absorbance, or whatever other quantity is being followed, at the end of the reaction, since each experimental reading must be subtracted from the time infinity value or the time infinity value must be subtracted from each experimental reading. The most common cause of deviations from first-order kinetics in reactions which are expected to be first order is an error in the value of this endpoint. The experimental readings near the end of a first-order experimental run show much smaller absolute changes than those near the beginning of the run and are especially susceptible to experimental error and to deviations caused by an incorrect endpoint. Experimental error usually appears as a scatter of the points, whereas an incorrect endpoint leads to an upward or downward curvature of the first-order plot near the end of the reaction.

Endpoints are usually obtained after about 10 half-times, when the reaction has proceeded 99.9% to completion. It may be desirable to make a preliminary estimate of the half-time and calculate the endpoint from the experimental measurement at seven half-times, at which the reaction is 99.2% complete, by adding a correction of 0.8% to the observed change in whatever property is being measured. In some cases it may be desirable to estimate the endpoint from a correction of this kind at even earlier times, but it is important to be certain beforehand that the reaction does, in fact, follow first-order kinetics. The amount of the reaction which has not yet taken place after different numbers of half-times is shown below:

Half-times	Percent of reaction not yet completed
4	6.25
5	3.1
6	1.5
7	0.8

Errors in endpoint determinations often arise from a slow secondary reaction, such as an oxidation of the products, which causes a change in the absorbance or other property which is being followed. It is sometimes useful to obtain endpoints from reaction mixtures in which the reaction of an identical amount of substrate has proceeded fast enough so that such secondary decomposition is insignificant. This may be done by adding a larger concentration of a second reactant, provided that a correction is made for any absorbance of this reactant, or by obtaining an artificial endpoint in a dummy reaction mixture. For example, the endpoint for the slow reaction of a phenyl ester with an amine, in which the reaction is followed by measuring the appearance of phenol spectrophotometrically, may be obtained by subjecting a known quantity of a relatively concentrated solution of phenyl acetate to alkaline hydrolysis, neutralizing it, and then adding it to a dummy reaction mixture containing amine to give the same final concentration as in the experimental run.

An alternative, but hazardous, method of obtaining a first-order rate constant when the endpoint is difficult to determine was described by Guggenheim.[2] When the value x of the property being measured is unknown at the endpoint x_∞, readings may be taken at a series of times t and at a series of times which are a constant amount later, $t + \Delta$ (Fig. 4). The measurements should be carried to well over one half-life of the reaction in order to obtain accurate rate constants. The readings at each time, x_t, are expressed for a first-order reaction in equation 14, and the readings at $t + \Delta$, x_Δ, are given in the same way in equation 15.

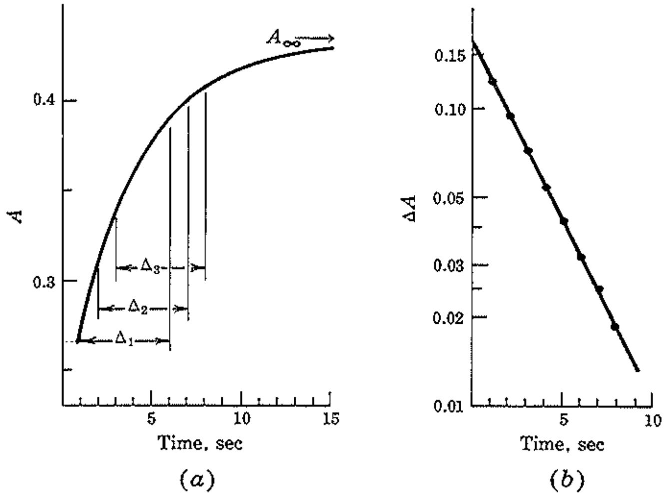


Fig 4. Application of the Guggenheim method to the reaction of 1-acetoxy-4-methoxypyridine cation with 5×10^{-4} *M* ethylenediamine in 0.01 *M* borate buffer at pH 8.36, ionic strength 1.0 *M*, 25°, followed with a recording spectrophotometer at 280 mμ. (*a*) Observed change in absorbance with time. (*b*) Semilogarithmic plot of the change in absorbance over successive 5-second time intervals.

$$x_t - x_\infty = (x_0 - x_\infty)\, e^{-kt} \tag{14}$$

$$x_\Delta - x_\infty = (x_0 - x_\infty) e^{-k(t+\Delta)} \tag{15}$$

Subtracting these two equations gives equation 16, which is converted to logarithmic form in equation 17. Now, the last term of

$$x_t - x_\Delta = (x_0 - x_\infty)\, e^{-kt}(1 + e^{-k\Delta}) \tag{16}$$

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[2] E. A. Guggenheim, *Phil. Mag.* **2**, 538 (1926).

$$\ln (x_t - x_\Delta) = -kt + \ln[(x_0 - x_\infty)(1 - e^{-k\Delta})] \tag{17}$$

equation 17, which contains the unknown quantity x_∞, is a constant and does not have to be evaluated for a first-order reaction. The rate constant k is obtained in the usual manner by simply plotting log $(x_t - x_\Delta)$ [or log $(x_\Delta - x_t)$] against time (Fig. 4). The danger of this method is that it may give linear plots for reactions that do not accurately follow first-order kinetics. It is important to be certain before using this method that the reaction does follow first-order kinetics and that secondary reactions are not affecting the readings at $t + \Delta$.

The demonstration that a reaction accurately follows first-order kinetics for three or four half-times on a logarithmic plot is convincing evidence that the reaction is, in fact, first order. Accurate rate constants can generally be obtained by following the reaction for two half-times if a satisfactory endpoint can be obtained. In certain experimental situations a reasonably accurate rate constant may be obtained from a reaction which is followed for one half-time, provided that it is certain that the reaction follows first-order kinetics. However, deviations from first-order kinetics because of an inaccurate endpoint or for other reasons may not be apparent in plots over one or even two half-times, so that rate constants that are seriously in error may be obtained if it is not certain that the reaction follows first-order kinetics accurately.

3. SECOND-ORDER REACTIONS

The integrated rate expression for a second-order reaction (equation 1) which follows the rate law of equation 2 is given in equation 18,

$$\frac{1}{B_0 - A_0} \ln \frac{A_0(B_0 - x)}{B_0(A_0 - x)} = kt \tag{18}$$

in which A_0 and B_0 refer to the concentrations of A and B at zero time and x refers to the amount of A and B which have reacted, which is equal to the amount of product. The rate constant k may be evaluated from a plot of ln $[(B_0 - x)/(A_0 - x)]$ against time.

In the special case in which the concentrations of A and B at zero time are identical ($A_0 = B_0$), the rate law is given by equations 19 and 20, in which C is the remaining concentration of A or B at any time. The rate constant k may then be obtained from a plot of $1/C$ against time.

$$-\frac{dC}{dt} = kC^2 \tag{19}$$

$$\frac{1}{C} - \frac{1}{C_0} = \cancel{kt} = 2kt \tag{20}$$

go through derivation

In the special case in which the concentration of A is much larger than that of B, the concentration of A does not change appreciably during the reaction and may be treated as a constant. The rate law for such a situation is given in equation 21, in which

$$v = k[A](B_0 - x) = k_{obs}(B_0 - x) \tag{21}$$

k_{obs} is a first-order rate constant equal to $k[A]$. Such a reaction is said to be *pseudo* first order because any individual experimental run follows first-order kinetics, but the first-order rate constant k_{obs} is a function of the concentration of the second reactant A, rather than a true constant. The second-order rate constant is obtained from the slope of a plot of a number of values of k_{obs}, determined at different concentrations of A, against [A]. Pseudo first-order rate constants provide a particularly useful method for the kinetic evaluation of reaction mechanisms because they make possible a separation of the variables which affect the reaction rate in a controlled manner. The great danger of such rate constants is their sensitivity to impurities which may be present in low concentration in the reactant present in great excess, A. If such impurities are much more reactive than A itself, the observed pseudo first-order reaction may be a reaction with the impurity rather than with A. For example, piperidine is prepared by the reduction of pyridine, and the 0.1% remaining pyridine impurity is responsible for most of the observed reaction of a redistilled piperidine solution with reactive acylating agents at pH 6.[3] This impurity and other troublesome impurities in amines, such as the methyl-substituted pyridines, can often be removed by repeated recrystallization of the amine hydrochloride.

4. INITIAL RATES

The measurement of initial rates of reaction is particularly useful for obtaining the rate constants of slow reactions. The simplifying

[3] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* **90**, 2622 (1968).

approximation of this method is that if a reaction is followed only 1 or 2% toward completion, the concentrations of all reactants are almost constant during the time of measurement, so that the rate constant may be evaluated directly from the rate of appearance of products and the concentrations of reactants, as shown for a second-order reaction in equation 22.

$$\frac{dP}{dt} = k[A][B] \approx kA_0B_0 \tag{22}$$

The experimental requirement for this technique is a method for the determination of small amounts of product in the presence of large amounts of starting materials. The concentrations of the reactants are ordinarily obtained from the amounts added to the reaction mixture or from analytical determinations of the concentrations in each reaction mixture. In experiments which are followed by spectrophotometry, it is often convenient to determine the concentration of that reactant which gives rise to the product being followed spectrophotometrically by forcing the reaction to completion in an aliquot of the reaction mixture and determining the absorbance after appropriate dilution. For example, the concentration of phenyl acetate in a reaction mixture may be determined by alkaline hydrolysis of the ester in an aliquot of the reaction mixture, followed by reneutralization to the pH of the reaction and spectrophotometric determination of the concentration of phenol after dilution. The advantage of this procedure is that it leads to the cancellation of any errors which might arise from uncertainty in the concentration or extinction coefficient of this component of the reaction mixture; it has the effect of treating the reaction of that component like a pseudo first-order reaction, which has a rate constant independent of the absolute concentration of the reactant. The dependence of rate constants obtained by measurements of initial rates of reaction upon the concentrations of the different reactants may be easily determined from experiments in which the concentrations of these reactants are varied separately. Small amounts of reactive impurities in the reactants may cause errors in kinetic measurements by the method of initial rates, as in pseudo first-order rate measurements.

5. REACTION ORDER

The order of a reaction is generally evident from the form of the rate law which is followed in a given experiment or, in the case of reactions in which pseudo first-order rate constants or initial rates are measured, from the dependence of the rate constants or rates obtained in individual experiments on changes in the concentrations of the reactants. An alternative method, which is useful when these criteria do not provide a clear-cut conclusion, gives the order of a reaction with respect to a particular reactant from the dependence of the half-time for its disappearance on its initial concentration. It is usually possible to determine the half-time for the disappearance of a given reactant regardless of the rate law which is followed for its disappearance. A logarithmic plot is made of the measured half-times of the reaction against the concentration of the reactant, as shown for the hydrolysis of phosphoramidate in the presence of formaldehyde in Fig. 5.[4] The order of the reaction is given by the negative slope of the resulting line plus 1.0. The half-time of phosphoramidate hydrolysis is independent of its concentration at low concentrations, as expected for a (pseudo) first-order reaction. As the concentration increases, the half-time decreases with a slope of −1 on the logarithmic plot as a term in the rate law which is second order with respect to phosphoramidate becomes significant. From this information, a minimal rate law may be written as shown in equation 23, in which the observed rate con-

$$-\frac{d[PA]}{dt} = k_1[PA] + k_2[PA]^2 \tag{23}$$

stants k_1 and k_2 are themselves dependent on the concentration of the other reactants. An alternative method of obtaining the reaction order for reactions up to third order is based on a plot of f/t against t, according to the approximate equation 24, in which f is the fraction to which the reaction has proceeded to completion, n is

$$\frac{t}{f} = \frac{1}{kA_0} + \frac{nt}{2} \tag{24}$$

the reaction order, A_0 is the initial concentration of the reactant, and k is the rate constant. The slope of such a plot is equal to one-half the reaction order, and the rate constant may be obtained from the intercept.[5]

[4] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* 86, 1410 (1964).

[5] R. W. Wilkinson, *Chem. Ind.* (*London*) 1961, 1395.

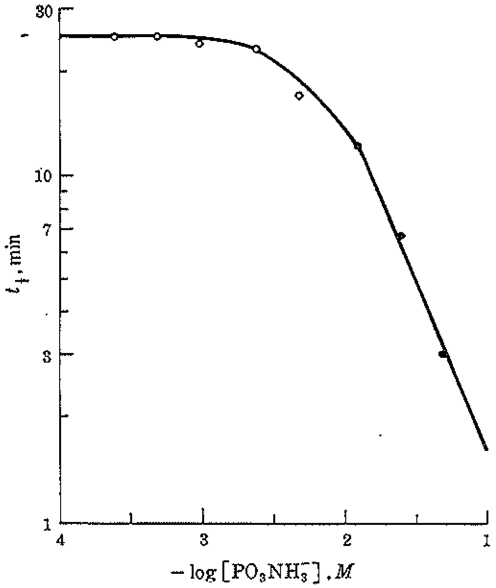


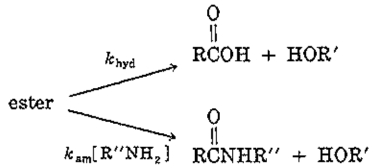
Fig 5. Logarithmic plot of the half-times for formaldehyde catalyzed hydrolysis of phosphoramidate against the concentration of phosphoramidate at 39°, ionic strength 1.0 *M*, pH 4.5. Solid circles: rates determined by automatic titration. Open circles: rates determined by measurement of the appearance of inorganic phosphate.[4]

B. THE UTILIZATION OF PSEUDO FIRST-ORDER RATE CONSTANTS

Pseudo first-order rate constants, obtained in the presence of a large excess of all the reactants except the one which gives rise to the change in whatever property of the solution is being followed, provide the most generally useful kinetic method for the elucidation of reaction mechanism, in the author's opinion. In the first place, it is often relatively easy to obtain a series of pseudo first-order rate constants for the disappearance of a substrate or the appearance of a product by spectrophotometry or by some other relatively simple analytical or physical measurement. Secondly, it is not necessary to know the exact concentration of the reactant or product which appears or disappears in a first-order reaction. The most important property of such rate constants, however, is that they make possible a facile separation of the variables that are involved in a given reaction, which is often difficult or impossible if the reaction is followed with the reactants at similar or equal concentrations. Some of the ways in which this can be done will be described in this section.

1. PARALLEL FIRST-ORDER REACTIONS

This separation of (pseudo) first-order rate constants is made possible by their additivity in parallel first-order reactions. If a substrate disappears by more than one concurrent first-order pathway, such as by hydrolysis and aminolysis of an ester in the presence of a large excess of amine (equation 25), the first-order rate constants for the reaction are additive (equations 26 and 27) so that the pseudo first-order rate constant for aminolysis k'_{am} may be obtained simply by subtracting that for hydrolysis, which can usually be measured in a separate experiment. The second-order rate constant for aminolysis may then be obtained by dividing the observed pseudo first-order rate constant for aminolysis by the concentration of free amine, *provided* that it is certain that the reaction with amine is first order with respect to amine concentration (i.e., is second order overall). It is usually desirable to plot the observed pseudo first-order rate constants against the concentration of the second reactant. The intercept of such a plot gives k_{hydrol}, and the slope, if the plot is linear, gives the second-order rate constant for aminolysis (Fig. 6).



$$\text{ester}\ \begin{cases} \xrightarrow{k_{hyd}} \mathrm{RC(=O)OH + HOR'} \\ \xrightarrow[k_{am}[\mathrm{R''NH_2}]]{} \mathrm{RC(=O)NHR'' + HOR'} \end{cases} \qquad (25)$$

$$v = \frac{-d[\mathrm{A}]}{dt} = \frac{d[\mathrm{R'OH}]}{dt} = k_{hyd}\,[\text{ester}] + k_{am}\,[\mathrm{R''NH_2}][\text{ester}]$$

$$= (k_{hyd} + k_{am}[\mathrm{R''NH_2}])[\text{ester}] \qquad (26)$$

$$k_{obs} = \frac{v}{[\text{ester}]} = k_{hyd} + k_{am}\,[\mathrm{R''NH_2}] = k_{hyd} + k'_{am} \qquad (27)$$

Another way to separate the component parts of an observed pseudo first-order rate constant is to determine the products at the

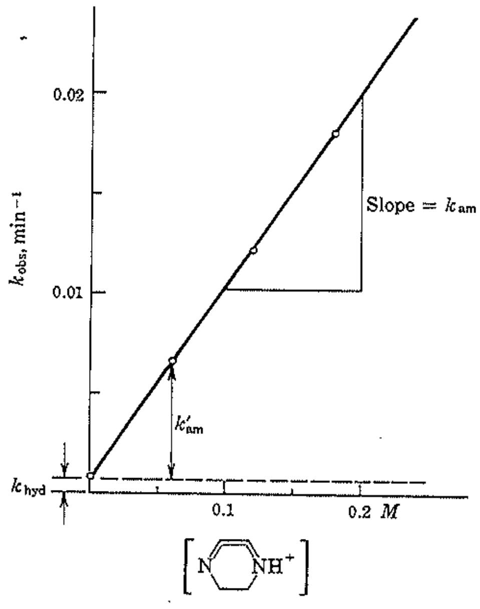


Fig 6. Pseudo first-order rate constants for the reaction of 2,4-dinitrophenyl acetate with triethylenediamine monocation in a buffer of 60% monocation-40% dication, pH 3.57, at an ionic strength maintained at 1.0 *M* with potassium chloride and 25°.

end of the reaction. Since all the pathways for the disappearance of the substrate are first order, the fraction of the substrate which disappears by each pathway during the course of the reaction is constant, as is the ratio of products from the different pathways. Consequently, the ratio of products at the end of the reaction is equal to the ratio of the pseudo first-order rate constants for the pathways from which they were derived. Thus, for the concurrent aminolysis and hydrolysis of an ester, the ratio and the absolute values of the pseudo first-order rate constants for aminolysis and hydrolysis can be obtained from the ratio of amide to acid product and k_{obs} (equations 27 and 28). However, in order to apply this

$$\frac{k_{hyd}}{k'_{am}} = \frac{[\mathrm{RCOOH}]_{final}}{[\mathrm{RCONHR''}]_{final}} \tag{28}$$

technique to the evaluation of rate constants, it is necessary to be certain that the reactions are what they are assumed to be. For example, an amine might cause ester disappearance by general base catalysis of ester hydrolysis as well as by aminolysis, so that not all of the kinetic term containing the amine concentration would represent aminolysis. In practice, determinations of products and product ratios are most often carried out to identify the chemical nature of a kinetic term, such as whether a reaction with an amine represents aminolysis, amine catalyzed hydrolysis, or both. It is, of course, necessary to be certain in any determination of products that the product being measured is stable under the conditions of the experiment.

Students are nearly always surprised to learn that the half-time or the observed rate constant for a reaction which proceeds by several concurrent first-order pathways is the same, regardless of what is being measured. Thus, for the concurrent hydrolysis and aminolysis of an ester (Fig. 7) the half-times are the same for ester disappearance and for appearance of the amide and of the acid (although the *absolute* rates, in units of moles per minute, are of course different). The pseudo first-order rate constant for the overall reaction may be determined just as well from the half-time for the small fraction of the reaction which gives hydrolysis as from any other measurement. This can be useful for the measurement of reactions which do not give an easily measurable change in the properties of reactants or products. If an additional first-order reaction which is easily measured is introduced into the system, this can serve as an indicator of the overall rate of substrate disappearance and, after correction for the known rate of the indicator reaction, as a means for the determination of the desired rate constant. The reason for the identity of the half-time for the several concurrent reactions is apparent after some consideration: When half of the substrate has reacted, one-half of the maximum amount of each product must be formed, and the absolute rate of each of the concurrent reactions is just one-half the initial rate (Fig. 7).

2. NONLINEAR DEPENDENCE OF k_{obs} ON THE CONCENTRATION OF ANOTHER REACTANT

It is sometimes found that the plot of observed pseudo first-order rate constants against the concentration of a reactant present in great excess is not linear. This means that the reaction is not first order with respect to that reactant, and that the rate law is more complicated than that of equation 27. These deviations often provide the most interesting information about the mechanism of the reaction. The two possible types of deviations—downward deviations and upward deviations—have an altogether different significance and are considered separately.

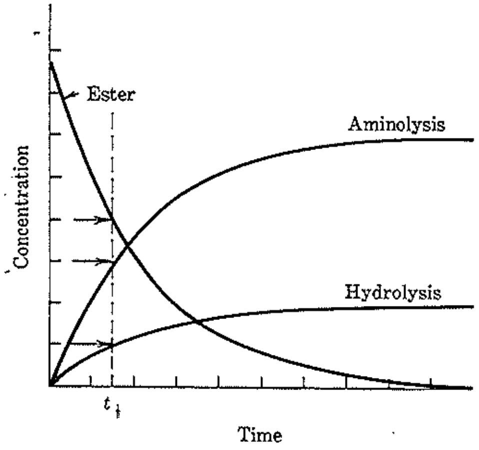


Fig 7. The time course of ester disappearance and of amide and acid appearance for concurrent aminolysis and hydrolysis of an ester by pseudo first-order reactions. The half-times for disappearance of the ester and for appearance of the two products are identical.

A downward deviation means that the reaction is proceeding more slowly than would be expected from the dependence on the concentration of the reactant at low concentrations; i.e., something is causing the reaction to proceed more slowly than predicted by a rate law of the form of equation 27. This may be caused either by some sort of complex formation of the reactants or by a change in rate-determining step. These possibilities are familiar to enzymologists in the leveling off of the rate of an enzymatic reaction with increasing substrate concentration, which can be caused either by formation of an enzyme-substrate complex at high substrate concentration (Michaelis complex, equation 29) or by a change in rate-

$$\mathrm{E+S} \overset{K}{\rightleftharpoons} \mathrm{ES} \xrightarrow{k} \text{products} \tag{29}$$

determining step from bimolecular formation of the complex to rate-determining monomolecular breakdown of the complex (Haldane interpretation, equation 30). An example of complex formation in a chemical reaction, the formation of an oxime from hydroxylamine

$$\mathrm{E+S} \xrightarrow{k_1} \mathrm{ES} \xrightarrow{k_2} \text{products} \tag{30}$$

and pyruvate, is shown in Fig. 8. At the pH of this experiment, 6.9, the dehydration of the addition compound I is rate determining, and the formation of this intermediate occurs in a rapid prior equilibrium step (equation 31). At low hydroxylamine concentrations a negligible fraction of pyruvate is present as the addition intermediate, so that the concentration of intermediate and the overall rate are directly proportional to the hydroxylamine concentration. At high hydroxylamine concentration all the pyruvate is converted to the addition compound, so that a further increase in hydroxylamine concentration does not increase the rate and the observed rate is simply the rate of breakdown of the intermediate.[6] The observed rate constant at any amine concentration is given by equation 32,

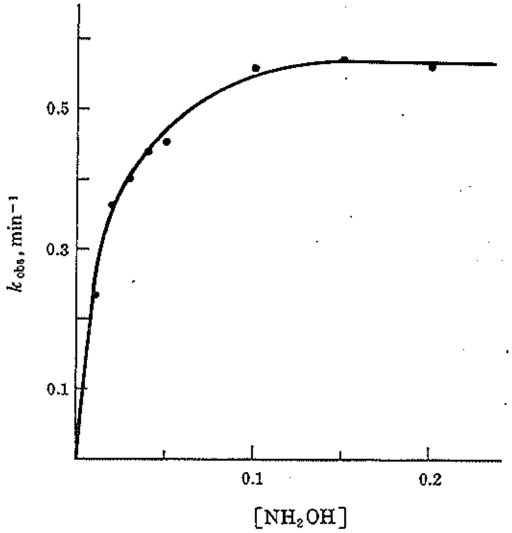
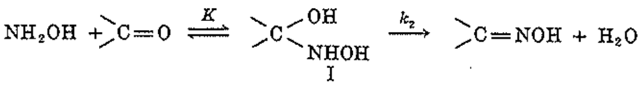


Fig 8. The leveling off of the rate of oxime formation from pyruvate in the presence of excess hydroxylamine caused by complete conversion of pyruvate to a hydroxylamine addition compound at pH 6.9, 25°, ionic strength maintained at 1.0 *M* with potassium chloride.[6]



$$\mathrm{NH_2OH} + {>}\mathrm{C{=}O} \overset{K}{\rightleftharpoons} {>}\mathrm{C}{<}^{\mathrm{OH}}_{\underset{\mathrm{I}}{\mathrm{NHOH}}} \xrightarrow{k_2} {>}\mathrm{C{=}NOH} + \mathrm{H_2O} \tag{31}$$

$$k_{\mathrm{obs}} = \frac{v}{[\mathrm{C{=}O}]_{\mathrm{tot}}} = k_2[\mathrm{NH_2OH}]\left(\frac{K}{1 + K[\mathrm{NH_2OH}]}\right) \tag{32}$$

which is derived from the fact that the rate is equal to the rate of breakdown of the intermediate (equation 33), the equilibrium constant

[6] W. P. Jencks, *Progr. Phys. Org. Chem.* 2, 63 (1964).

for formation of the intermediate (equation 34), and the conservation equation for the total added carbonyl compound $[C{=}O]_{tot}$ (equation 35). The equilibrium constant K may be obtained from the

$$v = k_2\,[I] \tag{33}$$

$$K = \frac{[I]}{[C{=}O][NH_2OH]} \tag{34}$$

$$[C{=}O]_{tot} = [C{=}O]_{free} + [I] \tag{35}$$

negative abscissa intercept of a plot of $1/k_{obs}$ against $1/[NH_2OH]$, which is analogous to the Lineweaver-Burk plot for enzymatic reactions.[7] This example involves covalent association of the reactants, but similar behavior is observed with association from any cause. Pyridines, for example, exhibit a self-association or some self-interaction effect which results in a decrease in activity coefficient with increasing pyridine concentration as well as in nonlinear kinetic behavior.[8,9] Pyridines and other compounds with hydrophobic constituents also associate with esters and other substrates to cause nonlinear kinetic behavior.[8,10,11]

If association can be ruled out as a cause for a negative deviation in a plot of k_{obs} against the concentration of a reactant or catalyst, the change in the form of the rate law means that there is a change in the rate-determining step of the reaction. This is a useful technique for the demonstration of an intermediate on the reaction path. A number of examples are described in Chap. 10.

Positive deviations in such plots (Fig. 9) mean that the reaction proceeds faster than expected from the results at low concentration; i.e., the reaction is more than first order with respect to the concentration of the varying reactant and an *additional* term must be added to the rate law to account for the observed rate. The

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[7] This procedure cannot be used if the reactant is a catalyst for the second step, so that the rate does not level off completely.

[8] A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.* 87, 3209 (1965).

[9] R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *J. Chem. Soc.* 1954, 3188; N. Ibl, G. Dändliker, and G. Trümpler, *Helv. Chim. Acta* 37, 1661 (1954).

[10] T. Higuchi and K. A. Connors, in C. N. Reilley (ed.), "Advances in Analytical Chemistry and Instrumentation," vol. IV, p. 117, Interscience Publishers, Inc., New York, 1965.

[11] J. A. Mollica, Jr. and K. A. Connors, *J. Am. Chem. Soc.* 89, 308 (1967).

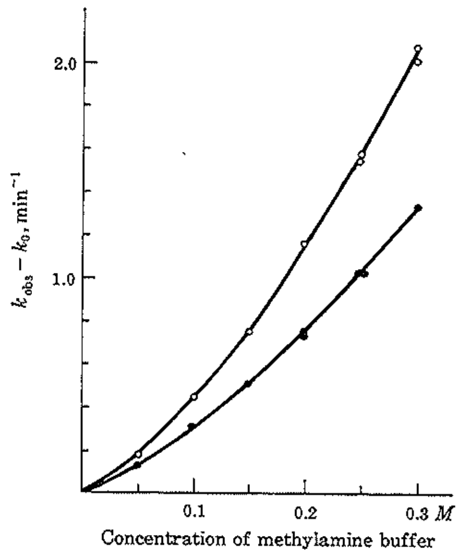

Fig 9. Pseudo first-order rate constants for the reaction of phenyl acetate with methylamine buffer, 40% free base, at 5°, ionic strength maintained at 1.0 with potassium chloride, showing the greater than first order dependence of the rate on the concentration of methylamine. Upper curve: in water. Lower curve: in deuterium oxide solution. k_0 is the rate of hydrolysis in the absence of amine.[12]

simplest way to evaluate this term is to calculate an apparent second-order rate constant $k_{2\,app}$ by dividing each observed rate constant by the concentration of the reactive species of the reactant (equation 36). The increase in $k_{2\,app}$ with increasing amine concen-

$$k_{2\,app} = \frac{k_{obs} - k_0}{[RNH_2]} \tag{36}$$

tration in ester aminolysis represents catalysis of the reaction by a second mole of amine. Consequently $k_{2\,app}$ is plotted against the concentration of amine (Fig. 10). The ordinate intercept of this plot gives the second-order rate constant for the uncatalyzed (or solvent catalyzed) aminolysis k_1, and the slope is the third-order constant for the amine catalyzed reaction k_{RNH_2}, according to the rate law of equation 37. If there is no intercept, all of the reaction is catalyzed;

$$\frac{v}{[\text{Ester}]} = k_{obs} = k_{hyd} + k_1[RNH_2] + k_{RNH_2}[RNH_2][RNH_2] + k_{OH^-}[RNH_2][OH^-] \tag{37}$$

i.e., there is no measurable second-order term, k_1.

If the reaction contains more than one third-order term, it is necessary to extrapolate each apparent second-order rate constant to zero concentration of the other reactants before plotting it against the concentration of the reactant in question. This proce-

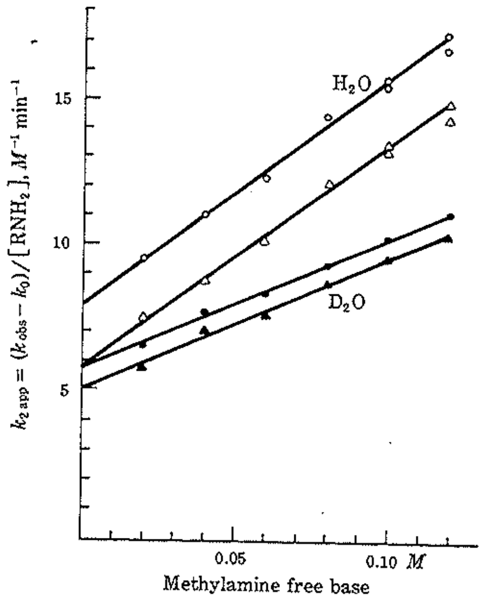

Fig 10. Apparent second-order rate constants for the reaction of phenyl acetate with methylamine in water (open symbols) and deuterium oxide (closed symbols) as a function of the concentration of methylamine. Circles: uncorrected rate constants. Triangles: corrected for hydroxide ion catalysis of aminolysis.[12]

dure, while laborious, makes possible the elucidation of the kinetics of reactions which would be difficult or impossible to evaluate by other techniques. The simplest procedure, if it is practicable, is to carry out the reaction at a sufficiently low concentration of the other reactants that only the first-order terms for these reactants are significant. The aminolysis of phenyl acetate is catalyzed by hydroxide ion as well as by a second molecule of amine (equation 37, k_{OH^-}). The observed rate constants may be separated into the contributions from k_{RNH_2} and k_{OH^-} by utilizing data obtained under conditions in which one of these terms makes the major contribution to the observed rate or change in rate and correcting for the contribution of the other, as shown in Figs. 10 and 11; the corrections may be made by successive approximations, if necessary, to obtain final values of the rate constants.[12]

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[12] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* 88, 104 (1966).

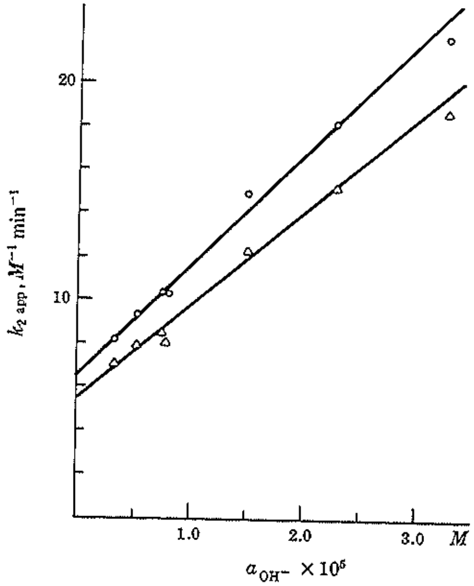
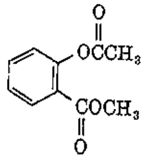


Fig 11. Apparent second-order rate constants, $k_{2\,app} = (k_{obs} - k_0)/[RNH_2]$, for the reaction of methylamine at a total buffer concentration of 0.05 M with phenyl acetate as a function of hydroxide ion activity. Circles: uncorrected values. Triangles: corrected for amine catalysis.[12]

3. EFFECT OF pH AND IONIZATION OF THE REACTANTS

Ester hydrolysis occurs through acid catalyzed, pH-independent, and hydroxide ion catalyzed terms according to equation 38, although one or more of these terms may not be significant for a given ester. The dependence on pH of the rate of hydrolysis of the phenyl ester moiety of methyl *o*-carboxyphenyl acetate (1) is shown in the *lower* curve of Fig. 12 as an example.[13] At low and high pH the rate constants increase with slopes of 1.0 in this logarithmic plot, cor-



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[13] T. St. Pierre and W. P. Jencks, *J. Am. Chem. Soc.* 90, 3817 (1968).

responding to acid and base catalyzed terms which are first order

$$\frac{v}{[\text{Ester}]} = k_{\text{obs}} = k_0 + k_{\text{H}^+}[\text{H}^+] + k_{\text{OH}^-}[\text{OH}^-] \quad (38)$$

with respect to hydrogen ion and hydroxide ion, respectively (k_{H^+} and k_{OH^-}, equation 38). The dashed line is the sum of the acid and base catalyzed reactions in the intermediate pH region. The increase in the observed rate above this dashed line corresponds to the pH-independent, "water" reaction. The kinetic constants are

evaluated from (linear) plots of k_{obs} against the concentration of hydrogen ion and hydroxide ion. (If the hydrolysis is catalyzed by buffers, the rate constants must first be determined at different buffer concentrations at each pH value and then extrapolated to zero buffer concentration.) The slopes of these plots give the second-order rate constants for the hydrogen and hydroxide ion catalyzed reaction, respectively, and the intercept of both plots is the pseudo first-order rate constant for the pH-independent, "water" reaction.

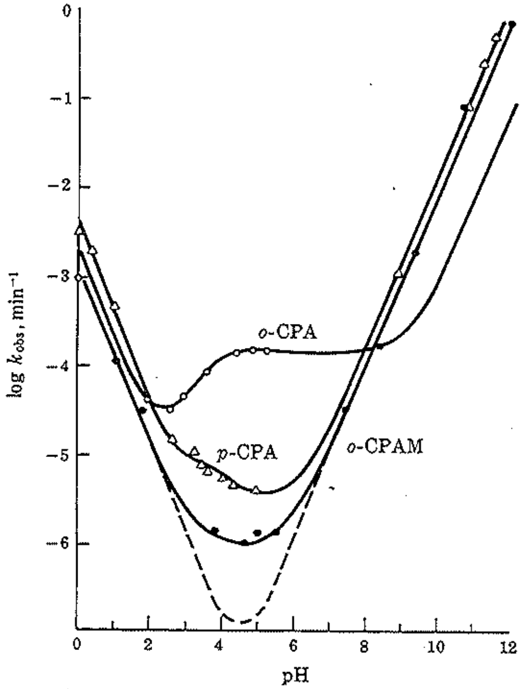


Fig 12. Logarithmic plots of the rate constants for the hydrolysis of aspirin (*o*-CPA), *p*-carboxyphenyl acetate (*p*-CPA), and methyl *o*-carboxyphenyl acetate (*o*-CPAM) as a function of pH. The dashed line shows the rate of hydrolysis of *o*-CPAM if hydrolysis proceeded with acid and base catalysis, but no pH-independent water reaction.[13]

It is not possible to determine the order of a reaction with respect to solvent molecules by ordinary kinetic techniques because the concentration of solvent cannot be varied without changing the nature of the solvent in a manner for which it is difficult or impossible to make a suitable correction. If the "water" hydrolysis is known or assumed to represent a second-order attack by water, it may be desirable to convert the experimental first-order constant to a second-order constant by dividing it by the concentration of water, 55.5 *M*. If both the acid and the base catalyzed reactions contribute significantly to the rate at a given pH value, it is necessary to correct each observed rate constant for the contribution of the base catalyzed reaction before plotting it against acid concentration, and vice versa, through a series of successive approximations. This is usually not difficult, since accurate rate constants may be evaluated from the observed rates at high acid and base concentrations, at which other reactions are not significant.

Kinetic results are ordinarily expressed in terms of the *concentrations* of the reactants. This presents no problem for acid and base catalyzed reactions which are measured in the presence of known concentrations of added acid or hydroxide ion. However, a rate measurement based on a measured pH gives a rate constant for an acid or base catalyzed reaction which is based on *activity*, not concentration. The pH is, or very nearly is, a measure of the hydrogen ion activity and K_w, the ionization constant of water, is a true constant at finite ionic strengths only for activities (equation 39). If a_{OH^-} is to be calculated from the measured pH and K_w, the

$$K_w = a_{\text{H}^+} \cdot a_{\text{OH}^-} = 10^{-14} \text{ at } 25^\circ \quad (39)$$

values of pH and K_w used must, of course, refer to the same temperature as the kinetic measurements. Rate constants which are based on activities should be so identified. They may be converted to a concentration basis by multiplication by the appropriate activity coefficients. For this purpose, the desired activity coefficients are most easily estimated from the measured pH of solutions containing a known concentration of hydrogen or hydroxide ion in the presence of the salt used to maintain the ionic strength of the reaction mixtures.

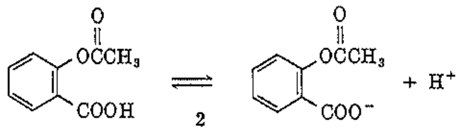
The complete rate law for a reaction of an ionizable reactant must refer to the rate of reaction of a particular ionic species of the reactant. It is desirable to convert observed rate constants to rate constants based on a particular ionic species of each reactant at an early stage in the evaluation of kinetic data. (It will be shown later that, because of the kinetic ambiguity of rate laws, it is generally not possible to decide by ordinary kinetic techniques whether a given ionic species is actually the species which is undergoing reaction, but it is still necessary to describe the rate of the reaction in terms of one or the other ionic species of each reactant; these may later be converted to kinetically equivalent forms if necessary.) The easiest way to do this is to divide the observed rate constant by the fraction of the material in a given ionic form. This fraction may be obtained from the Henderson-Hasselbalch equation 40, in which α is the fraction of the reactant in the basic

$$\mathrm{pH} = \mathrm{p}K_a' + \log\frac{[\text{base}]}{[\text{acid}]} = \mathrm{p}K_a' + \log\frac{\alpha}{1-\alpha} \tag{40}$$

form, and from the measured pH of the reaction mixture. The sensitivity of apparent ionization constants to variations in ionic strength, temperature, and other reaction conditions makes it essential that the pH value be measured for each kinetic run and that the $\mathrm{p}K_a'$ be determined under the exact experimental conditions of the kinetic run. It is not uncommon to obtain incorrect rate constants and even spurious additional terms in the rate law by calculating the value of α from measurements made under one set of experimental conditions and $\mathrm{p}K_a'$ values, perhaps taken from a table, which were measured under different conditions. For the same reason it is important to report the $\mathrm{p}K_a'$ values which are used for such calculations. For a reactant which is present in large excess, such as a buffer, it is far simpler and more accurate to obtain α from the stoichiometric composition of the buffer added to

the reaction mixture; this avoids the possibility of error in measurements of both the pH and the $\mathrm{p}K_a'$.[14]

If a constant value is not obtained by dividing the observed rate constants by α (or $1-\alpha$) for each reactant, there is either an additional hydrogen or hydroxide ion term in the rate law or both ionic forms of the substrate react at significant rates and terms must be included in the rate law for each of them. The most straightforward way to evaluate these terms is to plot the observed rate constant against α. The ordinate intercept is the rate constant for the reaction of the acidic form of this reactant and the intercept at 1.0 is the rate constant for the basic form. If more than a single reactant undergoes ionization in the pH region under observation, k_{obs} should be divided by α for one reactant (or, if the reactant is present in large excess, by the concentration of a given ionic species) before plotting against α for the other reactant.



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The curve with the open circles of Fig. 12 shows the dependence on pH of the rate of hydrolysis of aspirin, *o*-CPA. (2) The striking feature of this curve is the rapid pH-independent hydrolysis of aspirin anion between pH 5 and 8.[15] The rate constant for hydrolysis of the anion may be obtained from any point on this plateau without interference from the acid or base catalyzed hydrolysis reactions. The rate constant for the pH-independent hydrolysis of the acidic, uncharged species of aspirin is not large enough to account for most of the observed rate at any pH value and must be obtained

[14] This procedure is not valid at high and low pH values at which a significant fraction of the acidic or basic component of the added buffer must give off or take up a proton to attain the final pH of the solution. For example, to reach a pH of 2.0 the buffer must supply about 0.01 *M* hydrogen ion, which would cause a significant decrease in the acid component and a corresponding increase in the basic component of a half-neutralized 0.05 *M* buffer of p*K* 2.0. The simplest way to correct for this dissociation is probably to: (1) measure the pH of the solution; (2) calculate the concentration of hydrogen ion from the pH and the activity coefficient of hydrogen ion or from an empirical calibration curve of pH against hydrogen ion concentration under the conditions of the experiment; and (3) subtract this concentration from the acidic and add it to the basic component of the buffer. Alternatively, a series of buffer solutions of increasing concentration may be brought to a constant pH by the addition of strong acid to each reaction mixture.

[15] L. J. Edwards, *Trans. Faraday Soc.* **46**, 723 (1950).

from a plot against α of the observed rate constants, corrected for the rate of acid catalyzed hydrolysis. The hydrolysis of *p*-carboxyphenyl acetate, *p*–CPA, does not show the rapid monoanion reaction characteristic of the *ortho* carboxylate group of aspirin (Fig. 12), so that the observed rate constants must be corrected for both acid and base catalyzed hydrolysis and then plotted against α to obtain the rate constants for the pH–independent hydrolysis of the acidic and anionic species. The solid lines in Fig. 12 are calculated from rate constants obtained in this way according to the overall rate law of equation 41, in which the superscripts refer to the charge of

$$\text{Rate} = k_{\text{H}^+}[\text{SH}]a_{\text{H}^+} + k_a[\text{SH}] + k_b[\text{S}^-] + k_{\text{OH}^-}[\text{S}^-]a_{\text{OH}^-} \tag{41}$$

the various ionic species of the reactants and k_a and k_b are the rate constants for the uncatalyzed hydrolysis of the acidic and basic species of the reactant, respectively.

The rate constants for the reactions of the acidic and anionic forms of aspirin with semicarbazide, which undergoes protonation to the unreactive cation in the same pH region that aspirin undergoes dissociation to the anion, may be evaluated as shown in Fig. 13

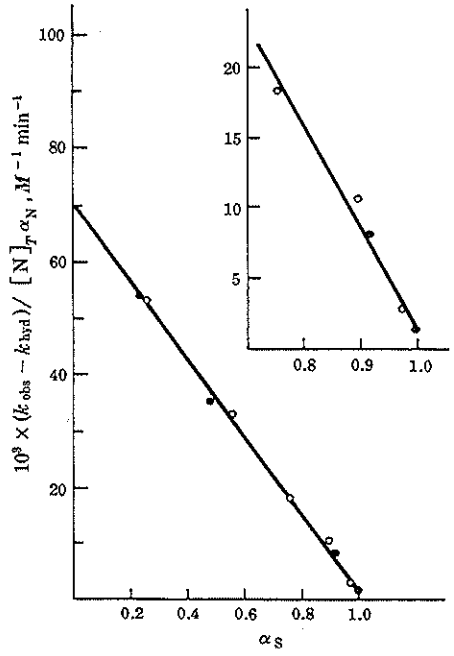

Fig 13. Apparent second-order rate constants for the reaction of semicarbazide with aspirin as a function of the fraction of aspirin present as the anion, α_S. $[\text{N}]_T$ and α_N refer to the total concentration of semicarbazide and the fraction of semicarbazide as the free base, respectively.[18]

according to the rate law of equation 42. The observed rate con-

$$v = k_a[o\text{–CPA}^0] + k_b[o\text{–CPA}^-] + k_3[o\text{–CPA}^0][\text{RNH}_2] + k_4[o\text{–CPA}^-][\text{RNH}_2] \tag{42}$$

stants, after correction for hydrolysis, are divided by the concentration of free semicarbazide and are then plotted against the fraction of aspirin as the anion at each pH. The fact that the ordinate intercept k_3 is much larger than the intercept at $\alpha = 1.0$, k_4, reflects the much larger susceptibility of aspirin acid than of aspirin anion to attack by semicarbazide.

In some instances the procedure may be reversed, and the variation in rate with pH is used to determine the ionization constant of a reactant. This is particularly useful if the compound is too unstable to permit determination of its p*K* by ordinary methods. There are no assumptions in such a procedure, except that the reaction does not undergo a change in rate-determining step in the pH region in question. For a reaction in which the rate constants at pH values well above and below the p*K* are accurately known and there is no interference from additional kinetic terms, the p*K* of the reactant may be simply read from the midpoint of the Δk, the difference in the rates of the reactions of the two species, in a plot of k_{obs} against pH. This is shown for the hydrolysis of acetyl phosphate monoanion and dianion in Fig. 14.[16, 17]

Several more accurate methods are available for obtaining p*K* values from kinetic data; they may also be applied to other types of p*K* determination. If the rate constants k_a and k_b for the reaction of the acidic and basic species of the reactant (equation 41) are known accurately, either by direct measurement or by correction of k_{obs} for the contributions of k_{H^+} and k_{OH^-}, the p*K* can be obtained from a plot of log $[k_{\text{obs}} - k_a)/(k_b - k_{\text{obs}})$ or log $[(k_a - k_{\text{obs}})/(k_{\text{obs}} - k_b)]$, against pH. The p*K* is the pH at which this quantity equals zero. This plot is simply an expression of the Henderson-Hasselbalch equation, modified to describe the dependence of k_{obs} on k_a, k_b, and the pH according to equation 43. Curvature near the upper

$$k_{\text{obs}} = k_b\alpha + k_a(1 - \alpha) \tag{43}$$

and lower limits of such a plot, which should include data covering

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[16] D. E. Koshland, Jr., *J. Am. Chem. Soc.* 74, 2286 (1952).

[17] G. Di Sabato and W. P. Jencks, *J. Am. Chem. Soc.* 83, 4400 (1961).

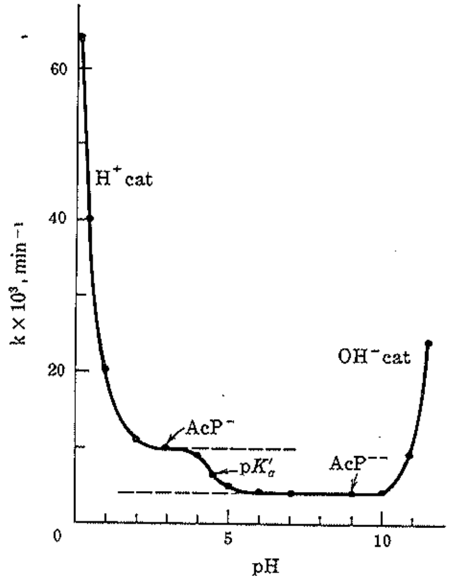

Fig 14. Dependence on pH of the hydrolysis of acetyl phosphate at 39°, showing the acid and base catalyzed reactions and the pH-independent hydrolyses of the acetyl phosphate monoanion and dianion; the pK'_a for dissociation of the monanion to the dianion is at the midpoint between the two latter rates.[16,17]

about two logarithmic units, usually means that the value of k_a or k_b is inaccurate. The slope of this plot *must* be 1.0 if only a single ionization is involved.

If only one ionic species reacts, but it is impossible to obtain an accurate rate constant in the pH region in which the reactant is entirely converted to the reactive form, it is necessary to obtain the pK and the desired rate constant by an extrapolation procedure. The most satisfactory procedure for this, if the basic form of the substrate is reacting, is to plot k'_{obs} against $k_{\text{obs}}a_{\text{H}^+}$ (equation 44).

$$k_{\text{obs}} = k_b - \frac{k_{\text{obs}}a_{\text{H}^+}}{K_a} \tag{44}$$

The values of k_b and the ionization constant are obtained from the ordinate intercept and the negative reciprocal of the slope, respectively, of this plot. If the acidic form is reactive, k_{obs} is plotted against $k_{\text{obs}}/a_{\text{H}^+}$, the ordinate intercept is k_a, and the slope is equal to $-K_a$ (equation 45). These equations are derived from the

$$k_{\text{obs}} = k_a - \frac{k_{\text{obs}}K_a}{a_{\text{H}^+}} \tag{45}$$

expression for the ionization constant of the reactant and the proportionality of k_{obs} to the amount of substrate in the reactive form.[18] In an alternate procedure, $1/k_{\text{obs}}$ is plotted against $1/a_{\text{H}^+}$, if the acidic species reacts, or against a_{H^+}, if the basic species reacts. The ordinate intercept is the reciprocal of k_a (or k_b) and the abscissa intercept is the negative of $1/K_a$ (or K_a). Double reciprocal plots of this kind, like the analogous Lineweaver-Burk plots for enzyme kinetics, have the disadvantage that the points near k_b (or k_a) are clustered near the ordinate, whereas the slower rate constants are spread out. They should be utilized with caution and with understanding of this characteristic. If both ionic species react, either of these types of plot may be utilized by subtracting the rate constant for the slower reacting species from k_{obs} before making the plot. The ordinate intercept will then give $k_b - k_a$ or $k_a - k_b$, instead of k_a or k_b. These extrapolation methods are also useful for the determination of pK values by the usual methods—by plotting changes in absorbance or the amount of added acid or base instead of the rate constant.

The effect of the concentration of hydrogen or hydroxide ion on the reaction rate should be interpreted in the same way as for other reactants: an increase in reaction rate that is not accounted for by the ionization of a reactant is ascribed to an additional term in the rate law containing hydrogen or hydroxide ion. A decrease in the rate which cannot be accounted for by ionization of a reactant means that there is a change in rate-determining step and an intermediate in the reaction, as described for a number of reactions in Chap. 10.

4. SALT AND SOLVENT EFFECTS

In order to avoid unnecessary changes in the reaction medium in a series of experiments, it is usually desirable to carry out reactions at a constant ionic strength and solvent composition. A standard set of experimental conditions should be chosen before undertaking any large series of experimental measurements. If it is necessary to increase a reactant or buffer to a high concentration, the substance itself will change the nature of the solvent in a manner for which it may be difficult to make a valid correction. The various theoretical equations for the effects of salts and solvents on reaction rates are subject to so many exceptions in practice as to be almost useless for making corrections to observed reaction rates in the

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[18] B. H. J. Hofstee, *Science* 131, 39, 1068 (1960).

absence of direct experimental data demonstrating their validity for the reaction in question. It is, therefore, desirable to make a direct experimental evaluation of the effect of unavoidable changes in reaction conditions if this is possible. Correction to a constant ionic strength will effectively eliminate electrostatic effects which follow the simple Debye-Hückel equation, but in even moderately concentrated solutions specific ion effects and solvent effects on the activity coefficients of the reactants and transition state (Chaps. 7 and 8) are likely to become much larger than the Debye-Hückel effect and may conceal or exaggerate important types of kinetic behavior. For example, general base and general acid catalysis of the aminolysis of phenyl acetate by alkylamines may be difficult to detect if the ionic strength is maintained constant with potassium chloride, which, in contrast to tetramethylammonium chloride, has a specific rate accelerating effect on the reaction.[12, 19] The effects of other changes in the nature of the solvent caused by reactants and buffers may be evaluated by examination of the effects of appropriate model compounds. For example, dioxane may be used as a model to evaluate the effect of the hydrocarbon-ether ring of morpholine. The fact that such model compounds and salts can never be entirely appropriate models for the reactant requires that one should regard small changes in rate constants, such as small catalytic terms which are obtained at high reactant concentrations, with considerable reserve, especially if the reaction is known to be sensitive to salt and solvent effects. The large sensitivity of some reactions of uncharged molecules to solvent effects is illustrated by the 50% decrease in the rate of hydrolysis of acetylsalicylic acid anhydride in the presence of 10% dioxane.[20]

5. REVERSIBLE REACTIONS

The kinetic equation for a reaction which proceeds to an equilibrium position instead of to completion is complicated if the reaction is more than first order in either direction. It is desirable, therefore, (1) to pull the reaction to completion by adding some second reaction which shifts the equilibrium (this could involve protonating, hydrolyzing, or trapping a product, for example), (2) to measure initial rates under conditions in which the reverse reaction is not significant, or (3) to examine the reaction under conditions in which it is (pseudo) first order in each direction.

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[19] T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Am. Chem. Soc.* 89, 2106 (1967).

[20] E. R. Garrett, *J. Am. Chem. Soc.* 82, 711 (1960).

It is initially surprising that the observed rate constant for a first-order reaction proceeding to equilibrium is *larger* than the first-order rate constant for the reaction in either the forward or reverse directions; in fact, it is equal to the sum of these rate constants (equation 46). The reason for this becomes clear from an

$$k_{\text{obs}} = k_f + k_r \tag{46}$$

inspection of the course of the reaction (Fig. 15) under conditions in which it is pulled to completion by a trapping reaction (upper curve) and conditions in which it proceeds to an equilibrium position (lower curve). The upper curve gives the half-time and the rate constant for the forward reaction without interference from the reverse reaction. The lower curve begins with the same initial rate of product formation, but the rate of product formation is soon slowed as the product accumulates and the back-reaction becomes significant. The necessary consequence is that both the endpoint and the half-time will be smaller (and the observed rate constant larger) for the reaction proceeding to equilibrium compared with the reaction proceeding to completion. This is one of several instances in which it is easy to become confused if a careful distinction is not made between the absolute rate (in moles per minute) and the rate *constant* of a reaction.

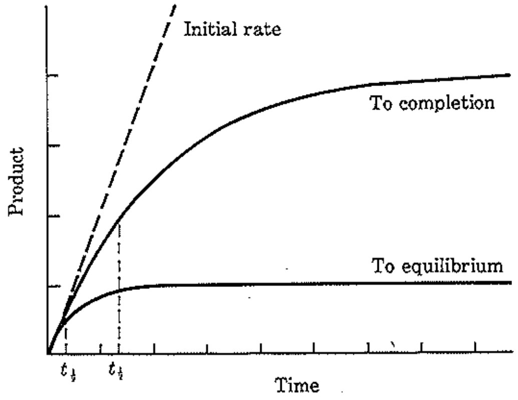

Fig 15. The course of a first-order reversible reaction which is forced to completion (upper curve) and which proceeds to equilibrium (lower curve).

The rate of a reversible first-order reaction is described by equation 47. If the apparent equilibrium constant K_{app} for a given

$$\ln\left(\frac{A_0-[A]_{\text{eq}}}{[A]-[A]_{\text{eq}}}\right) = (k_f+k_r)t = k_{\text{obs}}(t) \tag{47}$$

set of experimental conditions is known, the rate constants for the reaction in each direction are easily obtained from the observed rate constant for approach to equilibrium and equations 46 and 48. It

$$K_{\text{app}} = \frac{k_f}{k_r} \tag{48}$$

is often possible to measure the equilibrium constant for a reaction of the form of equation 49 with a nonabsorbing component B present in large excess simply by comparing the change in absorbance observed for the reaction proceeding to equilibrium with that observed when it goes to completion at a much higher concentration of B (equation 50); this does not require a knowledge of either the con-

$$A + B \rightleftharpoons C \tag{49}$$

$$K = \frac{[C]}{[A][B]} = \frac{\Delta A_{\text{eq}}}{\Delta A_{\max} - \Delta A_{\text{eq}}}\,\frac{1}{[B]} = K_{\text{app}}\,\frac{1}{[B]} \tag{50}$$

centration or the extinction coefficient of the product. In equation 50 ΔA_{eq} and $\Delta A_{\max}$ refer to the absorbance of the product at equilibrium and when the reaction is forced to completion, respectively. If necessary, the values of $\Delta A_{\max}$ and K_{app} may be obtained from the reciprocal ordinate intercept and negative abscissa intercept, respectively, of a plot of $1/\Delta A$ against $1/[B]$, or from the ordinate intercept and negative reciprocal of the slope, respectively, of a plot of ΔA against $\Delta A/[B]$. These are the same type of plots as for the evaluation of acid dissociation constants (Part 3). Once the values of k_f, k_r, and K_{app} have been evaluated for the (pseudo) first-order reaction at various concentrations of the reactant which is present in large excess, it is a simple matter to plot (for example) k_f against [B] to obtain the second-order rate constant for the forward reaction of equation 49, based on the relationship $k_f = k_1[B]$. Alternatively, the constants may be obtained graphically from a plot of k_{obs} against [B], which gives k_R as the ordinate intercept and $-1/K$ as the abscissa intercept.[21]

6. ISOTOPE EXCHANGE AT EQUILIBRIUM

It is frequently useful to measure the rate of a reaction under conditions in which there is no net change in the concentrations of the reactants by measuring the time required for a small quantity of an isotopically labeled reactant to give a labeled product. The change in the amount of label in the starting material or product always follows first-order kinetics, regardless of the order of the overall reaction.[22] What is desired, however, is not the rate of exchange of isotope, but the absolute rate, flux, or turnover of both the labeled and unlabeled reactant molecules to give the product. This rate R may be determined by measuring only the initial rate of incorporation or by multiplying the first-order rate constant for isotope incorporation, obtained in the usual way, by the factor $ab/(a+b)$, according to equation 51, which describes the first-order

$$-\ln\left(\frac{x_\infty - x}{x_\infty}\right) = \overset{\to\ \text{conc/time}}{R}\,\frac{(a+b)}{ab}\,t = \underset{\to\ \text{time}^{-1}}{k}t \tag{51}$$

exchange of labeled BX* to give labeled AX* according to equation 52. The terms are defined by equations 53 to 55. The kinetics of the overall reaction can usually be determined from the dependence of R on the concentrations of the reactants. The presence of a

$$BX^* + AX \rightleftharpoons AX^* + BX \tag{52}$$

$$[AX^*] = x \tag{53}$$

$$[AX] + [AX^*] = a \tag{54}$$

$$[BX] + [BX^*] = b \tag{55}$$

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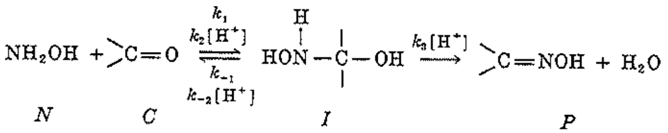
[21] I. W. Sizer and W. T. Jenkins, in E. E. Snell, P. M. Fasella, A. Braunstein, and A. Rossi Fanelli (eds.), "Chemical and Biological Aspects of Pyridoxal Catalysis," p. 123, Pergamon Press, New York, 1963.

[22] R. B. Duffield and M. Calvin, *J. Am. Chem. Soc.* 68, 557 (1946).

significant isotope effect, of course, will mean that the flux of isotope exchange is not an exact measure of the flux of the unlabeled molecules.

C. STEADY-STATE RATE EQUATIONS

The rate equation for a reaction which proceeds through several steps is usually derived by application of the steady-state assumption to the intermediates in a proposed mechanism for the reaction. This is best described by an example, for which we will take the reaction of an aldehyde with hydroxylamine to give an oxime through the intermediate formation of an addition compound, as described in Chap. 10. Near neutral pH, the addition of hydroxylamine to the aldehyde is rapid and reversible and is followed by a slow, rate-determining, acid catalyzed dehydration of the addition compound (equation 56). At low pH, as the concentration of free amine decreases and the rate of acid catalyzed dehydration becomes very fast, the attack of amine on the aldehyde becomes rate-determining and the rate drops below that predicted from the rate law which holds at higher pH; i.e., there is a change in rate-determining step. At very low pH the rate again levels off and becomes independent of pH as an acid catalyzed attack of free amine on the aldehyde becomes significant; the decrease in the concentration of free amine is exactly cancelled by the increase in the rate of acid catalyzed amine attack with increasing acidity. These steps of the mechanism are designated by appropriate rate constants in equation 56 and the concentrations of amine, carbonyl compound, and product will be indicated by N, C, and P, respectively.



$$\underset{N}{NH_2OH} + \underset{C}{>C{=}O} \underset{k_{-1}\atop k_{-2}[H^+]}{\overset{k_1\atop k_2[H^+]}{\rightleftharpoons}} \underset{I}{HON(H)-C-OH} \xrightarrow{k_3[H^+]} \underset{P}{>C{=}NOH} + H_2O \qquad (56)$$

The steady-state derivation is based on the assumption that the rate of change of the concentration of an intermediate is zero or insignificant compared with changes in other reactants and products (equation 57). This assumption has given rise to some confusion because the *flux* or turnover of the intermediate must be as fast as the accumulation of product, and the first-order rate constant for the change in the concentration of an intermediate in a reaction which follows overall first-order kinetics can be as large as that for the overall reaction. The point is that the *absolute* rate of change of the concentration of an intermediate which does not accumulate to a significant extent, in moles per liter per minute, is very small compared with that of the reactants and products. For the hydroxylamine reaction, the steady-state treatment may be applied to rate measurements at low pH, at which most of the hydroxylamine is protonated and there is no significant accumulation of the addition intermediate, but it cannot be applied to experimental data obtained at higher pH in the presence of concentrations of free hydroxylamine which are high enough to convert a significant fraction of the carbonyl compound to the addition intermediate.

$$\frac{dI}{dt} \approx 0 \qquad (57)$$

Now, the change in concentration of the intermediate with time is equal to its rate of formation minus its rate of disappearance by the pathways of equation 56, the proposed mechanism, so that equation 57 can be extended to give equation 58. This equation is solved for the unknown, the concentration of intermediate I, to give equation 59.

$$\frac{dI}{dt} = 0 = (k_1 + k_2\, a_{H^+})NC - (k_{-1} + k_{-2}a_{H^+} + k_3 a_{H^+})I \qquad (58)$$

$$I = \frac{(k_1 + k_2 a_{H^+})NC}{k_{-1} + k_{-2}a_{H^+} + k_3 a_{H^+}} \qquad (59)$$

For a reaction in which the formation of product is essentially irreversible under the conditions of measurement, the rate of product appearance is a function of the only possible path for product appearance from the intermediate I according to equation 60. The relationship of I to the rate constants for its formation and disappearance is known from equation 59, and substitution gives the complete steady-state rate equation 60. This equation can be evaluated from the experimental data. It is usually convenient to remove one or both of the variables N and C from the right-hand side of the equation and describe the experimental results in terms

$$v = \frac{dP}{dt} = k_3 a_{H^+} I = \frac{k_3 a_{H^+}(k_1 + k_2 a_{H^+})NC}{k_{-1} + k_{-2}a_{H^+} + k_3 a_{H^+}} \qquad (60)$$

of apparent first- or second-order rate constants. If the reaction is carried out in the presence of a large excess of N, the pseudo first-order rate constant is given by dividing both sides of the equation by C; the apparent second-order rate constant k' is given by dividing both sides of the equation by both N and C (equation 61). It is possible to include terms in the steady-state rate equation to correct

$$\frac{v}{NC} = k' = \frac{k_{\text{obs}}}{N} = \frac{k_3 a_{\text{H}^+}(k_1 + k_2 a_{\text{H}^+})}{k_{-1} + k_{-2} a_{\text{H}^+} + k_3 a_{\text{H}^+}} \tag{61}$$

for the ionization of each reactant, but this leads to an unnecessarily complicated equation and, in general, it is preferable to correct the observed rate constants to a reaction of one or the other ionic form of each reactant by dividing by the fraction of the reactant in the desired ionic form at each pH value.

The next step is to evaluate the meaning of equation 61 under limiting conditions, so that one can understand its mechanistic significance and be certain that it describes the important mechanistic features of the rate law from which it was derived (equation 56); this procedure also is useful in detecting errors in the derivation. The following limiting regions of pH are significant for oxime formation.

a) Low a_{H^+} (high pH). The terms in parenthesis and in the denominator of equation 61 which contain a_{H^+} become insignificant compared with other terms and may be neglected. Consequently, equation 61 reduces to the simple form of equation 62, in which K_1 is the equilibrium constant for the first step of the reaction. This equation, then, describes the reaction at high pH, at which hydroxylamine addition occurs in a rapid equilibrium step and the observed rate depends on the equilibrium concentration of addition compound and the rate of its acid catalyzed breakdown. The numerical value of $k_1 k_3/k_{-1}$ may be evaluated from the observed rate in this pH region (provided that the steady-state approximation is valid, i.e.,

$$\frac{k_{\text{obs}}}{N} = \frac{k_1}{k_{-1}} k_3 a_{\text{H}^+} = K_1 k_3 a_{\text{H}^+} \tag{62}$$

from experimental data obtained at sufficiently low hydroxylamine concentration that there is no significant accumulation of the intermediate).

b) Intermediate a_{H^+} and pH. In this region there is a change to rate-determining attack of amine on the carbonyl compound, which is equivalent to the statements: $k_3 a_{\text{H}^+} \gg k_{-1}$ and $k_3 a_{\text{H}^+} \gg k_{-2} a_{\text{H}^+}$. If an intermediate goes back to starting materials much faster than it goes on to products, it is in equilibrium with respect to starting materials and a subsequent step must be rate-determining; if it goes on to products much faster than it goes back to starting materials, every molecule of intermediate that is formed goes on to products and the rate of formation of intermediate is the rate-determining step of the overall reaction. It is important to understand this situation and remember that for a reaction under steady-state conditions it is not the absolute value of the rate constants for the two forward steps (for example, k_1 and $k_2 a_{\text{H}^+}$) that determines which step is rate-determining. It is perfectly possible (and not unusual) for the rate *constant* for the second step to be much larger than that for the first step when the second step is rate-determining. The *only* determinant of which step is rate-determining is the relative magnitude of the rates of breakdown of the intermediate to starting materials and products under a given set of experimental conditions (Fig. 4, Chap. 10). With the above inequalities and when $k_1 \gg k_2 a_{\text{H}^+}$ the rate equation for the hydroxylamine reaction reduces to equation 63. This is the expected equation for rate-determining attack of free amine, and the value of k_1 may be determined from the observed rates under conditions in which this step is rate-determining.

$$k_{\text{obs}} = \frac{k_3 a_{\text{H}^+} k_1 N}{k_3 a_{\text{H}^+}} = k_1 N \tag{63}$$

c) High a_{H^+} (low pH). At high acidity the acid catalyzed attack of free amine will become rate determining as $k_2 a_{\text{H}^+}$ becomes larger than k_1. The same inequalities with respect to k_3 hold as in the previous case, and the rate equation reduces to equation 64. Since

$$k_{\text{obs}} = k_2 a_{\text{H}^+} N \tag{64}$$

both the k_1 and $k_2 a_{\text{H}^+}$ terms are likely to contribute significantly to the observed rate of attack under most experimental conditions, their magnitude is best estimated by plotting k_{obs}/N against a_{H^+} to give k_2 and k_1 as the slope and intercept, respectively.

These limiting cases give numerical values for k_1, k_2, and, since k_1 is known, for k_3/k_{-1}. The equilibrium constant for the first step is the same regardless of which path is used to reach equilibrium, so that the value of k_3/k_{-2} may be evaluated from equation 65 and the known value of k_2. These rate constants—the

$$K_1 k_3 = \frac{k_1}{k_{-1}} k_3 = \frac{k_2}{k_{-2}} k_3 \tag{65}$$

constants for the first step and for the partitioning of the intermediate to starting materials and products—are all that can be obtained from a steady-state treatment. Steady-state experiments do not give information which can be used to obtain a value of K_1, the equilibrium constant for formation of the intermediate, or the absolute value of k_3, the rate constant for its breakdown.

With these rate constants it is possible to calculate the value of k_{obs} at any pH, and this should next be done in order to see if the steady-state rate equation provides an accurate description of the experimental results at intermediate pH values, at which more than a single step is rate-determining. For this purpose it is useful to recast equation 61 in the form of equation 66, in which all the quantities on the right side are known. The solid line in Fig. 1 of

$$k_{\text{obs}} = \frac{(k_1 + k_2 a_{\text{H}^+}) a_{\text{H}^+} N}{k_{-1}/k_3 + k_{-2} a_{\text{H}^+}/k_3 + a_{\text{H}^+}} \tag{66}$$

Chap. 10 is calculated from the steady-state rate equation 66; the rates for acid catalyzed dehydration of an equilibrium concentration of the addition intermediate and for hydroxylamine attack through uncatalyzed and acid catalyzed reactions are shown as dashed lines and dotted lines, respectively.[23]

The description to this point has been based on the assumption that the differences in the magnitudes of the various rate constants are large enough so that one or the other step of the reaction becomes almost completely rate-determining under the conditions of the experiments, and the rate constants for that step can be evaluated directly from the experimental rate constants. In practice, however, this is often not the case and both steps contribute to the observed rate under all experimentally attainable conditions. This is particularly likely to be the case if there are two kinetic terms with the same dependence on acidity, such as the k_2 and k_3 terms of equations 56 and 60; unless k_3 is much larger than k_2, for example, the dehydration step will be partially rate-determining even in strong acid solution. If preliminary calculations indicate that this is the case, the correct values of the rate constants must be obtained either by successive approximations or by calculation. Substitution of preliminary values of the rate constants in the steady-state rate equation will usually give an indication of what changes are necessary to take account of the fact that other steps are partially rate-determining, so that the numerical values may be adjusted until a satisfactory fit to the experimental data is obtained.

[23] W. P. Jencks, *J. Am. Chem. Soc.* 81, 475 (1959).

It is often possible to invert the steady-state rate equation and separate the variables so that the values of the rate constants may be obtained in a more elegant manner by reciprocal plots of the experimental data. For example, the reaction of protonated imido esters (IEH⁺) with amines (N) to give amidines (P) proceeds according to the mechanism of equation 67, with a change from rate-determining amine attack at high pH (k_1) to rate-determining breakdown

$$\begin{tikzcd} \text{IEH}^+ + \text{N} \arrow[r, shift left, "k_1"] & \text{IH}^+ \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "K_{\text{IH}^+}"] \arrow[d, "k_3"] & \text{I} + \text{H}^+ \arrow[l, shift left] \arrow[d, "k_2"] \\ & \text{PH}^+ & \text{P} \end{tikzcd} \tag{67}$$

of an addition intermediate (I and IH⁺) through uncharged (k_2) and positively charged (k_3) transition states at low pH.[24] The steady-state equation for this system (equation 68), in which f_{IEH^+} is the fraction of imido ester in the protonated form, may be converted to the reciprocal form (equation 69) to separate the rate constants.

$$\frac{d(P + PH^+)}{dt} = \frac{k_{\text{obs}}}{N f_{\text{IEH}^+}} = \frac{k_1 (k_3 + k_2 K_{\text{IH}^+}/a_{\text{H}^+})}{k_{-1} + k_3 + k_2 K_{\text{IH}^+}/a_{\text{H}^+}} \tag{68}$$

$$\frac{1}{k_{\text{obs}}/N f_{\text{IEH}^+}} = \frac{k_{-1} a_{\text{H}^+}}{k_1 k_3 a_{\text{H}^+} + k_1 k_2 K_{\text{IH}^+}} + \frac{1}{k_1} \tag{69}$$

A reciprocal plot of $k_{\text{obs}}/N f_{\text{IEH}^+}$ against a_{H^+} gives an initially straight line with an intercept equal to $1/k_1$ at $a_{\text{H}^+} = 0$ and

[24] E. Hand and W. P. Jencks, *J. Am. Chem. Soc.* 84, 3505 (1962).

slope $k_{-1}/k_1 k_2 K_{\mathrm{IH}^+}$. At higher acidity the $k_1 k_3 a_{\mathrm{H}^+}$ term becomes dominant, and the line levels off to the value $k_{-1}/k_1 k_3 + 1/k_1$. A third alternative is to evaluate the rate constants by either an iterative procedure or by direct calculation with a computer, but it often takes longer to derive or locate the appropriate computer program than to utilize more primitive methods.

It is worth emphasizing that steady-state kinetics reveals nothing about the nature of an intermediate except the charge, stoichiometry, and *relative* free energies of the transition states for its breakdown to starting materials and to products. It has already been pointed out that kinetics cannot provide information which determines the equilibrium constant for the formation or the absolute rate constants for the breakdown of an intermediate which is present only in steady-state concentrations. It is also not possible to determine the predominant state of ionization or the ionization constant of such an intermediate, so long as it does not accumulate in significant amounts. Consequently, it makes no difference whether a rate law is formulated as an acid catalyzed reaction of a neutral intermediate or as a reaction of the conjugate acid of the intermediate; the same applies to base catalysis. For example, the mechanism of imido ester aminolysis of equation 67 could equally well be formulated in terms of equation 70, in which a neutral intermediate breaks down by uncatalyzed and acid catalyzed pathways. Note that the transition states for the forward and the corresponding reverse steps must always have the same charge and composition, so that the k'_{-1} step, the reverse of the k'_1 step in this mechanism, must contain a proton to balance the proton in IEH$^+$. The steady-state expression for the mechanism of equation 70 is given in equation 71. This has precisely the same form and is kinetically indistinguishable from equation 68; the only difference is that k'_2 is substituted for $k_2 K_{\mathrm{IH}^+}$. A third formulation could be written with a protonated intermediate which breaks down by uncatalyzed and hydroxide ion catalyzed pathways. All these formulations are perfectly equivalent and indistinguishable kinetically, so that use of one or the other implies nothing about the detailed mechanism of the reaction.

$$\mathrm{IEH}^+ + \mathrm{N} \underset{k'_{-1}\mathrm{H}^+}{\overset{k'_1}{\rightleftharpoons}} \mathrm{I} \xrightarrow{\substack{k'_2 \\ k'_3\mathrm{H}^+}} \mathrm{P} \tag{70}$$

$$\frac{k_{\mathrm{obs}}}{Nf_{\mathrm{IEH}^+}} = \frac{k'_1(k'_3 + k'_2/a_{\mathrm{H}^+})}{k'_{-1} + k'_3 + k'_2/a_{\mathrm{H}^+}} \tag{71}$$

It is important to keep in mind that equilibrium requirements and microscopic reversibility must be satisfied in the application or simplification of steady-state rate equations for ordinary thermal reactions. For example, under conditions in which $k_1 \gg k_2[\mathrm{H}^+]$ in equations 56 and 61, it is also necessary that $k_{-1} \gg k_{-2}[\mathrm{H}^+]$. The relative importance of two pathways for a given reaction must be identical for the reaction in both directions. Thus, if it is decided that a particular kinetic term is insignificant for a reaction in one direction, the corresponding term for the opposite direction must also be insignificant.

In general, a requirement for steady-state kinetic treatment provides important evidence for the two-step nature and, hence, the existence of an intermediate in a reaction, but the kinetics do not give any indication of *which* step is rate-determining under a given set of conditions, and an equivalent mechanism can nearly always be written in which the assignment of rate-determining steps is reversed. For example, a kinetically equivalent mechanism for oxime formation could be written in which acid catalyzed formation of the addition intermediate is rate-determining at high pH and decomposition of the intermediate through neutral and cationic transition states is rate-determining at low pH. A choice between such kinetically indistinguishable assignments can sometimes be made on the basis of chemical reasonableness or analogy to the mechanism of related reactions, but usually the distinction is made by obtaining direct proof that formation of the intermediate is a fast step under a given set of conditions. This may be done by demonstrating its accumulation, as in the hydroxylamine reaction at high pH,[23] or by demonstrating exchange reactions which proceed through the intermediate, as in the exchange of amines into imido esters[24] or the exchange of labeled oxygen from water into thiol esters[25] at low pH. A number of examples are discussed in Chap. 10.

1. INHIBITION BY AN INITIAL PRODUCT IN A TWO-STEP REACTION

The 4-methylpyridine catalyzed hydrolysis of *p*-nitrophenyl acetate proceeds through the initial formation of an acetylpyridinium ion intermediate, which then undergoes hydrolysis at a rate which is too fast to measure by ordinary techniques (equation 72). However,

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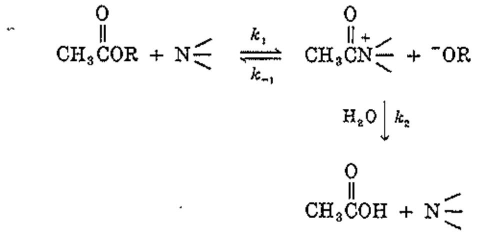
[25] M. L. Bender and H. d'A. Heck, *J. Am. Chem. Soc.* 89, 1211 (1967).



(72)

the *p*-nitrophenolate ion which is released in the first step may react with the intermediate to regenerate starting material faster than water reacts with the intermediate to give hydrolysis products.[3] This back-reaction causes an inhibition of the observed rate of hydrolysis. As shown in Fig. 16, the inhibition becomes significant at a low concentration of product because of the very high reactivity of *p*-nitrophenolate compared to water. The inhibition by this back-reaction causes a deviation from (pseudo) first-order kinetics, but this deviation may not be easily noticeable.

This type of inhibition is useful for two reasons. First, it shows that there must be an intermediate in the reaction when the intermediate cannot be observed directly. This is a method of demonstrating that the above reaction proceeds by nucleophilic rather than by general base catalysis and that carbonium ions are formed in reactions which are inhibited by the initial leaving group, for example. Second, it provides a simple method for determining the *relative* nucleophilic reactivities of the leaving group and of solvent toward the reactive intermediate. This provides a means for setting up a scale of relative reactivities. The mechanism of equation 72 is described by the steady-state equation 73. The value of k_{-1}/k_2 for a reaction of this kind may be evaluated from a plot of $1/k_{\text{obs}}$ against $[\text{RO}^-]$ (equation 74), based on a series of values of k_{obs} obtained under conditions in which the concentration of added RO^- is essentially constant.

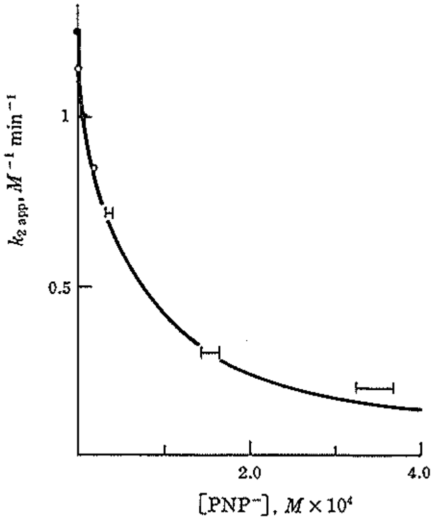


Fig 16. Inhibition of the 4-methylpyridine catalyzed hydrolysis of *p*-nitrophenyl acetate by added *p*-nitrophenolate ion PNP^- at 25°, ionic strength 1.0 *M*. Open circles: 50% free base. Solid symbols: 90% free base amine. The bars show the range of variation of the concentration of *p*-nitrophenolate ion during the experiment.[3]

$$k_{\text{obs}} = \frac{k_1 k_2}{k_2 + k_{-1}[\text{RO}^-]} \tag{73}$$

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k_1} + \frac{k_{-1}[\text{RO}^-]}{k_1 k_2} \tag{74}$$

D. APPLICATIONS OF TRANSITION-STATE THEORY

The transfer of an atom or group B from A—B to C can occur by the complete dissociation of B from A to give a radical which adds to C in a second step (equation 75), but often occurs by a more or less concerted path in which some bond formation develops between B and C before the bond to A is completely broken (equation 76).

$$\text{A—B} \overset{\pm\text{A}}{\rightleftharpoons} \text{B}\cdot \overset{\pm\text{C}}{\rightleftharpoons} \text{B—C} \tag{75}$$

$$\text{A—B} + \text{C} \rightleftharpoons [\text{A}\cdots\text{B}\cdots\text{C}]^{\ddagger} \rightleftharpoons \text{A} + \text{B—C} \tag{76}$$

The two-step pathway follows the energy curves for the dissociation of A—B and B—C, whereas the concerted reaction follows a lower-energy path which might be regarded as a composite of the separate A—B and B—C energy curves and is defined in terms of a "reaction coordinate," a function of the A—B and B—C distances (Fig. 17). The highest-energy point between A—B and

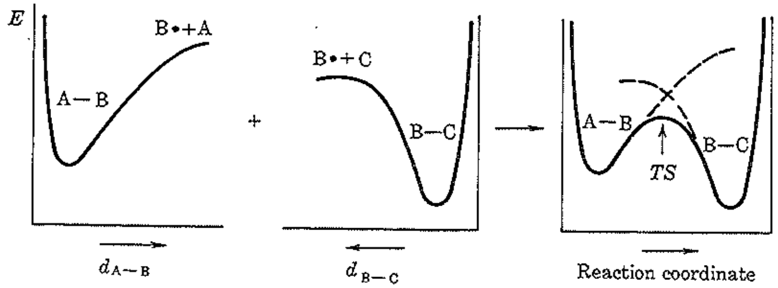


Fig 17. Energy curves for the dissociation of the molecules A—B and B—C and for the reaction of A—B with C to give B—C without complete dissociation.

B—C on this energy diagram is the transition state. The meaning of the reaction coordinate is apparent from an inspection of Fig. 18, in which the reaction coordinate, shown as the dashed line, represents the lowest-energy pathway from A—B to B—C as a function of changing A—B and B—C distances. This contour diagram shows that the B—C distance decreases considerably, as bond formation to C takes place, before the A—B distance has increased beyond that in which effective bonding can exist. If the reaction occurred through a carbonium ion or radical mechanism in which B separates completely from A before it reacts with C (equation 75 or 77), the reaction coordinate would pass through the energy hollow

$$\text{A—B} \overset{\pm A^-}{\rightleftharpoons} \text{B}^+ \overset{\pm C^-}{\rightleftharpoons} \text{B—C} \qquad (77)$$

for a carbonium ion or radical, shown by the dotted lines in Fig. 18. Such a reaction would show a dip in the transition-state diagram corresponding to the metastable intermediate (Fig. 19).

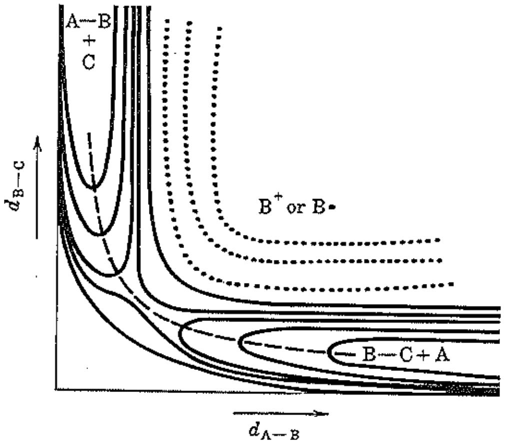


Fig 18. Contour diagram to show that the reaction coordinate (dashed line) is the lowest-energy pathway from A—B to B—C. The dotted lines represent the energy contours for a metastable intermediate carbonium ion or radical.

The great conceptual advantage of the transition-state treatment is that it permits the application to reaction rates of nearly all the considerations that are applied to reaction equilibria by treating the transition state as a chemical species which exists in a sort of pseudo equilibrium with the starting materials (equation 76). The rate of reaction depends on the "concentration" (not the activity) of transition states, almost all of which decompose to products with a transmission coefficient κ, close to 1.0. The observed rate constant k can then be described in terms of a pseudo equilibrium constant, $K^\ddagger$, for the formation of the transition state from the reactants according to equation 78, in which k_B is Boltzmann's constant and h is Planck's constant.

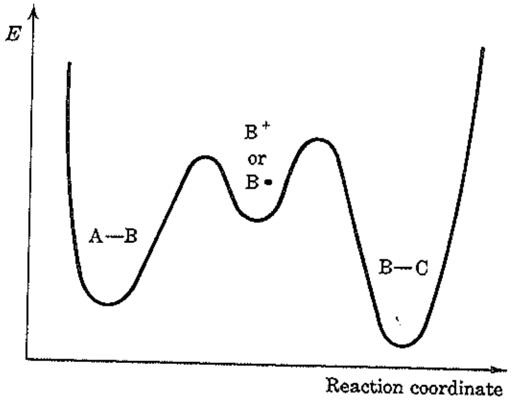


Fig 19. Reaction coordinate for a reaction which proceeds through a metastable carbonium ion or radical intermediate.

$$k = \kappa \frac{k_B T}{h} K^{\ddagger} \tag{78}$$

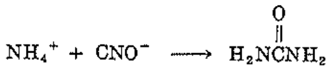
The pseudo equilibrium constant $K^{\ddagger}$ is, like other equilibrium constants, the ratio of the *activity* of the product (the transition state) to the activities of the reactants (equation 79). Since the rate depends on the *concentration* of the transition state and rate measurements are expressed in terms of rate laws based on the

$$K^{\ddagger} = \frac{a_{TS}}{a_A a_B} = \frac{C_{TS}}{C_A C_B} \frac{f_{TS}}{f_A f_B} \tag{79}$$

concentrations of the reactants, the rate may be expressed by equation 80, in which the activity-coefficient ratio $f_A f_B / f_{TS}$ describes the deviation from ideality of the transition state relative to the

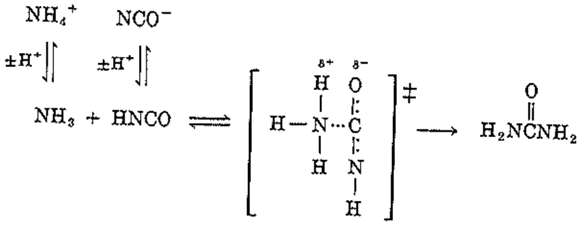
$$\text{Rate} \sim C_{TS} = K^{\ddagger} C_A C_B \frac{f_A f_B}{f_{TS}} \tag{80}$$

reactants. This relationship permits an enormous simplification of considerations of solvent, salt, and other activity-coefficient effects on reaction rates. It is often possible to predict or rationalize such effects simply by inspection of the nature of the reactants and a proposed transition state and a knowledge of the expected stabilizing or destabilizing effects of salts and solvents on the *difference* in structure and charge between the reactants and the transition state. Any such consideration must be based on the predominant ionic species of the reactants in solution, upon which the observed rate constant is based.



$$NH_4^+ + CNO^- \longrightarrow H_2N\overset{\overset{O}{\|}}{C}NH_2 \tag{81}$$

Consider, for example, the well known reaction of ammonium and isocyanate ions to give urea (equation 81). The mechanism of this reaction was the subject of extended controversy among physical chemists regarding whether it proceeds by a direct reaction of cyanate and ammonium ions or whether it proceeds by a preliminary pair of proton transfers to give free ammonia and cyanic acid, which then react with a rate constant k' to give urea (equation 82). It is easily shown algebraically that the rate laws for these two mechanisms are identical, with rate constants which are interrelated by the ionization constants of the reactants (equations 83 and 84).



(82)

$$\text{Rate} = k[NH_4^+][NCO^-] = k'[NH_3][HNCO]$$
$$= k' \frac{K_{NH_4^+}}{K_{HNCO}} [NH_4^+][NCO^-] \tag{83}$$

$$k = k' \frac{K_{NH_4^+}}{K_{HNCO}} \tag{84}$$

However, this conclusion may be reached more rapidly by simple inspection, which reveals that the stoichiometric composition and charge of the transition states for the two mechanisms are identical, so that the two mechanisms must follow the same rate law and be kinetically indistinguishable.

The effects of salts and solvents on this reaction may be evaluated for the two mechanisms by considering separately the effects on the starting materials, on the equilibria for the two ionization steps, and on each rate step, and a number of attempts were made to distinguish the two mechanisms by examination of the effects of salts and solvents on the observed rate.[26] However, the transition-state theory makes it possible to state immediately upon inspection that salt and solvent effects will be the same for these two mechanisms and cannot provide a means of distingushing them. In both cases the starting materials are charged and any reasonable transition state for either mechanism (for example, equation 82) will have either a similar charge or, more probably, a smaller charge than the starting materials. Therefore, the addition of a salt will probably stabilize (decrease the activity coefficient) of the starting materials more than the transition state and give a rate decrease,

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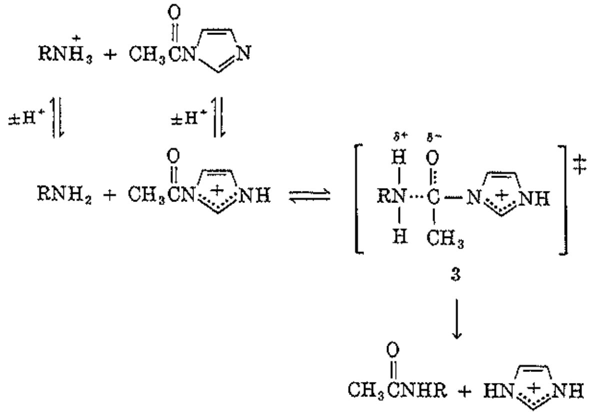
[26] A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," part B, p. 307 2nd ed., John Wiley & Sons, Inc., New York, 1961.

as is found experimentally, for either mechanism. The addition of most organic solvents will destabilize (increase the activity coefficient) of the starting materials compared with the transition state and give a rate increase, as is found experimentally, for either mechanism. The utility of the transition-state approach is that it permits one to ignore all the steps between the starting materials and the transition state.[27] Instead of considering the effect of a variation in reaction conditions on each individual equilibrium and rate step and then attempting to add these to predict the effects on the overall rate, one need only consider effects on the predominant ionic species of the reactants, according to which the observed rate constant is expressed, and on the transition state.

The same simplification applies to considerations of the effects of substituents on reaction rates. Consider, for example, the reaction of acetylimidazole with a series of substituted amines (equation 85).[28] The predominant species in solution near neutral pH are the protonated amine and uncharged acetylimidazole, but the reactive species are the kinetically indistinguishable free amine and protonated acetylimidazole. The effect of adding an electron-withdrawing



(85)

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[27] One cannot ignore any "intermediate" which is so unstable as to require a greater than diffusion-controlled rate for its further reaction in order to account for the observed rate of the overall reaction; such an "intermediate" cannot exist on the reaction path.

[28] W. P. Jencks and J. Carriuolo, *J. Biol. Chem.* 234, 1272, 1280 (1959); *J. Am. Chem. Soc.* 82, 1778 (1960).

substituent to the amine is to increase the observed rate. This may be accounted for by a consideration of each of the two steps of the reaction: an increased concentration of the reactive free amine will be brought about by the decrease in pK of the substituted amine, and this increase must be larger than the decrease in the reactivity of the free amine caused by its decreased basicity. Alternatively, one may simply note that the electron-withdrawing substituent destabilizes the starting material more than the transition state, 3, which will almost certainly have less charge on the nitrogen atom than the starting protonated amine. For more complicated reaction schemes the transition state approach can provide an even greater simplification.

1. THERMODYNAMIC ACTIVATION PARAMETERS

The dependence of observed reaction rates on temperature frequently follows the exponential equations 86 and 87, in which E_a is

$$k = PZe^{-E_a/RT} = Ae^{-E_a/RT} \tag{86}$$

$$\ln k = -E_a/RT + \ln PZ \tag{87}$$

the Arrhenius activation energy and PZ or A represents a "collision factor." The activation energy is given by equation 88, and is

$$\frac{d \ln k}{dT} = -\frac{E_a}{RT^2} \tag{88}$$

usually evaluated from the integrated equation 89 or from the slope

$$\log \frac{k_2}{k_1} = -\frac{E_a}{4.575}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \tag{89}$$

of a plot of log k against $1/T$ (in degrees Kelvin), which gives $-E_a/2.303R$. If this plot is nonlinear or if equation 89 does not give constant values of the activation energy over different temperature ranges, the reaction has a significant heat capacity of activation or there is a change in the nature of the rate-determining step with changing temperature.

The "collision factor" PZ (or A) is the so-called temperature-independent factor (although it is not altogether independent of temperature) and has a normal value of about 3×10^{11} M^{-1} sec^{-1} for a second-order reaction according to collision theory. According to this theory the collision frequency Z is given by equation 90, in which the subscripts A and B refer to two reacting molecules A and B, N is the number of molecules per cubic centimeter, d is the diameter, and m is the mass of the reacting molecules. The probability factor P is an adjustable parameter which in the simplest possible case might be a steric factor describing the fraction of collisions between A and B which occur with the proper orientation of A and B to lead to reaction. The difficulty with this nomenclature for reactions in solution is that this adjustable parameter must include many variables other than steric factors and may even have a value greater than 1. An extreme case is the denaturation of egg albumin, which has a frequency factor of 10^{72}.

$$Z = N_A N_B \left(\frac{d_A + d_B}{2}\right)^2 \sqrt{8\pi k_B T \left(\frac{1}{m_a} + \frac{1}{m_b}\right)} \tag{90}$$

The pseudo equilibrium for formation of the transition state according to transition-state theory makes possible the application to reaction rates of the same thermodynamic parameters that are used to describe ordinary equilibria. The free energy of activation is a direct logarithmic expression of the magnitude of the observed rate constant because of the direct relationship of the rate constant to the equilibrium constant for formation of the activated complex (equation 91). At 25°, $\Delta F^{\ddagger} = -1360 \log k + 17{,}400$ cal/mole, for rate constants expressed in units of time of sec^{-1}.

$$\Delta F^{\dagger} = -RT \ln K^{\dagger} = -RT \ln \frac{kh}{k_B T} \tag{91}$$

The free energy of activation has the usual relationship to the heat of activation $\Delta H^{\ddagger}$ and the entropy of activation $\Delta S^{\dagger}$ (equation 92). The relationship of $\Delta H^{\ddagger}$ to the Arrhenius activation energy is slightly different for different types of reactions, but for reactions in solution it differs

only by the factor RT (equation 93).

$$\Delta F^{\dagger} = \Delta H^{\dagger} - T\,\Delta S^{\dagger} \tag{92}$$

$$\Delta H^{\dagger} = E_a - RT \tag{93}$$

The entropy of activation corresponds to a logarithmic measure of the frequency factor PZ or A and may be calculated from equation 94 or 95, as well as from equations 91 and 92.

$$\Delta S^{\dagger} = R \ln k - R \ln \left(\frac{ek_B T}{h}\right) + \frac{E_a}{T} \tag{94}$$

$$\Delta S^{\ddagger} = 4.576 \log \frac{PZ}{T} - 49.203 \tag{95}$$

In calculating thermodynamic activation properties, particular care must be taken to take account of any rapid equilibrium steps, especially ionizations, which occur before the rate constant which is being examined. For example, a rate constant based on a_{OH^-} or on the free base species of a nucleophile at pH values below its pK must refer to each of these quantities at each temperature examined, so that pH measurements, values of K_w, and the ionization constant of each reactant must be obtained at each temperature in order to calculate the concentration of the reacting species at each temperature.

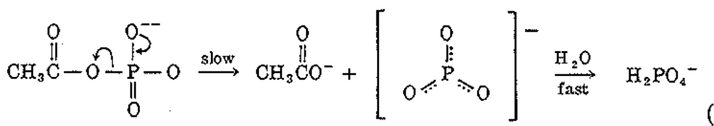
The physical meaning of the entropy of activation provides an intriguing subject for interpretation (and overinterpretation). In terms of the transition-state diagram of Fig. 18 the entropy of activation may be regarded as a measure of the *width* of the saddle point of energy over which reacting molecules must pass as activated complexes. The enthalpy of activation is a measure of the energy barrier which must be overcome by reacting molecules, whereas the entropy of activation is a measure of how many of the molecules which have this much energy can actually react. The activation entropy includes steric and orientation requirements, the entropy of dilution, concentration effects which result from the choice of some standard state in which to express equilibrium and rate constants, and solvent effects. Other things being equal, monomolecular reactions will have entropies of activation near zero because no concentration or orientation requirements ordinarily exist for such reactions. Bimolecular reactions which are described by rate constants with units of M^{-1} will have a negative entropy of activation simply as a result of the entropy requirement for bringing together two molecules from a 1 M solution to a single activated complex, and are likely to have still more negative entropies from steric and orientation requirements, including losses of translational and rotational degrees of freedom in the transition state. The entropy for the equilibrium hydration of an aldehyde, which might be regarded as a model for the combination of water and a carbonyl compound to give a transition state, is on the order of −18 e.u.[29] This is considerably more negative than the value of about −8 e.u. which would be required to bring a molecule of a reactant from a standard 1 *M* solution to a site adjacent to another molecule in preference to a molecule of solvent water.

In spite of uncertainties of quantitative interpretation, the entropy of activation provides a useful criterion to distinguish monomolecular from bimolecular (or polymolecular) reactions when the reaction order cannot be determined directly from the kinetics, as in the case of reactions which involve an unknown number of solvent molecules.[29] For example, the entropy of activation for the hydrolysis of the acetyl phosphate dianion is +3.7 e.u. This is consistent with a monomolecular mechanism in which acetate ion is expelled in the rate-determining step to give monomeric metaphosphate monoanion, which reacts with water in a subsequent fast step (equation 96). This mechanism is not available to acetyl phenyl phosphate, which decomposes more slowly with an entropy of activation of −28.8 e.u. This large negative entropy probably reflects a requirement for the orientation of several water molecules for nucleophilic attack on the *carbonyl* group with assistance by proton transfer (equation 97).[17] The same criteria may be used to interpret the mechanism of reactions which involve an equilibrium proton transfer before the rate-determining step, such as the hydrolysis of sucrose (equations 98 and 99). However, the observed entropy of activation

$$\mathrm{S} + \mathrm{H}^+_{\mathrm{solv}} \underset{K_a}{\rightleftharpoons} \mathrm{SH}^+ \tag{98}$$

$$\mathrm{SH}^+ \xrightarrow{k} \text{products} \tag{99}$$

for such reactions includes the entropy for the preliminary proton transfer (equation 98) as well as for the decomposition of the protonated intermediate (equation 99), which makes interpretation difficult unless the entropy of the proton transfer step can be measured directly or estimated. Nevertheless, there is an empirical correlation between entropy of activation and reaction order for a number of acid catalyzed reactions: monomolecular A_1 reactions have $\Delta S^{\ddagger}$ values which are near zero or positive; bimolecular A_2 reactions of acyl compounds have $\Delta S^{\ddagger}$ values which are usually more negative than −15 e.u., and other bimolecular reactions have $\Delta S^{\ddagger}$ values in the range −5 to −15 e.u., with overlap among these categories in a few cases.[29]



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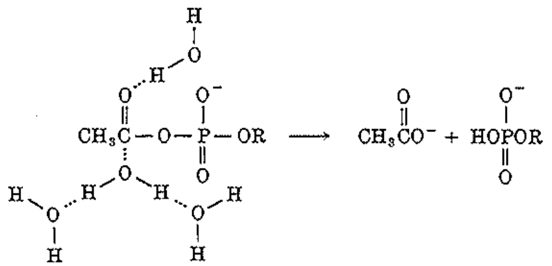

(97)

The *volume* of activation may provide a more direct approach to the estimation of reaction order.[30,31] The volumes of activation for the preliminary proton transfers in acid catalyzed reactions (for example, equation 98) are generally constant for a given type of ionization so that the observed volume of activation may easily be correlated with that for the rate-determining step. A monomolecular reaction is likely to have a transition state which is similar in size or is larger than the starting material, so that the volume of activation is zero or positive. The transition state for a bimolecular reaction is expected to be smaller than the starting materials because the reacting molecules are coming together to form a partial bond, so that the volume of activation is negative. The volume of activation[32] for the hydrolysis of acetyl phosphate dianion (equation 96) is 1.0 ± 1.0 cc/mole, whereas that for the hydrolysis of acetyl phenyl phosphate (equation 97) is −19 ± 2 cc/mole.

Both the volume and the entropy of activation are extremely sensitive to *solvent effects*. The orientation of solvent molecules around charges or developing charges results in a negative entropy

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[29] L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.* 1, 1 (1963).

[30] E. Whalley, *Trans. Faraday Soc.* 55, 798 (1959).

[31] W. J. Le Noble, *Progr. Phys. Org. Chem.* 5, 207 (1967).

[32] G. Di Sabato, W. P. Jencks, and E. Whalley, *Can. J. Chem.* **40**, 1220 (1962).

change, and the accompanying electrostriction will give a negative volume change. These effects may be as large or larger than those resulting from the molecularity of a reaction, so that the entropy and volume of activation may be used as criteria for molecularity only if it is reasonably certain that there is no large difference in charge between the reactants and the transition state. Conversely, if the order of the reaction is known, the entropy and volume of activation can provide an indication of whether the transition state requires more or less charge and solvent orientation than the starting materials.

Since ions can have a structure-breaking as well as a structure-making effect on water, it might be expected that polar transition states might exist with a positive entropy of activation. This does not appear to be a common phenomenon, perhaps because ordered water molecules around the developing charge have a specific catalytic or solvating role, but this possibility and the general difficulty of clearly defining "structural" effects in water suggest that detailed interpretations of reaction mechanisms based on thermodynamic activation parameters should be made with caution.

In considering reaction mechanisms in aqueous solution it is often more useful to evaluate the free energy of activation than the enthalpy of activation because of the difficulties of interpretation of the latter parameter, for reasons which have been noted at a number of points in this volume. Two-dimensional transition-state–reaction-coordinate diagrams may be drawn based on the free energy rather than the enthalpy of activation, and changes in these diagrams with changing reaction conditions or reactants may be useful in interpreting reaction mechanisms. However, it is important to keep in mind that the free energy of activation includes concentration-dependent terms, so that it is easy to make misleading interpretations for steps of different reaction order or for experimental situations in which the concentration of a reactant is varied. Furthermore, the absolute value of the standard free energy of activation is dependent on the concentration scale in which the rate constants are expressed. These concentration effects reflect the contribution of entropies of dilution or concentration to the free energy. The free energy of activation usually refers to a standard state of 1 *M* concentration for the reactants and products given in the rate laws for the forward and reverse reactions upon which the transition-state diagram is based, including hydrogen and hydroxide ions.

For some purposes it is useful to construct a transition-state diagram based on the free energy of activation for an *observed* rate constant, which changes with changing reaction conditions. For example, the nucleophilic displacement of phosphate from *p*-nitrophenyl phosphate by dimethylamine is a two-step reaction with the intermediate formation of a tetrahedral addition compound. The second step is subject to catalysis by hydroxide ion, so that there is a change in rate-determining step from rate-determining attack on the aromatic ring in strong base to rate-determining breakdown of the addition intermediate as the hydroxide ion concentration is decreased (Fig. 20).[33] When diagrams of this kind are used to compare the relative importance of different reaction pathways, it is important to be certain that the order of the reaction and the units of the rate constants are the same for the different pathways that are being compared. For the diagram of Fig. 20 the standard state is taken as 1 *M* for all reactants *except* hydroxide ion. Free-energy–reaction-coordinate diagrams cannot be drawn for irreversible processes, which have an infinitely large free energy. For this reason it is easy to be misled by reaction-coordinate diagrams for reactions which are studied under conditions in which one of the steps is essentially irreversible under the conditions of measurement. This is the case, for example, in enzymatic reactions in which two products are given off in different steps, so that both steps are irreversible under the conditions of initial rate measurements.

2. SUMMARY OF RULES FOR INTERPRETATION

Some of the principles which should be kept in mind when transition-state terminology and free-energy–reaction-coordinate diagrams are utilized for the interpretation of reaction kinetics and mechanism may be summarized as follows:

1. Ordinary kinetic techniques can determine the overall charge and stoichiometric composition of the transition state, but cannot determine the charge distribution or arrangement of atoms in the transition state. The demonstration that the rate of a reaction follows a particular rate law is consistent with a reaction which involves the reactants included in that rate law, but is also consistent with any chemically reasonable mechanism involving other reactants which are in a rapid equilibrium with those in the rate law, if they have the same total composition and charge.
2. It is permissible and often desirable to consider only the reactants in solution and the transition state, ignoring all metastable in-

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[33] A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.* 87, 3217 (1965).

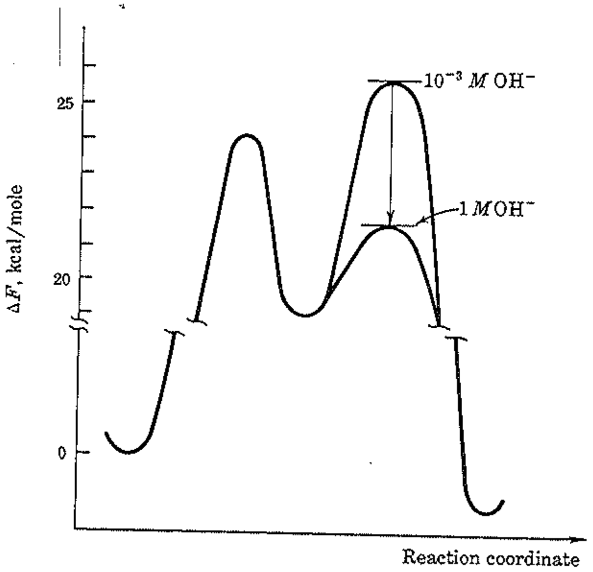

Fig 20. Transition-state diagram for the reaction of dimethylamine with p-nitrophenyl phosphate, based on observed second-order rate constants at 10^{-3} and 1.0 M hydroxide ion concentrations. The free energies of activation are based upon the observed rate constants, but the depth of the valley between the energy barriers for the two steps is arbitrary.[33]

termediates, in interpreting the significance of changes in solvents, salts, substituents, and thermodynamic activation parameters. However, it is essential to know what the reactants are; i.e., their state of ionization and whether a significant fraction of one or more reactants exists in some complexed form or intermediate. It is impossible to distinguish between transition states of identical composition and similar charge distribution by examining the effects of changes in any of the above variables.

3. The rate-determining step is the highest point on the reaction-coordinate diagram. If there is a steady-state intermediate in the reaction, the rate-determining step is determined by the relative rates of breakdown of the intermediate to starting materials and to products, not by the relative rates of its formation and breakdown (Fig. 4, Chap. 10).
4. If there is an unstable intermediate on the reaction path it is likely, but not certain, that this intermediate will resemble the transition state for the overall reaction and that factors which influence the stability of the intermediate will have a similar effect on the transition state.

5. The more unstable a starting material is relative to the products, the more the transition state is likely to occur early along the reaction coordinate and resemble the starting material. The converse holds for the transition state and products (Figs. 9, 10, and 12, Chap. 3). Points (4) and (5) provide the basis for many useful correlations of reaction rates with equilibra for overall or partial reactions.[34]
6. Free-energy diagrams are based on particular standard states, and free-energy barriers should be compared only for comparable standard states. For example, the energy barrier for an uncatalyzed reaction may be compared with that for an acid catalyzed reaction at the standard state of 1 M hydrogen ion. However, arbitrary standard states may be set up and used for comparisons; for example, an acid catalyzed reaction may be considered as a pseudo first-order reaction at some specified pH and compared with an uncatalyzed reaction at the same pH.
7. The baseline of transition-state–reaction-coordinate diagrams is arbitrary. If comparisons are made between related reactions, as in interpreting the effect of substituents on reaction rates, it is permissible to start from equal energies for all starting materials, transition states, or products, depending on the particular effect which is to be compared, because it is only the energy *differences* between starting materials, transition states, and products that are experimentally meaningful. For example, it is formally equally acceptable to speak of a substituent stabilizing the transition state (relative to the reactants) or destabilizing the starting materials (relative to the transition state) if it causes a rate acceleration; chemical intuition will usually lead to a preference for one or the other of these descriptions.
8. Reversible reactions must pass through the same transition state in both directions, so that the rate laws for the forward and reverse reactions must have the same stoichiometric composition and charge. If several reaction pathways are important, the energies of the different transition states and the fraction of the overall reaction that goes through each transition state are the

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[34] J. E. Leffler, *Science* 117, 340 (1953); G. S. Hammond, *J. Am. Chem. Soc.* 77, 334 (1955); J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, 1963.

same for the forward and reverse reactions. It is not uncommon to reach incorrect conclusions about reaction mechanisms by postulating that a certain pathway is important under a particular set of experimental conditions for a reaction in one direction only and that the reverse reaction proceeds by a different mechanism. These requirements arise from the principle of microscopic reversibility or detailed balance.

Name Index