12
Kinetics

In this chapter a study is made of the rates and mechanisms of reactions with particular emphasis on decomposition and stabilization of drug products. The experimental investigation of the possible breakdown of new drugs is not a simple matter. However, a small expenditure of time and energy in this direction can yield results that may save the pharmaceutical industry both money and reputation. Applications of kinetics in pharmacy result in the production of more stable drug preparations, the dosage and rationale of which may be established on sound scientific principles.

Although the manufacturer is primarily responsible for assuring the stability of marketed products, the community pharmacist also must have some understanding of stability characteristics to handle and store products under the proper conditions. He or she must also recognize that alterations may occur when a drug is combined with other ingredients. For example, if thiamine hydrochloride, which is most stable at a pH of 2 to 3 and is unstable above pH 6, is combined with a buffered vehicle of say pH 8 or 9, the vitamin is rapidly inactivated.[1] Knowing the rate at which a drug deteriorates at various hydrogen ion concentrations allows one to choose a vehicle that will retard or prevent the degradation.

Thus, as a result of current research involving the kinetics of drug systems, the pharmacist is able to assist the physician and patient regarding the proper storage and use of medicinal agents. This chapter brings out a number of factors that bear upon the formulation, stabilization, and administration of drugs. Concentration, temperature, light, and catalysts are important in relation to the speed and the mechanism of reactions and will be discussed in turn.

RATES AND ORDERS OF REACTIONS

The rate, velocity, or speed of a reaction is given by the expression, dc/dt, where dc is the increase or decrease of concentration over an infinitesimal time interval, dt. According to the law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules, a and b, of the substances A and B undergoing reaction. In the reaction

$$aA + bB + \ldots = \text{Products} \qquad (12\text{–}1)$$

the rate of the reaction is

$$\text{Rate} = -\frac{1}{a}\frac{d(A)}{dt}$$

$$= -\frac{1}{b}\frac{d(B)}{dt} = \ldots k(A)^a(B)^b \ldots \qquad (12\text{–}2)$$

in which k is the *rate constant*.

The overall *order* of a reaction is the sum of the exponents ($a + b$, for example, in equation (12–2) of the concentration terms, A and B. The order with respect to one of the reactants, A or B, is the exponent a or b of that particular concentration term. In the reaction of ethyl acetate with sodium hydroxide in aqueous solution, for example,

$$CH_3COOC_2H_5 + NaOH_{soln} \rightarrow CH_3COONa + C_2H_5OH$$

the rate expression is

$$\text{Rate} = -\frac{d[CH_3COOC_2H_5]}{dt}$$

$$= -\frac{d[NaOH]}{dt} = k[CH_3COOC_2H_5]^1[NaOH]^1 \qquad (12\text{–}3)$$

The reaction is first-order ($a = 1$) with respect to ethyl acetate and first-order ($b = 1$) with respect to sodium hydroxide solution; overall the reaction is second-order ($a + b = 2$).

Suppose that in this reaction, sodium hydroxide as well as water was in great excess and ethyl acetate was in a relatively low concentration. As the reaction proceeded, ethyl acetate would change appreciably from its original concentration, whereas the concentrations of NaOH and water would remain essentially unchanged since they are present in great excess. In this case the contribution of sodium hydroxide to the rate expression is considered constant and the reaction rate can be written as

$$-\frac{d(CH_3COOC_2H_5)}{dt} = k'(CH_3COOC_2H_5) \qquad (12\text{–}4)$$

in which $k' = k(\text{NaOH})$. The reaction is then said to be *pseudo-first-order*, for it depends only on the first power ($a = 1$) of the concentration of ethyl acetate. In general, when one of the reactants is present in such great excess that its concentration may be considered constant or nearly so, the reaction is said to be of *pseudo-order*.

Example 12–1. In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$$(CH_3CO)_2O + 2C_2H_5OH = 2CH_3CO_2C_2H_5 + H_2O$$

the rate of reaction is

$$Rate = -\frac{d([CH_3CO]_2O)}{dt}$$

$$= k([CH_3CO]_2O)(C_2H_5OH)^2 \qquad (12\text{–}5)$$

What is the order of the reaction with respect to acetic anhydride? With respect to ethyl alcohol? What is the overall order of the reaction?

If the alcohol, which serves here as the solvent for acetic anhydride, is in large excess such that a small amount of ethyl alcohol is used up in the reaction, write the rate equation for the process and state the order.

Answer: The reaction appears to be first-order with respect to acetic anhydride, second-order with respect to ethyl alcohol, and overall third-order. However, since alcohol is the solvent its concentration remains essentially constant and the rate expression may be written

$$-\frac{d([CH_3CO_2]O)}{dt} = k'([CH_3CO_2]O) \qquad (12\text{–}6)$$

Kinetically the reaction is therefore pseudo-first-order as noted by S. Glasstone, *Textbook of Physical Chemistry*, Van Nostrand, 1946, pp. 1051, 1052.

Molecularity. A reaction whose overall order is measured may be considered to occur through several steps or elementary reactions. Each of the elementary reactions has a stoichiometry giving the number of molecules taking part in that step. Since the order of an elementary reaction gives the number of molecules coming together to react in the step, it is common to refer to this order as the *molecularity* of the elementary reaction. If, on the other hand, a reaction proceeds through several stages, the term molecularity is not used in reference to the observed rate law: one step may involve two molecules, a second step only one molecule, and a subsequent step one or two molecules. Hence order and molecularity are ordinarily identical only for elementary reactions. Bimolecular reactions may or may not be second-order.

In simple terms molecularity is the number of molecules, atoms, or ions reacting in an elementary process. In the reaction

$$Br_2 \rightarrow 2Br$$

the process is *unimolecular*, since the single molecule, Br_2, decomposes to form two bromine atoms. In the single-step reaction

$$H_2 + I_2 \rightarrow 2HI$$

the process is *bimolecular*, since two molecules, one of H_2 and one of I_2, must come together to form the product HI. *Termolecular* reactions—that is, processes in which three molecules must come together simultaneously—are rare.

Chemical reactions that proceed through more than one step are known as *complex reactions*. The overall order determined kinetically may not be identical with the molecularity, for the reaction consists of several steps, each with its own molecularity. For the overall reaction

$$2NO + O_2 \rightarrow 2NO_2$$

the order has been found experimentally to be 2. The reaction is not termolecular, in which two molecules of NO would collide simultaneously with one molecule of O_2. Instead, the mechanism is postulated to consist of two elementary steps, each being bimolecular:

$$2NO \rightarrow N_2O_2$$

$$N_2O_2 + O_2 \rightarrow 2NO_2$$

Specific Rate Constant. The constant k appearing in the rate law associated with a single-step (elementary) reaction is called the *specific rate constant* for that reaction. Any change in the conditions of the reaction, for example, temperature, solvent, or a slight change in one of the reacting species, will lead to a rate law having a different value for the specific rate constant. Experimentally, a change of specific rate constant corresponds simply to a change in the slope of the line given by the rate equation. Variations in the specific rate constant are of great physical significance, for a

change in this constant necessarily represents a change at the molecular level as a result of a variation in the reaction conditions. This is further discussed on pages 295–301.

Rate constants derived from reactions consisting of a number of steps of different molecularity are functions of the specific rate constants for the various steps. Any change in the nature of a step due to a modification in the reaction conditions or in the properties of the molecules taking part in this step could lead to a change in the value of the overall rate constant. At times, variations in an overall rate constant can be used to provide useful information about a reaction, but quite commonly, anything that affects one specific rate constant will affect another; hence, it is quite difficult to attach significance to variations in the overall rate constant for these reactions.

Units of the Basic Rate Constants. To arrive at units for the rate constants appearing in zero-, first-, and second-order rate laws, the equation expressing the law is rearranged to have the constant expressed in terms of the variables of the equation. Thus, for a zero-order reaction,

$$k = -\frac{dA}{dt} = \frac{\text{moles/liter}}{\text{second}}$$

$$= \frac{\text{moles}}{\text{liter second}} = \text{moles liter}^{-1}\,\text{second}^{-1}$$

for a first-order reaction,

$$k = -\frac{dA}{dt}\frac{1}{A} = \frac{\text{moles/liter}}{\text{second-moles/liter}}$$

$$= \frac{1}{\text{second}} = \text{second}^{-1}$$

and for a second-order reaction,

$$k = -\frac{dA}{dt}\frac{1}{A^2} = \frac{\text{moles/liter}}{\text{second (moles/liter)}^2}$$

$$= \frac{\text{liter}}{\text{mole-second}} = \text{liter second}^{-1}\,\text{mole}^{-1}$$

where A is the molar concentration of the reactant. It is an easy matter to replace the units, moles/liter, by any other units (e.g., pressure in atmospheres), to obtain the proper units for the rate constants if quantities other than concentration are being measured.

Zero-Order Reactions. Garrett and Carper[2] found that the loss in color of a multisulfa product (as measured by the decrease of spectrophotometric absorbance at a wavelength of 500 nm) followed a zero-order rate. The rate expression for the change of absorbance A with time is therefore

$$-\frac{dA}{dt} = k_0 \qquad (12\text{–}7)$$

in which the minus sign signifies that the absorbance is decreasing (i.e., the color is fading). The velocity of fading is seen to be constant and independent of the concentration of the colorant used. The rate equation may be integrated between the initial absorbance A_0 corresponding to the original color of the preparation at $t = 0$, and A_t, the absorbance after t hours:

$$\int_{A_0}^{A_t} dA = -k_0 \int_0^t dt$$

$$A_t - A_0 = -k_0 t$$

or

$$A_t = A_0 - k_0 t \qquad (12\text{–}8)$$

The initial concentration corresponding to A_0 is ordinarily written as a and the concentration remaining at time t as c.

When this linear equation is plotted with c on the vertical axis against t on the horizontal axis, the slope of the line is equal to $-k_0$. Garrett and Carper obtained a value for k of 0.00082 absorbance decrease per hour at 60° C, signifying that the color was fading at this constant rate independent of concentration.

The half-period, or *half-life* as it is usually called, is the time required for one half of the material to disappear; it is the time at which A has decreased to $\frac{1}{2}A$. In the present illustration, $A_0 = 0.470$ and $\frac{1}{2}A_0 = 0.235$.

$$t_{1/2} = \frac{\frac{1}{2}A_0}{k_0} = \frac{0.235}{8.2 \times 10^{-4}} = 2.9 \times 10^2 \text{ hr.}$$

Suspensions. Apparent Zero-Order Kinetics.[3] Suspensions are another case of zero-order kinetics, in which the concentration in solution depends on the drug's solubility. As the drug decomposes in solution, more drug is released from the suspended particles so that the concentration remains constant. This concentration is, of course, the drug's equilibrium solubility in a particular solvent at a particular temperature. The important point is that the amount of drug in solution remains constant despite its decomposition with time. The reservoir of solid drug in suspension is responsible for this constancy.

The equation for an ordinary solution, with no reservoir of drug to replace that depleted, is the first-order expression, equation (12–11) (see p. 287):

$$\frac{-d[A]}{dt} = k[A]$$

in which A is the concentration of drug remaining undecomposed at time t, and k is known as a first-order rate constant. When the concentration $[A]$ is rendered constant, as in the case of a suspension, we may write

$$k[A] = k_0 \qquad (12\text{–}9)$$

so that the first-order rate law (12–11) becomes

$$-\frac{d[A]}{dt} = k_0 \qquad (12\text{–}10)$$

Equation (12–10) obviously is a zero-order equation. It is referred to as an *apparent zero-order equation*, being zero-order only because of the suspended drug reservoir that ensures constant concentration. Once all the suspended particles have been converted into drug in solution, the system changes to a first-order reaction.

Example 12–2. A prescription for a liquid aspirin preparation is called for. It is to contain 325 mg/5 mL or 6.5 g/100 mL. The solubility of aspirin at 25° C is 0.33 g/100 mL; therefore, the preparation will definitely be a suspension. The other ingredients in the prescription cause the product to have a pH of 6.0. The first-order rate constant for aspirin degradation in this solution is 4.5×10^{-6} sec^{-1}. Calculate the zero-order rate constant. Determine the shelf life for the liquid prescription, assuming that the product is satisfactory until the time at which it has decomposed to 90% of its original concentration (i.e., 10% decomposition) at 25° C.

Answer: $k_0 = k \times$ [aspirin in solution], from equation (12–9)

$$k_0 = (4.5 \times 10^{-6}\ \text{sec}^{-1}) \times (0.33\ \text{g/100 mL})$$

$$k_0 = 1.5 \times 10^{-6}\ \text{g/100 mL sec}^{-1}$$

$$*t_{90} = \frac{0.10[A]_0}{k_0} = \frac{(0.10)(6.5\ \text{g/100 mL})}{(1.5 \times 10^{-6}\ \text{g/100 mL sec}^{-1})}$$

$$= 4.3 \times 10^5\ \text{sec} = 5.0\ \text{days}$$

First-Order Reactions. In 1918, Harned showed that the decomposition rate of hydrogen peroxide, catalyzed by 0.02 *M* KI, was proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time. The data for the reaction

$$2H_2O_2 = 2H_2O + O_2$$

are given in Table 12–1. Although two molecules of hydrogen peroxide appear in the stoichiometric equation as just written, the reaction was found to be first-order. The rate equation is written

$$-\frac{dc}{dt} = kc \qquad (12\text{–}11)$$

in which c is the concentration of hydrogen peroxide remaining undecomposed at time t, and k is the first-order velocity constant. Integrating equation (12–11) between concentration c_0 at time $t = 0$ and concentration c at some later time t, we have

$$\int_{c_0}^{c} \frac{dc}{c} = -k \int_0^t dt$$

$$\ln c - \ln c_0 = -k(t - 0)$$

$$\ln c = \ln c_0 - kt \qquad (12\text{–}12)$$

Converting to common logarithms yields

$$\log c = \log c_0 - kt/2.303 \qquad (12\text{–}13)$$

or

$$k = \frac{2.303}{t} \log \frac{c_0}{c} \qquad (12\text{–}14)$$

*The equation for t_{90} is obtained by substituting $0.9[A]_0$ for $[A]$ into the zero-order equation $[A] = [A]_0 - k_0 t$.

TABLE 12–1. *Decomposition of Hydrogen Peroxide at 25° C in Aqueous Solution Containing 0.02 M KI.*

t (minutes)	$a - x$	k (min^{-1})
0	57.90	—
5	50.40	0.0278
10	43.90	0.0277
25	29.10	0.0275
45	16.70	0.0276
65	9.60	0.0276
∞	0	—

H. S. Harned, J. Am. Chem. Soc. 40, 1462, 1918.

In exponential form, equation (12–12) becomes

$$c = c_0 e^{-kt} \qquad (12\text{–}15)$$

and equation (12–13) becomes

$$c = c_0 10^{-kt/2.303} \qquad (12\text{–}16)$$

Equations (12–15) and (12–16) express the fact that, in a first-order reaction, the concentration decreases exponentially with time. As shown in Figure 12–1, the concentration begins at c_0 and decreases as the reaction becomes progressively slower. The concentration asymptotically approaches a final value c_∞ as time proceeds toward infinity.

Equation (12–14) is often written as

$$k = \frac{2.303}{t} \log \frac{a}{(a - x)} \qquad (12\text{–}17)$$

in which the symbol a is customarily used to replace c_0, x is the decrease of concentration in time t, and $(a - x) = c$.

The specific reaction rates listed in Table 12–1 were calculated by using equation (12–17). Probably the best way to obtain an average k for the reaction is to plot the logarithm of the concentration against the time, as shown in Figure 12–2. The linear expression in equation (12–13) shows that the slope of the line is $-k/2.303$ from which the rate constant is obtained. If a straight line is obtained, it indicates that the reaction is

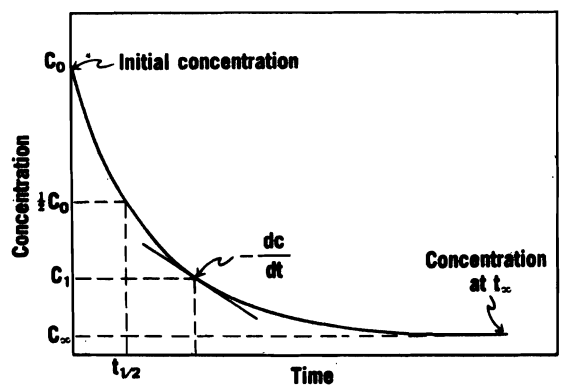


Fig. 12–1. Fall in concentration of a decomposing drug with time. In addition to C_0 and C_∞, $\frac{1}{2}C_0$ and the corresponding time, $t_{1/2}$, are shown. The rate of decrease of concentration with time $-dC/dt$ at an arbitrary concentration C_1 is also shown.

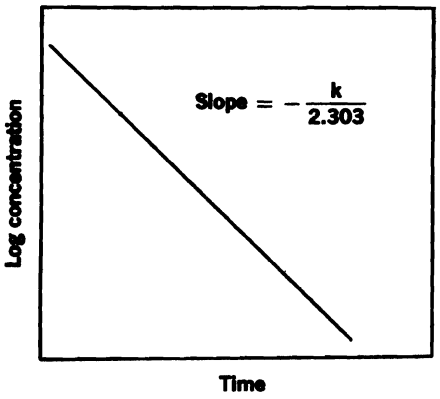


Fig. 12–2. A linear plot of log C versus time for a first-order reaction.

first-order. The tests for the order of a reaction are discussed in more detail on page 289.

Once the rate constant is known, the concentration of reactant remaining at a definite time may be computed as demonstrated in the following examples.

Example 12–3. The catalytic decomposition of hydrogen peroxide may be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 minutes, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.

(*a*) Calculate k using equation (12–14).

(*b*) How much hydrogen peroxide remained undecomposed after 25 minutes?

(*a*)

$$k = \frac{2.303}{65} \log \frac{57.90}{9.60} = 0.0277 \text{ min}^{-1}$$

(*b*)

$$0.0277 = \frac{2.303}{25} \log \frac{57.90}{c}; \; c = 29.01$$

Example 12–4. A solution of a drug contained 500 units per milliliter when prepared. It was analyzed after a period of 40 days and was found to contain 300 units per milliliter. Assuming the decomposition is first-order, at what time will the drug have decomposed to one half its original concentration?

(*a*)

$$k = \frac{2.303}{40} \log \frac{500}{300} = 0.0128 \text{ day}^{-1}$$

(*b*)

$$t = \frac{2.303}{0.0128} \log \frac{500}{250} = 54.3 \text{ days}$$

Half-Life. The period of time required for a drug to decompose to one half the original concentration as calculated in *Example 12–3* is the half-life, $t_{1/2}$, for a first-order reaction:

$$t_{1/2} = \frac{2.303}{k} \log \frac{500}{250} = \frac{2.303}{k} \log 2$$

$$t_{1/2} = \frac{0.693}{k} \qquad (12\text{–}18)$$

In *Example 12–4*, the drug has decomposed 250 units/milliliter in the first 54.3 days. Since the half-life is a constant, independent of the concentration, it remains at 54.3 days regardless of the amount of drug yet to be decomposed. In the second half-life of 54.3 days, half of the remaining 250 units or an additional 125 units/milliliter are lost; in the third half-life, 62.5 units/milliliter are decomposed, and so on.

The student should now appreciate the reason for stating the half-life rather than the time required for a substance to decompose completely. Except in a zero-order reaction, theoretically it takes an infinite period of time for a process to subside completely, as illustrated graphically in Figure 12–1. Hence, a statement of the time required for complete disintegration would have no meaning. Actually the rate ordinarily subsides in a finite period of time to a point at which the reaction may be considered to be complete, but this time is not accurately known, and the half-life, or some other fractional-life period, is quite satisfactory for expressing reaction rates.

The same drug may exhibit different orders of decomposition under various conditions. Although the deterioration of hydrogen peroxide catalyzed with iodine ions is first-order, it has been found that decomposition of concentrated solutions stabilized with various agents may become zero-order. In this case, in which the reaction is independent of drug concentration, decomposition is probably brought about by contact with the walls of the container or some other environmental factor.

Second-Order Reactions. The rates of bimolecular reactions, which occur when two molecules come together

$$A + B \rightarrow \text{products}$$

are frequently described by the second-order equation. When the speed of the reaction depends on the concentrations of A and B with each term raised to the first power, the rate of decomposition of A is equal to the rate of decomposition of B, and both are proportional to the product of the concentrations of the reactants:

$$-\frac{d[A]}{dt} = -\frac{d[B]}{dt} = k[A][B] \qquad (12\text{–}19)$$

If a and b are the initial concentrations of A and B and x is the concentration of each species reacting in time t, the rate law may be written

$$\frac{dx}{dt} = k(a - x)(b - x) \qquad (12\text{–}20)$$

in which dx/dt is the rate of reaction, and $(a - x)$ and $(b - x)$ are the concentrations of A and B remaining at time t. When, in the simplest case, both A and B are present in the same concentration so that $a = b$,

$$\frac{dx}{dt} = k(a - x)^2 \qquad (12\text{–}21)$$

Equation (12–21) is integrated, using the conditions that $x = 0$ at $t = 0$ and $x = x$ at $t = t$.

$$\int_0^x \frac{dx}{(a-x)^2} = k\int_0^t dt$$

$$\left(\frac{1}{a-x}\right) - \left(\frac{1}{a-0}\right) = kt$$

$$\frac{x}{a(a-x)} = kt \qquad (12\text{–}22)$$

or

$$k = \frac{1}{at}\left(\frac{x}{a-x}\right) \qquad (12\text{–}23)$$

When, in the general case, A and B are not present in equal concentrations, integration of equation (12–20) yields

$$\frac{2.303}{a-b}\log\frac{b(a-x)}{a(b-x)} = kt \qquad (12\text{–}24)$$

or

$$k = \frac{2.303}{t(a-b)}\log\frac{b(a-x)}{a(b-x)} \qquad (12\text{–}25)$$

It can be seen by reference to equation (12–22) that when $x/a(a-x)$ is plotted against t, a straight line results if the reaction is second-order. The slope of the line is k. When the initial concentrations, a and b, are not equal, a plot of $\log b(a-x)/a(b-x)$ against t should yield a straight line with a slope of $(a-b)k/2.303$. The value of k can thus be obtained. It is readily seen from equation (12–23) or (12–25) that the units in which k must be expressed for a second-order reaction are 1/(mole/liter) × 1/sec where the concentrations are given in mole/liter and the time in seconds. The rate constant k in a second-order reaction therefore has the dimensions, liter/(mole sec) or liter mole^{-1} sec^{-1}.

Example 12–5. Walker[4] investigated the saponification of ethyl acetate at 25° C:

$$CH_3COOC_2H_5 + NaOH \rightarrow CH_3COONa + C_2H_5OH$$

The initial concentrations of both ethyl acetate and sodium hydroxide in the mixture were 0.01000 M. The change in concentration x of alkali during 20 minutes was 0.000566 mole/liter; therefore $(a-x) = 0.01000 - 0.00566 = 0.00434$.

Compute (*a*) the rate constant and (*b*) the half-life of the reaction.

(*a*) Using equation (12–23)

$$k = \frac{1}{0.01 \times 20}\frac{(0.00566)}{(0.00434)} = 6.52 \text{ liter mole}^{-1}\text{ min}^{-1}$$

(*b*) The half-life of a second-order reaction is

$$t_{1/2} = \frac{1}{ak} \qquad (12\text{–}26)$$

It can be computed for the reaction only when the initial concentrations of the reactants are identical. In the present example,

$$t_{1/2} = \frac{1}{0.01 \times 6.52} = 15.3 \text{ min}$$

Determination of Order. The order of a reaction may be determined by several methods.

Substitution Method. The data accumulated in a kinetic study may be substituted in the integrated form of the equations that describe the various orders. When the equation is found in which the calculated k values remain constant within the limits of experimental variation, the reaction is considered to be of that order.

Graphic Method. A plot of the data in the form of a graph as shown in Figure 12–2 may also be used to ascertain the order. If a straight line results when concentration is plotted against t, the reaction is zero-order. The reaction is first-order if $\log(a-x)$ versus t yields a straight line; and it is second-order if $1/(a-x)$ versus t gives a straight line (in the case in which the initial concentrations are equal). When a plot of $1/(a-x)^2$ against t produces a straight line, with all reactants at the same initial concentration, the reaction is third-order.

Half-life Method. In a zero-order reaction, the half-life is proportional to the initial concentration, a, as observed in Table 12–2. The half-life of a first-order reaction is independent of a; $t_{1/2}$ for a second-order reaction, in which $a = b$, is proportional to $1/a$; and in a third-order reaction, in which $a = b = c$, it is proportional to $1/a^2$. The relationship between these results shows that, in general, the half-life of a reaction in which the concentrations of all reactants are identical is

$$t_{1/2} \propto \frac{1}{a^{n-1}} \qquad (12\text{–}27)$$

in which n is the order of the reaction. Thus if two reactions are run at different initial concentrations, a_1 and a_2, the half-lives $t_{1/2(1)}$ and $t_{1/2(2)}$ are related as follows:

$$\frac{t_{1/2(1)}}{t_{1/2(2)}} = \frac{(a_2)^{n-1}}{(a_1)^{n-1}} = \left(\frac{a_2}{a_1}\right)^{n-1} \qquad (12\text{–}28)$$

or in logarithmic form

$$\log\frac{t_{1/2(1)}}{t_{1/2(2)}} = (n-1)\log\frac{a_2}{a_1} \qquad (12\text{–}29)$$

and finally

$$n = \frac{\log(t_{1/2(1)}/t_{1/2(2)})}{\log(a_2/a_1)} + 1 \qquad (12\text{–}30)$$

The half-lives are obtained graphically by plotting a versus t at two different initial concentrations and reading the time at $\frac{1}{2}a_1$ and $\frac{1}{2}a_2$. The values for the half-lives and the initial concentrations are then substi-

TABLE 12–2. *Rate and Half-Life Equations*

Order	Integrated Rate Equation	Half-Life Equation
0	$x = kt$	$t_{1/2} = \frac{a}{2k}$
1	$\log\frac{a}{(a-x)} = \frac{k}{2.303}t$	$t_{1/2} = \frac{0.693}{k}$
2	$\frac{x}{a(a-x)} = kt$	$t_{1/2} = \frac{1}{ak}$
3	$\frac{2ax-x^2}{a^2(a-x)^2} = 2kt$	$t_{1/2} = \frac{3}{2}\frac{1}{a^2k}$

tuted into equation (12–30), from which the order n is obtained directly. Rather than using different initial concentrations, two concentrations during a single run may also be taken as a_1 and a_2 and the half-lives $t_{1/2(1)}$ and $t_{1/2(2)}$ determined in terms of these. If the reaction is first-order, $t_{1/2(1)} = t_{1/2(2)}$ since the half-life is independent of concentration in a first-order reaction. Then $\log (t_{1/2(1)}/t_{1/2(2)}) = \log 1 = 0$, and one can see from equation (12–30) that

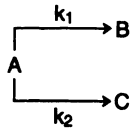
$$n = 0 + 1 = 1$$

Complex Reactions. Many reactions cannot be expressed by simple zero-, first-, and second-, or third-order equations. They involve more than one step or elementary reaction and accordingly are known as *complex reactions*. These processes include reversible, parallel, and consecutive reactions:

(1) Reversible reaction:

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C + D$$

(2) Parallel or side reactions:



(3) Series or consecutive reactions:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Reversible Reactions. The simplest reversible reaction is one in which both the forward and the reverse steps are first-order processes:

$$A \underset{k_r}{\overset{k_f}{\rightleftharpoons}} B$$

Although at first this equation appears to be that for an equilibrium between A and B, it must be pointed out that an equilibrium situation requires that the concentrations of A and B do not change with time. Since this expression is intended to explain a kinetic process, it must follow that the equation describes the approach to equilibrium. That is, the situation represented is one in which A decreases to form B and some of the product B reverts back to A. According to this description, the *net* rate at which A decreases will be given by the rate at which A decreases in the forward step less the rate at which A increases in the reverse step:

$$-\frac{dA}{dt} = k_f A - k_r B \qquad (12\text{–}31)$$

this rate law may be integrated by noting that

$$A_0 - A = B \qquad (12\text{–}32)$$

Substitution of equation (12–32) into equation (12–31) affords, upon integration,

$$\ln \frac{k_f A_0}{(k_f + k_r)A - k_r A_0} = (k_f + k_r)t \qquad (12\text{–}33)$$

Equation (12–33) may be simplified by introducing the equilibrium condition:

$$k_f A_{eq} = k_r B_{eq} \qquad (12\text{–}34)$$

in which

$$A_0 - A_{eq} = B_{eq} \qquad (12\text{–}35)$$

Equations (12–34) and (12–35) may be used to solve for the equilibrium concentration in terms of the starting concentration:

$$A_{eq} = \frac{k_r}{k_f + k_r} A_0 \qquad (12\text{–}36)$$

Use of equation (12–36) in equation (12–33) enables a simple form of the rate law to be given:

$$\ln \frac{A_0 - A_{eq}}{A - A_{eq}} = (k_f + k_r)t \qquad (12\text{–}37)$$

or

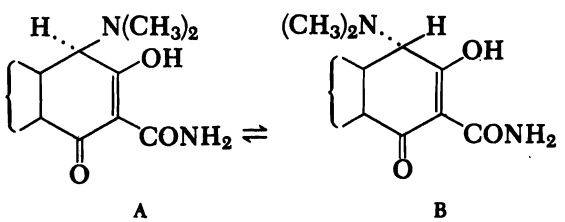
$$\log \frac{A_0 - A_{eq}}{A - A_{eq}} = \frac{(k_f + k_r)}{2.303} t \qquad (12\text{–}38)$$

Equation (12–38) has the advantage that the approach of A to equilibrium can be followed over a much wider range of concentrations than if an attempt is made to obtain the first-order rate constant k_f in the early stages of the reaction when $B \approx 0$. The equation corresponds to a straight line intersecting at zero and having a slope given by $\frac{k_f + k_r}{2.303}$. Since the equilibrium constant of the reaction is given by

$$K = \frac{k_f}{k_r} = \frac{B_{eq}}{A_{eq}} \qquad (12\text{–}39)$$

both the forward and reverse rate constants can be evaluated once the slope of the line and the equilibrium constant have been determined.

The tetracyclines and certain of their derivatives undergo a reversible isomerization at a pH in the range of 2 to 6. This isomerization has been shown to be an epimerization, resulting in *epi*tetracyclines, which show much less therapeutic activity than the natural form. Considering only that part of the tetracycline molecule undergoing change, the transformation can be represented by the equation



A B

The natural configuration of tetracycline has the $N(CH_3)_2$ group above the plane and the H group below

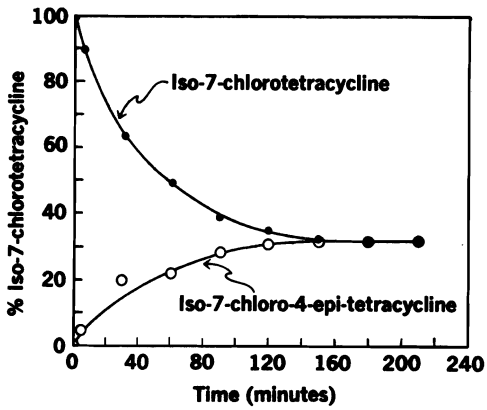


Fig. 12–3. Approach to equilibrium in the reversible epimerizations of iso-7-chloro-*epi*-tetracycline (○—○—○) and iso-7-chlorotetracycline (●—●—●). (After J. D. McCormick, S. M. Fox, L. L. Smith, *et al.* J. Am. Chem. Soc. 79, 2849, 1957.)

the plane of the page. Under acidic conditions, the natural compound A is converted reversibly to the *epi*-isomer B.

McCormick et al.[5] followed the epimerization of iso-7-chlorotetracycline and its *epi*-isomer and noted that each isomer led to the same equilibrium distribution of isomers (Fig. 12–3). In the solvent dimethylformamide containing 1 M aqueous NaH_2PO_4 at 25° C, the equilibrium distribution consisted of 32% iso-7-chlorotetracycline and 68% iso-7-chloro-4-*epi*-tetracycline, which gives an equilibrium constant

$$K = \frac{B_{eq}}{A_{eq}} = \frac{68}{32} = 2.1$$

The data used to arrive at Figure 12–3, when plotted according to equation (12–38), give the line shown in Figure 12–4. The slope of this line is 0.010 min^{-1}. Since from equation (12–38) the slope S is

$$S = \frac{k_f + k_r}{2.30} = 0.010 \text{ min}^{-1}$$

and from equation (12–39)

$$K = \frac{B_{eq}}{A_{eq}} = \frac{k_f}{k_r} = 2.1$$

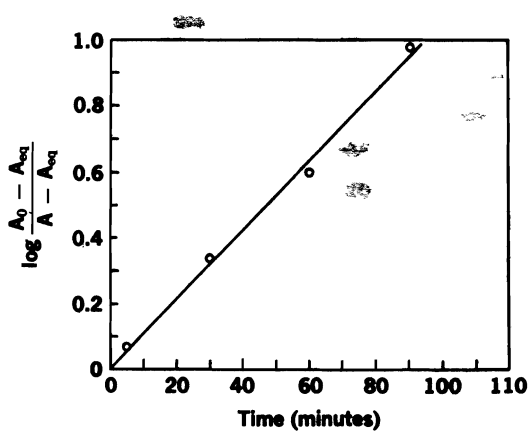


Fig. 12–4. Reversible epimerization of iso-7-chlorotetracycline in dimethylformamide containing 1 M NaH_2PO_4 at 25° C.

the elimination of k_f from these equations affords a value for k_r. Thus, it is found that

$$\frac{2.1k_r + k_r}{2.30} = 0.010 \text{ min}^{-1}$$

or

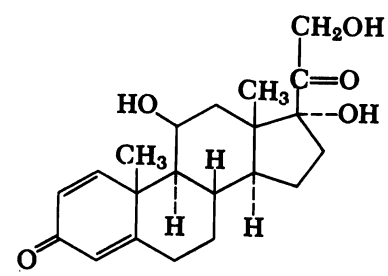
$$k_r = \frac{(0.010)(2.30)}{2.1 + 1} = 0.007 \text{ min}^{-1}$$

From this value, k_f is found to be

$$k_f = 2.30S - k_r = (2.30)(0.010) - 0.007$$
$$= 0.016 \text{ min}^{-1}$$

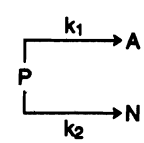
Parallel or Side Reactions. Parallel reactions are common in drug systems, particularly when organic compounds are involved. General acid–base catalysis, to be considered later (p. 303), belongs to this class of reactions.

The base-catalyzed degradation of prednisolone will be used here to illustrate the parallel-type process. Guttman and Meister[6] investigated the degradation of the steroid prednisolone in aqueous solutions containing sodium hydroxide as a catalyst. The runs were carried out at 35° C, and the rate of disappearance of the dihydroxyacetone side chain was followed by appropriate analytic techniques. The decomposition of prednisolone was found to involve parallel pseudo–first-order reactions with the appearance of acidic and neutral steroidal products.



Prednisolone

The mechanism of the reaction may be represented as



(12–40)

(12–41)

in which P, A, and N are the concentrations of prednisolone, an acid product, and a neutral product, respectively.

The corresponding rate equation is

$$-\frac{dP}{dt} = k_1P + k_2P = kP \qquad (12\text{–}42)$$

in which $k = k_1 + k_2$. This first-order equation is integrated to give

$$\ln (P_0/P) = kt \qquad (12\text{–}43)$$

or

$$P = P_0 e^{-kt} \tag{12-44}$$

The rate of formation of the acidic product can be expressed as

$$\frac{dA}{dt} = k_1 P = k_1 P_0 e^{-kt} \tag{12-45}$$

Integration of equation (12–45) yields

$$A = A_0 + \frac{k_1}{k} P_0(1 - e^{-kt}) \tag{12-46}$$

in which A is the concentration of the acid product at time t, and A_0 and P_0 are the initial concentrations of the acid and prednisolone, respectively. Actually, A_0 is equal to zero since no acid is formed before the prednisolone begins to decompose. Therefore,

$$A = \frac{k_1}{k} P_0(1 - e^{-kt}) \tag{12-47}$$

Likewise for the neutral product,

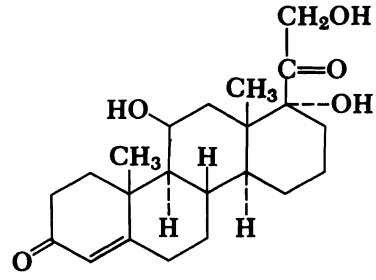
$$N = \frac{k_2}{k} P_0(1 - e^{-kt}) \tag{12-48}$$

Equations (12–47) and (12–48) suggest that for the base-catalyzed breakdown of prednisolone, a plot of the concentration A or N against $(1 - e^{-kt})$ should yield a straight line. At $t = 0$, the curve should pass through the origin, and at $t = \infty$, the function should have a value of unity. the value for k, the overall first-order rate constant, was obtained by a plot of log [prednisolone] against the time at various concentrations of sodium hydroxide. It was possible to check the validity of expression (12–47) using the k values that were now known for each level of hydroxide ion concentration. A plot of the acidic material formed against $(1 - e^{-kt})$ yielded a straight line passing through the origin as predicted by equation (12–47). The value of k_1, the rate constant for the formation of the acidic product, was then calculated from the slope of the line.

$$k_1 = \text{slope} \times k/P_0 \tag{12-49}$$

and the value of k_2, the rate constant for the formation of the neutral degradation product, was obtained by subtracting k_1 from k. The data, as tabulated by Guttman and Meister,[6] are found in Table 12–3.

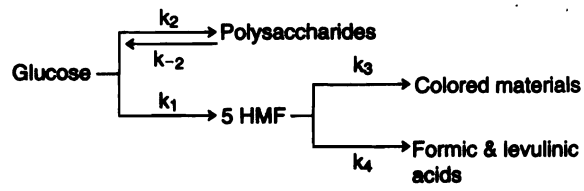
The stability of hydrocortisone was explored by Allen and Gupta[7] in aqueous and oil vehicles, water-washable ointment bases, and emulsified vehicles in the presence of other ingredients, at elevated temperatures and at



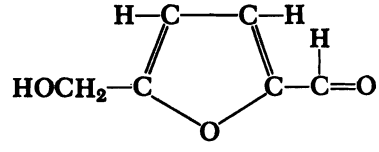
Hydrocortisone

various degrees of acidity and basicity. Hydrocortisone was unstable at room temperature in aqueous vehicles on the basic side of neutrality; alcohol and glycerin appeared to improve the stability. The decomposition in water and propylene glycol was pseudo–first-order. In highly acidic and basic media and at elevated temperatures, the decomposition of hydrocortisone was of a complex nature, following a parallel scheme.

Series or Consecutive Reactions. Consecutive reactions are common in radioactive series in which a parent isotope decays by a first-order process into a daughter isotope, and so on through a chain of disintegrations. We shall take a simplified version of the degradation scheme of glucose as illustrative of consecutive-type reactions. The depletion of glucose in acid solution may be represented by the scheme[8]



which is seen to involve all of the complex-type reactions–reversible, parallel, and consecutive processes. At low concentrations of glucose and acid catalyst, the formation of polysaccharides may be neglected. Furthermore, owing to the indefinite nature



5-Hydroxymethylfurfural
(5-HMF)

TABLE 12–3. ***Rate Constants for the Base-Catalyzed Degradation of Prednisolone in Air at 35° C***

NaOH (Normality)	k (hr^{-1})	k_1 (hr^{-1})	k_2 (hr^{-1})
0.01	0.108	0.090	0.018
0.02	0.171	0.137	0.034
0.03	0.233	0.181	0.052
0.04	0.258	0.200	0.058
0.05	0.293	0.230	0.063

of the breakdown products of 5-HMF, these may be combined together and referred to simply as constituent *C*. The simplified mechanism is therefore written as the series of reactions:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

in which *A* is glucose, *B* is 5-HMF and *C* is the final breakdown products. The rate of decomposition of glucose is given by the equation

$$-dA/dt = k_1A \qquad (12-50)$$

The rate of change in concentration of 5-HMF is

$$dB/dt = k_1A - k_2B \qquad (12-51)$$

and that of the breakdown products is

$$dC/dt = k_2B \qquad (12-52)$$

When these equations are integrated and proper substitutions made, we obtain

$$A = A_0e^{-k_1t} \qquad (12-53)$$

$$B = \frac{A_0k_1}{k_2 - k_1}(e^{-k_1t} - e^{-k_2t}) \qquad (12-54)$$

and

$$C = A_0\left[1 + \frac{1}{k_1 - k_2}(k_2e^{-k_1t} - k_1e^{-k_2t})\right] \qquad (12-55)$$

By the application of equations (12–53), (12–54), and (12–55), the rate constants k_1 and k_2 and the concentration of breakdown products *C* can be determined. Glucose is found to decompose by a first-order reaction. As glucose is depleted, the concentration of 5-HMF increases rapidly at the beginning of the reaction and then increases at a slower rate as time progresses. The decomposition products of 5-HMF increase slowly at first, indicating an induction or lag period, and then increase at a greater rate. These later products are responsible for the discoloration of glucose solutions that occurs when the solutions are sterilized at elevated temperatures.

Kinetic studies such as these have considerable practical application in pharmacy. When the mechanism of the breakdown of parenteral solutions is better understood, the manufacturing pharmacist should be able to prepare a stable product having a long shelf-life. Large supplies of glucose injection and similar products can then possibly be stockpiled for use in times of emergency.

Mauger et al.[9] studied the degradation of hydrocortisone hemisuccinate at 70° C over a narrow pH range and found the reaction to be another example of the consecutive first-order type. At pH 6.9, the rate constant k_1 was 0.023 hr^{-1} and k_2 was 0.50 hr^{-1}.

The Steady-State Approximation. Michaelis–Menten Equation. A number of kinetic processes cannot have their rate laws integrated exactly. In situations such as these, it is useful to postulate a reasonable reaction sequence and then to derive a rate law that applies to the postulated sequence of steps. If the postulate is reasonably accurate and reflects the actual steps involved in the reaction, the observed kinetics for the reaction should match the curve given by the derived rate law.

The *steady-state approximation* is commonly used to reduce the labor in deducing the form of a rate law. We will illustrate this approximation by deriving the Michaelis–Menten equation.

Michaelis and Menten[10] assumed that the interaction of a substrate *S* with an enzyme *E* to yield product *P* followed a reaction sequence given by

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} (E \cdot S) \xrightarrow{k_3} P$$

According to this scheme, the rate of product formation is

$$\frac{dP}{dt} = k_3(E \cdot S) \qquad (12-56)$$

We have no easy means of obtaining the concentration of enzyme–substrate complex, so it is necessary that this concentration be expressed in terms of easily measurable quantities. In an enzyme study, we can usually measure *S*, *P*, and E_0, the total concentration of enzyme.

The rate of formation of $(E \cdot S)$ is

$$\frac{d(E \cdot S)}{dt} = k_1(E)(S) - k_2(E \cdot S) - k_3(E \cdot S) \qquad (12-57)$$

or

$$\frac{d(E \cdot S)}{dt} = k_1(E)(S) - (k_2 + k_3)(E \cdot S) \qquad (12-58)$$

If the concentration of $E \cdot S$ is constant throughout most of the reaction and is always much less than the concentrations of *S* and *P*, we can write

$$\frac{d(E \cdot S)}{dt} = 0 \qquad (12-59)$$

It follows from equations (12–58) and (12–59) that

$$(E \cdot S)_{ss} = \frac{k_1(E)(S)}{k_2 + k_3} \qquad (12-60)$$

in which the subscript *ss* is used to designate the concentration referred to as the *steady-state* value.

The total concentration of enzyme E_0 is the sum of the concentrations of enzyme, both free *E* and bound $E \cdot S$,

$$E_0 = E + (E \cdot S)_{ss} \qquad (12-61)$$

Eliminating *E* from equations (12–60) and (12–61), we obtain

$$(E \cdot S)_{ss} = \frac{k_1SE_0}{(k_2 + k_3) + k_1S} \qquad (12-62)$$

or

$$(E \cdot S)_{ss} = \frac{SE_0}{K_m + S} \qquad (12-63)$$

in which

$$K_m = \frac{k_2 + k_3}{k_1} \qquad (12-64)$$

Thus, under steady-state conditions, the rate of product formation is given by

$$\frac{dP}{dt} = \frac{k_3 S E_0}{K_m + S} \qquad (12-65)$$

which may be recognized as the Michaelis–Menten equation. The Michaelis–Menten constant K_m indicates the tendency of the enzyme-substrate complex to decompose to starting substrate or to proceed to product, relative to the tendency of the complex to be formed.

It is useful to introduce a maximum velocity for the Michaelis–Menten scheme, namely $(dP/dt)_{\text{maximum}}$, which is usually written as V_m. When S is very large, all enzyme E_o is present as $E \cdot S$; that is, all enzyme is combined with the substrate and the reaction proceeds at maximum velocity. From equation (12–56), dP/dt becomes V_m, and $V_m = k_3 E_o$, since $E \cdot S$ is equivalent to E_o. Accordingly, from equation (12–65)

$$V = V_m \frac{S}{k_m + S} \qquad (12-66)$$

Equation (12–66) may be inverted to obtain a linear expression, known as the *Lineweaver–Burk equation:*

$$\frac{1}{V} = \frac{K_m + S}{V_m \cdot S} \qquad (12-67)$$

$$\frac{1}{V} = \frac{1}{V_m} + \frac{K_m}{V_m}\frac{1}{S} \qquad (12-68)$$

From equation (12–68) we see that a plot of $1/V$ versus $1/S$ yields a straight line with an intercept on the vertical axis of $1/V_m$ and a slope of K_m/V_m (Fig. 12–5). Knowing V_m from the intercept and obtaining K_m/V_m as the slope, it is possible to calculate K_m, the *Michaelis constant.*

Example 12–6. The velocity V of an enzymatic reaction at increasing substrate concentration $[S]$ was experimentally determined and is recorded here:

V [μg/(ℓ min)]	0.0350	0.0415	0.0450	0.0490	0.0505
$[S]$ (molarity, M)	0.0025	0.0050	0.0100	0.0167	0.0333

(a) Following the Lineweaver–Burk form of the Michaelis–Menten equation, plot $1/V$ versus $1/[S]$ using the data given below, and calculate V_m and K_m using linear regression analysis. The data for the Lineweaver–Burk plot and the regression analysis are:

$1/V$ [min/(μg/ℓ)]	28.57	24.10	22.22	20.41	19.80
$1/[S]$ (ℓ/mole)	400	200	100	59.88	30.0

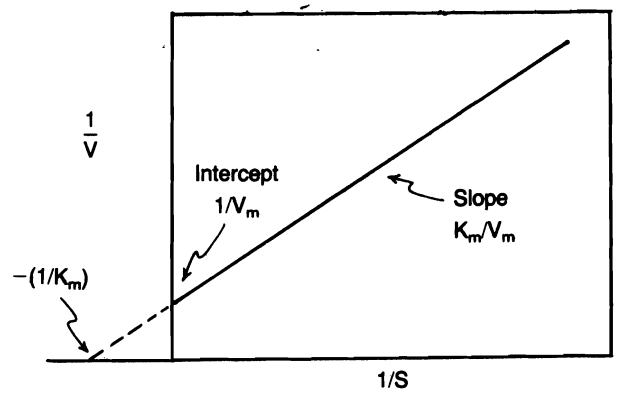


Fig. 12–5. A Lineweaver-Burk plot of Michaelis–Menten kinetics showing the calculation of K_m by two means.

(b) Extrapolate the line to the horizontal axis (x-axis) where the intercept is $-1/K_m$. Read $-1/K_m$ as accurately as possible by eye and obtain K_m as its reciprocal. Compare this value with that obtained by linear regression in *(a)* above.

Answer: (a) Linear regression analysis yields the expression

$1/V = 19.316 + 0.0234\ 1/[S]$; $r^2 = 0.990$

Intercept, $1/V_m = 19.316$; $V_m = 0.0518$ μg/(ℓ-min)

Slope $= K_m/V_m = 0.0234$ (ℓ-min/μg) M

$K_m = 0.0234$ (ℓ-min/μg) M × 0.0518 μg/ℓ-min

$= 0.0012$ M

(b) $-1/K_m$ by extrapolation $= -823\ \text{M}^{-1}$

$K_m = 0.0012$ M

Michaelis–Menten kinetics is used not only for enzyme reactions but also for biochemical processes in the body involving carriers that transport substances across membranes such as blood capillaries and the renal tubule. It is assumed, for example, that L-tyrosine is absorbed from the nasal cavity into systemic circulation by a carrier-facilitated process, and Michaelis–Menten kinetics is applied to this case in Chapter 19, *Problem 19–8.*

Rate-Determining Step. In a reaction sequence in which one step is much slower than all the subsequent steps leading to product, the rate at which the product is formed may depend on the rates of all the steps preceding the slow step but does not depend on any of the steps following. The slowest step in a reaction sequence is called, somewhat misleadingly, the *rate-determining step* of the reaction.

Consider the following mechanistic pathway,

$$A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \text{ (step 1 and step 2)}$$

$$B + C \xrightarrow{k_3} D \text{ (step 3)}$$

$$D \xrightarrow{k_4} P \text{ (step 4)}$$

which may be postulated for the observed overall reaction

$$A + C \rightarrow P$$

If the concentrations of the intermediates B and D are small, we may apply the steady-state approximation to

evaluate their steady-state concentrations. These are given by

$$B_{ss} = \frac{k_1 A}{k_2 + k_3 C}$$

and

$$D_{ss} = \frac{k_1 k_3 AC}{k_4(k_2 + k_3 C)}$$

For the rate of formation of product, we can write

$$\frac{dP}{dt} = k_4 D_{ss}$$

or

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{(k_2 + k_3 C)} \qquad (12\text{–}69)$$

If, in the mechanistic sequence, step 3 is the slow step (the rate-determining step), we may say that $k_2 \gg k_3 C$, *and equation (12–69) is simplified to a second-order expression,*

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{k_2} = k_0 AC \qquad (12\text{–}70)$$

On the other hand, if step 2, the reverse reaction, is the slow step, then $k_3 C \gg k_2$, and equation (12–69) reduces to a first-order expression,

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{k_3 C} = k_1 A \qquad (12\text{–}71)$$

Thus we see that reactions may exhibit a simple first- or second-order behavior, yet the detailed mechanism for these reactions may be quite complex.

INFLUENCE OF TEMPERATURE AND OTHER FACTORS ON REACTION RATES

Temperature. A number of factors other than concentration may affect the reaction velocity. Among these are temperature, solvents, catalysts, and light. The speed of many reactions increases about two to three times with each 10° rise in temperature. The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius,

$$k = Ae^{-E_a/RT} \qquad (12\text{–}72)$$

or

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT} \qquad (12\text{–}73)$$

in which k is the specific reaction rate, A is a constant known as the *Arrhenius factor* or the *frequency factor*, E_a is the *energy of activation*, R is the gas constant, 1.987 calories/deg mole, and T is the absolute temperature. The constants, A and E_a, will be considered further in later sections of the chapter. They may be evaluated by determining k at several temperatures and plotting $1/T$ against log k. As seen in equation (12–73), the slope of the line so obtained is $-E_a/2.303R$, and the intercept on the vertical axis is log A, from which E_a and A may be obtained.

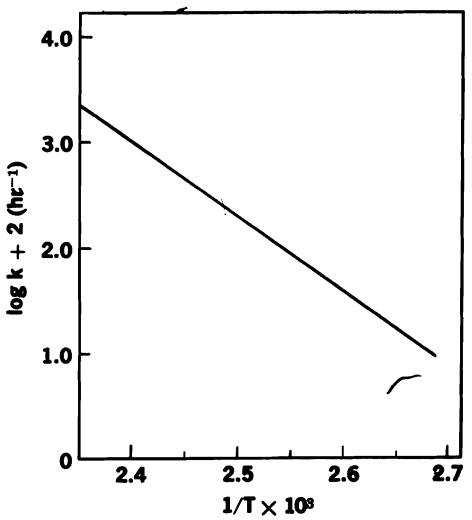


Fig. 12–6. A plot of log k against $1/T$ for the thermal decomposition of glucose.

The data, obtained from a study of the decomposition of glucose solutions between 100° and 140° C in the presence of 0.35 N hydrochloric acid, are plotted in this manner, as shown in Figure 12–6.* It should be observed that since the *reciprocal* of the absolute temperature is plotted along the horizontal axis, the temperature is actually *decreasing* from left to right across the graph. It is sometimes advantageous to plot log $t_{1/2}$ instead of log k on the vertical axis. The half-life for a first-order reaction is related to k by equation (12–18), $t_{1/2} = 0.693/k$, and in logarithmic form

$$\log k = \log 0.693 - \log t_{1/2} \qquad (12\text{–}74)$$

Substituting equation (12–74) into equation (12–73) gives

$$\log t_{1/2} = \log 0.693 - \log A + \frac{E_a}{2.303R}\frac{1}{T}$$

or

$$\log t_{1/2} = \frac{E_a}{2.303R}\frac{1}{T} + \text{constant}$$

and $E_a/2.303R$ is obtained as the slope of the line resulting from plotting log $t_{1/2}$ against $1/T$. Higuchi et al.[11] plotted the results of the alkaline hydrolysis of procaine in this manner, as shown in Figure 12–7.

E_a may also be obtained by writing equation (12–73) for a temperature T_2 as

*Notice that log k + 2 is plotted on the vertical axis of Figure 12–6. This is a convenient way of eliminating negative values along the axis. For example, if $k = 1.0 \times 10^{-2}$, 2.0×10^{-2}, etc., the logarithmic expressions are log 1.0 + log 10^{-2}, log 2.0 + log 10^{-2}, . . . or 0.0 − 2 = −2, 0.3 − 2 = −1.7, etc. The negative signs may be eliminated along the vertical axis if 2 is added to each value; hence the label, log k + 2.

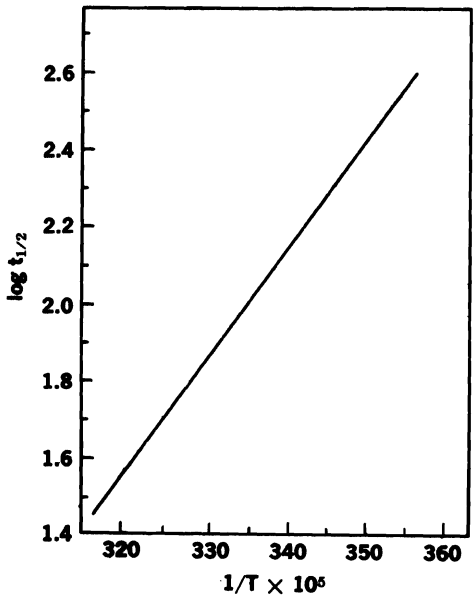


Fig. 12–7. A plot of log $t_{1/2}$ against $1/T$ for the alkaline hydrolysis of procaine. (After T. Higuchi et al[11].)

$$\log k_2 = \log A - \frac{E_a}{2.303R}\frac{1}{T_2}$$

and for another temperature T_1 as

$$\log k_1 = \log A - \frac{E_a}{2.303R}\frac{1}{T_1}$$

Subtracting these two expressions yields

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R}\left(\frac{T_2 - T_1}{T_2 T_1}\right)$$

Example 12–7. The rate constant k_1 for the decomposition of 5-hydroxymethylfurfural at 120° C (393° K) is 1.173 hr^{-1} or 3.258 × 10^{-4} sec^{-1} and k_2 at 140° C (413° K) is 4.860 hr^{-1}. What is the activation energy E_a in kcal/mole and the frequency factor A in sec^{-1} for the breakdown of 5-HMF within this temperature range?

$$\log \frac{4.860}{1.173} = \frac{E_a}{2.303 \times 1.987}\left(\frac{413 - 393}{413 \times 393}\right)$$

$$E_a = 23 \text{ kcal/mole}$$

At 120° C, using equation (12–73), one obtains

$$\log (3.258 \times 10^{-4}\ sec^{-1}) = \log A - \frac{23{,}000 \text{ cal}}{2.303 \times 1.987}\frac{1}{393}$$

$$A = 2 \times 10^9\ sec^{-1}$$

Classic Collision Theory of Reaction Rates. The Arrhenius equation is largely an empiric relation giving the effect of temperature on an observed rate constant. Relations of this type are observed for unimolecular and bimolecular reactions and often are also observed for complex reactions involving a number of bimolecular and unimolecular steps. Although it is extremely difficult, in most cases, to attach significance to the temperature dependence of complex reactions, the temperature dependence of uni- and bimolecular reactions appears to reflect a fundamental physical requirement that must be met for a reaction to occur.

The manner by which temperature affects molecular motion may be understood by considering a hypothetic situation in which all the molecules of a substance are moving in the same direction at the same velocity. If a molecule deviates from its course, it will collide with another molecule, causing both molecules to move off in different directions with different velocities. A chain of collisions between molecules can then occur, which finally results in random motion of all the molecules. In this case, only a certain fraction of the molecules have a velocity equivalent to the initial velocity of the ordered system. The net result is that for a fixed number of molecules at a given temperature, and therefore at a definite total energy, a distribution of molecular velocities varying from zero upward is attained. Since kinetic energy is proportional to the square of velocity, the distribution of molecular velocities corresponds to the distribution of molecular energies, and the fraction of the molecules having a given kinetic energy can be expressed by the *Boltzmann distribution law*

$$f_i = \frac{N_i}{N_T} = e^{-E_i/RT} \qquad (12\text{–}75)$$

From the Boltzmann distribution law we note that of the total number of moles N_T of a reactant, N_i moles have a kinetic energy given by E_i. The collision theory of reaction rates postulates that a collision must occur between molecules for a reaction to occur and, further, that a reaction between molecules does not take place unless the molecules are of a certain energy. By this postulate, the rate of a reaction can be considered proportional to the number of moles of reactant having sufficient energy to react, that is

$$\text{Rate} = PZN_i \qquad (12\text{–}76)$$

The proportionality constant in this relation is divided into two terms: the collision number Z which for a reaction between two molecules is the number of collisions per second per cubic centimeter, and the steric or probability factor P, which is included to take into account the fact that not every collision between molecules leads to reaction. That is, P gives the probability that a collision between molecules will lead to product.

Substituting for N_i in equation (12–76) yields

$$\text{Rate} = (PZe^{-E_i/RT})N_T \qquad (12\text{–}77)$$

which, when compared with the general rate law

$$\text{Rate} = k(\text{concentration of reactants}) \qquad (12\text{–}78)$$

leads to the conclusion that

$$k = (PZ)e^{-E_i/RT} \qquad (12\text{–}79)$$

Thus, collision state theory interprets the Arrhenius A factor in terms of the frequency of collision between molecules

$$A = PZ \qquad (12\text{–}80)$$

and the Arrhenius activation energy E_a as the minimum kinetic energy a molecule must possess in order to undergo reaction,

$$E_a = E_i \tag{12-81}$$

Yang[12] has shown the error possible in determining the activation energy E_a and the predicted shelf-life when the kinetic order in an accelerated stability test (pp. 313–315) is incorrectly assigned; for example, when an actual zero-order reaction can equally well be described by a first-order degradation.

Transition State Theory. An alternative to the collision theory is the *transition state theory* or absolute rate theory, according to which an equilibrium is considered to exist between the normal reactant molecules and an activated complex of these molecules. Decomposition of the activated complex leads to product. For an elementary bimolecular process, the reaction may be written as

$$\underset{\substack{\text{Normal reactant}\\ \text{molecules}}}{A + B} \rightleftharpoons \underset{\substack{\text{Activated reactant molecules in the transition state (activated complex)}}}{[A \cdots B]^{\ddagger}} \rightarrow \underset{\substack{\text{Product}\\ \text{molecules}}}{P} \tag{12-82}$$

A double dagger is used to designate the activated state, namely $[A \cdots B]^{\ddagger}$

The rate of product formation in this theory is given by

$$\text{Rate} = v[A \cdots B]^{\ddagger} \tag{12-83}$$

in which v is the frequency with which an activated complex goes to product. Since an equilibrium exists between the reactants and the activated complex,

$$K^{\ddagger} = \frac{[A \cdots B]^{\ddagger}}{[A][B]} \tag{12-84}$$

and this expression can be rearranged to

$$[A \cdots B]^{\ddagger} = K^{\ddagger}[A][B] \tag{12-85}$$

Hence,

$$\text{Rate} = [vK^{\ddagger}][A][B] \tag{12-86}$$

The general rate law for a bimolecular reaction is

$$\text{Rate} = k[A][B] \tag{12-87}$$

so it follows that

$$k = vK^{\ddagger} \tag{12-88}$$

It will be recalled from previous thermodynamic considerations (p. 70) that

$$\Delta G^{\circ} = -RT \ln K \tag{12-89}$$

or

$$K = e^{-\Delta G^{\circ}/RT} \tag{12-90}$$

and (p. 65)

$$\Delta G^{\circ} = \Delta H^{\circ} - T\,\Delta S^{\circ} \tag{12-91}$$

Replacing the ordinary K for present purposes with $K^{\ddagger}$, and by making similar substitutions for the thermodynamic quantities, it follows that

$$k = ve^{-\Delta G^{\ddagger}/RT} \tag{12-92}$$

and

$$k = (ve^{\Delta S^{\ddagger}/R})e^{-\Delta H^{\ddagger}/RT} \tag{12-93}$$

where $\Delta G^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta H^{\ddagger}$ are the respective differences between the standard free energy, entropy, and enthalpy in the transition state and in the normal reactant state.

In this theory, the Arrhenius A factor is related to the entropy of activation of the transition state:

$$A = ve^{\Delta S^{\ddagger}/R} \tag{12-94}$$

and the Arrhenius activation energy E_a is related to the enthalpy of activation of the transition state:

$$E_a = \Delta H^{\ddagger} = \Delta E^{\ddagger} + P\,\Delta V^{\ddagger} \tag{12-95}$$

For most practical purposes, $\Delta V^{\ddagger} = 0$; hence

$$E_a = \Delta E^{\ddagger} \tag{12-96}$$

In principle, the transition state theory gives the influence of temperature on reaction rates by the general equation

$$k = (ve^{\Delta S^{\ddagger}/R})e^{-\Delta E^{\ddagger}/RT} \tag{12-97}$$

in which the frequency of decomposition of the transition state complex v may vary depending on the nature of the reactants. Eyring[13] has shown that the quantity v may be considered, to a good approximation, as a universal factor for reactions, depending only on temperature, and that it may be written,

$$v = \left(\frac{RT}{Nh}\right) \tag{12-98}$$

in which R is the molar gas constant, T is the absolute temperature, N is Avogadro's number, and h is Planck's constant. The factor (RT/Nh) has a value of about 10^{12} to 10^{13} sec^{-1} at ordinary temperatures ($\cong 2 \times 10^{10}T$). In many unimolecular gas reactions in which $\Delta S^{\ddagger}$ is zero so that $e^{\Delta S^{\ddagger}/R} = 1$, the rate constant ordinarily has a value of about $10^{13}e^{-E_a/RT}$ or

$$k \cong \frac{RT}{Nh}\,e^{-\Delta H^{\ddagger}/RT} \cong 10^{13}e^{-E_a/RT} \tag{12-99}$$

When the rate deviates from this value, it can be considered as resulting from the $e^{\Delta S^{\ddagger}/R}$ factor. When the activated complex represents a more probable arrangement of molecules than found in the normal reactants $\Delta S^{\ddagger}$ is positive and the reaction rate will be greater than normal. Conversely, when the activated complex results only after considerable rearrangement of the structure of the reactant molecules, making the com-

plex a less probable structure, $\Delta S^{\ddagger}$ is negative, and the reaction will be slower than predicted from equation (12–99). The collision theory and the transition state theory are seen to be related by comparing equations (12–80), (12–94), and (12–98). One concludes that

$$PZ = \frac{RT}{Nh} e^{\Delta S^{\ddagger}/R} \qquad (12\text{–}100)$$

The collision number Z is identified with RT/Nh and the probability factor P with the entropy term $e^{\Delta S^{\ddagger}/R}$

Example 12–8. In the study of the acid-catalyzed hydrolysis of procaine, Marcus and Baron[14] obtained the first-order reaction rate k from a plot of log c versus t, and the activation energy E_a from an Arrhenius plot of log k versus $1/T$. The values were $k = 38.5 \times 10^{-6}$ sec^{-1} at 97.30° C and $E_a = 16.8$ kcal/mole.

Compute $\Delta S^{\ddagger}$ and the frequency factor A using equations (12–93) and (12–94), and the probability factor P. It is first necessary to obtain RT/Nh at 97.30° C or about 371° K:

$$v = \frac{RT}{Nh} = \frac{8.31 \times 10^{7} \text{ erg/mole deg} \times 371 \text{ deg}}{6.62 \times 10^{-27} \text{ erg sec/molecule} \times 6.02 \times 10^{23} \text{ molecule/mole}}$$

$$= 7.74 \times 10^{12} \text{ sec}^{-1}$$

Then, from equation (12–93), in which

$$\Delta H^{\ddagger} \cong E_a,$$

$$38.5 \times 10^{-6} = 7.74 \times 10^{12} e^{\Delta S^{\ddagger}/1.987} \times e^{-16{,}800/(1.987 \times 371)}$$

$$\Delta S^{\ddagger} = -33.9 \text{ cal/mole deg}$$

and from equation (12–94)

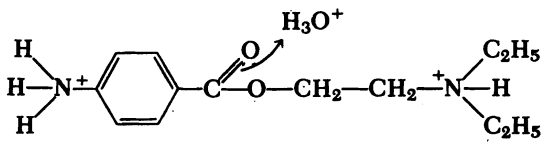
$$A = 7.74 \times 10^{12} e^{-33.9/1.987} = 3.02 \times 10^{5} \text{ sec}^{-1}$$

Finally, from the discussion accompanying equation (12–100)

$$P = e^{-33.9/1.987} = 3.9 \times 10^{-8}$$

Tables of e^{-x} values, available in handbooks of chemistry and physics, are convenient for handling calculations such as these, but hand calculators give the results directly.

Marcus and Baron[14] compared the kinetics of the acid-catalyzed hydrolyses of procainamide, procaine, and benzocaine. They found that the frequency factors for procainamide and procaine were considerably lower than the values expected for compounds of this type. Procainamide and procaine are diprotonated species in acid solution, that is, they have taken on two protons, and hydrolysis in the presence of an acid involves the interaction of positively charged ions, namely the diprotonated procaine molecule and the hydronium ion:



Diprotonated procaine under attack by a hydronium ion during acid hydrolysis

According to the authors, the two positively charged protonated centers on the procaine molecule exert a considerable repulsive effect on the attacking hydronium ions. This repulsion results in a low frequency factor. The $\Delta S^{\ddagger}$ is unusually negative (cf. *Example 12–8*) perhaps for the following reason. When the third proton finally attaches itself, the activated complex that results is a highly charged ion. The activated molecule is markedly solvated, reducing the freedom of the solvent and decreasing the entropy of activation. This effect, too, tends to lower the frequency factor.

Effect of the Solvent. The influence of the solvent on the rate of decomposition of drugs is a topic of great importance to the pharmacist. Although the effects are complicated and generalizations cannot usually be made, it appears that the reaction of nonelectrolytes is related to the relative internal pressures or solubility parameters of the solvent and solute (p. 224). The influence of the ionic strength and the dielectric constant of the medium on the rate of ionic reactions also are significant and will be discussed in subsequent sections.

Solutions are ordinarily nonideal, and equation (12–84) should be corrected by including activity coefficients. For the bimolecular reaction,

$$A + B \rightleftharpoons [A \cdots B]^{\ddagger} \rightarrow \text{Products}$$

the thermodynamic equilibrium constant should be written in terms of activities as

$$K^{\ddagger} = \frac{a^{\ddagger}}{a_A a_B} = \frac{C^{\ddagger}}{C_A C_B} \frac{\gamma^{\ddagger}}{\gamma_A \gamma_B} \qquad (12\text{–}101)$$

in which $a^{\ddagger}$ is the activity of the species in the transition state and a_A and a_B are the activities of the reactants in their normal state. Then the following expressions, analogous to equations (12–83) and (12–86), are obtained:

$$\text{Rate} = \frac{RT}{Nh} C^{\ddagger} = \frac{RT}{Nh} K^{\ddagger} C_A C_B \frac{\gamma_A \gamma_B}{\gamma^{\ddagger}} \qquad (12\text{–}102)$$

and

$$k = \frac{\text{Rate}}{C_A C_B} = \frac{RT}{Nh} K^{\ddagger} \frac{\gamma_A \gamma_B}{\gamma^{\ddagger}}$$

or

$$k = k_o \frac{\gamma_A \gamma_B}{\gamma^{\ddagger}} \qquad (12\text{–}103)$$

in which $k_0 = RTK^{\ddagger}/Nh$ is the rate constant in an infinitely dilute solution, that is, one that behaves ideally. It will be recalled from knowledge gained in previous chapters that the activity coefficients may relate the behavior of the solute in the solution under consideration to that of the solute in an infinitely dilute solution. When the solution is ideal the activity coefficients become unity and $k_0 = k$ in equation (12–103). This condition was tacitly assumed in equation (12–86).

Now, the activity coefficient γ_2 of a not too highly polar nonelectrolytic solute in a dilute solution is given by the expression (p. 224)

$$\log \gamma_2 = \frac{V_2}{2.303RT} (\delta_1 - \delta_2)^2 \qquad (12\text{–}104)$$

in which V_2 is the molar volume of the solute and δ_1 and δ_2 are the solubility parameters for the solvent and solute, respectively. The volume fraction term, Φ^2 on page 224 is assumed here to have a value of unity.

Writing equation (12–103) in logarithmic form

$$\log k = \log k_0 + \log \gamma_A + \log \gamma_B - \log \gamma^{\ddagger} \qquad (12\text{–}105)$$

and substituting for the activity coefficients from (12–104) gives

$$\log k = \log k_0 + \frac{V_A}{2.303RT}(\delta_1 - \delta_A)^2 + \frac{V_B}{2.303RT}(\delta_1 - \delta_B)^2 - \frac{V^{\ddagger}}{2.303RT}(\delta_1 - \delta^{\ddagger})^2 \qquad (12\text{–}106)$$

in which V_A, V_B, $V^{\ddagger}$, and the corresponding δ_A, δ_B, and $\delta^{\ddagger}$ are the molar volumes and solubility parameters of reactant A, reactant B, and the activated complex $(A\cdots B)^{\ddagger}$ respectively. The quantity δ_1 is the solubility parameter of the solvent.

Thus it is seen that the rate constant depends on the molar volumes and the solubility parameter terms. Since these three squared terms $(\delta_1 - \delta_A)^2$, $(\delta_1 - \delta_B)^2$, and $(\delta_1 - \delta^{\ddagger})^2$ represent the differences between solubility parameters or internal pressures of the solvent and the reactants, and the solvent and the activated complex, they may be symbolized respectively as $\Delta\delta_A$, $\Delta\delta_B$, and $\Delta\delta^{\ddagger}$. The molar volumes do not vary significantly, and the rate constant therefore depends primarily on the difference between $(\Delta\delta_A + \Delta\delta_B)$ and $\Delta\delta^{\ddagger}$. This is readily seen by writing equation (12–106) as

$$\log k = \log k_0 + \frac{V}{2.303RT}(\Delta\delta_A + \Delta\delta_B - \Delta\delta^{\ddagger})$$

It is assumed that the properties of the activated complex are quite similar to those of the products, so that $\Delta\delta^{\ddagger}$ may be taken as a squared term expressing the internal pressure difference between the solvent and the products. This equation indicates that if the internal pressure or "polarity" of the products is similar to that of the solvent, so that $\Delta\delta^{\ddagger} \cong 0$, and the internal pressures of the reactants are unlike that of the solvent, so that $\Delta\delta_A$ and $\Delta\delta_B > 0$, then the rate will be large in this solvent relative to the rate in an ideal solution. If, conversely, the reactants are similar in "polarity" to the solvent so that $\Delta\delta_A$ and $\Delta\delta_B \cong 0$, whereas the products are not similar to the solvent, that is, $\Delta\delta^{\ddagger} > 0$, then $(\Delta\delta_A + \Delta\delta_B) - \Delta\delta^{\ddagger}$ will have a sizable negative value and the rate will be small in this solvent.

As a result of this analysis, it can be said that polar solvents—those with high internal pressures—tend to accelerate reactions that form products having higher internal pressures than the reactants. If, on the other hand, the products are less polar than the reactants, they are accelerated by solvents of low polarity or internal pressure and retarded by solvents of high internal pressure. To illustrate this principle, the reaction between ethyl alcohol and acetic anhydride may be used:

$$C_2H_5OH + (CH_3CO)_2O = CH_3COOC_2H_5 + CH_3COOH$$

The activated complex, resembling ethyl acetate, is less polar than the reactants, and accordingly, the reaction should be favored in a solvent having a relatively low solubility parameter. The rate constants for the reaction in various solvents are given in Table 12–4 together with the solubility parameters of the solvents.[15] The reaction slows down in the more polar solvents as predicted.

Influence of Ionic Strength. In a reaction between ions, the reactants A and B have charges z_A and z_B, and the activated complex $(A\cdots B)^{\ddagger}$ has a charge of $(z_A + z_B)$. A reaction involving ions may be represented as

$$A^{z_A} + B^{z_B} \rightleftharpoons [A\cdots B]^{\ddagger(z_A+z_B)} \rightarrow \text{Products}$$

The activity coefficient γ_i of an ion in a dilute aqueous solution (<0.01 M) at 25° C is given by the Debye–Hückel equation (p. 135) as

$$\log \gamma_i = -0.51 z_i^2 \sqrt{\mu} \qquad (12\text{–}107)$$

in which μ is the ionic strength. Therefore, we can write

$$\begin{aligned}\log \gamma_A + \log \gamma_B - \log \gamma^{\ddagger} &= -0.51 z_A^2\sqrt{\mu} - 0.51 z_B^2\sqrt{\mu} + 0.51(z_A + z_B)^2\sqrt{\mu} \\ &= -0.51\sqrt{\mu}[z_A^2 + z_B^2 - (z_A^2 + 2z_Az_B + z_B^2)] \\ &= 0.51 \times 2 z_A z_B \sqrt{\mu} = 1.02 z_A z_B \sqrt{\mu} \qquad (12\text{–}108)\end{aligned}$$

Substituting into equation (12–105) results in the expression, at 25° C,

$$\log k = \log k_0 + 1.02 z_A z_B \sqrt{\mu} \qquad (12\text{–}109)$$

in which k_0 is the rate constant in an infinitely dilute solution in which $\mu = 0$. It follows from equation (12–109) that a plot of $\log k$ against $\sqrt{\mu}$ should give a straight line with a slope of $1.02 z_A z_B$. If one of the reactants is a neutral molecule, $z_A z_B = 0$ and the rate constant as seen from equation (12–109) should then be independent of the ionic strength in dilute solutions.

TABLE 12–4. *Influence of Solvents on Rate Constants*

Solvent	Solubility Parameter δ	k at 50° C
Hexane	7.3	0.0119
Carbon tetrachloride	8.6	0.0113
Chlorobenzene	9.5	0.0053
Benzene	9.2	0.0046
Chloroform	9.3	0.0040
Nitrobenzene	10.0	0.0024

Good agreement has been obtained between experiment and theory as expressed by equation (12–109).

If the reacting molecules are uncharged in a solution having a reasonable ionic strength, the rate expression is

$$\log k = \log k_0 + b\mu \qquad (12\text{–}110)$$

in which b is a constant obtained from experimental data. Carstensen[16] has considered the various ionic strength effects in pharmaceutical solutions.

Influence of Dielectric Constant. The effect of the dielectric constant on the rate constant of an ionic reaction, extrapolated to infinite dilution where the ionic strength effect is zero, is often a necessary piece of information in the development of new drug preparations. One of the equations by which this effect may be determined is

$$\ln k = \ln k_{\epsilon=\infty} - \frac{Nz_Az_Be^2}{RTr^\ddagger}\frac{1}{\epsilon} \qquad (12\text{–}111)$$

in which $k_{\epsilon=\infty}$ is the rate constant in a medium of infinite dielectric constant, N is Avogadro's number, z_A and z_B are the charges on the two ions, e is the unit of electric charge, $r^\ddagger$ is the distance between ions in the activated complex, and ϵ is the dielectric constant of the solution, equal approximately to the dielectric constant of the solvent in dilute solutions. The term $\ln k_{\epsilon=\infty}$ is obtained by plotting $\ln k$ against $1/\epsilon$ and extrapolating to $1/\epsilon = 0$, that is, to $\epsilon = \infty$. Such a plot, according to equation (12–111), should yield a straight line with a positive slope for reactant ions of opposite sign and a negative slope for reactants of like sign. For a reaction between ions of opposite sign, an increase in dielectric constant of the solvent results in a decrease in the rate constant. For ions of like charge, on the other hand, an increase in dielectric constant results in an increase in the rate of the reaction.

When a reaction occurs between a dipole molecule and an ion A, the equation is

$$\ln k = \ln k_{\epsilon=\infty} + \frac{Nz_A^2e^2}{2RT}\left(\frac{1}{r_A} - \frac{1}{r^\ddagger}\right)\frac{1}{\epsilon} \qquad (12\text{–}112)$$

in which z_A is the charge on the ion A, r_A is the radius of the ion, and $r^\ddagger$ is the radius of the activated complex. Equation (12–112) predicts that a straight line should be obtained when $\ln k$ is plotted against $1/\epsilon$, the reciprocal of the dielectric constant. Since $r^\ddagger$, being the radius of the combined ion and neutral molecule in the transition state, will be larger than r_A, the radius of the ion, the second term on the right side of the equation will always be positive, and the slope of the line will consequently be positive. Therefore, $\ln k$ will increase with increasing values of $1/\epsilon$, that is, the rate of reaction between an ion and a neutral molecule will increase with *decreasing* dielectric constant of the medium. This relationship, however, does not hold if different solvents are used or if the solutions are not dilute, in which ionic strength effects become significant.

The orientation of the solvent molecules around the solute molecules in solution will result in an effect that has not been accounted for in the equations given previously. When a solvent-mixture is composed of water and a liquid of low dielectric constant, water molecules will be oriented about the ions in solution, and the dielectric constant near the ion will be considerably greater than that in the bulk of the solution. Thus, when $\ln k$ is plotted against the reciprocal of the dielectric constant of the solvent mixture, deviations from the straight line predicted by equations (12–111) and (12–112) will frequently result.

A number of studies relating the dielectric constant of the solvent medium to the rate of reactions have been undertaken. Several investigations involving compounds of pharmaceutical interest are briefly reviewed here.

Amis and Holmes[17] studied the effect of the dielectric constant on the acid inversion of sucrose. When the dielectric constant was reduced by adding dioxane* to the aqueous solvent, the rate of the reaction was found to increase in accord with the theory of ion–dipole reactions as expressed by (12–112).

To determine the effect of dielectric constant on the rate of glucose decomposition in acidic solution, Heimlich and Martin[8] carried out tests in dioxane*–water mixtures. The results shown in Table 12–5 are those expected for a reaction between a positive ion and a dipole molecule. As observed in the table, the dielectric constant of the medium should be an important consideration in the stabilization of glucose solutions, since replacing water with a solvent of lower dielectric constant markedly increases the rate of breakdown of glucose. Marcus and Taraszka[18] studied the kinetics of the hydrogen-ion–catalyzed degradation of the antibiotic chloramphenicol in water–propylene glycol systems. The decrease in dielectric constant resulted in an increase in the rate of the reaction, a finding that agrees with the requirements for an ion–dipole reaction.

These findings have considerable pharmaceutical significance. The replacement of water with other solvents is often used in pharmacy as a means of stabilizing drugs against possible hydrolysis. The results of the investigations reviewed here suggest, however, that the use of a solvent mixture of lowered dielectric constant actually may increase rather than decrease the rate of decomposition. On the other hand, as pointed out by Marcus and Taraszka, a small increase in decomposition rate due to the use of nonaqueous solvents may be outweighed by enhancement of solubility of the drug in the solvent of lower dielectric constant. Thus, there is a need for thorough kinetic studies and cautious interpretations of the results before one can predict the optimum conditions for stabilizing drug products.

*Dioxane is toxic and cannot be used in pharmaceutical preparations. See Merck Index, 11th ed., p. 3297, 1989.

TABLE 12–5. *Decomposition of 0.278-M Solutions of Glucose at pH 1.27 and 100° C in Dioxane–Water Mixtures

Dioxane % by Weight	Dielectric Constant of the Solvent at 100° C	Rate Constant $k \times 10^5$ hr^{-1}
0	55	4.58
9.98	48	4.95
29.74	35	6.34
49.32	22	10.30

*See footnote on page 300.

Catalysis. As already noted, the rate of a reaction is frequently influenced by the presence of a catalyst. Although the hydrolysis of sucrose in the presence of water at room temperature proceeds with a decrease in free energy, the reaction is so slow as to be negligible. When the hydrogen ion concentration is increased by adding a small amount of acid, however, inversion proceeds at a measurable rate.

A *catalyst* is therefore defined as a substance that influences the speed of a reaction without itself being altered chemically. When a catalyst decreases the velocity of a reaction, it is called a *negative catalyst.* Actually, negative catalysts often may be changed permanently during a reaction, and should be called *inhibitors* rather than catalysts.

Since a catalyst remains unaltered at the end of a reaction, it does not change the overall $\Delta G°$ of the reaction and hence, according to the relationship

$$\Delta G° = -RT \ln K$$

it cannot change the position of the equilibrium of a reversible reaction. The catalyst increases the velocity of the reverse reaction to the same extent as the forward reaction, so that although the equilibrium is reached more quickly in the presence of the catalyst, the equilibrium constant

$$K = k_{\text{forward}}/k_{\text{reverse}}$$

remains the same and the product yield is not changed.

Catalysis is considered to operate in the following way. The catalyst combines with the reactant known as the *substrate* and forms an intermediate known as a *complex,* which then decomposes to regenerate the catalyst and yield the products. In this way, the catalyst decreases the energy of activation by changing the mechanism of the process, and the rate is accordingly increased. Alternatively, a catalyst may act by producing free radicals such as $CH_3\bullet$, which bring about fast *chain reactions.* Chain reactions are reactions consisting of a series of steps involving free atoms or radicals that act as intermediates. The chain reaction is begun by an initiating step and stopped by a chain-breaking or terminating step. Negative catalysts, or inhibitors, frequently serve as chain breakers in such reactions. Antiknock agents act as inhibitors in the explosive reactions attending the combustion of motor fuels.

Catalytic action may be homogeneous or heterogeneous and may occur in either the gaseous or liquid state. *Homogeneous catalysis* occurs when the catalyst and the reactants are in the same phase. Acid–base catalysis, the most important type of homogeneous catalysis in the liquid phase, will be discussed in some detail in the next section.

Heterogeneous catalysis occurs when the catalyst and the reactants form separate phases in the mixture. The catalyst may be a finely divided solid such as platinum, or it may be the walls of the container. The catalysis occurs at the surface of the solid and is therefore sometimes known as *contact catalysis.* The reactant molecules are adsorbed at various points or *active centers* on the rough surface of the catalyst. Presumably, the adsorption weakens the bonds of the reactant molecules and lowers the activation energy. The activated molecules then can react, and the products diffuse away from the surface.

Catalysts may be *poisoned* by extraneous substances that are strongly adsorbed at the active centers of the catalytic surface where the reactants would normally be held during reaction. Carbon monoxide is known to poison the catalytic action of copper in the hydrogenation of ethylene. Other substances, known as *promoters,* are found to increase the activity of a catalyst. For example, cupric ions promote the catalytic action of ferric ions in the decomposition of hydrogen peroxide. The exact mechanism of promoter action is not understood, although the promoter is thought to change the properties of the surface so as to enhance the adsorption of the reactants and thus increase the catalytic activity.

Specific Acid–Base Catalysis. Solutions of a number of drugs undergo accelerated decomposition upon the addition of acids or bases. If the drug solution is buffered, the decomposition may not be accompanied by an appreciable change in the concentration of acid or base, so that the reaction may be considered to be catalyzed by hydrogen or hydroxyl ions. When the rate law for such an accelerated decomposition is found to contain a term involving the concentration of hydrogen ion or the concentration of hydroxyl ion, the reaction is said to be subject to *specific acid–base catalysis.*

As an example of specific acid–base catalysis, we may consider the pH dependence for the hydrolysis of esters. In acidic solution, we can consider the hydrolysis to involve an initial equilibrium between the esters and a hydrogen ion followed by a rate-determining reaction with water, *R:*

$$S + H^+ \rightleftharpoons SH^+$$

$$SH^+ + R \rightarrow P$$

This general reaction scheme assumes that the products, P, of the hydrolysis reaction do not recombine to form ester.

For the generalized reaction, the rate of product formation is given by

$$\frac{dP}{dt} = k[SH^+][R] \qquad (12\text{–}113)$$

The concentration of the conjugate acid SH^+ can be expressed in terms of measurable quantities, because the pre-equilibrium requires that

$$K = \frac{[SH^+]}{[S][H^+]} \qquad (12-114)$$

Thus,

$$[SH^+] = K[S][H^+] \qquad (12-115)$$

and it follows that

$$\frac{dP}{dt} = kK[S][H^+][R] \qquad (12-116)$$

Since water, R, is present in great excess, equation (12–116) reduces to the apparent rate law

$$\frac{dP}{dt} = k_1[S][H^+] \qquad (12-117)$$

in which

$$k_1 = kK[R] \qquad (12-118)$$

The hydrogen ion concentration term in equation (12–117) indicates that the process is a specific hydrogen-ion–catalyzed reaction.

By studying the acid-catalyzed hydrolysis of an ester at various concentrations of hydrogen ion—that is, by hydrolyzing the ester in buffer solutions of differing pH—we can obtain a rate–pH profile for the reaction. At a given pH, an apparent first-order reaction is observed:

$$\frac{dP}{dt} = k_{obs}[S] \qquad (12-119)$$

in which

$$k_{obs} = k_1[H^+] \qquad (12-120)$$

Taking logarithms of equation (12–120)

$$\log k_{obs} = \log [H^+] + \log k_1 \qquad (12-121)$$

or, equivalently,

$$\log k_{obs} = -(-\log [H^+]) + \log k_1 \qquad (12-122)$$

We finally arrive at the expression

$$\log k_{obs} = -pH + \log k_1 \qquad (12-123)$$

Thus, a plot of $\log k_{obs}$ against the pH of the solution in which the reaction is run gives a line of slope equal to -1.

Consider, now, the specific hydroxide-ion–catalyzed decomposition of an ester, S. We may write the general reaction as

$$S + OH^- \rightarrow P$$

and the rate of product (P) formation is therefore given by

$$\frac{dP}{dt} = k_2[S][OH^-] \qquad (12-124)$$

Under buffer conditions, an apparent first-order reaction is again observed:

$$\frac{dP}{dt} = k_{obs}[S] \qquad (12-125)$$

in which now

$$k_{obs} = k_2[OH^-] \qquad (12-126)$$

or, since

$$K_w = [H^+][OH^-] \qquad (12-127)$$

$$k_{obs} = \frac{k_2K_w}{[H^+]} \qquad (12-128)$$

Taking the logarithm of equation (12–128)

$$\log k_{obs} = -\log [H^+] + \log k_2K_w \qquad (12-129)$$

we find that

$$\log k_{obs} = pH + \log k_2K_w \qquad (12-130)$$

In this case, a plot of $\log k_{obs}$ against pH should be linear with a slope equal to $+1$.

Figure 12–8 shows the rate–pH profile for the specific acid–base–catalyzed hydrolysis of methyl-*dl*-*o*-phenyl-2-piperidylacetate.[19] It is noted that an increase in pH from 1 to 3 results in a linear decrease in rate, as expected from equation (12–123), for specific hydrogen ion catalysis, while a further increase in pH from about 3 to 7 results in a linear increase in rate, as expected from equation (12–130), for specific hydroxide ion catalysis. Near pH 3, a minimum is observed that cannot be attributed to either hydrogen ion or hydroxyl ion participation in the reaction. This minimum is indicative of a solvent catalytic effect; that is, unionized water may be considered as the reacting species. Because of the pH independence of this reaction, the rate law is given by

$$\frac{dP}{dt} = k_0[S] \qquad (12-131)$$

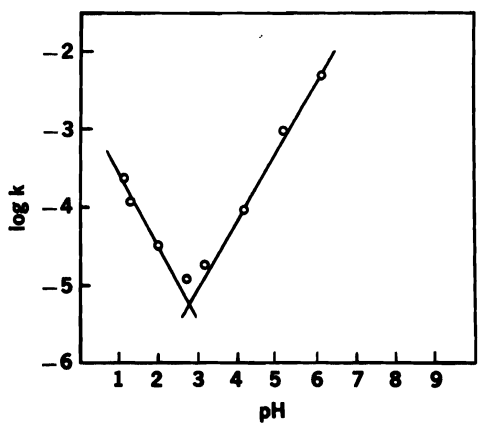


Fig. 12–8. Rate–pH profile for the specific acid–base catalyzed hydrolysis of methyl-dl-*o*-phenyl-2-piperidylacetate. (After S. Siegel, L. Lachmann, and L. Malspeis, J. Pharm. Sci. 48, 431, 1959, reproduced with permission of the copyright owner.)

so that

$$k_{obs} = k_0 \qquad (12-132)$$

Sometimes a minimum plateau extends over a limited pH region, indicating that solvent catalysis is the primary mode of reaction in this region.

Solvent catalysis may occur simultaneously with specific hydrogen ion or specific hydroxide ion catalysis, especially at pH values that are between the pH regions in which definitive specific ion and solvent catalytic effects are observed. Since each catalytic pathway leads to an increase in the same product, the rate law for this intermediate pH region may be written

$$\frac{dP}{dt} = (k_0 + k_1[H^+])[S] \qquad (12-133)$$

or

$$\frac{dP}{dt} = (k_0 + k_2[OH^-])[S] \qquad (12-134)$$

depending, respectively, on whether the pH is slightly lower or slightly higher than that for the solvent catalyzed case.

We may now summarize the pH dependency of specific acid–base–catalyzed reactions in terms of the general rate law

$$\frac{dP}{dt} = (k_0 + k_1[H^+] + k_2[OH^-])[S] \qquad (12-135)$$

for which

$$k_{obs} = k_0 + k_1[H^+] + k_2[OH^-] \qquad (12-136)$$

At low pH, the term $k_1[H^+]$ is greater than k_0 or $k_2[OH^-]$ because of the greater concentration of hydrogen ions, and specific hydrogen ion catalysis is observed. Similarly, at high pH at which the concentration of $[OH^-]$ is greater, the term $k_2[OH^-]$ outweighs the k_0 and $k_1[H^+]$ terms, and specific hydroxyl ion catalysis is observed. When the concentrations of H^+ and OH^- are low, or if the products $k_1[H^+]$ and $k_2[OH^-]$ are small in value, only k_0 is important, and the reaction is said to be *solvent catalyzed*. If the pH of the reaction medium is slightly acidic, so that k_0 and $k_1[H^+]$ are important and $k_2[OH^-]$ is negligible, both solvent and specific hydrogen ion catalysis operate simultaneously. A similar result is obtained when the pH of the medium is slightly alkaline, a condition that could allow concurrent solvent and specific hydroxide ion catalysis.

General Acid–Base Catalysis. In most systems of pharmaceutical interest, buffers are used to maintain the solution at a particular pH. Often, in addition to the effect of pH on the reaction rate, there may be catalysis by one or more species of the buffer components. The reaction is then said to be subject to *general acid* or *general base catalysis* depending, respectively, on whether the catalytic components are acidic or basic.

The rate–pH profile of a reaction that is susceptible to general acid–base catalysis exhibits deviations from the behavior expected on the basis of equations (12–123) and (12–130). For example, in the hydrolysis of the antibiotic streptozotocin, rates in phosphate buffer exceed the rate expected for specific base catalysis. This effect is due to a general base catalysis by phosphate anions. Thus, the alkaline branch of the rate–pH profile for this reaction is a line whose slope is different from 1 (Fig. 12–9).[20]

Other factors, such as ionic strength or changes in the pK_a of a substrate may also lead to apparent deviations in the rate–pH profile. Verification of a general acid or general base catalysis may be made by determining the rates of degradation of a drug in a series of buffers that are all at the same pH (i.e., the ratio of salt to acid is constant) but that are prepared with an increasing concentration of buffer species. Windheuser and Higuchi,[21] using acetate buffer, found that the degradation of thiamine is unaffected at pH 3.90, where the buffer is principally acetic acid. At higher pH values, however, the rate increases in direct proportion to the concentration of acetate. In this case, acetate ion is the general base catalyst.

Webb et al.[22] demonstrated the general catalytic action of acetic acid, sodium acetate, formic acid, and sodium formate in the decomposition of glucose. The equation for the overall rate of decomposition of glucose in water in the presence of acetic acid HAc and its conjugate base Ac^- can be written

$$-\frac{dG}{dt} = k_0[G] + k_H[H^+][G] + k_A[HAc][G] + k_{OH}[OH^-][G] + k_B[Ac^-][G] \qquad (12-137)$$

in which $[G]$ is the concentration of glucose, k_0 is the specific reaction rate in water alone, and the other k values, known as *catalytic coefficients*, represent the specific rates associated with the various catalytic

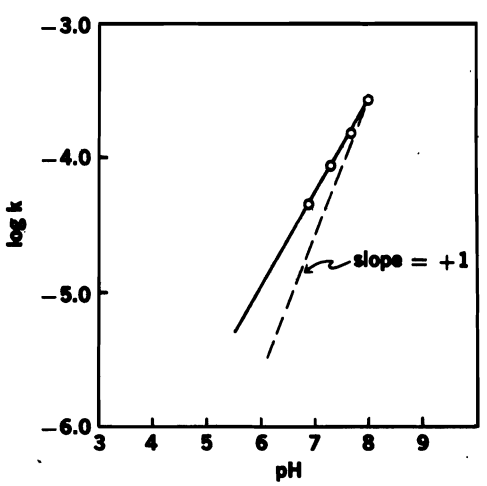


Fig. 12–9. Rate–pH profile of a reaction susceptible to general base catalysis. (After E. R. Garrett, J. Pharm. Sci. 49, 767, 1960, reproduced with permission of the copyright owner.)

species. The overall first-order rate constant k, which involves all effects, is written as follows:

$$k = -\frac{dG/dt}{[G]} = k_0 + k_H[H^+] + k_A[HAc] + k_{OH}[OH^-] + k_B[Ac^-] \qquad (12-138)$$

or, in general,

$$k = k_0 + \Sigma k_i c_i \qquad (12-139)$$

in which c_i is the concentration of the catalytic species i and k_i is the corresponding catalytic coefficient. In reactions in which only specific acid–base effects occur, that is, in which only $[H^+]$ and $[OH^-]$ act as catalysts, the equation is

$$k = k_0 + k_H[H^+] + k_{OH}[OH^-] \qquad (12-140)$$

Example 12–9. A sample of glucose was decomposed at 140° C in a solution containing 0.030 *M* HCl. The velocity constant k was found to be 0.0080 hr^{-1}. If the spontaneous rate constant k_0 is 0.0010 hr^{-1}, compute the catalytic coefficient k_H. The catalysis due to hydroxyl ions in this acidic solution may be considered as negligible.

The data are substituted in equation (12–140):

$$0.0080\ hr^{-1} = 0.0010\ hr^{-1} + k_H\ M^{-1}hr^{-1}\ (0.030)\ M$$

$$k_H = \frac{0.0080\ hr^{-1} - 0.0010\ hr^{-1}}{0.030\ M} = 0.233\ M^{-1}\ hr^{-1}$$

In 1928, Brönsted[23] showed that a relationship exists between the catalytic power as measured by the catalytic coefficients and the strength of general acids and bases as measured by their dissociation constants. The catalytic coefficient for a weak acid is related to the dissociation constant of the acid by the expression

$$k_A = aK_a^{\alpha} \qquad (12-141)$$

and the corresponding equation for catalysis by a weak base is

$$k_B = bK_a^{-\beta} \qquad (12-142)$$

K_a is the dissociation constant of the weak acid, and a, b, α, and β are constants for a definite reaction, solvent, and temperature. From this relationship, the catalytic effect of a Brönsted–Lowry acid or base on the specific reaction rate can be predicted if the dissociation constant of the weak electrolyte is known. The relationships in equations (12–141) and (12–142) hold because both the catalytic power and the dissociation constant of a weak electrolyte depend on the ability of a weak acid to donate a proton or a weak base to accept a proton.

Noncatalytic salts can affect the rate constant directly through their influence on ionic strength as expressed by equation (12–109). Secondly, salts also affect the catalytic action of some weak electrolytes because, through their ionic strength effect, they change the classic dissociation constant K_a of equations (12–141) and (12–142). These two influences, known respectively as the *primary* and *secondary salt effects*, are handled in a kinetic study by carrying out the reaction under conditions of constant ionic strength, or by obtaining a series of k values at decreasing ionic strengths and extrapolating the results to $\mu = 0$.

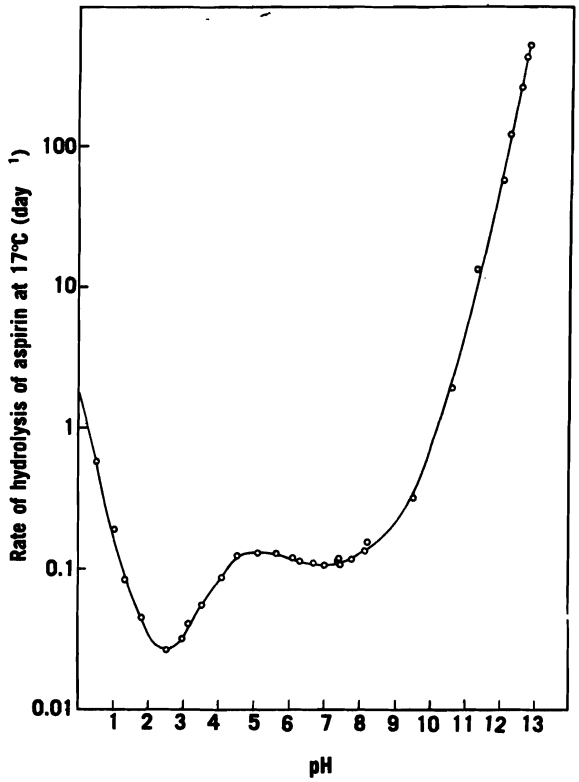
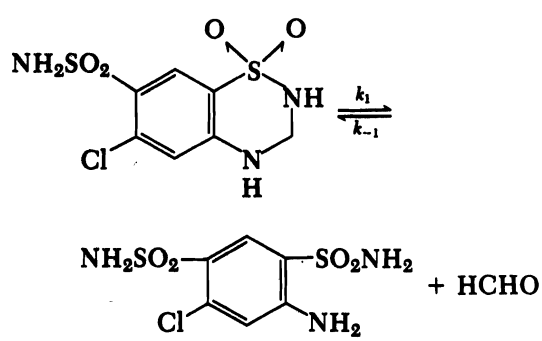


Fig. 12–10. Rate–pH profile for the hydrolysis of acetylsalicylic acid at 17° C. (After I. J. Edwards, Trans. Faraday Soc. 46, 723, 1950.)

An interesting rate–pH profile, shown in Figure 12–10, is obtained for the hydrolysis of acetylsalicylic acid. In the range of pH 0 to about 4, there is clearly specific acid–base catalysis and a pH-independent solvolysis, as first reported by Edwards.[24] Above pH 4, there is a second pH-independent region, the plateau extending over at least 3 pH units. Fersht and Kirby[25] and others have provided suggestions for the presence of this plateau.

The hydrolysis of hydrochlorothiazide was investigated by Mollica et al.[26] over a pH range from 1 to 13. The reaction was found to be reversible (p. 290), the fraction that had reacted at equilibrium X_e being about 0.4. The pH profile provides a complex curve (Fig. 12–11) indicating multiple steps and an intermediate involved in the reaction.



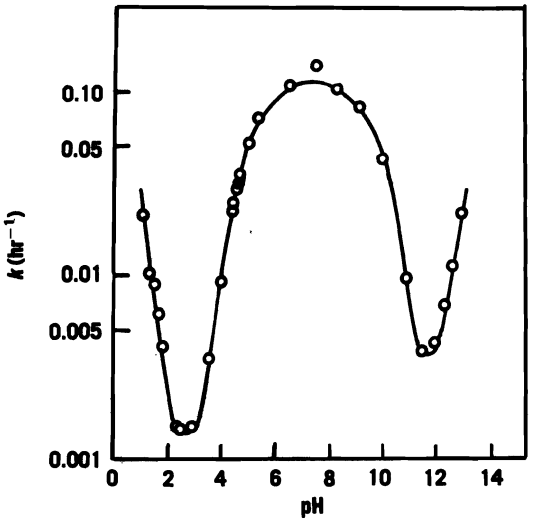


Fig. 12–11. The pH profile for the hydrolysis of hydrochlorothiazide. (From J. A. Mollica, C. R. Rohn and J. B. Smith, J. Pharm. Sci. 58, 636, 1969, reproduced with permission of copyright owner.)

DECOMPOSITION AND STABILIZATION OF MEDICINAL AGENTS

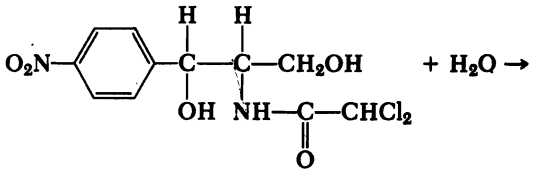
In recent years, various institutions and manufacturing companies have initiated programs to study systematically the decomposition of drugs. Some of the findings, not already referred to in this chapter, are briefly reviewed here. The interested reader should consult the original papers for the details of the methods and results.

Pharmaceutical decomposition can be classified as hydrolysis, oxidation, isomerization, epimerization, and photolysis, and these processes may affect the stability of drugs in liquid, solid, and semisolid products. Mollica et al.[27] have reviewed the many effects that the ingredients of dosage forms and environmental factors may have on the chemical and physical stability of pharmaceutical preparations.

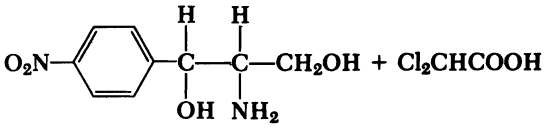
Hou and Poole[28] investigated the kinetics and mechanism of hydrolytic degradation of ampicillin in solution at 35° C and 0.5 ionic strength. The decomposition observed over a pH range of 0.8 to 10.0 followed first-order kinetics and was influenced by both specific and general acid–base catalysis. The pH–rate profile exhibited maximum stability in buffer solutions at pH 4.85 and in nonbuffered solutions at pH 5.85. The degradation rate is increased by the addition of various carbohydrates such as sucrose to the aqueous solution of ampicillin.[29] The Arrhenius plot shows the activation energy E_a to be 18 kcal/mole at pH 5 for the hydrolysis of ampicillin.

Alcohol is found to slow hydrolysis because of the decrease in the dielectric constant of the solvent. The half-life for the degradation of ampicillin in an acidified aqueous solution at 35° C is 8 hours; in a 50% alcohol solution the half-life is 13 hours.

Higuchi et al.[30] reported that chloramphenicol decomposed through hydrolytic cleavage of the amide linkage according to the reaction shown here.



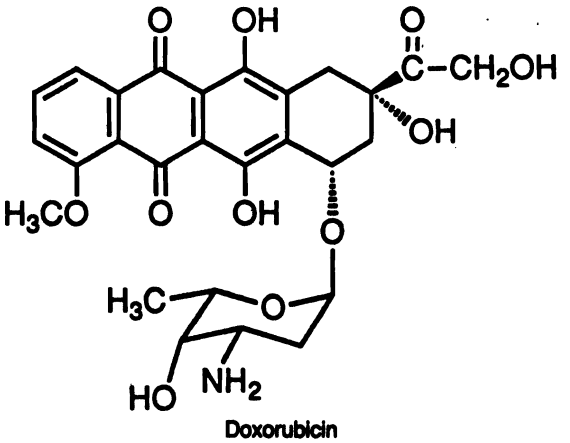
Chloramphenicol



The rate of degradation was low and independent of pH between 2 and 7 but was catalyzed by general acids and bases, including HPO_4^{2-} ions, undissociated acetic acid, and a citrate buffer. Its maximum stability occurs at pH 6 at room temperature, its half-life under these conditions being approximately 3 years. Below pH 2 the hydrolysis of chloramphenicol is catalyzed by hydrogen ions. In alkaline solution the breakdown is affected by both specific and general acid–base catalysis.[31]

The activation energy for the hydrolysis at pH 6 is 24 kcal/mole, and the half-life of the drug at pH 6 and 25° C is 2.9 years.

Beijnen et al.[32] investigated the stability of doxorubicin in aqueous solution using a stability-indicating



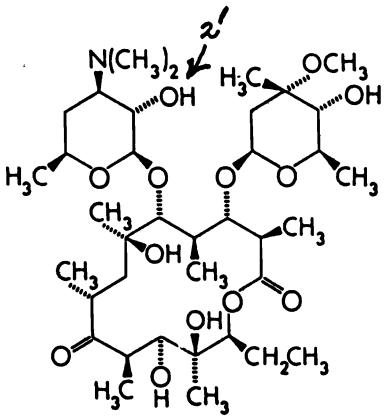
Doxorubicin

high-performance liquid chromatographic (HPLC) assay procedure. Doxorubicin has been used with success against various human neoplasms for the past 20 years. The decomposition of the drug has not been studied in depth, for it presents difficulties in analysis. It chelates with metal ions, self-associates in concentrated solutions, adsorbs to surfaces such as glass, and undergoes oxidative and photolytic decomposition.

Beijnen and associates studied the degradation kinetics of doxorubicin as a function of pH, buffer effects, ionic strength, temperature, and drug concentration. The decomposition followed pseudo–first-order kinetics at constant temperature and ionic strength at various

pH values. The pH–rate profile showed maximum stability of the drug at about pH 4.5. Some study was made of the degradation in alkaline solution, other systematic work having been done only with degradation of doxorubicin in acid solution below pH 3.5. Work has also been reported on the stability of doxorubicin infusions used in clinical practice.

Steffansen and Bundgaard[33] studied the hydrolysis of erythromycin and erythromycin esters in aqueous



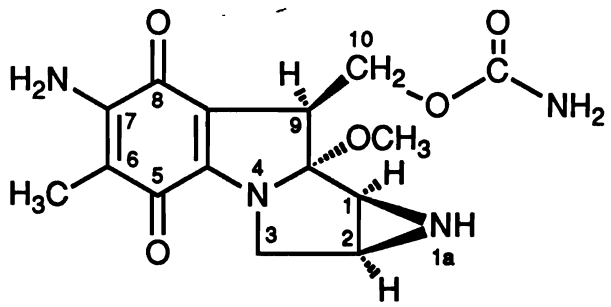
Erythromycin A

solution. Erythromycin is an antibiotic that acts against gram-positive and some gram-negative bacteria. It has the disadvantage of degradation in an acidic environment, as found in the stomach; and various methods have been suggested to protect the drug as it passes through the gastrointestinal tract. Most recent among these protective actions is the conversion of erythromycin into esters at the 2′ position. These are known as *prodrugs* (p. 513), since they are inactive until erythromycin is released from the esters by enzymatic hydrolysis in the body.

Vinckier et al.[34] studied the decomposition kinetics of erythromycin as a function of buffer type and concentration, ionic strength, pH, and temperature. Erythromycin was found to be most stable in a phosphate buffer and least stable in a sodium acetate buffer. Changes in ionic strength showed only a negligible effect on the kinetics of erythromycin. Log k–pH profiles were obtained over the pH range of about 2 to 5 and showed linearity with a slope of approximately 1, indicating specific acid catalysis in the decomposition of erythromycin at 22° C. Specific base catalysis occurs at higher pH values. Erythromycin base is most stable at pH 7 to 7.5.[35]

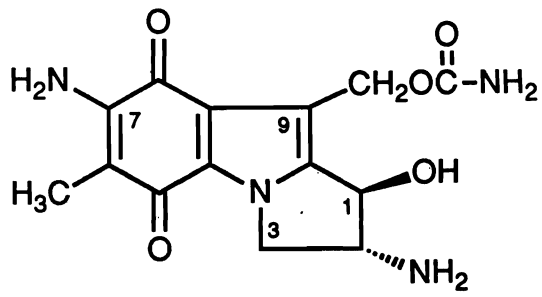
Atkins et al.[36] have also made a study of the kinetics of erythromycin decomposition in aqueous acidic and neutral buffers. They conclude that pH is the most important factor in controlling the stability of erythromycin A in acidic aqueous solutions.

The degradation of mitomycin C in acid solution was studied by Beijnen and Underberg.[37] Mitomycin C shows both strong antibacterial and antitumor activity. Degradation in alkaline solution involves the removal of an amino group and replacement by a hydroxyl group,



Mitomycin C

but the breakdown of mitomycin C is more complicated in acid solution, involving ring opening and the formation of two isomers, namely *trans* and *cis* mitosene (structures I and II).



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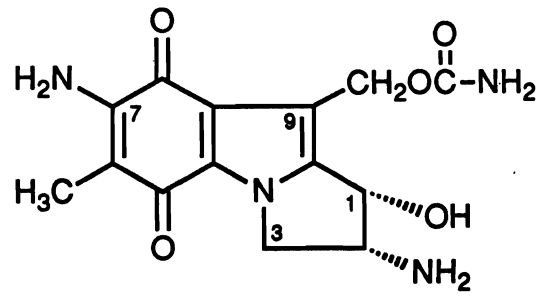


II

To study the mechanism of degradation the authors designed an HPLC assay that allows quantitative separation of the parent drug and its decomposition products.

The kinetics of mitomycin C in acid solution was studied at 20° C. To obtain pH values below 3 the solutions were acidified with aqueous perchloric acid, and for the pH range of 3 to 6 they were buffered with an acetic acid–acetate buffer. The degradation of mitomycin C shows first-order kinetics over a period of more than 3 half-lives.

The influence of pH and buffer species on the decomposition of mitomycin C is expressed as

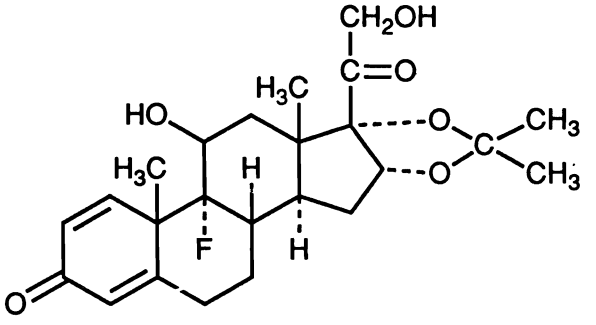
$$k = k_o + k_H[H^+] + k_A[HAc] + k_B[Ac^-] \qquad (12\text{–}143)$$

in which k_o is the first-order constant for decomposition in water alone and k_H is a second-order rate constant (catalytic coefficient) associated with catalysis due to the $[H^+]$. The second-order rate constants k_A and k_B

are catalytic coefficients for catalysis by the buffer components, [HAc] and [Ac^-], respectively (equation [12–138], p. 304). The term $k_{OH}[OH^-]$ is neglected because this study is conducted only in the acid region of the pH scale.

The log (rate-constant)–pH profile for the decomposition of mitomycin C at 20° C is seen in Figure 12–12. In other work, Beijnen and associates have shown that the inflection point in the curve is associated with the $pK_a = 2.6$ for mitomycin C. The straight-line portions of the curve—that is, below pH = 0 and above pH = 3—both exhibit slopes of approximately −1. Slopes of −1 in this region of the profile are an indication of specific acid catalysis for decomposition of the neutral form of mitomycin C (MMC) and for the protonated form ($MMCH^+$).

Procaine decomposes mainly by hydrolysis, the degradation being due primarily to the breakdown of the uncharged and singly charged forms.[38] The reaction of procaine is catalyzed by hydrogen and hydroxyl ions. Both the free base and the protonated form are subject to specific base catalysis. Marcus and Baron[39] obtained an activation energy $E_a = 16.8$ kcal/mole for procaine at 97.30°. Garrett[40] has reviewed the degradation and stability of procaine.



Triamcinolone Acetonide

Triamcinolone acetonide, a glucocorticoid (adrenal cortex) hormone, is a potent antiinflammatory agent when applied topically as a cream or suspension. Das Gupta[41] studied the stability of water–ethanol solutions at various pH values, buffer concentrations, and ionic strengths. The decomposition of triamcinolone acetonide followed first-order kinetics, the rate constant k_{obs} varying with the pH of phosphate, sodium hydroxide, and hydrochloric acid buffer solutions. The optimum pH for stability was found from a pH–rate profile to be about 3.4 and to be related to the concentration of the phosphate buffer. In the hydrochloric acid buffer solution, triamcinolone acetonide underwent hydrolysis to form triamcinolone and acetone. A study of the reaction in solvents of varying ionic strength showed that log k_{obs} decreased linearly with increasing values of $\sqrt{\mu}$, suggesting that reaction occurs between the protonated [H^+] form of the drug and the phosphate buffer species, $H_2PO_4^-/HPO_4^{2-}$.

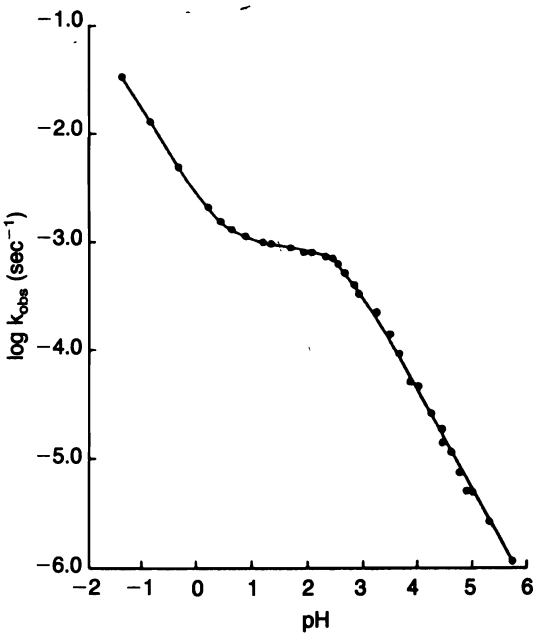


Fig. 12–12. pH–rate constant profile for mitomycin C decomposition. (From J. H. Beijnen and W. J. M. Underberg, Int. J. Pharm. 24, 219, 1985, reproduced with permission of the copyright owner.)

Vincristine and vinblastine are natural alkaloids used as cytotoxic agents in cancer chemotherapy (Fig. 12–13). Vendrig et al.[42] investigated the degradation kinetics of vincristine sulfate in aqueous solution within the pH range of −2.0 to 11 at 80° C. The drug exhibited first-order kinetics under these conditions; the rate constant k_{obs} was calculated using the first-order equation (equation [12–14], p. 287) at various pH values in order to plot the pH profile as seen in Figure 12–14. The degradation rates were found to be independent of buffer concentration and ionic strength within the pH range investigated. Vincristine appears to be most stable in aqueous solution between pH 3.5 and 5.5 at 80° C.

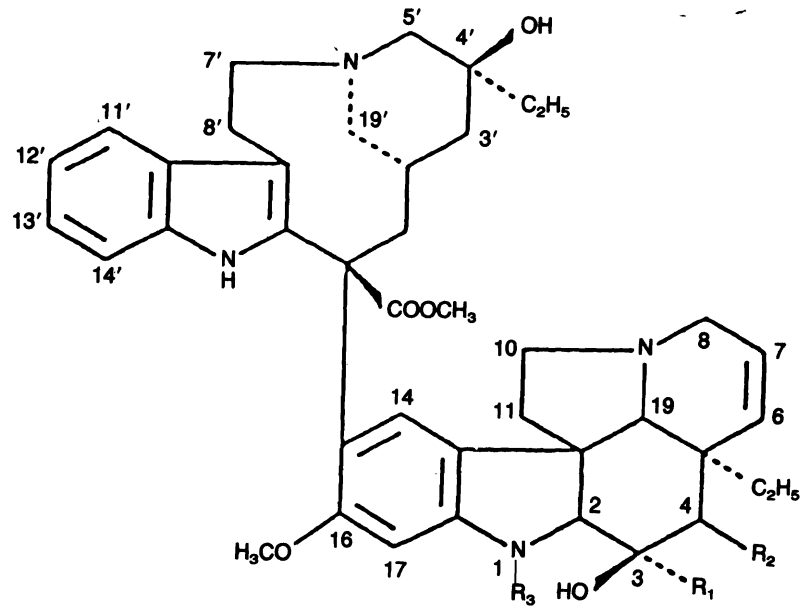
The effect of temperature on the degradation of vincristine at various pH values from 1.2 to 8.2 and within the temperature range of 60° to 80° C was assessed using the Arrhenius equation [equation (12–72) or (12–73), p. 295]. The activation energy Ea and the Arrhenius factor A are given in Table 12–6.

Example 12–10. Vendrig et al.[42] listed the activation energies in kJ $mole^{-1}$ for vincristine from pH 1.2 to 8.2. Convert the values for E_a given below to quantities expressed in cal/mole, as found in Table 12–6:

pH	1.2	3.5	5.2	7.0	8.2
E_a (kJ · $mole^{-1}$)	62	84	73	106	116

The conversion of units is obtained by writing a sequence of ratios so as to change SI to cgs units. For the first value above, that of E_a at pH 1.2:

$$62\ \frac{\text{kJ}}{\text{mole}} \times \frac{1000\ \text{J}}{\text{kJ}} \times \frac{10^7\ \text{erg}}{\text{J}} \times \frac{1\ \text{cal}}{4.184 \times 10^7\ \text{erg}}$$



	R_1	R_2	R3
VINBLASTINE	$COOCH_3$	$OCOCH_3$	CH_3
VINCRISTINE	$COOCH_3$	$OCOCH_3$	CHO
VINDESINE	$CONH_2$	OH	CH_3

Fig. 12–13. Chemical structures of the closely related antineoplastic agents vinblastine and vincristine, isolated from *Vinca rosea;* and vindesine, a synthetic derivative of vinblastine. (From D. Vendrig, J. H. Beijnen, O. van der Houwen and J. Holthuis, Int. J. Pharm. 50, 190, 1989, reproduced with permission of the copyright owner.)

or

$$62 \text{ mole}^{-1} \times 1000 \times 10^7 \times (1 \text{ cal}/4.184 \times 10^7) = 14818 \text{ cal/mole}$$

or

$$E_a = 1.4818 \times 10^4 \text{ cal/mole} \simeq 15 \text{ kcal/mole}$$

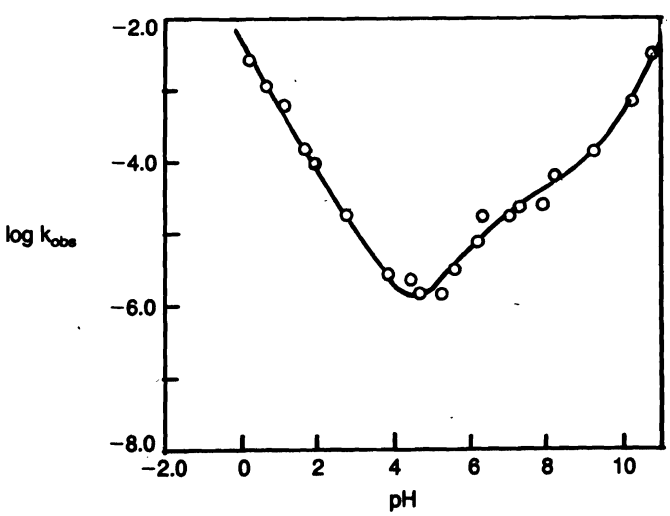


Fig. 12–14. Log *k*–pH profile for the decomposition of vincristine. (From D. Vendrig, J. H. Beijnen, O. van der Houwen and J. Holthuis, Int. J. Pharm. 50, 194, 1989, reproduced with permission of the copyright owner.)

In the *CRC Handbook of Chemistry and Physics*, we find the conversion factor, 1 J = 0.239045 cal; therefore, we can make the direct conversion:

$$62000 \text{ J/mole} \times 0.239045 \text{ cal/J} = 14821 \text{ cal/mole}$$

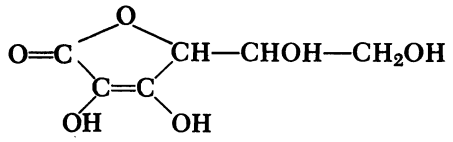
or

$$E_a = 1.4821 \times 10^4 \text{ cal/mole.}$$

The kinetic study of the autoxidation of ascorbic acid is an interesting research story that began about 50 years ago. Some of the reports are reviewed here as an illustration of the difficulties encountered in the study of free radical reactions. Although the decomposition kinetics of ascorbic acid probably has been studied more thoroughly than that of any other drug, we are only now beginning to understand the mechanism of the autoxidation. The overall reaction may be represented as

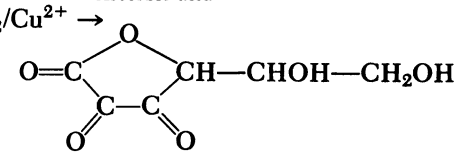
TABLE 12–6. *Activation Energies and Arrhenius Factors for Vincristine at Various pH Values at 80° C*[42]

pH	E_a cal/mole $\times 10^{-4}$	A (sec^{-1})
1.2	1.482	1×10^6
3.5	2.008	9×10^6
5.2	1.745	4×10^5
7.0	2.534	9×10^{10}
8.2	2.773	9×10^{12}



Ascorbic acid

$+ \frac{1}{2}O_2/Cu^{2+} \rightarrow$



Dehydroascorbic acid

One of the first kinetic studies of the autoxidation of ascorbic acid to dehydroascorbic acid was undertaken in 1936 by Barron et al.[43] These investigators measured the oxygen consumed in the reaction, using a Warburg type of vessel and a manometer to obtain the rate of decomposition of ascorbic acid. They found that when great care was taken to free the solution of traces of copper, ascorbic acid was not oxidized by atmospheric oxygen at a measurable rate except in alkaline solutions. Cupric ion was observed to oxidize ascorbic acid rapidly to dehydroascorbic acid, and KCN and CO were found to break the reaction chain by forming stable complexes with copper.

Dekker and Dickinson[44] suggested a scheme for oxidation of ascorbic acid by the cupric ion and obtained the following equations for the decomposition:

$$-\frac{d[H_2A]}{dt} = k\frac{[Cu^{2+}][H_2A]}{[H^+]^2} \qquad (12-144)$$

and in the integrated form,

$$k = \frac{2.303[H^+]^2}{[Cu^{2+}]t}\log\frac{[H_2A]_0}{[H_2A]} \qquad (12-145)$$

in which $[H_2A]_0$ is the initial concentration, and $[H_2A]$ is the concentration of ascorbic acid at time t. The experimental results compared favorably with those calculated from equation (12–145), and it was assumed that the initial reaction involved a slow oxidation of the ascorbate ion by cupric ion to a semiquinone, which was immediately oxidized by oxygen to dehydroascorbic acid. As the reaction proceeded, however, the specific reaction rate k was found to increase gradually.

Dekker and Dickinson observed that the reaction was retarded by increasing the initial concentration of ascorbic acid, presumably because ascorbic acid depleted the free oxygen. When oxygen was continually bubbled through the mixture, the specific rate of decomposition did not decrease with increasing ascorbic acid concentration.

Weissberger et al.[45] showed that the autoxidation of ascorbic acid involved both a singly and a doubly charged anion of L-ascorbic acid. Oxygen was found to react with the divalent ion at atmospheric pressure about 10^5 times as fast as with the monovalent ion of the acid at ordinary temperatures when metal catalysis was repressed. When copper ions were added to the reaction mixture, however, it was found that only the singly charged ion reaction was catalyzed. Copper was observed to be an extremely effective catalyst, since 2×10^{-4} mole/liter increased the rate of the monovalent ion reaction by a factor of 10,000.

Nord[46] showed that the rate of the copper-catalyzed autoxidation of ascorbic acid was a function of the concentrations of the monovalent ascorbate anion, the cuprous ion, the cupric ion, and the hydrogen ion in the solution. The kinetic scheme proposed by Nord appears to compare well with experimental findings.

Blaug and Hajratwala[47] observed that ascorbic acid degraded by aerobic oxidation according to the log rate constant–pH profile of Figure 12–15. The effects of buffer species were eliminated, so that only the catalysis due to hydrogen and hydroxyl ions was considered. Dehydroascorbic acid, the recognized breakdown product of ascorbic acid, was found to decompose further into ketogulonic acid, which then formed threonic and oxalic acids.

According to Rogers and Yacomeni,[48] ascorbic acid exhibits maximum degradation at pH 4 and minimum degradation at pH 5.6 in citric acid–phosphate buffers in the presence of excess oxygen at 25° C. The pH–rate profile can be fit closely to the experimental points using first- and second-order rate constants; $k_1 = 5.7 \times 10^{-6} M^{-1}s^{-1}$, $k_2 = 1.7\ s^{-1}$, and $k_3 = 7.4 \times 10^{-5} M^{-1}s^{-1}$ in the rate expression

$$k = k_1[H^+] + k_2 + k_3[OH^-] \qquad (12-146)$$

in which k_2 is the first-order solvent catalysis term, ordinarily written k_o, and k_1 and k_3 are the catalytic coefficients.

Takamura and Ito[49] studied the effect of metal ions and flavonoids on the oxidation of ascorbic acid, using polarography at pH 5.4. Transition metal ions increased the rate of first-order oxidation; the rate was increased by 50% in the presence of Cu^{2+}. Flavonoids are yellow

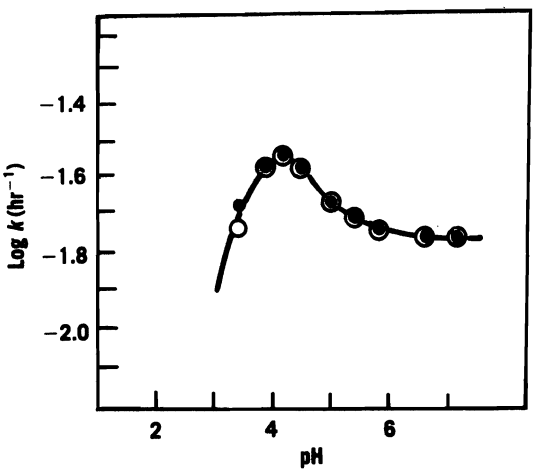


Fig. 12–15. The pH profile for the oxidative degradation of ascorbic acid. (From S. M. Blaug and B. Hajratwala, J. Pharm. Sci. **61**, 556, 1972; **63**, 1240, 1974, reproduced with permission of the copyright owner.) Key: ●, calculated rate constant; ○, rate constant extrapolated to zero buffer concentration where only the effect of hydrogen and/or hydroxyl ions is accounted for.

pigments found in higher plants. The flavonoid constituents, rutin and hesperidan, were used in the past to reduce capillary fragility and bleeding.[50] Takamura and Ito found that flavonoids inhibited the Cu^{2+}-catalyzed oxidation in the order of effectiveness: 3-hydroxyflavone < rutin < quercitin. This order of inhibition corresponded to the order of complexation of Cu^{2+} by the flavonoids, suggesting that the flavonoids inhibit Cu^{2+}-catalyzed oxidation by tying up the copper ion in solution.

Oxidation rates under conditions similar to those in pharmaceutical systems were examined by Fyhr and Brodin.[51] They investigated the iron-catalyzed oxidation of ascorbic acid at 35° C, at pH values of 4 to 6, at partial pressures of oxygen of 21 kPa (21 kilopascal), and at iron concentrations between 0.16 and 1.25 ppm. These workers found the oxidation of ascorbic acid to be first-order with respect to the total ascorbic acid concentration. Trace-element analysis was used to follow changes in iron concentration.

Akers[52] studied the *standard oxidation potentials* (pp. 207–209) of antioxidants in relation to stabilization of epinephrine in aqueous solution. He found that ascorbic acid or a combination of 0.5% thiourea with 0.5% acetylcysteine was the most effective in stabilizing parenteral solutions of epinephrine.

Thoma and Struve[53] attempted to protect epinephrine solutions from oxidative degradation by the addition of redox stabilizers (antioxidants) such as ascorbic acid. Sodium metabisulfite, $Na_2S_2O_5$, prevented discoloration of epinephrine solutions but improved the stability only slightly. The best stabilization of epinephrine in solution was provided by the use of nitrogen.

The decomposition of a new antiasthmatic agent (abbreviated here as HPAMB), which acts therapeutically by contraction of vascular and pulmonary smooth muscles, was investigated in the presence and absence of the antioxidant ascorbic acid, in phosphate buffer (pH 7.9), and in aqueous solution (pH 7.1).[54] As observed in Figure 12–16, the drug broke down rapidly at 25° C in water in the absence of ascorbic acid, whereas no loss in drug concentration occurred in the presence of 0.1% ascorbic acid. In two nonaqueous solvents, ethanol and dimethyl sulfoxide, the oxidative decomposition rate of HPAMB was much slower than in aqueous solution.

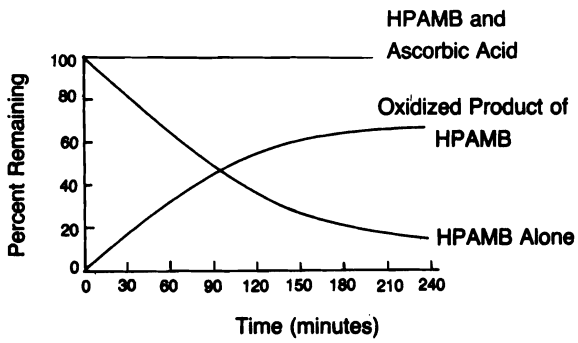


Fig. 12–16. Decomposition of HPAMB alone and in the presence of ascorbic acid. The curve for the oxidized product resulting from HPAMB breakdown is also shown. (From A. B. C. Yu and G. A. Portman, J. Pharm. Sci. 79, 915, 1990, reproduced with permission of the copyright owner.)

Influence of Light. Photodegradation. Light is not classified as a catalyst, and its effect on chemical reactions is treated as a separate topic. Light energy, like heat, may provide the activation necessary for a reaction to occur. Radiation of the proper frequency and of sufficient energy must be absorbed to activate the molecules. The energy unit of radiation is known as the *photon* and is equivalent to 1 *quantum* of energy. Photochemical reactions do not depend on temperature for activation of the molecules; therefore, the rate of activation in such reactions is independent of temperature. After a molecule has absorbed a quantum of radiant energy, however, it may collide with other molecules, raising their kinetic energy, and the temperature of the system will therefore increase. The initial photochemical reaction may often be followed by thermal reactions.

The study of photochemical reactions requires strict attention to control of the wavelength and intensity of light and the number of photons actually absorbed by the material. Reactions that occur by photochemical activation are usually complex and proceed by a series of steps. The rates and mechanisms of the stages can be elucidated through a detailed investigation of all factors involved, but in this elementary discussion of the effect of light on pharmaceuticals, we will not go into such considerations.

Examples of photochemical reactions of interest in pharmacy and biology are the irradiation of ergosterol and the process of photosynthesis. When ergosterol is irradiated with light in the ultraviolet region, vitamin D is produced. In photosynthesis, carbon dioxide and water are combined in the presence of a photosensitizer, chlorophyll. Chlorophyll absorbs visible light, and the light then brings about the photochemical reaction in which carbohydrates and oxygen are formed.

Some studies involving the influence of light on medicinal agents are reviewed here.

Moore[55] described the kinetics of photooxidation of benzaldehyde as determined by measuring the oxygen consumption with a polarographic oxygen electrode. Photooxidation of drugs is initiated by ultraviolet radiation according to one of two classes of reactions. The first is a free radical chain process in which a sensitizer, for example, benzophenone, abstracts a hydrogen atom from the drug. The free radical drug adds a molecule of oxygen and the chain is propagated by removing a hydrogen atom from another molecule of oxidant, a hydroperoxide, which may react further by a nonradical mechanism. The scheme for initiation, propagation, and termination of the chain reaction is shown in Figure 12–17.

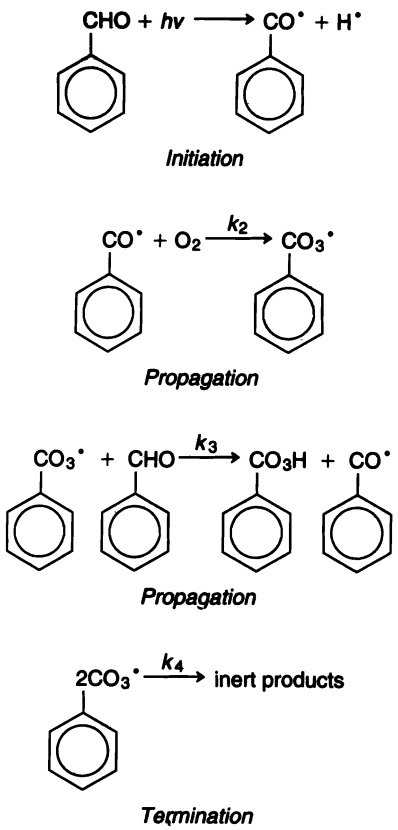


Fig. 12–17. Steps in the photooxidation of benzaldehyde. (From D. E. Moore, J. Pharm. Sci. 65, 1449, 1976. Reproduced with permission of the copyright owner.)

The second class of photooxidation is initiated by a dye such as methylene blue.

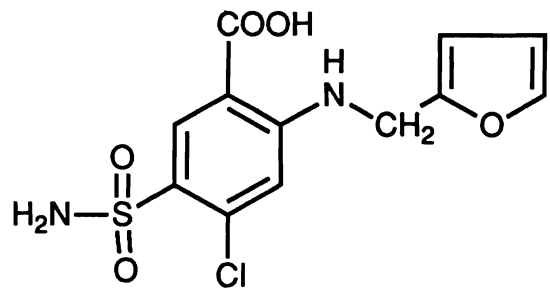
A manometer is usually used to measure the rate of absorption of oxygen from the gas phase into a stirred solution of the oxidizing drug. In some cases, as in the oxidation of ascorbic acid, spectrophotometry may be used if the absorption spectra of the reactant and product are sufficiently different. An oxygen electrode or galvanic cell oxygen analyzer has also been used to measure the oxygen consumption.

Earlier studies of the photooxidation of benzaldehyde in *n*-decane solution showed that the reaction involved a free radical mechanism. Moore proposed to show whether a free radical process also occurred in a dilute aqueous solution and to study the antioxidant efficiency of some polyhydric phenols. The photooxidation of benzaldehyde was found to follow a free radical mechanism, and efficiency of the polyhydric phenolic antioxidants ranked as follows: catechol > pyrogallol > hydroquinone > resorcinol > *n*-propyl gallate. These antioxidants could be classified as retarders rather than inhibitors for they slowed the rate of oxidation but did not inhibit the reaction.

Asker et al.[56] investigated the photostabilizing effect of DL-methionine on ascorbic acid solution. A 10-mg% concentration of DL-methionine was found to enhance the stability of a 40-mg% solution of ascorbic acid buffered by phosphate but not by citrate at pH 4.5.

Uric acid was found[57] to produce a photoprotective effect in buffered and unbuffered solutions of sulfathiazole sodium. The addition of 0.1% sodium sulfite assisted in preventing the discoloration of the sulfathiazole solution prepared in either a borate or a phosphate buffer.

Furosemide (Lasix) is a potent diuretic, available as tablets and as a sterile solution for injection. It is fairly stable in alkaline solution but degrades rapidly in acid solution.



Furosemide

Irradiation of furosemide with 365 nm of ultraviolet light in alkaline solutions and in methanol results in photooxidation and reduction, respectively, to yield a number of products. The drug is relatively stable in ordinary daylight or under fluorescent (room) lighting, but has a half-life of only about 4 hours in direct sunlight. Bundgaard et al.[58] discovered that it is the un-ionized acid form of furosemide that is most sensitive to photodegradation. In addition to investigating the photoliability of furosemide, these workers also studied the degradation of the ethyl, dimethylglycolamide, and diethylglycolamide esters of furosemide and found them to be very unstable in solutions of pH 2 to 9.5 in both daylight and artificial room lighting. The half-lives of photodegradation for the esters were 0.5 to 1.5 hours.

Andersin and Tammilehto[59] noted that apparent first-order photokinetics had been shown by other workers for adriamycin, furosemide, menadione, nifedipine, sulfacetamide, and theophylline. Photodegradation of the tromethamine* salt of ketorolac, an analgesic and antiinflammatory agent, appeared in ethanol to be an exception;[59] it showed apparent first-order kinetics at low concentrations, ≤2.0 μg/mL, of the drug (Fig. 12–18*a*). When the concentration of ketorolac tromethamine became ≥10 μg/mL, however, the kinetics exhibited non–first-order rates. That is to say, the plots of drug concentration versus irradiation time were no longer linear but rather were bowed at these higher concentrations (Fig. 12–18*b*).[60]

Nifedipine is a calcium antagonist used in coronary artery disease and in hypertension; unfortunately, it is sensitive to light both in solution and in the solid state.

*Tromethamine is "tris buffer," or TRIS, aminohydroxymethylpropanediol.

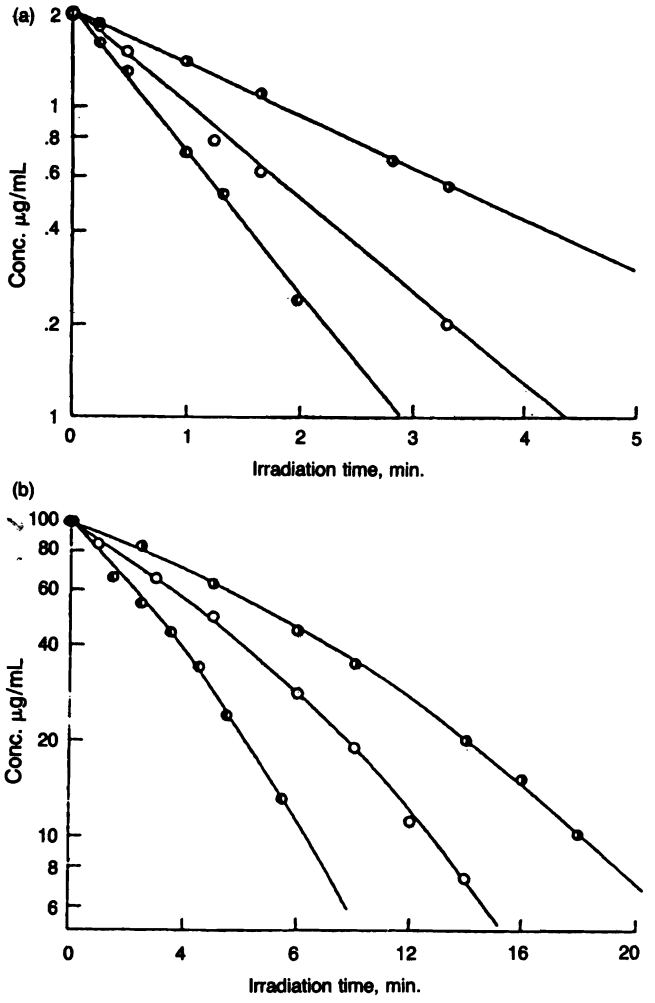


Fig. 12–18. A semilogarithmic plot of the photolysis of ketorolac tromethamine in ethyl alcohol. Key: ◐ under argon; ○ under air; ◑ under oxygen. *(a)* At low drug concentrations; *(b)* at high drug concentrations. (From L. Gu, H. Chiang and D. Johnson, Int. J. Pharm. 41, 109, 1988. Reproduced with permission of the copyright owner.)

Matsuda et al.[61] studied the photodegradation of nifedipine in the solid state when exposed to the radiation of mercury vapor and fluorescent light sources. The drug decomposed into four compounds, the main photoproduct being a nitrosopyridine. It readily degraded in ultraviolet and visible light with maximum decomposition occurring at a wavelength of about 380 nm (3.80×10^{-7} meter). The rate of degradation of nifedipine was much faster when exposed to a mercury vapor lamp than when subjected to the rays of a fluorescent lamp; however, the degradation in the presence of both light sources exhibited first-order kinetics. The drug is more sensitive to light when in solution. The photodecomposition of nifedipine in the crystalline solid state was found to be directly related to the *total irradiation intensity*. The total intensity was used as a convenient parameter to measure accelerated photodecomposition of nifedipine in the solid state and thus to estimate its photostability under ordinary conditions of light irradiation.

The photosensitivity of the dye FD&C Blue No. 2 causes its solution to fade and gradually to become colorless. Asker and Collier[62] studied the influence of an ultraviolet absorber, uric acid, on the photostability of FD&C Blue No. 2 in glycerin and triethanolamine. They found that the greater the concentration of uric acid in triethanolamine the more photoprotection was afforded the dye. Glycerin was not a suitable solvent for the photoprotector since glycerin accelerates the rate of color fading, possibly owing to its dielectric constant effect.

As would be expected for a reaction that is a function of light radiation and color change rather than concentration, these reactions follow zero-order kinetics. Photodegradation reactions of chlorpromazine, menadione, reserpine, and colchicine are also kinetically zero-order.

Asker and Colbert[63] assessed the influence of various additives on the photostabilizing effect that uric acid has on solutions of FD&C Blue No. 2. The agents tested for their synergistic effects belong to the classes: antioxidants, chelating agents, surfactants, sugars, and preservatives. It was found that the antioxidants DL-methionine and DL-leucine accelerated the photodegradation of the FD&C Blue No. 2 solutions. The addition of the surfactant Tween 80 (polysorbate 80) increased the photodegradation of the dye, as earlier reported by Kowarski[64] and other workers. Lactose has been shown by these authors and others to accelerate the color loss of FD&C Blue No. 2, and the addition of uric acid retards the photodegradation caused by the sugar. Likewise, methylparaben accelerates the fading of the blue color and the addition of uric acid counteracts this color loss. Chelating agents, such as disodium edetate (EDTA disodium) significantly increased the rate of color loss of the dye. EDTA disodium has also been reported to increase the rate of degradation of epinephrine, physostigmine, and isoproterenol, and it accelerates the photodegradation of methylene blue and riboflavine. Acids, such as tartaric and citric, tend to increase the fading of dye solutions.

Asker and Jackson[65] found a photoprotective effect by dimethyl sulfoxide on FD&C Red No. 3 solutions exposed to long- and short-wave ultraviolet light. Fluorescent light was more detrimental to photostability of the dye solution than were the ultraviolet light sources.

KINETICS IN THE SOLID STATE

The breakdown of drugs in the solid state is an important topic, but it has not been studied extensively in pharmacy. The subject has been reviewed by Garrett,[66] Lachman,[67] and Carstensen,[68] and is discussed here briefly.

Pure Solids. The decomposition of pure solids, as contrasted with the more complex mixture of ingredi-

ents in a dosage form, has been studied, and a number of theories have been proposed to explain the shapes of the curves obtained when decomposition of the compound is plotted against time. Carstensen and Musa[69] described the decomposition of solid benzoic acid derivatives, such as aminobenzoic acid, which broke down into the liquid, aniline, and the gas, carbon dioxide. The plot of concentration of decomposed drug vs. time yielded a sigmoidal curve (Fig. 12–19). After liquid begins to form, the decomposition becomes a first-order reaction in the solution. Such single-component pharmaceutical systems can degrade by either zero-order or first-order reaction, as observed in Figure 12–19. It is often diffficult to determine which pattern is being followed when the reaction cannot be carried through a sufficient number of half-lives to differentiate between zero- and first-order.

Solid Dosage Forms. The decomposition of drugs in solid dosage forms is understandably more complex than decay occurring in the pure state of the individual compound. The reactions may be zero- or first-order, but in some cases, as with pure compounds, it is difficult to distinguish between the two. Tardif[70] observed that ascorbic acid decomposed in tablets followed a pseudo-first-order reaction.

In tablets and other solid dosage forms, the possibility exists for solid–solid interaction. Carstensen et al.[71] have devised a program to test for possible incompatibilities of the drug with excipients present in the solid mixture. The drug is blended with various excipients in the presence and absence of 5% moisture, sealed in vials, and stored for 2 weeks at 55° C. Visual observation is done and the samples are tested for chemical interaction using thin-layer chromatography. The method is qualitative but, in industrial preformulation, provides a useful screening technique to uncover possible incompatibilities between active ingredient and pharmaceutical additives before deciding upon a suitable dosage form.

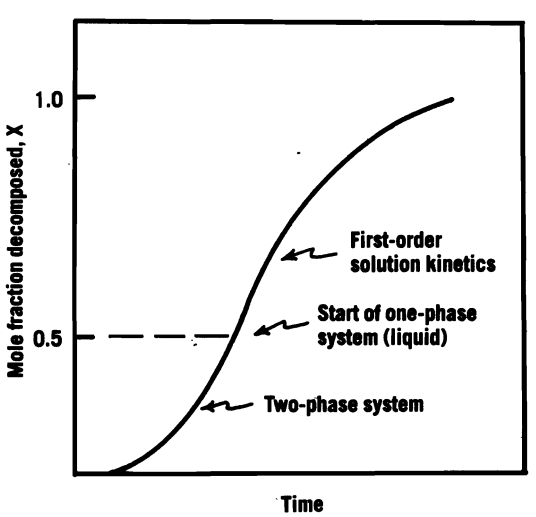


Fig. 12–19. Decomposition of a pure crystalline solid such as potassium permanganate, which involves gaseous reaction products. (From J. T. Carstensen, J. Pharm. Sci. 63, 4, 1974, reproduced with permission of the copyright owner.)

Lach and associates[72] used diffuse reflectance spectroscopy to measure interactions of additives and drugs in solid dosage forms. Blaug and Huang[73] used this spectroscopic technique to study the interaction of spray-dried lactose with dextroamphetamine sulfate.

Goodhart and associates[74] studied the fading of colored tablets by light (photolysis reaction) and plotted the results as color difference at various light energy values expressed in foot-candle hours.

Lachman, Cooper, and their associates[75] conducted a series of studies on the decomposition of FD&C colors in tablets and established a pattern of three separate stages of breakdown. The photolysis was found to be a surface phenomenon, causing fading of the tablet color to a depth of about 0.03 cm. Interestingly, fading did not occur further into the coating with continued light exposure, and the protected contents of the color-coated tablets were not adversely affected by exposure to light.

As noted by Monkhouse and Van Campen[76] solid-state reactions exhibit characteristics quite different than reactions in the liquid or gaseous state since the molecules of the solid are in the crystalline state. The quantitative and theoretical approaches to the study of solid-state kinetics is at its frontier, which, when opened, will probably reveal a new and fruitful area of chemistry and drug science. The authors[76] classify solid-state reactions as *addition* when two solids, *A* and *B*, interact to form the new solid *AB*. For example, picric acid reacts with naphthols to form what is referred to as *picrates*. A second kind of solid-state reaction is an *exchange* process in which solid *A* reacts with solid *BC* to form solid *AB* and release solid *C*. Solid–gas reactions constitute another class in which the oxidation of solid ascorbic acid and solid fumagillin are notable examples. Other types of solid-state processes include polymorphic transitions, sublimation, dehydration, and thermal decomposition.

Monkhouse and Van Campen[76] review the experimental methods used in solid-state kinetics, including reflectance spectroscopy, x-ray diffraction, thermal analysis, microscopy, dilatometry, and gas pressure–volume analysis. The review closes with sections on handling solid-state reaction data, temperature effects, application of the Arrhenius plot, equilibria expressions involved in solid-state degradation, and use of the van't Hoff equation for, say, a solid drug hydrate in equilibrium with its dehydrated form.

ACCELERATED STABILITY ANALYSIS

In the past it was the practice in many pharmaceutical manufacturing companies to evaluate the stability of pharmaceutical preparations by observing them for a year or more, corresponding to the normal time that

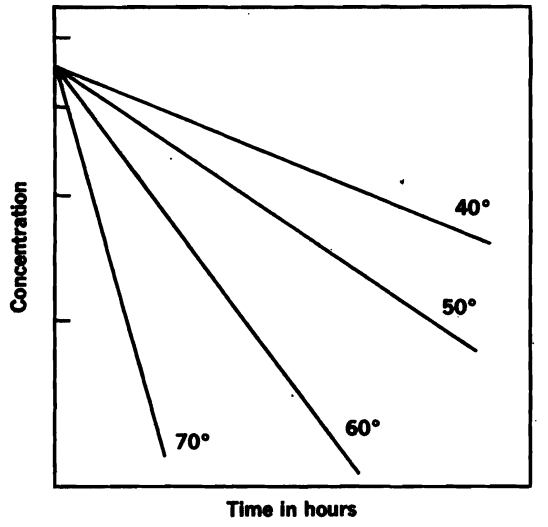


Fig. 12–20. Accelerated breakdown of a drug in aqueous solution at elevated temperature.

they would remain in stock and in use. Such a method was time-consuming and uneconomical. Accelerated studies at higher temperatures were also used by most companies, but the criteria were often arbitrary and were not based on fundamental kinetic principles. For example, some companies used the rule that the storage of liquids at 37° C accelerated the decomposition at twice the normal-temperature rate, while other manufacturers assumed that it accelerated the breakdown by 20 times normal. Levy[77] has pointed out that such arbitrary temperature coefficients of stability cannot be assigned to all liquid preparations and other classes of pharmaceuticals. The prediction of shelf-life must come instead from carefully designed analysis of the various ingredients in each product if the results are to be meaningful.

The method of accelerated testing of pharmaceutical products based on the principles of chemical kinetics was demonstrated by Garrett and Carper.[2] According to this technique, the k values for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some function of concentration against time, as seen in Figure 12–20 and already discussed in the early sections of this chapter. The logarithms of the specific rates of decomposition are then plotted against the reciprocals of the absolute temperatures as shown in Figure 12–21, and the resulting line is extrapolated to room temperature. The $k_{25°}$ is used to obtain a measure of the stability of the drug under ordinary shelf conditions.

Example 12–11. The initial concentration of a drug decomposing according to first-order kinetics is 94 units/mL. The specific decomposition rate k obtained from an Arrhenius plot is 2.09×10^{-5} hr^{-1} at room temperature, 25° C. Previous experimentation has shown that when the concentration of the drug falls below 45 units/mL it is not sufficiently potent for use and should be removed from the market. What expiration date should be assigned to this product?

$$t = \frac{2.303}{k} \log \frac{c_0}{c}$$

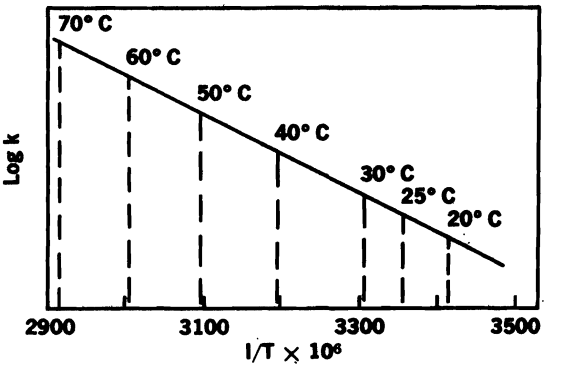


Fig. 12–21. Arrhenius plot for predicting drug stability at room temperatures.

$$t = \frac{2.303}{2.09 \times 10^{-5}} \log \frac{94}{45} = 3.5 \times 10^4 \text{ hr} \cong 4 \text{ years}$$

Free and Blythe and, more recently, Amirjahed[78] and his associates have suggested a similar method in which the fractional life-period (cf. *Example 12–2*) is plotted against reciprocal temperatures, and the time in days required for the drug to decompose to some fraction of its original potency at room temperature is obtained. The approach is illustrated in Figures 12–22 and 12–23. As observed in Figure 12–22, the log percent of drug remaining is plotted against time in days, and the time for the potency to fall to 90% of the original value, (i.e., t_{90}), is read from the graph. In Figure 12–23, the log time to 90% is then plotted against $1/T$, and the time at 25° C gives the shelf-life of the product in days. The decomposition data illustrated in Figure 12–22 result in a t_{90} value of 199 days. Shelf-life and expiration dates are estimated in this way; Baker and Niazi[79] have pointed out limitations of the method.

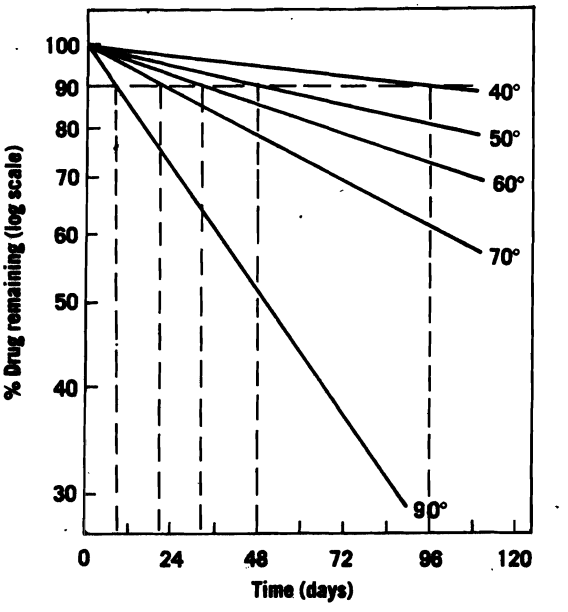


Fig. 12–22. Time in days required for drug potency to fall to 90% of original value. These times, designated t_{90}, are then plotted on a log scale in Figure 12–23.

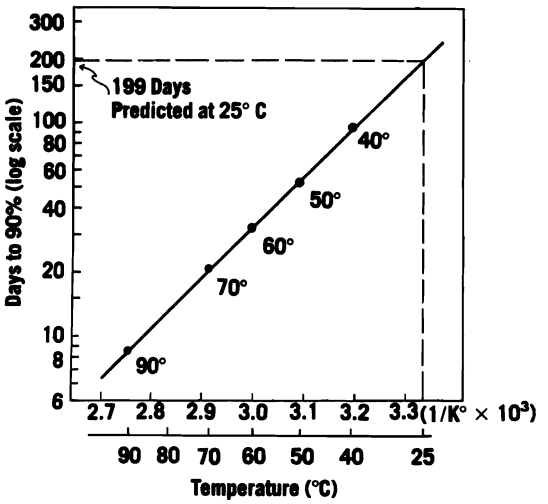


Fig. 12–23. A log plot of t_{90} (i.e., time to 90% potency) on the vertical axis against reciprocal temperature (both Kelvin and centigrade scales are shown) on the horizontal axis.

By either of these methods, the *overage*, that is, the excess quantity of drug that must be added to the preparation to maintain at least 100% of the labeled amount during the expected shelf-life of the drug, can be easily calculated and added to the preparation at the time of manufacture.

An improved approach to stability evaluation is that of nonisothermal kinetics, introduced by Rogers[80] in 1963. The activation energy, reaction rates, and stability predictions are obtained in a single experiment by programming the temperature to change at a predetermined rate. Temperature and time are related through an appropriate function, such as

$$1/T = 1/T_0 + at \qquad (12\text{–}147)$$

where T_0 is the initial temperature and a is a reciprocal heating rate constant. At any time during the run, the Arrhenius equation for time zero and time t may be written

$$\ln k_t = \ln k_0 - \frac{E_a}{R}\left(\frac{1}{T_t} - \frac{1}{T_0}\right) \qquad (12\text{–}148)$$

and substituting (12–147) into (12–148) yields

$$\ln k_t = \ln k_0 - \frac{E_a}{R}(at) \qquad (12\text{–}149)$$

Since temperature is a function of the time, t, a measure of stability, k_t, is directly obtained over a range of temperatures. A number of variations have been made on the method,[81–84] and it is now possible to change the heating rate during a run or combine programmed heating rate with isothermal studies and receive printouts of activation energy, order of reaction, and stability estimates for projected times and at various temperatures.

Although kinetic methods need not involve detailed studies of mechanism of degradation in the prediction of stability, they do demand the application of sound scientific principles if they are to be an improvement over extended room-temperature studies. Furthermore, before an older method, although somewhat less than wholly satisfactory, is discarded, the new technique should be put through a preliminary trial period and studied critically. Some general precautions regarding the use of accelerated testing methods are appropriate at this point.

In the first place, it should be re-emphasized that the results obtained from a study of the degradation of a particular component in a vehicle cannot be applied arbitrarily to other liquid preparations in general. As Garrett[85] has pointed out, however, once the energy of activation is known for a component, it probably is valid to continue to use this value although small changes of concentration (e.g., addition of overage) or slight formula changes are made. The known activation energy and a single-rate study at an elevated temperature may then be used to predict the stability of that component at ordinary temperatures.

Testing methods based on the Arrhenius law are valid only when the breakdown is a thermal phenomenon with an activation energy of about 10 to 30 kcal/mole. If the reaction rate is determined by diffusion or photochemical reactions, or if the decomposition is due to freezing, contamination by microorganisms, excessive agitation during transport, and so on, an elevated temperature study is obviously of little use in predicting the life of the product. Nor can elevated temperatures be used for products containing suspending agents such as methylcellulose that coagulate on heating, proteins that may be denatured, and ointments and suppositories that melt under exaggerated temperature conditions. Emulsion breaking involves aggregation and coalescence of globules, and some emulsions are actually more stable at elevated temperatures at which Brownian movement is increased. Lachman et al.[86] reviewed the stability testing of emulsions and suspensions and the effects of packaging on the stability of dosage forms.

Statistical methods should be used to estimate the errors in rate constants, particularly when assays are based on biologic methods; this is accomplished by the method of least squares as discussed by Garrett[85] and by Westlake.[87]

The investigator should be aware that the order of a reaction may change during the period of the study. Thus, a zero-order degradation may subsequently become first-order, second-order, or fractional-order, and the activation energy may also change if the decomposition proceeds by several mechanisms. At certain temperatures, autocatalysis (i.e., acceleration of decomposition by products formed in the reaction), may occur so as to make room temperature stability predictions from an elevated temperature study impractical.

In conclusion, the investigator in the product development laboratory must recognize the limitations of accelerated studies, both the classic and the more

recent kinetic type, and must distinguish between those cases in which reliable prognosis can be made and those in which, at best, only a rough indication of product stability can be obtained. Where accelerated methods are not applicable, extended aging tests must be employed under various conditions to obtain the desired information.

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*Problems**

12–1. The time and amount of decomposition of 0.056 M glucose at 140° C in an aqueous solution containing 0.35 N HCl was found to be

Data for *Problem 12–1*

Time (hr.)	Glucose, remaining (mole/liter × 10^2)
0.5	5.52
2	5.31
3	5.18
4	5.02
6	4.78
8	4.52
10	4.31
12	4.11

What is the order, the half-life, and the specific reaction rate of this decomposition? Can one unquestionably determine the order from the data given?

Answer: If first order, $k = 0.026\ hr^{-1}$, $t_{1/2} = 26.8$ hr

12–2. According to Connors et al.,[88] the first-order rate constant, k_1, for the decomposition of ampicillin at pH 5.8 and 35° C is $k_1 = 2 \times 10^{-7}\ sec^{-1}$. The solubility of ampicillin is 1.1 g/100 mL. If it is desired to prepare a suspension of the drug containing 2.5 g/100 mL, calculate (a) the zero-order rate constant, k_o, and (b) the shelf-life, i.e., the time in days required for the drug to decompose to 90% of its original concentration (at 35° C) in solution. (c) If the drug is formulated in solution rather than a suspension at this pH and temperature, what is its shelf-life? *Note:* 100 mL = 1 deciliter = 1 dL.

Answers: (a) $k_o = (2.2 \times 10^{-7}\ g\ dL^{-1}\ sec^{-1}$; (b) $t_{90} = 13.2$ days at 35° C (zero-order breakdown); (c) $t_{90} = 6.1$ days at 35° C (first-order breakdown).

12–3. (a) Menadione (vitamin K_3) is degraded by exposure to light, which is called *photodegradation* or *photolysis*. The rate constant of decomposition is $k = 4.863 \times 10^{-3}\ min^{-1}$. Compute the half-life.

(b) The formation of a complex of menadione with the quaternary ammonium compound cetylethylmorpholinium ethosulfate (I) in aqueous solution slows the rate of photodegradation by ultraviolet light. The rate of decomposition of 5.19×10^{-5} M of menadione containing a 5% (w/v) of the complexing agent (I) is as follows (the data are based on the paper by Kowarski and Ghandi[89]):

Time (min)	10	20	30	40
Menadione remaining (mole/liter × 10^5)	5.15	5.11	5.07	5.03

Compute the k value, $t_{1/2}$, and the percent decrease of k and increase of $t_{1/2}$ in the presence of the complexing agent.

**Problem 12–14* was provided by Professor Z. Zheng, Shanghai Medical University, Shanghai, China. *Problems 12–33, 12–34,* and *12–35* were prepared by Professor V. D. Gupta, University of Houston. *Problem 12–36* was suggested by J. K. Guillory, University of Iowa.

(c) What is the concentration after 5 hours with and without complexing agent? Use ln rather than log throughout the problem.

Answer: (a) $t_{1/2}$ = 142.5 min or 2 hr 22 min; (b) $k = 7.87\ 10^{-4}$ min^{-1}, $t_{1/2}$ = 880.56 min or 14 hr 41 min; k decreases by 84% and $t_{1/2}$ increases by 518%; (c) without (I) 1.2×10^{-5} M; with addition of (I), 4.10×10^{-5} M

12–4. Garrett and Carper[2] determined the zero-order rate constant for the degradation of the colorants in a multisulfa preparation. The results obtained at various temperatures are:

°C	40	50	60	70
k	0.00011	0.00028	0.00082	0.00196

(a) Plot these results according to the Arrhenius relationship and compute the activation energy E_a.

(b) Extrapolate the results to 25° C to obtain k at room temperature. You can also use regression analysis to answer (a) and (b).

(c) The rate of decrease of absorbance of the colored preparation at a wavelength of 500 nm was found to be zero-order and the initial absorbance A_o was 0.470. This preparation should be rejected when the spectrophotometric absorbance A falls to a value of 0.225. Therefore, to predict the absorbance of the preparation at any time t hr after preparation, the zero-order equation $A = A_o - k't$ is used. Calculate the predicted life of the preparation at 25° C.

Answers: (a) E_a = 20.8 kcal/mole; (b) k at 25° C = 1.99×10^{-5} absorbance units per hour (using regression analysis); (c) predicted life = 513 days (ca. 1.4 years)

12–5. In the saponification of methyl acetate at 25° C, the molar concentration of sodium hydroxide remaining after 75 min was 0.00552 M. The initial concentration of ester and of base was each 0.01 M. Calculate the second-order rate constant and the half-life of the reaction.

Answer: k = 1.082 (liter/mole) min^{-1}; $t_{1/2}$ = 92.4 min

12–6. Assume that under acidic conditions a compound undergoes reaction according to the following mechanism:

$$(1)\quad A + H^+ \underset{2}{\overset{1}{\rightleftarrows}} AH^+$$

$$(2)\quad AH^+ \overset{3}{\rightarrow} B$$

$$(3)\quad B \overset{4}{\rightarrow} \text{Products}$$

(a) What is the expression giving the steady-state concentration of B?

(b) What is the expression giving the steady-state concentration of AH^+ if the total concentration of acid added to the reaction mixture $[H^+_T]$ is related to the acid present during the reaction, both free $[H^+]$ and bound $[AH^+]$, by the equation

$$[H^+_T] = [H^+] + [AH^+]$$

(c) Give the rate law expressing the rate of formation of products if, instead of measuring the total concentration of acid added to the reaction mixture, a pH meter is used to measure the concentration of "free" acid $[H^+]$. Use the results of parts (a) and (b). See under Rate Determining Step, page 294 for help in solving this problem.

Answers: (a)

$$B_{ss} = \frac{k_3}{k_4}[AH^+];$$

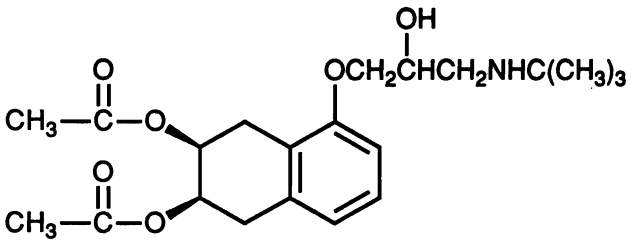
(b)

$$[AH^+]_{ss} = \frac{k_1[A][H^+_T]}{k_1[A] + (k_2 + k_3)}.$$

(c)

$$\text{rate} = \frac{d[P]}{dt} = \left(\frac{k_1k_3}{k_2 + k_3}\right)[A][H^+]$$

12–7. Diacetyl nadolol, used in ophthalmic preparations for glaucoma therapy, hydrolyzes in a series or consecutive reactions represented as $A \overset{k_1}{\rightarrow} B \overset{k_2}{\rightarrow} C$ where B and C are the intermediate and final



Diacetyl Nadolol

products, acetyl nadolol and nadolol, respectively. The apparent rate constants, k_1 and k_2, are first-order constants. The rate of decomposition $A \rightarrow B$ is given at pH 7.55 and 55° C by Chiang et al.[90]

Data for *Problem 12–7*

A (mM)	0.23	0.19	0.16	0.13	0.09	0.06
t (hr)	5	10	15	20	30	40

where mM in the table above stands for millimolar.

(a) Compute k_1 using least squares.

(b) The rate constant in the second step, k_2, was found by nonlinear regression analysis to be 0.0243 hr^{-1}. On the same graph plot the concentration of A remaining and the concentrations of B and C appearing as A hydrolyzes, versus the time in hours as given in the table. Prepare a table of concentrations of A, B, and C at various times, t, using the appropriate equations in the section on the complex reactions in this chapter, pages 290 to 293.

(c) Compute $t_{1/2}$ for A. What are the concentrations of B and C at this time?

Partial Answers: (a) k_1 = 0.0383 hr^{-1}; (b) at t = 5 hr, B = 0.046 mM and C = 0.004 mM; at t = 10 hr, B = 0.079 mM and C = 0.011 mM; (c) $t_{1/2}$ for A = 18.1 hr; the concentrations of B and C at 18.1 hr are 0.110 mM and 0.03 mM, respectively.

12–8. The initial stage of decomposition for a new drug according to a consecutive reaction was found to be first order. The initial concentration C_0 of the solution was 0.050 mole/liter and after 10 hours at 40° C, the drug concentration C was 0.015 mole/liter. Compute the specific rate at 40° C. What is the drug concentration after 2 hours? If the k value for this reaction at 20° C is 0.0020 hr^{-1}, what is the activation energy and the Arrhenius factor A for the reaction?

Answer: k = 0.120 hr^{-1}; concentration after 2 hours = 0.039 mole/liter, E_a = 37.4 kcal/mole, $A = 1.5 \times 10^{25}$ sec^{-1}

12–9. The hydrolysis of atropine base was found by Zvirblis et al.[91] to be first-order with respect to the base. The degradation constant k at 40° C was 0.016 sec^{-1}. If the energy of activation E_a is 7.7 kcal/mole, what is the Arrhenius factor A? What does the value of E_a suggest about the stability of atropine base at 40° C?

Answer: $A = 3.8 \times 10^3$ sec^{-1}

12–10. The following data for the first-order decomposition of penicillin are obtained from Swintosky et al.[92]

Data for *Problem 12–10*

First-order rate constant, k, hr^{-1}	0.0216	0.0403	0.119
Temperature (°C)	37	43	54

Plot the results and compute the activation energy. What is the Arrhenius factor A?

Answer: E_a = 20.3 kcal/mole, $A = 1.2 \times 10^9$ sec^{-1} (using regression analysis)

12–11. The rate constant, k_{OH^-}, for the base catalysis of cibenzoline, a new antiarrhythmic agent, varies with temperature as follows:[93]

Data for *Problem 12–11*

Temp. (°C)	25	35	50	80
k_{OH^-} (M^{-1} hr^{-1})	15.5	78.0	275	2100

Compute the Arrhenius factor, A, and the energy of activation, E_a

Answer: E_a = 18. kcal/mole, $A = 3.54 \times 10^{14}$ sec^{-1}

12–12. The first-order degradation of glucose in acid solution results in the formation of 5-hydroxymethylfurfural (5-HMF), and 5-HMF yields additional breakdown products that give the straw color to glucose solutions stored for long periods of time at high temperatures. These conditions exist, for example, in military warehouses and medical units.

The values of the rate constant for the breakdown of glucose in 0.35 N HCl solution at 110 to 150° C are given in the table.

Data for *Problem 12–12**

°C	°K	1/T (°K^{-1})	k (hr^{-1})	ln k
110	383	0.00261	0.0040	−5.521
130	403	0.00248	0.0267	−3.623
150	423	0.00236	0.1693	−1.776

*From K. R. Heimlich and A. Martin, J. Am. Pharm. Assoc., Sci. Ed. 49, 592, 1960.

Calculate the activation energy and the Arrhenius factor A for glucose in acid solution tested experimentally for accelerated breakdown over the temperature range of 110° to 150° C.

Answer: E_a = 29.8 kcal/mole, $A = 3.71 \times 10^{14}$ hr^{-1}

12–13. Methenamine is used to treat urinary tract infections, its antibacterial activity being derived from formaldehyde, which is produced upon hydrolysis in acidic media. About 0.75 mg/mL is the physiologic concentration of methenamine following a normal dose in humans. Methenamine circulates in the blood (pH 7.4) as the intact drug without degradation but is rapidly converted to formaldehyde when it reaches the acidic urine.

The Arrhenius activation energy, $E_a = \Delta E^{\ddagger}$ at pH 5.1, obtained in vitro at several temperatures, is 12 kcal/mole and the Arrhenius factor A at 37.5° C is 2×10^7 hr^{-1} (Strom and Jun[94]).

(a) Compute the entropy of activation, $\Delta S^{\ddagger}$, and the first-order rate of the reaction, k. Compute the free energy of activation, $\Delta G^{\ddagger}$ from equation (12–91). Assume that $E_a = \Delta H^{\ddagger} = \Delta E^{\ddagger}$.

(b) The drug remains in the bladder for about 6 hours and the effective concentration of formaldehyde is about 20 μg/mL. Compute the concentration of formaldehyde in the bladder after 6 hr assuming that the concentration of methenamine in the urine is that of the drug in plasma (0.75 mg/mL).

(c) When does formaldehyde reach the effective concentration, 20 μg/mL, in urine?

(d) Note that $\Delta H^{\ddagger}$ is a large positive value, $\Delta S^{\ddagger}$ is a relatively large negative value, $\Delta G^{\ddagger}$ is therefore positive, and the Arrhenius factor is small relative to A values normally found. Rationalize these factors in terms of the conversion of methenamine in the body to formaldehyde. See *Example 12–8* and the paragraph following it to assist you in your reasoning.

Answers: **(a)** $\Delta S^{\ddagger} = -41.5$ cal/mole, $k = 0.072$ hr^{-1}; $\Delta G^{\ddagger}$ = 24.9 kcal/mole; **(b)** 0.26 mg/mL; **(c)** 22.5 min

12–14. In a differential scanning calorimetric experiment of thermal degradation of cefamandole naftate, Zheng et al.[95] obtained the following data:

Data for *Problem 12–14*

Heating rate, β (°C/min)	5	2	1	0.5
Degradation peak temp., T_m (°K)	472	466	460	475

Let $x' = 1/T_m$ and $y' = \ln \dfrac{\beta}{T_m^2}$. One then casts the data in the transposed form:

Data for *Problem 12–14*

$x = x' \times 10^3$	2.119	2.146	2.174	2.188
$y = y' + 13$	2.2955	1.4048	0.7375	0.0575

Now one carries out regression analysis of y against x where the slope is $-E_a/R$, and solve for E_a. The degradation peak temperature T_m of a drug molecule depends on the rate of heating β in a differential scanning calorimeter; thus the slope is

$$-\frac{E_a}{R} = \frac{dy}{dx} = \frac{d\ln(\beta/T_m^2)}{d(1/T_m)}.$$

In this way one can obtain E_a values and rapidly scan a series of drug analogs for their stability or breakdown. This method is known as the Kissinger approach.[96]

Answer: E_a = 61.6 kcal/mole

12–15. The specific rate constant for the hydrolysis of procaine at 40° C is 0.011 sec^{-1} and the energy of activation is E_a = 13,800 cal/mole. Using the equation

$$k = \frac{RT}{Nh} e^{\Delta S^{\ddagger}/R} e^{-\Delta H^{\ddagger}/RT}$$

in which $\Delta H^{\ddagger} \approx E_a$, compute the entropy of activation $\Delta S^{\ddagger}$. Using the equation $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, compute the free energy of activation for the hydrolysis of procaine at 40° C. *Note:* The units in the above equation must cancel R in the terms $exp(\Delta S^{\ddagger}/R)$, and R in $exp(-\Delta H^{\ddagger}/RT)$ should be expressed as 1.9872 cal $mole^{-1}$ deg^{-1} and in RT/Nh as 8.314×10^7 erg deg^{-1} $mole^{-1}$.

Answer: $\Delta S^{\ddagger} = -23.5$ e.u.; $\Delta G^{\ddagger}$ = 21.2 kcal/mole

12–16. The first-order rate constant k for the acid-catalyzed hydrolysis of benzocaine is 140×10^{-6} sec^{-1}, and the energy of activation E_a is 18.6 kcal/mole at 97.3° C. Compute the entropy of activation $\Delta S^{\ddagger}$, the Arrhenius factor A, and the probability factor P.

Answer: $\Delta S^{\ddagger} = -26.4$ cal/(mole deg); $A = 1.31 \times 10^7$ sec^{-1}; $P = 1.7 \times 10^{-6}$

12–17.† The observed alkaline hydrolysis rate constants k_{obs} of maleimide[97] in dioxane–water mixtures (v/v %) at 30° C, containing 0.03 M NaOH, are given, on page 320, together with the solubility parameters[98] of the solvent mixtures, δ_1 (dioxane–water).

Plot k_{obs} (vertical axis) against the delta value, δ_1. Then plot the *log of* k_{obs} versus δ_1 on the same graph and find a simple linear relationship between the two variables. Does the addition of dioxane protect maleimide against hydrolysis? Explain. (The solubility parameter is related to polarity, as explained on pages 298–299; the larger is δ_1 the greater is the polarity of the dioxane–water mixture).

†Maleimide reacts with the sulfhydryl group of proteins and may one day become a useful drug. This problem deals with the chemical kinetics of the alkaline hydrolysis of an imide in an aqueous solvent, the dielectric constant of which is altered by the addition of dioxane.

Data for *Problem 12–17*

% (v/v) Dioxane	δ_1 (cal/cm^3)$^{1/2}$	$k_{obs} \times 10^3$ s^{-1}	log k_{obs}
5	22.78	10.68	−1.971
10	22.11	9.219	−2.035
15	21.43	7.612	−2.1185
20	20.76	6.572	−2.182
25	20.09	5.476	−2.262
30	19.42	4.580	−2.339
40	18.07	3.217	−2.493
50	16.73	2.223	−2.653
60	15.39	1.573	−2.803
70	14.04	1.199	−2.921

Would the toxicity of dioxane prevent its use in pharmaceutical products? See *Merck Index*, 11th ed., 1989, p. 521.

Partial Answer: log $k_{obs} = 0.111\ \delta_1 - 4.504$. A log k_{obs} against δ_1 plot results in a straight line.

12–18. The effect of ionic strength (μ) on the observed degradation rates of cefotaxime sodium, a potent third-generation cephalosporin, was studied in aqueous solution at several pH values, with the following results:[102]

Data for *Problem 12–18**

Ionic strength μ	$k_{obs} \times 10^3$ hr^{-1} (25° C)		
	pH 2.23	pH 5.52	pH 8.94
0.2	7.99	3.28	22.6
0.4	7.82	3.30	25.6
0.5	7.82	3.24	25.5
0.7	8.07	3.25	27.1
0.9	7.79	3.17	28.3

*Data from S. M. Berge, N. L. Henderson and M. J. Frank, J. Pharm. Sci. 72, 59, 1983.

(a) Does a primary salt effect exist at any of the pH values under study? If so, compute the rate constant k_o by plotting log k_{obs} versus $\sqrt{\mu}$ and extrapolating to $\mu = 0$.

(b) When you regress log k_{obs} versus $(\sqrt{\mu}/(1 + \sqrt{\mu}))$ instead of $\sqrt{\mu}$ at pH 8.94, the slope agrees better with the theoretical value, Az_Az_B, where $A_{(theor.)} = 0.51$ at 29° C. Why? See Carstensen.[16]

Answers: (a) $k_o = 0.019$ hr^{-1}; (b) check your answer with page 299, equation (12–109) and page 136, *Example 6–14*. The rate constant k_o changes to 0.0156 hr^{-1} when $\sqrt{\mu}/(1 - \sqrt{\mu})$ replaces $\sqrt{\mu}$ on the x-axis and the slope A becomes 0.5295, similar to the theoretical A value.

12–19. The following data were obtained for the decomposition of 0.056 M glucose at 140° C at various concentrations of the catalysts, HCl:

Data for *Problem 12–19*

k_{obs} (hr^{-1})	normality, [H_3O^+]
0.00366	0.0108
0.00580	0.0197
0.00818	0.0295
0.01076	0.0394
0.01217	0.0492

Plot the results and, from the graph, obtain k_o and the catalytic constant k_H. It may be assumed that hydroxyl ion catalysis is negligible in this acidic solution.

Answer: $k_H = 0.229$ M^{-1} hr^{-1} or liter mole^{-1} hr^{-1}; $k_o = 0.00135$ hr^{-1} by linear regression analysis. Extrapolation by eye yields 0.0013 hr^{-1}.

12–20. The moieties, $-CH_2NHCH_3$, $-CH_2N$, and $-CH_2NO$, were attached to a model peptide to form a prodrug known as a Mannich base (compounds 7, 8, and 9, respectively, of Bundgaard and Møss[99]). The pH–rate profile for the hydrolysis of the Mannich bases (Figure 12–24) exhibits sigmoidal shapes. The points of the three curves can be calculated using the equation

$$k = \frac{k_1 K_a}{[H^+] + K_a} + \frac{k_2 [H^+]}{[H^+] + K_a}$$

in which k_1 and k_2 are the first-order rate constants for degradation of the Mannich base, B, and the conjugate acid, BH^+, respectively. K_a is the ionization constant of the protonated Mannich base. The values at 37° C given by the authors for compound 9 are k_1 (min^{-1}) = 2.5×10^{-3}, k_2 (min^{-1}) = 1.0×10^{-2}, and pK_a = 5.1; Ka = 7.94×10^{-6}.

Calculate k, the first-order rate constant for the degradation of the Mannich base, compound 9, at pH 4. Check your answer at pH 4 by reading the log k value from Figure 12–24, and converting it to the rate constant k (min^{-1}) for hydrolysis. The student may care to calculate the k values for compounds 7 and 8. The rate data for the breakdown of compound 7 are: $k_1 = 0.024$ (min^{-1}), $k_2 = 1.8 \times 10^{-4}$ (min^{-1}) and pK_a = 7.2. The values for compound 8 are $k_1 = 0.42$ (min^{-1}), $k_2 = 1.7 \times 10^{-3}$ (min^{-1}) and pK_a = 7.2.

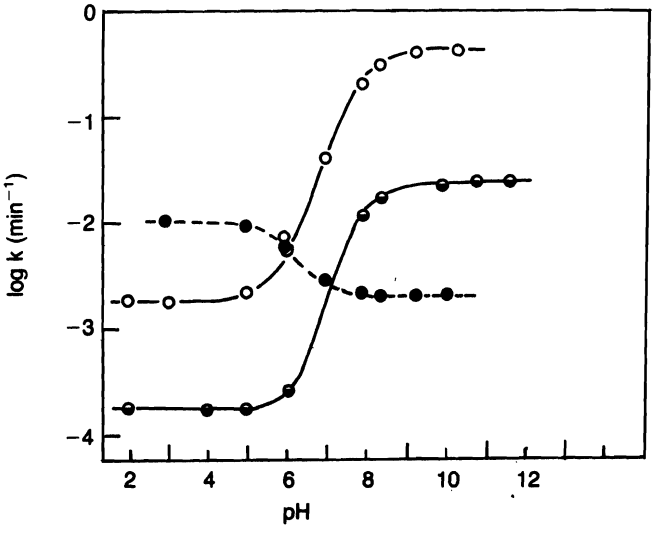


Fig. 12–24. (Figure 3 of H. Bundgaard and J. Møss, J. Pharm. Sci. 78, 122, 1989. pH profile for the Mannich base derivatives 7(◒), 8(○) and 9(●) in aqueous solution at 37° C. (Reproduced with permission of the copyright owner and altered according to the authors.)

Answer: From Figure 12–24, $\log k = -3.75$; $k = 1.78 \times 10^{-4}$ min^{-1}. From the calculation using the above equation, $k = 1.95 \times 10^{-4}$ min^{-1} for compound 7 at pH 4.

12–21. The degradation constant k_{obs} (sec^{-1}) for codeine sulfate may be calculated at 25° C using the expression

$$k_{obs}\,(sec^{-1}) = k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_0 = 2.46 \times 10^{-11}[H^+] + 3.22 \times 10^{-9}[OH^-] + 7.60 \times 10^{-11}$$

The constants k_{H^+} and k_{OH^-} associated with the concentrations of $[H^+]$ and $[OH^-]$ are expressed in M^{-1} sec^{-1}, where M^{-1} stands for reciprocal moles per liter, and k_0 is in sec^{-1}. Calculate the observed rate constant k_{obs} (sec^{-1}) for the decomposition of codeine at 25° C in codeine sulfate solutions, at pH 0.0, 2.0, 8.0, 10. Powell[100] shows that codeine sulfate solutions are subjected to general acid–base catalysis due to a buffer consisting of the phosphate ions, Na_2HPO_4 and NaH_2PO_4. Plot the log k_{obs} versus pH and compare with Figure 1, page 902 in the report by Powell. *Note:* At pH = 0.0, $[H^+]$ = 1 M. Above this concentration (> 1 M), pH values become negative. However, below pH 0 we do not use minus pH values but rather an acidity function known as H_0 (see Albert and Serjeant[101]).

Partial Answer: At pH = 2.0, $[H^+] = 0.01$ M, $[OH^-] = 1.0 \times 10^{-12}$ M, $k_{obs} = 7.62 \times 10^{-11}$ sec^{-1}, $\log k_{obs} = -10.12$. At pH = 8.0, $[H^+] = 10^{-8}$ M, $[OH^-] = 10^{-6}$ M, $k_{obs} = 7.60 \times 10^{-11}$ sec^{-1}, $\log k_{obs} = -10.12$

12–22. The hydrolysis of the prostaglandin, fenprostalene, in aqueous solution was studied at 80° C varying the buffer system. The total buffer concentration as well as the ionic strength was kept constant. Metal ions (Cu^{2+} or Fe^{3+}) were added to some solutions. The dependence of k_{obs} on the pH is given below (See **Data for *Problem 12–22***).

(a) Do the buffer systems, Cu^{2+} or Fe^{3+}, influence hydrolysis?

(b) Plot log k_{obs} versus pH and compute the catalytic constants k_1 and k_2 corresponding to the left and the right branches of the "V"-shaped plot. *Hint:* You will need two equations; one for the left branch of the line, another for the right branch. Using regression analysis, compute the intercept of each branch. Combine these intercepts with equations (12–123) and (12–130) to obtain the second-order rate constants for acid, $k_1 = k_{H^+}$ and base, $k_2 = k_{OH^-}$. K_w at 80° C is 12.63×10^{-14}.

Partial Answers: **(a)** The hydrolysis is due to specific acid-base catalysis. The regression equations of part **(b)** will substantiate this. **(b)** $k_1 = 5.62 \times 10^{-3}$ M^{-1} sec^{-1}; $k_2 = 6.10$ M^{-1} sec^{-1}

12–23. The pH–rate profile of cefotaxime sodium (log k_{obs} versus pH) at ionic strength $\mu = 0.5$ shows roughly slopes of −1, zero, and +1 within the pH ranges 0–4, 4–7, and 7–10, respectively.[102] **(a)** What kind of catalysis presumably occurs at each of the three pH ranges? **(b)** What is the value of the pH-independent rate constant if k_{obs} at pH 6 is 3.064×10^{-3} M^{-1} hr^{-1}? **(c)** Compute k_{obs} at pH 8. The specific acid and base constants are $k_{H^+} = 0.4137$ M^{-1} hr^{-1} and $k_{OH^-} = 1616.5$ M^{-1} hr^{-1}, where M stands for molarity (see equation (12–136)). The OH^- concentration at pH 8 and $\mu = 0.5$ is 1.38×10^{-6} M.

Answers: **(a)** Check your results with pages 302–303; **(b)** $k_0 = 3.064 \times 10^{-3}$ M^{-1} hr^{-1}; **(c)** $k_{obs} = 5.29 \times 10^{-3}$ hr^{-1}

12–24. Equation (12–128) may be written in logarithmic form to produce equation (12–130).

$$\log k_{obs} = \text{pH} + \log(K_w\, k_{OH^-})$$

This equation allows one to compute k_{OH^-} from the intercept of a regression of log k_{obs} against pH. Use the data of Khan[97] for the effect of pH on the alkaline hydrolysis rate constant of a new drug, maleimide, given in the table at the bottom of this page.

(a) Plot log k_{obs} (vertical axis) against pH. **(b)** Using least squares, compute the specific catalytic constant k_{OH^-} from the intercept.

Partial Answer: **(b)** The regression equation is $\log k_{obs} = 0.8689$ pH − 11.150. The value of k_{OH^-} is 7.08×10^2 sec^{-1}.

12–25. Strom and Jun[94] studied the kinetics of the hydrolysis of methenamine to produce formaldehyde in citrate–phosphate buffers from pH 2.0 to 7.4 at 37.5° C. The reaction half-life for the conversion of methenamine to formaldehyde was found to be pH dependent, decreasing from 13.8 hr at pH 5.8 to 1.6 hr at pH 2.0. **(a)** Using the data of the following table, plot the pH–rate profile from pH 2.0 to pH 5.8 and compute $t_{1/2}$ at these pH values.

Data (a) for *Problem 12–25*

k ($hr^{-1} \times 10^2$)	43.3	22.4	18.6	8.36	5.01
pH	2.0	3.4	4.6	5.1	5.8

(b) Prepare an Arrhenius plot of ln k against $1/T$ for the degradation of methenamine at various temperatures. Calculate the activation energy, E_a and the Arrhenius A factor at pH 5.1 over a range of temperatures from 37.5° to 67° C. The required data is as follows:

Data (b) for *Problem 12–25*

Temp. (°C)	37.5	47	57	67
k (hr^{-1})	0.0836	0.111	0.233	0.427

Partial Answer: **(a)** At pH 2, $t_{1/2} = 1.60$ hr; **(b)** $E_a = 11.9$ kcal/mole; $A = 1.87 \times 10^7$ hr^{-1} at pH 5

Data for *Problem 12–22**

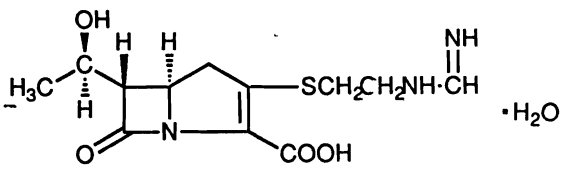
Buffer	HCl	Formate			Phosphate			Carbonate
Metal ion	—	Fe^{3+}	—	Cu^{2+}	Fe^{3+}	Cu^{2+}	—	—
$k_{obs} \times 10^7$ sec^{-1}	3360	35	22.1	21.6	18.6	21.4	84.5	8350
pH	1.15	2.99	3.21	3.22	6.51	6.57	7.21	9.22

*Selected data from D. M. Johnson, W. F. Taylor, G. Thompson and R. A. Pritchard, J. Pharm. Sci. 72, 946, 1983.

Data for *Problem 12–24*

pH	8.39	8.51	8.84	8.88	9.13	9.36	9.68	9.89	10.08
$k_{obs} \times 10^3$	0.1514	0.1750	0.330	0.3124	0.6510	0.9310	2.059	2.633	4.057

12–26. Thienamycin is an antibiotic with a structure somewhat related to the penicillins. Its decomposition accelerates as the concentration is increased; and a derivative, N-formimidoylthienamycin (imipemide, imipenen) has been introduced to improve the



Imipenem

stability and broad spectrum of activity. Smith and Schoenewaldt[103] studied the stability of imipenen in aqueous solution at 25° C and 40° C. A first-order reaction of ring opening occurred in dilute solution (1 or 2 mg/mL) and a second-order reaction became evident at higher concentrations. The pseudo–first-order rate constants k, hr^{-1}, at 25° C and 40° C are given in the following table at buffer pH from 5.0 to 8.0. The reaction rates were independent of general acid–base buffer effects, and the effect of ionic strength on rate was insignificant.

Data for *Problem 12–26*

Buffer pH	5.0	6.0	7.0	8.0
k (hr^{-1}), 25° C	0.0315	0.0069	0.0040	0.0083
k (hr^{-1}), 40° C	0.111	0.0257	0.0169	0.0462

The equation describing the rate–pH profiles of the drug at 25° and 40° C is

$$k_{obs} = k_1[H^+] + k_2 K_w/[H^+] + k_o \qquad (12\text{–}150)$$

in which k_{obs} is the experimentally determined first-order rate constant k at a definite pH, k_1 and k_2 are the second-order rate constants for hydrogen ion and hydroxyl ion catalysis, k_o is the first-order rate constant for water or "spontaneous" decomposition. $K_w/[H^+]$ is written in place of $[OH^-]$, where K_w is the ionization constant of water. Knowing the pH, one has by experiment both $[H^+]$ and $[OH^-] = K_w/[H^+]$. At 25° C, $K_w \cong 10^{-14.00}$ and at 40° C, $K_w = 10^{-13.54}$ (see p. 148).

(a) Plot the experimentally obtained points on the pH-profiles for the pseudo–first-order rate constants at 25° C and 40° C using the data of the table above. Draw the line obtained by use of equation (12–150) to determine how well the theory fits the experimental results. Using multiple least-squares regression, compute the values of k_o, k_1, and k_2 at both 25° C and 40° C. The researchers obtained the following results using a statistical method known as nonlinear regression.

Data for *Problem 12–26*

Temperature	k_o (hr^{-1})	k_1 ($M^{-1}\,hr^{-1}$)	k_2 ($M^{-1}\,hr^{-1}$)
40° C	0.01565	9730	10300
25° C	0.00403	2780	4150

Use the coefficients k_o, k_1, and k_2 to back-calculate $k_{25°}$ and $k_{40°}$.

Partial Answer: $k_{25°} = 0.0315\ hr^{-1}$ at pH 5, $k_{25°} = 0.0083$ at pH 8, $k_{40°} = 0.111$ at pH 5.

12–27. Notari[104] has studied the hydrolytic deamination of cytosine arabinoside in buffer solutions of varying composition prepared so as to maintain the pH and the ionic strength constant. He has reported the following data for the hydrolysis at 70° C:

Data for *Problem 12–27*

pH	Buffer composition			k, hr^{-1}
	$NaH_2PO_4 \cdot H_2O$	Na_2HPO_4	NaCl	
6.15	0.120	0.012	0.000	0.00311
	0.048	0.0048	0.094	0.00171
	0.024	0.0024	0.125	0.00118
6.90	0.040	0.040	0.000	0.00113
	0.029	0.029	0.043	0.000872
	0.016	0.016	0.092	0.000619

Using these data, determine which species in the buffer solution is functioning as a catalytic agent. Give your reasoning for choosing this agent. *Hint:* Plot k versus $[NaH_2PO_4]$ and versus $[Na_2HPO_4]$ on the same graph. If one or other of these catalytic species produces parallel lines at the two pH values, catalysis by this species is occurring.*

Answer: The $H_2PO_4^-$ ion is acting as a catalyst.

12–28. The degradation of phentolamine hydrochloride in phosphate buffer at pH 5.9 to 7.2 and 90° C is attributed to both the buffer species $H_2PO_4^-/HPO_4^{2-}$ and specific base catalysis. The value of the specific base catalysis constant k_{OH^-} was found to be 4.28×10^6 liter $mole^{-1}\ hr^{-1}$. The catalytic coefficients of the species $H_2PO_4^-$ and HPO_4^{2-} are $k_1 = 0.036$ and $k_2 = 1.470$ liter $mole^{-1}\ hr^{-1}$, respectively, and the total buffer concentration is 0.1 mole/liter. The equation for the overall rate constant is

$$k_{obs} = k_{OH^-}[OH^-] + k_1[H_2PO_4^-] + k_2[HPO_4^{2-}] \qquad (12\text{–}151)$$

The solvent effect is negligible and $k_o = 0$ (based in part on Wang et al.[105]).

(a) Compute the overall hydrolysis rate constant k at the pH values of 6, 6.5, 7, and 7.2 using the appropriate expression. At the pH range of 5.9 to 7 you can use the second dissociation constant of phosphoric acid, $pK_{a2} = 7.21$, to obtain the concentration of $H_2PO_4^-$ and HPO_4^{2-} at each pH value. Disregard the effect of the solvent alone. Then calculate the k_{obs} values at pH 6.5, 7.0 and 7.2. Finally convert the k values into log k and plot them versus pH.

(b) Plot the logarithm of the calculated k values against pH.

Partial Answer: **(a)** At pH 6, $k_{obs} = 0.0547\ hr^{-1}$; at pH 6.5, $k_{obs} = 0.162\ hr^{-1}$.

Hint: See page 303 and equations (12–138) and (12–139). To compute $[H_2PO_4^-]$ and $[HPO_4^{2-}]$ at each pH one uses the buffer equation

$$pH = pK_a + \log([HPO_4^{2-}] / [H_2PO_4^-]) \qquad (12\text{–}152)$$

in which pK_a is the second dissociation constant of H_3PO_4 (p. 147). At pH 6, one obtains $[HPO_4^{2-}]/[H_2PO_4^-] = 0.062/1$. Thus for 1 mole of buffer mixture, one has $0.062/(1 + 0.062) = 0.058$ mole HPO_4^{2-} and $(1 - 0.058) = 0.942$ mole $H_2PO_4^-$. Calculate the $[H_2PO_4^-]$ and $[HPO_4^{2-}]$ values at pH 6.0, 6.5, 7.0, and 7.2 for 0.1 mole/liter of buffer. The total rate constant at pH, say, 6 where $[OH^-] = 10^{-8}$ is $k_{(pH\ 6)} = (4.28 \times 10^6 \times 10^{-8}) + (0.036 \times 0.0942) + (1.470 \times 0.0058) = 0.0547\ hr^{-1}$. Then, calculate the k_{obs} values at pH 6.5, 7.0, and 7.2. **(b)** Finally, plot the log k_{obs} values versus pH.

12–29. The hydrolysis of mitomycin (see structure on p. 306 and Fig. 11–5*b*), an antitumor antibiotic, at pH 3.5 is due to the catalytic effect of water, the specific contribution of H^+ ions, and the effect of the phosphate buffer. At this pH value, phosphate buffers consist almost exclusively of $H_2PO_4^-$ ions so that the expression for k_{obs} is

*Dr. Keith Guillory, University of Iowa, suggested the test in *Problem 12–27* to determine what species is acting as the catalyst.

$$k_{obs} = k_o + k_{H^+}[H^+] + k_{H_2PO_4^-}[H_2PO_4^-]$$

The dependence of k_{obs} on the concentration of $H_2PO_4^-$ at a constant pH 3.5 is given in the table below.

Data for *Problem 12–29

$[H_2PO_4^-]$ (M)	0.01	0.05	0.1	0.2	0.3	0.4
$k_{obs} \times 10^3$ sec^{-1}	1.295	1.317	1.344	1.398	1.452	1.56

*From W. J. M. Underberg and H. Lingeman, J. Pharm. Sci. 72, 549, 1983.

Note: k_o and k_{H^+} are constants and since the pH is held at 3.5 $[H^+]$ is also constant.

(a) Plot k_{obs} versus $[H_2PO_4^-]$ and compute the equation of the line and the catalytic coefficient $k_{H_2PO_4^-}$ of $H_2PO_4^-$ from the slope.

(b) Compute k_{H^+} at pH 3.5, knowing that $k_o = 1 \times 10^{-6}$ sec^{-1}

Answers: **(a)** $k_{H_2PO_4^-} = 5.4 \times 10^{-4}$ M^{-1} sec^{-1}; **(b)** $k_{H^+} = 4.08$ M^{-1} sec^{-1}

12–30. The degradation in methanol of chlorthalidone, an oral diuretic sulfonamide, is catalyzed by ferric ions. The observed rate constants in methanol as solvent vary with the $FeCl_3$ concentration as follows:

Data (a) for *Problem 12–30*†

$[FeCl_3] \times 10^4$ M	0.64	1.93	3.78	4.96	6.22
k_{obs}, hr^{-1}	0.019	0.081	0.21	0.26	0.36

†From N. K. Pandit and J. S. Hinderliter, J. Pharm. Sci. 74, 857, 1985.

The addition of acetic acid to a chlorthalidone–methanol solution containing 6.15×10^{-4} mole/liter of $FeCl_3$ also influences hydrolysis. The variation of the observed rate constants with increasing concentrations of acetic acid, expressed as $[H^+]$, are as follows:

Data (b) for *Problem 12–30*

$[H^+] \times 10^7$	0.52	1.60	1.98	2.30
k_{obs}, hr^{-1}	0.436	0.672	0.764	0.772

The total k_{obs}, when both $[H^+]$ and $[FeCl_3]$ vary can therefore be represented as

$$k_{total} = k_o + k_M[M] + k'_M[M][H^+] \qquad (12\text{–}153)$$

where k_o is the first-order rate constant due to the catalytic effect of the solvent alone (methanol), k_M (M^{-1} sec^{-1}) is the pseudo–second-order constant for the metal ion catalyzed reaction, [M] is the concentration in mole/liter of $FeCl_3$, and k'_M (M^{-2} sec^{-1}) is the pseudo–third-order constant for the metal ion and acid-catalyzed reaction.

(a) Plot k_{obs} (vertical axis) against $[FeCl_3]$ from the first table of this problem and compute the equation of the line from which k_M is obtained. **(b)** Plot k_{obs} versus $[H^+]$ from the second table, and compute k'_M. *Hint:* Apply the general equation (12–153) given above to each part of the problem. That is, include the appropriate terms in the slope and intercept you get in (a) and (b).

Answer: **(a)** $k_M = 0.169$ M^{-1} sec^{-1}; **(b)** $k'_M = 9.03 \times 10^5$ M^{-2} sec^{-1}

12–31. A new drug product is found to be ineffective after it has decomposed 30%. The original concentration of one sample was 5.0 mg/mL; when assayed 20 months later, the concentration was found to be 4.2 mg/mL. Assuming that the decomposition is first order, what should be the expiration time on the label? What is the half-life of this product?

Answer: Expiration, 41 mo.; half-life = 79.5 mo.

12–32. Using the temperature lines of Figure 12–21, obtain the time necessary for a drug to decompose from 100% to 80% at the temperatures 50°, 60°, 70° and 90° C. Plot log (t_{80}) vs. the reciprocal of the absolute temperature (Figure 12–22) and determine the time in days required for the drug to degrade to 80% of its 100% value at 25° C

Answer: ca. 400 days.

12–33. The decomposition of ethacrinic acid in the presence of ammonium ion was determined to be reversible.[106] From the following k_f (forward) and k_r (reverse) values at 25° C determine the k_{obs}, k_o, and $k_{NH_4^+}$ values. *Hint:* You may solve the two equations simultaneously. You will need two equations: $k_{obs} = k_f/k_r$ and $k_{obs} = k_o + k_{NH_4^+}[NH_4^+]$.

Data for *Problem 12–33*

Value (hr^{-1})	Remarks
$k_r = 0.101$ $k_f = 0.026$	$[NH_4^+]$ concentration 0.04 M
$k_r = 0.108$ $k_f = 0.052$	$[NH_4^+]$ concentration 0.08 M

Answer: $k_{obs} = 0.257$ hr^{-1} at 0.04 M $[NH_4^+]$ and 0.482 hr^{-1} at 0.08 M $[NH_4^+]$; $k_{NH_4^+} = 5.625$ liter mole^{-1} hr^{-1}; $k_o = 0.032$ hr^{-1}

12–34. The hydrolysis of cefotaxime sodium at 25° C is first order[107]; and $k_{obs} = k_o + k_{H^+}[H^+] + k_{OH^-}[OH^-]$. The pH has very little effect in the range of 4.3 to 6.2 and k_{obs} in this pH range has the value 0.056 day^{-1}. The ionic strength and the phosphate buffer used have no effect on the decomposition constant. The k_{obs} values at pH 1.5 and 8.5 are 0.625 day^{-1} and 0.16 day^{-1}, respectively. Compute k_o, k_{H^+} and k_{OH^-} values.

Answer: $k_o = 0.056$ day^{-1}; $k_{H^+} = 18.0$ M^{-1} day^{-1}; and $k_{OH^-} = 3.3 \times 10^4$ M^{-1} day^{-1}

12–35. The hydrolysis of cocaine is catalyzed by the phosphate buffer.[108] The hydrolysis may be expressed using the following equation:

$$k_{obs} = k[OH^-] + k_2[H_2PO_4^-] + k_3[HPO_4^{2-}]$$

The equation may be rearranged to

$$k_{obs} = k + [H_2PO_4^-](k_2 + k_3/q)$$

where $k = k_1[OH^-]$ and is a constant at constant pH and

$$q = \frac{[H_2PO_4^-]}{[HPO_4^{2-}]}$$

On plotting k_{obs} (day^{-1}) versus $[H_2PO_4^{2-}]$ expressed in molar concentration, straight lines were obtained at the two pH values of 6.35 and 5.90. The q values at these pH values can be determined. The slope of the plots at pH values of 6.35 and 5.90 were 0.155 and 0.0556, respectively. **(a)** Compute the k_2 and k_3 values. **(b)** Which buffer ion is catalyzing the reaction?

Answers: **(a)** $k_3 = 1.09$ M^{-1} day^{-1}, $k_2 = 0.001$ M^{-1} day^{-1}; **(b)** HPO_4^{2-} catalyzes the reaction

12–36. Cyclophosphamide monohydrate is available as a sterile blend of dry drug and sodium chloride packaged in vials. A suitable aqueous vehicle is added and the sterile powder dissolved with agitation before the product is used parenterally. However, cyclophosphamide monohydrate is only slowly soluble in water, and a hospital pharmacist inquires concerning the advisability of briefly (for 15 min) warming the solution to 70° C to facilitate dissolution. Brooke et al. addressed this problem.[109] Assuming that degradation to 95% of the labeled amount is permitted for this compound, and given k at 25° C = 0.028 day^{-1}, $E_a = 25.00$ kcal/mole, what answer would you give?

Answer: $t_{95\%} = 10.4$ min. Degradation has occurred to the extent of 5% in 10.4 min, so heating at 70° C for a full 15 min would not be advisable. Brooke et al.[109] found by actual assay that heating at 50° C or 60° C produced less than 5% decomposition.