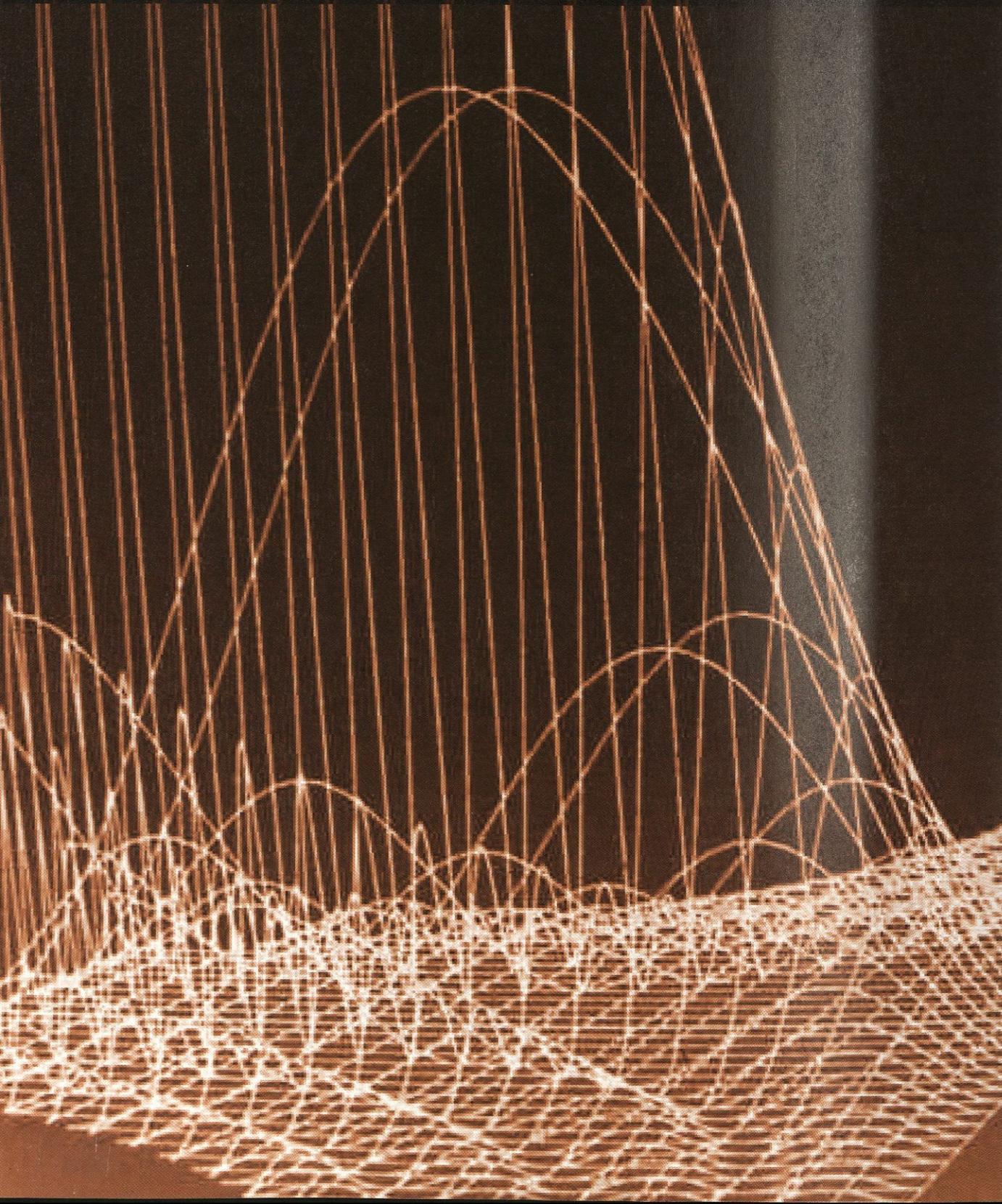


# PART IV

## KINETICS AND CATALYSIS

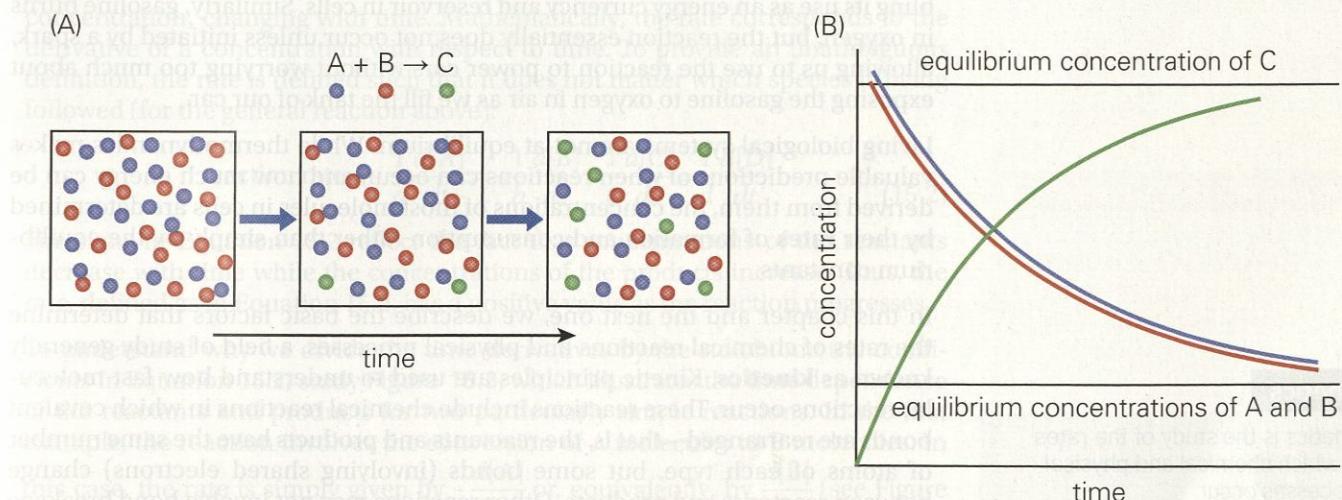


## The Rates of Molecular Processes

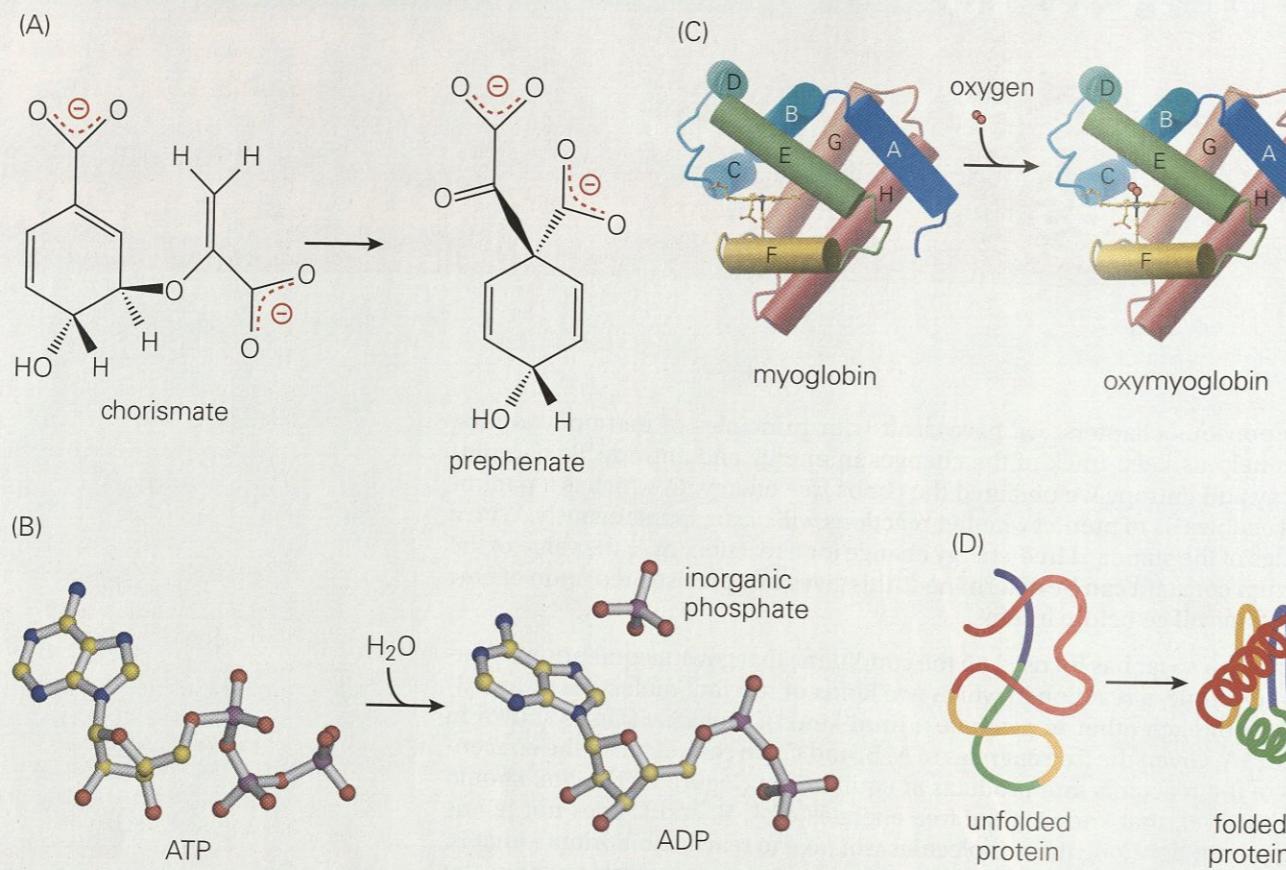
In the previous chapters, we have dealt with principles of thermodynamics, which help us keep track of the changes in energy and entropy. By combining energy and entropy we obtained the Gibbs free energy,  $G$ , which is a parameter that enables us to predict whether reactions will occur spontaneously. With a knowledge of the standard free-energy change for a reaction,  $\Delta G^\circ$ , the value of the equilibrium constant can be determined. This gives us a precise prediction of how far a reaction will go before it stops.

The discussion so far has focused on the conditions that govern equilibrium. Consider, for example, a reaction in which two kinds of reactant molecules (A and B) combine with each other to generate a third kind of molecule (C), as shown in **Figure 15.1A**. Given the free energies of A, B, and C, we can calculate the concentrations of the reactants and products at equilibrium (Figure 15.1B). You should realize, however, that knowing the free energies of A, B, and C does not tell us anything about how *long* these molecules will take to reach equilibrium—that is, how fast the reaction will occur. If we mix the reactants and products together, the concentrations of A, B, and C will relax towards their equilibrium values, as shown in Figure 15.1B. But *time* is a variable that we ignored in our analysis of energy, entropy, and free energy and, without additional information, we cannot predict how long the reaction will take.

Our intuition may tell us that if a reaction is very favorable—that is, if it is associated with a large, negative  $\Delta G^\circ$  value—then it will occur rapidly. While such reactions can sometimes be fast, there is no general correlation between how



**Figure 15.1 Time as a variable in the progress of a reaction.** (A) Schematic representation of a chemical reaction in which A and B molecules react with each other to produce C molecules. (B) The time course of the reaction. The system is initially not at equilibrium, but with time, A and B molecules are converted to C molecules until equilibrium is reached. Knowing thermodynamic parameters, such as the free-energy change of the reaction, does not inform us about how fast the reaction will go.



**Figure 15.2** Different kinds of reactions. (A) The conversion of chorismate to prephenate, an intramolecular rearrangement. (B) The hydrolysis of ATP. (C) The binding of oxygen to myoglobin. (D) Protein folding.

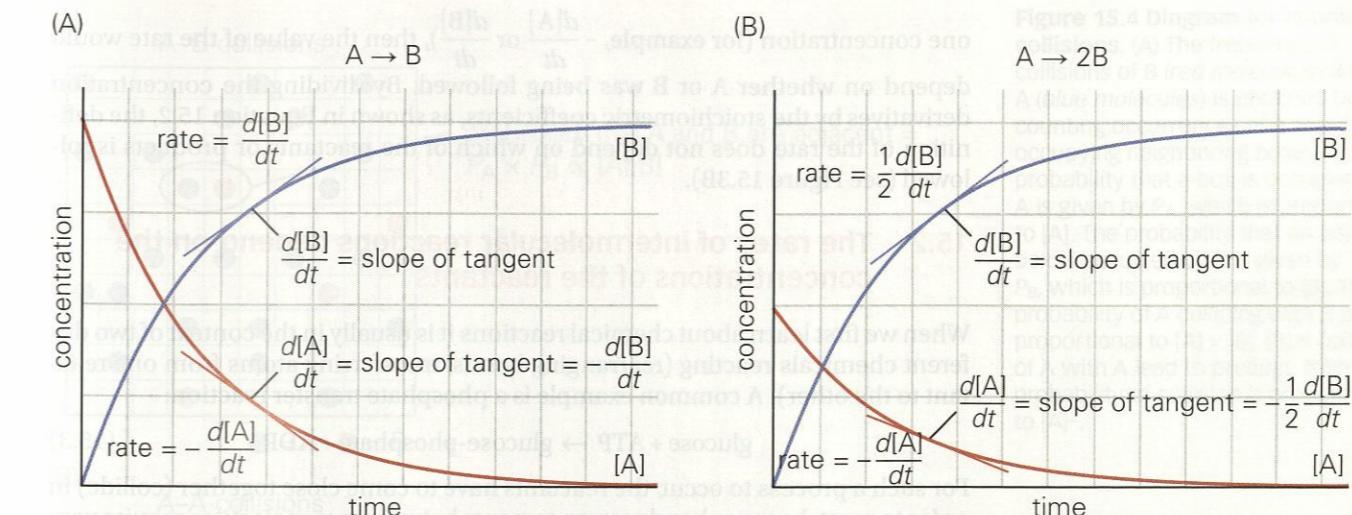
favorable a reaction is in terms of the change in free energy and how fast it occurs. Additionally, the same reaction may occur at very different rates under different circumstances. This is indeed fortunate, because it allows reactions occurring in biological systems to be controlled. For example, the hydrolysis of ATP to give ADP and phosphate by addition of water is favorable in terms of  $\Delta G^\circ$ , as discussed in previous chapters, but the reaction occurs very slowly unless catalyzed by interactions with proteins in the cell. Thus, ATP is not rapidly hydrolyzed by water, enabling its use as an energy currency and reservoir in cells. Similarly, gasoline burns in oxygen, but the reaction essentially does not occur unless initiated by a spark, allowing us to use the reaction to power cars without worrying too much about exposing the gasoline to oxygen in air as we fill the tank of our car.

Living biological systems are not at equilibrium. While thermodynamics makes valuable predictions of when reactions can occur, and how much energy can be derived from them, the concentrations of most molecules in cells are determined by their **rates** of formation and consumption rather than simply by the equilibrium constants.

In this chapter and the next one, we describe the basic factors that determine the rates of chemical reactions and physical processes, a field of study generally known as **kinetics**. Kinetic principles are used to understand how fast molecular reactions occur. These reactions include chemical reactions in which covalent bonds are rearranged—that is, the reactants and products have the same number of atoms of each type, but some bonds (involving shared electrons) change between reactants and products. Other reactions may not involve bond breakage or formation. Such processes include the rotational isomerization of molecules, the association (binding) of one molecule to another, the folding of a protein, or the release of light from an excited molecule (fluorescence). A few examples of different kinds of reactions are shown in Figure 15.2.

### Kinetics

Kinetics is the study of the rates at which chemical and physical processes occur.



## A. GENERAL KINETIC PRINCIPLES

### 15.1 The rate of reaction describes how fast concentrations change with time

A general chemical reaction can be written as follows:

$$aA + bB \rightarrow cC + dD \quad (15.1)$$

The uppercase letters represent the reactants and products. The lowercase letters are integers reflecting the stoichiometry (that is,  $a$ ,  $b$ ,  $c$ , and  $d$  are stoichiometric coefficients whose values are such that the reaction is balanced and atoms are neither created nor destroyed). Note that the arrow in Equation 15.1 points in only one direction. In principle, any reaction can go forward or backward, but we first focus our analysis on the forward direction, for simplicity, and later extend it to include both directions. A general reaction may have any number of reactants and/or products, but the simple reaction depicted in Equation 15.1 suffices to introduce the concept of reaction rates.

The rate of the reaction is how fast the reactant changes to product with time. Usually we think in terms of the amount in a particular volume of interest—that is, the concentration, changing with time. Mathematically, the rate corresponds to the derivative of a concentration with respect to time. To provide an unambiguous definition, the rate is defined such that it does not matter which species is being followed (for the general reaction above):

$$\text{reaction rate} = -\frac{1}{a} \frac{d[A]}{dt} = -\frac{1}{b} \frac{d[B]}{dt} = \frac{1}{c} \frac{d[C]}{dt} = \frac{1}{d} \frac{d[D]}{dt} \quad (15.2)$$

The signs in Equation 15.2 reflect the fact that concentrations of the reactants decrease with time while the concentrations of the products increase. Thus, the rate, defined as in Equation 15.2, has a positive value as the reaction progresses.

To understand why we divide the time derivatives by the stoichiometric coefficients in Equation 15.2, study Figure 15.3, which illustrates the time dependence of the reactants and products for two particularly simple reactions. In the first example, the reaction involves the conversion of  $A$  molecules to  $B$  molecules. In this case, the rate is simply given by  $-\frac{d[A]}{dt}$  or, equivalently, by  $\frac{d[B]}{dt}$  (see Figure 15.3A).

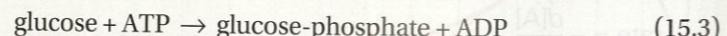
In the second example, one molecule of  $A$  is converted to two molecules of  $B$ . This means that the concentration of  $B$  increases twice as rapidly as the concentration of  $A$  decreases. If we were to define the rate as simply the time derivative of

**Figure 15.3** The dependence of reaction rates on stoichiometry. (A) The time dependence of the concentrations of reactants and products for the reaction  $A \rightarrow B$  is shown. The rate of the reaction is the derivative of the concentration of product,  $[B]$ , with time, which has a positive value. Because the stoichiometries of  $A$  and  $B$  are equal, the rate is equal to the negative of the derivative of  $[A]$  with time. (B) Concentrations of reactants and products for the reaction  $A \rightarrow 2B$ . The concentration of  $B$  increases twice as rapidly as the decrease in concentration of  $A$ . The rate of the reaction is defined as  $\frac{1}{2} \frac{d[B]}{dt}$ , which is the same as  $-\frac{d[A]}{dt}$ .

one concentration (for example,  $-\frac{d[A]}{dt}$  or  $\frac{d[B]}{dt}$ ), then the value of the rate would depend on whether A or B was being followed. By dividing the concentration derivatives by the stoichiometric coefficients, as shown in Equation 15.2, the definition of the rate does not depend on which of the reactants or products is followed (see Figure 15.3B).

## 15.2 The rates of intermolecular reactions depend on the concentrations of the reactants

When we first learn about chemical reactions it is usually in the context of two different chemicals reacting (rearranging bonds, transferring atoms from one reactant to the other). A common example is a phosphate transfer reaction:



For such a process to occur, the reactants have to come close together (collide) in order to react, because bond rearrangements between two molecules require very close proximity. The probability of the reaction occurring per unit time should therefore be related to the rates of collisions. The rates at which molecules collide with each other will be examined in detail in Chapter 17, but for now we just need to know how the rates of reaction depend on concentration.

In a mixture of molecules A and B, the frequency with which A-B collisions occur is proportional to the concentrations [A] and [B]. We can understand why this is so by using the approach applied in Chapter 7 to calculate entropy. We divide space into boxes that may be occupied or not, as shown in Figure 15.4. The probability of a box being occupied by an A molecule is  $P_A = N_A/n_{\text{total}}$ , where  $N_A$  is the number of A molecules in the box, and  $n_{\text{total}}$  is the number of boxes. The concentration, [A], is proportional to  $N_A/n_{\text{total}}$ . Likewise, the probability of a box being occupied by a B molecule is  $P_B = N_B/n_{\text{total}}$  and [B] is proportional to  $N_B/n_{\text{total}}$ . If we consider that a collision occurs when two neighboring boxes are occupied by A and by B, then the probability of this happening is  $P_A P_B$  (Figure 15.4). The collision rate will therefore be proportional to the product of the concentrations, [A][B]. If the formation of the collision complex, A•B, is all that is required for the reaction to proceed, then the reaction rate will also be proportional to [A][B].

## 15.3 Rate laws define the relationship between the reaction rates and concentrations

The relationship of the rate of a reaction to the concentrations of the chemical species that are involved in the reaction is called the **rate law** or **rate equation**. Rate equations can be derived from knowing the fundamental steps that occur during a reaction, as discussed in subsequent sections of this chapter. For example, if two molecules, A and B, combine and react directly to yield a product molecule, C, then the reaction,  $A + B \rightarrow C$ , is called an **elementary reaction**. We would expect the rate of this reaction to be proportional to the product of the concentrations of the reactants, [A][B] (Figure 15.5A).

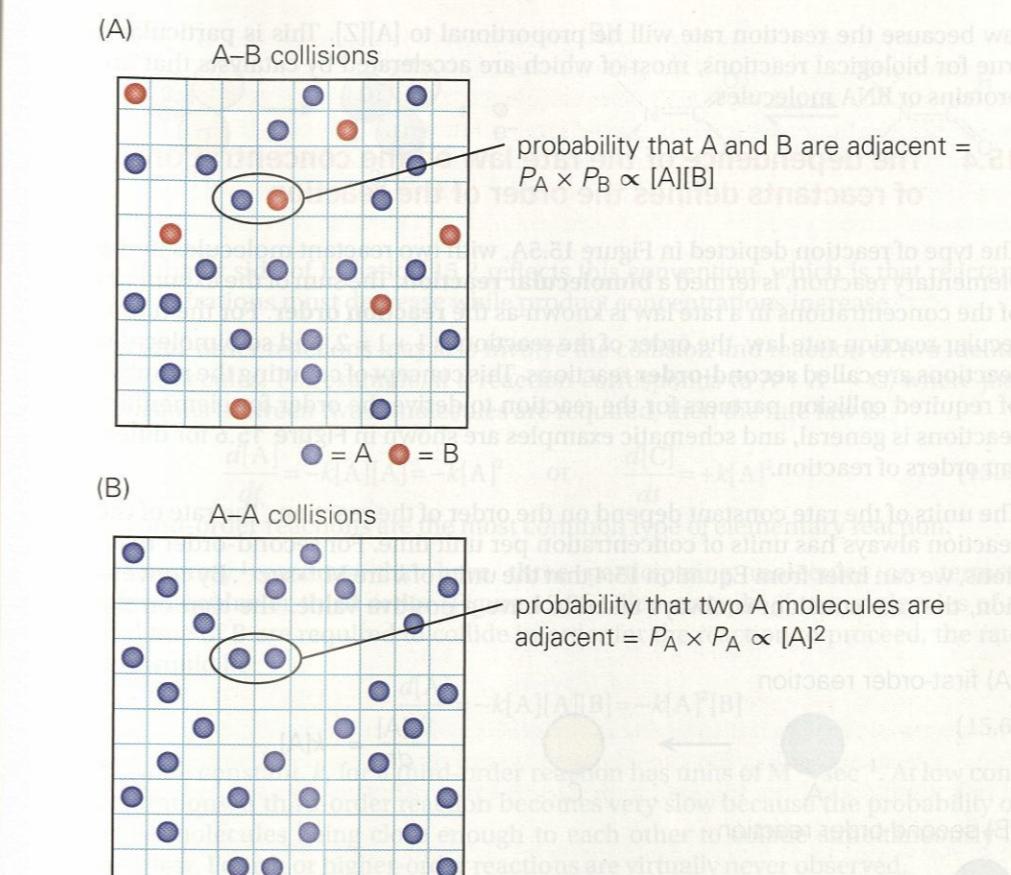
The rate law is the differential equation that describes the rate of change of concentration with time. For this elementary reaction, the rate law is:

$$\text{rate} = -\frac{d[A]}{dt} = \frac{d[C]}{dt} = k[A][B] \quad (15.4)$$

The proportionality constant,  $k$ , is called the **rate constant** of the reaction. What is the physical significance of the rate constant,  $k$ ? The rate constant must be related to the frequency of collisions between the reactants, as discussed above. For example, conditions in which molecules move faster will lead to more frequent collisions and therefore faster reactions. The rates of movement of molecules, determined by factors like the viscosity, are discussed in Chapter 17 in some detail.

### Rate laws and rate constants

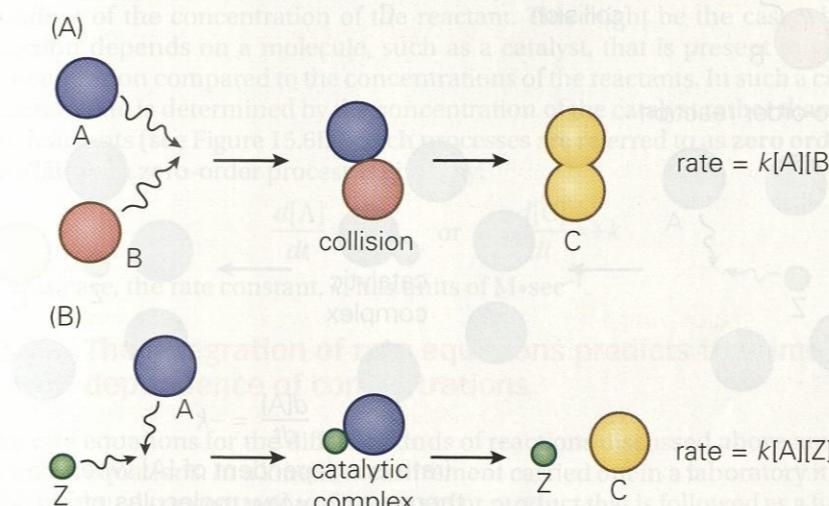
A rate law or **rate equation** is a differential equation that specifies how the reaction rate depends on the concentrations of species present in the reaction mixture including, but not limited to, reactants and products. The rate constant,  $k$ , is a proportionality constant between the reaction rate and the concentrations of species that determine the reaction rate.



**Figure 15.4 Diagram for counting collisions.** (A) The frequency of collisions of B (red molecules) with A (blue molecules) is obtained by counting occurrences of A and B occupying neighboring boxes. The probability that a box is occupied by A is given by  $P_A$ , which is proportional to [A]. The probability that an adjacent box is occupied by B is given by  $P_B$ , which is proportional to [B]. The probability of A colliding with B is proportional to  $[A] \times [B]$ . (B) If collisions of A with A lead to product, then the probability of collision is proportional to  $[A]^2$ .

The rate constant also reflects the fraction of collisions that actually lead to product formation, which is often very small. Most collisions are unproductive—that is, the two reactant molecules collide and then simply separate again without having undergone a reaction. The fraction of collisions that are productive depends on the chemical structure of the reactants and the energetics of the reaction. A more detailed analysis of the physical meaning of the rate constant is given in part C of this chapter.

Although it might be natural to think that the rate law would depend only on the concentrations of the reactants in the overall reaction, there are often other molecules present that do not appear in the overall reaction but still greatly affect the rate of reaction. For example, consider a reaction in which A molecules are converted to C molecules, but only if they collide with a catalyst, Z (see Figure 15.5B). Although the catalyst is unchanged by the reaction, it enters into the rate



### Elementary reaction

An elementary reaction represents the most basic step used to describe a reaction process. Many chemical mechanisms result from the combination of several elementary steps.

**Figure 15.5 Rate laws.** (A) Two molecules, A and B, collide to form a product molecule, C. The elementary reaction is  $A + B \rightarrow C$ , and the rate law (shown on the right) depends on the concentrations of A and B. (B) The rate law can depend on the concentrations of molecules that do not enter into the overall reaction. In this example, an A molecule is converted to a C molecule, but only when it encounters a catalyst (Z). The rate law depends on the concentrations of both A and Z.

**Reaction order**

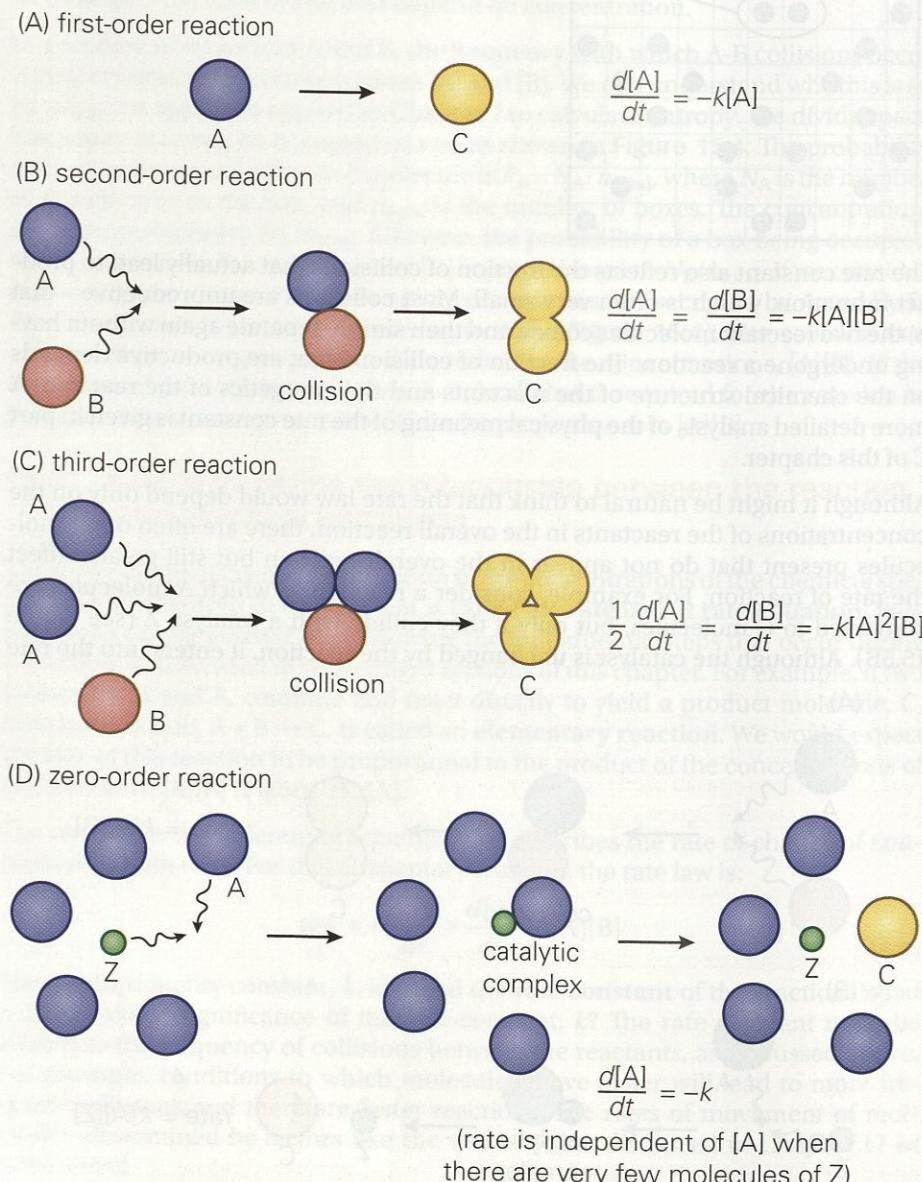
The order of the reaction is the sum of the concentration exponents in the rate law, which is the number of molecules colliding if it is an elementary reaction. An elementary bimolecular reaction has a reaction order of two.

law because the reaction rate will be proportional to  $[A][Z]$ . This is particularly true for biological reactions, most of which are accelerated by catalysts that are proteins or RNA molecules.

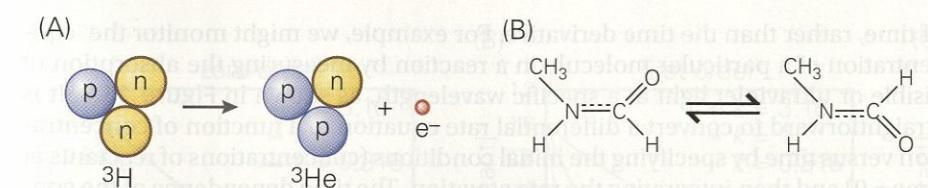
#### 15.4 The dependence of the rate law on the concentrations of reactants defines the order of the reaction

The type of reaction depicted in Figure 15.5A, with two reactant molecules in the elementary reaction, is termed a **bimolecular reaction**. The sum of the exponents of the concentrations in a rate law is known as the **reaction order**. For the bimolecular reaction rate law, the order of the reaction is  $1 + 1 = 2$ , and so bimolecular reactions are called **second-order** reactions. This concept of counting the number of required collision partners for the reaction to derive the order for elementary reactions is general, and schematic examples are shown in Figure 15.6 for different orders of reaction.

The units of the rate constant depend on the order of the reaction. The rate of the reaction always has units of concentration per unit time. For second-order reactions, we can infer from Equation 15.4 that the units of  $k$  are  $M^{-1} \cdot sec^{-1}$ . By convention, the rate constant is always taken to have a positive value. The sign on the



**Figure 15.6 Reaction order.**  
 Schematic illustration of (A) first-, (B) second-, and (C) third-order reactions occurring as elementary processes. In (D), a zero-order reaction is shown, for which the overall reaction,  $A \rightarrow C$ , is not an elementary process. The rate of  $Z$  colliding with  $A$  is fast compared to conversion of the catalytic complex to release product  $C$ . In this case, concentrations of reactants or products do not enter into the rate law because the rate-limiting step of the reaction involves collisions with the small number of  $Z$  molecules, and so the concentration of  $Z$  ends up controlling the reaction rate. Such behavior is common for enzymes with high concentrations of substrates, as discussed in detail in Chapter 16.



right-hand side of Equation 15.2 reflects this convention, which is that reactant concentrations must decrease while product concentrations increase.

Second-order reactions may also involve the collision and reaction of two identical molecules. For example, if a reaction corresponds to  $A + A \rightarrow C$ , where just collisions between two  $A$  molecules are required, then the rate law is:

$$\frac{d[A]}{dt} = -k[A][A] = -k[A]^2 \quad \text{or} \quad \frac{d[C]}{dt} = +k[A]^2 \quad (15.5)$$

Second-order reactions are the most common type of elementary reaction.

Elementary reactions that have three participating molecules are termed **termolecular** or **third order** (Figure 15.6C). For example, if two molecules of  $A$  and one of  $B$  are required to collide in order for the reaction to proceed, the rate law would be:

$$\frac{d[A]}{dt} = -k[A][A][B] = -k[A]^2[B] \quad (15.6)$$

The rate constant,  $k$ , for a third-order reaction has units of  $M^{-2} \cdot sec^{-1}$ . At low concentrations, a third-order reaction becomes very slow because the probability of three molecules being close enough to each other to collide simultaneously is very low. Fourth or higher-order reactions are virtually never observed.

It is also found experimentally that many reactions are **unimolecular**—that is, they depend linearly on the concentration of a single reactant. Such reactions obey **first-order kinetics**. For a first-order reaction of  $A \rightarrow C$ :

$$\frac{d[A]}{dt} = -k[A] \quad \text{or} \quad \frac{d[C]}{dt} = +k[A] \quad (15.7)$$

The rate constant,  $k$ , for a first-order reaction has units of  $sec^{-1}$ .

Although not very common in chemical processes in which bonds are made and broken, there are many physical processes that obey first-order kinetics. The radioactive decay of a nucleus is one example and is illustrated in Figure 15.7A. Other examples are provided by the emission of light from a molecule in an electronic excited state or by rearrangement reactions such as isomerizations (Figure 15.7B).

It is also possible to have situations in which the rate for a process is actually independent of the concentration of the reactant. This might be the case when the reaction depends on a molecule, such as a catalyst, that is present in very low concentration compared to the concentrations of the reactants. In such a case, the reaction rate is determined by the concentration of the catalyst rather than that of the reactants (see Figure 15.6D). Such processes are referred to as **zero order**. The rate law for a zero-order process is given by:

$$\frac{d[A]}{dt} = -k \quad \text{or} \quad \frac{d[C]}{dt} = +k \quad (15.8)$$

In this case, the rate constant,  $k$ , has units of  $M \cdot sec^{-1}$ .

#### 15.5 The integration of rate equations predicts the time dependence of concentrations

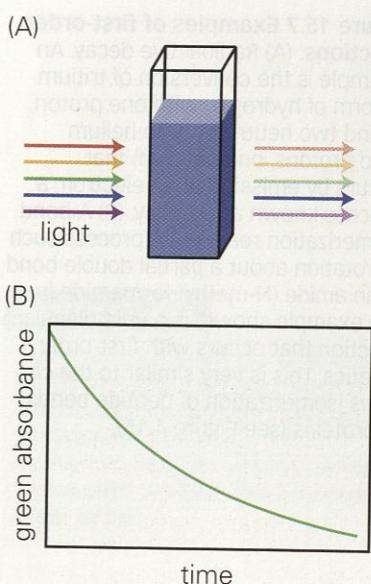
The rate equations for the different kinds of reactions discussed above are all differential equations. In a kinetic measurement carried out in a laboratory it is usually the actual concentration of a reactant or product that is followed as a function

**Figure 15.7 Examples of first-order reactions.** (A) Radioactive decay. An example is the conversion of tritium (a form of hydrogen with one proton,  $p$ , and two neutrons,  $n$ ) to helium (two protons, one neutron) that occurs by emission of an electron, a process known as  $\beta$  decay. (B) A bond isomerization reaction. A process such as rotation about a partial double bond in an amide ( $N$ -methyl formamide in the example shown) is a unimolecular reaction that occurs with first-order kinetics. This is very similar to the *cis-trans* isomerization of peptide bonds in proteins (see Figure 4.15).

**Unimolecular reaction**

A unimolecular or first-order reaction is one in which the rate depends only on the concentration of the reactant to the first power.

**Figure 15.10** A second-order reaction with just one type of reactant. Two  $A$  molecules collide and react to form one  $C$  molecule.



**Figure 15.8 Monitoring concentration during a reaction.** (A) Molecules absorb light at specific wavelengths, and this property allows their concentrations to be monitored during a reaction. In the example shown here, a reactant molecule absorbs some wavelengths more than others, leaving a blue color. (B) The change in concentration of reactants causes the amount of absorbance of green light, in this case, to decrease as the reaction progresses.

of time, rather than the time derivative. For example, we might monitor the concentration of a particular molecule in a reaction by measuring the absorption of visible or ultraviolet light at a specific wavelength, as shown in **Figure 15.8**. It is straightforward to convert a differential rate equation to a function of concentration versus time by specifying the initial conditions (concentrations of reactants at time = 0) and then integrating the rate equation. The time dependence of the concentration can be predicted in this way for each kind of elementary reaction. Comparison with experiment then helps determine the actual order of the reaction.

To set up the integration, we denote the initial concentrations of the various molecules by a subscript 0. For example, the initial concentration of a reactant, A, is denoted  $[A]_0$ . To integrate the equations, we separate the time and concentration variables, and then integrate from time = 0 to time =  $t$ . We now discuss reactions of various orders in turn.

### 15.6 Reactants disappear linearly with time for a zero-order reaction

Consider a reaction,  $A \rightarrow C$ , that proceeds with zero-order kinetics. This means that the rate law does not have any concentration terms in it, as given by Equation 15.8. By rearranging Equation 15.8, we get:

$$d[A] = -kdt \quad (15.9)$$

We can now integrate both sides of Equation 15.9 from the beginning of the reaction ( $t = 0$ ) to any time  $t$ . For the left-hand side of the equation, the limits on the concentration are from  $[A]_0$  (at  $t = 0$ ) to  $[A]$  (at  $t = t$ ). This results in the following expression:

$$\int_{[A]_0}^{[A]} d[A] = -k \int_0^t dt \quad (15.10)$$

which gives:

$$[A] - [A]_0 = -kt \quad (15.11)$$

According to Equation 15.11, the reactant disappears linearly with time for a zero-order reaction, as shown in **Figure 15.9A**. For the reaction,  $A \rightarrow C$ , the reactants are converted into a single product, C. It follows that the concentration of C increases linearly with time.

The concentration of a reactant can never be negative, and so Equation 15.11 applies only until the value of  $kt$  becomes equal to  $[A]_0$ , the initial concentration of A. At subsequent times, the concentration of A is zero. Note that the rate constant,  $k$ , has units of  $M \cdot sec^{-1}$  for a zero-order reaction.

### 15.7 The concentration of reactant decreases exponentially with time for a first-order reaction

Now consider a first-order reaction in which a single reactant is converted to a single product,  $A \rightarrow C$ . The rate law for such a reaction is given by Equation 15.7:

$$\frac{d[A]}{dt} = -k[A] \quad (15.7)$$

By rearranging this equation, we get:

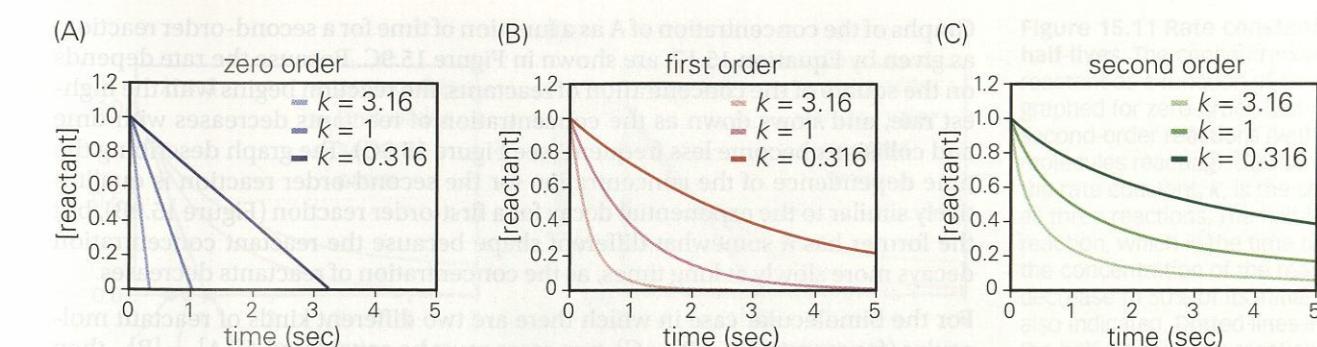
$$\frac{d[A]}{[A]} = -kdt \quad (15.12)$$

We now integrate both sides of Equation 15.12 to get:

$$\int_{[A]_0}^{[A]} \frac{d[A]}{[A]} = -k \int_0^t dt \quad (15.13)$$

This yields:

$$\ln[A] - \ln[A]_0 = -kt \quad (15.13)$$



**Figure 15.9 Concentration of reactant versus time for zero-order, first-order, and second-order kinetics.** Graphs of concentration versus time are shown for three values of the rate constant,  $k$ , spanning a factor of 10 in rate (the values of  $k$  are 0.316, 1, and 3.16). (A) Zero-order kinetics. (B) First-order kinetics. (C) Second-order kinetics with only one type of reactant.

$$[A] = [A]_0 e^{-kt} \quad (15.14)$$

According to Equation 15.14, the concentration of the reactant decays in a simple exponential fashion, as shown in **Figure 15.9B**. If the reactant is converted into a single product, C, then the concentration of C increases exponentially with time in the following way:

$$[C] = [A]_0 - [A] = [A]_0 (1 - e^{-kt}) \quad (15.15)$$

### 15.8 The reactants decay more slowly in second-order reactions than in first-order reactions, but the details depend on the particular type of reaction and the conditions

Second-order reactions are more complicated to analyze than first-order reactions, and it is helpful to consider different limiting cases. To start with, consider a second-order reaction with just one kind of reactant, as shown in **Figure 15.10**. The rate law for this reaction is given by Equation 15.5:

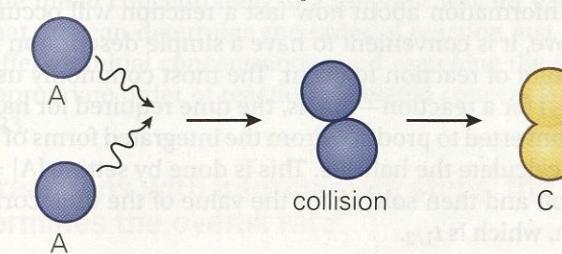
$$\frac{d[A]}{dt} = -k[A]^2$$

Rearranging, we get:

$$\frac{d[A]}{[A]^2} = -kdt \quad (15.16)$$

We now integrate Equation 15.16 to get an expression for the change in the concentration of A with time:

$$\begin{aligned} \int_{[A]_0}^{[A]} \frac{d[A]}{[A]^2} &= -k \int_0^t dt \\ \Rightarrow \frac{1}{[A]} - \frac{1}{[A]_0} &= -kt \\ \Rightarrow \frac{1}{[A]} &= \frac{1}{[A]_0} + kt = \frac{1 + [A]_0 kt}{[A]_0} \\ \Rightarrow [A] &= \frac{[A]_0}{1 + [A]_0 kt} \end{aligned} \quad (15.17)$$



$$\text{rate} = \frac{d[A]}{dt} = -k[A]^2$$

**Figure 15.10 A second-order reaction with just one type of reactant.** Two A molecules collide and react to form one C molecule.

Graphs of the concentration of A as a function of time for a second-order reaction, as given by Equation 15.17, are shown in Figure 15.9C. Because the rate depends on the square of the concentration of reactants, the reaction begins with the highest rate, and slows down as the concentration of reactants decreases with time and collisions become less frequent (see Figure 15.9C). The graph describing the time dependence of the concentration for the second-order reaction is qualitatively similar to the exponential decay for a first-order reaction (Figure 15.9B), but the former has a somewhat different shape because the reactant concentration decays more slowly at long times, as the concentration of reactants decreases.

For the bimolecular case in which there are two different kinds of reactant molecules (for example,  $A + B \rightarrow C$ ), two cases must be considered. If  $[A]_0 = [B]_0$ , then because of the stoichiometry, we know that  $[A] = [B]$  for all times, and mathematically the behavior is identical to the case in which two molecules of [A] react, as discussed above (that is, Equation 15.17 applies).

If the initial concentrations of A and B are different, then the integration of the rate equation is more complicated. Starting with the rate law (see Equation 15.6):

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

we obtain the integrated form, as explained in Box 15.1:

$$\ln\left(\frac{[A]}{[B]}\right) - \ln\left(\frac{[A]_0}{[B]_0}\right) = ([A]_0 - [B]_0)kt \quad (15.18)$$

Although Equation 15.18 looks complicated, if  $[A]_0 \gg [B]_0$  (or  $[B]_0 \gg [A]_0$ ), then it reduces to the case of a first-order reaction. To see why this is so, consider what happens when the initial concentration of A is very much greater than that of B (that is,  $[A]_0 \gg [B]_0$ ). As the reaction proceeds, A molecules react with B molecules, but because there are very few B molecules, the concentration of A is essentially unchanged and remains very close to  $[A]_0$ . In this case, the rate equation becomes:

$$\frac{d[A]}{dt} = -k[A][B] = -k[A]_0[B] = -k'[B] \quad (15.19)$$

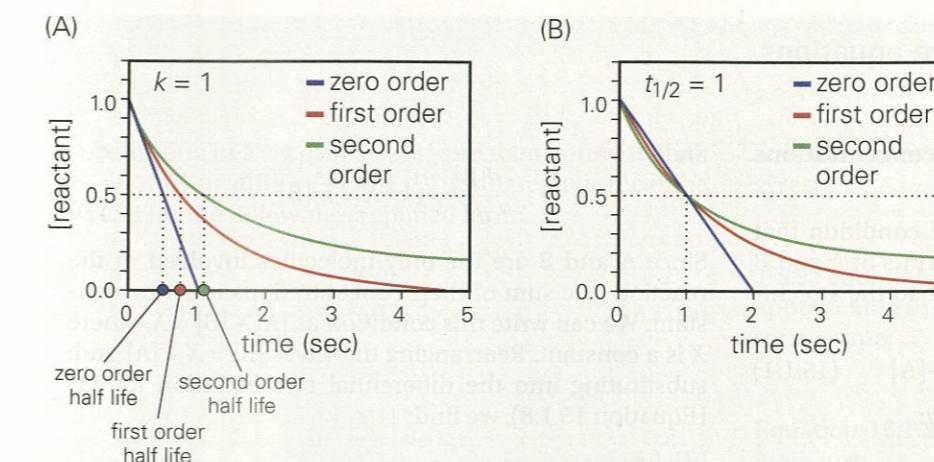
By comparing Equation 15.19 with Equation 15.7, you can see that the reaction behaves as if it were a first-order reaction with a rate constant,  $k'$ . The rate constant,  $k'$ , in Equation 15.19 is called a **pseudo-first-order rate constant** because it applies to a second-order reaction under a limiting condition (that is,  $[A]_0 \gg [B]_0$ ). The concept of a pseudo-first-order rate constant is an important one that we shall return to in Section 15.17, when we discuss the rates of reversible ligand binding to proteins.

When the initial concentrations of the reactants,  $[A]_0$  and  $[B]_0$ , are comparable, but not equal, Equation 15.18 must be applied. Although we shall not analyze this situation in detail, the changes in concentration with time are intermediate between first- and second-order reactions with one reactant.

### 15.9 The half-life for a reaction provides a measure of the speed of the reaction

Although all the information about how fast a reaction will occur is present in the equations above, it is convenient to have a simple description of how long it takes for some extent of reaction to occur. The most commonly used descriptor is the **half-life** ( $t_{1/2}$ ) for a reaction—that is, the time required for half of the initial reactant to have converted to product. From the integrated forms of the rate equations, it is easy to calculate the half-life. This is done by setting  $[A] = [A]_0/2$  in the integrated equation and then solving for the value of the time corresponding to this concentration, which is  $t_{1/2}$ .

For a zero-order reaction,  $t_{1/2} = [A]_0/2k$ . Since the rate of reaction (that is, the number of moles per unit time) is constant, it makes sense that more reactant being present means it takes longer for half of it to react.



**Figure 15.11 Rate constants and half-lives.** The concentration of reactant as a function of time is graphed for zero-order, first-order, and second-order reactions (with identical molecules reacting). (A) The value of the rate constant,  $k$ , is the same in all three reactions. The half-life of a reaction, which is the time taken for the concentration of the reactant to decrease to 50% of its initial value, is also indicated. Dotted lines indicate the half-life for each reaction. (B) The value of the half-life is the same in all three cases.

#### Half-life and time constant

The half-life of a reaction is the time for the concentration of a reactant to drop to half of its initial value. First-order processes are also commonly described by their time constants or lifetimes, which is the time required for the reactant to decay to  $\sim 37\%$  (that is,  $1/e$ ) of its initial value. The time constant for a first-order reaction is given by  $1/k$ , where  $k$  is the rate constant.

For a first-order reaction,  $t_{1/2} = \ln 2/k = 0.693/k$ . In this case, the half-life does not depend on the amount of reactant initially present. The values of half-lives are very commonly encountered in descriptions of the decay of radioactive elements. The fact that the half-life is independent of the starting amount is a critical feature for using the decay of “radiocarbon,”  $^{14}\text{C}$ , for determining the age of bones and other anthropological materials.

For first-order reactions, the **time constant**,  $\tau = 1/k$  (often referred to as the lifetime, especially for processes involving light, such as fluorescence), is used rather than half-life. The time constant is the time required for the concentration of the reactant to decay by a factor of  $e^{-1}$  (that is, to decay to  $\sim 37\%$  of its initial value). For a first-order reaction with a single product, the time constant is also the time taken for the concentration of the product to increase to  $\sim 63\%$  of its final value.

For a second-order reaction with two identical molecules reacting,  $t_{1/2} = 1/(k[A]_0)$ . As for the zero-order case, the half-life depends on the initial starting concentration, but in the opposite way. In the second-order case, a higher concentration of reactant results in collisions being more likely, leading to a faster initial reaction and, hence, a shorter half-life. For the  $A + B$  reaction, a half-life can be defined, but it depends on both  $[A]_0$  and  $[B]_0$  in a complex way and, hence, is not particularly useful.

Examples of concentration versus time curves are shown in Figure 15.11A for the three common types of elementary reactions: zero, first, and second order. In all of these examples, the rate constant is 1 (with appropriate units), and the initial concentration of reactant is taken as 1. For comparison, graphs are also shown in which the half-life is the same for all three kinds of reactions (Figure 15.11B). The latter case emphasizes the similarity of first- and second-order behavior toward the beginning of each reaction, but shows how differently they behave at longer times.

It is worth noting that, for these elementary reactions, the half-life for a reaction depends on the initial concentration in a different way for each reaction order. This means that one can determine the order of reaction just by measuring the half-life for different initial concentrations and matching the observed dependence to the appropriate order of reaction. A related concept is discussed further in Section 15.23.

### 15.10 For reactions with intermediate steps, the slowest step determines the overall rate

The elementary reactions discussed above are sufficient to describe any individual step of a reaction, but many real reactions have multiple steps or processes

### Box 15.1 Integrated forms of rate equations

**Second-order reaction with unequal concentrations of reactants:**  $A + B \rightarrow C$

For the second-order reaction with the condition that  $[A]_0 \neq [B]_0$ , we use the fact that the amounts of A and B that have reacted must be the same due to the stoichiometry:

$$[A]_0 - [A] = [B]_0 - [B] \text{ or } [B] = [B]_0 - [A]_0 + [A] \quad (15.1.1)$$

For convenience, we define the following:

$$\Delta = [B]_0 - [A]_0$$

so

$$[B] = \Delta + [A] \quad (15.1.2)$$

Using this, the basic kinetic equation becomes:

$$\frac{d[A]}{dt} = -k[A][B] = -k[A](\Delta + [A]) \quad (15.1.3)$$

Separating variables and then integrating Equation 15.1.3 from time 0 to  $t$  and from  $[A]_0$  to  $[A]$ , we get:

$$\int_0^t \frac{d[A]}{[A]_0 - k[A](\Delta + [A])} = \int_{[A]_0}^{[A]} \frac{d[A]}{-k\Delta[A] - k[A]^2} \quad (15.1.4)$$

Such polynomial integrals, of the form  $dt = dx/(a + bx + cx^2)$ , appear in standard mathematics tables. In this case, the general solution is:

$$t = \frac{1}{\sqrt{-q}} \log \left( \frac{2cx + b - \sqrt{-q}}{2cx + b + \sqrt{-q}} \right) \quad (15.1.5)$$

where  $q = 4ac - b^2$ . Then, using  $x = [A]$ ,  $a = 0$ ,  $b = -k\Delta$ ,  $c = -k$ , and Equation 15.1.4, Equation 15.1.5 becomes:

$$t = \frac{1}{k\Delta} \log \left( \frac{[A]}{[A] + [B]_0 - [A]_0} \right) - \frac{1}{k\Delta} \log \left( \frac{[A]_0}{[A]_0 + [B]_0 - [A]_0} \right)$$

$$= \frac{1}{k\Delta} \left[ \log \left( \frac{[A]}{[B]} \right) - \log \left( \frac{[A]_0}{[B]_0} \right) \right] \quad (15.1.6)$$

We now insert the definition of  $\Delta$  from Equation 15.1.2 and rearrange slightly to get Equation 15.18 in the main text:

$$\ln \left( \frac{[A]}{[B]} \right) - \ln \left( \frac{[A]_0}{[B]_0} \right) = ([A]_0 - [B]_0)kt \quad (15.1.7)$$

**Reversible reaction**  $A \xrightleftharpoons{k_r} B$

Using  $k_f$  and  $k_r$  as the rate constants for the forward and reverse reactions, respectively, the differential rate equations for concentrations have a term for the disappearance of A to make B and for the formation of A from B. The basic rate equations are then:

$$\frac{d[A]}{dt} = -k_f[A] + k_r[B] \quad (15.1.8)$$

and

$$\frac{d[B]}{dt} = +k_f[A] - k_r[B] \quad (15.1.9)$$

Since A and B are the only molecules involved in the reaction, the sum of their concentrations must be constant. We can write this condition as  $[A] + [B] = X$ , where  $X$  is a constant. Rearranging this gives  $[B] = X - [A]$  and, substituting into the differential rate equation for  $[A]$  (Equation 15.1.8), we find:

$$\frac{d[A]}{dt} = -k_f[A] + k_r(X - [A]) = -(k_f + k_r)[A] + k_rX \quad (15.1.10)$$

The variables  $[A]$  and  $t$  can be separated again. This is most easily seen by substituting in a new variable:

$$Z = -(k_f + k_r)[A] + k_rX \quad (15.1.11)$$

Using this in Equation 15.1.10, and recognizing that  $X$  is constant, we get:

$$\frac{dZ}{dt} = -(k_f + k_r)Z \quad (15.1.12)$$

Equation 15.1.12 can be integrated easily to give an exponential. To get back to  $[A]$  as the variable, substitute back in for  $Z$  and use the value of  $Z$  at time zero:

$$Z(0) = -(k_f + k_r)[A]_0 + k_rX \quad (15.1.13)$$

Following these steps gives:

$$[A] = \left( [A]_0 - \frac{k_r}{k_f + k_r} X \right) e^{-(k_f + k_r)t} + \frac{k_r}{k_f + k_r} X \quad (15.1.14)$$

Note that the forward and reverse rates must be equal at equilibrium, so:

$$k_f[A]_{eq} = k_r[B]_{eq} = k_r(X - [A]_{eq})$$

Then,

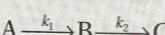
$$[A]_{eq} = \frac{k_r}{k_f + k_r} X \quad (15.1.15)$$

and so

$$[A] = ([A]_0 - [A]_{eq})e^{-(k_f + k_r)t} + [A]_{eq} \quad (15.1.16)$$

Equation 15.1.16 is the same as Equation 15.31 in the main text.

#### Steady-state situation for the series reaction



We begin by assuming that under steady-state conditions the concentration of  $[A]$  is held constant. We set  $[A] = [A]_0$  at all times, so:

$$\frac{d[B]}{dt} = +k_1[A]_0 - k_2[B] \quad (15.1.17)$$

Since there is just one time-dependent variable now,  $[B]$ , this is much easier to integrate than Equation 15.1.3. By

substituting in  $X = k_1[A]_0 - k_2[B]$  and then noting that  $dX = -k_2 d[B]$  or  $d[B] = (-1/k_2) dX$ , the integration can be written in the following simplified form:

$$\int_{X_0}^X \frac{-dX}{k_2 X} = \int_0^t dt \quad (15.1.18)$$

Thus,

$$\ln \left( \frac{X}{X_0} \right) = -k_2 t \quad (15.1.19)$$

Substituting back in for  $X$  and noting that  $X_0 = k_1[A]_0$  gives:

$$[B] = \frac{k_1}{k_2} [A]_0 (1 - e^{-k_2 t}) \quad (15.1.20)$$

These equations show that  $[B]$  increases, asymptotically approaching  $[B]_{ss}$  (with a time constant  $1/k_2$ ), and that at steady state:

$$[B]_{ss} = \frac{k_1}{k_2} [A]_0 \quad (15.1.21)$$

Equation 15.1.21 is the same as Equation 15.42 in the main text.

#### Intermediate

An intermediate is a chemical species that appears during the reaction but disappears when the reaction is complete.

between the reactants and final products. Consider, for example, a reaction in which an **intermediate**, B, is formed, that then goes on to product, C:



The letter  $k$  above the arrow for a step indicates the rate constant for that step in the reaction.

Many chemical reactions have intermediates. Intermediates are also important for many other processes, including protein folding. As we discuss in Section 18.8, an unfolded protein often collapses to a partially folded intermediate, which then converts to the native and functional conformation of the protein (Figure 15.12).

If the elementary reactions of the two steps,  $A \rightarrow B$  and  $B \rightarrow C$ , are each first order, then there are two rate equations that govern the reaction. First, there is the rate equation for A converting to B. This is similar to the first-order rate equation given in Equation 15.7:

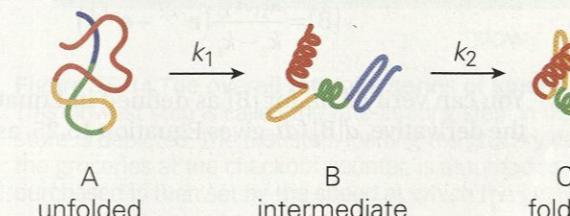
$$\frac{d[A]}{dt} = -k_1[A] \quad (15.21)$$

The rate equation for the concentration of B is more complex, because the concentration of B can change in two ways. B is produced from A, but it is also converted to C. By considering both of these processes, we obtain the rate equation for B:

$$\frac{d[B]}{dt} = +k_1[A] - k_2[B] \quad (15.22)$$

As for A, the rate equation for C is simple, because its concentration changes only when it is generated from or converted to B:

$$\frac{d[C]}{dt} = +k_2[B] \quad (15.23)$$



**Figure 15.12 A reaction with an intermediate.** A protein folding reaction is shown in which the unfolded protein first converts to an intermediate conformation that then progresses to the folded conformation. The rate constants associated with the two steps are denoted  $k_1$  and  $k_2$ , respectively.

The integrated form of the equation for A is the same as if there was no reaction beyond B:

$$[A] = [A]_0 e^{-k_1 t} \quad (15.24)$$

To get the integrated equation for [B], we substitute the expression for [A] given in Equation 15.24 into Equation 15.22:

$$\frac{d[B]}{dt} = +k_1[A] - k_2[B] = k_1[A]_0 e^{-k_1 t} - k_2[B] \quad (15.25)$$

As explained in Box 15.2, Equation 15.25 is integrated to yield the following expression for [B]:

$$[B] = \frac{k_1 [A]_0}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \quad (15.26)$$

To get the equation for the product, C, the solution for [B] is inserted into the differential equation, Equation 15.23, and the integration can again be performed with separation of variables to give:

$$[C] = [A]_0 \left[ 1 - \frac{1}{k_2 - k_1} (k_2 e^{-k_1 t} - k_1 e^{-k_2 t}) \right] \quad (15.27)$$

The values of [A], [B], and [C] are plotted versus time in Figure 15.13 for two different ratios of the rate constants,  $k_1$  and  $k_2$ . In one case, shown in Figure 15.13A, the first step is the slow one. In the second case, the second step is the slow one (see Figure 15.13B). The behavior is intuitively what one expects. The reactant A decreases in a simple, first-order, exponential way—unaffected by what happens subsequently. The intermediate, B, increases with the same time constant as that for the decrease of A, and then B converts to C in a first-order manner with rate constant,  $k_2$ . If the production of B is much slower than its subsequent conversion to C (that is, if  $k_1 \ll k_2$ ), then [B] never gets very high. On the other hand, if the first step is fast (that is,  $k_1 \gg k_2$ ), then most of the A converts to B before it goes on to form C, as is seen in the graphs.

### Box 15.2 Integrating the rate equation for a reaction with intermediate steps

We seek to integrate Equation 15.25 in the main text:

$$\frac{d[B]}{dt} = +k_1[A] - k_2[B] = k_1[A]_0 e^{-k_1 t} - k_2[B] \quad (15.25)$$

Equation 15.25 has just [B] and  $t$  as variables, so it can be integrated. This integration is not straightforward, because the variables cannot easily be separated. However, the general form of Equation 15.25 derives from an application of the product rule for differentiation. Notice that Equation 15.25 is equivalent to a differential equation of the general form:

$$\frac{dy}{dx} + cy = g(x) \quad (15.2.1)$$

If we apply the product rule for differentiation to an exponential function, we get the following:

$$\frac{d}{dx}(e^{cx}y) = ce^{cx}y + e^{cx}\frac{dy}{dx} = e^{cx}\left(\frac{dy}{dx} + cy\right) \quad (15.2.2)$$

By combining Equations 15.2.1 and 15.2.2, we get:

$$\frac{d}{dx}(e^{cx}y) = e^{cx}g(x) \quad (15.2.3)$$

Equation 15.2.3 is then integrated to give:

$$\int \frac{d}{dx}(e^{cx}y) dx = e^{cx}y = \int e^{cx}g(x) dx \quad (15.2.4)$$

To apply Equation 15.2.4 to integrate the rate equation (Equation 15.25), we use the initial condition that  $[B]_0 = 0$  and substitute as follows:

$$x = t$$

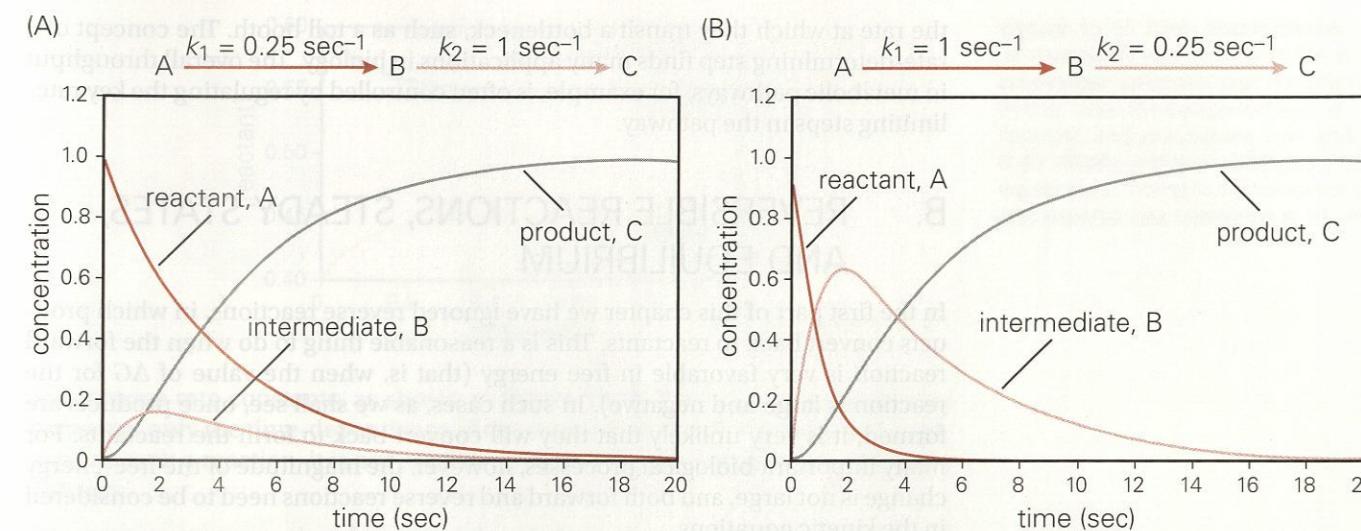
$$g(x) = k_1[A]_0 \exp(-k_1 t)$$

$$y = [B] \text{ (which is a function of } x = t)$$

This gives us Equation 15.21 in the main text:

$$[B] = \frac{k_1 [A]_0}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t})$$

You can verify that, for [B] as defined in Equation 15.26, the derivative,  $d[B]/dt$ , gives Equation 15.25, as it should.



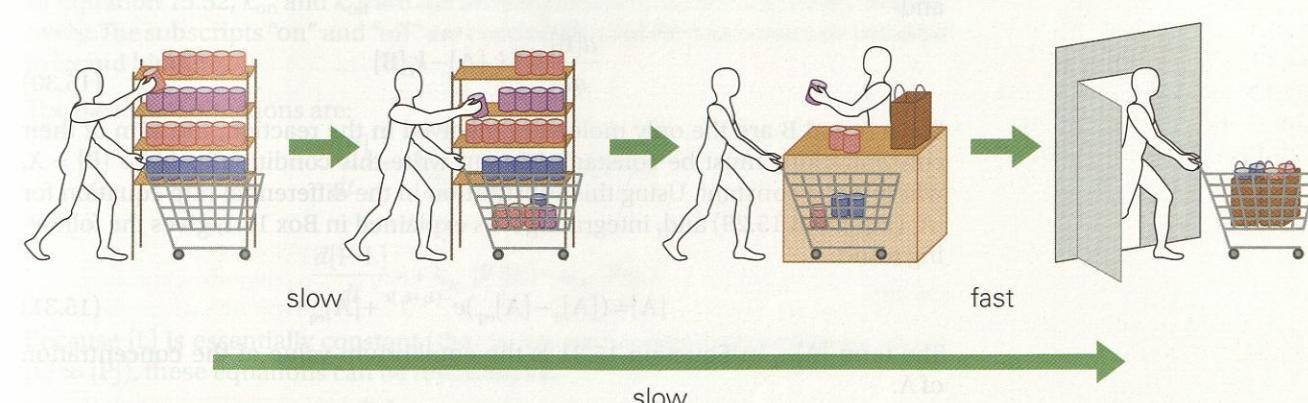
**Figure 15.13 Time dependence of concentrations for the reaction  $A \rightarrow B \rightarrow C$ .** (A) The rate constants for the conversion of A to B and of B to C are  $k_1 = 0.25 \text{ sec}^{-1}$  and  $k_2 = 1.0 \text{ sec}^{-1}$ , respectively. The first step is slower than the second step and the intermediate does not build up very much, because it is rapidly converted to product. (B) The values of the rate constants,  $k_1$  and  $k_2$ , are  $1.0 \text{ sec}^{-1}$  and  $0.25 \text{ sec}^{-1}$ , respectively. The second step is slower than the first step. The intermediate builds up to a greater extent. The rate of final product formation is the same regardless of whether the first or the second step is slower, because the slower step has the same rate constant in both cases.

An important principle emerges when we compare Figures 15.13A and 15.13B. Note that the rate at which the product, C, builds up is the same in the two cases. This is because it is always the slowest step in a chain of reactions that limits the overall reaction rate. In the examples shown in Figure 15.13, the rate constant for the slower step is the same in the two cases, and so the rate of buildup of the product is the same. But, more generally, for any complex set of series reactions, the rate for the slowest step determines the rate of the overall process. That slowest step is called the **rate-determining step** for the reaction.

The graphs shown in Figure 15.13 are based on Equations 15.24, 15.26, and 15.27, which seem rather complicated. Nevertheless, the principle that the slowest step in a process limits the overall speed of the process is one that you can recognize from many aspects of everyday life. The rate at which you can move through a grocery store, for example, limits the speed at which you can exit the store (Figure 15.14). The rate at which cars move along a multilane highway is determined by

### Rate-determining step

The rate-determining step in a series of reactions is the slowest step, which therefore ultimately limits the rate of formation of product.



**Figure 15.14 The overall rate of a series of kinetic steps is determined by the rate of the slowest step.** This slowest step is called the rate-limiting step. In this illustration, the process of purchasing groceries at a store is depicted. The first step, loading the grocery cart, is assumed to be slow. The second step, paying for the groceries at the checkout counter, is assumed to be fast. The overall speed with which the groceries are purchased is then set by the speed at which the grocery cart is loaded.