# 14 Chemical Kinetics and Stability

**Chapter Objectives**

**At the conclusion of this chapter the student should be able to:**

1. Define reaction rate, reaction order, and molecularity.
2. Understand and apply apparent zero-order kinetics to the practice of pharmacy.
3. Calculate half-life and shelf life of pharmaceutical products and drugs.
4. Understand Michaelis–Menten (nonlinear) kinetic behavior and linearization techniques.
5. Interpret pH–rate profiles and kinetic data.
6. Understand the basis for transition-state theory and its application to chemical kinetics.
7. Describe the influence of temperature, ionic strength, solvent, pH, and dielectric constant on reaction rates.
8. Calculate the increase in rate constant as a function of temperature ($Q_{10}$).
9. Describe the factors that influence solid-state chemical kinetics.
10. Identify and describe methods for the stabilization of pharmaceutical agents.
11. Understand stability-testing protocols and regulatory requirements.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. Although the pharmaceutical scientist plays a critical role in determining the stability of pharmaceuticals, practicing pharmacists should be able to interpret this information for their patients. This chapter introduces the rates and mechanisms of reactions with particular emphasis on decomposition and stabilization of drug products. It is essential for pharmacists and pharmaceutical scientists to study, understand, and interpret conditions of instability of pharmaceutical products as well as to be able to offer solutions for the stabilization of these products. Pharmaceutical manufacturers routinely utilize the principles covered in this chapter; however, with the resurgence of pharmaceutical compounding, it is essential for practicing pharmacists to understand drug product stability as well. If a community pharmacist is asked to compound a prescription product, there are many factors that he or she must consider. The pharmacist must recognize that alterations in stability 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. Patients expect that products will have a reasonable shelf life. Even though pharmaceutical manufacturers label prescription and over-the-counter drug products with expiration dating to guide the patient/consumer in these matters, patients may store these products in a bathroom medicine cabinet where the humidity and temperature are higher than the typical storage place for medications. How does this affect the shelf life of the product? A community pharmacy practitioner should be able to understand this and advise patients on these matters.

The experimental investigation of the possible breakdown of new drugs is not a simple matter. Applications of chemical 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. 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 on the formulation, stabilization, and administration of drugs. Concentration, temperature, light, pH, and catalysts are important in relation to the speed and the mechanism of reactions and will be discussed in turn.

## Fundamentals and Concentration Effects

## *Rates, Order, and Molecularity 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*, respectively, undergoing reaction. In the reaction

$$aA + bB + \cdots = \text{Products} \qquad \textbf{(14–1)}$$

the rate of the reaction is

$$\text{Rate} = \frac{1}{a}\frac{d[A]}{dt} = \frac{1}{b}\frac{d[B]}{dt} = \cdots k[A]^a[B]^b \cdots \qquad \textbf{(14–2)}$$

where *k* is the *rate constant*.

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The overall *order* of a reaction is the sum of the exponents [*a* + *b*, e.g., in equation (14-2)] 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

$$\text{Rate} = \frac{d[CH_3COOC_2H_5]}{dt} = -\frac{d[NaOH]}{dt} = k[CH_3COOC_2H_5]^1\,[NaOH]^1 \qquad \textbf{(14–3)}$$

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 because 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

$$\frac{d[CH_3COOC_2H_5]}{dt} = k'[CH_3COOC_2H_5] \qquad \textbf{(14–4)}$$

where *k*′ = *k*[NaOH]. The reaction is then said to be a *pseudo–first-order* reaction because 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 14-1**
**Reaction Order**

In the reaction of acetic anhydride with ethyl alcohol to form ethyl acetate and water,

$$(CH_3CO)_2O + 2C_2H_5OH \rightarrow 2CH_3CO_2C_2H_5 + H_2O$$

the rate of reaction is

$$\text{Rate} = -\frac{d[(CH_3CO)_2O]}{dt} = k[(CH_3CO)_2O]\,[C_2H_5OH]^2 \qquad \textbf{(14–5)}$$

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, because alcohol is the solvent, its concentration remains essentially constant, and the rate expression can be written as

$$-\frac{d[(CH_3CO)_2O]}{dt} = k'[(CH_3CO)_2O] \qquad (14\text{–}6)$$

Kinetically the reaction is therefore a pseudo–first-order reaction, as noted by Glasstone.2

## Molecularity

A reaction whose overall order is measured can 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. Because 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* because 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* because 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 because 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:

$$2NO \rightarrow N_2O_2$$

$$N_2O_2 + O_2 \rightarrow 2NO_2$$

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# *Rate Constants, Half-Life, Shelf Life, and Apparent or Pseudo-order*

## 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, in temperature or 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 because a change in this constant necessarily represents a change at the molecular level as a result of a variation in the reaction conditions.

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,

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

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

**Key Concept**

**Apparent or Pseudo-Order**

"Apparent" or "pseudo"-order describes a situation where one of the reactants is present in large excess or does not effect the overall reaction and can be held constant. For example, many hydrolysis decomposition reactions of drug molecules are second order. Usually the amount of water present is in excess of what is needed for the reaction to proceed. In other words, the concentration of water is essentially constant throughout the reaction. In this case, the second-order reaction behaves like a first-order reaction and is called an apparent or pseudo–first-order reaction.

**Key Concept**

**Half-Life and Shelf Life**

The *half-life* is the time required for one-half of the material to disappear; it is the time at which *A* has decreased to ½ *A*. The shelf life is the time required for 10% of the material to disappear; it is the time at which *A* has decreased to 90% of its original concentration (i.e., 0.9 *A*).

and for a second-order reaction,

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

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

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 Carper3 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

$$-\frac{dA}{dt} = k_0 \qquad \textbf{(14–7)}$$

where 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 can 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

$$A_t = A_0 - k_0 t \qquad \textbf{(14–8)}$$

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

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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 Carper3 obtained a value for *k* of 0.00082 absorbance decrease per hour at 60°C, indicating that the color was fading at this constant rate independent of concentration. Because the *half-life* is the time required for one-half of the material to disappear, in the present case $A_0 = 0.470$ 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 Kinetics4

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 **(**14-11**)**:

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

where [*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 can write

$$k[A] = k_0 \qquad \textbf{(14–9)}$$

so that the first-order rate law **(**14-11**)** becomes

$$-\frac{d[A]}{dt} = k_0 \qquad \textbf{(14–10)}$$

Equation **(**14-10**)** 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, which ensures constant concentration. Once all the suspended particles have been converted into drug in solution, the system changes to a first-order reaction.

**Key Concept**

**Shelf Life and Expiration Dating**

*Shelf life* (also referred to as the expiration dating period) is the time period during which a drug product is expected to remain within the approved specification for use, provided that it is stored under the conditions defined on the container label.

*Expiration date* is the date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions and after which it must not be used.

**Example 14-2**
**Shelf Life of an Aspirin Suspension**
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 $4.5 \times 10^{-6}$ $sec^{-1}$. Calculate the zero-order rate constant. Determine the shelf life, $t_{90}$, 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 (14-9).
Thus,

$$k_0 = (4.5 \times 10^{-6}\ \text{sec}^{-1}) \times (0.33\ \text{g}/100\ \text{mL})$$
$$k_0 = 1.5 \times 10^{-6}\ \text{g}/100\ \text{mL sec}^{-1}$$
$$t_{90} = \frac{0.10[A]_0}{k_0} = \frac{(0.10)(6.5\ \text{g}/100\ \text{mL})}{(1.5 \times 10^{-6}\ \text{g}/100\ \text{mL sec}^{-1})}$$
$$= 4.3 \times 10^5\ \text{sec} = 5.0\ \text{days}$$

## First-Order Reactions

In 1918, Harned5 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

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

are given in Table 14-1. 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 as

$$-\frac{dc}{dt} = kc \qquad \textbf{(14–11)}$$

where $c$ is the concentration of hydrogen peroxide remaining undecomposed at time $t$ and $k$ is the first-order velocity constant. Integrating equation (14-11) between concentration $c_0$ at time $t = 0$ and concentration $c$ at some later time, $t$, we have

$$\int_{c_0}^{c} \frac{dc}{c} = -k \int_0^t dt$$
$$\ln c - \ln c_0 = -k(t - 0)$$
$$\ln c = \ln c_0 - kt \qquad \textbf{(14–12)}$$



**Table 14-1 Decomposition of Hydrogen Peroxide at 25°C in Aqueous Solution Containing 0.02 m KI***

| *t* (min) | *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 | – |

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

Converting to common logarithms yields

$$\log c = \log c_0 - kt/2.303 \qquad \textbf{(14–13)}$$

or

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

In exponential form, equation (14-12) becomes

$$c = c_0 e^{-kt} \qquad \textbf{(14–15)}$$

and equation (14-13) becomes

$$c = c_0 10^{-kt/2.303} \qquad \textbf{(14–16)}$$

Equations (14-15) and (14-16) express the fact that, in a first-order reaction, the concentration decreases exponentially with time. As shown in Figure 14-1, the concentration begins at $c_0$ and decreases as the reaction becomes progressively slower. The concentration asymptotically approaches a final value $c_\infty$ as time proceeds toward infinity.

Equation (14-14) is often written as

$$k = \frac{2.303}{t} \log \frac{a}{a - x} \qquad \textbf{(14–17)}$$

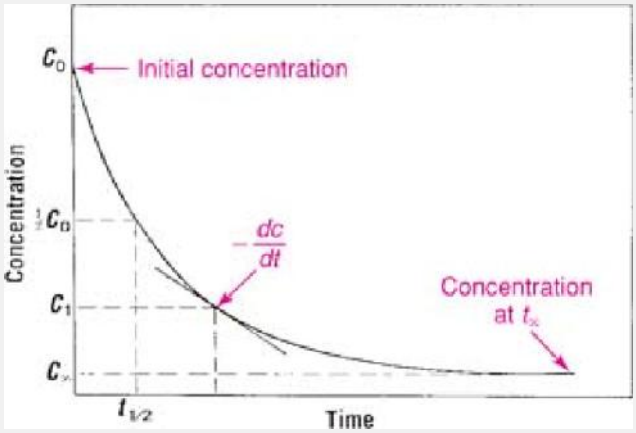



**Fig. 14-1.** Fall in concentration of a decomposing drug with time. In addition to $C_0$and $C_\infty$, $\frac{1}{2}C_0$ and the corresponding time, $t_{½}$, are shown. The rate of decrease of concentration with time, $-dC/dt$, at an arbitrary concentration,$C_1$, is also shown.

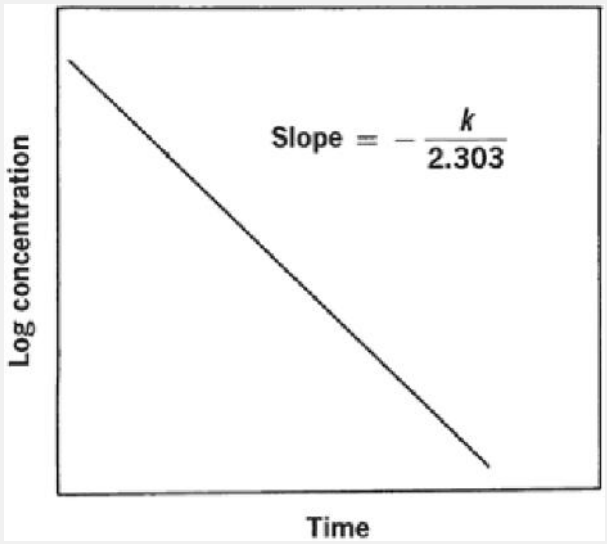


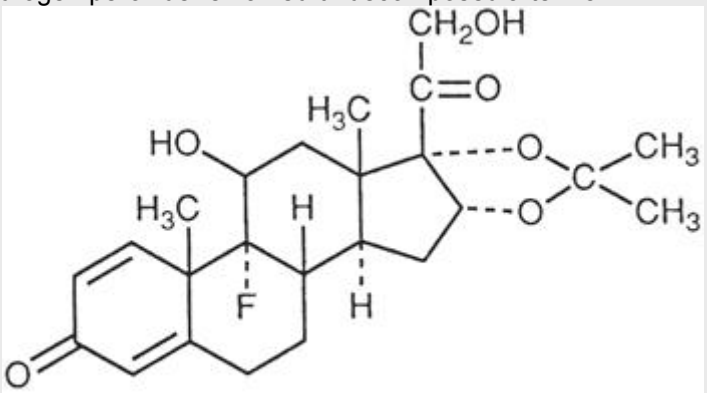

**Fig. 14-2.** A linear plot of log $C$ versus time for a first-order reaction.

where 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 14-1 were calculated by using equation (14-17). 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 14-2. The linear expression in equation(14-13) 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 first order. Once the rate constant is known, the concentration of reactant remaining at a definite time can be computed as demonstrated in the following examples.

**Example 14-3**
**Decomposition of Hydrogen Peroxide**

The catalytic decomposition of hydrogen peroxide can 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 min, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90.
(a) Calculate *k* using equation (14-14).
(b) How much hydrogen peroxide remained undecomposed after 25 min?



Triamcinolone acetonide

**Example 14-4**
**First-Order Half-Life**
A solution of a drug contained 500 units/mL when prepared. It was analyzed after 40 days and was found to contain 300 units/mL. Assuming the decomposition is first order, at what time will the drug have decomposed to one-half of its original concentration?
We have

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

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

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## Half-Life

The period of time required for a drug to decompose to one-half of the original concentration as calculated in Example 14-3 is the half-life, $t_{1/2}$, for a first-order reaction:

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

$$t_{1/2} = \frac{0.693}{k} \qquad (14\text{–}18)$$

In Example 14-4, the drug has decomposed by 250 units/mL in the first 54.3 days. Because 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/mL, or an additional 125 units/mL, are lost; in the third half-life, 62.5 units/mL 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 14-1. 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:

$$-\frac{d[A]}{dt} = \frac{d[B]}{dt} = k[A][B] \qquad \textbf{(14–19)}$$

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

$$\frac{dx}{dt} = k(a - x)(b - x) \qquad \textbf{(14–20)}$$

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

$$\frac{dx}{dt} = k(a - x)^2 \qquad \textbf{(14–21)}$$

Equation **(**14-21**)** is integrated, using the conditions that *x* = 0 at *t* = 0 and *x* = *x* at *t* = *t*.

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

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

$$\frac{x}{a(a - x)} = kt \qquad \textbf{(14–22)}$$

or

$$k = \frac{1}{at}\left(\frac{x}{a - x}\right) \qquad \textbf{(14–23)}$$

When, in the general case, *A* and *B* are not present in equal concentrations, integration of equation **(**14-20**)** yields

$$\frac{2.303}{a - b}\log\frac{b(a - x)}{a(b - x)} = kt \qquad \textbf{(14–24)}$$

or

$$k = \frac{2.303}{t(a - b)}\log\frac{b(a - x)}{a(b - x)} \qquad \textbf{(14–25)}$$

It can be seen by reference to equation **(**14-22**)** 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 **(**14-23**)** or **(**14-25**)**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 $\text{mole}^{-1}$ $\text{sec}^{-1}$.

### Example 14-5

### Saponification of Ethyl Acetate

Walker6 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 min 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 (14-23), we obtain

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

b. The half-life of a second-order reaction is

$$t_{1/2} = \frac{1}{ak} \qquad (14\text{–}26)$$

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

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

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## Determination of Order

The order of a reaction can be determined by several methods.

### *Substitution Method*

The data accumulated in a kinetic study can 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 14-2 can 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 14-2. 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

$$t_{1/2} \propto \frac{1}{a^{n-1}} \qquad (14\text{–}27)$$

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

$$\frac{t_{1/2(1)}}{t_{1/2(2)}} = \frac{(a_2)^{n-1}}{(a_1)^{n-1}} = \left(\frac{a_2}{a_1}\right)^{n-1} \qquad (14\text{–}28)$$

| 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 | $\frac{2ax - x^2}{a^2(a-x)^2} = 2kt$ | $t_{1/2} = \frac{3}{2}\frac{1}{a^2k}$ |

**Table 14-2 Rate and Half-Life Equations**

or, in logarithmic form,

$$\log \frac{t_{1/2(1)}}{t_{1/2(2)}} = (n-1)\log \frac{a_2}{a_1} \qquad \textbf{(14–29)}$$

and finally

$$n = \log \frac{(t_{1/2(1)}/t_{1/2(2)})}{\log(a_2/a_1)} + 1 \qquad \textbf{(14–30)}$$

The half-lives are obtained graphically by plotting *a* versus *t* at two different initial concentrations and reading the time at $1/2a_1$ and $1/2a_2$. The values for the half-lives and the initial concentrations are then substituted into equation **(**14-30**)**, from which the order *n* is obtained directly. Rather than using different initial concentrations, one can take two concentrations during a single run as $a_1$ and $a_2$and determine the half-lives $t_{1/2(1)}$ and $t_{1/2(2)}$ in terms of these. If the reaction is first order, $t_{1/2(1)} = t_{1/2(2)}$ because 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 **(**14-30**)**that

$$n = 0 + 1 = 1$$

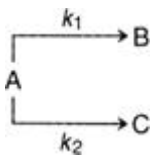
## Complex Reactions

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

a. Reversible reaction:

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

b. Parallel or side reactions:



c. 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. Because 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

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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:

$$-\frac{dA}{dt} = k_f A - k_r B \qquad \textbf{(14–31)}$$

This rate law can be integrated by noting that

$$A_0 - A = B \qquad \textbf{(14–32)}$$

Substitution of equation (14-32) into equation (14-31) affords, upon integration,

$$\ln \frac{k_f A_0}{(k_f + k_r)A - k_r A_0} = (k_f + k_r)t \qquad \textbf{(14–33)}$$

Equation (14-33) can be simplified by introducing the equilibrium condition

$$k_f A_{eq} = k_r B_{eq} \qquad \textbf{(14–34)}$$

where

$$A_0 - A_{eq} = B_{eq} \qquad \textbf{(14–35)}$$

Equations (14-34) and (14-35) can be used to solve for the equilibrium concentration in terms of the starting concentration:

$$A_{eq} = \frac{k_r}{k_f + k_r} A_0 \qquad \textbf{(14–36)}$$

Use of equation (14-36) in equation (14-33) enables us to give a simple form of the rate law:

$$\ln \frac{A_0 - A_{eq}}{A - A_{eq}} = (k_f + k_r)t \qquad \textbf{(14–37)}$$

or

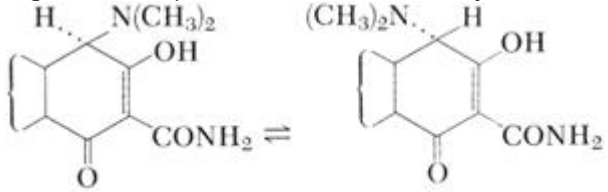
$$\log \frac{A_0 - A_{eq}}{A - A_{eq}} = \frac{k_f + k_r}{2.303} t \qquad \textbf{(14–38)}$$

Equation **(14-38)** 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 $\frac{k_f+k_r}{2.303}$ Because the equilibrium constant of the reaction is given by

$$K = \frac{k_f}{k_r} - \frac{B_{eq}}{A_{eq}} \qquad (14\text{–}39)$$

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, we can represent the transformation by the scheme




A B

The natural configuration of tetracycline has the $N(CH_3)_2$ group above the plane and the H group below the plane of the page. Under acidic conditions, the natural compound A is converted reversibly to the *epi* isomer B.

McCormick et al.7 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. 14-3). 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 14-3, when plotted according to equation **(**14-38**)**, give the line shown in Figure 14-4. The slope of this line is 0.010 $min^{-1}$. Because from equation **(**14-38**)** the slope *S*is

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

and from equation **(**14-39**)**

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

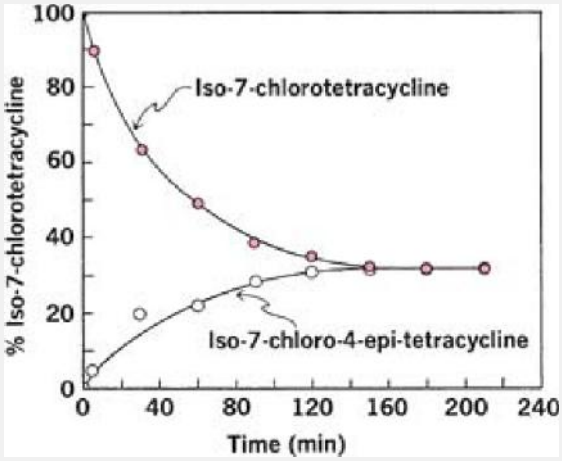



**Fig. 14-3.** Approach to equilibrium in the reversible epimerizations of iso-7-chloro-*epi*-tetracycline ^—^—^ and iso-7-chlorotetracycline •—•—•. (From J. D. McCormick, J. R. D. et al., J. Am. Chem. Soc. **79,** 2849, 1957.)



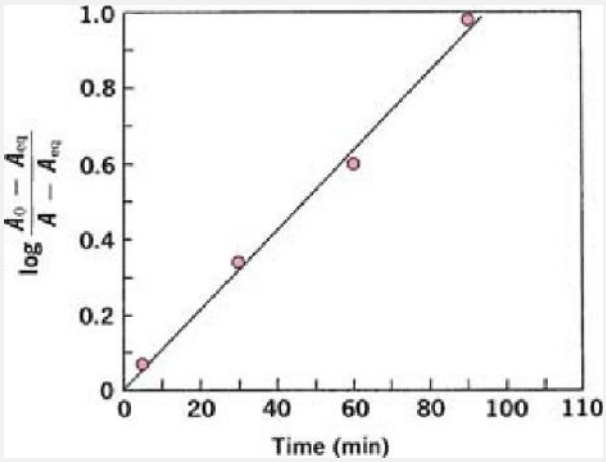



**Fig. 14-4.** Reversible epimerization of iso-7-chlorotetracycline in dimethylformamide containing 1 M $NaH_2PO_4$ at 25°C.

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

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

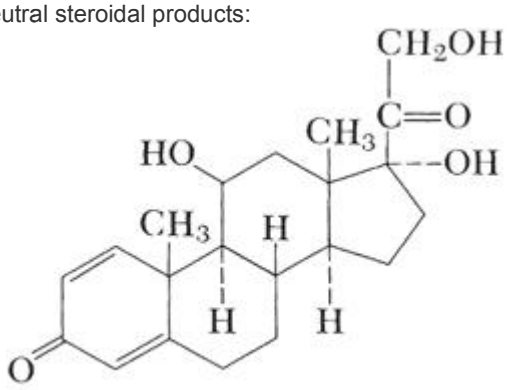
From this value, $k_f$ is found to be

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

## *Parallel or Side Reactions*

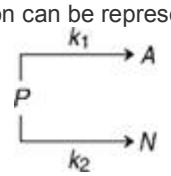
Parallel reactions are common in drug systems, particularly when organic compounds are involved. General acid–base catalysis, to be considered later, belongs to this class of reactions.

The base-catalyzed degradation of prednisolone will be used here to illustrate the parallel-type process. Guttman and Meister8investigated 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 can be represented as




(14–40)

(14–41)

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

The corresponding rate equation is

$$-\frac{dP}{dt} = k_1 P + k_2 P = kP \qquad \textbf{(14–42)}$$

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

$$\ln(P_0/P) = kt \qquad \textbf{(14–43)}$$

or

$$P = P_0 e^{-kt} \qquad \textbf{(14–44)}$$

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

$$\frac{dA}{dt} = k_1 P = k_1 P_0 e^{-kt} \qquad \textbf{(14–45)}$$

Integration of equation (14-45) yields

$$A = A_0 + \frac{k_1}{k} P_0 (1 - e^{-kt}) \qquad \textbf{(14–46)}$$

where *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 because no acid is formed before the prednisolone begins to decompose. Therefore,

$$A = \frac{k_1}{k} P_0 (1 - e^{-kt}) \qquad \textbf{(14–47)}$$

Likewise, for the neutral product,

$$N = \frac{k_2}{k} P_0 (1 - e^{-kt}) \qquad \textbf{(14–48)}$$

Equations (14-47) and (14-48) 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 (14-47) 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 (14-47). The value of $k_1$, the rate constant for the formation of the acidic product, was then calculated from the slope of the line,

$$k_1 = \text{Slope} \times k/P_0 \qquad \textbf{(14–49)}$$

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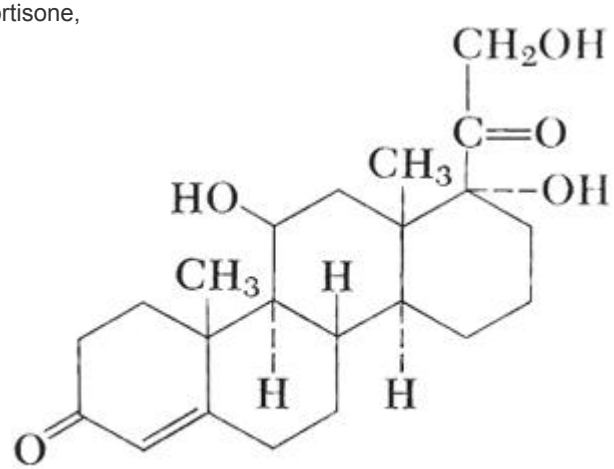
**Table 14-3 Rate Constants for the Base-Catalyzed Degradation of Prednisolone in Air at 35°C**

| 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 |

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,8 are given in Table 14-3. The stability of hydrocortisone,



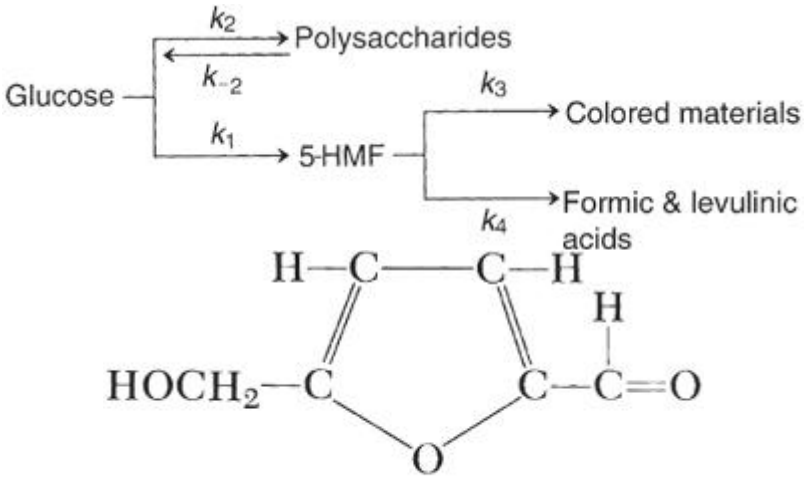

Hydrocortisone

was explored by Allen and Gupta9 in aqueous and oil vehicles, water-washable ointment bases, and emulsified vehicles in the presence of other ingredients, at elevated temperatures and at 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 a pseudo–first-order reaction. 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 take a simplified version of the degradation scheme of glucose as illustrative of consecutive-type reactions. The depletion of glucose in acid solution can be represented by the following scheme,10 where 5-HMF is 5-hydroxymethylfurfural:






5-Hydroxymethylfurfural
(5-HMF)

The scheme 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 can be neglected. Furthermore, owing to the indefinite nature of the breakdown products of 5-HMF, these can be combined together and referred to simply as constituent *C*. The simplified mechanism is therefore written as the series of reactions

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

where *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

$$-dA/dt = k_1 A \qquad \textbf{(14–50)}$$

The rate of change in concentration of 5-HMF is

$$dB/dt = k_1 A - k_2 B \qquad \textbf{(14–51)}$$

and that of the breakdown products is

$$dC/dt = k_2 B \qquad \textbf{(14–52)}$$

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

$$A = A_0 e^{-k_1 t} \qquad \textbf{(14–53)}$$

$$B = \frac{A_0 k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t}) \qquad \textbf{(14–54)}$$

and

$$C = A_0\left[1 + \frac{1}{k_1 - k_2}\left(k_2 e^{-k_1 t} - k_1 e^{-k_2 t}\right)\right] \qquad \textbf{(14–55)}$$

By the application of equations **(**14-53**)** through **(**14-55**)**, 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.11 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 postulated sequence 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 illustrate this approximation by deriving the Michaelis–Menten equation.

Michaelis and Menten12 assumed that the interaction of a substrate,*S*, with an enzyme, *E*, to yield a product, *P*, followed a reaction sequence given by

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

According to this scheme, the rate of product formation is

$$\frac{dP}{dt} = k_3 (E \cdot S) \qquad \textbf{(14–56)}$$

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

$$\frac{d(E \cdot S)}{dt} = k_1(E)(S) - k_2(E \cdot S) - k_3(E \cdot S) \qquad \textbf{(14–57)}$$

or

$$\frac{d(E \cdot S)}{dt} = k_1(E)(S) - (k_2 + k_3)(E \cdot S) \qquad \textbf{(14–58)}$$

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

$$\frac{d(E \cdot S)}{dt} = 0 \qquad \textbf{(14–59)}$$

It follows from equations (14-58) and (14-59) that

$$(E \cdot S)_{ss} = \frac{k_1(E)(S)}{k_2 + k_3} \qquad \textbf{(14–60)}$$

where 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, $E \cdot S$,

$$E_0 = E + (E \cdot S)_{ss} \qquad \textbf{(14–61)}$$

Eliminating *E* from equations (14-60) and (14-61), we obtain

$$(E \cdot S)_{ss} = \frac{k_1 S E_0}{(k_2 + k_3) + k_1 S} \qquad \textbf{(14–62)}$$

or

$$(E \cdots S)_{ss} = \frac{SE_0}{K_m + S} \qquad (14\text{–}63)$$

where

$$K_m = \frac{k_2 + k_3}{k_1} \qquad (14\text{–}64)$$

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

$$\frac{dP}{dt} = \frac{k_3 SE_0}{K_m + S} \qquad (14\text{–}65)$$

which can 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 $(dP/dt)_{maximum}$, which is usually written as $V_m$. When $S$ is very large, all enzyme $E_0$ is present as $E{\cdot}S$, that is, all enzyme is combined with the substrate and the reaction proceeds at maximum velocity. From equation (14-56), $dP/dt$ becomes $V_m$ and $V_m = k_3E_0$ because $E \cdot S$ is equivalent to $E_0$. Accordingly, from equation (14-65),

$$V = V_m \frac{S}{k_m + S} \qquad (14\text{–}66)$$

Equation (14-66) can be inverted to obtain a linear expression known as the *Lineweaver–Burk equation*:

$$\frac{1}{V} = \frac{K_m + S}{V_m \cdot S} \qquad (14\text{–}67)$$

$$\frac{1}{V} = \frac{1}{V_m} + \frac{K_m}{V_m}\frac{1}{S} \qquad (14\text{–}68)$$

From equation (14-68) 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. 14-5). Knowing $V_m$ from the intercept and obtaining $K_m/V_m$ as the slope, we can calculate $K_m$, the *Michaelis constant*.

**Example 14-6**

**Linear Transformations of the Michaelis–Menten Equation**

The velocity, $V$, of an enzymatic reaction at increasing substrate concentration [$S$] was experimentally determined to be as follows:

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

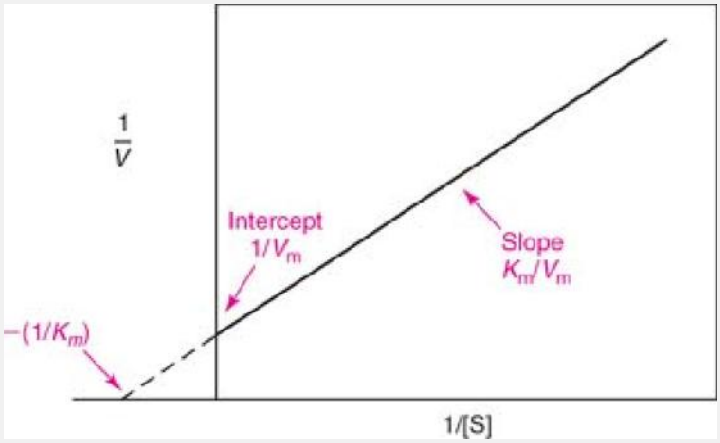



**Fig. 14-5.** A Lineweaver–Burk plot of Michaelis–Menten kinetics showing the calculation of $K_m$ by two means.

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

| | | | | | |
|---|---|---|---|---|---|
| 1/*V*[min/(μg/liter)] | 28.57 | 24.10 | 22.22 | 20.41 | 19.80 |
| 1/[*S*] (liters/mole) | 400 | 200 | 100 | 59.88 | 30.0 |

(*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*).

*Answer:* (*a*) Linear regression analysis yields

$$1/V = 19.316 + 0.0234\,(1/[S]);\ r^2 = 0.990$$
$$\text{Intercept, } 1/V_m = 19.316;\ V_m = 0.0518\ \mu\text{g/(liter} \cdot \text{min)}$$
$$\text{Slope} = K_m/V_m = 0.0234\ (\text{liter} \cdot \text{min}/\mu\text{g})\ \text{M}$$
$$K_m = 0.0234\ (\text{liter} \cdot \text{min}/\mu\text{g})\ \text{M} \times 0.0518\ \mu\text{g/liter} \cdot \text{min}$$
$$= 0.0012\ \text{M}$$

(*b*) By extrapolation,

$$-1/K_m = -823\ \mathrm{M}^{-1}$$
$$K_m = 0.0012\ \mathrm{M}$$

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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.

## Rate-Determining Step

In a reaction sequence in which one step is much slower than all the subsequent steps leading to the 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 mechanistic pathway

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

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

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

which can be postulated for the observed overall reaction

$$A + C \rightarrow P$$

If the concentrations of the intermediates *B* and *D* are small, we can 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 the product, we can write

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

or

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{k_2 + k_3 C} \qquad \textbf{(14–69)}$$

If, in the mechanistic sequence, step 3 is the slow step (the rate-determining step), we can say that $k_2 \gg k_3\ C$, and equation (14-69)is simplified to a second-order expression,

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{k_2} = k_0 AC \qquad \textbf{(14–70)}$$

On the other hand, if step 2, the reverse reaction, is the slow step, then $k_3 C \gg k_2$, and equation (14-69) reduces to a first-order expression,

$$\frac{dP}{dt} = \frac{k_1 k_3 AC}{k_3 C} = k_1 A \qquad \textbf{(14–71)}$$

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.

## Temperature Effects

A number of factors other than concentration may affect the reaction velocity. Among these are temperature, solvents, catalysts, and light. This section discusses the effect of temperature covered.

## *Collision Theory*

Reaction rates are expected to be proportional to the number of collisions per unit time. Because the number of collisions increases as the temperature increases, the reaction rate is expected to increase with increasing temperature. In fact, the



speed of many reactions increases about two to three times with each 10° rise in temperature. As a reaction proceeds from reactants to products, the system must pass through a state whose energy is greater than that of the initial reactants. This "barrier" is what prevents the reactants from immediately becoming products. The activation energy, $E_a$, is a measure of this barrier. The effect of temperature on reaction rate is given by the equation, first suggested by Arrhenius,

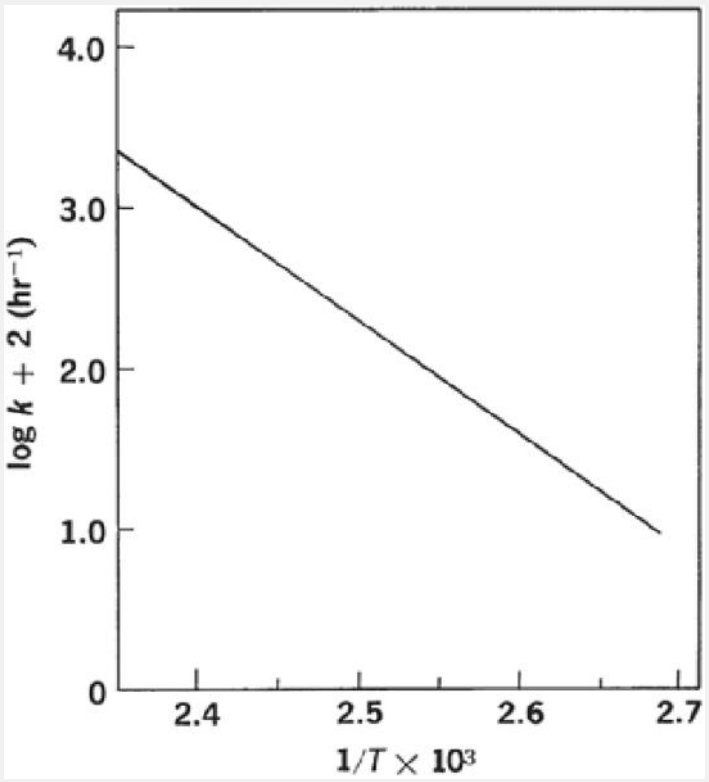



**Fig. 14-6.** A plot of log $k$ against $1/T$ for the thermal decomposition of glucose.

$$k = Ae^{-E_a/RT} \qquad (14\text{–}72)$$

or

$$\log k = \log A - \frac{E_a}{2.303}\frac{1}{RT} \qquad (14\text{–}73)$$

where $k$ 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 can be evaluated by determining $k$ at several temperatures and plotting $1/T$ against log $k$. As seen in equation **(**14-73**)**, the slope of the line so obtained is $-E_a/2.303\ R$, and the intercept on the vertical axis is log $A$, from which$E_a$ and $A$ can be obtained.

Data obtained from a study of the decomposition of glucose solutions between 100°C and 140°C in the presence of 0.35 N hydrochloric acid are plotted in this manner in Figure 14-6.* It should be observed that because 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 (14-18), $t_{1/2} = 0.693/k$, and in logarithmic form

$$\log k = \log 0.693 - \log t_{1/2} \qquad \textbf{(14–74)}$$

Substituting equation (14-74) into equation (14-73) 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.13 plotted the results of the alkaline hydrolysis of procaine in this manner, as shown in Figure 14-7. $E_a$ can also be obtained by writing equation (14-73) for a temperature $T_2$ as

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

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

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

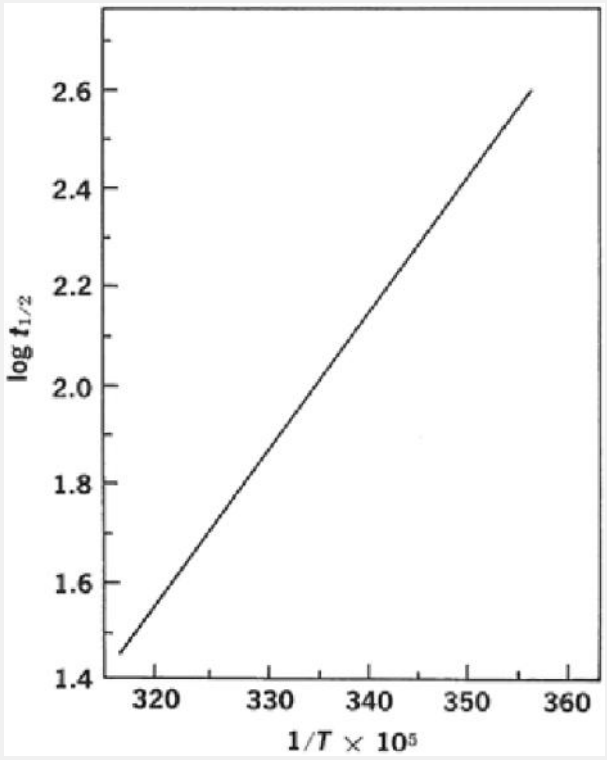



**Fig. 14-7.** A plot of log $t_{1/2}$ against $1/T$ for the alkaline hydrolysis of procaine. (From T. Higuchi, A. Havinga, and L. W. Busse, J. Am. Pharm. Assoc. Sci. Ed. **39,** 405, 1950.)

**Example 14-7**
**Decomposition of 5-HMF**

The rate constant $k_1$ for the decomposition of 5-hydroxymethylfurfural at 120°C (393 K) is 1.173 $hr^{-1}$ or $3.258 \times 10^{-4}$ $sec^{-1}$ 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?

We have

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

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

At 120°C, using equation (14-73), we obtain

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

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

## *Classic Collision Theory of Reaction Rates*

The Arrhenius equation is largely an empirical 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 can be understood by considering a hypothetical 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. Because 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*,

$$f_i = \frac{N_i}{N_T} = e^{-Ei/RT} \qquad (14\text{–}75)$$

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,

$$\text{Rate} = PZN_i \qquad (14\text{–}76)$$

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 (14-76) yields

$$\text{Rate} = (PZe^{-Ei/RT})N_T \qquad (14\text{–}77)$$

which, when compared with the general rate law

$$\text{Rate} = k \times \text{Concentration of reactants} \qquad (14\text{–}78)$$

leads to the conclusion that

$$k = (PZ)e^{-Ei/RT} \qquad (14\text{–}79)$$

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

$$A = PZ \qquad (14\text{–}80)$$

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

$$E_a = E_i \qquad (14\text{–}81)$$

Yang14 showed the error possible in determining the activation energy, $E_a$, and the predicted shelf life when the kinetic order in an accelerated stability test is incorrectly assigned, for example, when an actual zero-order reaction can equally well be described by a first-order degradation.

## $Q_{10}$ Calculations

In an excellent reference text for pharmacists, Connors et al.1described a straightforward calculation that facilitates a practical understanding of temperature effects. Using this method, one can estimate the effect of a 10° rise in temperature on the stability of pharmaceuticals. Just as was done in Example 14-7, this so-called$Q_{10}$ method relies on the ratio of reaction rate constants at two different temperatures. The quantity $Q_{10}$ was originally defined by Simonelli and Dresback15 as

$$Q_{10} = \frac{k_{(T+10)}}{k_T} \qquad (14\text{–}82)$$

$Q_{10}$ is the factor by which the rate constant increases for a 10°C temperature increase. The $Q_{10}$ factor can be calculated from the following equation:

$$Q_{10} = \exp\left[-\frac{E_a}{R}\left(\frac{1}{T+10} - \frac{1}{T}\right)\right] \qquad (14\text{–}83)$$



If the activation energy is known, the corresponding $Q_{10}$ value can be obtained from equation (14-83). The $Q_{10}$ approximation method is useful for making quick approximations. As noted by Connors et al.,1the activation energies for drug decompositions usually fall in the range of 12 to 24 kcal/mole, with typical values 19 to 20 kcal/mole. To make approximations when $E_a$ is unknown, it is reasonable to use these typical values to calculate $Q_{10}$ values. For example, using Equation (14-83), we have $Q_{10}$ = 2, 3, and 4 when $E_a$ = 12.2, 19.4, and 24.5, respectively, when the temperature rises from 20°C to 30°C. This simple calculation demonstrates that the degradation rate of most pharmaceutical agents will increase by two to four times, with an average of three times, for a 10°C rise in temperature in a range (from 20°C to 30°C) that typical consumers will experience. The more advanced student may be interested in generalizing the $Q_{10}$ approach to estimate the effect of increasing or decreasing the temperature by variable amounts. To do this, use the following equation:

$$Q_{\Delta T} = \frac{k_{(T+\Delta T)}}{k_T} = Q_{10}^{(\Delta T/10)} \qquad (14\text{–}84)$$

**Example 14-8**
**Effect of Temperature Increase/Decrease on Rate Constants**
Calculate the factors by which rate constants may change for (*a*) a 25°C to 50°C temperature change and (*b*) a 25°C to 0°C temperature change.
*Answer*:

a. Using equation (14-84), with $\Delta T$ = +25, we obtain

$$Q_{+25} = Q_{10}^{25/10}$$
$$= 5.7, 15.6, 32 \quad \text{for} \quad Q_{10} = 2, 3, 4, \text{ respectively.}$$

Thus, the rate increases between 6-fold and 32-fold, with a probable average increase of about 16-fold.

b. When $\Delta T = -1$, we have

$$Q_{-25} = Q_{10} = \frac{1}{5.7}, \frac{1}{15.6}, \frac{1}{32} \quad \text{for } Q_{10} = 2, 3, 4, \text{ respectively}$$

Thus, the rate decreases to between 1/6 and 1/32 of the initial rate.

## *Shelf-Life Calculations*

The following examples illustrate situations that pharmaceutical scientists and practicing pharmacists are likely to encounter.

**Example 14-9**

**Increased Shelf Life of Aspirin** (Connors et al.,[1] pp. 12–18)

Aspirin is most stable at pH 2.5. At this pH the apparent first-order rate constant is $5 \times 10^{-7}$ $sec^{-1}$ at 25°C. The shelf life of aspirin in solution under these conditions can be calculated as follows:

$$t_{90} = \frac{0.10^5}{5 \times 10^{-7}} = 2.1 \times 10^5 \text{ sec} = 2 \text{ days}$$

As one can see, aspirin is very unstable in aqueous solution. Would making a suspension increase the shelf life of aspirin?

The solubility of aspirin is 0.33 g/100 mL. At pH 2.5, the apparent zero-order rate constant for an aspirin suspension is

$$k_0 = 5 \times 10^{-7} \text{ sec}^{-1} \times 0.33 \text{ g/100 mL} = 1.65 \times 10^{-7} \text{ g/mL} \cdot \text{sec}$$

If one dose of aspirin at 650 mg per teaspoonful is administered, then one has 650 mg/5 mL = 13 g/100 mL.

For this aspirin suspension,

$$t_{90} = \frac{(0.1)(13)}{1.65 \times 10^{-7}} = 7.9 \times 10^6 \text{ sec} = 91 \text{ days}$$

The increase in the shelf life of suspensions as compared to solutions is a result of the interplay between the solubility and the stability of the drug. In the case of aspirin, the solid form of the drug is stable, whereas when aspirin is in solution it is unstable. As aspirin in solution decomposes, the solution concentration is maintained as additional aspirin dissolves up to the limit of its aqueous solubility.

**Example 14-10**

**How Long Can a Product Be Left Out at Room Temperature?**

Reconstituted ampicillin suspension is stable for 14 days when stored in the refrigerator (5°C). If the product is left at room temperature for 12 hr, what is the reduction in the expiration dating?

To solve this problem we must use the following equation:

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} \qquad (14\text{–}85)$$

The estimate of $t_{90}(T_2)$ is independent of order. In other words, it is not necessary to know the reaction order to make this estimate.

# Other Factors—A Molecular Viewpoint

## *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 can be written as

$$\underset{\substack{\text{Normal reactant}\\ \text{molecules}}}{A + B} \quad \rightleftharpoons \quad \underset{\substack{\text{Activated}\\ \text{molecules in the}\\ \text{transition state}\\ \text{(activated complex)}}}{[A \cdots B]^{\ddagger}} \quad \rightarrow \quad \underset{\substack{\text{Product}\\ \text{molecules}}}{P} \qquad \textbf{(14–86)}$$

A double dagger is used to designate the activated state, namely [A … B]‡.

The rate of product formation in this theory is given by

$$\text{Rate} = \nu[A \cdots B]^{\ddagger} \qquad \textbf{(14–87)}$$

where *v* is the frequency with which an activated complex goes to product. Because an equilibrium exists between the

P.333

reactants and the activated complex,

$$K^{\ddagger} = \frac{[A \cdots B]^{\ddagger}}{[A][B]} \qquad \textbf{(14–88)}$$

and this expression can be rearranged to

$$[A \cdots B]^{\ddagger} = K^{\ddagger}[A][B] \qquad \textbf{(14–89)}$$

Hence,

$$\text{Rate} = \nu K^{\ddagger}[A][B] \qquad \textbf{(14–90)}$$

The general rate law for a bimolecular reaction is

$$\text{Rate} = k[A][B] \qquad \textbf{(14–91)}$$

so it follows that

$$k = \nu K^{\ddagger} \qquad \textbf{(14–92)}$$

It will be recalled from previous thermodynamic considerations that

$$\Delta G^{\circ} = -RT \ \ln \ K \qquad \textbf{(14–93)}$$

or

$$K = e^{-\Delta G^{\circ}/RT} \qquad \textbf{(14–94)}$$

and

$$\Delta G^{\circ} = \Delta H^{\circ} - T\,\Delta S^{\circ} \qquad \textbf{(14–95)}$$

Replacing the ordinary *K* for present purposes with *K*‡ and making similar substitutions for the thermodynamic quantities, we obtain

$$k = \nu e^{-\Delta G^{\ddagger}/RT} \qquad \textbf{(14–96)}$$

and

$$k = \left(\nu e^{-\Delta S^{\ddagger}/R}\right) e^{-\Delta H^{\ddagger}/RT} \qquad \textbf{(14–97)}$$

where Δ*G*‡, Δ*S*‡, and Δ*H*‡ 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 factor *A* is related to the entropy of activation of the transition state:

$$A = \nu e^{\Delta S^{\ddagger}/R} \qquad \textbf{(14–98)}$$

and the Arrhenius activation energy, $E_a$, is related to the entropy of activation of the transition state:

$$E_a = \Delta H^{\ddagger} = \Delta E^{\ddagger} + P\,\Delta V^{\ddagger} \qquad \textbf{(14–99)}$$

For most practical purposes, Δ*V*‡ = 0; hence,

$$E_a = \Delta E^{\ddagger} \qquad \textbf{(14–100)}$$

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

$$k = \left(\nu e^{\Delta S^{\ddagger}/R}\right) e^{-\Delta E^{\ddagger}/RT} \qquad \textbf{(14–101)}$$

where the frequency of decomposition of the transition-state complex, *v*, may vary depending on the nature of the reactants. Eyring16 showed that the quantity *v* can be considered, to a good approximation, as a universal factor for reactions, depending only on temperature, and that it can be written as

$$v = \frac{RT}{Nh} \qquad (14\text{–}102)$$

where $R$ 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 (~2 × $10^{10}$ $T$). In many unimolecular gas reactions in which $\Delta S‡$ is zero so that $e^{\Delta S‡/R} = 1$, the rate constant ordinarily has a value of about $10^{13}e^{-E_a/RT}$, or

$$k \cong \frac{RT}{Nh}e^{-\Delta H^‡/RT} \cong 10^{13}e^{-E_a/RT} \qquad (14\text{–}103)$$

When the rate deviates from this value, it can be considered as resulting from the $e^{\Delta S‡/R}$ factor. When the activated complex represents a more probable arrangement of molecules than found in the normal reactants, $\Delta S‡$ 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 complex a less probable structure, $\Delta S‡$ is negative, and the reaction will be slower than predicted from equation (14-103). The collision theory and the transition-state theory are seen to be related by comparing equations (14-80), (14-98), and (14-102). One concludes that

$$PZ = \frac{RT}{Nh}e^{\Delta S^‡/R} \qquad (14\text{–}104)$$

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

**Example 14-11**

**Acid-Catalyzed Hydrolysis of Procaine**

In the study of the acid-catalyzed hydrolysis of procaine, Marcus and Baron17 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 × $10^{-6}$ $sec^{-1}$ at 97.30°C and $E_a$ = 16.8 kcal/mole.

Compute $\Delta S‡$ and the frequency factor, $A$, using equations (14-97) and (14-98), and the probability factor $P$. It is first necessary to obtain $RT/Nh$ at 97.30°C or about 371 K:

$$v = \frac{RT}{Nh} = \frac{8.31 \times 10^7 \text{ ergs/mole deg} \times 371 \text{ deg}}{6.62 \times 10^{-27}\text{erg sec/molecule} \times 6.02 \times 10^{23} \text{ molecules/mole}}$$
$$= 7.74 \times 10^{12}\,\text{sec}^{-1}$$

Then, from equation (14-97), in which

$$\Delta H^‡ \cong E_a$$
$$38.5 \times 10^{-6} = 7.74 \times 10^{12}e^{\Delta S^‡/1.987} \times e^{-16{,}800/(1.987\times 371)}$$
$$\Delta S^‡ = -24.73\,\text{cal/mole}$$

and from equation (14-98),

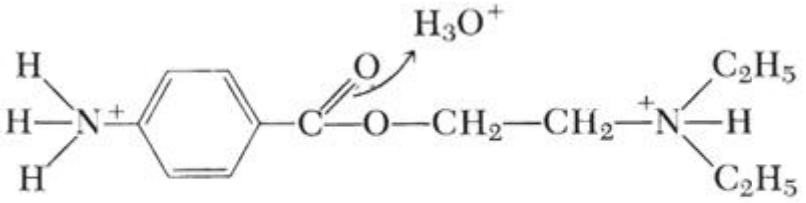
$$A = 7.74 \times 10^{12}e^{-33.9/1.987} = 3.05 \times 10^7\,\text{sec}^{-1}$$

Finally, from the discussion accompanying equation (14-104),

$$P = e^{-33.9/1.987} = 3.9 \times 10^{-6}$$



Marcus and Baron17 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 these 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 (Example 14-8) 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 also tends to lower the frequency factor.

## *Medium Effects: Solvent, Ionic Strength, Dielectric Constant*

### 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 the solute. The effects of the ionic strength and the dielectric constant of the medium on the rate of ionic reactions are also significant and will be discussed in subsequent sections.

Solutions are ordinarily nonideal, and equation (14-88) 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

$$K^{\ddagger} = \frac{a^{\ddagger}}{a_A a_B} = \frac{C^{\ddagger}}{C_A C_B} \frac{\gamma^{\ddagger}}{\gamma_A \gamma_B} \qquad \textbf{(14–105)}$$

where $a\ddagger$ 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 (14-87) and (14-90), are obtained:

$$\text{Rate} = \frac{RT}{Nh} C^{\ddagger} = \frac{RT}{NH} K^{\ddagger} C_A C_B \frac{\gamma_A \gamma_B}{\gamma^{\ddagger}} \quad \textbf{(14–106)}$$

or

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

or

$$k = k_0 \frac{\gamma_A \gamma_B}{\gamma^{\ddagger}} \qquad \textbf{(14–107)}$$

where $k_0 = RTK\ddagger/Nh$ is the rate constant in an infinitely dilute solution, that is, one that behaves ideally. It will be recalled from 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 (14-107). This condition was tacitly assumed in equation (14-90).

Now, the activity coefficient $\Delta_2$ of a not too highly polar nonelectrolytic solute in a dilute solution is given by the expression

$$\log \gamma_2 = \frac{V_2}{2.303RT} (\delta_1 - \delta_2)^2 \qquad \textbf{(14–108)}$$

where $V_2$ is the molar volume of the solute and $\Delta_1$ and $\Delta_2$ are the solubility parameters for the solvent and solute, respectively. The volume fraction term, $F^2$, is assumed here to have a value of unity.

Writing equation (14-107) in logarithmic form,

$$\log k = \log k_0 + \log \gamma_A + \log \gamma_B - \log \gamma^{\ddagger} \quad \textbf{(14–109)}$$

and substituting for the activity coefficients from (14-108) gives

$$\log k = \log k_0 + \frac{V_A}{2.303RT}(\delta_1 - \delta_A)^2 + \frac{V_B}{2.303RT}(\delta_1 - \delta_B)^2 - \frac{V^{\ddagger}}{2.303RT}(\delta_1 - \delta^{\ddagger})^2 \quad \textbf{(14–110)}$$

where $V_A$, $V_B$, $V‡$, and the corresponding $\delta_A$, $\delta_B$, and δ‡ are the molar volumes and solubility parameters of reactant *A*, reactant *B*, and the activated complex $(A \cdots B)‡$, respectively. The quantity $\Delta_1$ 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. Because these three squared terms, $(\delta_1 - \delta_A)2$, $(\delta_1 - \delta_B)2$, and $(\delta_1 - \delta‡)2$ represent the differences between solubility parameters or internal pressures of the solvent and the reactants, and the solvent and the activated complex, they can be symbolized, respectively, as $\Delta\delta_A$, $\Delta\delta_B$, and Δδ‡. 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 Δδ‡. This is readily seen by writing equation (14-110) as

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

It is assumed that the properties of the activated complex are quite similar to those of the products so that Δδ‡ can 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 Δδ‡ [congruent] 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 $\Delta\delta_B$ [congruent] 0, whereas the products are not similar to the solvent, that is, Δδ‡ > 0, then $(\Delta\delta_A + \Delta\delta_B)$ - Δδ‡ 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, we can use the reaction between ethyl alcohol and acetic anhydride:

$$C_2H_5OH + (CH_3CO)_2O \rightarrow CH_3COOC_2H_5 + CH_3COOH$$

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 14-4together with the solubility parameters of the solvents.18 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 $z_B$, respectively, and the activated complex $(A \cdots B)‡$ has a charge of $z_A + z_B$. A reaction involving ions can be represented as

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

**Table 14-4 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 |

The activity coefficient, $\gamma_i$, of an ion in a dilute aqueous solution (<0.01 M) at 25°C is given by the Debye–Hückel equation as

$$\log \gamma_i = -0.51 z_i^2 \sqrt{\mu} \qquad \textbf{(14–111)}$$

where $\mu$ is the ionic strength. Therefore, we can write

$$\begin{aligned} &\log \gamma_A + \log \gamma_B - \log \gamma^{\ddagger} \\ &= -0.51 z_A^2 \sqrt{\mu} - 0.51 z_B^2 \sqrt{\mu} + 0.51 (z_A + z_B)^2 \sqrt{\mu} \\ &= -0.51 \sqrt{\mu}\, [z_A^2 + z_B^2 - (z_A^2 + 2 z_A z_B + z_B^2)] \\ &= 0.51 \times 2 z_A z_B \sqrt{\mu} = 1.02 z_A z_B \sqrt{\mu} \qquad \textbf{(14–112)} \end{aligned}$$

Substituting into equation (14-109) results in the expression, at 25°C,

$$\log k = \log k_0 + 1.02 z_A z_B \sqrt{\mu} \qquad \textbf{(14–113)}$$

where $k_0$ is the rate constant in an infinitely dilute solution in which $\mu = 0$. It follows from equation (14-113) 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 (14-113), should then be independent of the ionic strength in dilute solutions. Good agreement has been obtained between experiment and theory as expressed by equation(14-113).

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

$$\log k = \log k_0 + b\mu \qquad \textbf{(14–114)}$$

where $b$ is a constant obtained from experimental data. Carstensen19 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 can be determined is

$$\ln k = \ln k_{\epsilon=\infty} - \frac{N z_A z_B e^2}{R T r^{\ddagger}} \frac{1}{\epsilon} \qquad \textbf{(14–115)}$$

where $k_{\varepsilon=\infty}$ 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 $k_{\varepsilon=\infty}$ is obtained by plotting ln *k*against 1/ε and extrapolating to 1/ε = 0, that is, to ε = ∞. Such a plot, according to equation **(**14-115**)**, 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.
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When a reaction occurs between a dipole molecule and an ion *A*, the equation is

$$\ln k = \ln k_{\epsilon=\infty} + \frac{N z_A^2 e^2}{2RT}\left(\frac{1}{r_A} - \frac{1}{r^\ddagger}\right)\frac{1}{\epsilon} \qquad \textbf{(14–116)}$$

where $z_A$ is the charge on the ion *A*, $r_A$ is the radius of the ion, and *r*‡ is the radius of the activated complex. Equation **(**14-116**)** predicts that a straight line should be obtained when ln *k* is plotted against 1/ε, the reciprocal of the dielectric constant. Because *r*‡, 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/ε, 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 case 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 **(**14-115**)** and **(**14-116**)**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 Holmes20 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 equation **(**14-116**)**.

To determine the effect of dielectric constant on the rate of glucose decomposition in acidic solution, Heimlich and Martin10 carried out tests in dioxane–water mixtures. The results shown in Table 14-5are 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 because replacing water with a solvent of lower dielectric constant markedly increases the rate of breakdown of glucose. Marcus and Taraszka21 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.

**Table 14-5 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 |

*Dioxane is toxic and cannot be used in pharmaceutical preparations.

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,21 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 interpretation of the results before one can predict the optimum conditions for stabilizing drug products.

## *Catalysis: Specific and General Acid–Base and pH Effects*

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.

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

$$\Delta G^\circ = -RT \ln K$$

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 $\dot{C}H_3$, 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 the 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 on 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 can 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, 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

$$\frac{dP}{dt} = k[SH^+][R] \qquad \textbf{(14–117)}$$

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

$$K = \frac{[SH^+]}{[S][H^+]} \qquad (14\text{–}118)$$

Thus,

$$[SH^+] = K[S][H^+] \qquad (14\text{–}119)$$

and it follows that

$$\frac{dP}{dt} = kK[S][H^+][R] \qquad (14\text{–}120)$$

Because water, R, is present in great excess, equation (14-120)reduces to the apparent rate law

$$\frac{dP}{dt} = k_1[S][H^+] \qquad (14\text{–}121)$$

where

$$k_1 = kK[R] \qquad (14\text{–}122)$$

The hydrogen ion concentration term in equation (14-121) 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:

$$\frac{dP}{dt} = k_{obs}[S] \qquad (14\text{–}123)$$

where

$$k_{obs} = k_1[H^+] \qquad (14\text{–}124)$$

Taking logarithms of equation (14-124) gives

$$\log k_{obs} = \log [H^+] + \log k_1 \qquad (14\text{–}125)$$

or, equivalently,

$$\log k_{obs} = -(-\log [H^+]) + \log k_1 \qquad (14\text{–}126)$$

We finally arrive at the expression

$$\log k_{obs} = -pH + \log k_1 \qquad (14\text{–}127)$$

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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 can write the general reaction as

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

and the rate of product, *P*, formation is therefore given by

$$\frac{dP}{dt} = k_2[S][OH^-] \qquad (14\text{–}128)$$

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

$$\frac{dP}{dt} = k_{obs}[S] \qquad (14\text{–}129)$$

where now

$$k_{obs} = k_2[OH^-] \qquad (14\text{–}130)$$

or, because

$$K_w = [H^+][OH^-] \qquad (14\text{–}131)$$

$$k_{obs} = \frac{k_2 K_w}{[H^+]} \qquad (14\text{–}132)$$

Taking the logarithm of equation (14-132),

$$\log k_{obs} = -\log [H^+] + \log k_2 K_w \qquad (14\text{–}133)$$

we find that

$$\log k_{obs} = \text{pH} + \log k_2 K_w \qquad \textbf{(14–134)}$$

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

Figure 14-8 shows the rate–pH profile for the specific acid–base–catalyzed hydrolysis of methyl-*dl*-*o*-phenyl-2-piperidylacetate.22 Note that an increase in pH from 1 to 3 results in a linear decrease in rate, as expected from equation (14-127), for specific hydrogen ion catalysis, whereas a further increase in pH from about 3 to 7 results in a linear increase in rate, as expected from equation (14-134), 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, un-ionized water may be considered as the reacting species. Because of the pH independence of this reaction, the rate law is given by

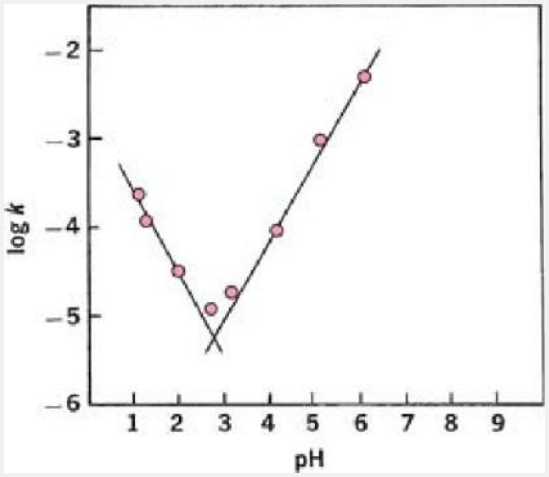


**Fig. 14-8.** Rate–pH profile for the specific acid–base–catalyzed hydrolysis of methyl-*dl*-*o*-phenyl-2-piperidylacetate. (From S. Siegel, L. Lachmann, and L. Malspeis, J. Pharm. Sci. **48,**431, 1959. With permission.)

$$\frac{dP}{dt} = k_0[\text{S}] \qquad \textbf{(14–135)}$$

so that

$$k_{obs} = k_0 \qquad \textbf{(14–136)}$$

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. Because each catalytic pathway leads to an increase in the same product, the rate law for this intermediate pH region can be written as:

$$\frac{dP}{dt} = (k_0 + k_1[\text{H}^+])[\text{S}] \qquad \textbf{(14–137)}$$

or

$$\frac{dP}{dt} = (k_0 + k_2[\text{OH}^-])[\text{S}] \qquad \textbf{(14–138)}$$

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

We can now summarize the pH dependence of specific acid–base–catalyzed reactions in terms of the general rate law,

$$\frac{dP}{dt} = (k_0 + k_1[\text{H}^+] + k_2[\text{OH}^-])[\text{S}] \qquad \textbf{(14–139)}$$

for which

$$k_{obs} = k_0 + k_1[H^+] + k_2[OH^-] \qquad (14\text{–}140)$$

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

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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 **(**14-127**)** and **(**14-134**)**. 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. 14-9).23

Other factors, such as ionic strength or changes in the p$K_a$ 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,24 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.25 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 as

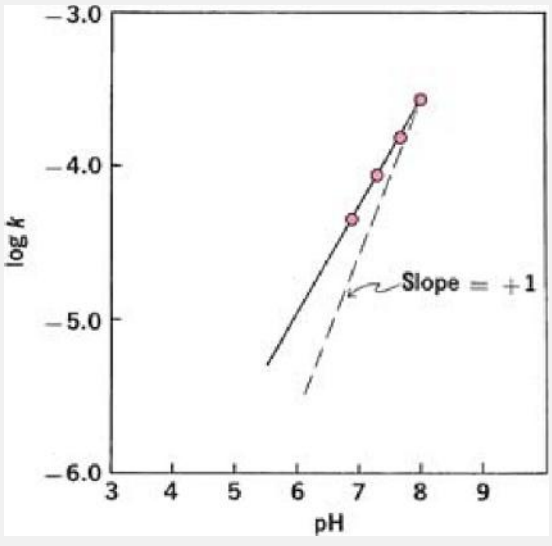


**Fig. 14-9.** Rate–pH profile of a reaction susceptible to general base catalysis. (From E. R. Garrett, J. Pharm. Sci. **49,** 767, 1960. With permission.)

$$-\frac{dG}{dt} = k_0[G] + k_{\mathrm{H}}[\mathrm{H}^+][G] + k_A[\mathrm{HAc}][G] + k_{\mathrm{OH}}[\mathrm{OH}^-][G] + k_B[\mathrm{Ac}^-][G] \qquad \textbf{(14–141)}$$

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

$$k = \frac{dG/dt}{[G]} = k_0 + k_{\mathrm{H}}[\mathrm{H}^+] + k_A[\mathrm{HAc}] + k_{\mathrm{OH}}[\mathrm{OH}^-] + k_B[Ac^-] \qquad \textbf{(14–142)}$$

or, in general,

$$k = k_0 + \Sigma k_i c_i \qquad \textbf{(14–143)}$$

where $c_i$ 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

$$k = k_0 + k_{\mathrm{H}}[\mathrm{H}^+] + k_{\mathrm{OH}}[\mathrm{OH}^-] \qquad \textbf{(14–144)}$$

**Example 14-12**
**Catalytic Coefficient of Glucose Decomposition**

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 can be considered as negligible. The data are substituted in equation (14-144):

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

$$k_{\mathrm{H}} = \frac{0.0080\ \mathrm{hr}^{-1} - 0.0010\ \mathrm{hr}^{-1}}{0.030\ \mathrm{M}} = 0.233\ \mathrm{M}^{-1}\mathrm{hr}^{-1}$$

In 1928, Brönsted26 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

$$k_A = aK_{\mathrm{a}}^{\alpha} \qquad \textbf{(14–145)}$$

and the corresponding equation for catalysis by a weak base is

$$k_B = bK_{\mathrm{a}}^{-\beta} \qquad \textbf{(14–146)}$$

Here $K_a$ 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 **(**14-145**)** and **(**14-146**)** 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.

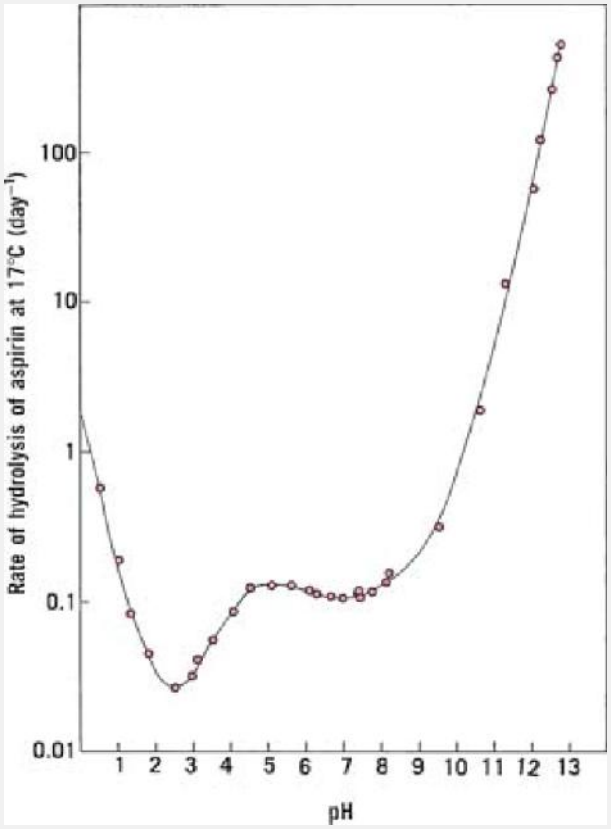
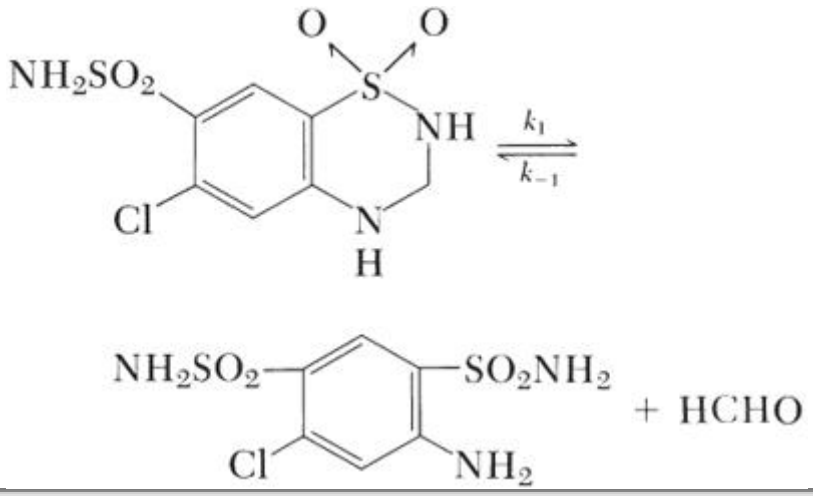



**Fig. 14-10.** Rate–pH profile for the hydrolysis of acetylsalicylic acid at 17°C. (From I. J. Edwards, Trans. Faraday Soc. **46,** 723, 1950.)

Noncatalytic salts can affect the rate constant directly through their influence on ionic strength as expressed by equation **(**14-113**)**. Second, 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 **(**14-145**)** and **(**14-146**)**. 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 $\mu = 0$.

An interesting rate–pH profile is obtained for the hydrolysis of acetylsalicylic acid (Fig. 14-10). In the range of pH from 0 to about 4, there is clearly specific acid–base catalysis and a pH-independent solvolysis, as first reported by Edwards.27 Above pH 4, there is a second, pH-independent region, the plateau extending over at least 3 pH units. Fersht and Kirby28 and others have provided suggestions for the presence of this plateau.

The hydrolysis of hydrochlorothiazide,



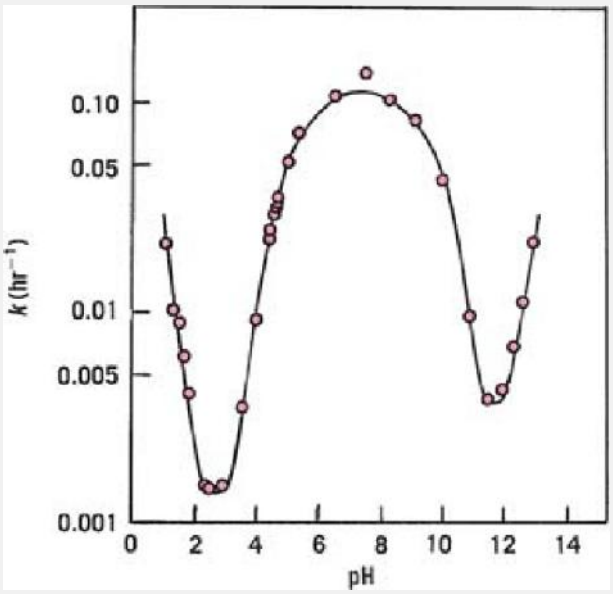




**Fig. 14-11.** The pH profile for the hydrolysis of hydrochlorothiazide. (From J. A. Mollica, C. R. Rohn, and J. B. Smith, J. Pharm. Sci. **58,** 636, 1969. With permission.)

was studied by Mollica et al.29 over a pH range from 1 to 13. The reaction was found to be reversible, the fraction that had reacted at equilibrium, $X_e$, being about 0.4. The pH profile provides a complex curve (Fig. 14-11), indicating multiple steps and an intermediate involved in the reaction.

## Stability of Pharmaceuticals

### *Decomposition and Stabilization of Medicinal Agents*

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.30 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 Poole31 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.32 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 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 hr; in a 50% alcohol solution the half-life is 13 hr.

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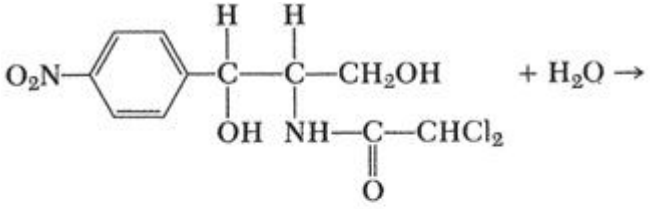
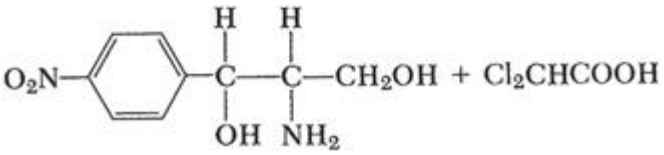
Higuchi et al.33 reported that chloramphenicol decomposed through hydrolytic cleavage of the amide linkage according to the reaction.



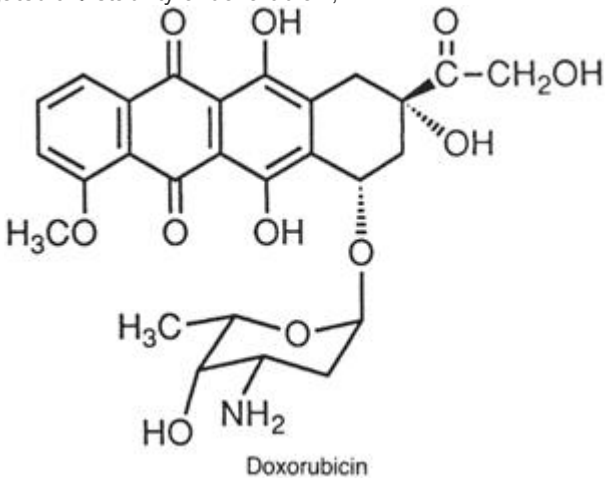
Chloramphenicol



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.34

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.35 investigated the stability of doxorubicin,



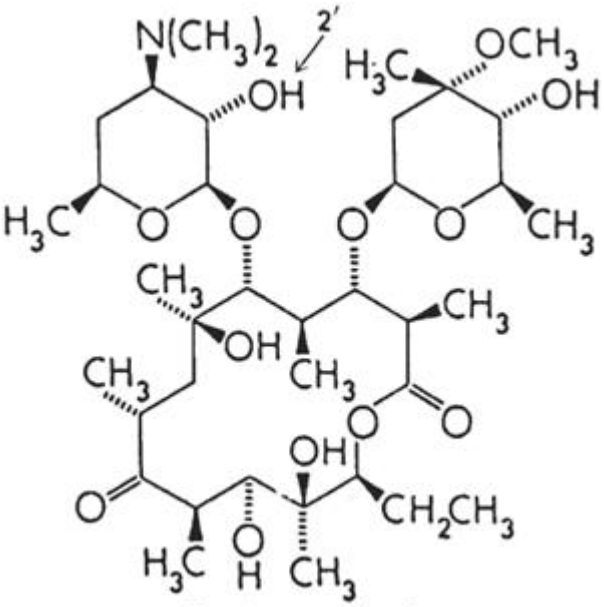
Doxorubicin

in aqueous solution using a stability-indicating high-performance liquid chromatographic assay procedure. Doxorubicin has been used with success against various human neoplasms for the last 20 years. The decomposition of the drug has not been studied in depth because 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 associates35 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 Bundgaard36 studied the hydrolysis of erythromycin and erythromycin esters in aqueous solution:

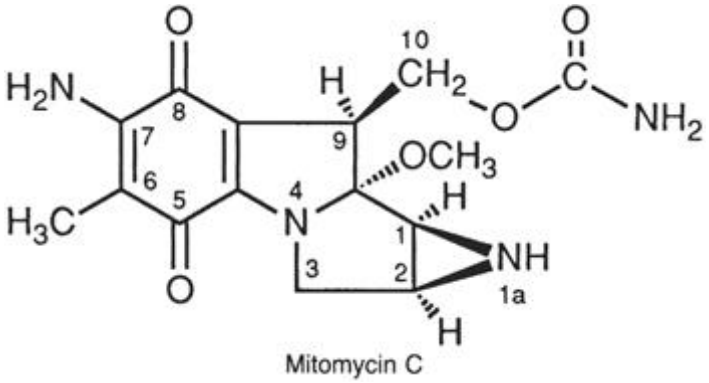



Erythromycin A

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; 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* because they are inactive until erythromycin is released from the esters by enzymatic hydrolysis in the body.

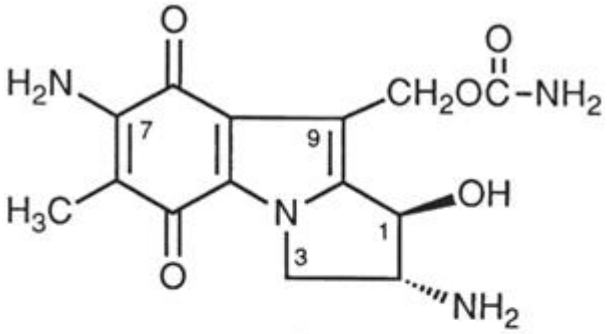
Vinckier et al.37 studied the decomposition kinetics of erythromycin as a function of buffer type and concentration, ionic strength, pH, and temperature. Erythromycin was found to be most stable in a phosphate buffer and least stable in a sodium acetate buffer. Changes in ionic strength showed only a 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 7.5.38

Atkins et al.39 also studied the kinetics of erythromycin decomposition in aqueous acidic and neutral buffers. They concluded that pH is the most important factor in controlling the stability of erythromycin A in acidic aqueous solutions.

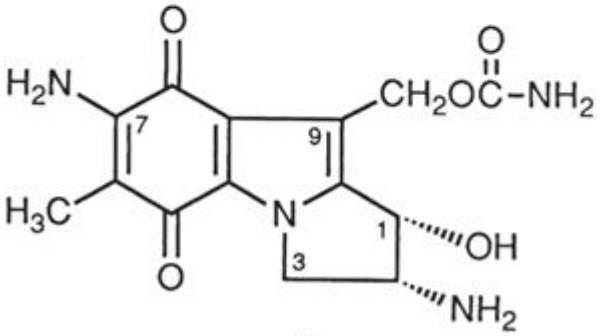



Mitomycin C

The degradation of mitomycin C in acid solution was studied by Beijnen and Underberg.40 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, 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:




I




II

To study the mechanism of degradation the authors designed a high-performance liquid chromatographic 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 three half-lives.

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

$$k = k_0 + k_H[H^+] + k_A[HAc] + k_B[Ac^-] \qquad \textbf{(14–147)}$$

where $k_0$ 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 **(**14-142**)]**. 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 shown in Figure 14-12. In other work, Beijnen and associates40 showed 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 ($MMCH^+$).

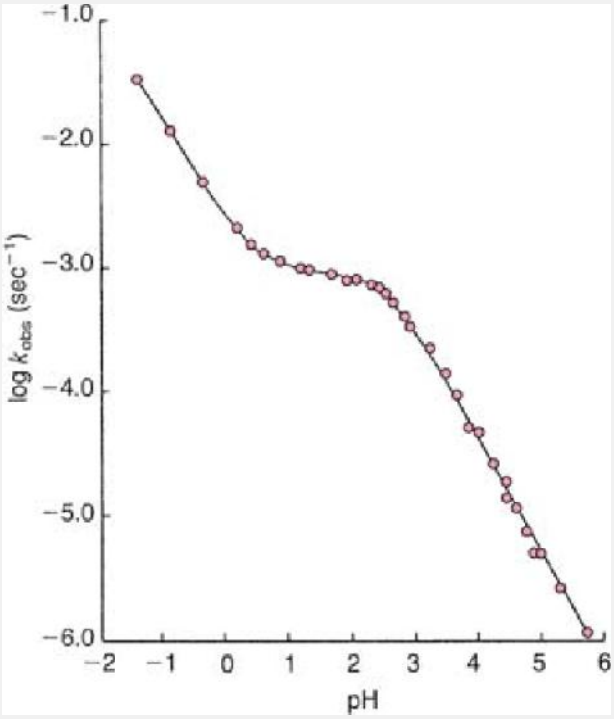
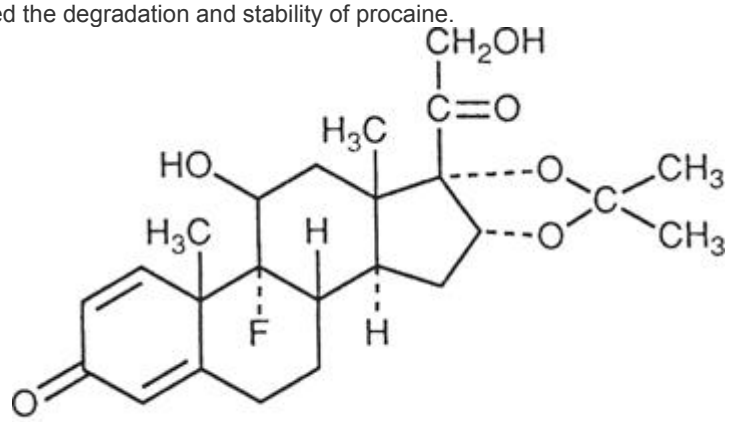



**Fig. 14-12.** The pH–rate constant profile for mitomycin C decomposition at 20°C. (From J. H. Beijnen and W. J. M. Underberg, Int. J. Pharm.**24,** 219, 1985. With permission.)

Procaine decomposes mainly by hydrolysis, the degradation being due primarily to the breakdown of the uncharged and singly charged forms.13 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 Baron17 obtained an activation energy, $E_a$, of 16.8 kcal/mole for procaine at 97.30°C.
Garrett41 reviewed the degradation and stability of procaine.



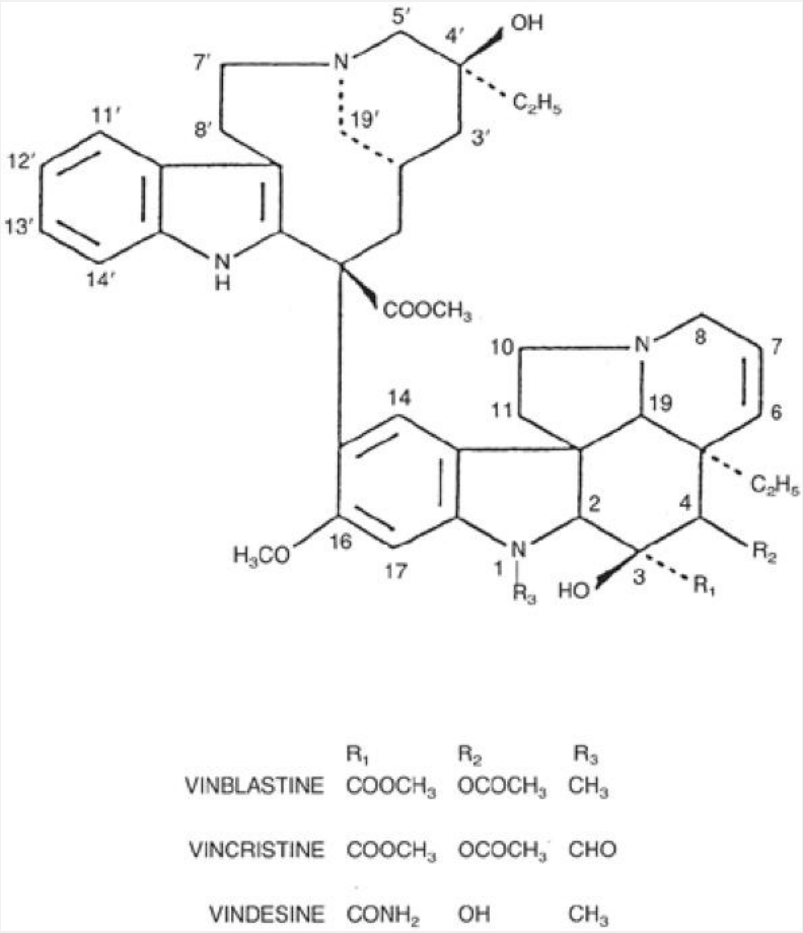

Triamcinolone acetonide

Triamcinolone acetonide, a glucocorticoid (adrenal cortex) hormone, is a potent anti-inflammatory agent when applied topically as a cream or suspension. Gupta42 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, $H_2PO_4^-/HPO_4^{2-}$.




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| VINBLASTINE | $COOCH_3$ | $OCOCH_3$ | $CH_3$ |
| VINCRISTINE | $COOCH_3$ | $OCOCH_3$ | CHO |
| VINDESINE | $CONH_2$ | OH | $CH_3$ |

**Fig. 14-13.** 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. With permission.)

Vincristine and vinblastine are natural alkaloids used as cytotoxic agents in cancer chemotherapy (Fig. 14-13). Vendrig et al.43investigated the degradation kinetics of vincristine sulfate in aqueous solution within the pH range of -1.0 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 **(**14-14**)**] at various pH values to plot the pH profile as seen in Figure 14-14. 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°C to 80°C was assessed using the Arrhenius equation [equation **(**14-72**)** or **(**14-73**)**]. The

activation energy, $E_a$, and the Arrhenius factor, $A$, are given in Table 14-6.

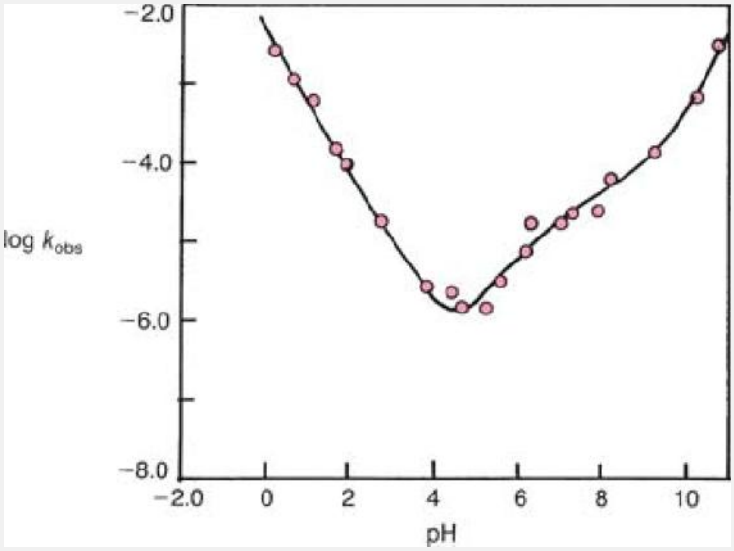



**Fig. 14-14.** Log $k$–pH profile for the decomposition of vincristine. (From D. Vendrig, J. H. Beijnen, O. van der Houwen, and J. Holthuis, Int. J. Pharm. **50,** 194, 1989. With permission.)

**Table 14-6 Activation Energies and Arrhenius Factors for Vincristine at various pH values at 80°C***

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

*Based on D. E. M. M. Vendrig, J. H. Beijnen, O. A. G. J. van der Houwen, and J. J. M. Holthuis, Int. J. Pharm. **50,** 189, 1989.

**Example 14-13**
**Vincristine**

Vendrig et al.43 listed the activation energies in kJ/mole for vincristine from pH 1.2 to 8.2. Convert the following values for $E_a$ to quantities expressed in cal/mole, as found in Table 14-6:

| pH | 1.2 | 3.5 | 5.2 | 7.0 | 8.2 |
|---|---|---|---|---|---|
| $E_a$(kJ/mole) | 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, that of $E_a$ at pH 1.2,

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

or

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

or

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

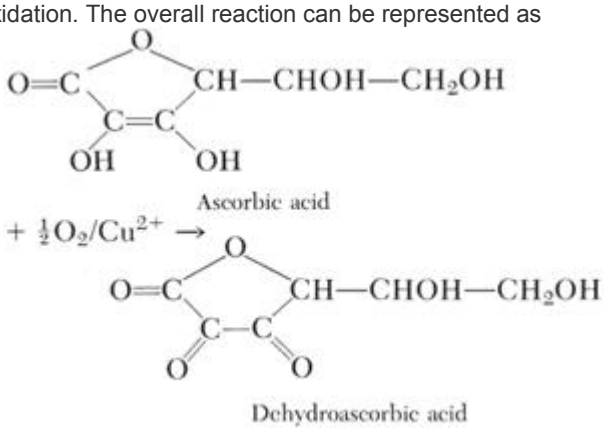
In the *CRC Handbook of Chemistry and Physics*, we find the conversion factor 1 joule = 0.239045 cal; therefore, we can make the direct conversion

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

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 can be represented as




Ascorbic acid

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.44These 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 Dickinson45 suggested a scheme for oxidation of ascorbic acid by the cupric ion and obtained the following equations for the decomposition:

$$-\frac{d[H_2A]}{dt} = k\frac{[Cu^{2+}][H_2A]}{[H^+]^2} \qquad \textbf{(14–148)}$$

and in the integrated form,

$$k = \frac{2.303[H^+]^2}{[Cu^{2+}]t}\log\frac{[H_2A]_0}{[H_2A]} \qquad \textbf{(14–149)}$$

where $[H_2 A]_0$ 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 (14-149), 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 Dickinson45 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.46 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 because $2 \times 10^{-4}$ mole/liter increased the rate of the monovalent ion reaction by a factor of 10,000.

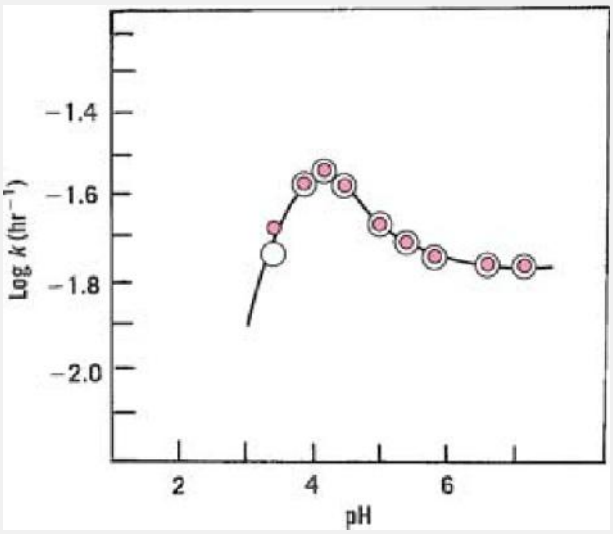



**Fig. 14-15.** The pH profile for the oxidative degradation of ascorbic acid. Key: • = calculated rate constant; ^ = rate constant extrapolated to zero buffer concentration

where only the effect of hydrogen and/or hydroxyl ions is accounted for. (From S. M. Blaug and B. Hajratwala, J. Pharm. Sci. **61,** 556, 1972; **63,** 1240, 1974. With permission.)

Nord47 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 Hajratwala48 observed that ascorbic acid degraded by aerobic oxidation according to the log(rate constant)–pH profile ofFigure 14-15. 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,49 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 $k_1 = 5.7 \times 10^{-6}$ $M^{-1}$ $sec^{-1}$, $k_2 = 1.7$ $sec^{-1}$, and $k_3 = 7.4 \times 10^{-5}$ $M^{-1}$ $sec^{-1}$ in the rate expression

$$k = k_1[H^+] + k_2 + k_3[OH^-] \qquad \textbf{(14–150)}$$

where $k_2$ is the first-order solvent catalysis term, ordinarily written as$k_0$, and $k_1$ and $k_3$ are the catalytic coefficients.

Takamura and Ito50 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 pigments found in higher plants. The flavonoid constituents rutin and hesperidan were used in the past to reduce capillary fragility and bleeding.51 Takamura and Ito50 found that flavonoids inhibited the $Cu^{2+}$-catalyzed oxidation in the following 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.52 They investigated the iron-catalyzed oxidation of ascorbic acid at 35°C at pH values of 4 to 6 and partial pressures of oxygen of 21 kilopascal (kPa) 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.

Akers53 studied the *standard oxidation potentials* 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 Struve54 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 (2-[(4-hydroxyphenyl)amino]-5-methoxybenzenemethanol or 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).55 As shown in Figure 14-16, 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.

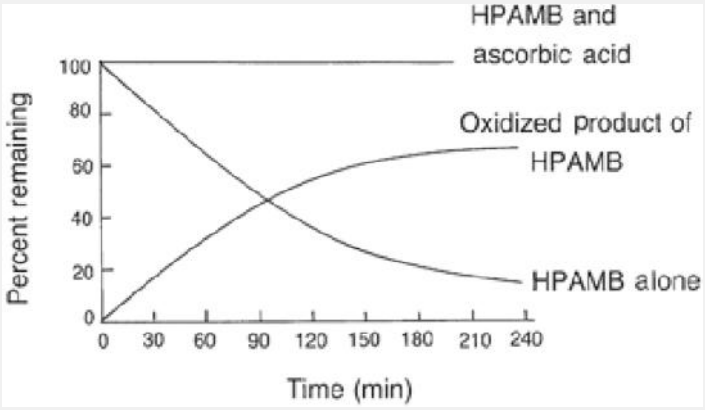



**Fig. 14-16.** Decomposition of HPAMB alone and in the presence of ascorbic acid. The curve for the oxidized product resulting from HPAMB breakdown is also shown. (From A. B. C. Yu and G. A. Portman, J. Pharm. Sci. **79,** 913, 1990. With permission.)

## *Photodegradation*

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 one*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.

Moore56 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 14-17.

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.

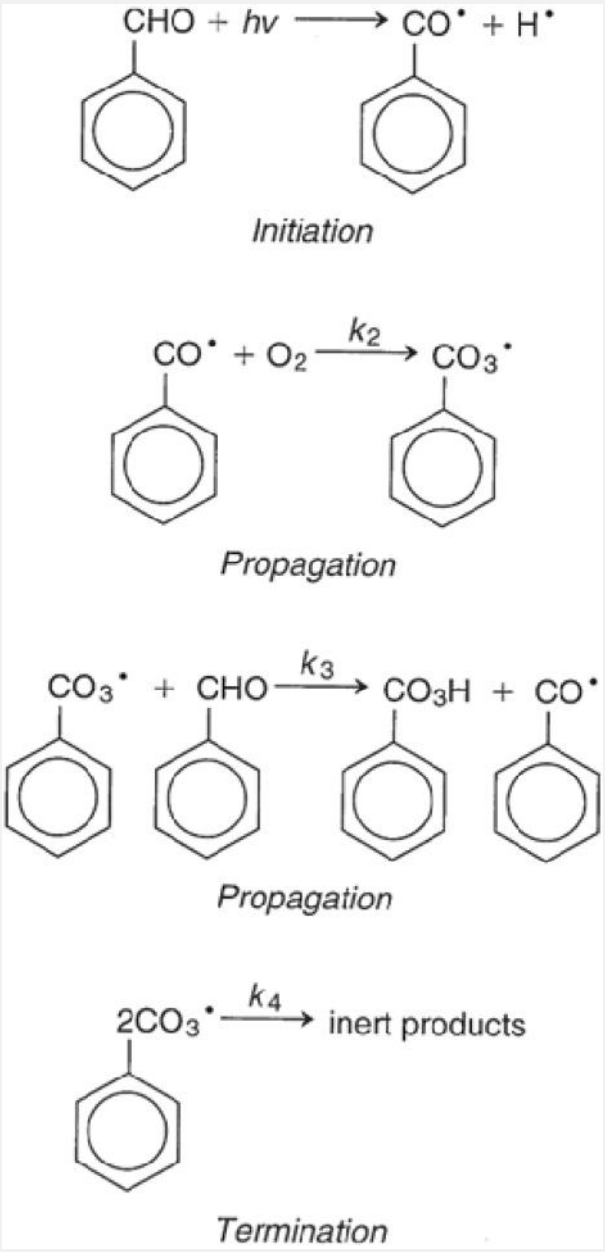



**Fig. 14-17.** Steps in the photooxidation of benzaldehyde. (From D. E. Moore, J. Pharm. Sci. **65,** 1449, 1976. With permission.)

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

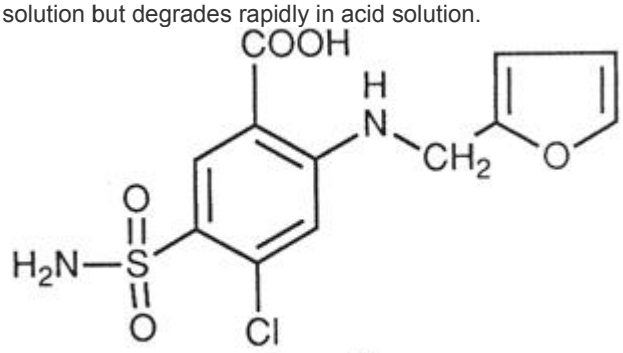
> *n*-propyl gallate. These antioxidants could be classified as retarders rather than inhibitors because they slowed the rate of oxidation but did not inhibit the reaction.

Asker et al.57 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 to produce a photoprotective effect in buffered and unbuffered solutions of sulfathiazole sodium.58 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 hr in direct sunlight. Bundgaard et al.59discovered 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 hr.

Andersin and Tammilehto60 noted that apparent first-order photokinetics had been shown by other workers for adriamycin, furosemide, menadione, nifedipine, sulfacetamide, and theophylline. Photodegradation of the tromethamine (TRIS buffer, aminohydroxymethylpropanediol) salt of ketorolac, an analgesic and anti-inflammatory agent, appeared in ethanol to be an exception60; it showed apparent first-order kinetics at low concentrations, 2.0 µg/mL or less, of the drug (Fig. 14-18a). When the concentration of ketorolac tromethamine became 10 µg/mL or greater, however, the kinetics exhibited non–first-order rates. That is, the plots of drug concentration versus irradiation time were no longer linear but rather were bowed at these higher concentrations (Fig. 14-18b).61

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. Matsuda et al.62 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 ($3.80 \times 10^{-7}$ m). 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.

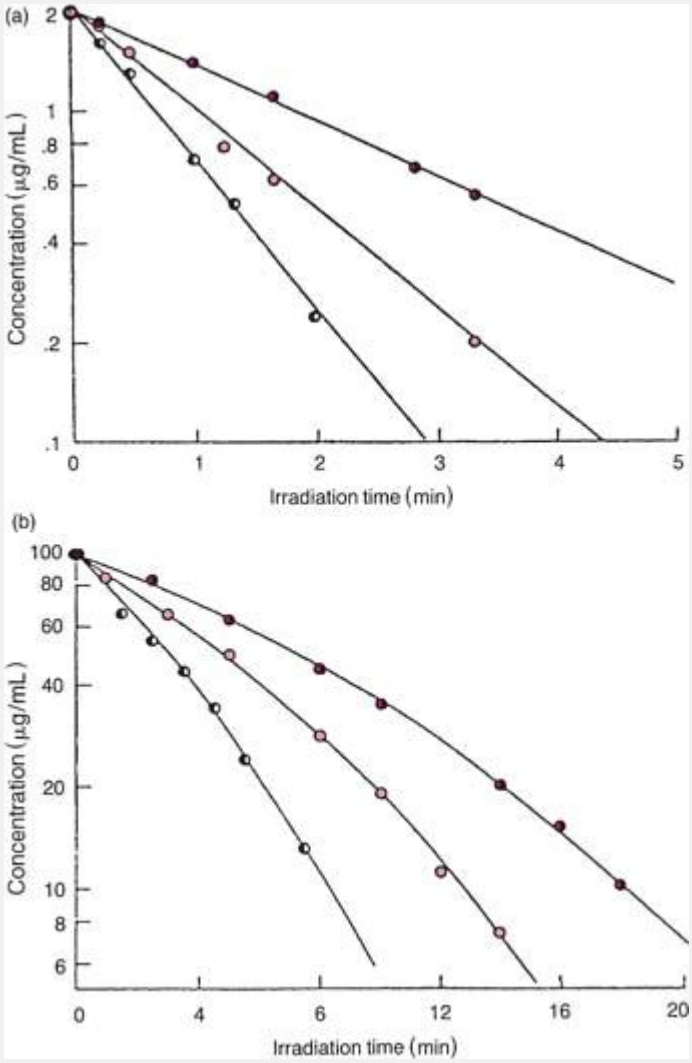



**Fig. 14-18.** A semilogarithmic plot of the photolysis of ketorolac tromethamine in ethyl alcohol. Key: ◐ = under argon; ^ = under air; [circle with right half black] = under oxygen. (*a*) At low drug concentrations; (*b*) at high drug concentrations. (From L. Gu, H. Chiang, and D. Johnson, Int. J. Pharm. **41,** 109, 1988. With permission.)

The photosensitivity of the dye FD&C Blue No. 2 causes its solution to fade and gradually to become colorless. Asker and Collier63studied 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 because 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 Colbert64 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 following 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 Kowarski65 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 Jackson66 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.

## *Accelerated Stability and Stress Testing*

The Federal Food, Drug, and Cosmetic Act requires that manufacturers establish controls for the manufacture, processing, packing, and holding of drug products to ensure their safety, identity, strength, quality, and purity [§501(a)(2)(B)]. Requirements for these controls, also known as current good manufacturing practices, are established and monitored by the Food and Drug Administration (FDA). Stability studies should include testing of those attributes of the drug substance or drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biologic, and microbiologic attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). As part of the current good manufacturing practice regulations, the FDA requires that drug products bear an expiration date determined by appropriate stability testing (21 Code of Federal Regulations 211.137 and 211.166). The stability of drug products needs to be evaluated over time in the same container-closure system in which the drug product is marketed. In some cases, accelerated stability studies can be used to support tentative expiration dates in the event that full shelf-life studies are not available. When a manufacturer changes the packaging of a drug product (e.g., from a bottle to unit dose), stability testing must be performed on the product in its new packaging, and expiration dating must reflect the results of the new stability testing. Accelerated stability studies are designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes. Stress testing of the drug substance or drug product can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

**Key Concept**

**Stress Testing**

Stress testing to elucidate the intrinsic stability of the *drug substance* is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing. The testing typically includes the effects of temperature [in 10°C increments (e.g., 50°C–60°C) above that for accelerated testing], humidity (e.g., 75% relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance.

Stress testing of the *drug product* is undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing and specific testing of certain products (e.g., metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

The method of accelerated testing of pharmaceutical products based on the principles of chemical kinetics was demonstrated by Garrett and Carper.3 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 shown in Figure 14-19 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 14-20, 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.



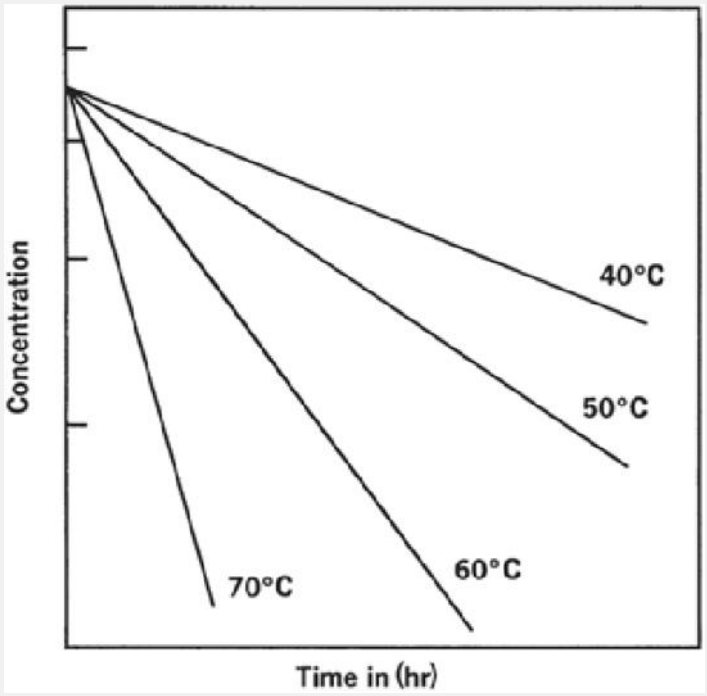



**Fig. 14-19.** Accelerated breakdown of a drug in aqueous solution at elevated temperature.

**Example 14-14**
**Expiration Dating**

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 $2.09 \times 10^{-5}$ $hr^{-1}$ 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?

We have

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

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

Free and Blythe and, more recently, Amirjahed67 and his associates suggested a similar method in which the fractional life period (Example 14-2) 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 14-21 and 14-22. As observed in Figure 14-21, 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 14-22, 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 14-21 result in a $t_{90}$ value of 199 days. Shelf life and expiration dates are estimated in this way; Baker and Niazi68 pointed out limitations of the method.

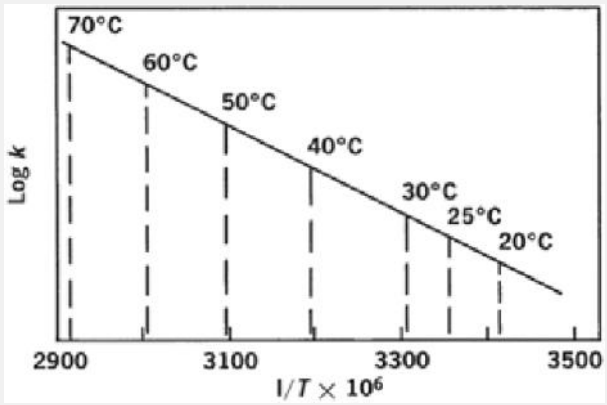



**Fig. 14-20.** Arrhenius plot for predicting drug stability at room temperatures.

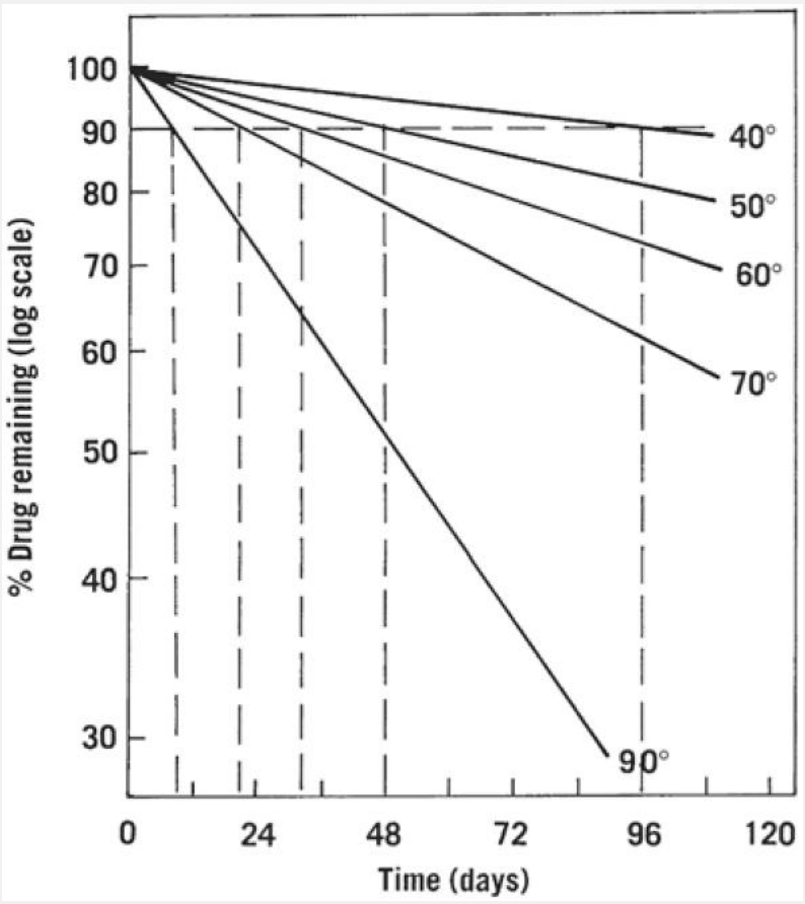



**Fig. 14-21.** Time in days required for drug potency to fall to 90% of original value. These times, designated $t_{90}$, are then plotted on a log scale in Figure 14-22.

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.

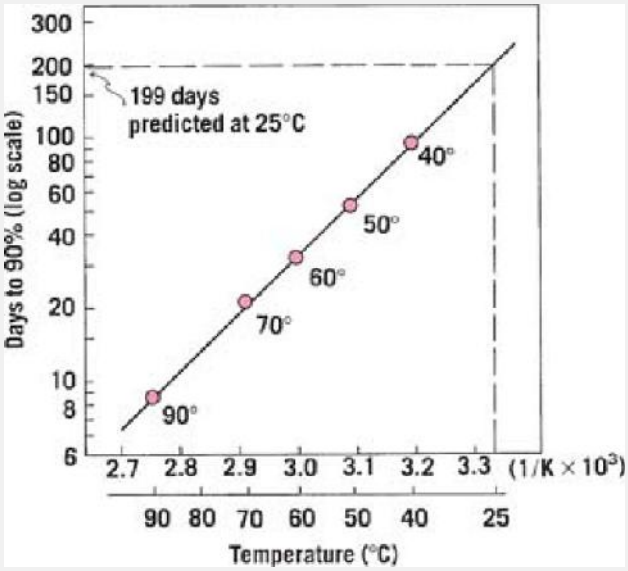



**Fig. 14-22.** A log plot of $t_{90}$ (i.e., time to 90% potency) on the vertical axis against reciprocal temperature (both Kelvin and centigrade scales are shown) on the horizontal axis.

An improved approach to stability evaluation is that of nonisothermal kinetics, introduced by Rogers[69] 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

$$1/T = 1/T_0 + at \qquad \textbf{(14–151)}$$

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 $t$ can be written as

$$\ln k_t = \ln k_0 - \frac{E_a}{R}\left(\frac{1}{T_t} - \frac{1}{T_0}\right) \qquad \textbf{(14–152)}$$

and substituting (14-151) into (14-152) yields

$$\ln k_t = \ln k_0 - \frac{E_a}{R}at \qquad \textbf{(14–153)}$$

Because 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,[70,71,72,73] and it is now possible to change the heating rate during a run or combine a 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 reemphasized 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[74] 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.75 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 Garrett74 and Westlake.76

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 prediction 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.

## *Containers and Closures*

The information for this section is largely taken from the FDA Guidances for Containers and Closures. The interested student should refer to the specific guidances for additional information. A container closure or packaging system refers to the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. Packaging components are typically made from glass, high-density polyethylene resin, metal, or other materials. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals), overwraps, administration accessories, and container labels. A package or market package refers to the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink wrap). A market package is the article



provided to a pharmacist or retail customer upon purchase and does not include packaging used solely for the purpose of shipping such articles. There are many issues that relate to container closure systems, including protection, compatibility, safety, and performance of packaging components and/or systems. The purpose of this section is to raise the student's awareness of the stability aspects related to container closure systems.

The United States Pharmacopeial Convention has established requirements for containers that are described in many of the drug product monographs in *United States Pharmacopeia* (USP). For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well closed, or light-resistant). For injectable products, materials of construction are also addressed (e.g., “Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light”). These requirements are defined in the General Notices and Requirements (Preservation,

Packaging, Storage, and Labeling) section of the USP. The requirements for materials of construction are defined in the General Chapters of the USP.

The type and extent of stability information required for a particular drug product depends on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid because a liquid-based dosage form is more likely to interact with the packaging components. The suitability of a container closure system for a particular pharmaceutical product is ultimately proven by full shelf-life stability studies. A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a reduction in the quality of that dosage form over its shelf life. As discussed earlier in this chapter, there are numerous causes of degradation such as exposure to light, loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth. Not every drug product is susceptible to degradation by all of these factors. Not all drug products are light sensitive. Not all tablets are subject to loss of quality due to absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Light protection is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The USP test for light transmission is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid- and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the USP monograph recommendation. Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., due to the buildup of pressure during storage). Leaks can also occur in tubes due to a failure of the crimp seal. Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of a low-density polyethylene bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

## *Biotechnology Products*

Biotechnological/biologic products have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence, of biologic activity is dependent on noncovalent as well as covalent forces. Examples of these products are cytokines (interferons, interleukins, colony-stimulating factors, tumor necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. These products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. To ensure maintenance of biologic activity and to avoid degradation, stringent conditions for their storage are usually necessary. The evaluation of stability may necessitate complex analytical methodologies. Assays for biologic activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit their use. The shelf lives of biotechnological/biologic products may vary from days to several years. With only a few exceptions, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. This takes into account the fact that degradation of biotechnological/biologic products may not be governed by the same factors during different intervals of a long storage period. Therefore, if the

expected shelf life is within this range, the FDA makes certain recommendations in their Guidance to Industry. When shelf lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter. For products with proposed shelf lives of greater than 1 year, the studies should be conducted every 3 months during the first



year of storage, every 6 months during the second year, and annually thereafter.

## *Solid-State Stability*

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,77 Lachman,78 and Carstensen,79 and is discussed here briefly.

### Pure Solids

The decomposition of pure solids, as contrasted with the more complex mixture of ingredients 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 Musa80 described the decomposition of solid benzoic acid derivatives, such as aminobenzoic acid, which broke down into a liquid, aniline, and a gas, carbon dioxide. The plot of concentration of decomposed drug versus time yielded a sigmoidal curve (Fig. 14-23). 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 inFigure 14-23. It is often difficult 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 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. Tardif81 observed that ascorbic acid decomposed in tablets by a pseudo–first-order reaction.

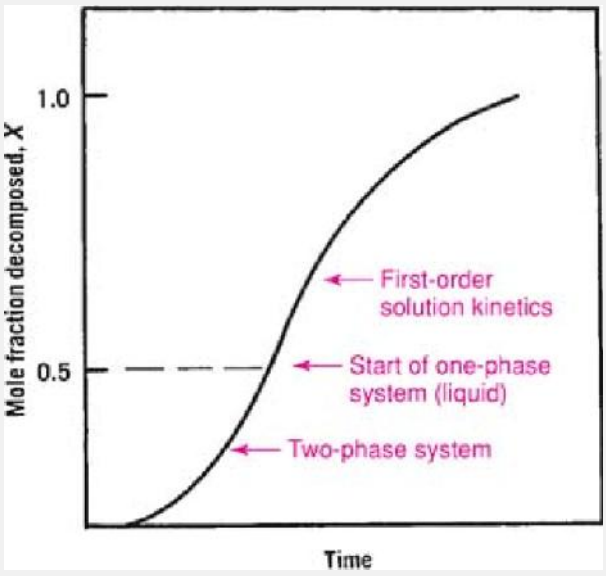



**Fig. 14-23.** Decomposition of a pure crystalline solid such as potassium permanganate, which involves gaseous reaction products. (From J. T. Carstensen, J. Pharm. Sci. **63,** 4, 1974. With permission.)

In tablets and other solid dosage forms, the possibility exists for solid–solid interaction. Carstensen et al.82 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 by thin-layer chromatography. The method is qualitative but, in industrial preformulation, provides a useful screening technique for uncovering possible incompatibilities between active ingredient and pharmaceutical additives before deciding on a suitable dosage form.

Lach and associates83 used diffuse reflectance spectroscopy to measure interactions of additives and drugs in solid dosage forms. Blaug and Huang84 used this spectroscopic technique to study the interaction of spray-dried lactose with dextroamphetamine sulfate.

Goodhart and associates85 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 associates86 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,87 solid-state reactions exhibit characteristics quite different from reactions in the liquid or gaseous state because the molecules of the solid are in the crystalline state. The quantitative and theoretical approaches to the study of solid-state kinetics are at their frontier, which, when opened, will probably reveal a new and fruitful area of chemistry and drug science. The authors87 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 are 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, of 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 Campen87 reviewed the experimental methods used in solid-state kinetics, including reflectance spectroscopy, x-ray diffraction, thermal analysis, microscopy, dilatometry, and gas pressure–volume analysis. Their 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.



## Chapter Summary

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. This fundamental topic was covered in this chapter. This chapter introduces the rates and mechanisms of reactions with particular emphasis on decomposition and stabilization of drug products. It is essential for pharmacists and pharmaceutical scientists to study, understand, and interpret conditions of instability of pharmaceutical products as well as to be able to offer solutions for the stabilization of these products. It is also essential for them to define reaction rate, reaction order, and molecularity, while understanding and applying apparent zero-order kinetics to the practice of pharmacy. By the conclusion of this chapter and some practice, the student should be able to calculate half-life and shelf life of pharmaceutical products and drugs as well as interpret pH–rate profiles and kinetic data. You should also be able to describe the influence of temperature, ionic strength, solvent, pH, and dielectric constant on reaction rates. Be

familiar with $Q_{10}$ calculations as they aid in the understanding of the relationship between reaction rate constant and temperature. Finally, stabilizing pharmaceutical agents is critical for making acceptable products in the industrial and community pharmacy setting. Therefore, you should understand stabilization techniques, stability testing protocols, and regulatory requirements.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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## Recommended Readings

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K. Huynh-Ba (Ed.), *Handbook of Stability Testing in Pharmaceutical Development: Regulations, Methodologies and Best Practices*, 1st Ed., Springer, New York, 2008.

*Notice that log $k$ + 2 is plotted on the vertical axis of Figure 14-6. This is a convenient way of eliminating negative values along the axis. For example, if $k = 1.0 \times 10^{-2}$, $2.0 \times 10^{-2}$, etc., the logarithmic expressions are log 1.0 + log $10^{-2}$, log 2.0 + log $10^{-2}$, etc., or 0.0 - 1 = -1, 0.3 - 1 = -1.7, etc. The negative signs can be eliminated along the vertical axis if 2 is added to each value; hence the label, log $k$ + 2.

### Chapter Legacy

**Fifth Edition:** published as Chapter 15 (Chemical Kinetics and Stability). Updated by Patrick Sinko.
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