Chapter 6

Energy and Metabolism

Chapter Outline

Introduction

Life can be viewed as a constant flow of energy, channeled by organisms to do the work of living. Each of the significant properties by which we define life—order, growth, reproduction, responsiveness, and internal regulation—requires a constant supply of energy. Both the lion and the giraffe need to eat to provide energy for a wide variety of cellular functions. Deprived of a source of energy, life stops. Therefore, a comprehensive study of life would be impossible without discussing ***bioenergetics,*** *the analysis of how energy powers the activities of living systems. In this chapter, we focus on energy—what it is and how it changes during chemical reactions.*

6.1 The Flow of Energy in Living Systems

Learning Outcomes

1. *Explain what energy is and describe its different forms.*
2. *Identify the source of energy for the biosphere.*
3. *Contrast oxidation and reduction reactions.*

Thermodynamics is the branch of chemistry concerned with energy changes. Cells are governed by the laws of physics and chemistry, so we must understand these laws in order to understand how cells function.

Energy can take many forms

Energy is defined as the capacity to do work. We think of energy as existing in two states: kinetic energy and potential energy (figure 6.1). **Kinetic energy** is the energy of motion. Moving objects perform work by causing other matter to move. **Potential energy** is stored energy. Objects that are not actively moving but have the capacity to do so possess potential energy. A boulder perched on a hilltop has gravitational potential energy. As it begins to roll downhill, some of its potential energy is converted into kinetic energy. Much of the work that living organisms carry out involves transforming potential energy into kinetic energy.

Energy can take many forms: mechanical energy, heat, sound, electric current, light, or radioactivity. Because it can exist in so many forms, energy can be measured in many ways. Heat is the most convenient way of measuring energy because all other forms of energy can be converted into heat. In fact, the term *thermodynamics* means "heat changes."

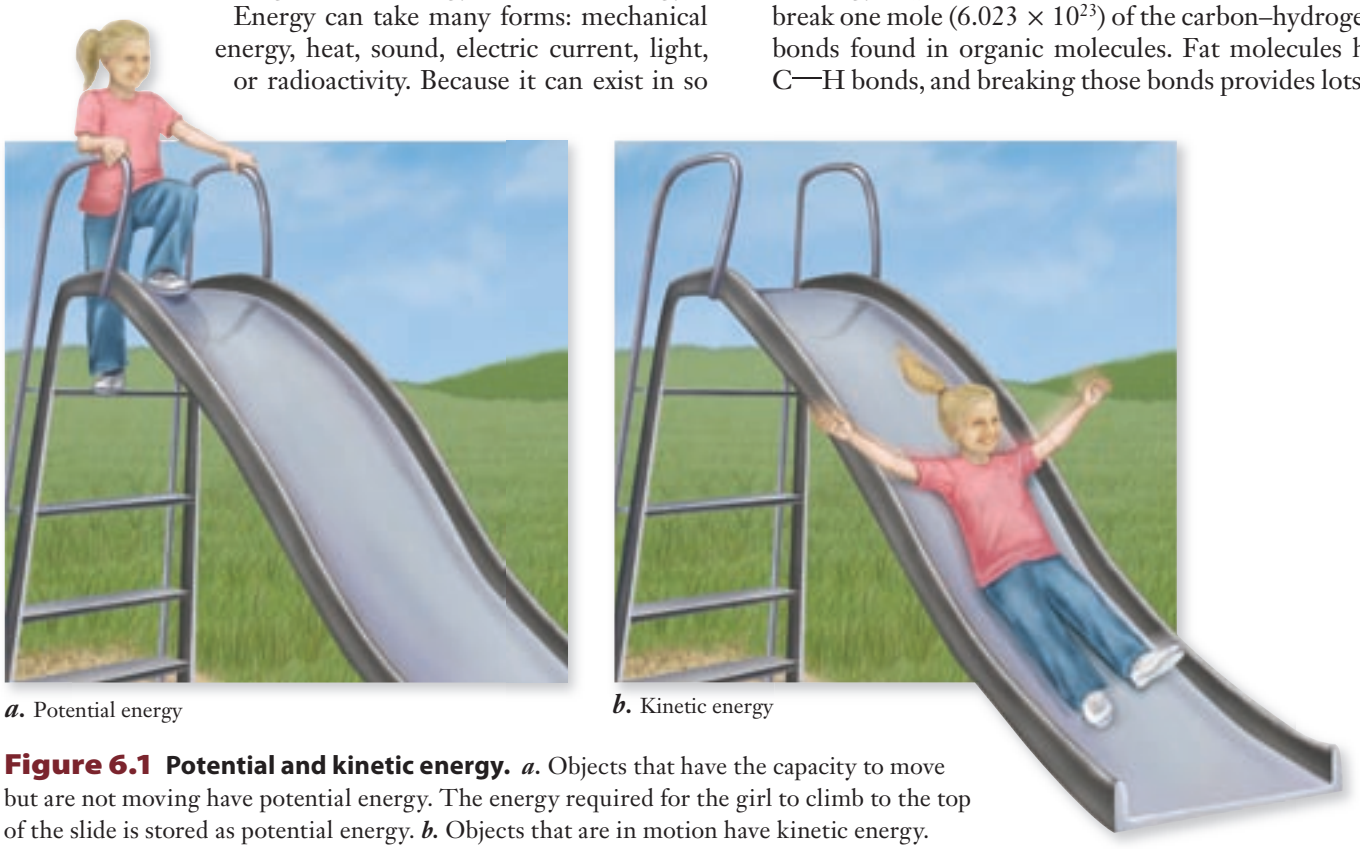
The unit of heat most commonly employed in biology is the kilocalorie (kcal). One kilocalorie is equal to 1000 calories (cal). One calorie is the heat required to raise the temperature of one gram of water one degree Celsius (°C). (You are probably more used to seeing the term *Calorie* with a capital C. This is used on food labels and is actually the same as kilocalorie.) Another energy unit, often used in physics, is the *joule;* one joule equals 0.239 cal.

The sun provides energy for living systems

Energy flows into the biological world from the Sun. It is estimated that the Sun provides the Earth with more than 13×10^{23} calories per year, or 40 million billion calories per second! Plants, algae, and certain kinds of bacteria capture a fraction of this energy through photosynthesis.

In photosynthesis, energy absorbed from sunlight is used to combine small molecules (water and carbon dioxide) into more complex ones (sugars). This process converts carbon from an inorganic to an organic form. In the process energy from the Sun is stored as potential energy in the covalent bonds between atoms in the sugar molecules.

Breaking the bonds between atoms requires energy. In fact, the strength of a covalent bond is measured by the amount of energy required to break it. For example, it takes 98.8 kcal to break one mole (6.023×10^{23}) of the carbon–hydrogen (C—H) bonds found in organic molecules. Fat molecules have many C—H bonds, and breaking those bonds provides lots of energy.



a. Potential energy

b. Kinetic energy

Figure 6.1 Potential and kinetic energy. ***a.*** Objects that have the capacity to move but are not moving have potential energy. The energy required for the girl to climb to the top of the slide is stored as potential energy. ***b.*** Objects that are in motion have kinetic energy. The stored potential energy is released as kinetic energy as the girl slides down.

This is one reason animals store fat. The oxidation of one mole of a 16-carbon fatty acid that is completely saturated with hydrogens yields 2340 kcal.

Oxidation–reduction reactions transfer electrons while bonds are made or broken

During a chemical reaction, the energy stored in chemical bonds may be used to make new bonds. In some of these reactions, electrons actually pass from one atom or molecule to another. An atom or molecule that loses an electron is said to be oxidized, and the process by which this occurs is called **oxidation.** The name comes from the fact that oxygen is the most common electron acceptor in biological systems. Conversely, an atom or molecule that gains an electron is said to be reduced, and the process is called *reduction.* The reduced form of a molecule has a higher level of energy than the oxidized form (figure 6.2).

Oxidation and reduction always take place together, because every electron that is lost by one atom through oxidation is gained by another atom through reduction. Therefore, chemical reactions of this sort are called **oxidation–reduction,** or **redox,** *reactions.* Oxidation–reduction reactions play a key role in the flow of energy through biological systems.

In the next two chapters, you will learn the details of how organisms derive energy from the oxidation of organic compounds via respiration, as well as from the energy in sunlight via photosynthesis.

Learning Outcome Review 6.1

Energy is defined as the capacity to do work. The two forms of energy are kinetic energy, or energy of motion, and potential energy, or stored energy. The ultimate source of energy for living systems is the Sun. Organisms derive their energy from oxidation–reduction reactions. In oxidation, a molecule loses an electron; in reduction, a molecule gains an electron.

- ***What energy source might ecosystems at the bottom of the ocean use?***

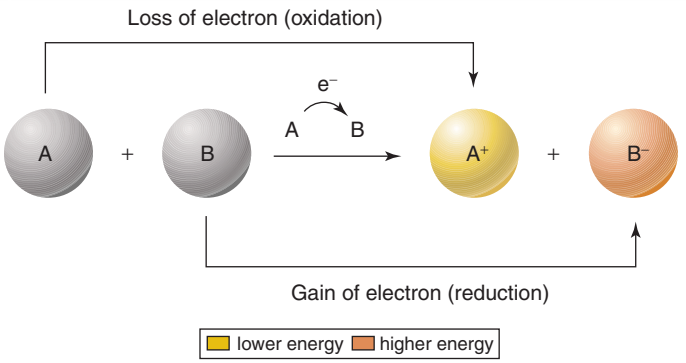


Figure 6.2 Redox reactions. Oxidation is the loss of an electron; reduction is the gain of an electron. In this example, the charges of molecules A and B appear as superscripts in each molecule. Molecule A loses energy as it loses an electron, and molecule B gains that energy as it gains an electron.

6.2 The Laws of Thermodynamics and Free Energy

Learning Outcomes

1. ***Explain the laws of thermodynamics.***
2. ***Recognize how free energy can be used to predict the outcome of chemical reactions.***
3. ***Contrast the course of a reaction with and without an enzyme catalyst.***

All activities of living organisms—growing, running, thinking, singing, reading these words—involve changes in energy. A set of two universal laws we call the laws of thermodynamics govern all energy changes in the universe, from nuclear reactions to a bird flying through the air.

The First Law states that energy cannot be created or destroyed

The **First Law of Thermodynamics** concerns the amount of energy in the universe. Energy cannot be created or destroyed; it can only change from one form to another (from potential to kinetic, for example). The total amount of energy in the universe remains constant.

The lion eating a giraffe at the beginning of this chapter is acquiring energy. Rather than creating new energy or capturing the energy in sunlight, the lion is merely transferring some of the potential energy stored in the giraffe's tissues to its own body, just as the giraffe obtained the potential energy stored in the plants it ate while it was alive.

Within any living organism, chemical potential energy stored in some molecules can be shifted to other molecules and stored in different chemical bonds. It can also be converted into other forms, such as kinetic energy, light, or electricity. During each conversion, some of the energy dissipates into the environment as **heat,** which is a measure of the random motion of molecules (and therefore a measure of one form of kinetic energy). Energy continuously flows through the biological world in one direction, with new energy from the Sun constantly entering the system to replace the energy dissipated as heat.

Heat can be harnessed to do work only when there is a heat gradient—that is, a temperature difference between two areas. Cells are too small to maintain significant internal temperature differences, so heat energy is incapable of doing the work of cells. Instead, cells must rely on chemical reactions for energy.

Although the total amount of energy in the universe remains constant, the energy available to do work decreases as more of it is progressively lost as heat.

The Second Law states that some energy is lost as disorder increases

The **Second Law of Thermodynamics** concerns the transformation of potential energy into heat, or random molecular motion. It states that the disorder in the universe, more formally called **entropy,** is continuously increasing. Put simply, disorder is more likely than order. For example, it is much more likely that a column of bricks will tumble over than that a pile of bricks will arrange themselves spontaneously to form a column.

In general, energy transformations proceed spontaneously to convert matter from a more ordered, less stable form to a less ordered, but more stable form. For this reason, the second law is sometimes called "time's arrow." Looking at the photographs in figure 6.3, you could put the pictures into correct sequence using the information that time had elapsed with only natural processes occurring. Although it might be great if our rooms would straighten themselves up, we know from experience how much work it takes to do so.

The Second Law of Thermodynamics can also be stated simply as "entropy increases." When the universe formed, it held all the potential energy it will ever have. It has become progressively more disordered ever since, with every energy exchange increasing the amount of entropy.

Chemical reactions can be predicted based on changes in free energy

It takes energy to break the chemical bonds that hold the atoms in a molecule together. Heat energy, because it increases atomic motion, makes it easier for the atoms to pull apart. Both chemical bonding and heat have a significant influence on a molecule. Chemical bonding reduces disorder; heat increases it. The net effect, the amount of energy actually available to break and subsequently form other chemical bonds, is called the *free energy* of that molecule. In a more general sense, **free energy** is defined as the energy available to do work in any system.

For a molecule within a cell, where pressure and volume usually do not change, the free energy is denoted by the symbol G (for "Gibbs' free energy"). G is equal to the energy contained in a molecule's chemical bonds (called **enthalpy** and designated H) together with the energy term (TS) related to the degree of disorder in the system, where S is the symbol for *entropy* and T is the absolute temperature expressed in the Kelvin scale (K = °C + 273):

$$G = H - TS$$

Chemical reactions break some bonds in the reactants and form new ones in the products. Consequently, reactions can produce changes in free energy. When a chemical reaction occurs under conditions of constant temperature, pressure, and volume—as do most biological reactions—the change symbolized by the Greek capital letter delta, Δ, in free energy (ΔG) is simply:

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

We can use the change in free energy, or ΔG, to predict whether a chemical reaction is spontaneous or not. For some reactions, the ΔG is positive, which means that the products of the reaction contain *more* free energy than the reactants; the bond energy (H) is higher, or the disorder (S) in the system is lower. Such reactions do not proceed spontaneously because they require an input of energy. Any reaction that requires an input of energy is said to be **endergonic** ("inward energy").

For other reactions, the ΔG is negative. In this case, the products of the reaction contain less free energy than the reactants; either the bond energy is lower, or the disorder is higher, or both. Such reactions tend to proceed spontaneously. These reactions release the excess free energy as heat and are thus said to be **exergonic** ("outward energy"). Any chemical reaction tends to proceed spontaneously if the difference in disorder ($T\Delta S$) is *greater* than the difference in bond energies between reactants and products (ΔH).

Note that *spontaneous* does not mean the same thing as *instantaneous*. A spontaneous reaction may proceed very slowly. Figure 6.4 sums up endergonic and exergonic reactions.

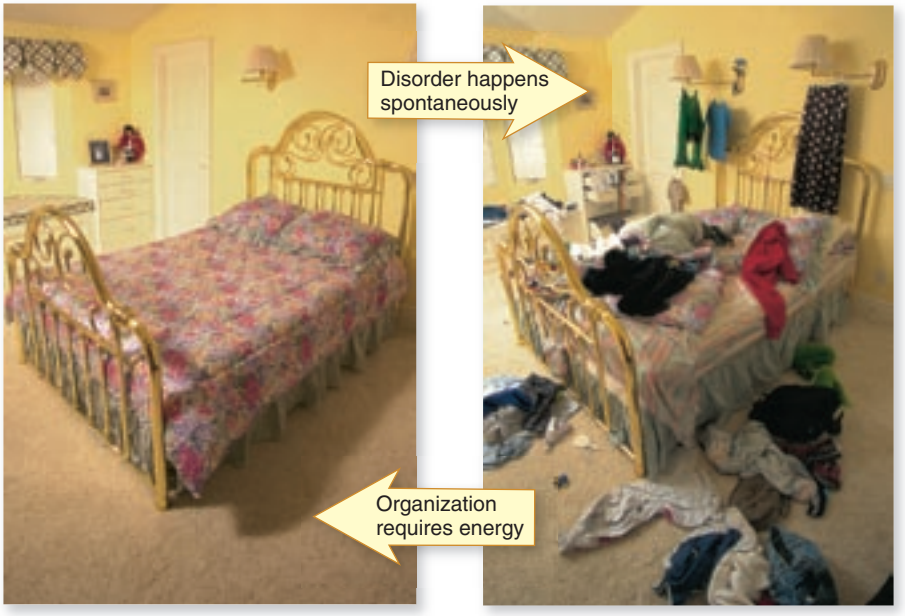
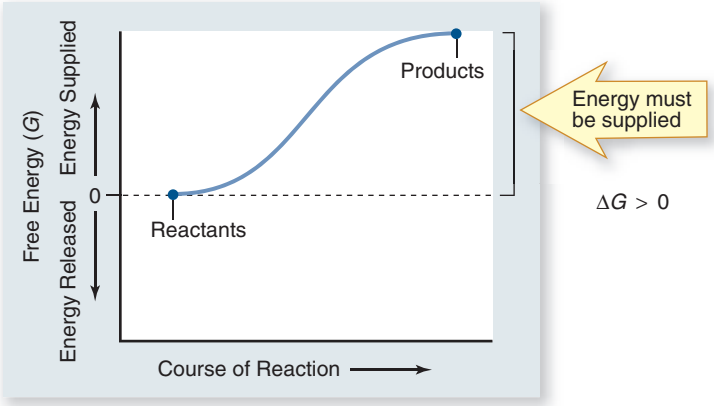
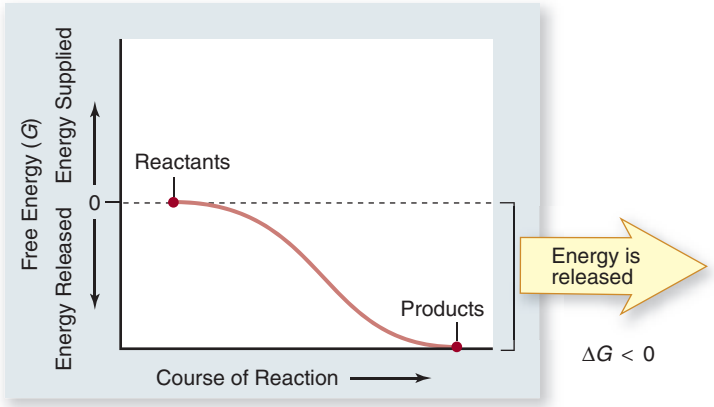


Figure 6.3 Entropy in action. As time elapses, the room shown at right becomes more disorganized. Entropy has increased in this room. It takes energy to restore it to the ordered state shown at left.



a.



b.

Figure 6.4 Energy in chemical reactions. ***a.*** In an endergonic reaction, the products of the reaction contain more energy than the reactants, and the extra energy must be supplied for the reaction to proceed. ***b.*** In an exergonic reaction, the products contain less energy than the reactants, and the excess energy is released.

Because chemical reactions are reversible, a reaction that is exergonic in the forward direction will be endergonic in the reverse direction. For each reaction, an equilibrium exists at some point between the relative amounts of reactants and products. This equilibrium has a numeric value and is called the *equilibrium constant*. This characteristic of reactions provides us with another way to think about free energy changes: an exergonic reaction has an equilibrium favoring the products, and an endergonic reaction has an equilibrium favoring the reactants.

Spontaneous chemical reactions require activation energy

If all chemical reactions that release free energy tend to occur spontaneously, why haven't all such reactions already occurred? Consider the gasoline tank of your car: The oxidation of the hydrocarbons in gasoline is an exergonic reaction, but your gas tank does not spontaneously explode. One reason is that most reactions require an input of energy to get started. In the case of your car, this input consists of the electrical sparks in the engine's cylinders, producing a controlled explosion.

Activation energy

Before new chemical bonds can form, even bonds that contain less energy, existing bonds must first be broken, and that requires energy input. The extra energy needed to destabilize existing chemical bonds and initiate a chemical reaction is called **activation energy** (figure 6.5).

The rate of an exergonic reaction depends on the activation energy required for the reaction to begin. Reactions with larger activation energies tend to proceed more slowly because fewer molecules succeed in getting over the initial energy hurdle. The rate of reactions can be increased in two ways: (1) by increasing the energy of reacting molecules or (2) by lowering activation energy. Chemists often drive important industrial reactions by increasing the energy of the reacting molecules, which is frequently accomplished simply by heating up the reactants. The other strategy is to use a catalyst to lower the activation energy.

How catalysts work

Activation energies are not constant. Stressing particular chemical bonds can make them easier to break. The process of influencing chemical bonds in a way that lowers the activation energy needed to initiate a reaction is called **catalysis,** and substances that accomplish this are known as *catalysts* (see figure 6.5).

Catalysts cannot violate the basic laws of thermodynamics; they cannot, for example, make an endergonic reaction proceed spontaneously. By reducing the activation energy, a catalyst accelerates both the forward and the reverse reactions by exactly the same amount. Therefore, a catalyst does not alter the proportion of reactant that is ultimately converted into product.

To understand this, imagine a bowling ball resting in a shallow depression on the side of a hill. Only a narrow rim of dirt below the ball prevents it from rolling down the hill. Now imagine digging away that rim of dirt. If you remove enough dirt from below the ball, it will start to roll down the hill—but

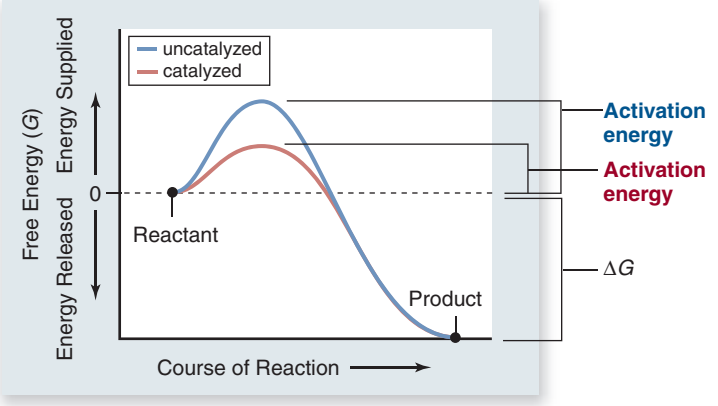


Figure 6.5 Activation energy and catalysis. Exergonic reactions do not necessarily proceed rapidly because activation energy must be supplied to destabilize existing chemical bonds. Catalysts accelerate particular reactions by lowering the amount of activation energy required to initiate the reaction. Catalysts do not alter the free-energy change produced by the reaction.

removing dirt from below the ball will *never* cause the ball to roll up the hill. Removing the lip of dirt simply allows the ball to move freely; gravity determines the direction it then travels.

Similarly, the direction in which a chemical reaction proceeds is determined solely by the difference in free energy between reactants and products. Like digging away the soil below the bowling ball on the hill, catalysts reduce the energy barrier that is preventing the reaction from proceeding. Only exergonic reactions can proceed spontaneously, and catalysts cannot change that. What catalysts *can* do is make a reaction proceed much faster. In living systems, enzymes act as catalysts.

Learning Outcome Review 6.2

The First Law of Thermodynamics states that energy cannot be created or destroyed. The Second Law states that the loss of energy results in greater disorder, or entropy. Free-energy changes (ΔG) can predict whether chemical reactions take place. Reactions with a negative ΔG occur spontaneously, and those with a positive ΔG do not. Energy needed to initiate a reaction is termed activation energy. Catalysts, such as enzymes in living systems, lower this activation energy to speed up reactions.

- ***Can an enzyme make an endergonic reaction exergonic?***

6.3 ATP: The Energy Currency of Cells

Learning Outcomes

1. *Describe the role of ATP in short-term energy storage.*
2. *Explain what "high-energy" bonds are in ATP.*

The chief "currency" all cells use for their energy transactions is the nucleotide *adenosine triphosphate (ATP)*. ATP powers almost every energy-requiring process in cells, from making sugars, to supplying activation energy for chemical reactions, to actively transporting substances across membranes, to moving through the environment and growing.

Cells store and release energy in the bonds of ATP

You saw in chapter 3 that nucleotides serve as the building blocks for nucleic acids, but they play other cellular roles as well. ATP is used as a building block for RNA molecules, and it also has a critical function as a portable source of energy on demand for endergonic cellular processes.

The structure of ATP

Like all nucleotides, ATP is composed of three smaller components (figure 6.6). The first component is a five-carbon sugar, ribose, which serves as the framework to which the other two subunits are attached. The second component is adenine, an organic molecule composed of two carbon–nitrogen rings. Each of the nitrogen atoms in the ring has an unshared pair of electrons and weakly attracts hydrogen ions, making adenine chemically a weak base. The third component of ATP is a chain of three phosphates.

How ATP stores energy

The key to how ATP stores energy lies in its triphosphate group. Phosphate groups are highly negatively charged, and thus they strongly repel one another. This electrostatic repulsion makes the covalent bonds joining the phosphates unstable. The molecule is often referred to as a "coiled spring," with the phosphates straining away from one another.

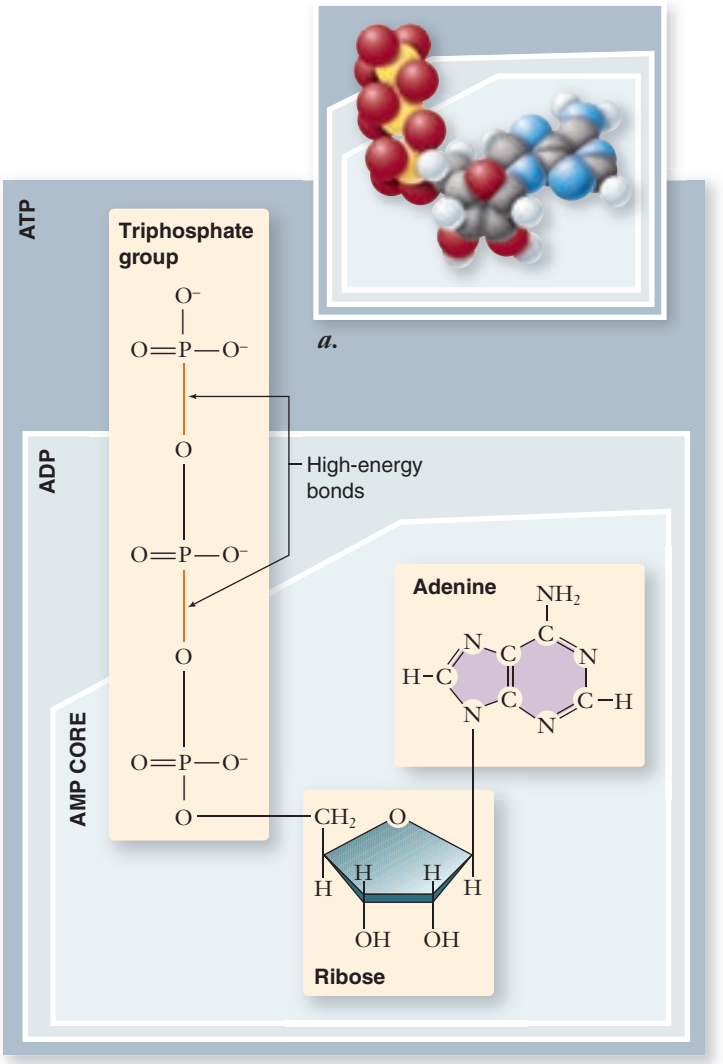


Figure 6.6 The ATP molecule. The model *(a)* and the structural diagram *(b)* both show that ATP has a core of AMP. Addition of one phosphate to AMP yields ADP, and addition of a second phosphate yields ATP. These two terminal phosphates are attached by high-energy bonds so that removing either by hydrolysis is an exergonic reaction that releases energy. ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate.

The unstable bonds holding the phosphates together in the ATP molecule have a low activation energy and are easily broken by hydrolysis. When they break, they can transfer a considerable amount of energy. In other words, the hydrolysis of ATP has a negative ΔG, and the energy it releases can be used to perform work.

In most reactions involving ATP, only the outermost high-energy phosphate bond is hydrolyzed, cleaving off the phosphate group on the end. When this happens, ATP becomes *adenosine diphosphate (ADP)* plus an **inorganic phosphate (P_i),** and energy equal to 7.3 kcal/mol is released under standard conditions. The liberated phosphate group usually attaches temporarily to some intermediate molecule. When that molecule is dephosphorylated, the phosphate group is released as P_i.

Both of the two terminal phosphates can be hydrolyzed to release energy, leaving *adenosine monophosphate (AMP)*, but the third phosphate is not attached by a high-energy bond. With only one phosphate group, AMP has no other phosphates to provide the electrostatic repulsion that makes the bonds holding the two terminal phosphate groups high-energy bonds.

ATP hydrolysis drives endergonic reactions

Cells use ATP to drive endergonic reactions. These reactions do not proceed spontaneously because their products possess more free energy than their reactants. However, if the cleavage of ATP's terminal high-energy bond releases more energy than the other reaction consumes, the two reactions can be coupled so that the energy released by the hydrolysis of ATP can be used to supply the endergonic reaction with the energy it needs. Coupled together, these reactions result in a net release of energy ($-\Delta G$) and are therefore exergonic and proceed spontaneously. Because almost all the endergonic reactions in cells require less energy than is released by the cleavage of ATP, ATP can provide most of the energy a cell needs.

Inquiry question

When ATP hydrolysis is coupled with an endergonic reaction and supplies more than enough energy, is the overall process endergonic or exergonic? Would the ΔG for the overall process be negative or positive?

ATP cycles continuously

The same feature that makes ATP an effective energy donor—the instability of its phosphate bonds—prevents it from being a good long-term energy-storage molecule. Fats and carbohydrates serve that function better.

The use of ATP can be thought of as a cycle: Cells use exergonic reactions to provide the energy needed to synthesize ATP from ADP + P_i; they then use the hydrolysis of ATP to provide energy to drive the endergonic reactions they need (figure 6.7).

Most cells do not maintain large stockpiles of ATP. Instead, they typically have only a few seconds' supply of ATP at any given time, and they continually produce more from ADP and P_i. It is estimated that even a sedentary individual turns over an amount of ATP in one day roughly equal to his body weight. This statistic makes clear the importance of ATP synthesis. In the next two chapters we will explore in detail the cellular mechanisms for synthesizing ATP.

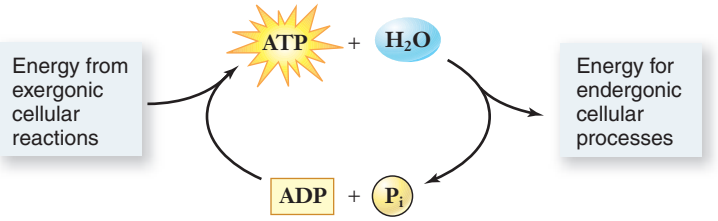


Figure 6.7 The ATP cycle. ATP is synthesized and hydrolyzed in a cyclic fashion. The synthesis of ATP from ADP + P_i is endergonic and is powered by exergonic cellular reactions. The hydrolysis of ATP to ADP + P_i is exergonic, and the energy released is used to power endergonic cellular functions such as muscle contraction. ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate.

Learning Outcome Review 6.3

ATP is a nucleotide with three phosphate groups. Endergonic cellular processes can be driven by coupling to the exergonic hydrolysis of the two terminal phosphates. The bonds holding the terminal phosphate groups together are easily broken, releasing energy like a coiled spring. The cell is constantly building ATP using exergonic reactions and breaking it down to drive endergonic reactions.

- ***If the molecular weight of ATP is 507.18 g/mol, and the ΔG for hydrolysis is –7.3 kcal/mol how much energy is released over the course of the day by a 100-kg man?***

6.4 Enzymes: Biological Catalysts

Learning Outcomes

1. *Discuss the specificity of enzymes.*
2. *Explain how enzymes bind to their substrates.*
3. *List the factors that influence the rate of enzyme-catalyzed reactions.*

The chemical reactions within living organisms are regulated by controlling the points at which catalysis takes place. Life itself, therefore, can be seen as regulated by catalysts. The agents that carry out most of the catalysis in living organisms are called enzymes. Most enzymes are proteins, although increasing evidence indicates that some enzymes are actually RNA molecules, as discussed later in this chapter.

An enzyme alters the activation energy of a reaction

The unique three-dimensional shape of an enzyme enables it to stabilize a temporary association between **substrates**—the molecules that will undergo the reaction. By bringing two substrates together in the correct orientation or by stressing particular chemical bonds of a substrate, an enzyme lowers the

activation energy required for new bonds to form. The reaction thus proceeds much more quickly than it would without the enzyme.

The enzyme itself is not changed or consumed in the reaction, so only a small amount of an enzyme is needed, and it can be used over and over.

As an example of how an enzyme works, let's consider the reaction of carbon dioxide and water to form carbonic acid. This important enzyme-catalyzed reaction occurs in vertebrate red blood cells:

$$\underset{\text{carbon dioxide}}{CO_2} + \underset{\text{water}}{H_2O} \rightleftharpoons \underset{\text{carbonic acid}}{H_2CO_3}$$

This reaction may proceed in either direction, but because it has a large activation energy, the reaction is very slow in the absence of an enzyme: Perhaps 200 molecules of carbonic acid form in an hour in a cell in the absence of any enzyme. Reactions that proceed this slowly are of little use to a cell. Vertebrate red blood cells overcome this problem by employing an enzyme within their cytoplasm called *carbonic anhydrase* (enzyme names usually end in "–ase"). Under the same conditions, but in the presence of carbonic anhydrase, an estimated 600,000 molecules of carbonic acid form every *second!* Thus, the enzyme increases the reaction rate by more than one million times.

Thousands of different kinds of enzymes are known, each catalyzing one or a few specific chemical reactions. By facilitating particular chemical reactions, the enzymes in a cell determine the course of metabolism—the collection of all chemical reactions—in that cell.

Different types of cells contain different sets of enzymes, and this difference contributes to structural and functional variations among cell types. For example, the chemical reactions taking place within a red blood cell differ from those that occur within a nerve cell, in part because different cell types contain different arrays of enzymes.

Active sites of enzymes conform to fit the shape of substrates

Most enzymes are globular proteins with one or more pockets or clefts, called **active sites,** on their surface (figure 6.8). Substrates bind to the enzyme at these active sites, forming an **enzyme–substrate complex** (figure 6.10). For catalysis to occur within the complex, a substrate molecule must fit precisely into an active site. When that happens, amino acid side groups of the enzyme end up very close to certain bonds of the substrate. These side groups interact chemically with the substrate, usually stressing or distorting a particular bond and consequently lowering the activation energy needed to break the bond. After the bonds of the substrates are broken, or new bonds are formed, the substrates have been converted to products. These products then dissociate from the enzyme, leaving the enzyme ready to bind its next substrate and begin the cycle again.

Proteins are not rigid. The binding of a substrate induces the enzyme to adjust its shape slightly, leading to a better *induced fit* between enzyme and substrate (see figure 6.9).

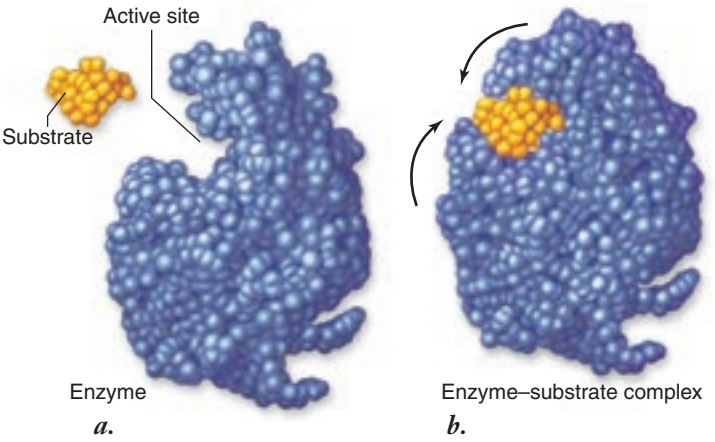


Figure 6.8 Enzyme binding its substrate. ***a.*** The active site of the enzyme lysozyme fits the shape of its substrate, a peptidoglycan that makes up bacterial cell walls. ***b.*** When the substrate, indicated in yellow, slides into the groove of the active site, the protein is induced to alter its shape slightly and bind the substrate more tightly. This alteration of the shape of the enzyme to better fit the substrate is called induced fit.

This interaction may also facilitate the binding of other substrates; in such cases, one substrate "activates" the enzyme to receive other substrates.

Enzymes occur in many forms

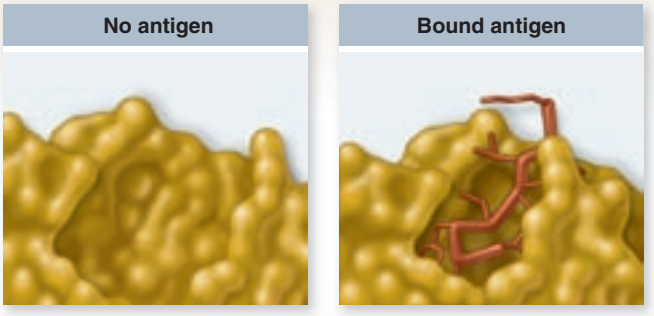
Although many enzymes are suspended in the cytoplasm of cells, not attached to any structure, other enzymes function as

SCIENTIFIC THINKING

Hypothesis: *Protein structure is flexible not rigid.*

Prediction: *Antibody–antigen binding can involve a change in protein structure.*

Test: *Determine crystal structure of a fragment of a specific antibody with no antigen bound, and with antigen bound for comparison.*



Result: *After binding, the antibody folds around the antigen forming a pocket.*

Conclusion: *In this case, binding involves an induced-fit kind of change in conformation.*

Further Experiments: *Why is this experiment easier to do with an antibody than with an enzyme? Can this experiment be done with an enzyme?*

Figure 6.9 Induced-fit binding of antibody to antigen.

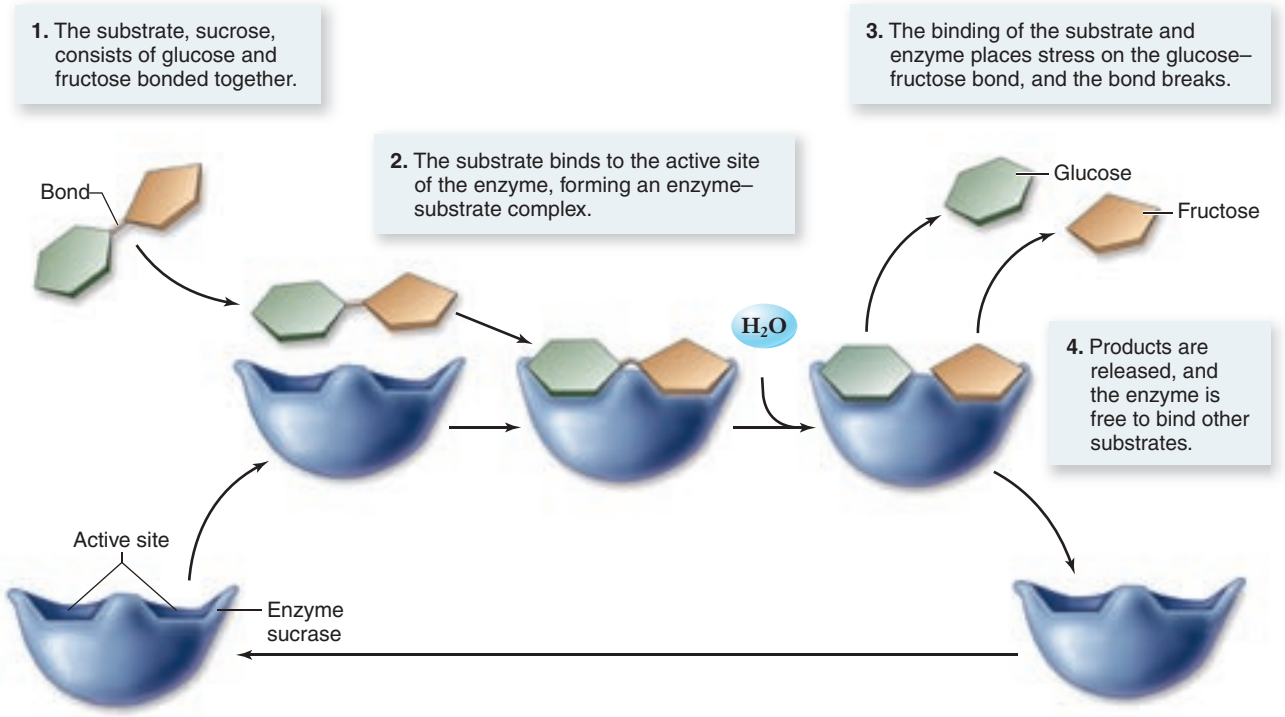


Figure 6.10 The catalytic cycle of an enzyme. Enzymes increase the speed at which chemical reactions occur, but they are not altered permanently themselves as they do so. In the reaction illustrated here, the enzyme sucrase is splitting the sugar sucrose into two simpler sugars: glucose and fructose.

integral parts of cell membranes and organelles. Enzymes may also form associations called *multienzyme complexes* to carry out reaction sequences. And, as mentioned earlier, evidence exists that some enzymes may consist of RNA rather than being only protein.

Multienzyme complexes

Often several enzymes catalyzing different steps of a sequence of reactions are associated with one another in noncovalently bonded assemblies called **multienzyme complexes.** The bacterial pyruvate dehydrogenase multienzyme complex, shown in figure 6.11, contains enzymes that carry out three sequential reactions in oxidative metabolism. Each complex has multiple copies of each of the three enzymes—60 protein subunits in all. The many subunits work together to form a molecular machine that performs multiple functions.

Multienzyme complexes offer the following significant advantages in catalytic efficiency:

1. The rate of any enzyme reaction is limited by how often the enzyme collides with its substrate. If a series of sequential reactions occurs within a multienzyme complex, the product of one reaction can be delivered to the next enzyme without releasing it to diffuse away.
2. Because the reacting substrate doesn't leave the complex while it goes through the series of reactions, unwanted side reactions are prevented.
3. All of the reactions that take place within the multienzyme complex can be controlled as a unit.

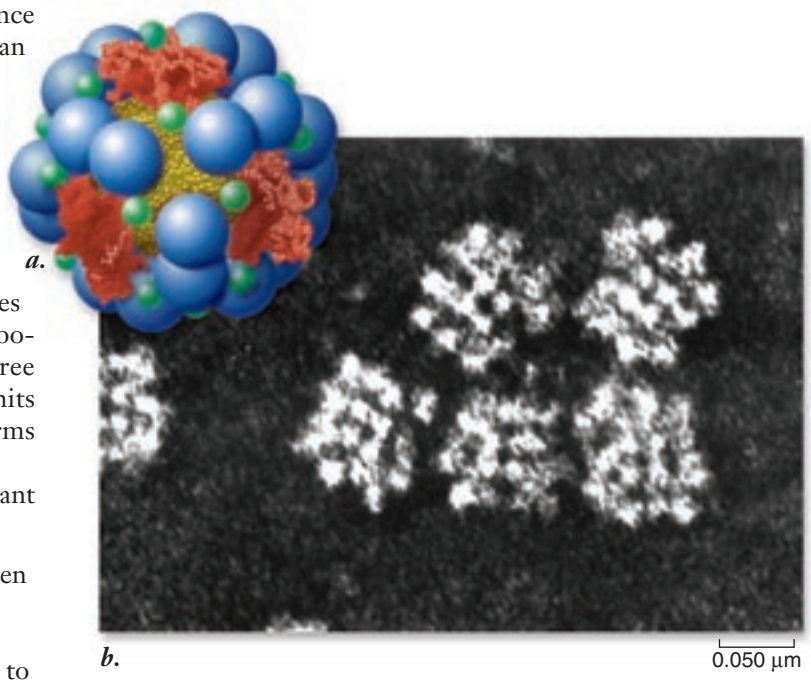


Figure 6.11 A complex enzyme: pyruvate dehydrogenase. Pyruvate dehydrogenase, which catalyzes the oxidation of pyruvate, is one of the most complex enzymes known. ***a.*** A model of the enzyme showing the arrangement of the 60 protein subunits. ***b.*** Many of the protein subunits are clearly visible in the electron micrograph.

In addition to pyruvate dehydrogenase, which controls entry to the Krebs cycle during aerobic respiration (see chapter 7), several other key processes in the cell are catalyzed by multienzyme complexes. One well-studied system is the fatty acid synthetase complex that catalyzes the synthesis of fatty acids from two-carbon precursors. Seven different enzymes make up this multienzyme complex, and the intermediate reaction products remain associated with the complex for the entire series of reactions.

Nonprotein enzymes

Until a few years ago, most biology textbooks contained statements such as "Proteins called enzymes are the catalysts of biological systems." We can no longer make that statement without qualification.

Thomas J. Cech and colleagues at the University of Colorado reported in 1981 that certain reactions involving RNA molecules appear to be catalyzed in cells by RNA itself, rather than by enzymes. This initial observation has been corroborated by additional examples of RNA catalysis. Like enzymes, these RNA catalysts, which are loosely called "ribozymes," greatly accelerate the rate of particular biochemical reactions and show extraordinary substrate specificity.

Research has revealed at least two sorts of ribozymes. Some ribozymes have folded structures and catalyze reactions on themselves, a process called *intra*molecular catalysis. Other ribozymes act on other molecules without being changed themselves, a process called *inter*molecular catalysis.

The most striking example of the role of RNA as enzyme is emerging from recent work on the structure and function of the ribosome. For many years it was thought that RNA was a structural framework for this vital organelle, but it is now clear that ribosomal RNA plays a key role in ribosome function. The ribosome itself is a ribozyme.

The ability of RNA, an informational molecule, to act as a catalyst has stirred great excitement because it seems to answer the question—Which came first, the protein or the nucleic acid? It now seems at least possible that RNA evolved first and may have catalyzed the formation of the first proteins.

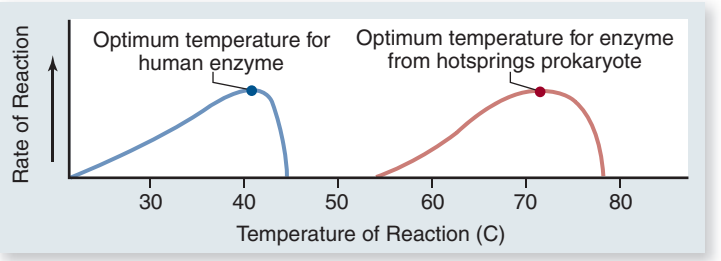
Environmental and other factors affect enzyme function

The rate of an enzyme-catalyzed reaction is affected by the concentrations of both the substrate and the enzyme that works on it. In addition, any chemical or physical factor that alters the enzyme's three-dimensional shape—such as temperature, pH, and the binding of regulatory molecules—can affect the enzyme's ability to catalyze the reaction.

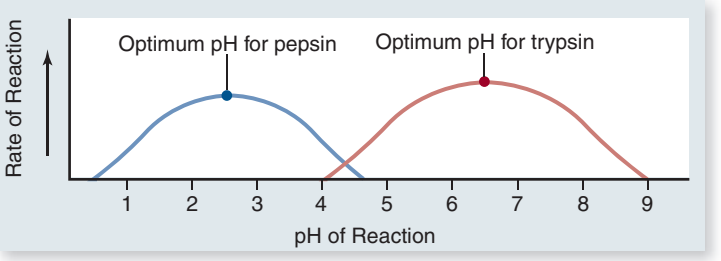
Temperature

Increasing the temperature of an uncatalyzed reaction increases its rate because the additional heat increases random molecular movement. This motion can add stress to molecular bonds and affect the activation energy of a reaction.

The rate of an enzyme-catalyzed reaction also increases with temperature, but only up to a point called the *optimum temperature* (figure 6.12*a*). Below this temperature, the hydrogen bonds and hydrophobic interactions that determine the enzyme's shape are not flexible enough to permit the induced fit that is optimum for catalysis. Above the optimum temperature, these forces are too weak to maintain the enzyme's shape against the increased random movement of the atoms in the enzyme. At higher temperatures, the enzyme denatures, as described in chapter 3.



a.



b.

Figure 6.12 Enzyme sensitivity to the environment. The activity of an enzyme is influenced by both ***(a)*** temperature and ***(b)*** pH. Most human enzymes, such as the protein-degrading enzyme trypsin, work best at temperatures of about 40°C and within a pH range of 6 to 8. The hot springs prokaryote tolerates a higher environmental temperature and a correspondingly higher temperature optimum for enzymes. Pepsin works in the acidic environment of the stomach and has a lower optimum pH.

Most human enzymes have an optimum temperature between 35°C and 40°C—a range that includes normal body temperature. Prokaryotes that live in hot springs have more stable enzymes (that is, enzymes held together more strongly), so the optimum temperature for those enzymes can be 70°C or higher. In each case the optimal temperature for the enzyme corresponds to the "normal" temperature usually encountered in the body or the environment, depending on the type of organism.

pH

Ionic interactions between oppositely charged amino acid residues, such as glutamic acid (–) and lysine (+), also hold enzymes together. These interactions are sensitive to the hydrogen ion concentration of the fluid in which the enzyme is dissolved, because changing that concentration shifts the balance between positively and negatively charged amino acid residues. For this reason, most enzymes have an *optimum pH* that usually ranges from pH 6 to 8.

Enzymes able to function in very acidic environments are proteins that maintain their three-dimensional shape even in

the presence of high hydrogen ion concentrations. The enzyme pepsin, for example, digests proteins in the stomach at pH 2, a very acidic level (figure 6.12*b*).

Inhibitors and activators

Enzyme activity is also sensitive to the presence of specific substances that can bind to the enzyme and cause changes in its shape. Through these substances, a cell is able to regulate which of its enzymes are active and which are inactive at a particular time. This ability allows the cell to increase its efficiency and to control changes in its characteristics during development. A substance that binds to an enzyme and *decreases* its activity is called an **inhibitor.** Very often, the end product of a biochemical pathway acts as an inhibitor of an early reaction in the pathway, a process called *feedback inhibition* (discussed later in this chapter).

Enzyme inhibition occurs in two ways: **Competitive inhibitors** compete with the substrate for the same active site, occupying the active site and thus preventing substrates from binding; **noncompetitive inhibitors** bind to the enzyme in a location other than the active site, changing the shape of the enzyme and making it unable to bind to the substrate (figure 6.13).

Many enzymes can exist in either an active or inactive conformation; such enzymes are called *allosteric enzymes*. Most noncompetitive inhibitors bind to a specific portion of the enzyme called an **allosteric site.** These sites serve as chemical on/off switches; the binding of a substance to the site can switch the enzyme between its active and inactive configurations. A substance that binds to an allosteric site and reduces enzyme activity is called an **allosteric inhibitor** (figure 6.13*b*).

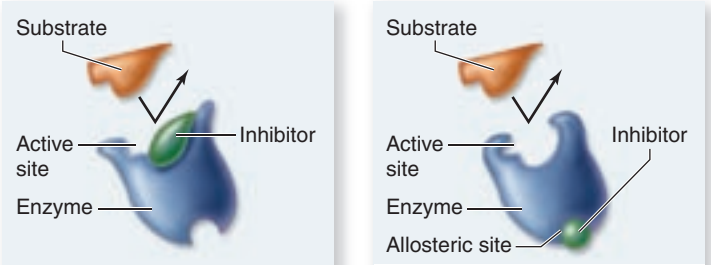
This kind of control is also used to activate enzymes. An **allosteric activator** binds to allosteric sites to keep an enzyme in its active configuration, thereby *increasing* enzyme activity.

Enzyme cofactors

Enzyme function is often assisted by additional chemical components known as **cofactors.** These can be metal ions that are often found in the active site participating directly in catalysis. For example, the metallic ion zinc is used by some enzymes, such as protein-digesting carboxypeptidase, to draw electrons away from their position in covalent bonds, making the bonds less stable and easier to break. Other metallic elements, such as molybdenum and manganese, are also used as cofactors. Like zinc, these substances are required in the diet in small amounts.

When the cofactor is a nonprotein organic molecule, it is called a **coenzyme.** Many of the small organic molecules essential in our diets that we call vitamins function as coenzymes. For example the B vitamins B_6 and B_{12}, both function as coenzymes for a number of different enzymes. Modified nucleotides are also used as coenzymes.

In numerous oxidation–reduction reactions that are catalyzed by enzymes, the electrons pass in pairs from the active site of the enzyme to a coenzyme that serves as the electron acceptor. The coenzyme then transfers the electrons to a different enzyme, which releases them (and the energy they bear) to the substrates in another reaction. Often, the electrons combine with protons (H^+) to form hydrogen atoms. In this way, coenzymes shuttle energy in the form of hydrogen atoms from one enzyme to another in a cell. The role of coenzymes and the specifics of their action will be explored in detail in the following two chapters.



a. Competitive inhibition ***b.*** Noncompetitive inhibition

Figure 6.13 How enzymes can be inhibited. *a.* In competitive inhibition, the inhibitor has a shape similar to the substrate and competes for the active site of the enzyme. ***b.*** In noncompetitive inhibition, the inhibitor binds to the enzyme at the allosteric site, a place away from the active site, effecting a conformational change in the enzyme, making it unable to bind to its substrate.

Learning Outcome Review 6.4

Enzymes are biological catalysts that accelerate chemical reactions inside the cell. Enzymes bind to their substrates based on molecular shape, which allows them to be highly specific. Enzyme activity is affected by conditions such as temperature and pH and the presence of inhibitors or activators. Some enzymes also require an inorganic cofactor or an organic coenzyme.

- ***Why do proteins and RNA function as enzymes but DNA does not?***

6.5 Metabolism: The Chemical Description of Cell Function

Learning Outcomes

1. ***Explain the kinds of reactions that make up metabolism.***
2. ***Discuss what is meant by a metabolic pathway.***
3. ***Recognize that metabolism is a product of evolution.***

Living chemistry, the total of all chemical reactions carried out by an organism, is called **metabolism.** Those chemical reactions that expend energy to build up molecules are called *anabolic* reactions, or **anabolism.** Reactions that harvest energy by breaking down molecules are called *catabolic* reactions, or **catabolism.** This section presents a general overview of metabolic processes that will be described in much greater detail in later chapters.

Biochemical pathways organize chemical reactions in cells

Organisms contain thousands of different kinds of enzymes that catalyze a bewildering variety of reactions. Many of these reactions in a cell occur in sequences called **biochemical pathways.** In such pathways, the product of one reaction becomes the substrate for the next (figure 6.14). Biochemical pathways are the organizational units of metabolism—the elements an organism controls to achieve coherent metabolic activity.

Many sequential enzyme steps in biochemical pathways take place in specific compartments of the cell; for example, the steps of the Krebs cycle (see chapter 7), occur in the matrix inside mitochondria in eukaryotes. By determining where many of the enzymes that catalyze these steps are located, we can "map out" a model of metabolic processes in the cell.

Biochemical pathways may have evolved in stepwise fashion

In the earliest cells, the first biochemical processes probably involved energy-rich molecules scavenged from the environment. Most of the molecules necessary for these processes are thought to have existed independently in the "organic soup" of the early oceans.

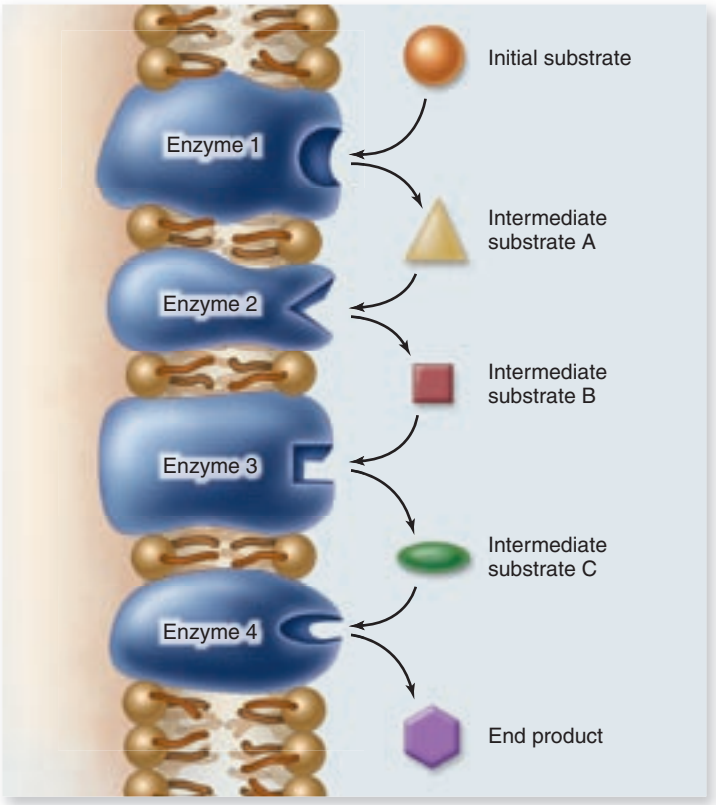


Figure 6.14 A biochemical pathway. The original substrate is acted on by enzyme 1, changing the substrate to a new intermediate, substrate A, recognized as a substrate by enzyme 2. Each enzyme in the pathway acts on the product of the previous stage. These enzymes may be either soluble or arranged in a membrane as shown.

The first catalyzed reactions were probably simple, one-step reactions that brought these molecules together in various combinations. Eventually, the energy-rich molecules became depleted in the external environment, and only organisms that had evolved some means of making those molecules from other substances could survive. Thus, a hypothetical reaction,

$$\begin{matrix} F \\ + \\ G \end{matrix} \longrightarrow H$$

where two energy-rich molecules (F and G) react to produce compound H and release energy, became more complex when the supply of F in the environment ran out.

A new reaction was added in which the depleted molecule, F, is made from another molecule, E, which was also present in the environment:

$$E \longrightarrow \begin{matrix} F \\ + \\ G \end{matrix} \longrightarrow H$$

When the supply of E was in turn exhausted, organisms that were able to make E from some other available precursor, D, survived. When D was depleted, those organisms in turn were replaced by ones able to synthesize D from another molecule, C:

$$C \longrightarrow D \longrightarrow E \longrightarrow \begin{matrix} F \\ + \\ G \end{matrix} \longrightarrow H$$

This hypothetical biochemical pathway would have evolved slowly through time, with the final reactions in the pathway evolving first and earlier reactions evolving later.

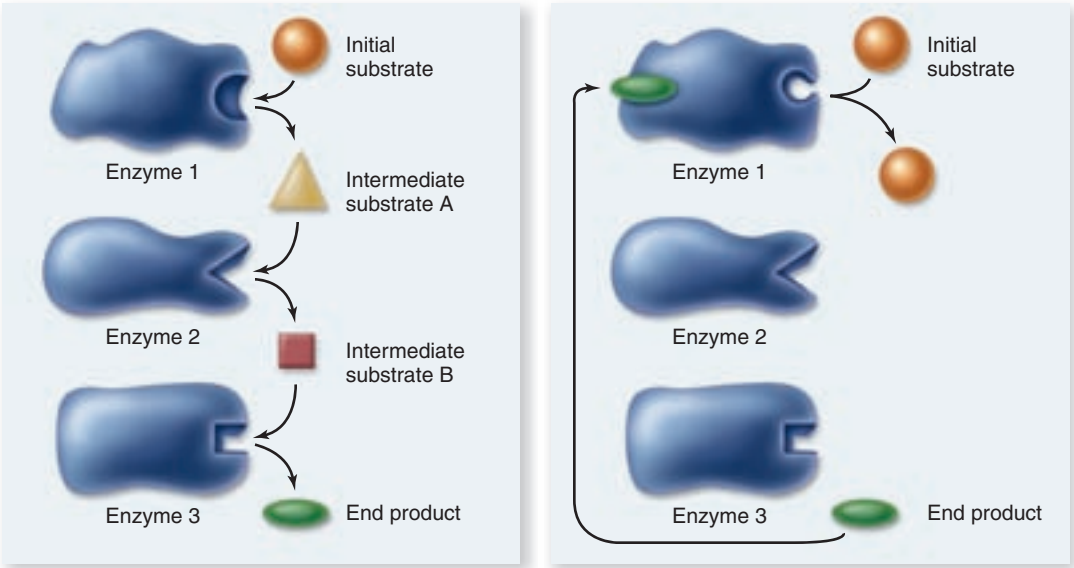
Looking at the pathway now, we would say that the "advanced" organism, starting with compound C, is able to synthesize H by means of a series of steps. This is how the biochemical pathways within organisms are thought to have evolved—not all at once, but one step at a time, backwards.

Feedback inhibition regulates some biochemical pathways

For a biochemical pathway to operate efficiently, its activity must be coordinated and regulated by the cell. Not only is it unnecessary to synthesize a compound when plenty is already present, but doing so would waste energy and raw materials that could be put to use elsewhere. It is to the cell's advantage, therefore, to temporarily shut down biochemical pathways when their products are not needed.

The regulation of simple biochemical pathways often depends on an elegant feedback mechanism: The end-product of the pathway binds to an allosteric site on the enzyme that catalyzes the first reaction in the pathway. This mode of regulation is called **feedback inhibition** (figure 6.15).

In the hypothetical pathway we just described, the enzyme catalyzing the reaction C ⟶ D would possess an allosteric site for H, the end-product of the pathway. As the pathway churned out its product and the amount of H in the cell increased, it would become more likely that an H molecule would encounter



a. *b.*

Figure 6.15 Feedback inhibition. ***a.*** A biochemical pathway with no feedback inhibition. ***b.*** A biochemical pathway in which the final end-product becomes the allosteric inhibitor for the first enzyme in the pathway. In other words, the formation of the pathway's final end-product stops the pathway. The pathway could be the synthesis of an amino acid, a nucleotide, or another important cellular molecule.

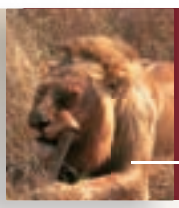
the allosteric site on the C ⟶ D enzyme. Binding to the allosteric site would essentially shut down the reaction C ⟶ D and in turn effectively shut down the whole pathway.

In this chapter we have reviewed the basics of energy and its transformations as carried out in living systems. Chemical bonds are the primary location of energy storage and release, and cells have developed elegant methods of making and breaking chemical bonds to create the molecules they need. Enzymes facilitate these reactions by serving as catalysts. In the following chapters you will learn the details of the mechanisms by which organisms harvest, store, and utilize energy.

Learning Outcome Review 6.5

Metabolism is the sum of all chemical reactions in a cell. Anabolic reactions use energy to build up molecules. Catabolic reactions release energy by breaking down molecules. In a metabolic pathway, the end-product of one reaction is the substrate for the next reaction. Evolution may have favored organisms that could use precursor molecules to synthesize a nutrient. Over time, more reactions would be linked together as novel enzymes arose by mutation.

- ***Is a catabolic pathway likely to be subject to feedback inhibition?***



Chapter Review

6.1 The Flow of Energy in Living Systems

Thermodynamics is the study of energy changes.

Energy can take many forms.

Energy is the capacity to do work. Potential energy is stored energy, and kinetic energy is the energy of motion. Energy can take many forms: mechanical, heat, sound, electric current, light, or radioactive radiation. Energy is measured in units of heat known as kilocalories.

The Sun provides energy for living systems.

Photosynthesis stores light energy from the Sun as potential energy in the covalent bonds of sugar molecules. Breaking these bonds in living cells releases energy for use in other reactions.

Oxidation–reduction reactions transfer electrons while bonds are made or broken.

Oxidation is a reaction involving the loss of electrons. Reduction is the gain of electrons (see figure 6.2). These two reactions take place together and are therefore termed redox reactions.

6.2 The Laws of Thermodynamics and Free Energy

The First Law states that energy cannot be created or destroyed.

Virtually all activities of living organisms require energy. Energy changes form as it moves through organisms and their biochemical systems, but it is not created or destroyed.

The Second Law states that some energy is lost as disorder increases.

The disorder, or entropy, of the universe is continuously increasing. In an open system like the Earth, which is receiving energy from the Sun, this may not be the case. To increase order however, energy must be expended. In energy conversions, some energy is always lost as heat.

Chemical reactions can be predicted based on changes in free energy.

Free energy (G) is the energy available to do work in any system. Changes in free energy (ΔG) predict the direction of reactions. Reactions with a negative ΔG are spontaneous (exergonic) reactions, and reactions with a positive ΔG are not spontaneous (endergonic).

Endergonic chemical reactions absorb energy from the surroundings, whereas exergonic reactions release energy to the surroundings.

Spontaneous chemical reactions require activation energy.

Activation energy is the energy required to destabilize chemical bonds and initiate chemical reactions (see figure 6.5). Even exergonic reactions require this activation energy. Catalysts speed up chemical reactions by lowering the activation energy.

6.3 ATP: The Energy Currency of Cells

Adenosine triphosphate (ATP) is the molecular currency used for cellular energy transactions.

Cells store and release energy in the bonds of ATP.

The energy of ATP is stored in the bonds between its terminal phosphate groups. These groups repel each other due to their negative charge and therefore the covalent bonds joining these phosphates are unstable.

ATP hydrolysis drives endergonic reactions.

Enzymes hydrolyze the terminal phosphate group of ATP to release energy for reactions. If ATP hydrolysis is coupled to an endergonic reaction with a positive ΔG with magnitude less than that for ATP hydrolysis, the two reactions together will be exergonic.

ATP cycles continuously.

ATP hydrolysis releases energy to drive endergonic reactions, and it is synthesized with energy from exergonic reactions (see figure 6.7).

6.4 Enzymes: Biological Catalysts

An enzyme alters the activation energy of a reaction.

Enzymes lower the activation energy needed to initiate a chemical reaction.

Active sites of enzymes conform to fit the shape of substrates.

Substrates bind to the active site of an enzyme. Enzymes adjust their shape to the substrate so there is a better fit (see figure 6.8).

Enzymes occur in many forms.

Enzymes can be free in the cytosol or exist as components bound to membranes and organelles. Enzymes involved in a biochemical pathway can form multienzyme complexes. While most enzymes are proteins, some are actually RNA molecules, called ribozymes.

Environmental and other factors affect enzyme function.

An enzyme's functionality depends on its ability to maintain its three-dimensional shape, which can be affected by temperature and pH. The activity of enzymes can be affected by inhibitors. Competitive inhibitors compete for the enzyme's active site, which leads to decreased enzyme activity (see figure 6.13). Enzyme activity can be controlled by effectors. Allosteric enzymes have a second site, located away from the active site, that binds effectors to activate or inhibit the enzyme. Noncompetitive inhibitors and activators bind to the allosteric site, changing the structure of the enzyme to inhibit or activate it. Cofactors are nonorganic metals necessary for enzyme function. Coenzymes are nonprotein organic molecules, such as certain vitamins, needed for enzyme function. Often coenzymes serve as electron acceptors.

6.5 Metabolism: The Chemical Description of Cell Function

Metabolism is the sum of all biochemical reactions in a cell. Anabolic reactions require energy to build up molecules, and catabolic reactions break down molecules and release energy.

Biochemical pathways organize chemical reactions in cells.

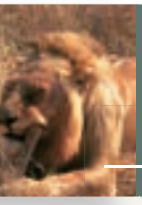
Chemical reactions in biochemical pathways use the product of one reaction as the substrate for the next.

Biochemical pathways may have evolved in stepwise fashion.

In the primordial "soup" of the early oceans, many reactions were probably single-step reactions combining two molecules. As one of the substrate molecules was depleted, organisms having an enzyme that could synthesize the substrate would have a selective advantage. In this manner, biochemical pathways are thought to have evolved "backward" with new reactions producing limiting substrates for existing reactions.

Feedback inhibition regulates some biochemical pathways.

Biosynthetic pathways are often regulated by the end product of the pathway. Feedback inhibition occurs when the end-product of a reaction combines with an enzyme's allosteric site to shut down the enzyme's activity (see figure 6.15).



Review Questions

UNDERSTAND

1. A covalent bond between two atoms represents what kind of energy?
   a. Kinetic energy
   b. Potential energy
   c. Mechanical energy
   d. Solar energy
2. During a redox reaction the molecule that gains an electron has been
   a. reduced and now has a higher energy level.
   b. oxidized and now has a lower energy level.
   c. reduced and now has a lower energy level.
   d. oxidized and now has a higher energy level.
3. An endergonic reaction has the following properties
   a. $+\Delta G$ and the reaction is spontaneous.
   b. $+\Delta G$ and the reaction is not spontaneous.
   c. $-\Delta G$ and the reaction is spontaneous.
   d. $-\Delta G$ and the reaction is not spontaneous.
4. A spontaneous reaction is one in which
   a. the reactants have a higher free energy than the products.
   b. the products have a higher free energy than the reactants.
   c. an input of energy is required.
   d. entropy is decreased.

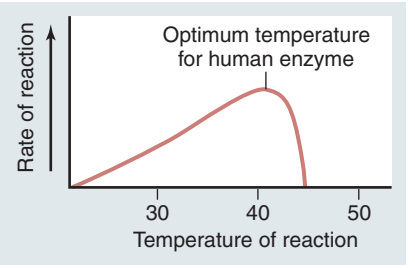
5. What is *activation energy*?
   a. The thermal energy associated with random movements of molecules
   b. The energy released through breaking chemical bonds
   c. The difference in free energy between reactants and products
   d. The energy required to initiate a chemical reaction
6. Which of the following is NOT a property of a catalyst?
   a. A catalyst reduces the activation energy of a reaction
   b. A catalyst lowers the free energy of the reactants
   c. A catalyst does not change as a result of the reaction
   d. A catalyst works in both the forward and reverse directions of a reaction
7. Where is the energy stored in a molecule of ATP?
   a. Within the bonds between nitrogen and carbon
   b. In the carbon-to-carbon bonds found in the ribose
   c. In the phosphorus-to-oxygen double bond
   d. In the bonds connecting the two terminal phosphate groups

APPLY

1. Cells use ATP to drive endergonic reactions because
   a. ATP is the universal catalyst.
   b. energy released by ATP hydrolysis makes ΔG for coupled reactions more negative.
   c. energy released by ATP hydrolysis makes ΔG for coupled reactions more positive.
   d. the conversion of ATP to ADP is also endergonic.
2. Which of the following statements is NOT true about enzymes?
   a. Enzymes use the three-dimensional shape of their active site to bind reactants.
   b. Enzymes lower the activation energy for a reaction.
   c. Enzymes make ΔG for a reaction more negative.
   d. Enzymes can catalyze the forward and reverse directions of a reaction.
3. What is the function of the *active site* of an enzyme?
   a. Bind the substrate, forming an enzyme–substrate complex
   b. Side groups within the active site interact with the substrate
   c. Bind to regulatory molecules, thereby altering the enzymes conformation
   d. Both a and b
4. The discovery of ribozymes meant that
   a. only proteins have catalytic function.
   b. only nucleic acids have catalytic function.
   c. RNAs can act as enzymes.
   d. RNA has the same function as protein.
5. Enzymes have similar responses to both changes in temperature and pH. The affect of both is on the
   a. rate of movement of the substrate molecules.
   b. strength of the chemical bonds within the substrate.
   c. three-dimensional shape of the enzyme.
   d. rate of movement of the enzyme.
6. In feedback inhibition, the
   a. first enzyme in a pathway is inhibited by its own product.
   b. last enzyme in a pathway is inhibited by its own product.
   c. first enzyme in a pathway is inhibited by the end-product of the pathway.
   d. last enzyme in a pathway is inhibited by the end-product of the pathway.

SYNTHESIZE

1. Examine the graph showing the rate of reaction versus temperature for an enzyme–catalyzed reaction in a human.
   a. Describe what is happening to the enzyme at around 40°C.
   b. Explain why the line touches the *x*-axis at approximately 20°C and 45°C.
   c. Average body temperature for humans is 37°C. Suggest a reason why the temperature optimum of this enzyme is greater than 37°C.



2. Phosphofructokinase functions to add a phosphate group to a molecule of fructose-6-phosphate. This enzyme functions early in glycolysis, an energy-yielding biochemical pathway discussed in chapter 7. The enzyme has an active site that binds fructose and ATP. An allosteric inhibitory site also binds ATP when cellular levels of ATP are very high.
   a. Predict the rate of the reaction if the levels of cellular ATP are low.
   b. Predict the rate of the reaction if levels of cellular ATP are very high.
   c. Describe what is happening to the enzyme when levels of ATP are very high.

ONLINE RESOURCE

www.ravenbiology.com

Understand, Apply, and Synthesize—enhance your study with animations that bring concepts to life and practice tests to assess your understanding. Your instructor may also recommend the interactive eBook, individualized learning tools, and more.