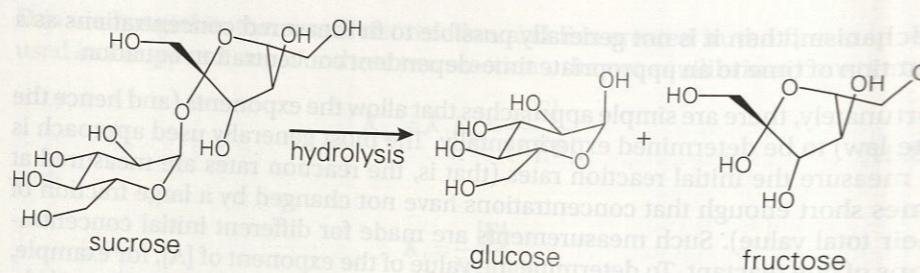


**Figure 15.30 Structures of sucrose and its hydrolysis products, glucose and fructose.** The process of sucrose hydrolysis is known as inversion because it was first followed by measuring how much the plane of polarization of light was rotated by passing through the solution. As the reaction proceeds in this case, the sense of rotation inverts for products relative to reactants.



The kinetics of sucrose hydrolysis was studied many years ago by following the reaction through observation of the rotation of polarized light by solutions containing sucrose. A solution of sucrose is dextrorotatory (that is, it rotates light in a counterclockwise fashion, as explained in Section 3.4). Glucose is dextrorotatory and fructose is levorotatory, but because fructose rotates the polarization of light more strongly than glucose, the net polarization of light by the products is levorotatory. Thus, as the reaction proceeds, the polarization of light by the solution switches from counterclockwise to clockwise (that is, the polarization inverts). This phenomenon led to the hydrolysis of sucrose being referred to as an **inversion reaction**.

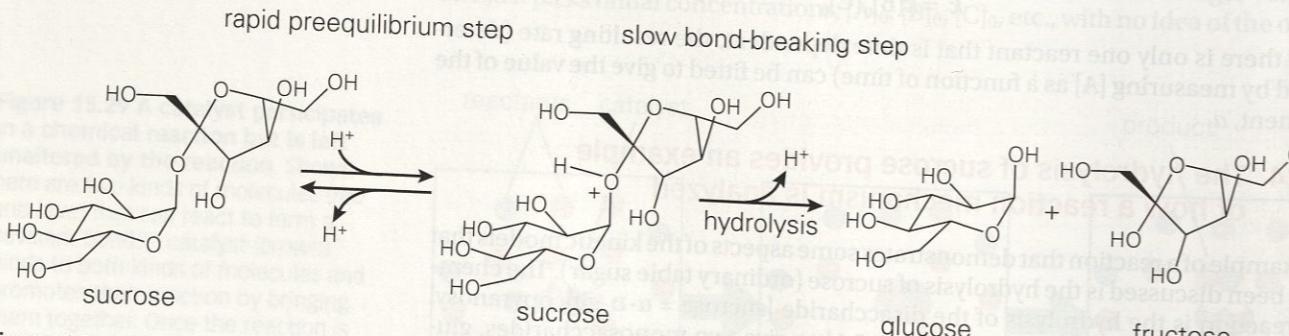
The mechanism of sucrose hydrolysis can be deduced from three important observations concerning the kinetics of the reaction. The first observation is that although the hydrolysis reaction is very slow in pure water, the rate increases dramatically as the pH is lowered (that is, as the proton concentration increases). The nature of the acid used to lower the pH of the solution does not matter.

The second observation is that during the course of the reaction the pH of the solution does not change. Thus, although protons are clearly participating in the reaction (because the rate depends on the pH), the protons must be acting as catalysts.

The third observation is that the reaction is first order in proton concentration and also first order in sucrose. Thus, the rate law seems to be:

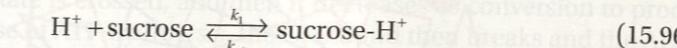
$$\frac{d[\text{sucrose}]}{dt} = k[\text{sucrose}][\text{H}^+] \quad (15.95)$$

We now combine these observations with some chemical knowledge to deduce the chemical mechanism. First, in reactions that break bonds, the stability of the leaving group is very important. From a study of other organic reactions, it is known that protonation of an oxygen can create a better leaving group ( $\text{HOCH}$  is a better leaving group than the unstable  $\text{-OCH}$  group). In this case, it is the bridging oxygen in sucrose that must be protonated (Figure 15.31). But this is unfavorable, because ether oxygens ( $\text{C}-\text{O}-\text{C}$ ) have a very low  $\text{pK}_a$  value. Nevertheless,



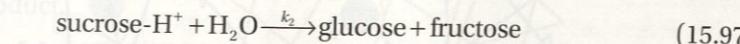
**Figure 15.31 Mechanism of sucrose hydrolysis.** A mechanism that is consistent with the observed rate law is shown. It involves reversible protonation followed by bond cleavage in the protonated form of sucrose to give glucose + fructose. The water molecule that reacts is not shown.

in solution we know that there will be a small amount of the protonated sugar present. This reaction is:



and the rates for protonation/deprotonation reactions are generally rapid.

If we assume that the protonated sucrose reacts with water, then we can write:



The back reaction is not included because the forward reaction is thermodynamically favorable and the reaction goes essentially to completion (that is, all of the sucrose is converted to glucose and fructose). We can now develop a kinetic model from these two reactions.

First, note that product formation is an elementary reaction of sucrose- $\text{H}^+$  with  $\text{H}_2\text{O}$ , so the rate law is:

$$\frac{d[\text{glucose}]}{dt} = \frac{d[\text{fructose}]}{dt} = k_2[\text{sucrose-H}^+][\text{H}_2\text{O}] \quad (15.98)$$

To obtain an expression for  $[\text{sucrose-H}^+]$ , we consider the reaction depicted in Equation 15.96. Protonation/deprotonation is much faster than the bond-breaking step that occurs in the reaction depicted in Equation 15.97. This means that the rate constants for the protonation/deprotonation step,  $k_1$  and  $k_{-1}$ , are much greater than the rate constant for the bond-breaking step,  $k_2$ . This fact allows us to make a **"preequilibrium" approximation**—that is, we assume that the following is true:

$$[\text{sucrose-H}^+] \approx \frac{k_1}{k_{-1}}[\text{sucrose}][\text{H}^+] \quad (15.99)$$

Equation 15.99 is equivalent to stating that the protonated and deprotonated sucrose essentially remains at equilibrium throughout the reaction—that is, we are equating the ratio of the two rate constants to the equilibrium constant for the reaction (compare Equation 15.67). Then, by inserting Equation 15.99 into Equation 15.98, we find that the rate of product production is given by:

$$\begin{aligned} \frac{d[\text{glucose}]}{dt} &= k_2 \frac{k_1}{k_{-1}} [\text{sucrose}][\text{H}^+][\text{H}_2\text{O}] \\ &= k_2 \frac{k_1}{k_{-1}} [\text{sucrose}][\text{H}^+] \end{aligned} \quad (15.100)$$

In the last step we have taken  $k_2 = k_2[\text{H}_2\text{O}]$  because the reaction is in water (where  $[\text{H}_2\text{O}] = 55 \text{ mol}\cdot\text{L}^{-1}$ ), and the concentration of water does not change significantly during the reaction.

This kinetic model, which is shown in Figure 15.31 and consists of a reversible protonation step followed by an essentially irreversible hydrolysis step, is consistent with experimental observation. The rate depends linearly on sucrose concentration and also on hydrogen ion concentration. It is important to note, however, that this agreement does not prove that this kinetic model is correct. It is often the case that there are other kinetic models that can give the same concentration dependence and, hence, would also be consistent with the kinetic observations. To distinguish among such possibilities we would need to carry out more complicated experiments, such as those that probe whether other intermediates are present.

### 15.25 The fastest possible bimolecular reaction rate is determined by the diffusion-limited rate of collision

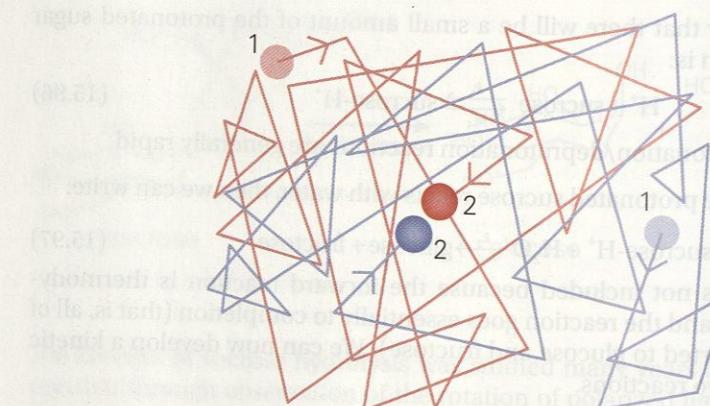
In Section 15.2, we noted that the rate constant,  $k$ , for a bimolecular reaction must reflect the frequency of collisions per unit concentration. The rate constant also depends on the fraction of collisions that lead to formation of product. Both of these factors depend on reaction conditions, including temperature.

Figure 15.32 illustrates the effect of concentration on the rate of a bimolecular reaction. The figure shows a series of reaction coordinate diagrams for a reaction between two molecules, A and B, that proceed through different transition states. The diagrams illustrate how the reaction rate increases as the initial concentrations of A and B increase. The diagrams also show that the activation energy for the reaction is relatively constant across different concentrations, but the overall rate of the reaction increases with concentration.

### Preequilibrium approximation

A preequilibrium approximation refers to a case in which there are forward and backward reactions that are both much faster than subsequent reaction steps. In this case, the reactants and products for this fast step always remain at relative concentrations determined as if they were fully at equilibrium.

**Figure 15.32 The diffusion time limits the rate of reaction.** Two molecules in solution are shown here (red and blue). As they move around, they collide with water molecules (not shown), which changes their trajectories. Starting from the points indicated by 1, the molecules move randomly until they collide (indicated by the red and blue lines, ending in the positions marked 2). The frequency of such collisions is determined by the viscosity of the solution and the temperature.



For gases it is quite straightforward to calculate the rate at which collisions occur,  $N_{\text{collision}}$ . The rate of intermolecular collisions in air is given by:

$$N_{\text{collision}} = k_{\text{collision}} [A][B] \quad (15.101)$$

in which  $k_{\text{collision}}$  is the rate constant for collisions. For molecules in air at 1 atm, the rate constant,  $k_{\text{collision}}$ , has a value of about  $6 \times 10^{10} \text{ M}^{-1} \cdot \text{sec}^{-1}$ . In spite of this high collision rate, molecules in gases move very significant distances between collisions (an average on the order of 500 molecular diameters).

For molecules moving in solution, as is the case for essentially all biological reactions, the movement of the molecules changes to that of much slower diffusion (see Figure 15.32), which is developed in detail in Chapter 17. It would seem that large molecules should collide more often, but they also move more slowly, which decreases the rate of collisions. For water at 25°C, the value of  $k_{\text{collision}}$  is about  $1 \times 10^{10} \text{ M}^{-1} \cdot \text{sec}^{-1}$ , surprisingly similar to the value predicted for gas-phase collisions of molecules in air with each other.

If every collision between reactants in a solution leads to product, then  $k_{\text{collision}}$  will be the value for the bimolecular rate constant. There are some reactions that do indeed reach this **diffusion-limited reaction** rate. An example of a reaction that occurs at the diffusion limit is that of iodine atoms reacting to form molecular iodine:  $2\text{I}^* \rightarrow \text{I}_2$ . In this case, the delocalized electrons in the outermost orbitals on each atom must simply come close together to form the bond, and this can happen during any collision, with no orientational constraint. There are a few biological reactions that occur at rates close to this diffusion limit, but most do not.

### Diffusion-limited reaction

A diffusion-limited reaction is one in which every collision between reactants leads to products. The rate of reaction in this case is limited by the rate of collisions, which is affected just by the rates of diffusion. The rate constant for collisions between molecules in water is about  $1 \times 10^{10} \text{ M}^{-1} \cdot \text{sec}^{-1}$ . A reaction that occurs with a rate constant close to this value is said to be diffusion-limited.

### 15.26 Most reactions occur more slowly than the diffusion-limited rate

Most observed reaction rate constants are much smaller than the diffusion-limited value. The reason is that most collisions of reactants do not lead to products—that is, after a collision the molecules usually remain as reactants (Figure 15.33). By comparing the observed rate constant for a bimolecular reaction,  $k_{\text{obs}}$ , to that for the expected rate constant for collisions ( $\sim 10^{10} \text{ M}^{-1} \cdot \text{sec}^{-1}$ ), one can calculate the fraction of collisions that do lead to products. It turns out that very fast reactions have values of  $k_{\text{obs}}=10^6 \text{ M}^{-1} \cdot \text{sec}^{-1}$ , which means that only 1 collision in  $10^4$  leads to products. For a slow reaction, with  $k_{\text{obs}}=1 \text{ M}^{-1} \cdot \text{sec}^{-1}$ , it is just 1 collision in  $10^{10}$  that is productive.

There are two important factors that limit reaction rates. First, as shown in Figure 15.33, for the reaction to occur, the reactants must come together in a rather specific orientation. The importance of the correct orientation is illustrated in Figure 15.34, which shows how a hydroxide ion attacks ATP, resulting in the hydrolysis of ATP. The oxygen atom of the hydroxide ion must come in close and be in line with the P-O bond that will break. In this orientation, the attacking oxygen can get close enough to the phosphorous to begin to make a bond, forming a transient structure known as the **transition state**. The transition state is a point of commitment

to the conversion of reactants to products. The energy of the reactants increases until the transition state is crossed, and then it decreases as conversion to product occurs. In the case of ATP hydrolysis, the O-P bond then breaks and the ADP departs. If the hydroxide comes into contact with any other part of the phosphate, then the transition state cannot form, and no reaction will occur. Thus, only collisions with “correct” relative positions and orientations form the transition state that leads to product.

As the analysis of the ATP hydrolysis reaction makes clear, to get the number of collisions that can lead to product, the total rate of collisions must be multiplied by  $f_p$ , the fraction of collisions that can actually lead to product. This fraction is specific for the particular pair of reactants, differing widely depending on the structures involved and the nature of the chemical transformation. The collision rate, corrected for orientation, is given the symbol  $A$  and is the rate of collisions multiplied by the fraction that are productive,  $f_p$ :

$$A = k_{\text{collision}} f_p \quad (15.102)$$

This corrected collision rate is called the **preexponential factor**, for reasons that are explained in Section 15.28.

The second factor limiting reaction rates is that the collision must provide enough energy for the reaction to occur, as discussed in the next section.

### 15.27 The activation energy is the minimum energy required to convert reactants to products during a collision between molecules

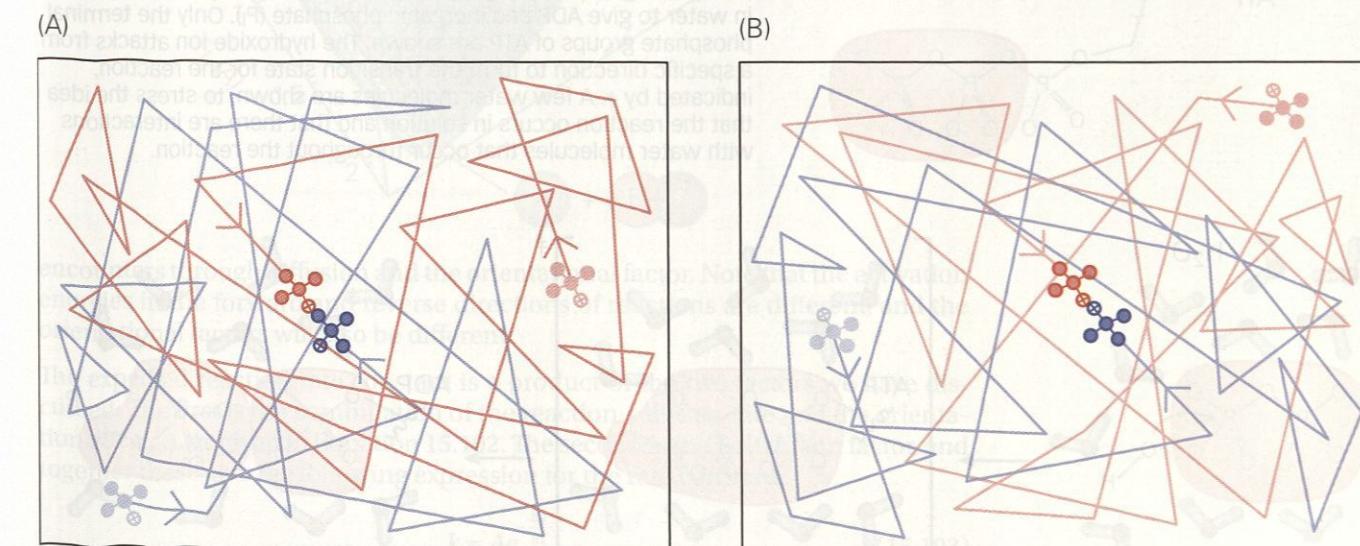
When the hydroxide ion approaches the ATP from the correct direction, the phosphate oxygens must be pushed away from their equilibrium tetrahedral geometry toward a planar position in order for the electronic orbitals of the hydroxide to overlap with those on the phosphorous to initiate bonding, and this requires energy. There is a minimum energy required to bring the reactants sufficiently close together to react, which is called the **activation energy** and is denoted  $E_A$ . This can be visualized by plotting the energy of the system as a function of a single **reaction coordinate**—a variable defined to describe whether colliding molecules are more like reactants or products, as shown in Figure 15.35. The activation

### Transition state

In a pathway connecting reactants to products, the potential energy increases until it has a maximum value at the transition state. Once the transition state is crossed, the reaction is downhill in terms of potential energy.

### Reaction coordinate

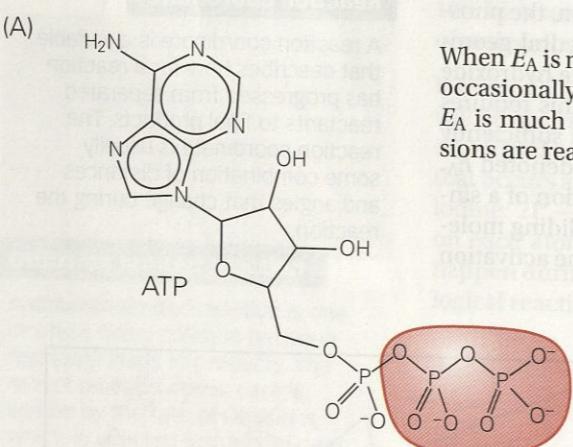
A reaction coordinate is a variable that describes how far a reaction has progressed from separated reactants to final products. The reaction coordinate is usually some combination of distances and angles that change during the reaction.



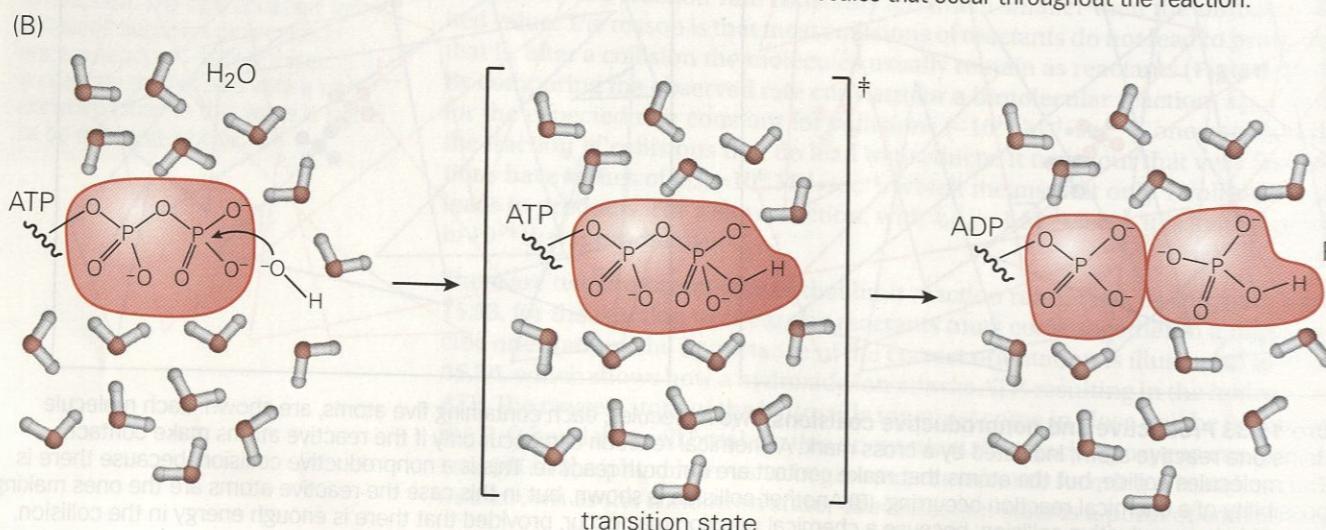
**Figure 15.33 Productive and nonproductive collisions.** Two molecules, each containing five atoms, are shown. Each molecule contains one reactive atom, indicated by a cross mark. A chemical reaction can occur only if the reactive atoms make contact. (A) The molecules collide, but the atoms that make contact are not both reactive. This is a nonproductive collision, because there is no possibility of a chemical reaction occurring. (B) Another collision is shown, but in this case the reactive atoms are the ones making contact. This is a productive collision, because a chemical reaction may occur, provided that there is enough energy in the collision.

**Activation energy**

The activation energy is the minimum increase in potential energy for reactants to be converted to products, and hence the minimum energy that reactants must have to be able to react. The requirement that the reactants have sufficient energy,  $E_A$ , to cross from reactants to products limits the rate of most reactions.



**Figure 15.34 Importance of the attacking group orientation in the hydrolysis of ATP.** (A) The structure of ATP. The terminal phosphate groups are highlighted. (B) Attack by a hydroxide group in water to give ADP and inorganic phosphate ( $P_i$ ). Only the terminal phosphate groups of ATP are shown. The hydroxide ion attacks from a specific direction to form the transition state for the reaction, indicated by  $\ddagger$ . A few water molecules are shown, to stress the idea that the reaction occurs in solution and that there are interactions with water molecules that occur throughout the reaction.



energy is the difference in potential energy between the unreacted molecules and the transition state of the reaction.

Describing the reaction as occurring along just one coordinate is a great oversimplification, but this description provides useful insights into the fundamental aspects of the processes. A more complete diagram of energy versus distances for the exchange of a single atom with a diatomic molecule is also shown in Figure 15.35. Trajectories of the atoms as they go through a reaction correspond to lines on this potential energy surface and, in a complete description, would include vibrational motions as well as the relative translation.

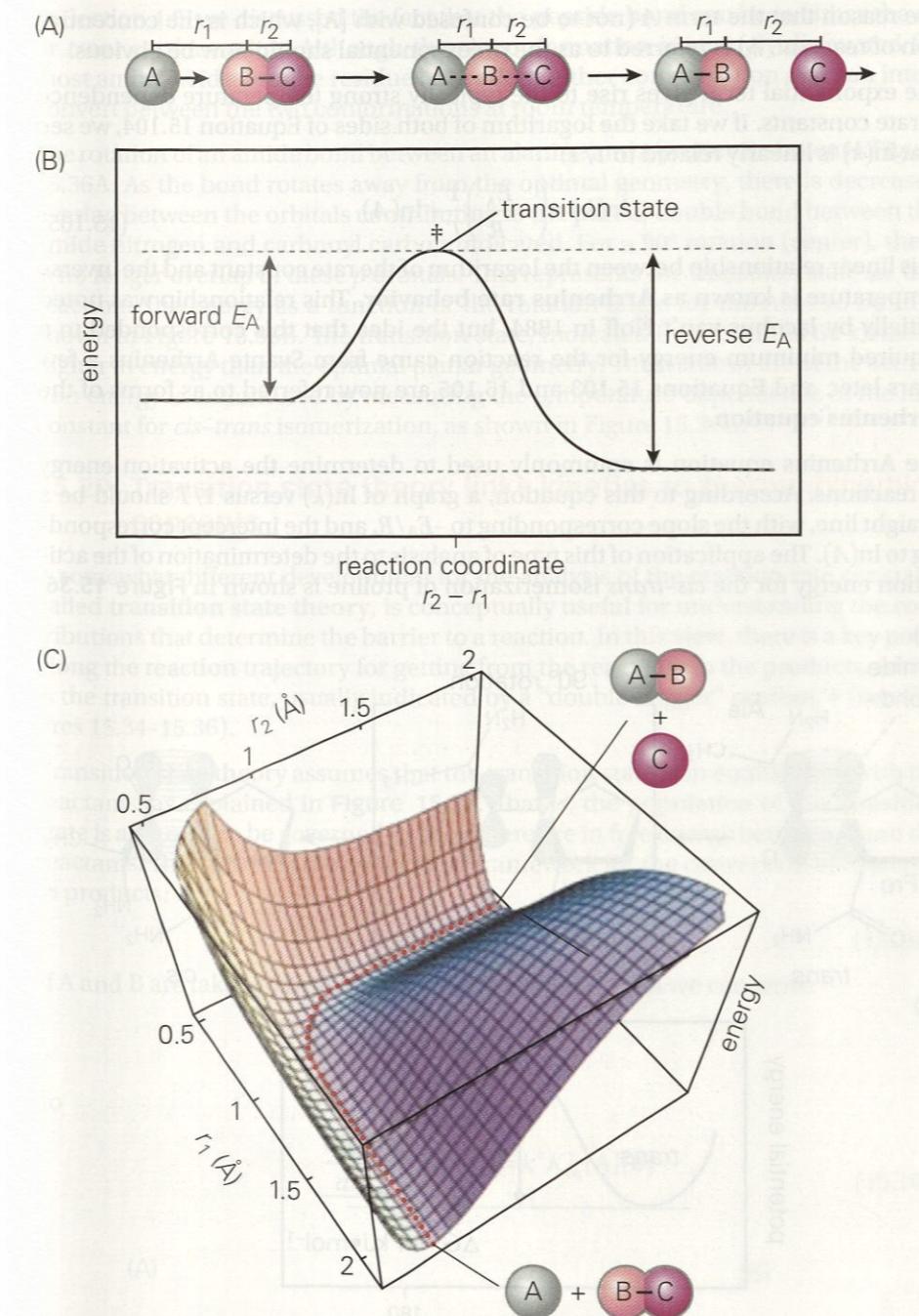
As molecules come together to undergo a chemical reaction, there is an increase in the potential energy, converted from kinetic energy of the reactants (which includes vibrational and rotational energy). The minimum increase in potential energy of the system along the reaction coordinate in order for the reaction to proceed is  $E_A$ , the activation energy. If the reacting molecules have sufficient energy to get past this point, then they can convert to products, releasing energy as they do. The value of  $E_A$  is specific for the particular reactants, as is the shape of the energy versus reaction coordinate plot.

### 15.28 The reaction rate depends exponentially on the activation energy

Recall from part B of Chapter 8 that energy is distributed among molecules according to the Boltzmann distribution. The fraction of molecules that have energy equal to  $E_A$  (expressed in  $J \cdot mol^{-1}$ ) is proportional to the Boltzmann factor:

$$e^{-\frac{E_A}{RT}}$$

When  $E_A$  is much larger than  $RT$ , then this Boltzmann factor is very small and only occasionally do colliding molecules have sufficient energy to react. If, however,  $E_A$  is much less than  $RT$  (equivalent to saying  $E_A \approx 0$ ), then essentially all collisions are reactive from the energy viewpoint and the rate becomes limited just by



**Figure 15.35 Energy vs. reaction coordinate diagram.** (A) A simple atom exchange reaction is shown. The reaction coordinate is the difference in separation of atom 1 and 2 ( $r_1$ ) and atoms 2 and 3 ( $r_2$ ). (B) The energy as a function of the reaction coordinate. The maximum point on this curve is the transition state marked with  $\ddagger$ . The energy barriers that must be overcome to bring the atoms together in the forward and reverse directions are indicated by  $E_A$ . (C) A more complete energy diagram. The reaction pathway shown by the red dotted line represents the minimum energy path from reactants to products and, drawn as a function of a single variable, it would look like the curve in (B). (C, adapted from C.M. Dobson, A. Šali and M. Karplus, *Angew. Chemie* 37: 868–893, 1998. With permission from John Wiley & Sons.)

encounters through diffusion and the orientational factor. Note that the activation energies in the forward and reverse directions of reactions are different, and the orientational factors will also be different.

The expected reaction rate constant is a product of the two factors we have discussed. The first is the combination of the reaction collision rate and the orientation effect,  $A$ , as given in Equation 15.102. The second is the Boltzmann factor, and together these give the following expression for the rate constant:

$$k = Ae^{-\frac{E_A}{RT}} \quad (15.103)$$

An overall kinetic equation for a bimolecular reaction can therefore be written as follows:

$$\frac{d[C]}{dt} = Ae^{-\frac{E_A}{RT}} [A][B] \quad (15.104)$$

The reason that the term  $A$  (not to be confused with  $[A]$ , which is the concentration of reactant,  $A$ ) is referred to as the preexponential should now be obvious. The exponential term gives rise to the typically strong temperature dependence of rate constants. If we take the logarithm of both sides of Equation 15.104, we see that  $\ln(k)$  is linearly related to  $1/T$ :

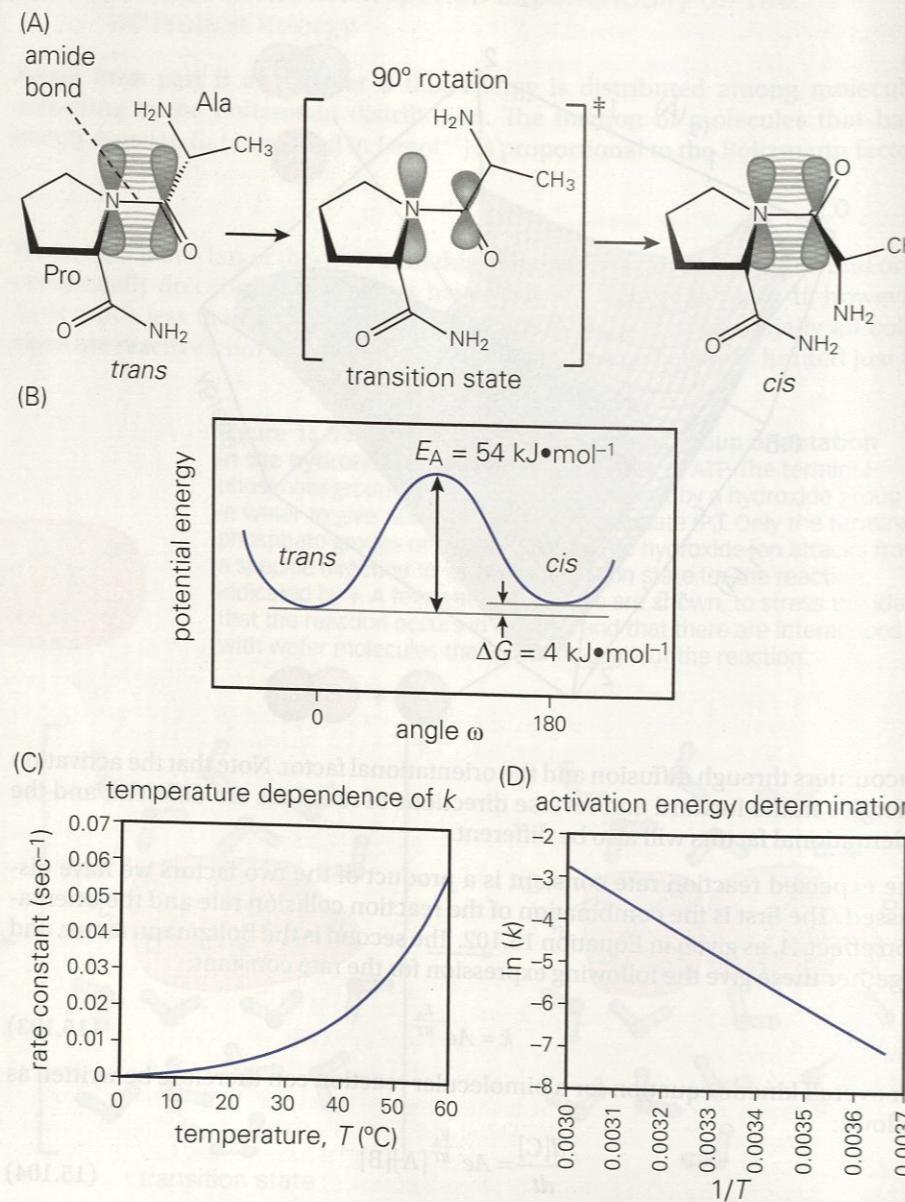
$$\ln(k) = \left( -\frac{E_A}{R} \right) \frac{1}{T} + \ln(A) \quad (15.105)$$

### Arrhenius rate behavior

Arrhenius rate behavior gives an exponential dependence of the rate on temperature,  $k \propto \exp(-E_A/RT)$ .

This linear relationship between the logarithm of the rate constant and the inverse temperature is known as **Arrhenius rate behavior**. This relationship was noted initially by Jacobus van't Hoff in 1884, but the idea that this corresponded to a required minimum energy for the reaction came from Svante Arrhenius a few years later, and Equations 15.103 and 15.105 are now referred to as forms of the **Arrhenius equation**.

The Arrhenius equation is commonly used to determine the activation energy of reactions. According to this equation, a graph of  $\ln(k)$  versus  $1/T$  should be a straight line, with the slope corresponding to  $-E_A/R$ , and the intercept corresponding to  $\ln(A)$ . The application of this type of analysis to the determination of the activation energy for the *cis-trans* isomerization of proline is shown in Figure 15.36.



**Figure 15.36 Activation energy analysis for peptide bond isomerization.** (A) Rotation of the amide bond between alanine and proline is shown, with the orbitals contributing to the partial double bond between the amide nitrogen and carbonyl carbon indicated. (B) Energy as a function of the rotation angle for the Ala-Pro bond. (C) A plot of the rate constant for proline isomerization vs. temperature,  $T$ . (D)  $\ln(k)$  vs.  $1/T$ . From the plot in part (D), the slope of the line gives the value of  $(-E_A/R)$ , with  $E_A = 54 \text{ kJ}\cdot\text{mol}^{-1}$  in this case.

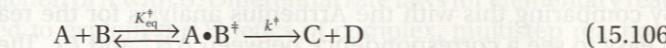
In Section 4.8, we discussed the fact that the peptide bond can be in either the *cis* or *trans* conformation. Although the *cis* conformation is strongly disfavored for most amino acids, proline residues can adopt either conformation and can interconvert between the two conformations at room temperature.

The rotation of an amide bond between an alanine and a proline is shown in Figure 15.36A. As the bond rotates away from the optimal geometry, there is decreased overlap between the orbitals contributing to the partial double bond between the amide nitrogen and carbonyl carbon indicated. For a  $90^\circ$  rotation (center), there is no longer overlap of these  $p$  orbitals. This represents the transition state for this reaction. The energy as a function of the rotation angle for the Ala-Pro bond is shown in Figure 15.36B. The transition state, indicated by  $\ddagger$ , is about  $54 \text{ kJ}\cdot\text{mol}^{-1}$  higher in energy than the optimal planar geometry. This value of the activation energy is determined by measuring the temperature dependence of the rate constant for *cis-trans* isomerization, as shown in Figure 15.36C.

### 15.29 Transition state theory links kinetics to thermodynamic concepts

A somewhat different development for the analysis of the reaction rate constant, called **transition state theory**, is conceptually useful for understanding the contributions that determine the barrier to a reaction. In this view, there is a key point along the reaction trajectory for getting from the reactants to the products, which is the transition state, usually indicated by a “double dagger” symbol,  $\ddagger$  (see Figures 15.34–15.36).

Transition state theory assumes that the transition state is in equilibrium with the reactants, as explained in Figure 15.37. That is, the population of the transition state is assumed to be governed by the difference in free energy between it and the reactants. This provides the conceptual framework for the conversion of reactants to products:

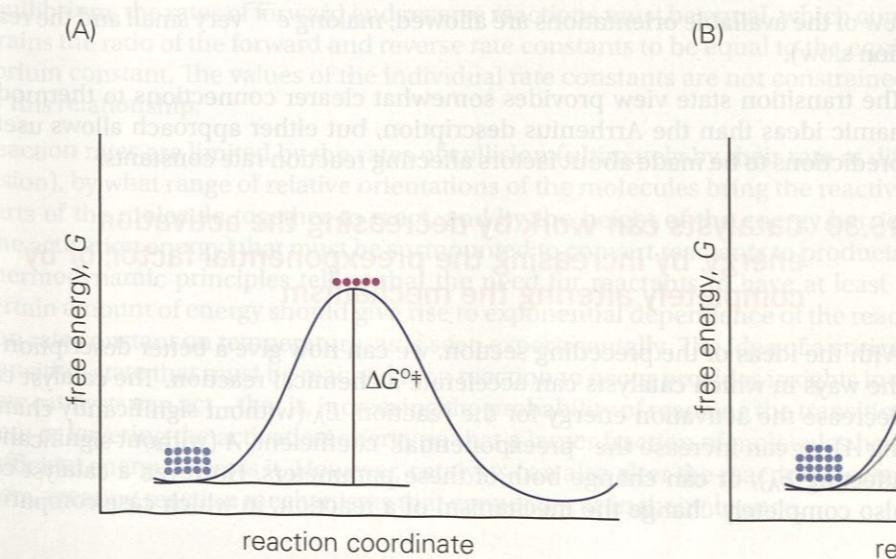


If A and B are taken to be in equilibrium with  $A \cdot B^{\ddagger}$ , then we can write:

$$K_{eq}^{\ddagger} = \frac{[A \cdot B^{\ddagger}]}{[A][B]}$$

so

$$\frac{d[C]}{dt} = k^{\ddagger}[A \cdot B^{\ddagger}] = k^{\ddagger} K_{eq}^{\ddagger} [A][B] \quad (15.107)$$

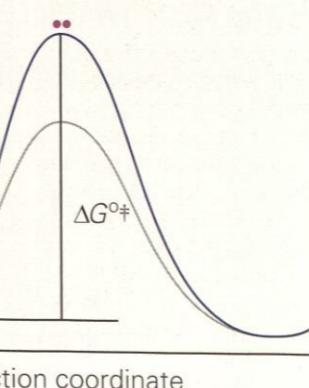


### Transition state theory

Transition state theory uses the concept of an equilibrium between the ground state and the transition state for a reaction to predict the temperature dependence of the reaction rate.

### Figure 15.37 Transition state theory.

In this theory, it is assumed that the number of molecules that are in the transition state for the reactions is determined by the equilibrium constant between the reactants and the transition state. (A) The graph shows the free energy as a function of the reaction coordinate for a reaction. The relative population of molecules in the reactant state and in the transition state is shown schematically by circles. (B) If the transition state has higher free energy, then the number of molecules in the transition state decreases.



In this analysis, we need to estimate  $k^\ddagger$ . Since the transition state is at a relative maximum in energy, it is intrinsically unstable, and any movement of atoms leads to a lower energy. Movements of atoms in molecules, even in this kind of transition state, correspond to vibrations. Because the bond being changed becomes weak in the transition state, the rate of crossing the transition state can be estimated as the rate of motion due to the vibration. The vibration frequency should be significantly lower than that typical of a stable, fully bonded molecule. This can be expressed as  $k^\ddagger = \kappa v$ , in which  $\kappa$  is a transmission coefficient (the fraction of molecules that do not reform the original bond after crossing the barrier, normally a value near 1), and  $v$  is the frequency of the relevant vibration. These ideas lead to the following expression for  $k^\ddagger$ :

$$k^\ddagger = \kappa \frac{k_B T}{h} \quad (15.108)$$

in which  $k_B$  is Boltzmann's constant,  $h$  is Planck's constant,  $\kappa \approx 1$  as described above. Understanding the basis for Equation 15.108 requires a more complicated analysis than is possible here, and you can consult advanced textbooks on kinetics to see how this equation arises.

Using the thermodynamic concepts of an equilibrium constant that were developed earlier:

$$\Delta G^\ddagger = -RT \ln K_{eq}^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (15.109)$$

Or, in exponential form:

$$K_{eq}^\ddagger = e^{-\frac{\Delta G^\ddagger}{RT}} = e^{-\frac{\Delta H^\ddagger}{RT}} e^{\frac{\Delta S^\ddagger}{R}} \quad (15.110)$$

Thus, together these ideas give the following expression for the rate:

$$\frac{d[C]}{dt} = \frac{k_B T}{h} e^{-\frac{\Delta H^\ddagger}{RT}} e^{\frac{\Delta S^\ddagger}{R}} [A][B] \quad (15.111)$$

By comparing this with the Arrhenius analysis for the reaction rate constant, it is easy to see a correspondence between  $\Delta H^\ddagger$  and  $E_A$ . The transition state viewpoint predicts an extra temperature dependence from the linear  $k_B T$  term, but this temperature dependence is very weak relative to that of the exponential, so that the correspondence between  $\Delta H^\ddagger$  and  $E_A$  in determining the overall temperature dependence is good.

The entropy change in getting to the transition state,  $\Delta S^\ddagger$ , and the restriction on angles that lead to products in the preexponential term,  $A$ , also have a clear connection. If the orientation for reaction is extremely restrictive, then there is a large loss of entropy in getting to the transition state ( $\Delta S^\ddagger$  is negative and large because few of the available orientations are allowed, making  $e^{\frac{\Delta S^\ddagger}{R}}$  very small and the reaction slow).

The transition state view provides somewhat clearer connections to thermodynamic ideas than the Arrhenius description, but either approach allows useful predictions to be made about factors affecting reaction rate constants.

### 15.30 Catalysts can work by decreasing the activation energy, by increasing the preexponential factor, or by completely altering the mechanism

With the ideas of the preceding section, we can now give a better description of the ways in which catalysts can accelerate a chemical reaction. The catalyst can decrease the activation energy for the reaction,  $E_A$  (without significantly changing  $A$ ), or can increase the "preexponential" coefficient,  $A$  (without significantly affecting  $E_A$ ), or can change both of these parameters. However, a catalyst can also completely change the mechanism of a reaction, in which case comparing

the kinetic parameters is not very meaningful. Serine proteases, discussed in the following chapter, provide an example in which the mechanism for an enzyme-catalyzed hydrolysis reaction is changed from that which occurs in water alone.

In presenting the idea of an activation energy, we noted that the potential energy reaches a maximum at the transition state. One common way for biological catalysts to accelerate the rate of a reaction is to have favorable interactions with the transition state, thereby lowering its energy, without changing the energy of the reactants or products substantially. This lowers the activation energy,  $E_A$ , and thereby increases the rate of reaction, as shown in Figure 15.38. This effect can be quite dramatic, because the activation energy enters the rate equation in an exponent.

The preexponential term,  $A$ , reflects a combination of the rates of collisions and the fraction of these that are in the correct orientation to actually react when sufficient energy is available. A catalyst can increase the rate of collisions or can cause more collisions to occur in a productive orientation by interacting with the reactants.

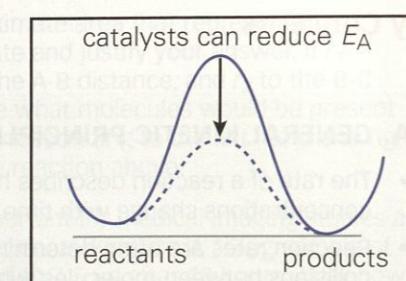
In biological systems, a vast majority of reactions are catalyzed by enzymes, which are discussed in the next chapter. Enzyme-catalyzed reactions in cells are critical for accelerating slow reactions sufficiently to meet the needs of the cells for specific compounds. The regulation of enzyme activity enables the rates of production of many metabolites to be controlled in response to the requirements of the cell.

### Summary

In this chapter, we have developed equations that describe the rates at which chemical reactions occur. Differential rate equations can be derived from the molecular mechanism of the reaction by using simple ideas predicted from the rates of collision for elementary reactions—for example, rate =  $k[A][B]$  for the direct, bimolecular reaction of A with B. Differential rate laws for elementary reactions can be combined to explain the kinetics of complex, multistep reactions. Integration of these differential rate laws predicts how concentrations of reactants and products change with time during a reaction. Experimentally determined rate laws can be used to test the consistency of mechanisms with the experimental data, providing important insight into how the reaction occurs.

Situations giving rise to steady-state concentrations in series reactions can be easily understood with these ideas. Steady-state conditions are important in many metabolic processes and will be used in understanding enzyme reactions. In systems with equilibrium constants that are close to unity, both the forward and reverse reactions have to be considered to correctly predict kinetic behavior. At equilibrium, the rates of forward and reverse reactions must be equal, which constrains the ratio of the forward and reverse rate constants to be equal to the equilibrium constant. The values of the individual rate constants are not constrained by this relationship.

Reaction rates are limited by the rates of collision (ultimately by their rate of diffusion), by what range of relative orientations of the molecules bring the reactive parts of the molecule together to react, and by the height of the energy barrier (the activation energy) that must be surmounted to convert reactants to products. Thermodynamic principles tell us that the need for reactants to have at least a certain amount of energy should give rise to exponential dependence of the reaction rate constant on temperature, as is seen experimentally. The idea of a critical transition state that must be reached for a reaction to occur provides insights into how catalysts can act—that is, increasing the probability of reaching the transition state or lowering the activation energy so that a larger fraction of molecules have sufficient energy to cross it. However, catalysts can also alter the reaction mechanism, creating reaction mechanisms that cannot occur in their absence.



**Figure 15.38 Schematic drawing of the effect of a catalyst.** One effect of a catalyst can be to lower the activation energy. The arrow indicates the decreased barrier; the energy for the catalyzed reaction is shown as a dashed line.

## Key Concepts

### A. GENERAL KINETIC PRINCIPLES

- The rate of a reaction describes how fast concentrations change with time.
- Reaction rates are often determined by the rate of collisions between molecules, which depends on the concentrations.
- Rate laws define the relationship between the reaction rates and concentrations.
- The dependence of the rate law on the concentrations of reactants defines the order of the reaction.
- The integration of rate equations predicts the time dependence of concentrations.
- The concentration of reactants decreases exponentially with time for a first-order reaction.
- The reactants decay more slowly in second-order reactions than in first-order reactions with the same rate constant, but the details depend on the particular type of reaction and the conditions.
- The half-life for a reaction provides a measure of the speed of the reaction.
- For a reaction with intermediate steps, the slowest step determines the overall rate.
- Multistep reactions have intermediates that build up as the reaction is initiated, but disappear as the reaction goes to completion.
- A steady-state condition in a reaction means that a concentration does not change with time although the reaction is occurring.
- Steady-state reactions are important in metabolism.
- For reactions with alternative products, the relative values of rate constants determine the distribution of products.
- Measurement of fluorescence provides an easy way to monitor kinetics.

## Problems

### True/False and Multiple Choice

- What is the order of this elementary reaction:  
 $A + 2B \rightarrow 1C$ 
  - 2
  - 7
  - 4
  - 3
  - 8
- The addition of a catalyst increases the rate of the reaction but not the equilibrium constant.  
 True/False
- For a reaction with a larger  $\Delta G$  compared to a reaction with a smaller  $\Delta G$ ,
  - The reaction with the larger  $\Delta G$  is always the faster reaction.
  - The reaction with the larger  $\Delta G$  is always the slower reaction.
  - The two rates are equal.
  - It is impossible to decide which reaction is faster.
- For elementary reactions of zero and second order with a rate constant of 1 (with appropriate units),

### B. REVERSIBLE REACTIONS

- For reversible reactions (that is, ones for which the equilibrium constant is close to unity), both forward and reverse reactions must be considered in calculating the approach to equilibrium.
- The ratio of forward and reverse rate constants must equal the equilibrium constant.
- Relaxation methods provide a way to obtain rate constants for reversible reactions.
- Temperature jump experiments can be used to determine the association and dissociation rate constants for reactions such as dimerization.
- The rate constants for a cyclic set of reactions are coupled.

### C. FACTORS THAT AFFECT THE RATE CONSTANT

- Catalysts accelerate the rates of chemical reactions without being consumed in the process.
- Rate laws for reactions must be determined experimentally.
- The fastest possible reaction rate is determined by the diffusion-limited rate of collision.
- Most reactions occur more slowly than the diffusion-limited rate.
- The activation energy is the minimum energy required to convert reactants to products during a collision between molecules.
- The activation energy gives rise to an exponential dependence of rate on temperature through a Boltzmann factor.
- Transition state theory links kinetics to thermodynamic concepts.
- Catalysts for reactions can accelerate a reaction by lowering the activation energy or by affecting collision rates or orientation factors.

the second-order reaction half-life is a shorter period of time.

True/False

5. The most basic step used to describe a reaction process is:

- The transition state.
- An elementary reaction.
- A unimolecular reaction.
- The steady state.
- The equilibrium rate.

6. The probability of a bimolecular reaction occurring is related to the rate of collisions between the two species of molecules.

True/False

7. After excitation, the intensity of light emitted by a sample of fluorescent molecules drops exponentially with time.

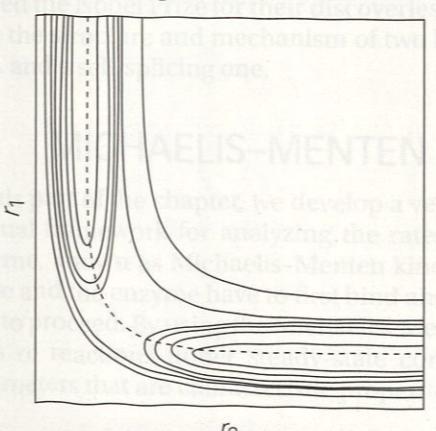
True/False

### Fill in the Blank

- The symbol “‡” is used to represent the \_\_\_\_\_ of the reaction.
- The rate law gives the relationship between the rate of a reaction and the \_\_\_\_\_ of the chemical species involved in the reaction.
- The rate constant for a \_\_\_\_\_-order elementary reaction is  $M^{-1}\cdot sec^{-1}$ .
- The rate of product formation at the end of a pathway is determined by the rate of the \_\_\_\_\_ step.
- Catalysts can work by changing the reaction mechanism, \_\_\_\_\_, or \_\_\_\_\_.

### Quantitative/Essay

- How do the kinetics of hydrolysis of ATP to ADP and phosphate by water make it a good energy reservoir for the cell?
- Below is a two-dimensional energy versus reaction coordinate diagram for the reaction  $AB + C \rightarrow A + BC$ .



Circle the approximate area that represents the transition state and justify your answer. If  $r_1$  corresponds to the A-B distance, and  $r_2$  to the B-C distance, indicate what molecules would be present in the regions corresponding to the left hand and right hand sides of the reaction above.

- Iodine-123 is important for medical imaging studies and follows first-order decay kinetics. A 15- $\mu g$  sample of I-123 has decayed to 7.5  $\mu g$  after 13 hours. After how much time will it decay to only 1.5  $\mu g$ ?
- A reaction is half complete after 20 minutes. After 40 minutes the reaction is two-thirds complete. When will the reaction be 90% complete?
- A protein (P) can either fold properly into the native state (N) or aggregate into a misfolded form (A). Both processes obey first-order kinetics. The branching ratio ( $[N]/[A]$ ) is 9 and the effective rate constant,  $k_{eff}$ , is 15  $sec^{-1}$ . What is the rate constant for native state folding?
- Upon excitation, a modified green fluorescent protein emits photons that yield an initial intensity of 10,000 units in the fluorimeter. After 2 nanoseconds, the signal has decayed to 300 units. If the rate constant for fluorescent production of light ( $k_f$ ) is 0.1  $nsec^{-1}$ , what are the values of the rate constant for heat production ( $k_h$ ) and the fluorescence lifetime ( $\tau_f$ )?
- An experiment is performed to measure the affinity of the human proline isomerase hCypA to the inhibitor cyclosporin, analogous to the experiments described for imatinib in this chapter. At 25  $\mu M$  cyclosporin, the value of  $k_{obs}$  is measured to be 12.55  $sec^{-1}$ . Given that the off-rate is 0.01  $sec^{-1}$ , what is the on-rate?
- A homologous proline isomerase, vCypA, is isolated from a deadly virus. The kinetics of cyclosporin binding to vCypA were measured. The off-rate is 0.1  $sec^{-1}$  and the on-rate is 0.05  $\mu M^{-1}\cdot sec^{-1}$ . What concentration of cyclosporin was used to yield  $k_{obs} = 120 sec^{-1}$ ?
- Several experiments indicate that the vCypA is essential for viral replication. Use the parameters calculated in Problems 19 and 20, and assume that the concentration of cyclosporin would be much larger than the concentration of either vCypA or hCypA. For each protein, calculate the value of  $K_D$  for cyclosporin. Given the ratio of the two  $K_D$  values, explain whether cyclosporin could be an effective treatment for this virus.
- The activation energy for proline isomerization of a peptide depends on the identity of the preceding residue and obeys Arrhenius rate behavior. Experiments are conducted on the isomerization of an alanine-proline peptide. At 25°C (298 K) the observed rate constant is 0.05  $sec^{-1}$  and the value of  $E_A$  is calculated to be 60  $kJ\cdot mol^{-1}$ . What is the value of the preexponential factor ( $A$ )? Similar measurements are performed on a phenylalanine-proline peptide at 25°C, with a measured rate constant of 0.005  $sec^{-1}$ . Assuming an identical preexponential factor as the alanine-proline peptide, what is the activation energy for this peptide?