

lems which prevent a final conclusion about a reaction's feasibility. In the first place, most reactions of interest occur in solution, and the enthalpy, entropy, and free energy associated with any reaction depend strongly on the solvent medium. There is only a limited amount of tabulated thermochemical data that is directly suitable for treatment of reactions in organic solvents. Molecular orbital calculations usually refer to the isolated (gas phase) molecule. Estimates of solvation effects must be made in order to apply either experimental or theoretical data to reactions occurring in solution.

There is an even more basic limitation to the usefulness of thermodynamic data for making predictions about reactions: Thermodynamics provides no information about the energy requirements of the pathways that a potential reaction can follow; that is, thermodynamics provides no information about the *rates of chemical reactions*. In the absence of a relatively low-energy pathway, two molecules that can potentially undergo a highly favorable reaction will coexist without reacting. Thus, even if a reaction is thermodynamically feasible, it may not occur at a significant rate. It is therefore extremely important to develop an understanding of reaction mechanisms and the energy requirements and rates of the various steps by which organic reactions proceed.

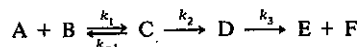
## 4.2. Kinetic Data

Kinetic data are capable of providing much detailed insight into reaction mechanisms. The rate of a given reaction can be determined by following the disappearance of a reactant or the appearance of product. The extent of reaction is often measured spectroscopically, since spectroscopic techniques provide a rapid, continuous means of monitoring changes in concentration. Numerous other methods are available, however, and may be preferable in certain cases. For example, continuous pH measurement or acid-base titration can be used to follow the course of reactions that consume or generate acid or base. Conductance measurements provide a means for determining the rate of reactions that generate ionic species; polarimetry is a convenient way of following reactions involving optically active materials. In general, any property that can be measured and related to the concentration of a reactant or product can be used to determine a reaction rate.

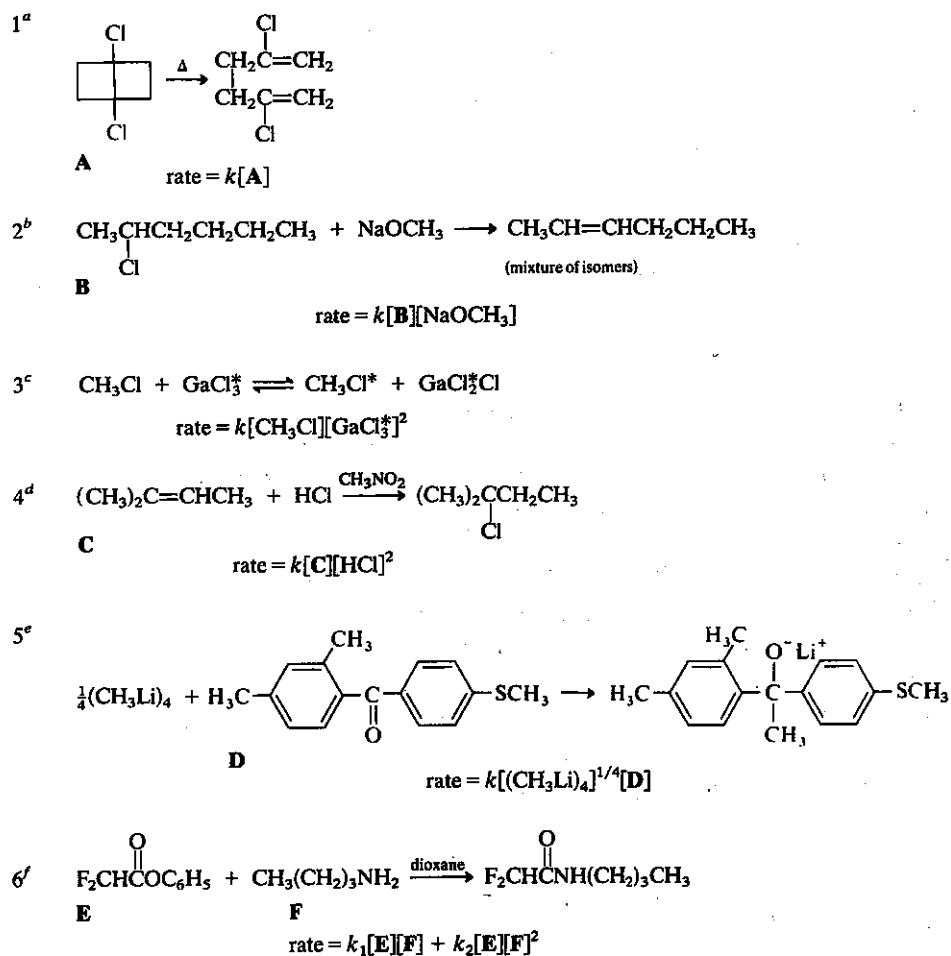
The goal of a kinetic study is to establish the quantitative relationship between the concentration of reactants and catalysts and the rate of the reaction. Typically, such a study involves rate measurements at enough different concentrations of each reactant so that the *kinetic order* with respect to each reactant can be assessed. A complete investigation allows the reaction to be described by a rate law, which is an algebraic expression containing one or more *rate constants* as well as the concentrations of all reactant species that are involved in the rate-determining step and steps prior to the rate-determining step. In the rate law, each concentration has an exponent that is the order of the reaction with respect to that component. The overall kinetic order of the reaction is equal to the sum of all the exponents in the

rate expression. Several examples of rate laws which illustrate the variety observed are presented in Scheme 4.1. Some are simple; others are more complex.

The relationship between a kinetic expression and a reaction mechanism can be appreciated by considering the several individual steps that constitute the overall reaction mechanism. The expression for the rate of any *single step* in a reaction mechanism will contain a term for the concentration of each reacting species. Thus, for the reaction sequence



Scheme 4.1. Some Representative Rate Laws



- a. E. N. Cain and R. K. Solly, *J. Am. Chem. Soc.* **95**, 7884 (1973).  
 b. R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.* **90**, 408 (1968).  
 c. F. P. DeHaan, H. C. Brown, D. C. Conway, and M. G. Gibby, *J. Am. Chem. Soc.* **91**, 4854 (1969).  
 d. Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Am. Chem. Soc.* **91**, 4199 (1969).  
 e. S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.* **94**, 7059 (1972).  
 f. A. S. A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.* **89**, 3020 (1967).

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the rates for the successive steps are

$$\text{step 1: } \frac{d[\text{C}]}{dt} = k_1[\text{A}][\text{B}] - k_{-1}[\text{C}]$$

$$\text{step 2: } \frac{d[\text{D}]}{dt} = k_2[\text{C}]$$

$$\text{step 3: } \frac{d[\text{E}]}{dt} = \frac{d[\text{F}]}{dt} = k_3[\text{D}]$$

Let us further specify that the first step is a very rapid but unfavorable equilibrium, and that  $k_2 \ll k_3$ , i.e., that the second step is slow relative to the third step. Under these circumstances, the overall rate of the reaction will depend on the rate of the second step, and the second step is called the *rate-determining step*.

Kinetic data provide information only about the rate-determining step and steps preceding it. In the hypothetical reaction under consideration, the final step follows the rate-determining step, and since its rate will not affect the rate of the overall reaction,  $k_3$  will not appear in the overall rate expression. The rate of the overall reaction is governed by the second step, which is the bottleneck in the process. The rate of this step is equal to  $k_2$  multiplied by the molar concentration of intermediate C, which may not be directly measurable. It is therefore necessary to express the rate in terms of the concentration of reactants. In the case under consideration, this can be done by recognizing that [C] is related to [A] and [B] by an equilibrium constant

$$K = \frac{[\text{C}]}{[\text{A}][\text{B}]}$$

Furthermore,  $K$  is related to  $k_1$  and  $k_{-1}$  by the requirement that no net change in composition occur at equilibrium.

$$k_{-1}[\text{C}] = k_1[\text{A}][\text{B}]$$

$$[\text{C}] = \frac{k_1}{k_{-1}} [\text{A}][\text{B}]$$

The rate of step 2 can therefore be written in terms of [A] and [B]:

$$\frac{d[\text{D}]}{dt} = k_2[\text{C}] = k_2 \frac{k_1}{k_{-1}} [\text{A}][\text{B}] = k_{\text{obs}}[\text{A}][\text{B}]$$

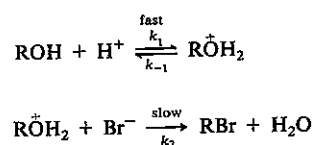
Experimentally, it would be observed that the reaction rate would be proportional to both [A] and [B]. Kinetic data are normally handled using the integrated forms of the differential equations. The integrated rate equations for simple first-order and second-order reactions are

$$\text{first-order reaction: } k = \frac{1}{t} \ln \left( \frac{c_0}{c} \right)$$

$$\text{second-order reaction: } k = \frac{1}{t(a_0 - b_0)} \ln \frac{b_0(a)}{a_0(b)}$$

where  $a$ ,  $b$ , and  $c$  refer to concentrations of reactants at time  $t$ , and  $a_0$ ,  $b_0$ , and  $c_0$  to initial concentrations. As reaction mechanisms become more complex, the mathematical form of their rate expressions and their solutions become increasingly complex. For the simple rate expressions, graphical or numerical analysis of the data directly provides a value for the appropriate rate constant. More complex rate expressions may be analyzed by a variety of graphical or analytical techniques, in conjunction with sufficient changes in the reactant concentrations and other variables to determine the kinetic expression and rate constants.

Most organic reactions involve more than one step. It is therefore necessary to consider the kinetic expressions that arise from some of the more important cases of multistep reactions. There may be a rapid equilibrium preceding the rate-determining step. Such a mechanism may operate, for example, in the reaction of an alcohol with hydrobromic acid to give an alkyl bromide:



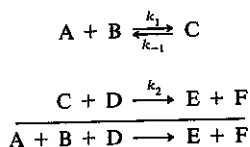
The overall rate being measured is that of step 2, but there may be no means of directly measuring  $[\text{ROH}_2^+]$ . The concentration of the protonated intermediate  $\text{ROH}_2^+$  can be expressed in terms of the concentration of the starting material by taking into consideration the equilibrium constant, which relates  $[\text{ROH}]$ ,  $[\text{Br}^-]$ , and  $[\text{H}^+]$ :

$$K = \frac{[\text{ROH}_2^+]}{[\text{ROH}][\text{H}^+]}$$

$$[\text{ROH}_2^+] = K[\text{ROH}][\text{H}^+]$$

$$\text{rate} = k_2 K [\text{ROH}][\text{H}^+][\text{Br}^-] = k_{\text{obs}} [\text{ROH}][\text{H}^+][\text{Br}^-]$$

A useful approach that is often used in analysis and simplification of kinetic expressions is the *steady-state approximation*. It can be illustrated with a hypothetical reaction scheme:



If C is a reactive, unstable species, its concentration will never be very large. It must then be consumed at a rate that closely approximates the rate at which it is formed. Under these conditions, it is a valid approximation to set the rate of formation of C equal to its rate of destruction:

$$k_1[\text{A}][\text{B}] = k_2[\text{C}][\text{D}] + k_{-1}[\text{C}]$$

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Rearrangement of this equation provides an expression for [C]:

$$\frac{k_1[A][B]}{k_2[D] + k_{-1}} = [C]$$

By substituting into the rate for the second step, the following expression is obtained:

$$\text{rate} = k_2[C][D] = k_2 \frac{k_1[A][B]}{k_2[D] + k_{-1}} [D]$$

If  $k_2[D]$  is much greater than  $k_{-1}$ , the rate expression simplifies to

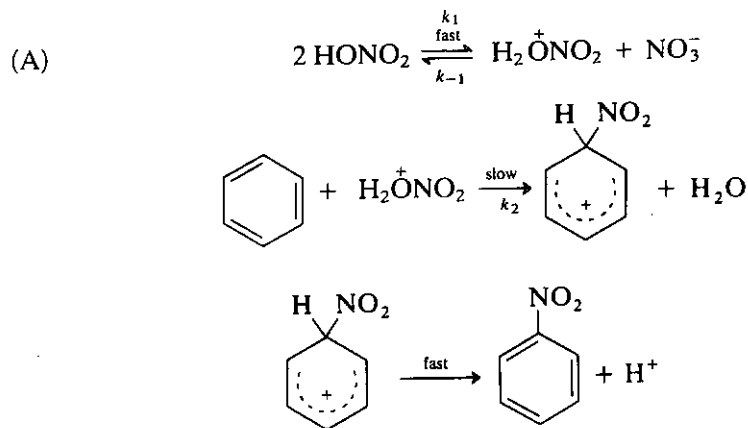
$$\text{rate} = \frac{k_2 k_1 [A][B][D]}{k_2[D]} = k_1 [A][B]$$

On the other hand, if  $k_2[D]$  is much less than  $k_{-1}$ , the observed rate expression becomes

$$\text{rate} = \frac{k_1 k_2 [A][B][D]}{k_{-1}}$$

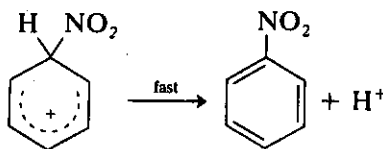
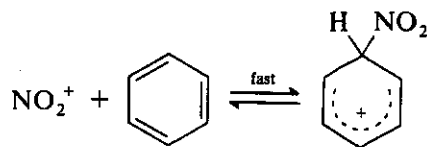
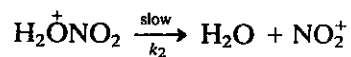
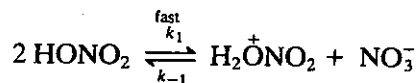
The first situation corresponds to the first step being rate-determining. In the second case, it is the second step that is rate-determining, with the first step being a preequilibrium.

The normal course of a kinetic investigation involves the postulation of likely mechanisms and comparison of the observed rate law with those expected for the various mechanisms. Those mechanisms that are incompatible with the observed kinetics can be eliminated as possibilities. Let us consider aromatic nitration by nitric acid in an inert solvent as a typical example and restrict the mechanisms being considered to the three shown below. In an actual case, such arbitrary restriction would not be imposed, but instead all mechanisms compatible with existing information would be considered.



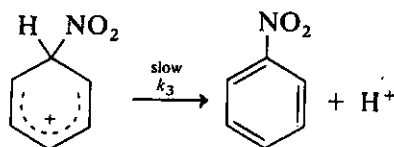
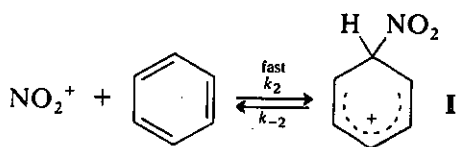
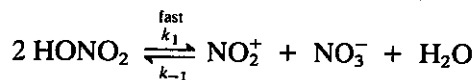
$$\begin{aligned} \text{rate} &= k_2 [\text{H}_2\text{ONO}_2^+][\text{benzene}] = \frac{k_2 k_1 [\text{HONO}_2]^2}{k_{-1} [\text{NO}_3^-]} [\text{benzene}] \\ &= k_{\text{obs}} \frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]} [\text{benzene}] \end{aligned}$$

(B)



$$\text{rate} = \frac{k_1 k_2 [\text{HONO}_2]^2}{k_{-1} [\text{NO}_3^-]} = k_{\text{obs}} \frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]}$$

(C)



The third step is rate-controlling, so

$$\text{rate} = k_3[\text{I}]$$

[I] can be expressed in terms of the rapid equilibria involved in its formation:

$$k_{-2}[\text{I}] = k_2[\text{NO}_2^+][\text{benzene}]$$

$$[\text{NO}_2^+] = \frac{k_1[\text{HNO}_3]^2}{k_{-1}[\text{NO}_3^-][\text{H}_2\text{O}]}$$

$$\text{rate} = k_3 \frac{k_2[\text{benzene}]k_1[\text{HNO}_3]^2}{k_{-2}k_{-1}[\text{NO}_3^-][\text{H}_2\text{O}]}$$

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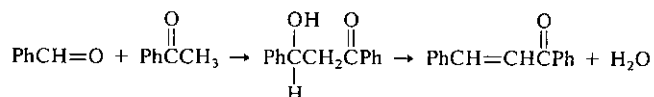
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$$\begin{aligned} \text{rate} &= \frac{k_{\text{obs}}[\text{HNO}_3]^2[\text{benzene}]}{[\text{NO}_3^-][\text{H}_2\text{O}]} \\ &= k_{\text{obs}} \frac{[\text{HNO}_3]^2[\text{benzene}]}{[\text{NO}_3^-]} \quad \text{if } [\text{H}_2\text{O}] \gg [\text{benzene}] \end{aligned}$$

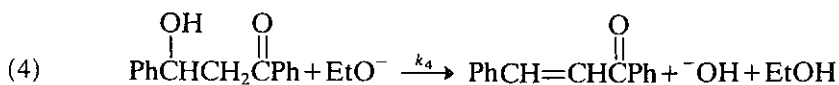
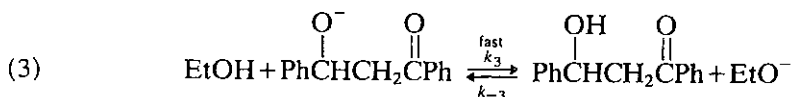
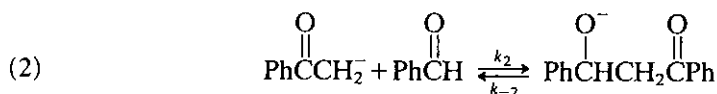
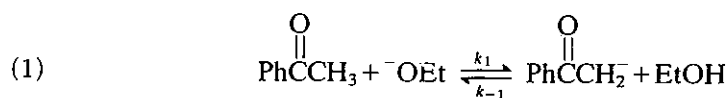
Mechanism B has the distinctive feature that it is zero-order in the reactant benzene, since the rate-determining step occurs prior to the involvement of benzene. Mechanism B has, in fact, been established for nitration of benzene in several organic solvents, and the absence of a benzene concentration term in the rate law is an important part of the evidence for this mechanism.<sup>8</sup>

Mechanisms A and C, on the other hand, provide kinetic expressions that are rather similar in form, differing only in the inclusion of water in the expression for mechanism C. This might not be a detectable difference. If the concentration of water is several times larger than that of benzene, its overall concentration will change little during the course of the reaction. In this circumstance, the term for the concentration of water would disappear (by becoming a component of the observed rate constant  $k$ ) so that the form of the kinetic expression alone would not distinguish between mechanisms A and C.

To illustrate the development of a kinetic expression from a postulated reaction mechanism, let us consider the base-catalyzed reaction of benzaldehyde and acetophenone.



Based on general knowledge of base-catalyzed reactions of carbonyl compounds, a reasonable sequence of steps can be written, but the relative rates of the steps are an open question. Furthermore, it is known that reactions of this type are generally reversible so that the potential reversibility of each step must be taken into account. A completely reversible mechanism is as follows:



8. J. H. Ridd, *Acc. Chem. Res.* **4**, 248 (1971); J. H. Ridd, in *Studies on Chemical Structure and Reactivity*, J. H. Ridd (ed.), John Wiley and Sons, New York, 1966, Chapter 7; J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitrogen and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971; K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980.

Since proton transfer reactions between oxygen atoms are usually very fast, step 3 can be assumed to be a rapid equilibrium. With the above mechanism assumed, let us examine the rate expressions that would result, depending upon which of the steps is rate-determining.

If step 1 is rate-controlling, the rate expression would be

$$\text{rate} = k_1[\text{PhCOCH}_3][^-\text{OEt}]$$

Under these conditions, the concentration of the second reactant, benzaldehyde, would not enter into the rate expression.

If step 1 is an equilibrium and step 2 is rate-controlling, we obtain the rate expression

$$\text{rate} = k_2[\text{PhCOCH}_2^-][\text{PhCHO}]$$

which on substituting in terms of the rapid prior equilibrium gives

$$\text{rate} = k_2K_1[\text{PhCOCH}_3][^-\text{OEt}][\text{PhCHO}]$$

since

$$[\text{PhCOCH}_2^-] = K_1[\text{PhCOCH}_3][^-\text{OEt}]$$

where  $K_1$  is the equilibrium constant for the deprotonation in the first step.

If the final step is rate-controlling, the rate is



The concentration of the intermediate



can be expressed in terms of the three prior equilibria. Using I for the intermediate and  $\text{I}^-$  for its conjugate base and neglecting  $[\text{EtOH}]$ , since EtOH is the solvent and its concentration will remain constant, gives the relationships:

$$K_3 = \frac{[\text{I}][^-\text{OEt}]}{[\text{I}^-]} \quad \text{and} \quad [\text{I}] = K_3 \frac{[\text{I}^-]}{[^-\text{OEt}]}$$

and, since  $[\text{I}^-] = K_2[\text{PhCOCH}_2^-][\text{PhCHO}]$ , substituting for  $[\text{I}^-]$  gives

$$[\text{I}] = K_3 \frac{K_2[\text{PhCOCH}_2^-][\text{PhCHO}]}{[^-\text{OEt}]}$$

Substituting for  $[\text{PhCOCH}_2^-]$  from the equilibrium expression for step 1 gives

$$[\text{I}] = \frac{K_3K_2[\text{PhCHO}]}{[^-\text{OEt}]} K_1[\text{PhCOCH}_3][^-\text{OEt}] = K'[\text{PhCHO}][\text{PhCOCH}_3]$$

and this provides the final rate expression

$$\text{rate} = k_{\text{obs}}[^-\text{OEt}][\text{PhCHO}][\text{PhCOCH}_3]$$



The form of this third-order kinetic expression is identical to that in the case where the second step is rate-determining.

Experimental studies of this base-catalyzed condensation have revealed that it is third-order, indicating that either the second or fourth step must be rate-determining. Studies on the intermediate I obtained by an alternative synthesis have shown that  $k_4$  is about four times as large as  $k_{-3}$  so that about 80% of the intermediate goes on to product. These reactions are faster than the overall reaction under the same conditions, so the second step must be rate-controlling.<sup>9</sup>

These examples illustrate the relationship between kinetic results and the determination of reaction mechanism. Kinetic results can exclude from consideration all mechanisms that require a rate law different from the observed one. It is often true, however, that related mechanisms give rise to identical predicted rate expressions. In this case, the mechanisms are "kinetically equivalent," and a choice between them is not possible on the basis of kinetic data. A further limitation on the information that kinetic studies provide should also be recognized. Although the data can give the *composition* of the activated complex for the rate-determining step and preceding steps, they provide no information about the *structure* of the intermediate. Sometimes the structure can be inferred from related chemical experience, but it is never established by kinetic data alone.

The nature of the rate constants  $k$ , can be discussed in terms of *transition state theory*. This is a general theory for analyzing the energetic and entropic components of a reaction process. In transition state theory, a reaction is assumed to involve the attainment of an activated complex that goes on to product at an extremely rapid rate. The rate of decomposition of the activated complex has been calculated from the assumptions of the theory to be  $6 \times 10^{12} \text{ s}^{-1}$  at room temperature and is given by the expression<sup>10</sup>

$$\text{rate of activated complex decomposition} = \frac{\kappa k T}{h} \quad (4.3)$$

in which  $\kappa$  is the transmission coefficient, which is usually taken to be 1,  $k$  is Boltzmann's constant,  $h$  is Planck's constant, and  $T$  is absolute temperature.

$$\text{rate of reaction} = \frac{\kappa k T}{h} [\text{activated complex}]$$

If the activated complex is considered to be in equilibrium with its component molecules, the attainment of the transition state (T.S.) can be treated as being

9. E. Coombs and D. P. Evans, *J. Chem. Soc.*, 1295 (1940); D. S. Noyce, W. A. Pryor, and A. H. Bottini, *J. Am. Chem. Soc.* **77**, 1402 (1955).
10. For a complete development of these relationships, see M. Boudart, *Kinetics of Chemical Processes*, Prentice-Hall, Englewood Cliffs, New Jersey, 1968, pp. 35-46; K. Amdur and C. G. Hammes, *Chemical Kinetics, Principles and Selected Topics*, McGraw-Hill, New York, 1966, pp. 43-58; J. W. Moore and R. G. Pearson, *Kinetics and Mechanism*, Wiley, New York, 1981, pp. 159-169; M. M. Kreevoy and D. G. Truhlar, in *Investigation of Rates and Mechanisms of Reactions*, C. F. Bernasconi (ed.), *Techniques of Chemistry*, Fourth Edition, Vol. VI, Part 1, Wiley-Interscience, New York, 1986.