CHAPTER 6

Energy and Metabolism

All living things require energy because life processes involve work. It may seem obvious that cells need energy to grow and reproduce, but even nongrowing cells need energy simply to maintain themselves. The sun is the ultimate source of almost all the energy that powers life. Plants and other photosynthetic organisms capture a tiny portion of the sun's energy and, in the process of photosynthesis, convert it to chemical energy in organic molecules. The chemical energy captured by photosynthesis and stored in seeds and leaves is transferred to animals, such as this black-tailed prairie dog, when they eat. Plants, animals, or other organisms need the energy stored in these organic molecules, and they commonly use the process of cellular respiration to break them apart and convert their energy to more immediately usable forms.

Because energy cannot be created or destroyed, cells have no way to produce new energy. Energy is captured from the environment, temporarily stored, and then used to perform biological work. However, not all of the captured energy can be used for work; at every step some inevitably becomes converted to heat and is dispersed back into the environment.

Cells obtain energy in many forms, but seldom can that energy be used directly to power cellular processes. For this reason cells have mechanisms that convert energy from one form to another. Because most of the components of these energy conversion systems evolved very early in the history of life, many aspects of energy metabolism tend to be very similar in a wide range of organisms.

This chapter focuses on some of the basic principles that govern how cells capture, transfer, store, and use energy. We discuss the functions of ATP and other molecules used in energy conversions, including those that transfer electrons in redox reactions. We also pay particular attention to the essential role of enzymes in cellular energy dynamics. In Chapter 7 we will explore some of the main metabolic pathways used in cellular respiration, and in Chapter 8 we will discuss the energy transformations of photosynthesis. The flow of energy in ecosystems is discussed in Chapter 53.

(Barbara Gerlach/Visuals Unlimited)

Learning Objectives

After you have studied this chapter you should be able to

1. Define energy, emphasizing how it is related to work and to heat.
2. Use examples to contrast potential energy and kinetic energy.
3. State the first and second laws of thermodynamics and discuss the implications of these laws as they relate to organisms.
4. Discuss how changes in free energy in a reaction are related to changes in entropy and enthalpy.
5. Compare the energy dynamics of a reaction at equilibrium with the dynamics of a reaction not at equilibrium.
6. Distinguish between exergonic and endergonic reactions and give examples of how they may be coupled.
7. Explain how the chemical structure of ATP allows it to transfer a phosphate group. Discuss the central role of ATP in the overall energy metabolism of the cell.
8. Relate the transfer of electrons (or hydrogen atoms) to the transfer of energy.
9. Explain how an enzyme lowers the required energy of activation for a reaction.
10. Describe some of the ways enzymes are regulated.

Biological Work Requires Energy

Energy, one of the most important concepts in biology, can be understood in the context of **matter,** which is anything that has mass and takes up space. **Energy** can be defined as the capacity to do **work,** which is any change in the state or motion of matter.

Biologists generally express energy in units of work **(kilojoules, kJ)** or units of heat energy **(kilocalories, kcal).** One kilocalorie equals 4.184 kilojoules. Because heat energy cannot do cellular work, the kilojoule is the unit preferred by most biologists today (see *Making the Connection: Energy, Work, and Heat*). However, we will use both units because references to the kilocalorie are common in the scientific literature.

Many of the activities performed by an organism are mechanical. At this very moment you are expending considerable energy to carry out such activities as breathing and circulating your blood. In these processes, the state or position of matter is changed in some way. However, these forms of mechanical work are the consequence of cellular activities. For example, the cells of the heart muscle use a great deal of energy to contract, thereby pumping the blood through your body. As we will see, however, not all of the work of cells is mechanical. A great deal of it is chemical. For example, heart muscle cells expend energy to synthesize the proteins required for contraction. Energy can be converted to many different forms, including not only mechanical and chemical energy, but also heat energy, electrical energy, and radiant energy.

Making the Connection

Energy, Work, and Heat

Why can we express energy both in units of work (kilojoules) and in units of heat energy (kilocalories)? We can because of a conceptual breakthrough that came about in the 1800s, after the invention of the steam engine. Scientists studying the connections among the heat energy that powered the engine, the mechanical work that the engine was able to perform, and the heat that was transferred to the environment were able to demonstrate that all these forms of energy are interconvertable.

Today we know that not only mechanical work but all forms of energy can be converted to heat. In fact, the study of energy and its transformations has been named thermodynamics, that is, heat dynamics. (Recall from Chapter 2 that *heat* refers to the total amount of kinetic energy in a sample of a substance, whereas *temperature* refers to the average kinetic energy of the particles.) **Heat energy** is energy that can flow from an object with a higher temperature (known as the heat source) to an object with a lower temperature (the heat sink).

Cells cannot work as heat engines because they are isothermal; they are too small to have regions that differ in temperature. Therefore, heat cannot be used to do biological work. Nevertheless, the fact that all forms of energy can be converted to heat is useful to scientists because heat energy is particularly convenient to measure.

Nutritionists use the kilocalorie to express the potential energy of foods and usually refer to it as a Calorie (with a capital C; see Chapter 45). For example, the energy content of 10 grams, about 2 teaspoons, of table sugar (sucrose) is about 36 Calories (36 kcal or 151 kJ), whereas the energy content of 20 potato chips is about 150 Calories (150 kcal or 628 kJ). A person weighing 58 kilograms (130 pounds) uses about 1 kcal (4.184 kJ) per minute to maintain the body while sleeping and up to 10 kcal (41.84 kJ) per minute when engaged in strenuous activity.

Organisms carry out conversions between potential energy and kinetic energy

When an archer draws a bow, **kinetic energy,** which is energy of motion, is used and work is done (Fig. 6–1). The resulting tension in the bow and string represents stored energy, or **potential energy.** Potential energy is the capacity to do work owing to position or state. When the string is released, this potential energy is converted to kinetic energy in the motion of the bow, which propels the arrow.

Most of the actions of an organism involve a complex series of energy transformations that occur as kinetic energy is converted to potential energy or as potential energy is converted to kinetic energy. For example, potential energy derived from chemical energy of food molecules is converted to kinetic energy in the muscles of the archer.

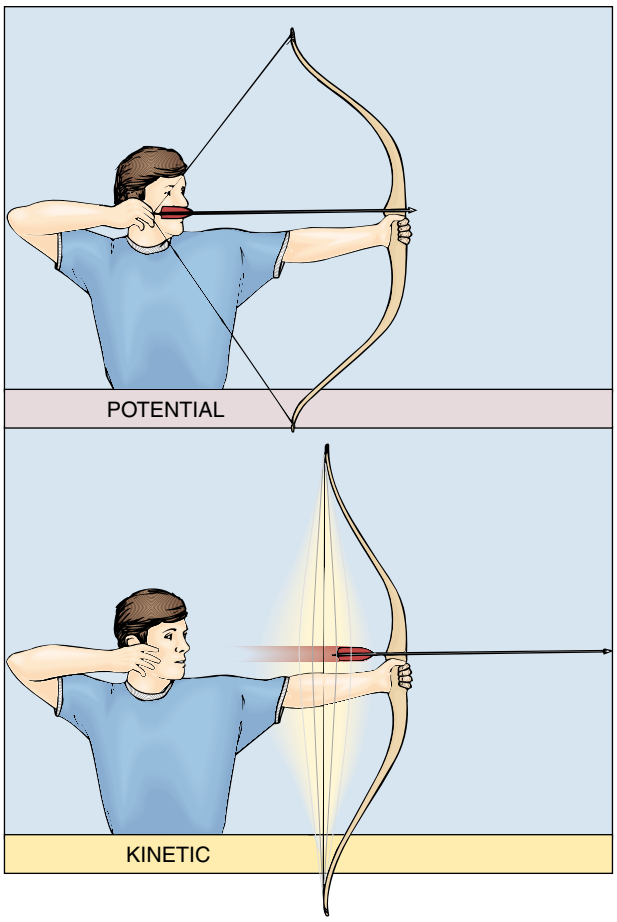


Figure 6–1 Potential versus kinetic energy. The potential chemical energy released by cellular respiration is converted to kinetic energy in the muscles, which do the work of drawing the bow. The potential energy stored in the drawn bow is transformed into kinetic energy as the bowstring pushes the arrow toward its target.

TWO LAWS OF THERMODYNAMICS GOVERN ENERGY TRANSFORMATIONS

All the activities of our universe, from the life and death of cells to the life and death of stars, are governed by **thermodynamics,** which is the study of energy and its transformations. When considering thermodynamics, scientists use the term *system* to refer to an object that is being studied, whether it is a cell, an organism, or planet Earth. The rest of the universe other than the system being studied is known as the *surroundings*. A **closed system** is one that does not exchange energy or matter with its surroundings, whereas an **open system** is one that can exchange matter and energy with its surroundings (Fig. 6–2). There are two laws about energy that apply to all things in the universe. These are known as the first and second laws of thermodynamics.

The total energy in the universe does not change

According to the **first law of thermodynamics,** energy cannot be created or destroyed, although it can be transferred or changed from one form to another. As far as we know, the energy present in the universe at its formation, approximately 15 to 20 billion years ago, equals the amount of energy present in the universe today.[1] This is all the energy that can ever be present in the universe. Similarly, the energy of any system and its surroundings is constant. A system may absorb energy from its surroundings, or it may give up some energy into its surroundings, but the total energy content of that system and its surroundings is always the same.

[1]Technically, mass is a form of energy, and so we should say that the total mass-energy of the universe is a constant. Energy can be produced from mass (recall Einstein's famous equation $E = mc^2$). This is the basis behind the energy generated by the sun and stars. More than 4 billion kilograms of matter per second are converted to energy in our sun.

As specified by the first law of thermodynamics, then, organisms cannot create the energy that they require to live. Instead, they must capture energy from the environment to use for biological work, a process involving the transformation of energy from one form to another. In photosynthesis, for example, plants absorb the radiant energy of the sun and convert it into the chemical energy contained in the bonds of carbohydrate molecules. Some of that chemical energy may later be transformed by the plant to do various types of cellular work or by some animal that eats the plant and might convert it to the mechanical energy of muscle contraction or some other needed form.

The entropy of the universe is increasing

As each energy transformation occurs, some of the energy is converted to heat energy that is then given off into the cooler surroundings. This energy can never again be used by any organism for biological work; it is lost from the biological point of view. However, it is not really gone from a thermodynamic

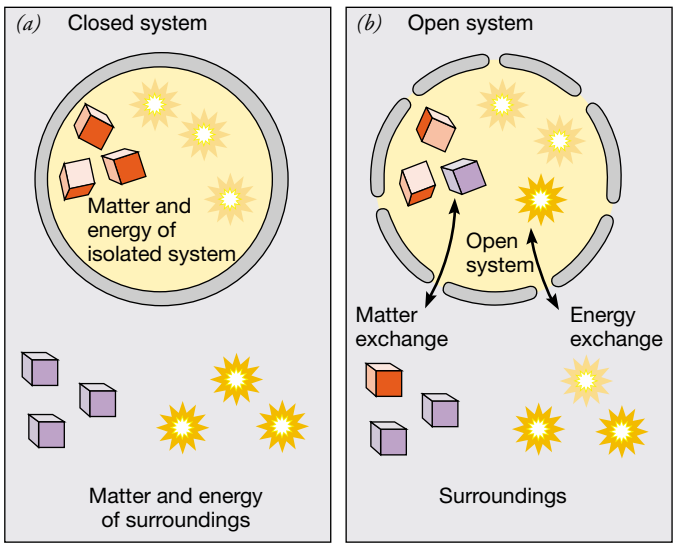
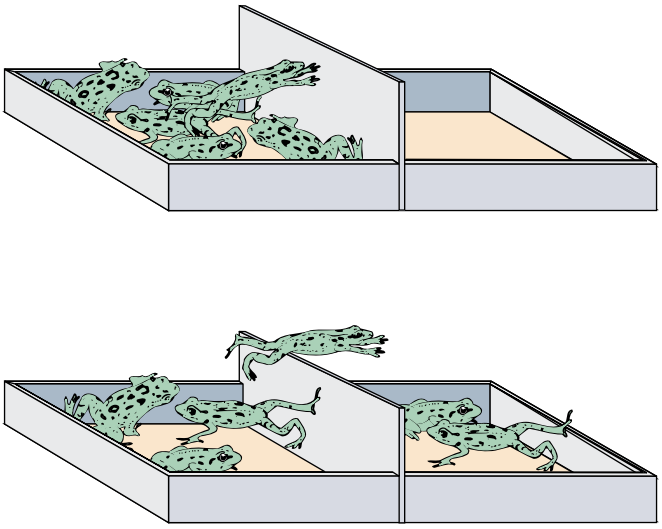


Figure 6–2 Closed and open systems. *(a)* Matter and energy are not exchanged between a closed system and its surroundings. *(b)* Matter and energy are exchanged between an open system and its surroundings. *(Adapted from Tobin and Morel)*



(a)

(b)

Figure 6–3 Entropy. *(a)* Entropy as demonstrated by frogs. The frogs are placed on one side of a box with partitions to represent a highly ordered system. As the frogs hop into the other side and back again so that they are randomly distributed throughout both sides of the box, they represent a system of greater entropy. *(b)* Similarly, the beaker on the left, in which all marbles of the same color are located together, represents a highly organized system with low entropy. The beaker on the right, in which the marbles are randomly arranged, regardless of color, represents a more disorganized system with greater entropy. *(a, Adapted from Tobin and Morel; b, Dennis Drenner)*

point of view because it still exists in the surroundings. For example, the use of food to enable us to walk or run does not destroy the chemical energy that was once present in the food molecules. After we have performed the task of walking or running, the energy still exists in the surroundings as heat.

The **second law of thermodynamics** can be stated most simply as follows: when energy is converted from one form to another, some usable energy, that is, energy available to do work, is degraded into a less usable form, heat, that disperses into the surroundings. As a result, the amount of usable energy available to do work in the universe decreases over time.

It is important to understand that the second law of thermodynamics is consistent with the first law; that is, the total amount of energy in the universe is *not* decreasing with time. However, the energy available to do work is being degraded to less-usable energy with time.

Less-usable energy is more diffuse, or disorganized. **Entropy (*S*)** is a measure of this disorder or randomness; organized, usable energy has a low entropy, whereas disorganized energy such as heat has a high entropy (Fig. 6–3). The total entropy of the universe is continuously increasing in all natural processes. It may be that at some time, billions of years from now, all energy will exist as heat uniformly distributed throughout the universe. If that happens, the universe will cease to operate because no work will be possible. Everything will be at the same temperature, so there will be no way to convert the thermal energy of the universe into usable mechanical energy.

Another way to explain the second law of thermodynamics, then, is that entropy, or disorder, in a closed system tends to increase spontaneously over time. (The word *spontaneously* in this context means that entropy occurs naturally rather than being caused by some external influence.)

As a result of the second law of thermodynamics, no process requiring an energy conversion is ever 100% efficient, because much of the energy is dispersed as heat, resulting in an increase in entropy. For example, an automobile engine, which converts the chemical energy of gasoline to mechanical energy, is between 20% and 30% efficient. That is, only 20% to 30% of the original energy stored in the chemical bonds of

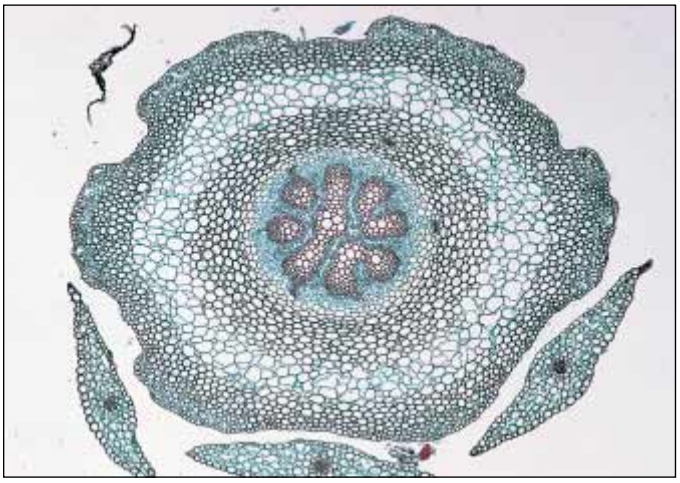


Figure 6–4 LM of club moss stem cross section. The highly organized cellular structure of this *Lycopodium clavatum* stem is developed and maintained only by the constant input of energy from the sun. Thus, the high degree of organization of living things does not refute the second law of thermodynamics. *(John D. Cunningham/Visuals Unlimited)*

the gasoline molecules is actually transformed into mechanical energy; the other 70% to 80% is dissipated as waste heat. Energy utilization in our cells is about 40% efficient, with the remaining energy given to the surroundings as heat.

Organisms have a high degree of organization, and at first glance they appear to refute the second law of thermodynamics (Fig. 6–4). As organisms grow and develop, they maintain a high level of order and do not appear to become more disorganized. However, organisms are able to maintain their degree of order over time only with the constant input of energy from their surroundings. That is why plants must photosynthesize and animals must eat. Although the order of organisms might tend to increase temporarily, the total entropy of the universe (organisms plus surroundings) will increase over time.

Metabolic reactions involve energy transformations

The chemical reactions that enable an organism to carry on its activities—to grow, move, maintain and repair itself, reproduce, and respond to stimuli—together make up its **metabolism.** Metabolism was defined in Chapter 1 as the sum of all the chemical activities that take place in an organism. An organism's metabolism consists of many intersecting series of chemical reactions, or pathways, which are of two main types. **Anabolism** refers to the various pathways in which complex molecules are synthesized from simpler substances, such as the linking of amino acids to form proteins. **Catabolism** includes the pathways in which larger molecules are broken down into smaller ones, such as the degradation of starch to form monosaccharides.

As we will see, these changes not only involve alterations in the arrangement of atoms, but also various energy transformations. Catabolism and anabolism are complementary processes; catabolic pathways involve an overall release of energy, some of which is used to power the anabolic pathways, which have an overall energy requirement. In the following sections we will discuss how to predict whether a particular chemical reaction requires energy or releases it.

Enthalpy is the total potential energy of a system

In the course of any chemical reaction, including the metabolic reactions of a cell, chemical bonds break, and new and different bonds may form. Every specific type of chemical bond has a certain amount of **bond energy,** defined as the energy required to break that bond. The total bond energy is essentially equivalent to the total potential energy of the system, a quantity known as **enthalpy (*H*).** Because energy can be conveniently measured as heat, enthalpy is often referred to as the heat content of the system.

Free energy is energy that is available to do cellular work

Entropy and enthalpy are related by a third dimension of energy, termed **free energy (*G*),** which is the amount of energy available to do work under the conditions of a biochemical reaction. Free energy, the only kind of energy that can do cellular work, is the aspect of thermodynamics of greatest interest to a biologist.

Entropy (S) and free energy (G) are related inversely; as entropy increases, the amount of free energy decreases. The two are related by the following equation:

$$G = H - TS$$

in which G is the free energy, H is the enthalpy of the system, T is the absolute temperature expressed in degrees Kelvin, and S is entropy. If we assume that entropy is zero, the free energy is simply equal to the total potential energy (enthalpy); an increase in entropy reduces the amount of free energy.

What is the significance of the temperature (T)? Remember that as the temperature increases, there is an increase in random molecular motion that contributes to disorder and multiplies the effect of the entropy term.

Chemical reactions involve changes in free energy

Biologists need ways to analyze the role of energy in the many reactions that comprise metabolism. Although the total free energy of a system (G) cannot be effectively measured, the equation $G = H - TS$ can be extended to predict whether any

particular chemical reaction will release energy or require an input of energy. This is because *changes* in free energy can be measured. We use the Greek letter delta (Δ) to denote any change that occurs in the system between its initial state before the reaction and its final state after the reaction. To express what happens with respect to energy in a chemical reaction, the equation becomes:

$$\Delta G = \Delta H - T\Delta S$$

Notice that the temperature does not change; it is held constant during the reaction. Thus the change in free energy (ΔG) during the reaction is equal to the change in enthalpy (ΔH) minus the product of the absolute temperature (T) multiplied by the change in entropy (ΔS). ΔG and ΔH are expressed in kilojoules or kilocalories per mole; ΔS is expressed in kilojoules per degree or in kilocalories per degree.

Free energy decreases during an exergonic reaction

In accordance with the second law of thermodynamics, no chemical reaction is 100% efficient. No reaction can take place without a decrease in enthalpy, an increase in entropy, or both (see *Making the Connection: Energy and Diffusion*). For this reason, the total free energy of the system in its final state is always less than the total free energy of the system in its initial state. When calculated in this way, ΔG is a negative number. Such a reaction, with a $-\Delta G$, is referred to as an **exergonic reaction** (Fig. 6–5*a*).

An exergonic reaction releases energy and is said to be a spontaneous or a "downhill" reaction. The term *spontaneous* may give the false impression that such reactions are always instantaneous. In fact, spontaneous reactions do not necessarily occur readily; some are extremely slow. This is because energy, known as activation energy, is required to initiate every reaction, even a spontaneous one. Activation energy will be discussed later in the chapter.

Free energy increases during an endergonic reaction

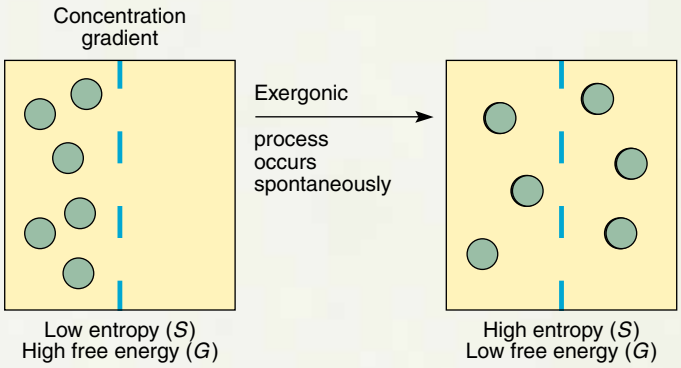
An **endergonic reaction** is a reaction in which there is a gain of free energy (Fig. 6–5*b*). Because the free energy of the products is greater than the free energy of the reactants, ΔG has a positive value. Such a reaction cannot take place in isolation. Instead, it must occur in such a way that energy can be supplied from the surroundings. Of course, many energy-requiring reactions take place in cells, and, as we will see, metabolic mechanisms have evolved that supply the energy needed to "drive" these nonspontaneous cellular reactions in a particular direction.

MAKING THE CONNECTION

Energy and Diffusion

What is the source of energy for diffusion? In Chapter 5 we saw that randomly moving particles can diffuse down their own **concentration gradient** (see figure). That is, although the movements of the individual particles are random, net movement of the group of particles seems to be directional. What provides the energy for this seemingly directed process? A concentration gradient, with a region of higher concentration and another region of lower concentration, is an orderly state. A cell must expend energy to produce a concentration gradient. Because work must be done to produce this order, the concentration gradient is a form of potential energy. As the particles move about randomly, disorder increases. Although there is no change in enthalpy, entropy increases. The process is spontaneous because there is an overall decrease in free energy ($-\Delta G$); diffusion is paid for by an increase in entropy.

In cellular respiration and photosynthesis, the potential energy stored in a concentration gradient of hydrogen ions (H^+) can be transformed into chemical energy in ATP as the hydrogen ions pass through a membrane down the concentration gradient. This important concept, known as **chemiosmosis,** will be discussed further in Chapters 7 and 8.



Energy, entropy, and diffusion. The tendency of entropy to increase can be used to produce work, in this case, diffusion. *(Left)* A concentration gradient is a form of potential energy. *(Right)* When molecules are evenly distributed, they have a high entropy.

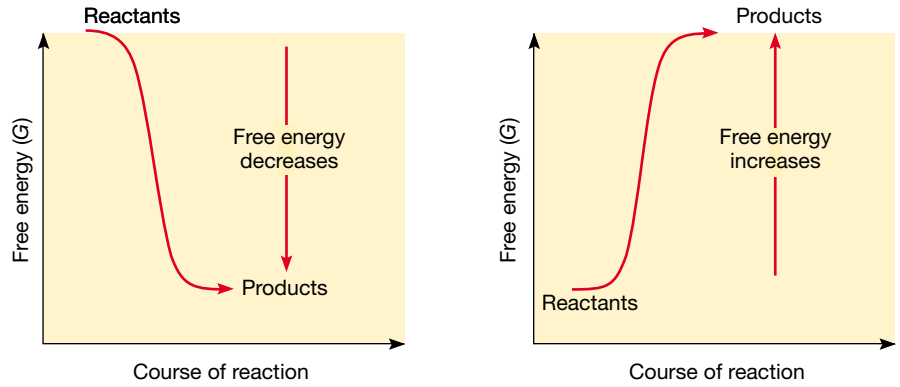


Figure 6–5 **Exergonic and endergonic reactions.** *(a)* In an exergonic reaction there is a net loss of free energy. The products have less free energy than was present in the reactants, and the reaction proceeds spontaneously. *(b)* In an endergonic reaction there is a net gain in free energy. The products have more free energy than was present in the reactants. An endergonic reaction occurs only if energy lost from some other system is fed into the reaction. *(Adapted from Tobin and Morel)*

Free energy changes depend on the concentrations of reactants and products

According to the second law of thermodynamics, any process that increases entropy (S) can do work. Differences in concentration of a substance, for example, between two different parts of a cell, represent a more orderly state than when the substance is diffused homogeneously throughout the cell. We have seen that free energy changes in any chemical reaction depend mainly on the difference in bond energies (enthalpy, H) between reactants and products. Free energy also depends on *concentrations* of both reactants and products. The change in molecules from a more concentrated to a less concentrated state increases entropy because it is movement from a more orderly to a less orderly state.

In most biochemical reactions there is little intrinsic free energy difference between reactants and products. Such reactions are reversible, a fact that is indicated by drawing double arrows ($\rightleftharpoons$) between the reactants and the products.

$$A \rightleftharpoons B$$

At the beginning of a reaction, only the reactant molecules (A) may be present. As the reaction proceeds, the concentration of the reactant molecules decreases, and the concentration of the product molecules (B) increases. As the concentration of the product molecules increases, they may have enough free energy to initiate the reverse reaction. The reaction thus proceeds in both directions simultaneously; if undisturbed it could eventually reach a state of **dynamic equilibrium,** in which the rate of the reverse reaction is equal to the rate of the forward reaction. At equilibrium there is no net change in the system; every forward reaction is balanced by a reverse reaction.

Knowledge that a system is at equilibrium tells us nothing about the relative concentrations of reactants and products at equilibrium. If the reactants have much greater intrinsic free energy than the products, the reaction goes almost to completion; that is, it reaches equilibrium at a point at which most of the reactants have been converted to products. Reactions in which the reactants have much less intrinsic free energy than the products reach equilibrium at a point where very few of the reactant molecules have been converted to products.

If we increase the initial concentration of A, then the equilibrium will "shift to the right," and more A will be converted to B; a similar effect can be obtained if B is removed from the reaction mixture. The opposite effect occurs if the concentration of B is increased, or if A is removed; here the equilibrium "shifts to the left." The actual free energy change that occurs during a reaction is defined mathematically to include these effects, which are a consequence of the relative initial concentrations of reactants and products.

Cells manipulate the relative concentrations of reactants and products of almost every reaction. Cellular reactions are virtually never at equilibrium. By displacing their reactions far from equilibrium, cells are able to supply energy to endergonic reactions and direct their metabolism in accordance with their needs.

Cells drive endergonic reactions by coupling them to exergonic reactions

Many metabolic reactions such as protein synthesis are anabolic and endergonic. Because an endergonic reaction cannot take place without an input of energy, endergonic reactions are coupled to exergonic reactions. In **coupled reactions,** the thermodynamically favorable exergonic reaction provides the energy required to drive the thermodynamically unfavorable endergonic reaction. The endergonic reaction can proceed only if it absorbs free energy released by the exergonic reaction to which it is coupled.

Consider the free energy change, ΔG, in the following reaction:

$$(1)\ A \longrightarrow B \qquad \Delta G = +20.9 \text{ kJ/mole } (+5 \text{ kcal/mole})$$

Because ΔG has a positive value, we know that the product of this reaction has more free energy than the reactant. This is an endergonic reaction. It is not spontaneous and does not take place without an energy source.

By contrast, consider the following reaction:

(2) C $\longrightarrow$ D $\quad \Delta G = -33.5$ kJ/mole (-8 kcal/mole)

The negative value of ΔG tells us that the free energy of the reactant is greater than the free energy of the product. This exergonic reaction can proceed spontaneously.

We can sum up Reactions 1 and 2 as follows:

(1) A $\longrightarrow$ B	$\Delta G = +20.9$ kJ/mole ($+5$ kcal/mole)
(2) C $\longrightarrow$ D	$\Delta G = -33.5$ kJ/mole (-8 kcal/mole)
Overall	$\Delta G = -12.6$ kJ/mole (-3 kcal/mole)

Because thermodynamics considers the overall changes in these two reactions, which show a net negative value of ΔG, the two reactions taken together are exergonic.

The fact that we can write reactions this way is a useful bookkeeping device, but it does not mean that an exergonic reaction can mysteriously transfer energy to an endergonic "bystander" reaction. However, these reactions can be coupled if their pathways are altered such that they are linked by a common intermediate. Reactions 1 and 2 might be coupled by an intermediate (I) in the following way:

(3) A + C $\longrightarrow$ I	$\Delta G = -8.4$ kJ/mole (-2 kcal/mole)
(4) I $\longrightarrow$ B + D	$\Delta G = -4.2$ kJ/mole (-1 kcal/mole)
Overall	$\Delta G = -12.6$ kJ/mole (-3 kcal/mole)

Note that Reactions 3 and 4 are sequential. Thus the reaction pathways have changed, but overall the reactants and products are the same, and the free energy change is the same.

Generally, for each endergonic reaction occurring in a living cell, there is a coupled exergonic reaction to drive it. Often, the exergonic reaction involves the breakdown of adenosine triphosphate (ATP). We now examine specific examples of the role of ATP in energy coupling.

ATP IS THE ENERGY CURRENCY OF THE CELL

In all living cells, energy is temporarily packaged within a remarkable chemical compound called **adenosine triphosphate (ATP),** which holds readily available energy for very short periods of time. We may think of ATP as the energy currency of the cell. When you work to earn money, you might say that your energy is symbolically stored in the money you earn. The energy the cell requires for immediate use is temporarily stored in ATP, which is like cash. When you earn extra money, you might deposit some in the bank; similarly, a cell might deposit energy in the chemical bonds of lipids, starch, or glycogen. Moreover, just as you dare not make less money than you spend, so too the cell must avoid energy bankruptcy, which would mean its death. Finally, just as you (alas) do not keep what you make very long, so too the cell continuously spends its ATP, which must be replaced immediately.

ATP is a nucleotide consisting of three main parts: adenine, a nitrogen-containing organic base; ribose, a five-carbon sugar; and three phosphate groups, identifiable as phosphorus atoms surrounded by oxygen atoms (Fig. 6–6*a*). Notice that the phosphate groups are bonded to the end of the molecule in a series, rather like three cars behind a locomotive, and, like the cars of a train, they can be attached and detached.

ATP donates energy through the transfer of a phosphate group

When the terminal phosphate is removed from ATP, the remaining molecule is **adenosine diphosphate (ADP)** (Fig. 6–6*b*). If the phosphate group is not transferred to another molecule, it is released as inorganic phosphate (P_i). This is an exergonic reaction. ATP is sometimes called a "high-energy" compound because the hydrolysis reaction that releases a phosphate has a relatively large $-\Delta G$.[2]

(5) ATP + H_2O $\longrightarrow$ ADP + P_i
$\Delta G = -32$ kJ/mole (or -7.6 kcal/mole)

Reaction 5 can be coupled to endergonic reactions in cells. Consider the following endergonic reaction in which the disaccharide sucrose is formed from two monosaccharides, glucose and fructose.

(6) Glucose + Fructose $\longrightarrow$ Sucrose + H_2O
$\Delta G = +27$ kJ/mole (or $+6.5$ kcal/mole)

With a free energy change of -32 kJ/mole (-7.6 kcal/ mole), the hydrolysis of ATP in Reaction 5 can drive Reaction 6, but only if the reactions can be coupled through a common intermediate. The following series of reactions is a simplified version of an alternative pathway used by some bacteria.

(7) Glucose + ATP $\longrightarrow$ Glucose-P + ADP

(8) Glucose-P + Fructose $\longrightarrow$ Sucrose + P_i

Reaction 7 is a **phosphorylation reaction,** one in which a phosphate group is transferred to some other compound. Glucose is phosphorylated to form glucose phosphate (glucose-P), the intermediate that links the two reactions. Glucose-P, which corresponds to "I" in Reactions 3 and 4, reacts exergonically with fructose to form sucrose. For energy coupling to work in this way, Reactions 7 and 8 must occur in sequence. It is convenient to summarize the reactions in the following way:

(9) Glucose + Fructose + ATP $\longrightarrow$ Sucrose + ADP + P_i
$\Delta G = -5$ kJ/mole (-1.2 kcal/mole)

When encountering an equation written in this way, remember that it is actually a summary of a series of reactions and that transitory intermediate products are sometimes not shown.

[2]Calculations of the free energy of ATP hydrolysis vary somewhat, but range between about -28 and -37 kJ/mole (-6.8 to -8.7 kcal/mole).

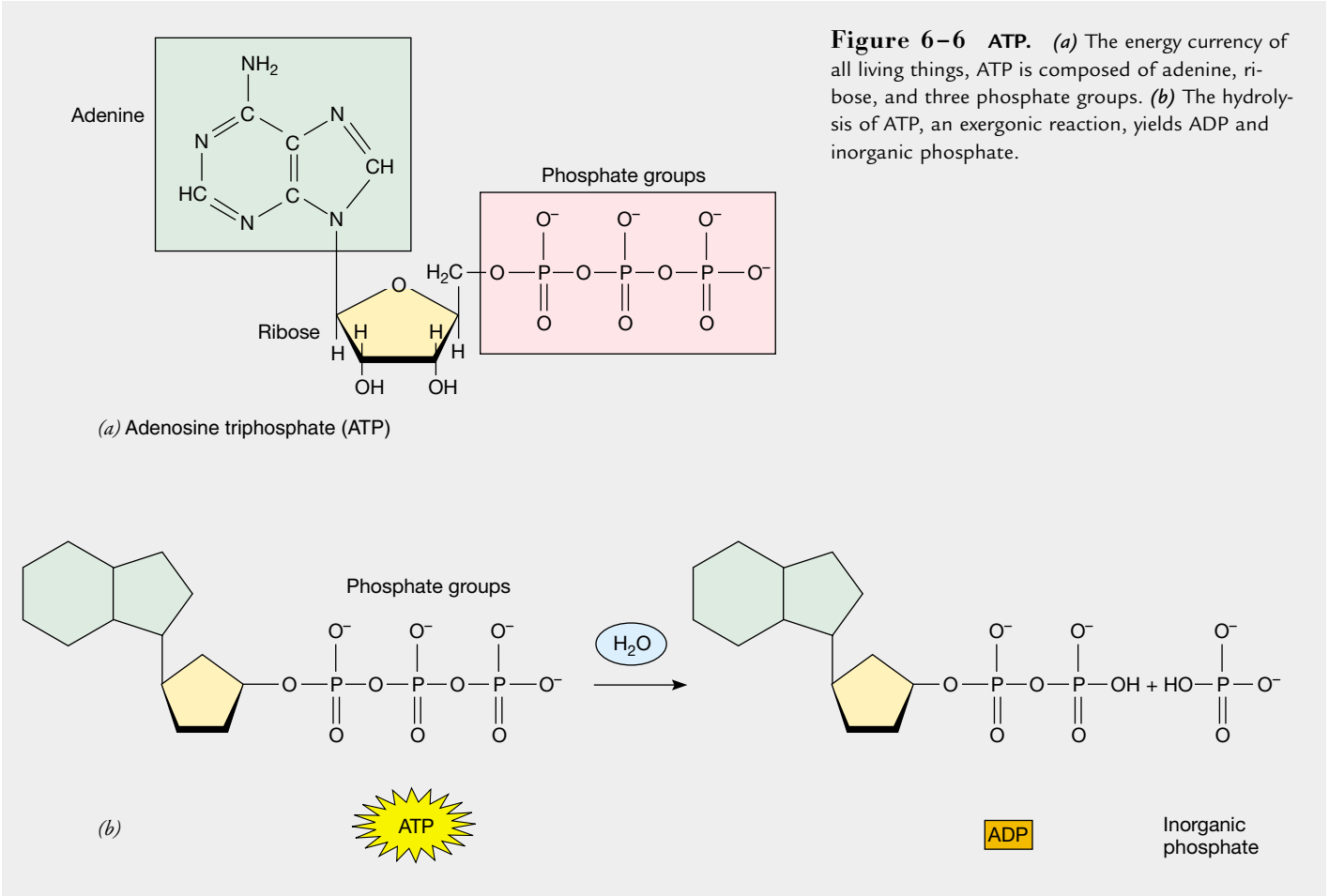


Figure 6–6 ATP. *(a)* The energy currency of all living things, ATP is composed of adenine, ribose, and three phosphate groups. *(b)* The hydrolysis of ATP, an exergonic reaction, yields ADP and inorganic phosphate.

ATP links exergonic and endergonic reactions

We have just discussed how the transfer of a phosphate group from ATP to some other compound can be coupled to endergonic reactions in the cell. Conversely, adding a phosphate group to AMP (forming ADP) or to ADP (forming ATP) requires coupling to exergonic reactions in the cell.

$$AMP + P_i + \text{Energy} \longrightarrow ADP$$
$$ADP + P_i + \text{Energy} \longrightarrow ATP$$

Thus ATP occupies an intermediate position in the metabolism of the cell and is an important link between exergonic reactions, which are generally components of catabolic pathways, and endergonic reactions, which are generally part of anabolic pathways (Fig. 6–7).

The cell maintains a very high ratio of ATP to ADP

The cell maintains the ratio of ATP to ADP far from the equilibrium point. ATP is constantly formed from ADP and inorganic phosphate as nutrients are oxidized in cellular respiration or as the radiant energy of sunlight is trapped in photosynthesis (see Chapters 7 and 8). At any point in time,

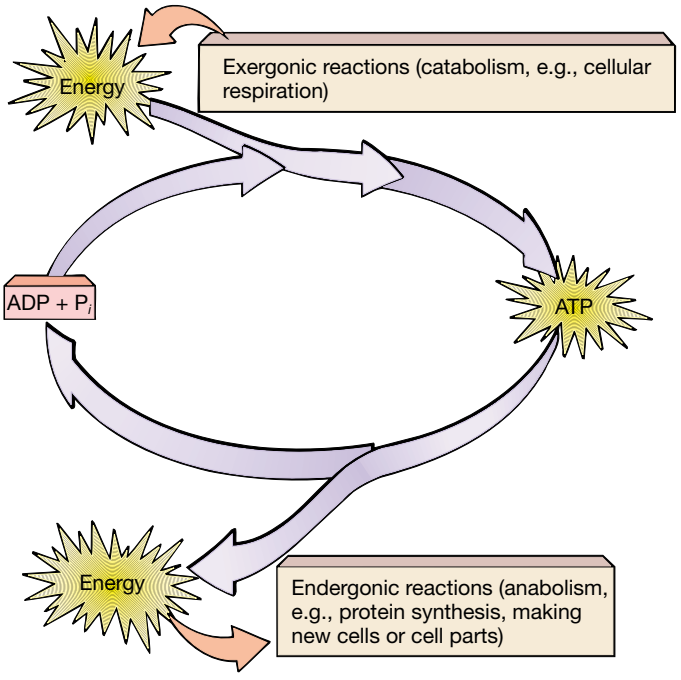


Figure 6–7 ATP links exergonic and endergonic reactions. Because ATP is responsible for coupling many exergonic and endergonic reactions, it is an important link between catabolism and anabolism in cells.

a typical cell contains more than ten ATP molecules for every ADP molecule. The fact that the cell maintains the ATP concentration at such a high level (relative to the concentration of ADP) makes its hydrolysis reaction even more strongly exergonic and more able to drive the endergonic reactions to which it is coupled.

Although the cell maintains a high ratio of ATP to ADP, large quantities of ATP cannot be stored in the cell. The concentration of ATP is always very low, less than 1 millimole per liter. In fact, studies suggest that a bacterial cell has no more than a one-second supply of ATP. Thus, ATP molecules are used almost as quickly as they are produced. A human at rest uses about 45 kilograms (99 pounds) of ATP each day, but the amount present in the body at any given moment is less than 1 gram (0.035 ounce). Every second in every cell, an estimated 10 million molecules of ATP are made from ADP and phosphate, and an equal number of ATPs transfer their phosphate groups along with their energy to whatever chemical reactions may require them.

CELLS TRANSFER ENERGY BY REDOX REACTIONS

We have seen that cells can transfer energy through the transfer of a phosphate group from ATP. Energy can also be transferred through the transfer of electrons. As discussed in Chapter 2, **oxidation** is the chemical process in which a substance loses electrons, whereas **reduction** is the complementary process in which a substance gains electrons. Because electrons released during an oxidation reaction cannot exist in the free state in living cells, every oxidation reaction must be accompanied by a reduction reaction, in which the electrons are accepted by another atom, ion, or molecule. Oxidation and reduction reactions are often called **redox reactions** because they occur simultaneously. The substance that becomes oxidized gives up energy as it releases electrons, and the substance that becomes reduced receives energy as it gains electrons.

Redox reactions often occur in a series as electrons are transferred from one molecule to another. These electron transfers, which are equivalent to energy transfers, are an essential part of cellular respiration, photosynthesis, and many other chemical reactions. Redox reactions, for example, release the energy stored in food molecules so that ATP can be synthesized using that energy.

Most electron carriers carry hydrogen atoms

Generally it is not easy to remove one or more electrons from a covalent compound; it is much easier to remove a whole atom. For this reason, redox reactions in cells usually involve the transfer of a hydrogen atom rather than just an electron. A hydrogen atom contains an electron and a proton that does not participate in the oxidation/reduction.

When an electron, either singly or as part of a hydrogen atom, is removed from an organic compound, it takes with it some of the energy stored in the chemical bond of which it was a part. That electron, along with its energy, is transferred to an acceptor molecule. An electron progressively loses free energy as it is transferred from one acceptor to another.

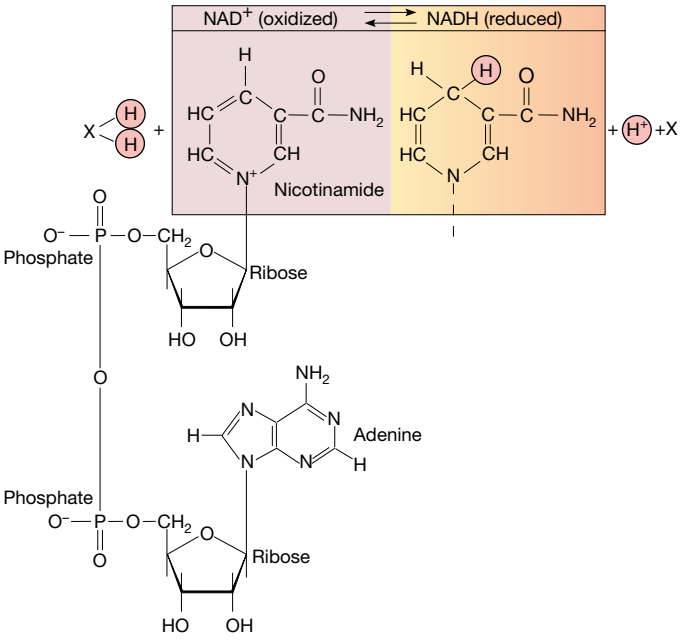


Figure 6–8 NAD+. The acceptor molecule NAD^+ is composed of two nucleotides joined together. The oxidized form, NAD^+, becomes reduced (NADH) by the transfer of two electrons and one proton from another organic compound, which becomes oxidized in the process.

One of the most frequently encountered acceptor molecules is **nicotinamide adenine dinucleotide (NAD^+).** When NAD^+ becomes reduced, it temporarily stores large amounts of free energy. Here is a generalized equation showing the transfer of hydrogen from a compound we call X to NAD^+:

$$XH_2 + NAD^+ \longrightarrow X + NADH + H^+$$

(Oxidized) (Reduced)

Note that the NAD^+ becomes reduced when it combines with hydrogen. NAD^+ is an ion with a net charge of +1. When two electrons and one proton are added, the charge is neutralized and the reduced form of the compound, **NADH,** is produced (Fig. 6–8).[3] Some of the energy stored in the bonds holding the hydrogen atoms to molecule X has been transferred by this redox reaction and is temporarily held by NADH. When NADH transfers the electrons to some other molecule, some of their energy is transferred. This energy is usually then transferred through a complex series of reactions that result in the formation of ATP (see Chapter 7).

Nicotine adenine dinucleotide phosphate ($NADP^+$) is a hydrogen acceptor that is chemically similar to NAD^+ but

[3]Although the correct way to write the reduced form of NAD^+ is $NADH + H^+$, for simplicity we will present the reduced form as NADH in this and succeeding chapters.

with an extra phosphate group. Unlike NADH, the reduced form of $NADP^+$ (abbreviated **NADPH**) is not involved in ATP synthesis. Instead, the electrons of NADPH are used more directly to provide energy for certain reactions, including certain essential reactions of photosynthesis (see Chapter 8).

Other important hydrogen acceptors or electron acceptors include **flavin adenine dinucleotide (FAD)** and the **cytochromes.** FAD is a nucleotide that accepts hydrogen atoms and their electrons; its reduced form is **$FADH_2$.** The cytochromes are proteins that contain iron; the iron component accepts electrons from hydrogen atoms and then transfers these electrons to some other compound. Like NAD^+ and $NADP^+$, FAD and the cytochromes are electron transfer agents. Each can exist in a reduced state in which it has more free energy or in an oxidized state in which it has less. Each is an essential component of many redox reaction sequences in cells.

Enzymes are chemical regulators

The principles of thermodynamics help us predict whether a reaction can occur, but they tell us nothing about the speed of the reaction. The breakdown of glucose, for example, is an exergonic reaction, yet a glucose solution keeps virtually indefinitely in a bottle if kept free of bacteria and molds and not subjected to high temperature or strong acids or bases. Cells cannot wait for centuries for glucose to break down, nor can they use extreme conditions to cleave glucose molecules. Cells regulate the rates of chemical reactions with **enzymes,** which are protein **catalysts** that affect the speed of a chemical reaction without being consumed by the reaction.[4]

Cells require a steady release of energy, and they must be able to regulate that release to meet metabolic energy requirements. Metabolism generally proceeds by a series of steps so that a molecule may go through as many as 20 or 30 chemical transformations before it reaches some final state. Even then, the seemingly completed molecule may enter yet another chemical pathway and become totally transformed or consumed to produce energy. The changing needs of the cell require a system of flexible metabolic control. The key directors of this control system are enzymes.

The catalytic ability of some enzymes is truly remarkable. For example, hydrogen peroxide (H_2O_2) breaks down extremely slowly if the reaction is uncatalyzed, but a single molecule of the enzyme catalase brings about the decomposition of 5 million molecules of hydrogen peroxide per minute at 0°C! Catalase protects cells because hydrogen peroxide is a poisonous substance produced as a byproduct of some cellular reactions. The bombardier beetle uses the enzyme catalase as a defense mechanism (Fig. 6–9).

[4]In recent years scientists have learned that protein enzymes are not the only cellular catalysts; some types of RNA molecules have catalytic activity as well (see Chapter 12).

Figure 6–9 Catalase. When threatened, a bombardier beetle uses the enzyme catalase to decompose hydrogen peroxide. The oxygen gas formed in the decomposition ejects water and other chemicals with explosive force. Because the reaction releases a great deal of heat, the water comes out as steam. (The beetle is immobilized by a wire attached to its back by a drop of adhesive. His leg was just prodded with the dissecting needle on the left to trigger the ejection.) *(Thomas Eisner and Daniel Aneshansley/Cornell University)*

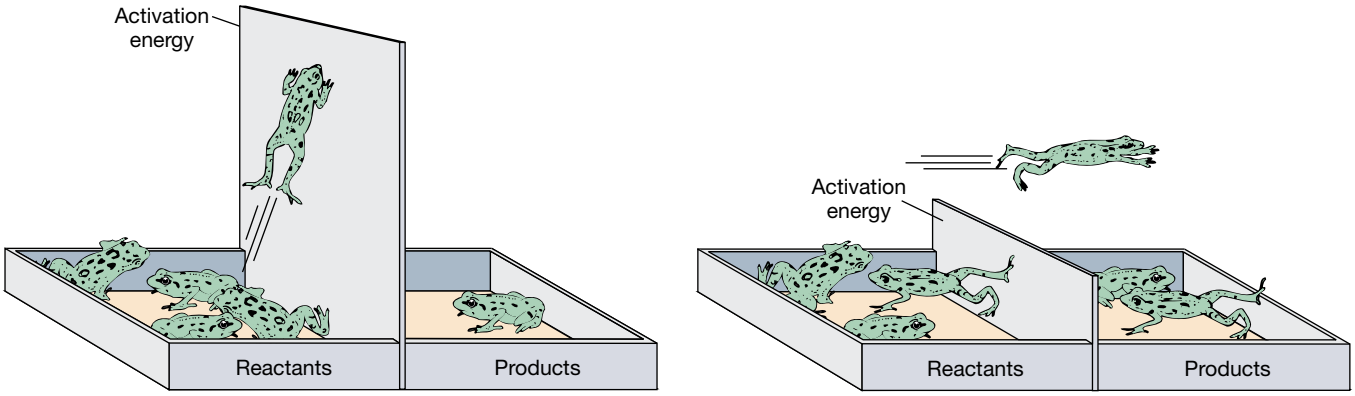
All reactions have a required energy of activation

All reactions have an energy barrier known as the **energy of activation (E_A)** or **activation energy.** The energy barrier is the energy required to break the existing bonds and begin the reaction. In a population of molecules of any kind, some have a relatively high energy content, while others have a lower energy content. Only molecules with a relatively high energy content are likely to react to form the product (Fig. 6–10*a*).

Even a strongly exergonic reaction, one that releases a substantial quantity of energy as it proceeds, may be prevented from proceeding by the activation energy required to begin the reaction. For example, molecular hydrogen and molecular oxygen can react explosively to form water:

$$2\ H_2 + O_2 \longrightarrow 2\ H_2O$$

This reaction is spontaneous (exergonic), yet hydrogen and oxygen can be safely mixed as long as all sparks are kept away. This is because the required energy of activation for this particular reaction is relatively high. A tiny spark provides the activation energy that allows a few molecules to react. Their reaction liberates so much heat that the rest react, producing an explosion. Such an explosion occurred on the Hindenburg, an airship that used hydrogen gas, which is lighter than air, for buoyancy (Fig. 6–11). At the end of a transatlantic voyage in 1937, it exploded on landing, probably because a small spark supplied the activation energy for the reaction of hydrogen with oxygen from the air.



(a) Uncatalyzed reaction, high activation energy

(b) Catalyzed reaction, low activation energy

Figure 6–10 **Kinetic energy in molecules and activation energy, as demonstrated by frogs.** ***(a)*** If a reaction is uncatalyzed, only a small fraction of reactant molecules (frogs) have sufficient energy to overcome the barrier of activation energy and undergo a chemical reaction to form product molecules (jump into the adjacent compartment). ***(b)*** An enzyme lowers the activation energy barrier and increases the fraction of molecules (frogs) that can react (jump). *(Adapted from Tobin and Morel)*

An enzyme lowers a reaction's activation energy

As do all catalysts, enzymes affect the rate of a reaction by lowering the energy needed to initiate the reaction. An enzyme greatly reduces the activation energy necessary to initiate a chemical reaction (Figs. 6–10*b* and 6–12). If molecules need less energy to react because the activation barrier is lowered, a larger fraction of the reactant molecules reacts at any one time. As a result, the reaction proceeds more quickly.

Although an enzyme lowers the activation energy for a reaction, it has no effect on the overall free energy change. That is, an enzyme can only promote a chemical reaction that could proceed without it. No catalyst can cause a reaction to proceed in a thermodynamically unfavorable direction or can influence the final concentrations of reactants and products if the reaction goes to equilibrium. Enzymes simply speed up reaction rates.

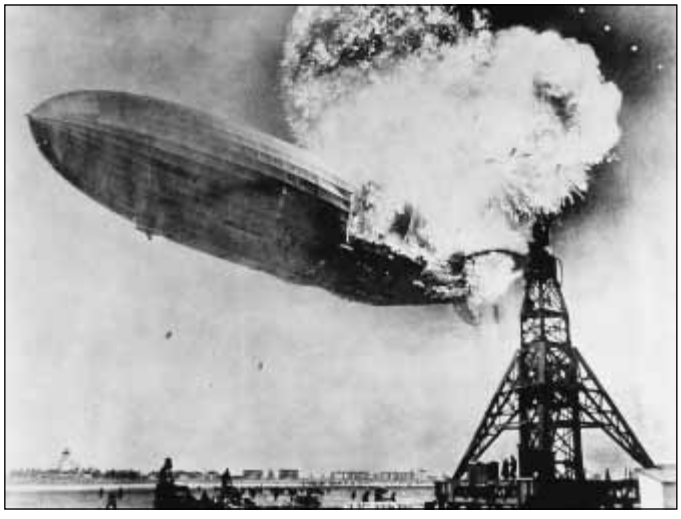


Figure 6–11 **The Hindenburg explosion.** This disaster resulted when a spark triggered an explosive, exergonic reaction between hydrogen in the airship and oxygen in the atmosphere. *(Archive Photos)*

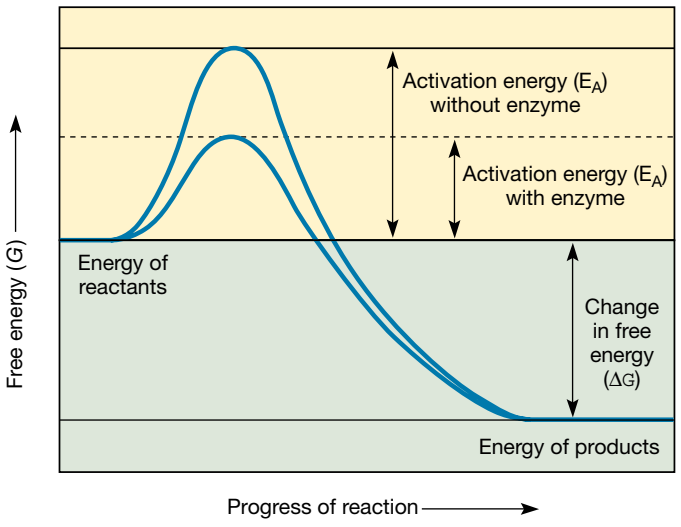
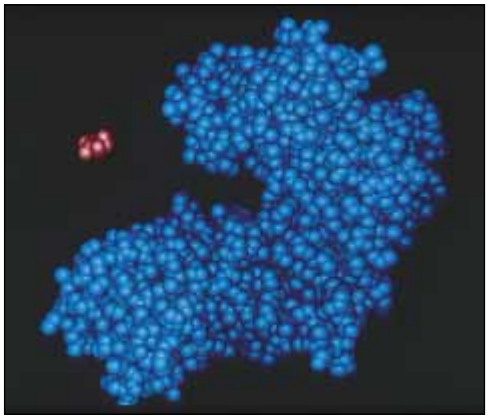
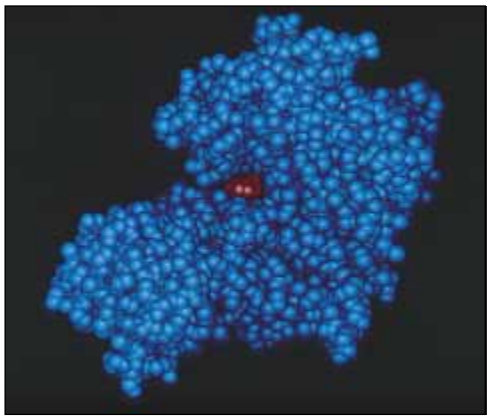


Figure 6–12 **Activation energy and enzymes.** An enzyme speeds up a reaction by lowering its activation energy (E_A). In the presence of an enzyme, it takes less activation energy for reacting molecules to complete a reaction.



(a)



(b)

Figure 6–13 Active site and induced fit. ***(a)*** Computer graphic model of the enzyme hexokinase *(blue)* and its substrate, glucose *(red),* before forming an ES complex. The active site of the enzyme is the furrow where glucose will bind. ***(b)*** The binding of glucose to the active site of hexokinase changes the shape of the enzyme, a phenomenon known as induced fit. Hexokinase, which is involved in cellular respiration, catalyzes the transfer of a phosphate group from ATP to glucose. *(Courtesy of Thomas A. Steitz)*

An enzyme works by forming an enzyme-substrate complex

An uncatalyzed reaction depends on random collisions among reactants. Because of its ordered structure, an enzyme is able to reduce this reliance on random events and thereby control the reaction. The enzyme is thought to accomplish this by forming an unstable intermediate complex with the **substrate,** the substance on which it acts. When the **enzyme-substrate complex,** or **ES complex,** breaks up, the product is released; the original enzyme molecule is regenerated and is free to form a new ES complex.

$$\text{Enzyme} + \text{Substrate(s)} \longrightarrow \text{ES complex}$$

$$\text{ES complex} \longrightarrow \text{Enzyme} + \text{Product(s)}$$

The enzyme itself is not permanently altered or consumed by the reaction and can be reused.

As shown in Figure 6–13*a*, every enzyme contains one or more **active sites,** regions to which the substrate binds, forming the ES complex. The active sites of some enzymes are grooves or cavities in the enzyme molecule, formed by amino acid side chains. The active sites of most enzymes are located close to the surface. During the course of a reaction, substrate molecules occupying these sites are brought close together and react with one another.

The shape of the enzyme does not seem to be exactly complementary to that of the substrate. When the substrate binds to the enzyme molecule, it causes a change, known as **induced fit,** in the shape of the enzyme molecule. Usually the shape of the substrate also changes slightly, in a way that may distort its chemical bonds (Fig. 6–13*b*). The proximity and orientation of the reactants, together with strains in their chemical bonds, facilitate the breakage of old bonds and the formation of new ones. Thus the substrate is changed into product, which moves away from the enzyme. The enzyme is then free to catalyze the reaction of more substrate molecules to form more product molecules.

Most enzyme names end in *-ase*

Enzymes are usually named by the addition of the suffix *-ase* to the name of the substrate. The enzyme sucrase, for example, splits sucrose into glucose and fructose. A few enzymes retain traditional names that do not end in *-ase;* some of these end in *-zyme*. For example, lysozyme (from the Greek *lysis*, "to dissolve") is an enzyme found in tears and saliva; this enzyme breaks down bacterial cell walls. Other examples of enzymes with traditional names include pepsin and trypsin, which break internal peptide bonds in proteins.

Enzymes are specific

Virtually every chemical reaction that takes place in an organism is catalyzed by an enzyme. Because there is a close relationship between the shape of the active site and the shape of the substrate, the majority of enzymes are highly specific. Most are capable of catalyzing only a few closely related chemical reactions or, in many cases, only one particular reaction. For example, the enzyme urease, which decomposes urea to ammonia and carbon dioxide, attacks no other substrate. The enzyme sucrase splits only sucrose; it does not act on other disaccharides such as maltose or lactose.

A few enzymes are specific only to the extent that they require the substrate to have a certain kind of chemical bond. For example, lipase secreted by the pancreas splits the ester linkages connecting the glycerol and fatty acids of a wide variety of fats.

Enzymes that catalyze similar reactions are classified into groups, although each particular enzyme in the group may catalyze only one specific reaction. Some of the important classes of enzymes and their roles are listed in Table 6–1. Each class is divided into many subclasses. For example, sucrase, mentioned above, is referred to as a glycosidase because it cleaves a glycosidic linkage. Glycosidases are a subclass of the hydrolases.

TABLE 6–1 Some Important Classes of Enzymes

Enzyme Class	Function
Oxidoreductases	Catalyze oxidation-reduction reactions
Transferases	Catalyze the transfer of a functional group from a donor molecule to an acceptor molecule
Hydrolases	Catalyze hydrolysis reactions
Isomerases	Catalyze conversion of a molecule from one isomeric form to another
Ligases	Catalyze certain reactions in which two molecules are joined
Lyases	Catalyze certain reactions in which double bonds are formed or broken.

Many enzymes require cofactors

Some enzymes, for example, pepsin, which is secreted by the stomach, consist only of protein. Others have two components: a protein referred to as the **apoenzyme** and an additional chemical component called a **cofactor.** Neither the apoenzyme nor the cofactor alone has catalytic activity; only when the two are combined does the enzyme function. A cofactor may be inorganic, or it may be an organic molecule.

Some enzymes require a specific metal ion as a cofactor. Two very common inorganic cofactors are magnesium ions and calcium ions. Most of the trace elements, such as iron, copper, zinc, and manganese, all of which are required in very small amounts, function as cofactors.

An organic, nonpolypeptide compound that binds to the apoenzyme and serves as a cofactor is called a **coenzyme.** Most coenzymes are carrier molecules that transfer electrons or part of a substrate from one molecule to another. Some examples of coenzymes have already been introduced in this chapter. NADH, NADPH, and $FADH_2$ are coenzymes; they transfer electrons. ATP functions as a coenzyme; it is responsible for transferring phosphate groups. Yet another coenzyme, **coenzyme A,** is involved in the transfer of groups derived from organic acids. Most vitamins, which are organic compounds that an organism requires in small amounts but cannot synthesize itself, are coenzymes or components of coenzymes (see Table 45–4).

Enzymes are most effective at optimal conditions

Enzymes generally work best under certain narrowly defined conditions, such as appropriate temperature, pH, and ion concentration. Any departure from optimal conditions adversely affects enzyme activity.

Each enzyme has an optimal temperature

Most enzymes have an optimal temperature at which the rate of reaction is fastest. For human enzymes, the temperature optima are near body temperature (35° to 40°C). Enzymatic reactions occur slowly or not at all at low temperatures. As the temperature increases, molecular motion increases, resulting in more molecular collisions. The rates of most enzyme-controlled reactions therefore increase as the temperature increases, within limits (Fig. 6–14*a*). High temperatures rapidly denature most enzymes; the molecular conformation of the protein

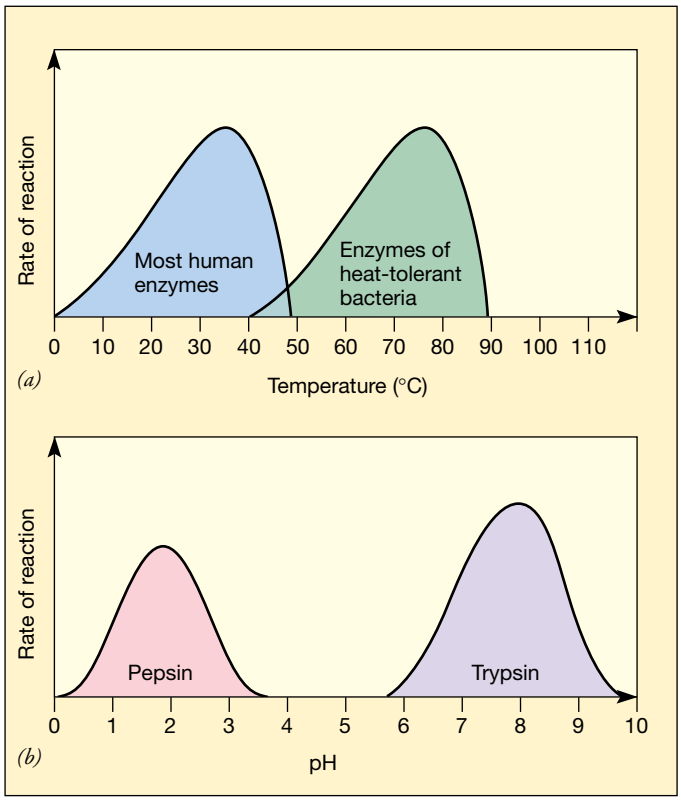


Figure 6–14 Effect of temperature and pH on enzyme activity. Substrate and enzyme concentrations are held constant in the reactions illustrated. *(a)* Generalized curves for the effect of temperature on enzyme activity. As temperature increases, enzyme activity increases until it reaches an optimal temperature. Enzyme activity abruptly falls after it exceeds the optimal temperature because the enzyme, being a protein, denatures. *(b)* Enzyme activity is very sensitive to pH. Pepsin is a protein-digesting enzyme in the very acidic stomach juice. Trypsin, secreted by the pancreas into the slightly alkaline small intestine, digests polypeptides.

becomes altered as the hydrogen bonds responsible for its secondary, tertiary, and quaternary structures are broken. Because this inactivation is usually not reversible, activity is not regained when the enzyme is cooled.

Most organisms are killed by even a short exposure to high temperature; their enzymes are denatured, and they are unable to continue metabolism. A few remarkable exceptions to this rule exist: certain species of bacteria can survive in the waters of hot springs, such as those in Yellowstone Park, where the temperature is almost 100°C; these organisms are responsible for the brilliant colors in the terraces of the hot springs. Still other bacteria live at temperatures much above that of boiling water, near deep-sea vents, where the extreme pressure keeps water in its liquid state (see Chapter 23 and *Focus On: Life Without the Sun* in Chapter 52).

Each enzyme has an optimal pH

Most enzymes are active only over a narrow pH range and have an optimal pH at which the rate of reaction is fastest. The optimal pH for most human enzymes is between 6 and 8. Pepsin, a protein-digesting enzyme secreted by cells lining the stomach, is remarkable in that it works only in a very acid medium, optimally at pH 2 (Fig. 6–14*b*). In contrast, trypsin, the protein-splitting enzyme secreted by the pancreas, functions best under slightly basic conditions.

The activity of an enzyme may be markedly changed by any alteration in pH, which in turn alters charges on the enzyme. Changes in charge affect the ionic bonds that contribute to tertiary and quaternary structure, thus changing the protein's conformation and activity. Many enzymes become inactive, and usually irreversibly denatured, when the medium is made very acidic or very basic.

Enzymes are organized into teams in metabolic pathways

Enzymes play an essential role in energy coupling because they usually work in sequence, with the product of one enzyme-controlled reaction serving as the substrate for the next. We can picture the inside of a cell as a factory with many different assembly (and disassembly) lines operating simultaneously. An assembly line is composed of a number of enzymes. Each enzyme carries out one step, such as changing molecule A into molecule B. Then molecule B is passed along to the next enzyme, which converts it into molecule C, and so on. Such a series of reactions is referred to as a **metabolic pathway.**

$$A \xrightarrow{\text{Enzyme 1}} B \xrightarrow{\text{Enzyme 2}} C$$

Each of these reactions is theoretically reversible, and the fact that it is catalyzed by an enzyme does not change that fact. An enzyme does not itself determine the direction of the reaction it catalyzes. However, the overall reaction sequence is portrayed as proceeding from left to right. You will recall that if there is little intrinsic free energy difference between the reactants and products for a particular reaction, its direction will be determined mainly by the relative concentrations of reactants and products.

In biological pathways, both intermediate and final products are often removed and converted to other chemical compounds. Such removal drives the sequence of reactions in a particular direction. Let us assume that Reactant A is being constantly supplied and that its concentration remains constant. Enzyme 1 converts Reactant A to Product B. The concentration of B is always lower than the concentration of A because B is removed as it is converted to C in the reaction catalyzed by Enzyme 2. If C is removed as quickly as it is formed (perhaps by leaving the cell), the entire pathway is "pulled" toward C.

The cell regulates enzymatic activity

Enzymes regulate the chemistry of the cell, but what controls the enzymes? One mechanism depends simply on controlling the amount of enzyme produced. The synthesis of each type of enzyme is directed by a specific gene. The gene, in turn, may be switched on by a signal from a hormone or by some other type of cellular product. When the gene is switched on, the enzyme is synthesized. The amount of enzyme present then influences the rate of the reaction.

If the pH and temperature are kept constant, the rate of the reaction can be affected by the substrate concentration or by the enzyme concentration. If an excess of substrate is present, the enzyme concentration is the rate-limiting factor. The initial rate of the reaction is then directly proportional to the concentration of enzyme present (Fig. 6–15*a*).

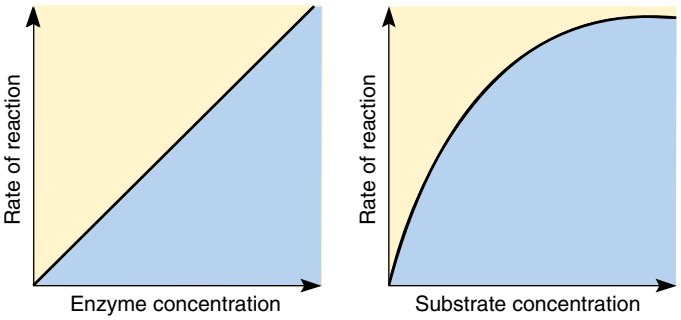


Figure 6–15 **Effect of enzyme concentration and substrate concentration on the rate of a reaction.** ***(a)*** In this example, the rate of reaction is measured at different enzyme concentrations, and an excess of substrate is present at all times. The rate of the reaction is therefore directly proportional to the enzyme concentration. ***(b)*** In this example, the rate of reaction is measured at different substrate concentrations, and enzyme concentration is constant. If the substrate concentration is relatively low, then the reaction rate is directly proportional to substrate concentration. However, higher substrate concentrations do not increase the reaction rate because the enzyme molecules become saturated with substrate.

If the enzyme concentration is kept constant, the initial rate of an enzymatic reaction is proportional to the concentration of substrate present. Substrate concentration is the rate-limiting factor at lower concentrations; the rate of the reaction is therefore directly proportional to the substrate concentration. However, at higher substrate concentrations the enzyme molecules become saturated with substrate, and increasing the substrate concentration does not increase the reaction rate (Fig. 6–15*b*).

The product of one enzymatic reaction may control the activity of another enzyme, especially in a complex sequence of enzymatic reactions. For example, in the following metabolic pathway,

$$A \xrightarrow{\text{Enzyme 1}} B \xrightarrow{\text{Enzyme 2}} C \xrightarrow{\text{Enzyme 3}} D \xrightarrow{\text{Enzyme 4}} E$$

each step is catalyzed by a different enzyme, and the final product E may inhibit the activity of Enzyme 1. When the concentration of E is low, the sequence of reactions proceeds rapidly. However, an increasing concentration of E serves as a signal for Enzyme 1 to slow down and eventually to stop functioning. Inhibition of Enzyme 1 stops the entire reaction sequence. This type of enzyme regulation, in which the formation of a product inhibits an earlier reaction in the sequence, is called **feedback inhibition** (Fig. 6–16).

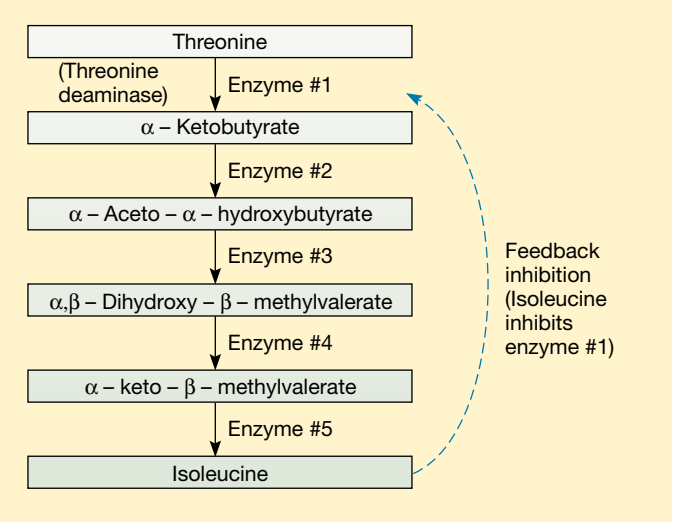


Figure 6–16 Feedback inhibition. Bacteria synthesize the amino acid isoleucine from the amino acid threonine. The isoleucine synthetic pathway involves five steps, each catalyzed by a different enzyme. When enough isoleucine accumulates in the cell, the isoleucine inhibits the enzyme that catalyzes the first step in this pathway.

Another important method of enzymatic control depends on the activation of enzyme molecules. In their inactive form the active sites of the enzyme are inappropriately shaped, so that the substrates do not fit. Among the factors that influence the shape of the enzyme are pH, the concentration of certain ions, and the addition of phosphate groups to certain amino acids in the enzyme.

Some enzymes possess a receptor site, called an **allosteric site,** on some region of the enzyme molecule other than the active site. (The word *allosteric* means "another space.") Substances that affect enzyme activity by binding to allosteric sites are called **allosteric regulators.** Some allosteric regulators are inhibitors that keep the enzyme in its inactive shape. Other allosteric regulators are activators that result in an enzyme with a functional active site.

The enzyme cyclic AMP-dependent protein kinase is an allosteric enzyme with a regulator that is a protein that binds reversibly to the allosteric site and inactivates the enzyme. Protein kinase is in this inactive form most of the time (Fig. 6–17). When protein kinase activity is needed, the compound cyclic AMP (cAMP; see Fig. 3–25) contacts the enzyme-inhibitor complex and removes the inhibitory protein, thereby activating the protein kinase. Activation of protein kinases by cAMP is an important aspect of the mechanism of action of certain hormones (see Chapter 47).

Enzymes can be inhibited by certain chemical agents

Most enzymes may be inhibited or even destroyed by certain chemical agents. Enzyme inhibition may be reversible or irreversible. **Reversible inhibition** occurs when an inhibitor forms

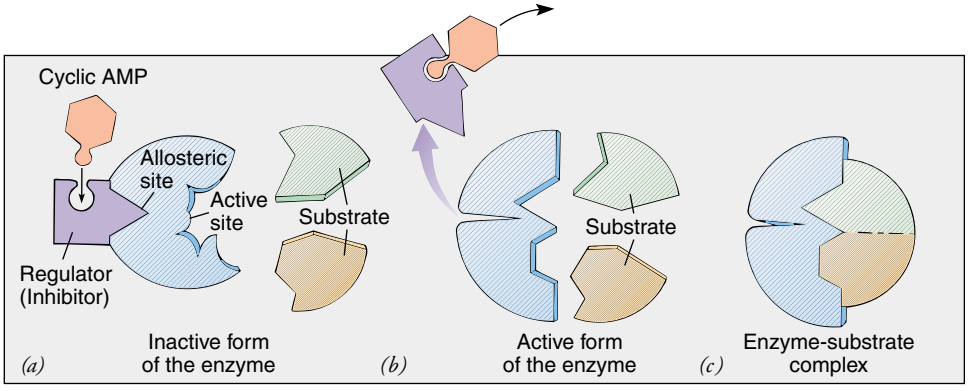
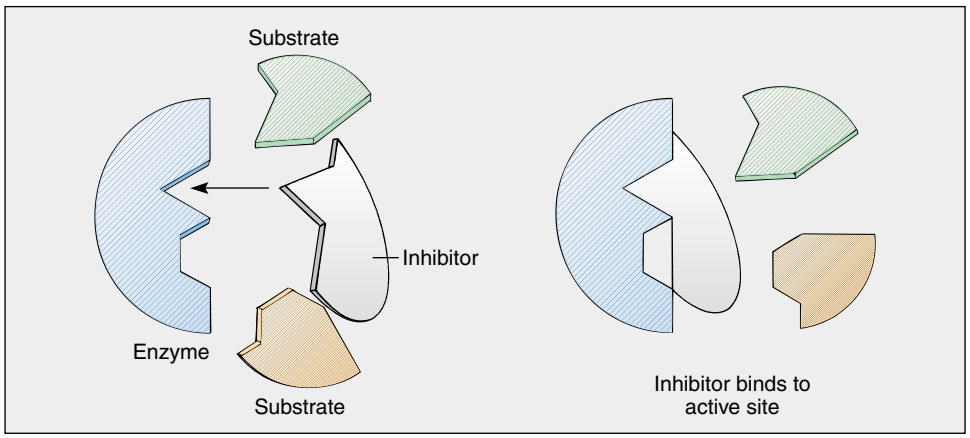
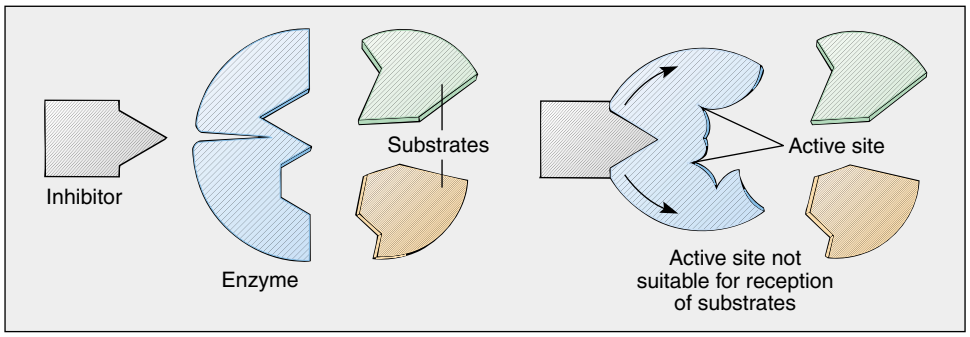


Figure 6–17 Allosteric enzyme. *(a)* The enzyme protein kinase is inhibited by a regulatory protein that binds reversibly to its allosteric site. When the enzyme is in this inactive form, the shape of the active site is modified so that the substrate cannot combine with it. *(b)* Cyclic AMP removes the allosteric inhibitor and activates the enzyme. The substrate can then combine with the active site *(c)*.



(a) Competitive inhibition



(b) Noncompetitive inhibition

Figure 6–18 Competitive and noncompetitive inhibition. *(a)* In competitive inhibition, the inhibitor competes with the normal substrate for the active site of the enzyme. A competitive inhibitor occupies the active site only temporarily. *(b)* In noncompetitive inhibition, the inhibitor binds with the enzyme at a site other than the active site, altering the shape of the enzyme and thereby inactivating it. Noncompetitive inhibition may be reversible.

weak chemical bonds with the enzyme. Reversible inhibition can be competitive or noncompetitive.

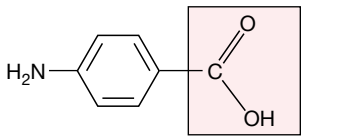
In **competitive inhibition,** the inhibitor competes with the normal substrate for binding to the active site of the enzyme (Fig. 6–18*a*). Usually a competitive inhibitor is structurally similar to the normal substrate and so fits into the active site and combines with the enzyme. However, it is not similar enough to substitute fully for the normal substrate in the chemical reaction, and the enzyme cannot attack it to form product molecules. A competitive inhibitor occupies the active site only temporarily and does not permanently damage the enzyme. In competitive inhibition, an active site is occupied by the inhibitor part of the time and by the normal substrate part of the time. If the concentration of the substrate is increased relative to the concentration of the inhibitor, the active site will usually be occupied by the substrate. Competitive inhibition is demonstrated experimentally by the fact that it can be reversed by increasing the substrate concentration.

In **noncompetitive inhibition,** the inhibitor binds with the enzyme at a site other than the active site (Fig. 6–18*b*). Such an inhibitor inactivates the enzyme by altering its shape so that the active site cannot bind with the substrate. Many important noncompetitive inhibitors are metabolic substances that regulate enzyme activity by combining reversibly with the enzyme. Noncompetitive inhibition has some features in common with allosteric inhibition discussed previously.

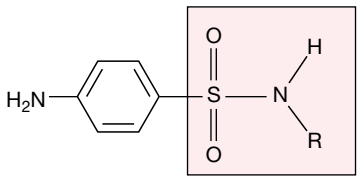
In **irreversible inhibition,** an inhibitor permanently inactivates or destroys an enzyme when it combines with one of its functional groups. Many poisons are irreversible enzyme inhibitors. For example, heavy metals such as mercury and lead bind irreversibly to and denature many proteins, including enzymes. Certain nerve gases poison the enzyme acetylcholinesterase, which is important to the function of nerves and muscles. Cytochrome oxidase, one of the enzymes that transports electrons in cellular respiration, is especially sensitive to cyanide. Death results from cyanide poisoning because cytochrome oxidase is irreversibly inhibited and can no longer transfer electrons from substrate to oxygen. A number of insecticides and drugs are irreversible enzyme inhibitors. Irreversible inhibition may also occur if a protein is denatured by heat or organic solvents.

Some drugs are enzyme inhibitors

Many bacterial infections are treated with drugs that directly or indirectly inhibit bacterial enzyme activity. For example, sulfa drugs have a chemical structure similar to that of the nutrient para-aminobenzoic acid (PABA) (Fig. 6–19). When PABA is available, microorganisms can synthesize the vitamin folic acid, which is necessary for growth. Humans do not synthesize folic acid from PABA, and that is why sulfa drugs selectively affect bacteria.



Para-aminobenzoic acid
(PABA)



Generic sulfonamide
(Sulfa drug)

Figure 6–19 Para-aminobenzoic acid and sulfonamides. Sulfa drugs owe their antibiotic properties to their similarity in structure to para-aminobenzoic acid, a precursor in the synthesis of folic acid. Sulfa drugs block the synthesis of folic acid, an important vitamin necessary for growth. Animals, including humans, obtain folic acid in their diets, but many bacteria synthesize it.

When a sulfa drug is present, competitive inhibition occurs within the bacterium: the drug competes with PABA for the active site of the bacterial enzyme. When bacteria use the sulfa drug instead of PABA, they synthesize a compound that cannot be used to make folic acid. Therefore, the bacterial cells are unable to grow.

Penicillin and related antibiotics irreversibly inhibit a bacterial enzyme called transpeptidase. This enzyme is responsible for establishing some of the chemical linkages in the bacterial cell wall. Susceptible bacteria cannot produce properly constructed cell walls and are prevented from multiplying effectively. Human cells do not have cell walls and do not employ this enzyme. Thus, except for individuals allergic to it, penicillin is harmless to humans. Unfortunately, during the years since it was introduced, resistance to penicillin has evolved in many bacterial strains. The resistant bacteria fight back with an enzyme of their own, penicillinase, which breaks down the penicillin and renders it ineffective. Because bacteria evolve at such a rapid rate, drug resistance is a growing problem in medical practice (see *Making the Connection: Tuberculosis, Bacterial Resistance to Antibiotics, and Evolution* in Chapter 17). Although new antibacterial drugs are constantly under development, certain serious infections, such as tuberculosis, are becoming increasingly difficult to treat.

SUMMARY WITH KEY TERMS

I. **Energy** can be defined as the capacity to do work (expressed in **kilojoules, kJ**).
   A. All life depends on a continuous input of energy. Most producers capture energy during photosynthesis and incorporate some of it into the chemical bonds of organic compounds. Some of this chemical energy then becomes available to consumers and decomposers.
   B. All forms of energy are interconvertable.
      1. **Potential energy** is stored energy; **kinetic energy** is energy of motion.
      2. Energy can be conveniently measured as **heat energy;** the unit of heat energy is the **kilocalorie (kcal),** which is equal to 4.184 kilojoules. Heat energy cannot do cellular work.

II. The **first law of thermodynamics** states that energy cannot be created or destroyed but can be transferred and changed in form. The **second law of thermodynamics** states that disorder (**entropy**) in the universe is continuously increasing.
   A. The first law explains why organisms cannot produce energy but must continuously capture it from the surroundings.
   B. The second law explains why no process requiring energy is ever 100% efficient. In every energy transaction, some energy is dissipated as heat, which contributes to entropy.

III. When a chemical reaction is in a state of **dynamic equilibrium,** the rate of change in one direction is exactly the same as the rate of change in the opposite direction; the system can do no work because the **free energy** difference between the reactants and products is zero.
   A. As entropy (S) increases, the amount of free energy (G) decreases, as shown in the equation $G = H - TS$, in which G is the free energy, H is the **enthalpy** (total potential energy of the system), T is the absolute temperature (expressed in degrees Kelvin), and S is entropy.
   B. The equation $\Delta G = \Delta H - T\Delta S$ indicates that the change in free energy (ΔG) during a chemical reaction is equal to the change in enthalpy (ΔH) minus the product of the absolute temperature (T) multiplied by the change in entropy (ΔS).

IV. A **spontaneous reaction** releases free energy and can perform work.
   A. Free energy decreases in an **exergonic reaction.** Exergonic reactions are spontaneous.
   B. Free energy increases in an **endergonic reaction.** The input of free energy required to drive an endergonic reaction may be supplied by **coupling** it to an exergonic reaction.

V. **Adenosine triphosphate (ATP)** is the immediate energy currency of the cell; it generally transfers energy through the transfer of its terminal phosphate group to acceptor molecules.
   A. ATP is formed by the **phosphorylation** of **ADP,** an endergonic process that requires an input of energy.
   B. ATP is the common cellular link between exergonic and endergonic reactions and between **catabolism** and **anabolism.**

VI. Energy can be transferred in **oxidation-reduction (redox) reactions.**
   A. A substance that becomes oxidized gives up one or more electrons (and energy) to a substance that becomes reduced. Electrons are typically transferred as part of hydrogen atoms.
   B. **NAD^+** and **$NADP^+$** accept electrons as part of hydrogen atoms and become reduced to form NADH and NADPH, respectively. These electrons (along with some of their energy) can be transferred to other acceptors.

VII. An **enzyme** is a biological **catalyst;** it greatly increases the speed of a chemical reaction without being consumed.
   A. An enzyme lowers the **activation energy** necessary to get a reaction going.
   B. An **active site** of an enzyme is a three-dimensional region where **substrates** come into close contact and thereby react more readily. A substrate binds to an active site, causing an **induced fit** in which the shape of the enzyme changes slightly.
   C. Some enzymes consist of an **apoenzyme** and a **cofactor.**
      1. Most inorganic cofactors are metal ions.
      2. A **coenzyme** is an organic cofactor; many coenzymes transfer electrons or part of a substrate from one molecule to another.
   D. Enzymes work best at specific temperature and pH conditions.

E. A cell can regulate enzymatic activity by controlling the amount of enzyme produced and by regulating metabolic conditions that influence the shape of the enzyme.
   1. Some enzymes have **allosteric sites,** noncatalytic sites to which a substance can bind, changing the enzyme's activity.
   2. Allosteric enzymes are subject to **feedback inhibition,** in which the formation of an end product inhibits an earlier reaction in the sequence.

F. Most enzymes can be inhibited by certain chemical substances. Inhibition may be reversible or irreversible.
   1. **Reversible inhibition** occurs when an inhibitor forms weak chemical bonds with the enzyme. Reversible inhibition may be **competitive,** in which the inhibitor competes with the substrate for the active site, or **noncompetitive,** in which the inhibitor binds with the enzyme at a site other than the active site.
   2. **Irreversible inhibition** occurs when an inhibitor combines with an enzyme and permanently inactivates it.

POST-TEST

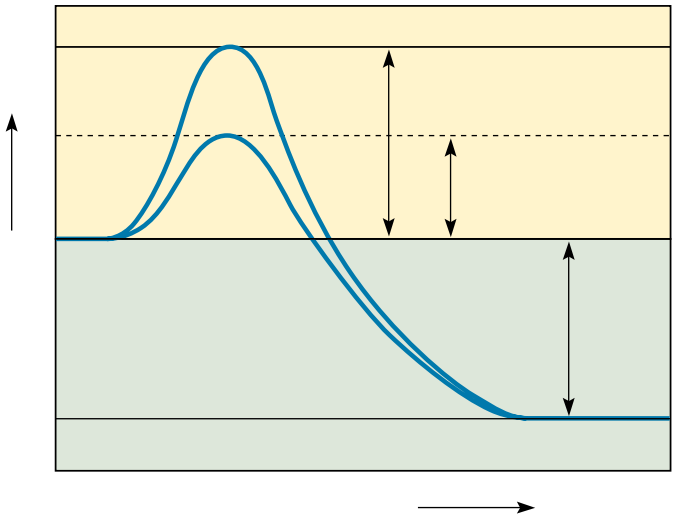
1. According to the first law of thermodynamics (a) energy may be changed from one form to another but is neither created nor destroyed (b) much of the work an organism does is mechanical work (c) the disorder of the universe is increasing (d) free energy is available to do cellular work (e) a cell is in a state of dynamic equilibrium
2. According to the second law of thermodynamics (a) energy may be changed from one form to another but is neither created nor destroyed (b) much of the work an organism does is mechanical work (c) the disorder of the universe is increasing (d) free energy is available to do cellular work (e) a cell is in a state of dynamic equilibrium
3. In thermodynamics, _____ is a measure of the amount of disorder in the system. (a) bond energy (b) catabolism (c) entropy (d) enthalpy (e) work
4. The _____ of a system is that part of the total energy available to do cellular work. (a) activation energy (b) bond energy (c) kinetic energy (d) free energy (e) heat energy
5. A reaction that requires a net input of free energy is described as (a) exergonic (b) endergonic (c) spontaneous (d) both a and c (e) both b and c
6. A reaction that releases energy is described as (a) exergonic (b) endergonic (c) spontaneous (d) both a and c (e) both b and c
7. A spontaneous reaction is one in which the change in free energy (ΔG) has a _____ value. (a) positive (b) negative (c) positive or negative (d) none of these (ΔG has no value)
8. To drive a reaction that requires an input of energy (a) an enzyme-substrate complex must form (b) the concentration of ATP must be decreased (c) the activation energy must be increased (d) some reaction that yields energy must be coupled to it (e) some reaction that requires energy must be coupled to it
9. The energy required to initiate a reaction is called (a) activation energy (b) bond energy (c) kinetic energy (d) free energy (e) heat energy
10. A biological catalyst that affects the rate of a chemical reaction without being consumed by the reaction is a(an) (a) product (b) cofactor (c) coenzyme (d) substrate (e) enzyme
11. The region of an enzyme molecule that combines with the substrate is the (a) allosteric site (b) reactant (c) active site (d) coenzyme (e) product
12. This inhibitor binds to the active site of an enzyme. (a) noncompetitive inhibitor (b) competitive inhibitor (c) irreversible inhibitor (d) allosteric regulator
13. Which of the following reactions could be coupled to an endergonic reaction with $\Delta G = +3.56$ kJ/mole? (a) A → B, $\Delta G = +6.08$ kJ/mole (b) C → D, $\Delta G = +3.56$ kJ/mole (c) E → F, $\Delta G = -1.22$ kJ/mole (d) G → H, $\Delta G = -5.91$ kJ/mole
14. In the following reaction series, which enzyme is most likely to have an allosteric site to which the end product E binds?

$$A \xrightarrow{\text{Enzyme 1}} B \xrightarrow{\text{Enzyme 2}} C \xrightarrow{\text{Enzyme 3}} D \xrightarrow{\text{Enzyme 4}} E$$

(a) enzyme 1 (b) enzyme 2 (c) enzyme 3 (d) enzyme 4

REVIEW QUESTIONS

1. Why can we express energy either in kilojoules or in kilocalories? Which is more convenient to measure? Which has more meaning in biology?
2. You exert tension on a spring and then release it. Explain how these actions relate to work, potential energy, and kinetic energy.
3. Life is sometimes described as a constant struggle against the second law of thermodynamics. How do organisms succeed in this struggle without violating the second law?
4. Consider the free energy change in a reaction in which enthalpy decreases and entropy increases. Is ΔG zero, or does it have a positive value or a negative value? Is the reaction endergonic or exergonic?
5. Why do coupled reactions typically have common intermediates? Give a generalized example involving ATP. Why is ATP able to serve as an important link between exergonic and endergonic reactions?
6. What is activation energy? What effect does an enzyme have on activation energy?
7. Give the function of each of the following (a) active site of an enzyme (b) coenzyme (c) allosteric site
8. Describe three factors that influence how an enzyme functions.
9. Label the diagram. Use Figure 6–12 to check your answers.



YOU MAKE THE CONNECTION

1. Reaction 1 and Reaction 2 happen to have the same free energy change: $\Delta G = -41.8$ kJ/mole (-10 kcal/mole). Reaction 1 is at equilibrium, but Reaction 2 is far from equilibrium. Is either reaction capable of performing work? If so, which one?
2. You are doing an experiment in which you are measuring the rate at which succinic acid is converted to fumaric acid by the enzyme succinic dehydrogenase. You decide to add a little malonic acid to make things interesting. You observe that the reaction rate slows markedly and conclude that malonic acid must be acting as an inhibitor. Design an experiment that will help you decide if malonic acid is acting as a competitive inhibitor or a noncompetitive inhibitor.
3. Based on what you have learned in this chapter, explain why an extremely high fever (above 105°F or 40°C) is often lethal.

RECOMMENDED READINGS

Adams, S. "No Way Back." *New Scientist,* 22 Oct. 1994. Examines the second law of thermodynamics.

Atkins, P.W. *The Second Law*. W.H. Freeman, San Francisco, 1984. A basic, understandable introduction to thermodynamics with an extensive section devoted to its biological implications.

Hinrichs, R.A. *Energy: Its Use and the Environment,* 2nd ed. Saunders College Publishing, Philadelphia, 1996. The focus of this introductory text is the physical principles behind energy use and its effects on the environment.

Tobin, A.J., and R.E. Morel. *Asking About Cells.* Saunders College Publishing, Philadelphia, 1997. A readable cell biology text with excellent coverage of cellular energetics.

• Visit our website at **http://www.saunderscollege.com/lifesci/titles.html** and click on Solomon/Berg/Martin Biology for links to chapter-related resources on the World Wide Web.