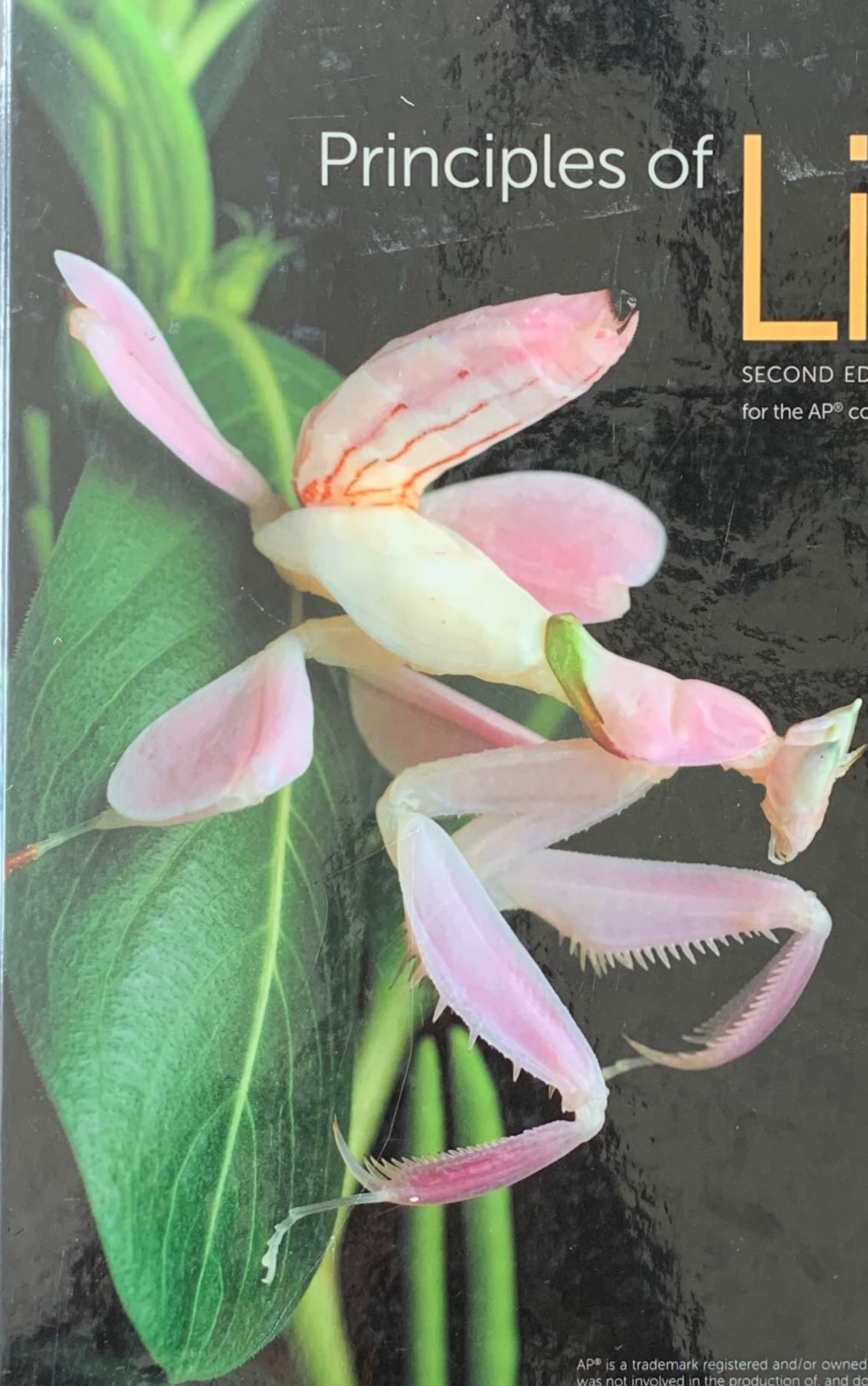
Principles of Life

SECOND EDITION

for the AP® course



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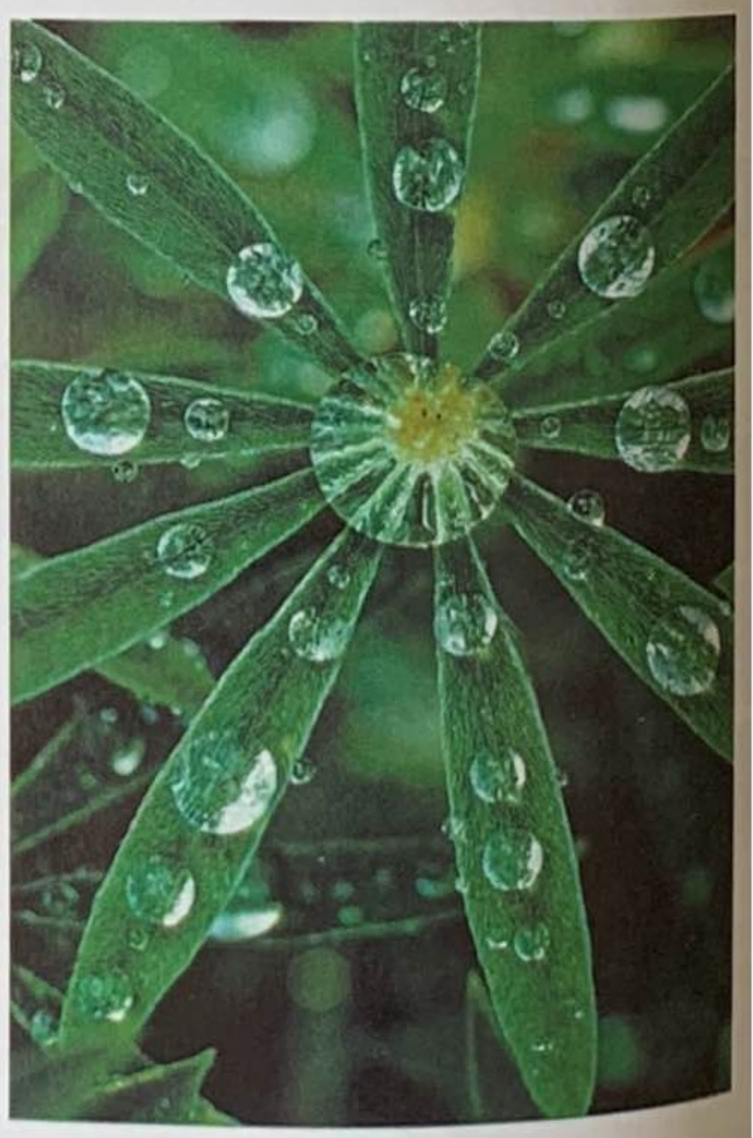

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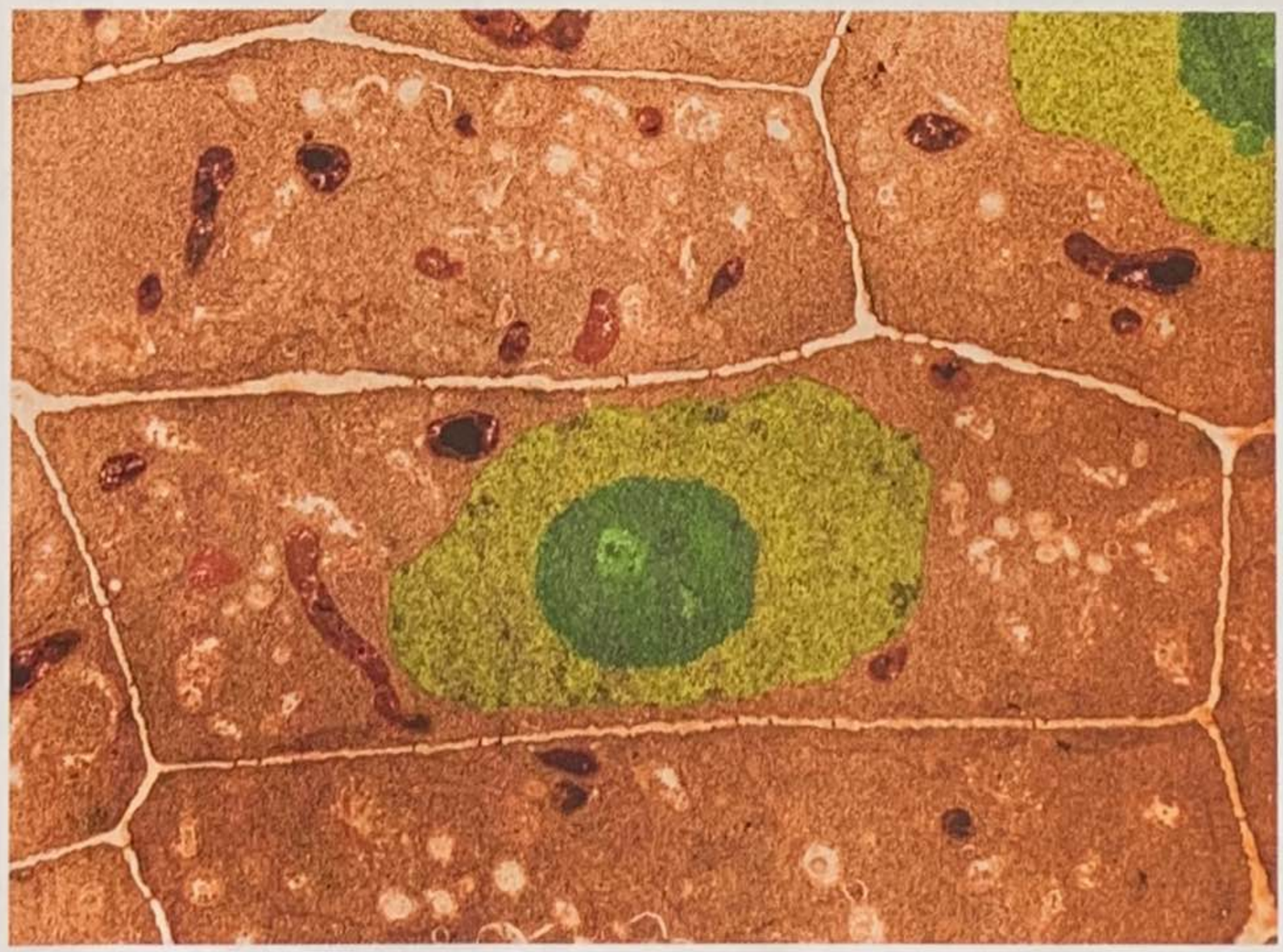

1

Principles of Life

KEY CONCEPTS

1.1 Living Organisms Share Common Aspects of Structure, Function, and Energy Flow

1.2 Life Depends on Organization and Energy

1.3 Genetic Systems Control the Flow, Exchange, Storage, and Use of Information

1.4 Evolution Explains the Diversity as Well as the Unity of Life

1.5 Science Is Based on Quantitative Observations, Experiments, and Reasoning

What principles of life are illustrated in this scene?

When you take a walk through the woods and fields or a park near your home, what do you see? Like most people, you probably notice the trees, colorful flowers, and some animals. But do you spend more than a little time thinking about how these living things survive, reproduce, interact with one another, or affect their environment? With the introduction to biology in this book, we would like to inspire you to ask questions about what life is, how living systems work, and how the living world came to be as we observe it today.

Biologists have amassed a huge amount of information about the living world, and some introductory biology classes focus on memorizing these details. In this book we take a different approach, focusing on the major principles of life that underlie everything in biology.

What do we mean by "principles of life"? Look at the photograph. Why is the view so overwhelmingly green? A fundamental principle of life, namely that all living organisms require energy to grow, move, reproduce, and maintain their bodies, can explain the color. Ultimately, most of that energy comes from the sun. The leaves of plants contain chlorophyll, a green pigment that captures energy from the sun and uses it to transform water and carbon dioxide into sugar and oxygen (in the process called photosynthesis). That sugar stores some of the energy from the sun in its chemical bonds. The plant, or other organisms that eat the plant, can then obtain energy by breaking down the sugar. The frog in the photo used energy to climb up the tree. That energy came from molecules in the bodies of insects eaten by the frog. The insects, in turn, had built up their bodies by ingesting tissues of plant leaves, which grew by using some of the sun's energy captured through photosynthesis. The frog, like the plants, is ultimately solar-powered, as is the human observer who took this photograph.

The photograph also illustrates other principles of biology. One is that living organisms often survive and thrive by interacting with one another in complex ways. You probably noticed the frog and the trees. But did you notice the patches of growth on the trunk of the tree? Most of those are lichens, a complex interaction between a fungus and a photosynthetic organism (in this case, a kind of alga). In lichens, the fungus and the alga depend on each other for survival. Many other organisms in this scene are too small to be seen, but they are critical components for keeping this living system functioning over time.

After reading this book, you should understand the main principles of life. You'll be able to describe how organisms capture and transform energy; pass genetic information to their offspring in reproduction; grow, develop, and behave; and interact with other organisms and with their physical environment. You will also have learned how this system of life on Earth evolved, and how it continues to change. May a walk in the park never be the same for you again!

CONCEPT 1.1 Living Organisms Share Common Aspects of Structure, Function, and Energy Flow

Biology is the scientific study of life, which encompasses all living things, or **organisms**. The living things we know about are all descended from a single-celled ancestor that lived on Earth almost 4 billion years ago. We can imagine that something with some similarities to life as we know it might have originated differently, perhaps on other planets. But the evidence suggests that all of life on Earth today has a single origin—a single common ancestor—and we consider all the organisms that descended from that common ancestor to be a part of life.

Life as we know it had a single origin

The overwhelming evidence for the common ancestry of life lies in the many characteristics that are shared among living organisms. Typically, living organisms

- are composed of a common set of chemical parts, such as nucleic acids (one example is DNA, which is the important molecule that carries our genetic information) and amino acids (the chemical building blocks that make up proteins), and similar structures, such as cells enclosed within membranes
- depend on intricate interactions among structurally complex parts to maintain the living state
- contain genetic information that uses a nearly universal code to specify how proteins are assembled
- convert molecules obtained from their environment into new biological molecules
- extract energy from the environment and use it to carry out life functions
- replicate their genetic information in the same manner when reproducing themselves
- share structural similarities among a fundamental set of genes
- evolve through gradual changes in their genetic information

Taken together, these shared characteristics logically lead to the conclusion that all life has a common ancestry, and that the diverse organisms that exist today originated from one life form. If life had multiple origins, there would be little reason to expect a nearly universal genetic code, or the similarities among many genes, or a common set of amino acids. If we were to discover something similar to life, such as a self-replicating system that originated independently on another planet, we would expect it to be fundamentally different in these aspects. It might be similar in some ways to life on Earth, such as using genetic information to reproduce. But we would not expect the details of its genetic code, for example, to be like ours.

The simple list of shared characteristics above, however, does not describe the incredible complexity and diversity of life. Some forms of life may not even display all of these characteristics all of the time. For example, the seed of a desert plant may exist for many years in a dormant state in which it doesn't extract energy from the environment, convert molecules, or reproduce. Yet the seed is alive.

And then there are viruses, which are not composed of cells and cannot carry out physiological functions on their own. Instead they use the cells they invade to perform these functions for them. Yet viruses contain genetic information, and they mutate and evolve. So even though viruses are not independent cellular organisms, their existence depends on cells, and there is strong evidence that viruses evolved from cellular life forms. For these reasons, most biologists consider viruses to be a part of life. But as viruses illustrate, the boundaries between "living" and "nonliving" are not always clear, and all biologists do not agree exactly on where we should draw the lines.

Major steps in the history of life are compatible with known physical and chemical processes

Geologists estimate that Earth formed between 4.6 and 4.5 billion years ago. At first the planet was not a very hospitable place. It was some 600 million years or more before the earliest life evolved. If we picture the history of Earth as a 30-day month, with each day representing about 150 million years, life first appeared somewhere toward the end of the first week (**FIGURE 1.1**).

How might life have arisen from nonliving matter? In thinking about this question, we must take into account that the young Earth's atmosphere, oceans, and climate all were very different than they are today. Biologists have conducted many experiments that simulate the conditions on early Earth. These experiments have confirmed that the formation of complex organic molecules under such conditions is possible, even probable.

The critical step for the evolution of life, however, was the appearance of **nucleic acids**—molecules that could reproduce themselves and also contain the information for the synthesis, or manufacture, of large molecules with complex but stable shapes. These large, complex molecules were proteins. Their shapes varied enough to enable them to participate in increasing numbers and kinds of chemical reactions with other molecules.

CELLULAR STRUCTURE EVOLVED IN THE COMMON ANCESTOR OF LIFE In the next big step in the origin of life, a membrane surrounded and enclosed complex proteins and other biological molecules, forming a tiny **cell**. This membrane kept the enclosed components separate from the surrounding external environment. Molecules called fatty acids played a critical role because these molecules form membrane-like films instead of dissolving in water. When agitated, these films can form hollow spheres, which could have enveloped assemblages of biological molecules. The creation of a cell interior, separate from the external environment, allowed the reactants and products of chemical reactions to be concentrated, opening up the possibility that those reactions could be integrated and controlled. This natural process of membrane formation likely resulted in the first cells with the ability to reproduce—the evolution of the first cellular organisms.

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For more than 2 billion years after cells originated, every organism consisted of only one cell. These first organisms were **prokaryotes**, which are made up of single cells containing genetic material and other biochemical structures enclosed in a membrane (**FIGURE 1.2**). Vast numbers of their descendants, such as bacteria, exist in similar form today. Early prokaryotes were confined to the oceans, which had an abundance of complex molecules they could use as raw materials and sources of energy. The oceans also shielded them from the damaging effects of ultraviolet (UV) light, which was intense at that time because there was little or no oxygen (O_2) in the atmosphere, and for that reason, no protective ozone (O_3) layer in the upper atmosphere.

PHOTOSYNTHESIS ALLOWED LIVING ORGANISMS TO CAPTURE THE SUN'S ENERGY To fuel the chemical reactions inside them, the earliest prokaryotes took in molecules directly from their environment and broke down these small molecules to release and use the energy contained in their chemical bonds. Many modern prokaryotes still function this way, and very successfully.

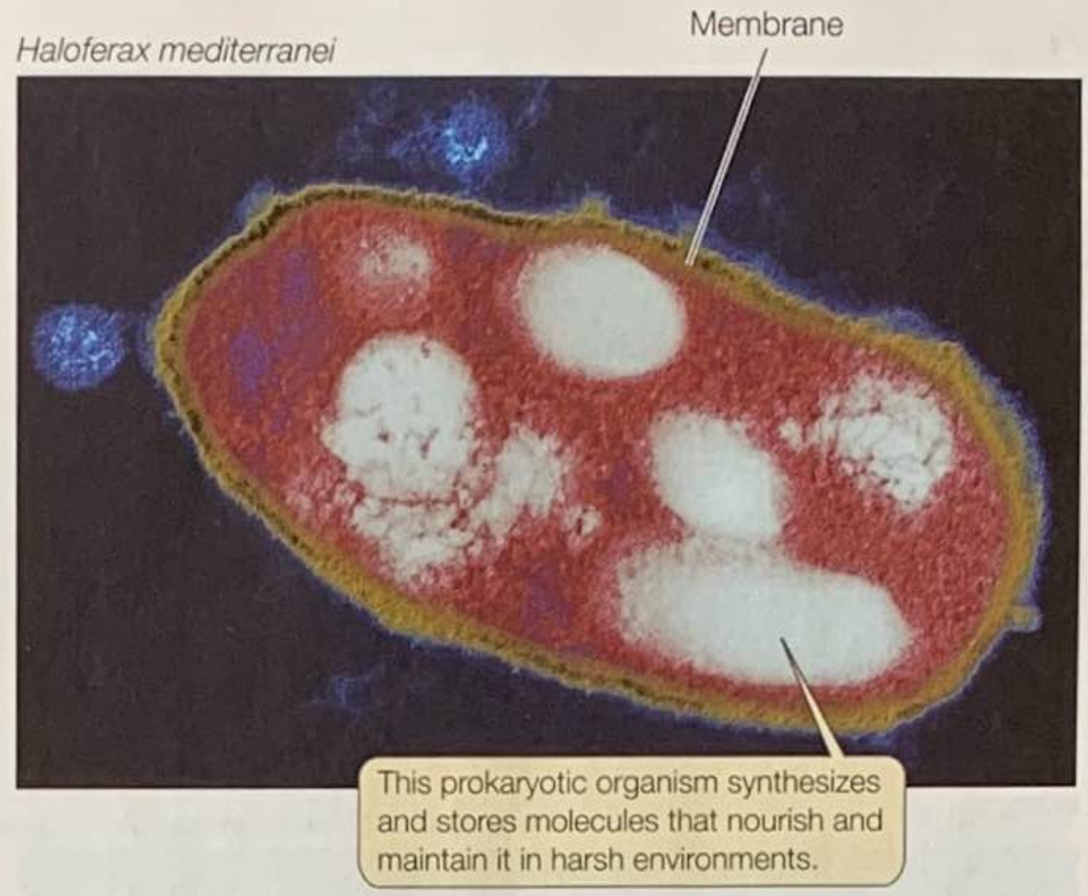


FIGURE 1.2 The Basic Unit of Life Is the Cell The concentration of reactions within the enclosing membrane of a cell allowed the evolution of integrated organisms. Today all organisms, even the largest and most complex, are made up of cells. Single-celled organisms such as this one, however, remain the most abundant living organisms (in absolute numbers) on Earth.

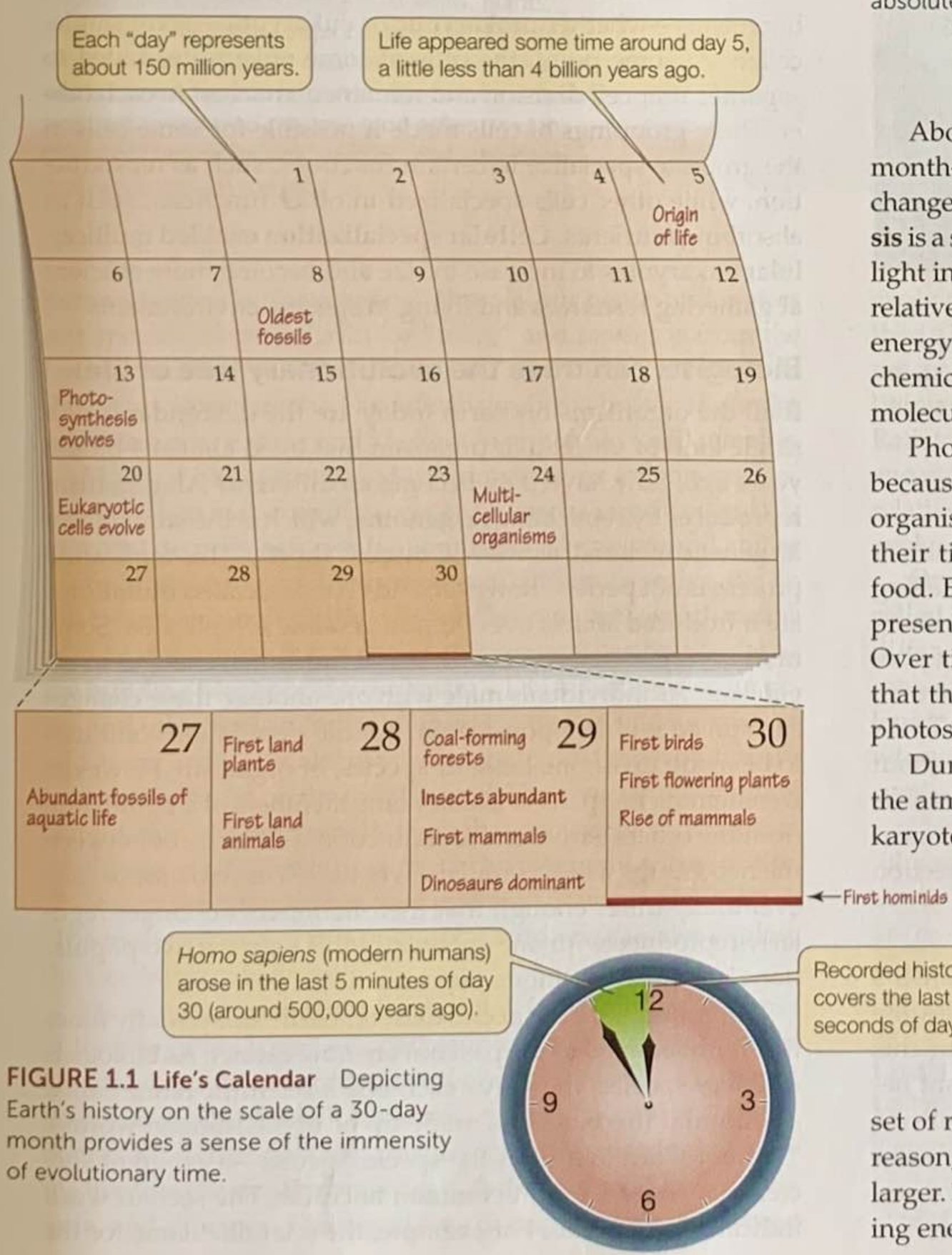


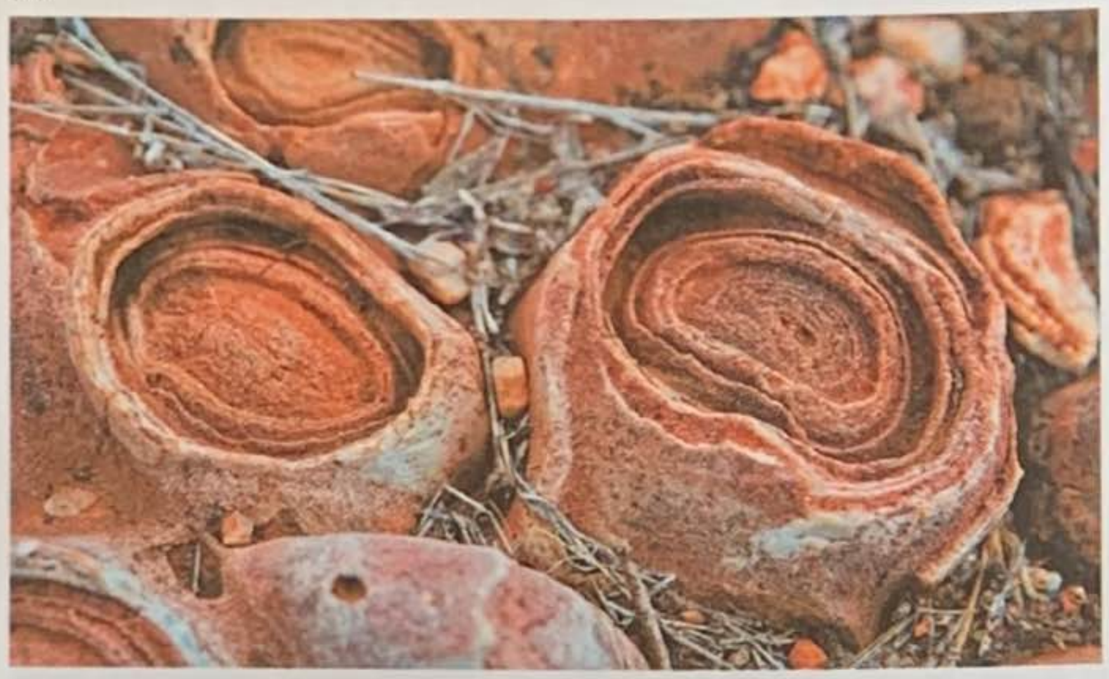
FIGURE 1.1 Life's Calendar Depicting Earth's history on the scale of a 30-day month provides a sense of the immensity of evolutionary time.

About 2.7 billion years ago, or on day 13 of our imaginary month-long calendar of life, the emergence of photosynthesis changed the nature of life on Earth (see Figure 1.1). **Photosynthesis** is a set of chemical reactions that transforms the energy of sunlight into chemical-bond energy of the sugar glucose and other relatively small biological molecules. In turn, the chemical-bond energy of these small molecules can be tapped to power other chemical reactions inside cells, including the synthesis of large molecules, such as proteins, that are the building blocks of cells.

Photosynthesis is the basis of much of life on Earth today because its energy-capturing processes provide food for other organisms. Photosynthetic organisms use solar energy to build their tissues, and then other organisms use those tissues as food. Early photosynthetic cells were probably similar to the present-day prokaryotes called cyanobacteria (**FIGURE 1.3**). Over time, photosynthetic prokaryotes became so abundant that they produced vast quantities of O_2 as a by-product of photosynthesis.

During the early eons of life on Earth, there was no O_2 in the atmosphere. In fact, O_2 was poisonous to many of the prokaryotes that lived at that time. But those organisms that tolerated O_2 were able to proliferate as O_2 slowly began to accumulate in the atmosphere. The presence of O_2 opened up vast new avenues of evolution. **Aerobic metabolism**, a set of chemical reactions that releases energy from life's molecules by using O_2, proved to be more efficient than **anaerobic metabolism**, a set of reactions that extracts energy without using O_2. For this reason, O_2 allowed organisms to live more intensely and grow larger. The majority of living organisms today use O_2 in extracting energy from molecules.

(A)



(B)

FIGURE 1.3 Photosynthetic Organisms Changed Earth's Atmosphere Cyanobacteria were the first photosynthetic organisms on Earth. (A) Colonies of cyanobacteria called stromatolites are known from the ancient fossil record. (B) Living stromatolites are still found in suitable environments on Earth today.

Oxygen in the atmosphere also made it possible for life to move onto land. For most of life's history, UV radiation falling on Earth's surface was so intense that it destroyed any living cell that was not well shielded by water. But as a result of photosynthesis, O_2 accumulated in the atmosphere for more than 2 billion years and gradually resulted in a layer of ozone in the upper atmosphere. By about 500 million years ago, or about day 28 on our imaginary calendar of life, the ozone layer was sufficiently dense and absorbed enough of the sun's UV radiation to make it possible for organisms to leave the protection of the water and live on land (see Figure 1.1).

EUKARYOTIC CELLS AROSE THROUGH ENDOSYMBIOSIS Another important, earlier step in the history of life was the evolution of cells with membrane-enclosed compartments called **organelles**. Organelles were—and are—important because specialized cellular functions could be performed inside them, separated from the rest of the cell. The first organelles probably appeared about 2.5 billion years after life first appeared on Earth, or about day 20 on Figure 1.1.

One of these organelles, the **nucleus**, came to contain the cell's genetic information. The nucleus (Latin *nux*, "nut" or "core") gives these cells their name: **eukaryotes** (Greek *eu*, "true"; *karyon*, "kernel" or "core"). The eukaryotic cell is distinct from the cells of prokaryotes (*pro*, "before"), which lack nuclei and other internal compartments.

Some organelles are hypothesized to have originated by **endosymbiosis**, which means "living inside another" and may have occurred when larger cells ingested smaller ones. The **mitochondria** that release energy for use by a eukaryotic cell probably evolved from engulfed prokaryotic organisms. And **chloroplasts**—the organelles specialized to conduct photosynthesis in eukaryotic photosynthetic organisms—could have originated when larger eukaryotes ingested photosynthetic prokaryotes. If the larger cell failed to break down this intended food object, a partnership could have evolved in which the ingested prokaryote provided sugars from photosynthesis and the host cell provided a good environment for its smaller partner.

MULTICELLULARITY ALLOWED SPECIALIZATION OF TISSUES AND FUNCTIONS For the first few billion years of life, all organisms—whether prokaryotic or eukaryotic—were single-celled. At some point, the cells of some eukaryotes failed to separate after cell division and remained attached to each other. These groupings of cells made it possible for some cells in the group to specialize in certain functions, such as reproduction, while other cells specialized in other functions, such as absorbing nutrients. **Cellular specialization** enabled multicellular eukaryotes to increase in size and become more efficient at gathering resources and living in specific environments.

Biologists can trace the evolutionary tree of life

If all the organisms on Earth today are the descendants of a single kind of unicellular organism that lived almost 4 billion years ago, how have they become so different? An organism reproduces by replicating its **genome**, which is the sum total of its genetic material, as we will discuss shortly. This replication process is not perfect, however, and changes, called **mutations**, are introduced almost every time a genome is replicated. Some mutations give rise to structural and functional changes in organisms. As individuals mate with one another, these changes can spread within a population, but the population continues to be made up of one kind, or species, of organism. However, if something happens to isolate some members of a population from the others, structural and functional differences between the two groups will accumulate over time. The two groups may eventually differ enough that their members no longer regularly reproduce with one another. In this way the two populations become two different species.

Tens of millions of species exist on Earth today. Many times that number lived in the past but are now extinct. As biologists discover species, they give each one a scientific name called a **binomial** (because it is made up of two Latinized words). The first word identifies the species' genus—a group of species that share a recent common ancestor. The second word indicates the species. For example, the scientific name for the

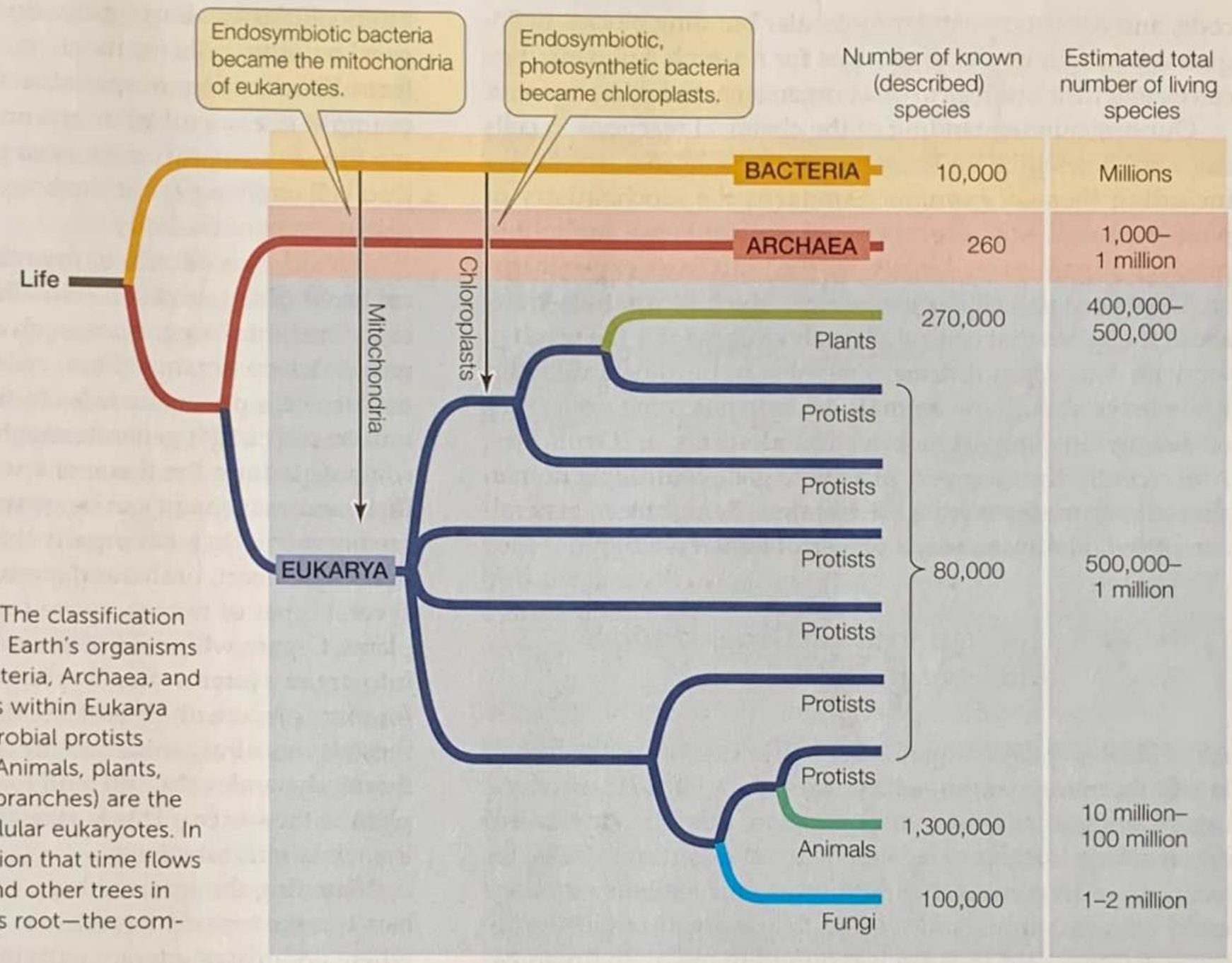


FIGURE 1.4 The Tree of Life The classification system used in this book divides Earth's organisms into three primary domains: Bacteria, Archaea, and Eukarya. The dark blue branches within Eukarya represent various groups of microbial protists (mostly unicellular eukaryotes). Animals, plants, and fungi (green and turquoise branches) are the most familiar groups of multicellular eukaryotes. In this book we adopt the convention that time flows from left to right, so this tree (and other trees in this book) lies on its side, with its root—the common ancestor—at the left.

human species is *Homo sapiens*: *Homo* is our genus and *sapiens* our species. *Homo* is Latin for "man," and *sapiens* is from the Latin word for "wise" or "rational." Our closest relatives in the genus *Homo* are the Neanderthals (*Homo neanderthalensis*), which are now extinct and are known only from fossil remains.

Much of biology is based on comparisons among species. Our ability to make relevant comparisons has improved greatly in recent decades as a result of our relatively newfound ability to study and compare the genomes of different species. We do this by sequencing a genome (in whole or in part), which means we can determine the order of the nucleotides that serve as the building blocks of the organism's DNA. Genome sequencing and other molecular techniques have allowed biologists to add a vast array of molecular evidence to existing evolutionary knowledge based on the fossil record. The result is the ongoing compilation of **phylogenetic trees** that document and diagram evolutionary relationships as part of an overarching **tree of life**. The broadest categories of this tree are shown in **FIGURE 1.4**. (The tree is expanded in Appendix A, and you can also explore the tree interactively online.)

Many details remain to be clarified, but the broad outlines of the tree of life have been determined. Its branching patterns are based on a rich array of evidence from fossils, structures, chemical processes, behavior, and molecular analyses of genomes. Molecular data in particular have been used to separate the tree into three major branches called **domains**: Archaea, Bacteria, and Eukarya. The organisms of each domain have been evolving separately from those in the other domains for more than a billion years. Note that all organisms that are alive today descended from common ancestors in the past. In other words, living species did not evolve from other species living today. Rather, all living organisms evolved from now-extinct common ancestors. For example, humans did not evolve from our close relatives, the chimpanzees, but humans and chimpanzees both evolved from a common (now extinct) ancestral species.

Organisms in the domains **Archaea** and **Bacteria** are single-celled prokaryotes. However, members of these two groups differ so fundamentally that they are thought to have separated into distinct evolutionary lineages very early. Species belonging to the third domain—**Eukarya**—have eukaryotic cells whose mitochondria and chloroplasts originated from endosymbioses with bacteria, as we have described.

Plants, fungi, and animals are examples of familiar multicellular eukaryotes. We know that multicellularity arose independently in each of these three multicellular groups because they are each most closely related to different groups of unicellular eukaryotes (commonly called protists), as you can see from the branching pattern of Figure 1.4.

Life's unity allows discoveries in biology to be generalized

Knowledge gained from investigations of one kind of organism can, with care, be generalized to other organisms because all life is related by descent from a common ancestor, shares a genetic

code, and consists of similar molecular building blocks. Biologists use certain **model organisms** for research, knowing they can extend their findings to other organisms, including humans.

Our basic understanding of the chemical reactions in cells came from research on bacteria but is applicable to all cells, including those of humans. Similarly, the biochemistry of photosynthesis—the process by which plants use sunlight to produce sugars—was largely worked out from experiments on *Chlorella*, a unicellular green alga. Much of what we know about the genes that control plant development is the result of work on *Arabidopsis thaliana*, a member of the mustard family. Knowledge about how animals develop has come from work on sea urchins, frogs, chickens, roundworms, and fruit flies. And recently, the discovery of a major gene controlling human skin color came from work on zebrafish. Being able to generalize from model systems is a powerful tool in biology.

CONCEPT 1.2 Life Depends on Organization and Energy

All of life depends on organization. Physics gives us the second law of thermodynamics, which states that, left to themselves, organized entities tend to become more random. Any loss of organization threatens the well-being of organisms. Cells, for example, must combat the thermodynamic tendency for their molecules, structures, and systems to lose organization—to become disorganized. Energy is required to maintain organization. For this reason, cells require energy throughout their lives.

Organization is apparent in a hierarchy of levels from molecules to ecosystems

Cells synthesize, or manufacture, proteins and other complex molecules by assembling atoms into new, highly organized configurations. Such complex molecules give cells their structure and enable them to function. For example, a fatty acid molecule that the cell synthesizes may become part of a membrane that structures the inside of the cell by dividing it into compartments. Or a protein made by a cell may enable a specific chemical reaction to take place in the cell by helping start or speed up the reaction—that is, by acting as a catalyst for the reaction.

Organization is also essential for many cells to function together in a multicellular organism. As we have seen, multicellularity allows individual cells to specialize and depend on other cells for functions they themselves do not perform. But the different specialized cells also work together. For example, division of labor in a multicellular organism usually requires a circulatory system so that the functions of specialized cells in one part of the body are of use to cells in other, distant parts of the body.

Overall, a multicellular organism exhibits many hierarchical levels of organization (**FIGURE 1.5A**). Small molecules are organized into larger ones, such as DNA and proteins. Large molecules are organized into cells, and assemblages of differentiated cells are organized into **tissues**. For example, a single muscle cell cannot generate much force, but when many cells combine to form the tissue of a working muscle, considerable force and movement can be generated. Different tissue types are organized to form **organs** that accomplish specific functions. The heart, brain, and stomach are each constructed of several types of tissues, as are the roots, stems, and leaves of plants. Organs whose functions are interrelated can be grouped into **organ systems**; the esophagus, stomach, and intestines, for example, are all part of the digestive system. Because all these levels of organization are subject to the second law of thermodynamics, they all tend to degrade unless energy is applied to the system. This is why an organism must use energy to maintain its functions.

Matching the internal hierarchy of an individual organism is an external hierarchy in the larger biological world where organisms interact with their physical environment—an **ecological system**, often shortened to **ecosystem** (**FIGURE 1.5B**). Individual organisms interacting with their immediate

FIGURE 1.5 Life Consists of Organized Systems at a Hierarchy of Scales (A) The hierarchy of systems within a multicellular organism. DNA—a molecule—encodes the information for cells—a higher level of organization. Cells, in turn, are the components of still higher levels of organization: tissues, organs, and the organism itself. (B) Organisms interacting with their external environment form ecological systems on a hierarchy of scales. Individual organisms form the smallest ecological system. Individuals of a species form populations, which interact with other populations to form communities. Multiple communities in turn interact within landscapes at progressively larger scales until they include all the landscapes and organisms of Earth: the entire biosphere.

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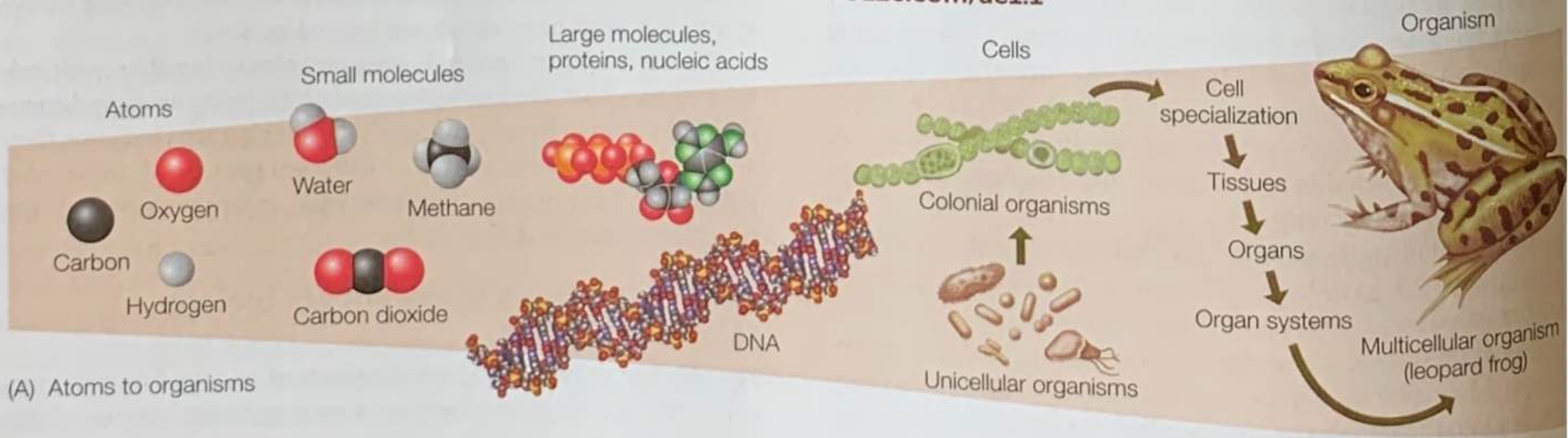

environment form the smallest ecological system. Groups of individuals of any one species live together and interact in **populations**, and populations of different species that live and interact in a single area form ecological **communities**. Multiple communities interact within **landscapes**. The landscape of the entire Earth and all its life is known as the **biosphere**.

But there are some important differences between biological systems at the organismal level and these larger scales. All the hierarchical levels of organization within an individual organism are encoded by its single genome, so that these levels generally interact harmoniously. By contrast, the external hierarchy of populations, communities, and landscapes involves interactions among multiple species with multiple genomes, so that interactions are not always harmonious. For example, individuals often prevent others of their own species from exploiting a necessary resource such as food, or they exploit members of their own or different species as food.

Each level of biological organization consists of systems

We have already discussed organ systems and ecological systems. More generally, a **system** is a set of interacting parts in which neither the parts nor the whole can be understood without taking into account the interactions. A simple biological system might consist of a few **components** (e.g., proteins, pools of nutrients, or organisms) and the **processes** by which the components interact (e.g., protein synthesis, nutrient metabolism, or grazing) (**FIGURE 1.6**).

Consider, for example, the system within a cell that synthesizes and controls the quantity of a particular protein, which we'll call Protein T (**FIGURE 1.7A**). The components of the system are the amino acids from which Protein T is made, Protein T, and the breakdown products of Protein T. The processes are the biochemical pathways that synthesize and break down Protein T. To understand how the cell controls the amount of Protein T, we must understand how all the other components and processes in this system function.

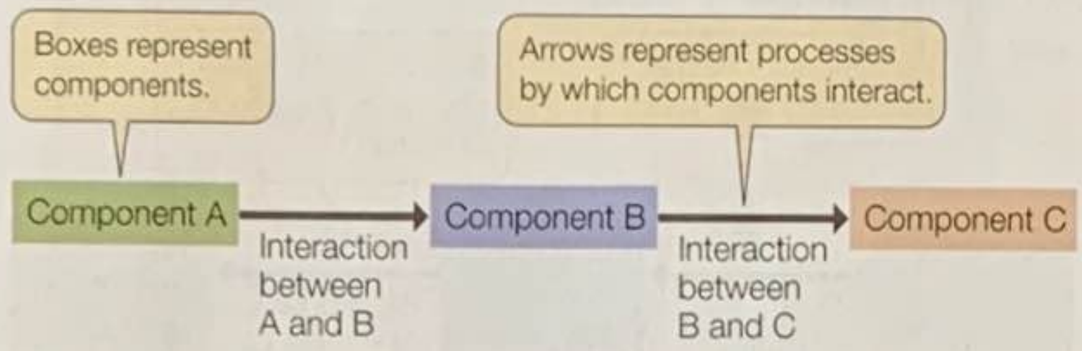

FIGURE 1.6 A Generalized System Systems in cells, whole organisms, and ecosystems can be represented with boxes and arrows.

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System Simulation
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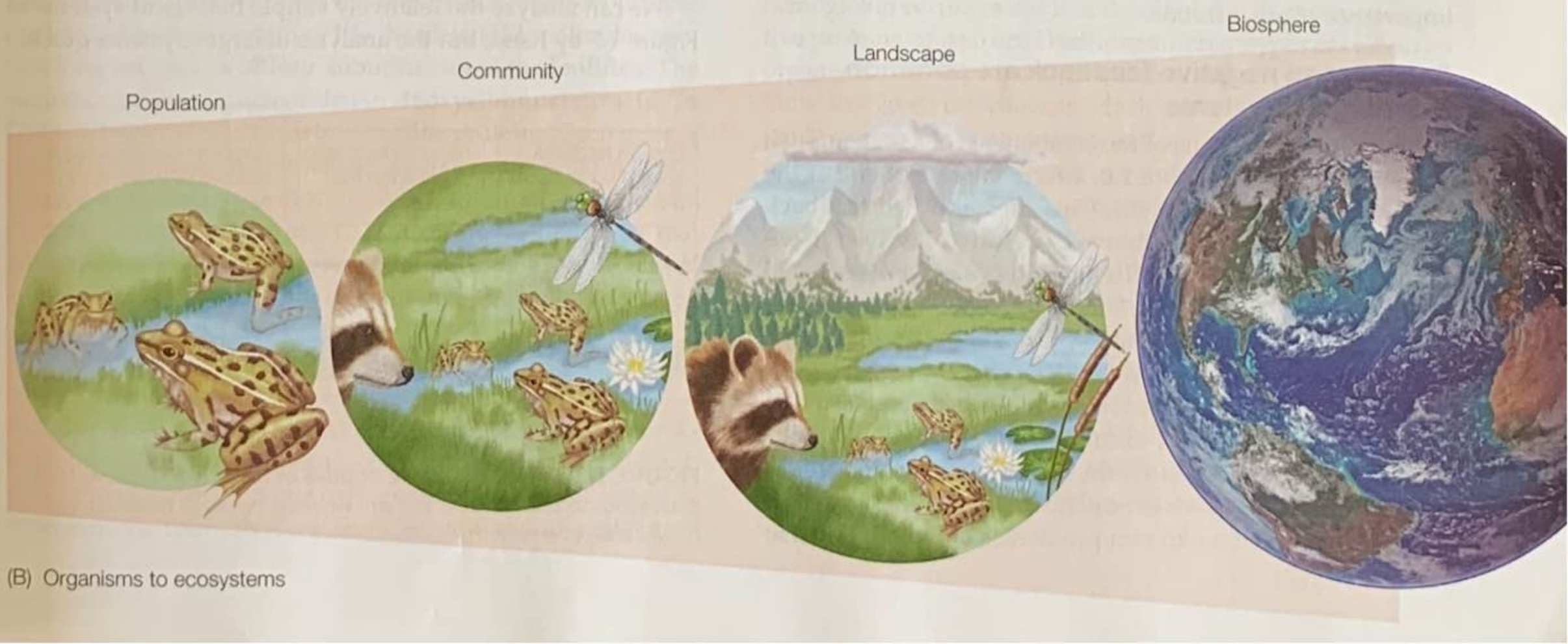
Systems are found at every level of biological organization. For example, our bodies have a physiological system that controls the amount of sodium (Na^+) in our body fluids (**FIGURE 1.7B**). Grass, voles, and predators (foxes and owls) are components of a community-level system (**FIGURE 1.7C**).

Biological systems are highly dynamic even as they maintain their essential organization

Given the central importance of organization, you might think that biological systems are inflexible and static. Actually, they are often incredibly dynamic—characterized by rapid flows of matter and energy. On average, for example, a cell in your body breaks down and rebuilds 2–3 percent of its protein molecules per day. Each day it also makes and uses more than 100,000 trillion (10^{14}) molecules of adenosine triphosphate (ATP), the molecule responsible for shuttling energy from sources to uses. Collectively, all the cells in your body liberate more than 90 grams of hydrogen every day from the foods they break down to obtain energy. Your cells also combine that hydrogen with oxygen (O_2) to make almost a liter of water every day.

This dynamic aspect of biological systems means that they constantly exchange energy and matter with their surroundings. For example, even after a single-celled or multicellular



(B) Organisms to ecosystems

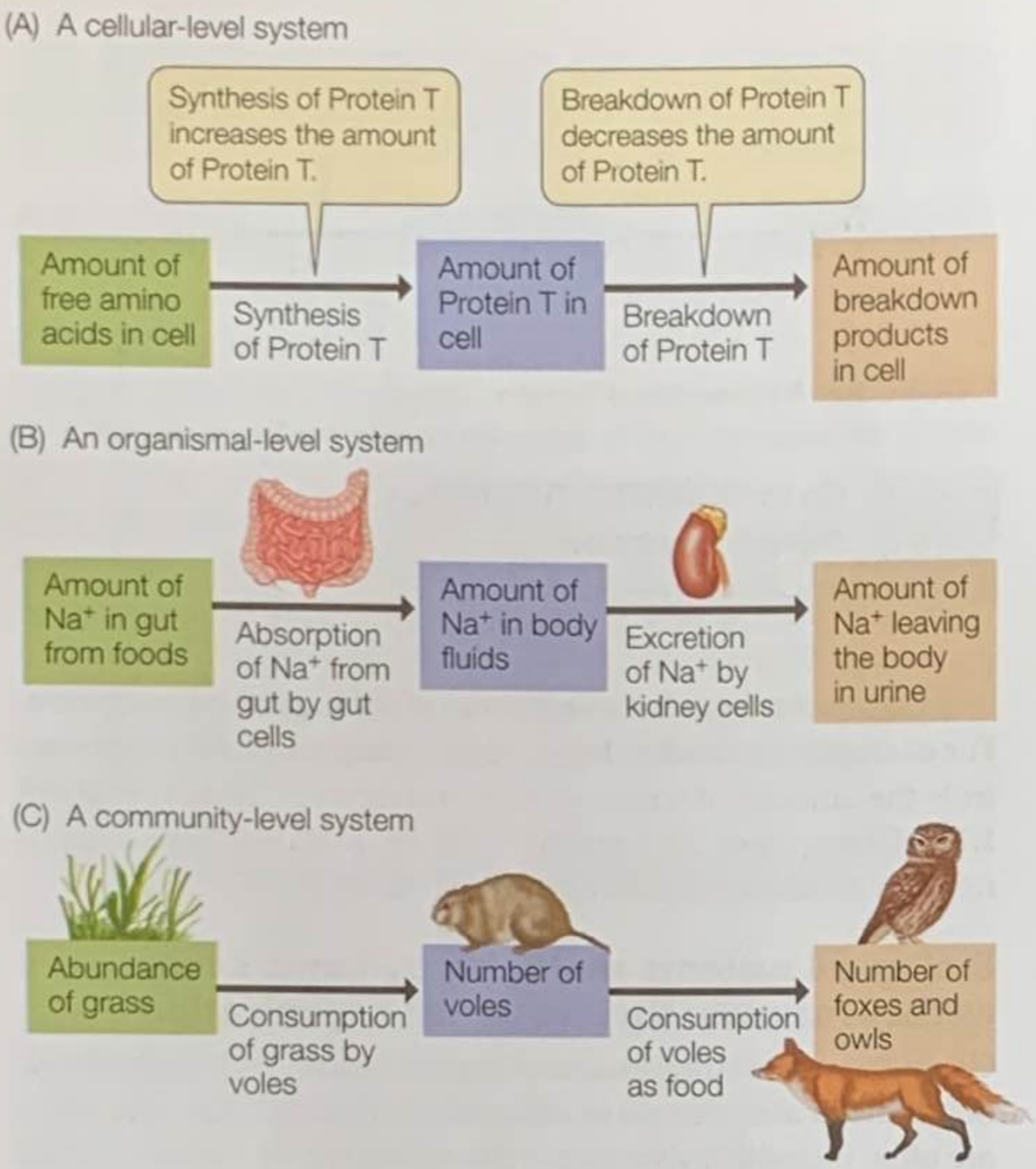


FIGURE 1.7 Organized Systems Exist at Many Levels (A) This cellular-level system synthesizes and breaks down a cell protein called Protein T. (B) This organismal-level system determines the amount (and thus the concentration) of sodium (Na^+) in the blood plasma and other extracellular body fluids of a human. (C) This community-level system helps determine the number of meadow voles (*Microtus pennsylvanicus*) in a field in the spring.

organism has reached maturity, most of its molecules are steadily replaced. In this ceaseless, dynamic process, atoms are lost from the cells in the organism to the surrounding soil, air, or water, and they are replaced with atoms from the soil, air, or water. Yet as the atomic building blocks of any particular cell come and go, the organization of the molecules, structures, and systems in the cell persists. This fact emphasizes the central importance of organization.

Positive and negative feedback are common in biological systems

Often, the amount of one of the components of a system, such as component C in **FIGURE 1.8**, affects the rate of one of the earlier processes in the system. This effect is called **feedback** and may be described as positive or negative. Feedback is often diagrammed simply with a line and symbol, but its actual mechanism may be complex.

Positive feedback occurs in a system when a product of the system *speeds up* an earlier process. The effect of positive feedback is to cause the product to be produced faster and faster. To return to one of our earlier examples, if the breakdown products of Protein T sped up synthesis of Protein T, this would lead to more breakdown products, then even more Protein T, then even more breakdown products, and so on. Positive feedback tends to destabilize a system, but destabilization can sometimes be advantageous, provided it is ultimately brought under control.

Negative feedback occurs when a product of a system *slows down* an earlier process in the system. Often, as the product increases in amount or concentration, it exerts more and more of a slowing effect. Negative feedback stabilizes the amount of the product in this way: if a high amount of the product accumulates, that accumulation tends to reduce further production of the product. For example, if an increase in the amount of breakdown products of Protein T slowed down synthesis of Protein T, this would lead to a decreased amount of breakdown products and a return to the previous rate of Protein T synthesis. Negative feedback is very common in **regulatory systems**, which are systems that tend to stabilize amounts or concentrations.

Systems analysis is a conceptual tool for understanding all levels of organization

Biologists today employ an approach known as **systems analysis** to understand how biological systems function. In systems analysis, we identify the parts or components of a biological system and specify the processes by which the components interact (see Figure 1.6). We may also be able to specify the *rates* of these interactions and how the rates are affected by feedback. What we can do then is analyze how the system will change through time. Will the amounts of different components increase or decrease, and how quickly, and how will this depend on the rates of the interactions? Will there be any stable balance, or equilibrium, that the system eventually reaches?

To do the analysis we write out mathematical equations that express the amounts of the different components and that include the processes and their rates. Expressed in words, such an equation for component B in Figure 1.6 has the following form:

The amount of B present at some time in the future = the amount of B now + the amount of A converted into B − the amount of B converted into C

We write out a similar equation for each component in the system.

We can analyze the relatively simple biological systems in Figure 1.7 by hand, but the analysis of larger systems quickly

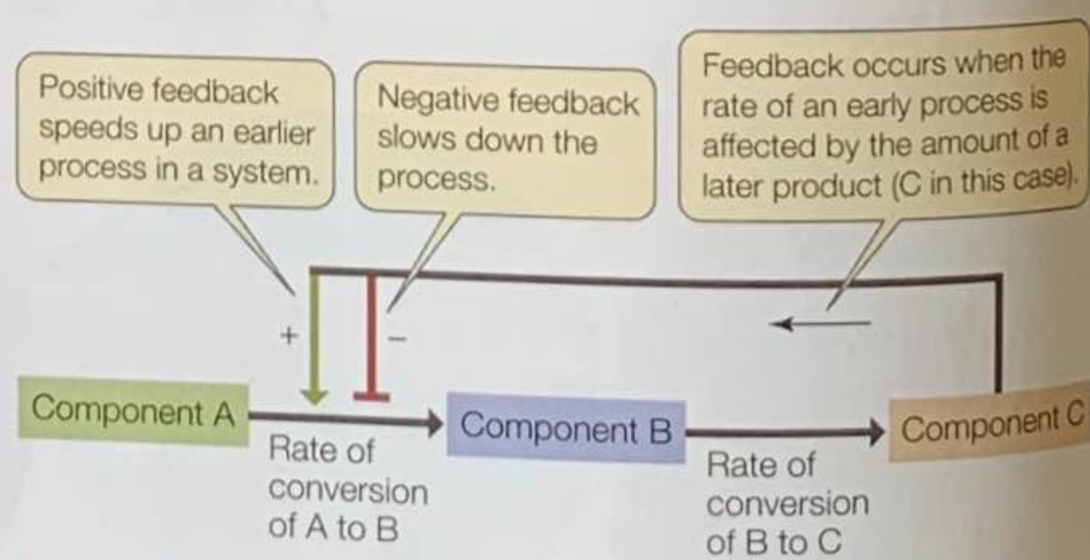
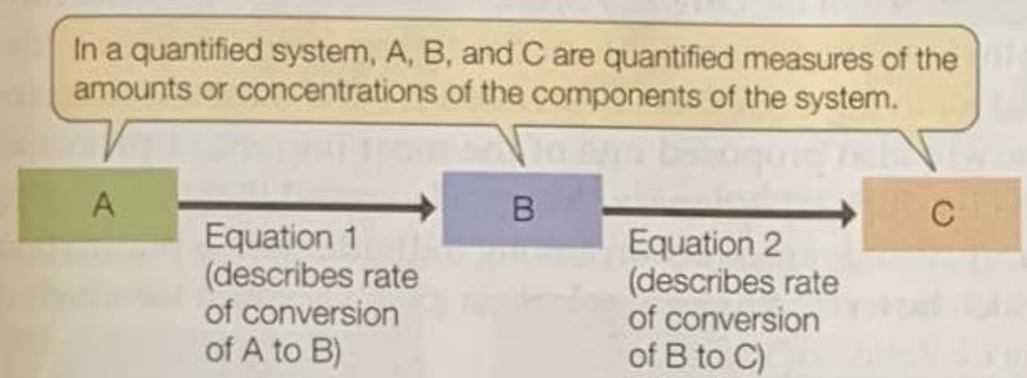


FIGURE 1.8 Feedback Can Be Positive or Negative Positive feedback tends to destabilize a system, whereas negative feedback typically stabilizes a system.

becomes very complicated and is typically carried out using computers. The approach, however, is the same: We express the rates of all processes as mathematical equations.



After this analysis is done, we have a **computational model** of the biological system. If the computational model is well grounded in factual knowledge of the biological system, the model will mimic the biological system.

An important use of computational models is prediction. For instance, if atmospheric temperature affects a biological system, we can use a computational model to develop a hypothetical prediction of the future behavior of the system in a warming world by adjusting the model to take into account the expected increases in temperature.

CONCEPT 1.3 Genetic Systems Control the Flow, Exchange, Storage, and Use of Information

The information required for an organism to function—the "blueprint" for its existence—is contained in the organism's genome, which as we noted earlier is the sum total of all the information encoded by its genes. The presence of genetic information and the processes by which organisms "decode" and use it to build the proteins that underlie a body's structure and function involve fundamental principles that we will discuss and expand on throughout the book, especially in Chapters 10–14.

Genomes encode the proteins that govern an organism's structure

Early in the chapter we noted the importance of self-replicating nucleic acids in the origin of life. Nucleic acid molecules contain long sequences of four subunits called **nucleotides**. The sequence of these nucleotides in **deoxyribonucleic acid**, or **DNA**, allows the organism to assemble **proteins**. Each **gene** is a specific segment of DNA whose sequence carries the information for building, or controlling the building of, one or more proteins (**FIGURE 1.9**). Proteins, in turn, are the molecules that govern the chemical reactions within cells and form much of an organism's structure. For these reasons, in biology we often say that genes "encode" proteins.

By analogy with a book, the nucleotides of DNA are like the letters of an alphabet. The sentences in the book are genes that encode proteins, which means that the genes provide instructions for making the proteins at a particular time or place. If you were to write out your own genome using four letters to represent the four DNA nucleotides, you would write more

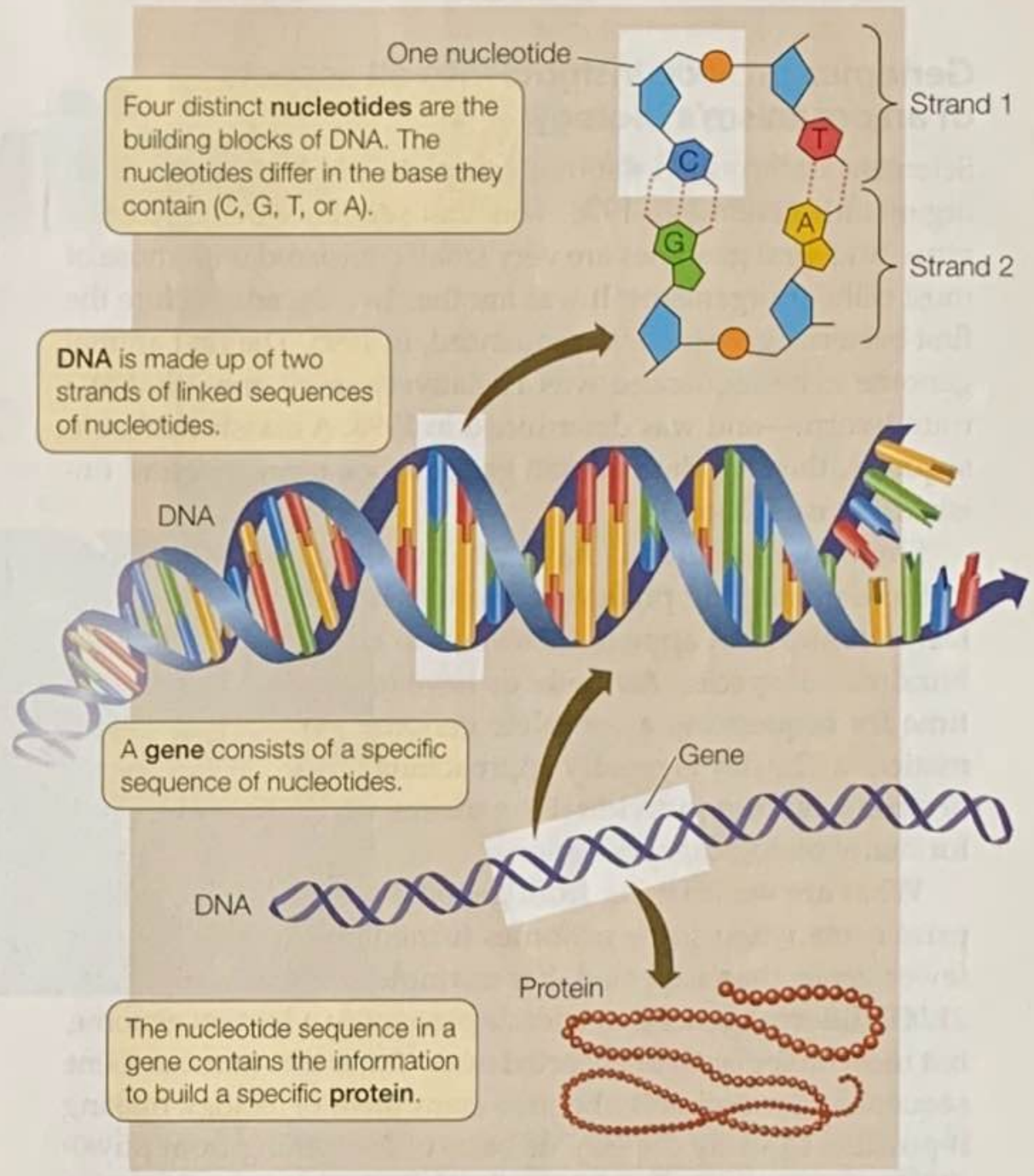


FIGURE 1.9 DNA Is Life's Blueprint The instructions for life are contained in the sequences of nucleotides in DNA molecules. Specific DNA nucleotide sequences comprise genes. The average length of a single human gene is 27,000 nucleotides. The information in each gene provides the cell with the information it needs to manufacture molecules of a specific protein.

than 3 billion letters. Using the size type you are reading now, your genome would fill more than 1,000 books the size of this one.

All the cells of a given multicellular organism contain the same genome, yet the different cells have different functions and form different proteins. For example, oxygen-carrying hemoglobin occurs in red blood cells, gut cells produce digestive proteins, and so on. Therefore different types of cells in an organism must express, or use, different parts of the genome. How any given cell controls which genes it expresses, or uses (and which genes it suppresses, or doesn't use), is a major focus of current biological research.

The genome of an organism contains thousands of genes. If mutations alter the nucleotide sequence of a gene, the protein that the gene encodes is often altered as well. Mutations may occur spontaneously, as happens when mistakes take place during replication of DNA. Mutations can also be caused by certain chemicals (such as those in cigarette smoke) and radiation (including UV radiation from the sun). Most mutations either are harmful or have no effect. Occasionally a mutation improves the functioning of the organism under the environmental conditions the individual encounters. Mutations are the raw material of evolution.

Genomes provide insights into all aspects of an organism's biology

Scientists determined the first complete DNA sequence of an organism's genome in 1976. This first sequence belonged to a virus, and viral genomes are very small compared with those of most cellular organisms. It was another two decades before the first bacterial genome was sequenced, in 1995. The first animal genome to be sequenced was a relatively small one—that of a roundworm—and was determined in 1998. A massive effort to sequence the complete human genome began in 1990 and finished 13 years later.

Since then, scientists have used the methods developed in these pioneering projects, as well as new DNA sequencing technologies that appear each year, to sequence genomes of hundreds of species. As methods have improved, the cost and time for sequencing a complete genome have dropped dramatically. The day is rapidly approaching when the sequencing of genomes from individual organisms will be commonplace for many biological applications.

What are we learning from genome sequencing? One surprise came when some genomes turned out to contain many fewer genes than expected. For example, there are only about 21,000 different genes that encode proteins in a human genome, but most biologists had expected many times that number. Gene sequence information is a boon to many areas of biology, making it possible to study the genetic basis of everything from physical structures to inherited diseases. Biologists can also compare genomes from many species to learn how and why one species differs from another. Such comparative genomic studies allow biologists to trace the evolution of genes through time and to document how particular changes in gene sequences result in changes in structure and function.

The vast amount of information being collected from genome studies has led to rapid development of the field of bioinformatics, the study of biological information. In this emerging field, biologists and computer scientists work together closely to develop new computational tools to organize, process, and study databases used in comparing genomes.

CONCEPT 1.4 Evolution Explains the Diversity as Well as the Unity of Life

Evolution—change in the genetic makeup of biological populations through time—is a major unifying principle of biology. Any process that can lead to changes in the frequencies of genes in a population from generation to generation is an evolutionary process. A common set of evolutionary processes is at work in populations of all organisms. The constant change that occurs in these populations gives rise to all the diversity we see in life. These two themes—unity and diversity—provide a framework for organizing and thinking about the evolution of life. The similarities of life allow us to make comparisons and predictions from one species to another, as we have discussed. The differences are what make biology such a rich and exciting field for investigation and discovery.

Natural selection is an important process of evolution

Charles Darwin compiled factual evidence for evolution in his 1859 book *On the Origin of Species*. Since then, biologists have gathered massive amounts of data supporting Darwin's idea that all living organisms descended from a common ancestor. Darwin also proposed one of the most important processes that produce evolutionary change. He argued that the differing survival and reproduction among individuals in a population, which he termed **natural selection**, could account for much of the evolution of life.

When Darwin proposed that living organisms descended from a common ancestor and are therefore related to one another, he did not have the advantage we have today of understanding the processes of genetic inheritance. Those processes, which we will cover in depth in Chapters 7–9, were not widely understood until the early 1900s. But he knew that offspring differed from their parents, even though they showed strong similarities. And he knew that any population of a plant or animal species displays variation.

Darwin himself bred pigeons, and he knew that if you selec breeding pairs on the basis of some particular trait, then tha trait is more likely to be present in their offspring than in th general population. He was well aware of how pigeon fanci ers selected breeding pairs to produce offspring with unusua feather patterns, beak shapes, or body sizes. He realized tha if humans could select for specific traits in organisms such a pigeons, a similar process could operate in nature. Darwin em phasized that human-imposed selection, which he called "arti ficial selection," has been practiced on crop plants and domesti cated animals since the dawn of human civilization. In coinin the term "natural selection," he argued that a similar proces occurs in nature. But in nature, the "selection" occurs not b human choice but by the fact that some individuals contribut more offspring to future generations than others.

How does natural selection work? Darwin thought that di fering probabilities of survival and reproductive success coul account for evolutionary change. He reasoned that the repr ductive capacity of plants and animals, if unchecked, would r sult in unlimited growth of populations, but we do not obser such growth in nature. In most species, only a small percenta of offspring survive to reproduce. For this reason, any trait w spread in the population if that trait gives an individual orga ism even a small increase in the probability that the individu will survive and reproduce.

Because organisms with certain traits survive and rep duce best under specific sets of conditions, natural selecti leads to **adaptations**: structural, physiological, or behavio traits that increase an organism's chances of surviving a reproducing in its environment. For example, remember t frog in the opening photograph of this chapter? Look at t frog's feet and notice that the frog's toes appear to be grea expanded. These expanded toes would be especially obvic if you could compare them with the toes of frog species t do not live in trees. Expanded toes increase the ability of t frogs to climb trees, which allows them to hunt insects for fo in the treetops and to escape predators on the ground. For t

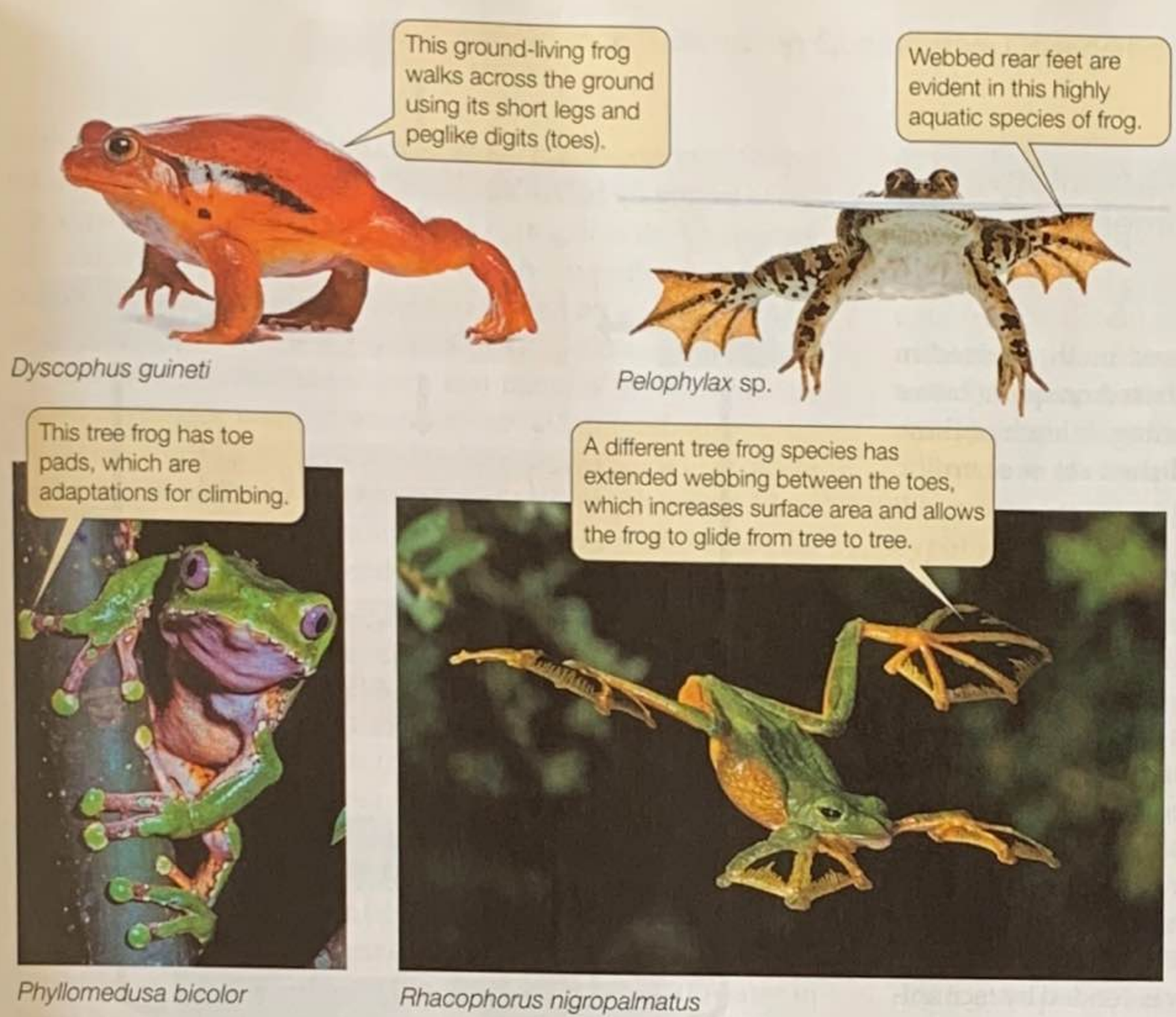


FIGURE 1.10 Adaptations to the Environment The limbs of frogs show adaptations to the different environments of each species.

Go to MEDIA CLIP 1.1 Wallace's Flying Frog PoL2e.com/mc1.1

reason the expanded toe pads of tree frogs are an adaptation to life in trees. **FIGURE 1.10** shows other adaptations in the limbs of frogs to different environments.

Biologists often think about two different kinds of explanations for adaptations. On the one hand, we can consider the immediate genetic, physiological, neurological, and developmental processes that explain how an adaptation works. We call these **proximate explanations**. For example, a proximate explanation for the toes of tree frogs might examine the physical structure of the toe pads and explain how expansion of the toe leads to greater adhesion to a substrate. Such an explanation tells us how the adaptation works, but it does not explain how tree frogs came to possess such toe pads. An **ultimate explanation**, on the other hand, concerns the processes that led to the evolution of toe pads in various groups of climbing frogs. Ultimate explanations involve comparison of variation within and among species and describe how a given trait affects an organism's chances for survival and reproduction.

Natural selection has been demonstrated in countless biological investigations, but it is not the only process that results in evolution, as we will explore in Chapters 15–18. An example of another evolutionary process is genetic drift, which refers to random changes in gene frequencies in a population because of chance events. As a result of the various evolutionary processes, all biological populations evolve through time. All the evolutionary processes operating over the long history of Earth have led to the remarkable diversity of life on our planet.

Evolution is a fact, as well as the basis for broader theory

The famous biologist Theodosius Dobzhansky once wrote that "Nothing in biology makes sense except in the light of evolution." Dobzhansky was emphasizing the need to include an evolutionary perspective and approach in all aspects of biological study. Everything in biology is a product of evolution, and biologists need a perspective of change and adaptation to fully understand biological systems.

You may have heard someone say that evolution is "just a theory," implying that there is some question about whether or not biological populations evolve. This is a common misunderstanding that originates in part from the different meanings of the word "theory" in everyday language and in science. In everyday speech, some people use the word "theory" to mean "hypothesis" or even—disparagingly—"a guess." In science, however, a **theory** is *a body of scientific work in which rigorously tested and well-established facts and principles are used to make predictions about the natural world.* In short, evolutionary theory is both (1) a body of knowledge supported by facts and (2) the resulting understanding of the various processes by which biological populations have changed and diversified over time, and by which Earth's populations continue to evolve.

We can observe and measure evolution directly, and many biologists conduct experiments on evolving populations. We constantly observe changes in the genetic makeup of populations over relatively short time periods. For example, every year health agencies need to produce new flu vaccines, because populations of influenza viruses evolve so quickly that last year's vaccines may not be effective against this year's populations of viruses. In addition, we can directly observe a record of the history of evolution in the fossil record over the almost unimaginably long periods of geological time. Exactly *how* biological populations change through time is something that is subject to testing and experimentation. The fact that biological populations evolve, however, is not disputed among biologists.

CONCEPT 1.5 Science Is Based on Quantitative Observations, Experiments, and Reasoning

Regardless of the many different tools and methods used in research, all scientific investigations are based on quantitative observation, experimentation, and reasoning. In each of these areas, scientists are guided by an established set of scientific methodological principles.

Observing and quantifying are important skills

Many biologists are motivated by their observations of the living world. Learning *what to observe* in nature is a skill that develops with experience in biology. An intimate understanding of the **natural history** of a group of organisms—how the organisms get their food, reproduce, behave, regulate their functions, and interact with other organisms—leads to better observations and prompts biologists to ask questions about those observations. The more a biologist knows about general principles of life, the more he or she is likely to gain new insights from observing nature.

Biologists have always observed the world around them, but today our ability to observe is greatly extended by technologies such as electron microscopes, rapid genome sequencing, magnetic resonance imaging, and global positioning satellites. These technologies allow us to observe everything from the distribution of molecules in the body (by using electron microscopes) to the daily movement of animals across continents and oceans (by using global positioning satellites).

Observation is a basic tool of biology, but as scientists we must also be able to **quantify** our observations—turn the observations into explicit counts or measures. Whether we are testing a new drug or mapping the migrations of whales, mathematical and statistical calculations are essential. For example, biologists once classified organisms entirely on the basis of qualitative descriptions of the physical differences among them. There was no way of objectively determining evolutionary relationships of organisms, and biologists had to depend on the fossil record for insight. Today our ability to quantify the molecular and physical differences among species, combined with explicit mathematical models of the evolutionary process, enables quantitative analyses of evolutionary history. These mathematical calculations, in turn, make it easier to compare all other aspects of the biology of different organisms.

Scientific methods combine observation, experimentation, and logic

Often, science textbooks describe "*the* scientific method," as if there is a single flow chart that all scientists follow. This view is an oversimplification. Such flow charts include much of what scientists do, but you should not conclude that scientists necessarily go through these steps in one prescribed, linear order.

Observations lead to questions, and scientists make additional observations and often do experiments to answer those questions. This approach, called the hypothesis–prediction method, has five steps: (1) making observations; (2) asking questions; (3) forming hypotheses, or tentative answers to the questions; (4) making predictions based on the hypotheses; and (5) testing the predictions by making additional observations or conducting experiments. These are the steps in traditional flow charts such as the one shown in **FIGURE 1.11**.

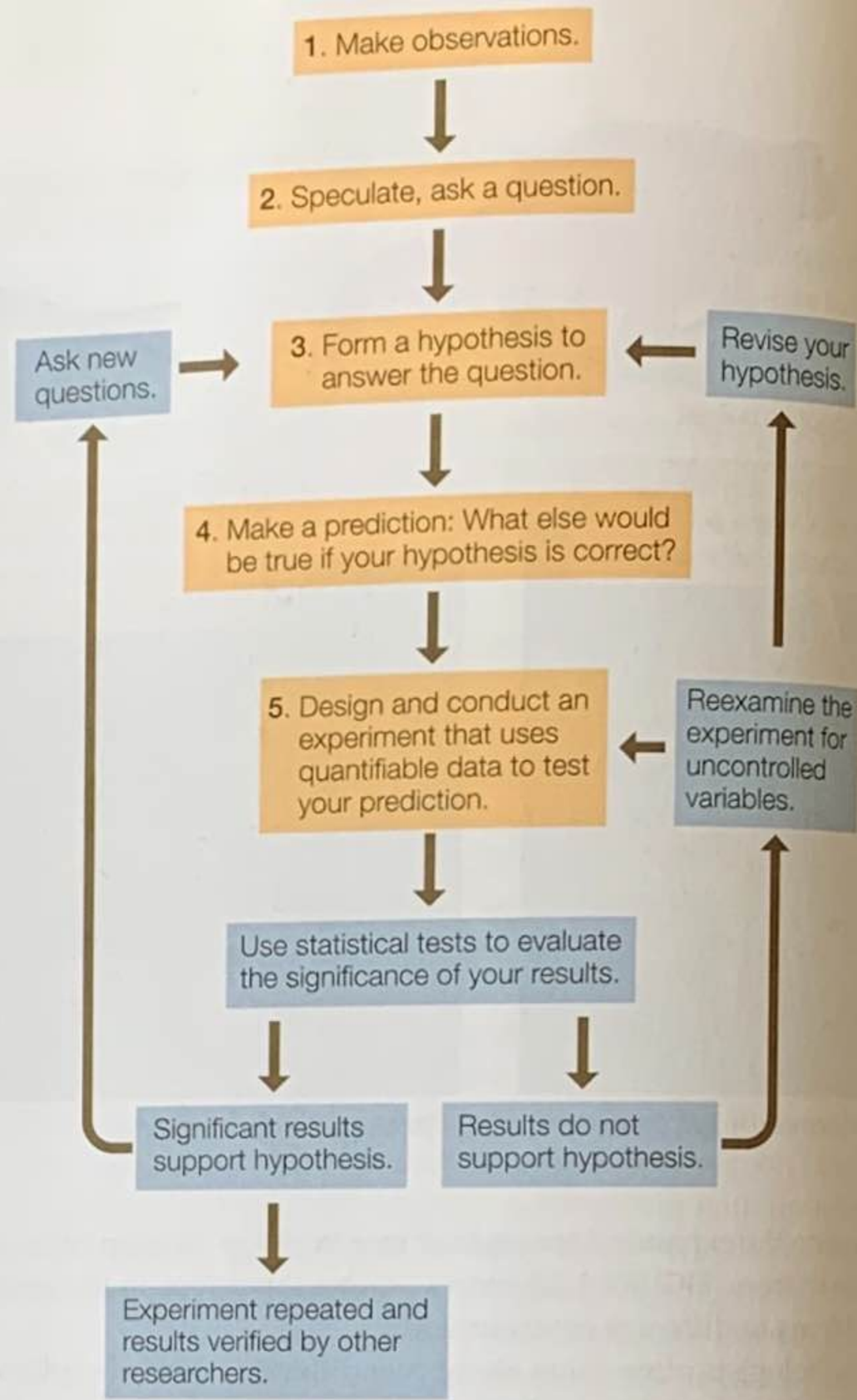


FIGURE 1.11 Scientific Methodology The process of observation, speculation and questioning, hypothesis formation, prediction, and experimentation is a cornerstone of modern science, although scientists may initiate their research at any of several different points.

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Using Scientific Methodology
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Getting from questions to answers

Let's consider an example of how scientists start with a general question and work to find answers. Amphibians—such as the frog in the opening photograph of this chapter—have been around for a long time. They watched the dinosaurs come and go. But today scientists have observed that amphibian populations around the world are in dramatic decline. In quantitative terms, more than a third of the world's amphibian species are threatened with extinction. Why is this happening?

To answer big questions like this, biologists begin by sifting through what is already known to arrive at possible answers, or **hypotheses**. In the case of amphibians, biologists know that instances of recent population declines have been associated

with various environmental changes such as loss of moist habitats, changing climate, pathogens, or increased quantities of environmental toxins. Tyrone Hayes, a biologist at the University of California at Berkeley, chose to test the hypothesis that frog populations have been adversely affected by agricultural insecticides and herbicides (weed killers). He did so even though several prior studies had shown that many of these chemicals tested at realistic concentrations do not kill amphibians.

Hayes focused on atrazine, the most widely used herbicide in the world and a common contaminant in fresh water. More than 70 million pounds of atrazine are applied to farmland in the United States every year, and it is used in at least 20 countries. Atrazine kills several types of weeds that can choke fields of important crops such as corn. The chemical is usually applied before weeds emerge in the spring—at the same time many amphibians are breeding and thousands of tadpoles swim in the ditches, ponds, and streams that receive runoff from farms.

In his laboratory, Hayes and his associates raised frog tadpoles in water containing no atrazine and in water with concentrations ranging from 0.01 parts per billion (ppb) up to 25 ppb. The U.S. Environmental Protection Agency considers environmental levels of atrazine of 10–20 ppb of no concern, and it considers 3 ppb a safe level in drinking water. Rainwater in Iowa has been measured to contain 40 ppb. In Switzerland, where the use of atrazine is illegal, the chemical has been measured at approximately 1 ppb in rainwater.

In the Hayes laboratory, an atrazine concentration as low as 0.1 ppb had a dramatic effect on tadpole development: it feminized the males. In some of the adult males that developed from these tadpoles, the vocal structures used in mating calls were smaller than normal, female sex organs developed, and eggs were found growing in the testes. In other studies, normal adult male frogs exposed to 25 ppb had a tenfold reduction in levels of the male sex hormone testosterone and did not produce sperm. You can imagine the disastrous effects these changes could have on the capacity of frogs to breed and reproduce.

But Hayes's experiments were performed in the laboratory, with a species of frog bred for laboratory use. Could atrazine be affecting frogs in nature? If so, then developmental abnormalities in natural frog populations should occur where atrazine is present in their environment. Hayes and his students traveled across the middle of North America, sampling water and collecting frogs to test this prediction. They analyzed the water for atrazine and examined the frogs. In the only site where atrazine was undetectable in the water, the frogs were normal. In all the other sites, male frogs had abnormalities of the sex organs.

Like other biologists, Hayes made observations. He then made predictions based on those observations, and designed and carried out experiments to test his predictions. Some of the conclusions from his experiments, described below, could have profound implications not only for amphibians but also for other animals, including humans.

Well-designed experiments have the potential to falsify hypotheses

Once predictions are made from a hypothesis, experiments can be designed to test those predictions. The most informative experiments have the ability to show that the prediction is wrong. If the prediction is wrong, the hypothesis must be modified or rejected.

There are two general types of experiments. Both compare data from different groups or samples. A **controlled experiment** changes, or manipulates, one or more of the factors being tested. A **comparative experiment** compares unmanipulated data gathered from different sources.

In a controlled experiment, we start with groups or samples that are as similar as possible. We predict on the basis of our hypothesis that some critical factor, or **variable**, has an effect on the phenomenon we are investigating. We devise some method to manipulate *only that variable* in an "experimental" group, and we compare the resulting data with data from an unmanipulated "control" group. If the predicted difference occurs, we then apply statistical tests to find the probability that the manipulation created the difference (as opposed to the difference being the result of random chance). **FIGURE 1.12** describes one of the many controlled experiments performed by the Hayes laboratory to quantify the effects of atrazine on male frogs.

The basis of controlled experiments is that one variable is manipulated while all others are held constant. The variable that is manipulated is called the independent variable (because an investigator can manipulate it independently of other considerations). The response that is measured is the dependent variable (because it is not manipulated directly by the investigator but is permitted to vary in ways that depend on the independent variable). A perfectly controlled experiment is not easy to design because biological variables are so interrelated that it is difficult to alter just one.

A comparative experiment starts with the prediction that there will be a difference among naturally existing samples or groups based on the hypothesis. In comparative experiments, we do not control any of the variables, and often we cannot even identify all the variables that are present. We simply gather and compare data from different naturally occurring sample groups.

When his controlled experiments indicated that atrazine indeed affects reproductive development in frogs, Hayes and his colleagues performed a comparative experiment. They collected frogs and water samples from eight widely separated sites across the United States and compared the percentages of abnormal frogs from environments with very different levels of atrazine (**FIGURE 1.13**). Of course, the sample sites differed in many ways besides the level of atrazine present.

The results of experiments frequently reveal that the situation is more complex than the hypothesis anticipated, thus raising new questions. There are no "final answers" in science. As a result, biologists often develop new questions, hypotheses, and experiments as they collect more data. The process of science is open-ended in this regard, and continued research leads to an ever-better understanding of the living world, with practical implications for agriculture, medicine, conservation of species, and other endeavors.

Statistical methods are essential scientific tools

Whether we do controlled or comparative experiments, at the end we have to decide whether there is a difference among the

INVESTIGATION

FIGURE 1.12 Controlled Experiments Manipulate a Variable
The Hayes laboratory created controlled environments that differed only in the concentrations of atrazine in the water. Eggs from leopard frogs (*Rana pipiens*) raised specifically for laboratory use were allowed to hatch and the tadpoles were separated into experimental tanks containing water with different concentrations of atrazine.[a]

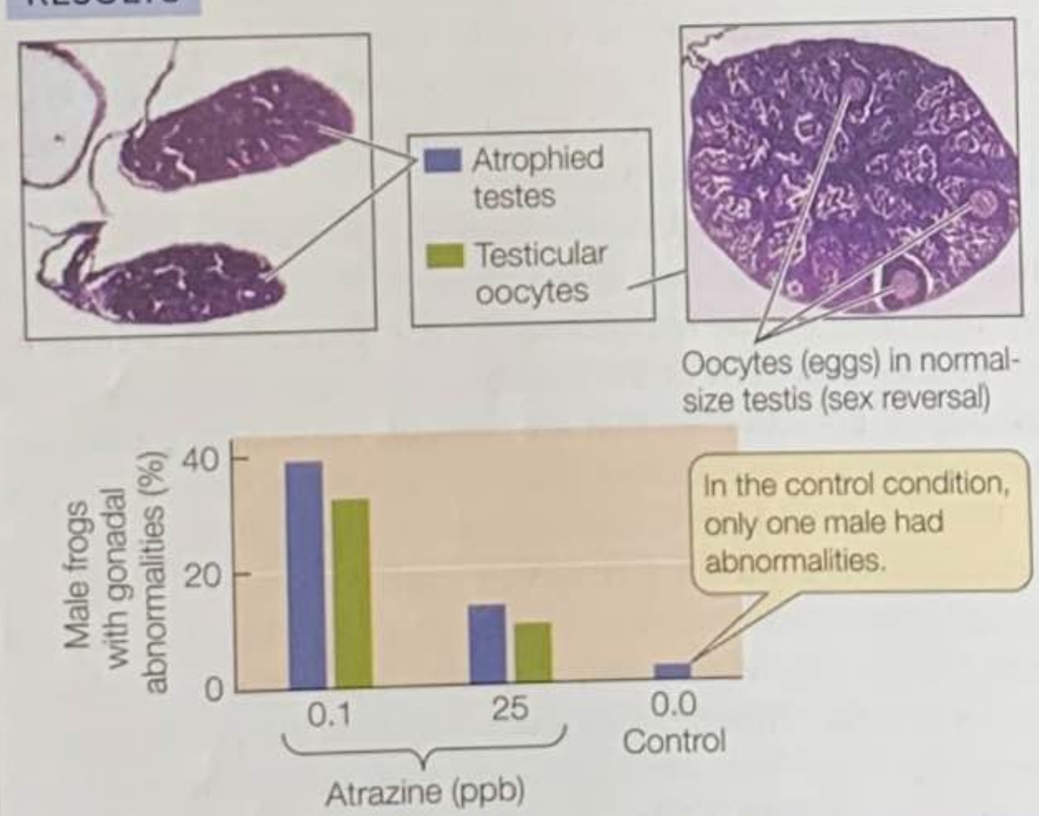
HYPOTHESIS

Exposure to atrazine during larval development causes abnormalities in the reproductive tissues of male frogs.

METHOD

1. Establish 9 tanks in which all attributes are held constant except the water's atrazine concentration. Establish 3 atrazine conditions (3 replicate tanks per condition): 0 ppb (control condition), 0.1 ppb, and 25 ppb.
2. Place *Rana pipiens* tadpoles from laboratory-reared eggs in the 9 tanks (30 tadpoles per tank).
3. When tadpoles have transitioned into adults, sacrifice the animals and evaluate their reproductive tissues.
4. Test for relationship between degree of atrazine exposure and the presence of abnormalities in the gonads (testes) of male frogs.

RESULTS



CONCLUSION

Exposure to atrazine at concentrations as low as 0.1 ppb induces abnormalities in the gonads of male frogs. The effect is not proportional to the level of exposure.

Go to **LaunchPad** for discussion and relevant links for all **INVESTIGATION** figures.

[a]T. Hayes et al. 2003. *Environmental Health Perspectives 111*: 568–575.

samples, individuals, groups, or populations in the study. How do we decide whether a measured difference is enough to support or reject a hypothesis? In other words, how do we decide in an unbiased, objective way whether the measured difference is meaningful, or significant?

Statistical significance refers to the extent to which a result is unlikely to be due to chance alone. Scientists use statistics because they recognize that variation is always present in any set of measurements. Statistical tests calculate the probability that the differences observed in an experiment could be due to random variation. The results of statistical tests are therefore probabilities. Many statistical tests start with a **null hypothesis**—the premise that any observed differences are simply the result of random differences that arise from drawing two samples from the same population. When scientists collect quantified observations, or **data**, they apply statistical methods to those data to calculate the likelihood that the null hypothesis is correct.

More specifically, statistical methods tell us the probability of obtaining a particular result by chance alone, even if the samples being tested are drawn from the same population. As scientists, we need to eliminate, insofar as possible, the possibility that any differences seen are simply due to chance variation in the samples. Appendix B in this book is a short primer on statistical methods that you can refer to as you analyze data that will be presented throughout the text.

Not all forms of inquiry into nature are scientific

Science is a human endeavor that is bounded by certain standards of practice. Other areas of scholarship share with science the practice of making observations and asking questions, but scientists are distinguished by what they do with their observations and how they answer their questions. Data, subjected to appropriate statistical analysis, are critical in testing hypotheses. Science is the most powerful approach humans have devised for learning about the world and how it works.

Scientific explanations for natural processes are objective and reliable because the hypotheses proposed *must be testable* and *must have the potential of being rejected* by direct observations and experiments. Scientists must clearly describe the methods they use to test hypotheses so that other scientists can repeat their experiments to see if they get the same results. Not all experiments are repeated, but surprising or controversial results are always subjected to independent verification. Scientists worldwide share this process of testing and rejecting hypotheses, contributing to a common body of scientific knowledge.

If you understand the methods of science, you can distinguish science from non-science. Art, music, and literature all contribute to the quality of human life, but they are not science. They do not use scientific methods to establish what is fact. Religion is not science, although religions have historically attempted to explain natural events ranging from unusual weather patterns to crop failures to human diseases. Most such phenomena that at one time were mysterious can now be explained in terms of scientific principles. Fundamental tenets of religious faith, such as the existence of a supreme deity or deities, cannot be confirmed or refuted by experimentation and for this reason are outside the realm of science.

The power of science derives from the uncompromising objectivity and absolute dependence on evidence that comes from reproducible and quantifiable observations. A religious or spiritual explanation of a natural phenomenon may be

INVESTIGATION

FIGURE 1.13 Comparative Experiments Look for Differences among Groups To see whether the presence of atrazine correlates with testicular abnormalities in male frogs, the Hayes lab collected frogs and water samples from different locations around the U.S. The analysis that followed was "blind," meaning that the frogs and water samples were coded so that experimenters working with each specimen did not know which site the specimen came from.[a]

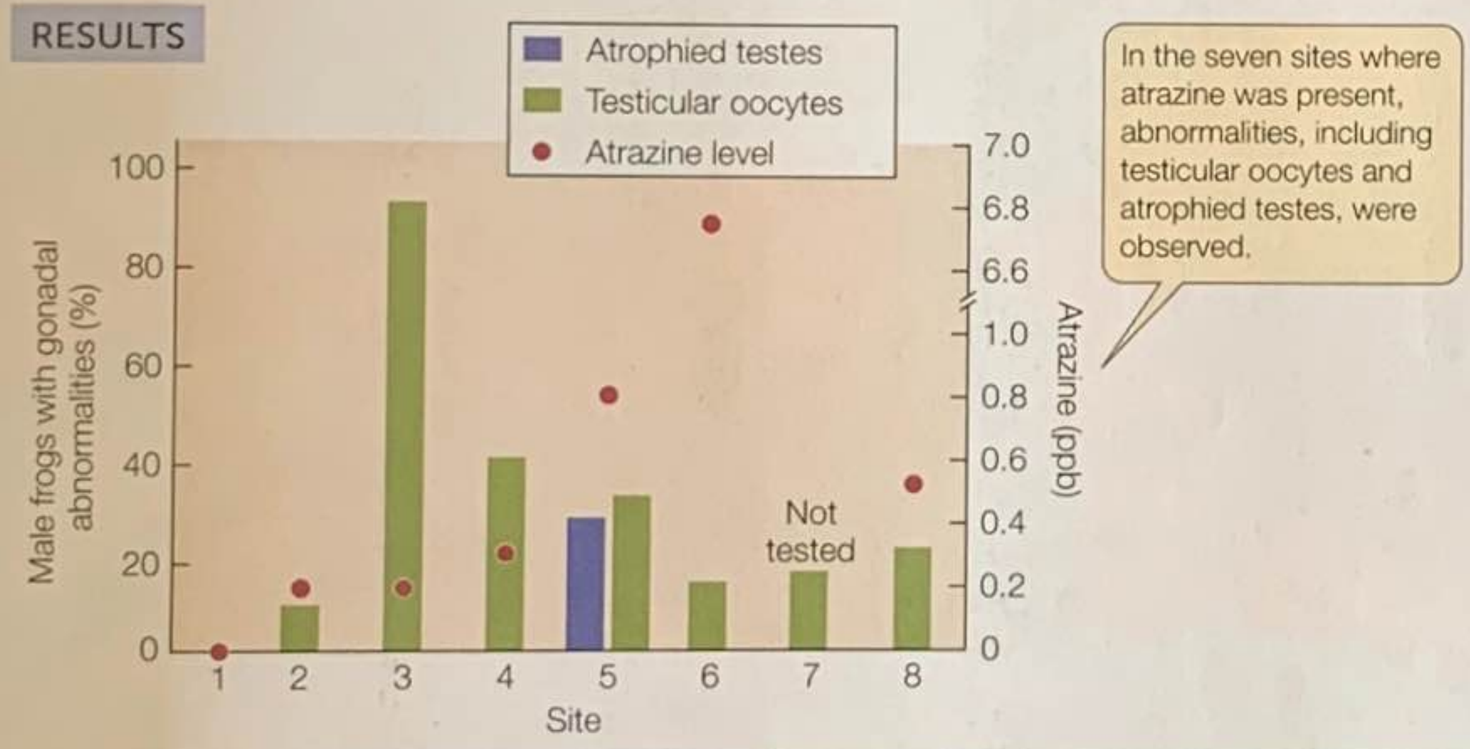
HYPOTHESIS

Presence of the herbicide atrazine in environmental water correlates with gonadal abnormalities in frog populations.

METHOD

1. Based on commercial sales of atrazine, select 4 sites (sites 1–4) less likely and 4 sites (sites 5–8) more likely to be contaminated with atrazine.
2. Visit all sites in the spring (i.e., when frogs have transitioned from tadpoles into adults); collect frogs and water samples.
3. In the laboratory, sacrifice frogs and examine their reproductive tissues, documenting abnormalities.
4. Analyze the water samples for atrazine concentration (the sample for site 7 was not tested).
5. Quantify and correlate the incidence of reproductive abnormalities with environmental atrazine concentrations.

RESULTS



CONCLUSION

Reproductive abnormalities exist in frogs from environments in which aqueous atrazine concentration is 0.2 ppb or above. The frequency of abnormalities does not appear to be proportional to atrazine concentration at the time of transition to adulthood.

Go to **LaunchPad** for discussion and relevant links for all **INVESTIGATION** figures.

[a]T. Hayes et al. 2002. *Nature* 419: 895–896.

coherent and satisfying for the person holding that view, but it is not testable and therefore it is not science. To invoke a supernatural explanation (such as a "creator" or "intelligent designer" with no known bounds) is to depart from the world of science. Science does not say that untestable religious beliefs are necessarily wrong, just that they are not something that we can address using scientific methods.

Science describes how the world works. It is silent on the question of how the world "ought to be." Many scientific advances that contribute to human welfare also raise major ethical issues. Recent developments in genetics and developmental biology may enable us to select the sex of our children, to use stem cells to repair our bodies, and to modify the human genome. Scientific knowledge allows us to do these things, but science cannot tell us whether or not we should do so, or if we choose to do them, how we should regulate them. Such questions are as crucial to human society as the science itself. A responsible scientist does not lose sight of these questions or neglect the contributions of the humanities in attempting to come to grips with them.

Consider the big themes of biology as you read this book

You will see evolution and the other fundamental principles of life introduced in this chapter at work in each part of this book. In Part 1 you will learn about the molecular organization of life. We will discuss the origin of life, the energy in atoms and molecules, and how proteins and nucleic acids became the self-replicating cellular systems of life. Part 2 will describe how these self-replicating systems work and the genetic principles that explain heredity and mutation, which are the basis of evolution. In Part 3 we will describe the processes of evolution and go into detail about how evolution works. Part 4 will examine the products of evolution: the vast diversity of life and the many different ways organisms solve common problems such as how to reproduce, defend themselves, and obtain nutrients. Parts 5 and 6 will explore the physiological adaptations that allow plants and animals to survive and function in a wide range of physical environments. Finally, in Part 7 we will discuss these environments and the integration of individual organisms, populations, and communities into the interrelated ecological systems of Earth.

You may enjoy returning to this chapter occasionally as the course progresses. The brief explanations we have given here should become more meaningful as you read about the facts and phenomena that underlie the principles. Our knowledge of the "facts" of biology, however, is not based just on reading, contemplation, or discussion, although all of these activities are important. Scientific knowledge is based on active and always-ongoing research.

PART 1

Cells

2

The Chemistry and Energy of Life

KEY CONCEPTS

2.1 Atomic Structure Is the Basis for Life's Chemistry

2.2 Atoms Interact and Form Molecules

2.3 Carbohydrates Consist of Sugar Molecules

2.4 Lipids Are Hydrophobic Molecules

2.5 Biochemical Changes Involve Energy

Polar ice caps, as shown here, have been observed on Mars for a long time, but recent evidence also shows water at the milder mid-latitudes of Mars. Finding water on Mars may indicate that it is or was hospitable to life.

A major discovery of biology was that living things are composed of the same chemical elements as the vast nonliving portion of the universe. This mechanistic view—that life is chemically based and obeys the universal laws of chemistry and physics—is relatively new in human history. Until the nineteenth century, many scientists thought that a "vital force," distinct from the forces governing the inanimate world, was responsible for life. Many people still assume that such a vital force exists. However, the mechanistic view of life has led to great advances in biological science, and it underpins many of the applications of biology to medicine and agriculture. We use a mechanistic view throughout this book.

Among the most abundant chemical elements in the universe are hydrogen and oxygen, and life as we know it requires the presence of these elements as water (H_2O). Water makes up about 70 percent of the bodies of most organisms, and those that live on land have evolved elaborate ways to retain the water in their bodies. Aquatic organisms do not need these water-retention mechanisms; thus biologists think that life originated in a watery environment.

Life has been found in some surprising places, often in extreme conditions. There are organisms living in hot springs at temperatures above the boiling point of water, 5 kilometers below Earth's surface, at the bottom of the ocean, and in extremely acid or salty conditions.

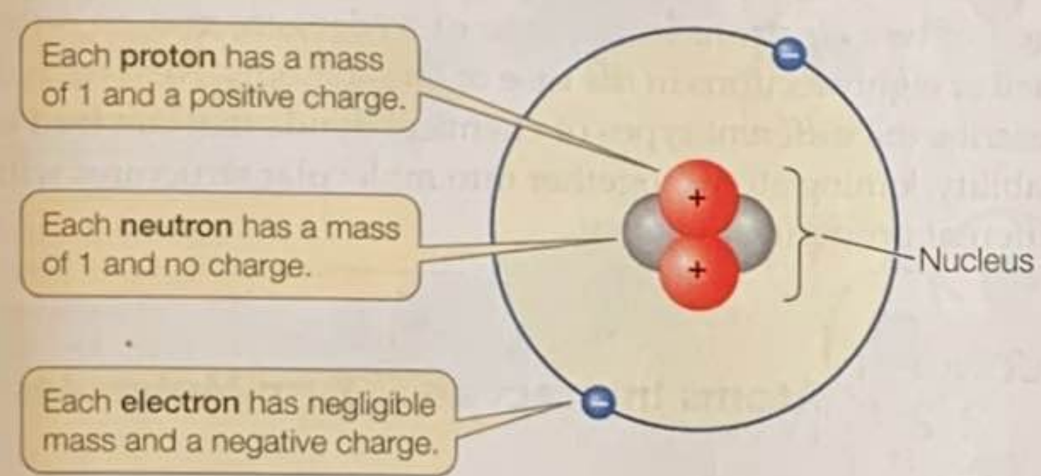
Life has been found even below the Antarctic ice, a finding especially relevant to the search for life beyond Earth. Some moons that orbit Jupiter and Saturn have ice on their surfaces, overlaying oceans of water much larger than the oceans on Earth. The subsurface water on these moons may be maintained as a liquid in large part because ice is a good insulator and traps heat generated by tidal forces between the moons and their planets. Europa is a moon of Jupiter that is slightly smaller than Earth's moon. It has an atmosphere composed primarily of oxygen, and scientists speculate that Europa's subsurface oceans could harbor life, just as the Antarctic ice lakes do. Mars also has ice on its surface, with some evidence of subsurface water. Two of NASA's highest priorities are to launch missions to Mars and Europa to bring back samples from these lakes to Earth.

Q Why is the search for water important in the search for life?

You will find the answer to this question on page 34

CONCEPT 2.1 Atomic Structure Is the Basis for Life's Chemistry

Living and nonliving matter is composed of **atoms**. Each atom consists of a dense, positively charged **nucleus**, with one or more negatively charged **electrons** moving around it. The nucleus contains one or more positively charged **protons**, and may contain one or more **neutrons** with no electrical charge:



Charges that are different (+/−) attract each other, whereas charges that are alike (+/+, −/−) repel one another. Most atoms are electrically neutral because the number of electrons in an atom equals the number of protons.

The standard unit of measure for the mass of an atom (atomic mass) is the dalton—named after the English chemist John Dalton. A single proton or neutron has a mass of about 1 dalton (Da), which is 1.7×10^{-24} grams, but an electron is even tinier, at 0.0005 Da (9×10^{-28} g). Because the mass of an electron is only about 1/2,000th of the mass of a proton or neutron, the contribution of electrons to the mass of an atom can usually be ignored when chemical measurements and calculations are made.

An element consists of only one kind of atom

An **element** is a pure substance that contains only one kind of atom. The element hydrogen consists only of hydrogen atoms, the element gold only of gold atoms. The atoms of each element have characteristics and properties that distinguish them from the atoms of other elements.

There are 94 elements in nature, and at least another 24 have been made in physics laboratories. Most of the 94 natural elements have been detected in living organisms, but just a few predominate. About 98 percent of the mass of every living organism (bacterium, turnip, or human) is composed of just six elements:

Carbon (symbol C)	Hydrogen (H)	Nitrogen (N)
Oxygen (O)	Phosphorus (P)	Sulfur (S)

The chemistry of these six elements will be our primary concern in this chapter, but other elements found in living organisms are important as well. Sodium and potassium, for example, are essential for nerve function; calcium can act as a biological signal; iodine is a component of a human hormone; and magnesium is bound to chlorophyll in green plants.

The physical and chemical (reactive) properties of atoms depend on the numbers of protons, neutrons, and electrons they contain. The atoms of an element differ from those of other elements by the number of protons in their nuclei. The number of protons is called the **atomic number**, and it is unique to and characteristic of each element. A carbon atom has six protons and thus an atomic number of 6; the atomic number of oxygen is 8. For electrical neutrality, each atom has the same number of electrons as protons, so a carbon atom has six electrons and an oxygen atom has eight.

Along with a definitive number of protons, every element except hydrogen has one or more neutrons. The **mass number** of an atom is the total number of protons and neutrons in its nucleus. The number of neutrons may vary among atoms of a particular element. For example, carbon atoms with six, seven, and eight neutrons are found in nature. These variants are referred to as **isotopes**. The most common carbon isotope has six neutrons and a mass number of 12, and is referred to as carbon-12 (often written ^{12}C). The most common oxygen isotope (^{16}O) has eight protons and eight neutrons, and a mass number of 16.

Go to MEDIA CLIP 2.1
The Elements Song
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Electrons determine how an atom will react

The **Bohr model** for atomic structure (see diagram in previous column) provides a concept of an atom that is largely empty space, with a central nucleus surrounded by electrons in orbits, or **electron shells**, at various distances from the nucleus. This model is much like our solar system, with planets orbiting around the sun. Although highly oversimplified (you will learn about the reality of atomic structure in physical chemistry courses), the Bohr model is useful for describing how atoms behave. Specifically, *the behaviors of electrons determine whether a chemical bond will form and what shape the bond will have.* These are two key properties for determining biological changes and structure.

In the Bohr model, each electron shell is a certain distance from the nucleus. Since electrons are negatively charged and protons are positive, an electron needs energy to escape from the attraction of the nucleus. The farther away an electron shell is from the nucleus, the more energy the electron must have. We will return to this topic when we discuss biological energetics in Chapter 6.

The electron shells, in order of their distance from the nucleus, can be filled with electrons as follows:

- First shell: up to 2 electrons
- Second shell: up to 8 electrons
- Third shell: up to 18 electrons
- Fourth and subsequent shells: up to 32 electrons

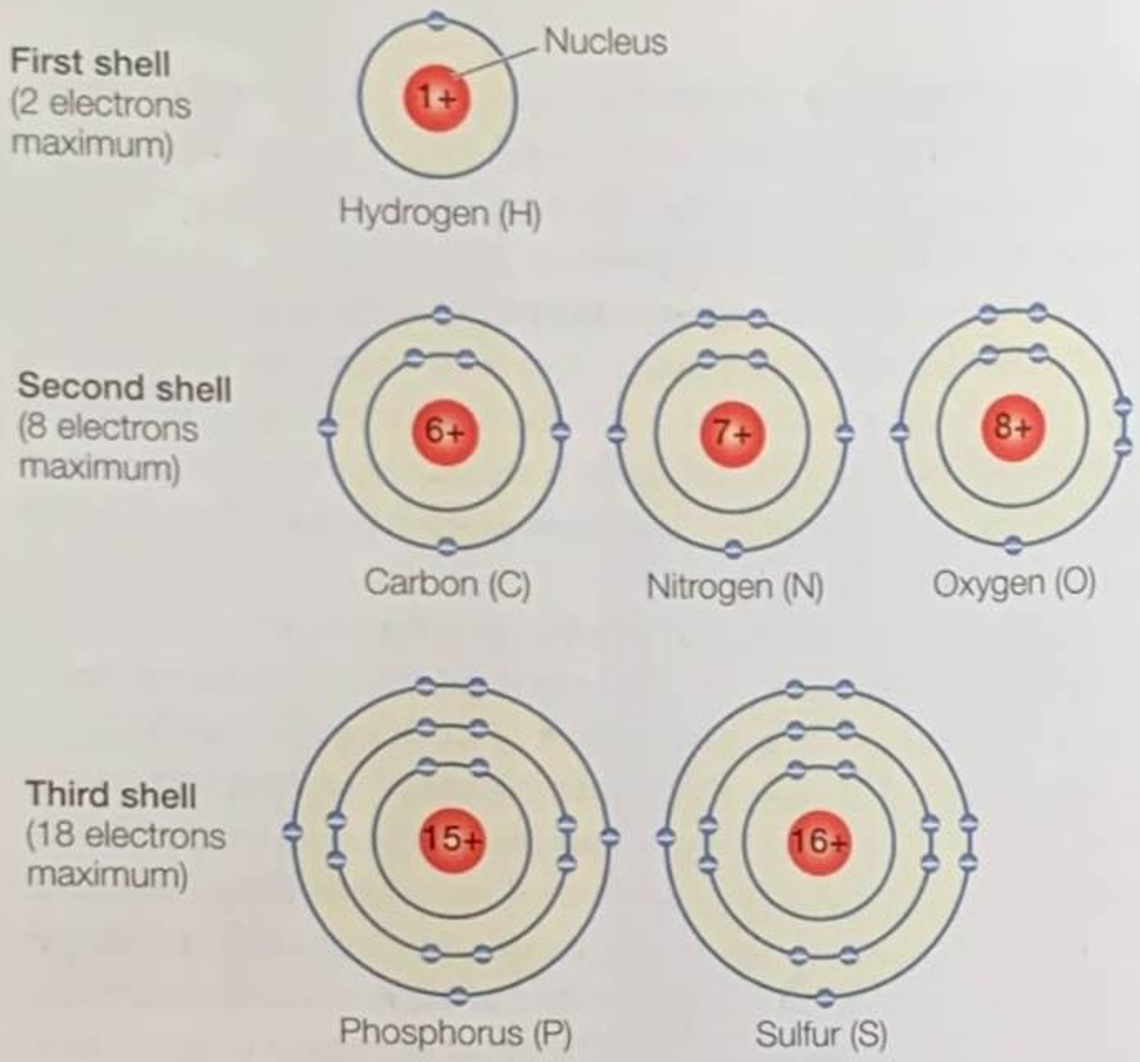


FIGURE 2.1 Electron Shells Each shell can hold a specific maximum number of electrons and must be filled before electrons can occupy the next shell. The energy level of an electron is higher in a shell farther from the nucleus. An atom with fewer than eight electrons in its outermost shell (or two in the case of hydrogen) can react (bond) with other atoms.

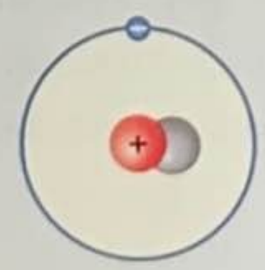
Electrons fill shells closest to the nucleus before occupying shells farther from the nucleus. **FIGURE 2.1** illustrates the electron shell configurations for the six major elements found in living systems.

For elements with atomic numbers between 6 and 20 there is a chemical rule of thumb called the **octet rule**, which states that an atom will lose, gain, or share electrons in order to achieve a stable configuration of eight electrons in its outermost shell. Oxygen, for example, which has six electrons in its outermost shell, will undergo chemical reactions to gain two electrons. When atoms share electrons, they form stable associations called **molecules**. Most atoms in biologically important molecules—for example, carbon and nitrogen—follow the octet rule. However, very small atoms such as hydrogen (with one proton and one electron) tend to gain, lose, or share electrons such that their single shell contains its maximum number of two electrons.

CHECKpoint CONCEPT 2.1

- ✓ What is the arrangement of protons, neutrons, and electrons in an atom?
- ✓ Sketch the electron shell configuration of a sodium atom (symbol Na), which has 11 protons. According to the octet rule, what would be the simplest way for a sodium atom to achieve electron stability?
- ✓ Many elements have isotopes, which are rare variants of the element with additional neutrons in the nucleus. Deuterium is an isotope of hydrogen that has one neutron (normal hydrogen has no neutrons).

Does the neutron change the chemical reactivity of deuterium, compared with normal hydrogen? Explain why or why not.



Deuterium
1 proton
1 neutron

We have introduced the basic unit of matter that makes up all living organisms—the atom. We have discussed the tendency of atoms to attain stable configurations of electrons: a single shell of two electrons in the case of hydrogen, and an outer shell of eight electrons in the case of larger atoms. Next we will describe the different types of chemical bonds that can lead to stability, joining atoms together into molecular structures with different properties.

CONCEPT 2.2 Atoms Interact and Form Molecules

A **chemical bond** is an attractive force that links two atoms together in a molecule. There are several kinds of chemical bonds (**TABLE 2.1**; see p. 22). In this section we will begin with covalent bonds, the strong bonds that result from the sharing of electrons. Next we will consider weaker interactions, including hydrogen bonds, which are enormously important to biology. We will then examine ionic attractions, which form when an atom gains or loses electrons to achieve stability. Finally, we will see how atoms are bonded to make functional groups—groups of atoms that give important properties to biological molecules.

Go to ANIMATED TUTORIAL 2.1
Chemical Bond Formation
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Covalent bonds consist of shared pairs of electrons

A **covalent bond** forms when two atoms attain stable electron numbers in their outermost shells by *sharing* one or more pairs of electrons. In this case, each atom contributes one member of each electron pair. Consider two hydrogen atoms coming close together, each with just one electron in its single shell (**FIGURE 2.2**). When the electrons pair up, a stable association is formed, and this links the two hydrogen atoms in a covalent bond, forming the molecule H_2.

Let's see how covalent bonds are formed in the somewhat more complicated methane molecule (CH_4). The carbon atom has six electrons: two electrons fill its inner shell, and four electrons are in its outer shell. Because of the octet rule, carbon is most stable when it shares electrons with four other atoms—*it can form four covalent bonds* (**FIGURE 2.3A**). Methane forms when an atom of carbon reacts with four hydrogen atoms. As a result of electron sharing, the outer shell of the carbon atom is now filled with eight electrons—a stable configuration. The single shell of each hydrogen atom is also filled. Four covalent bonds—four shared electron pairs—hold methane together

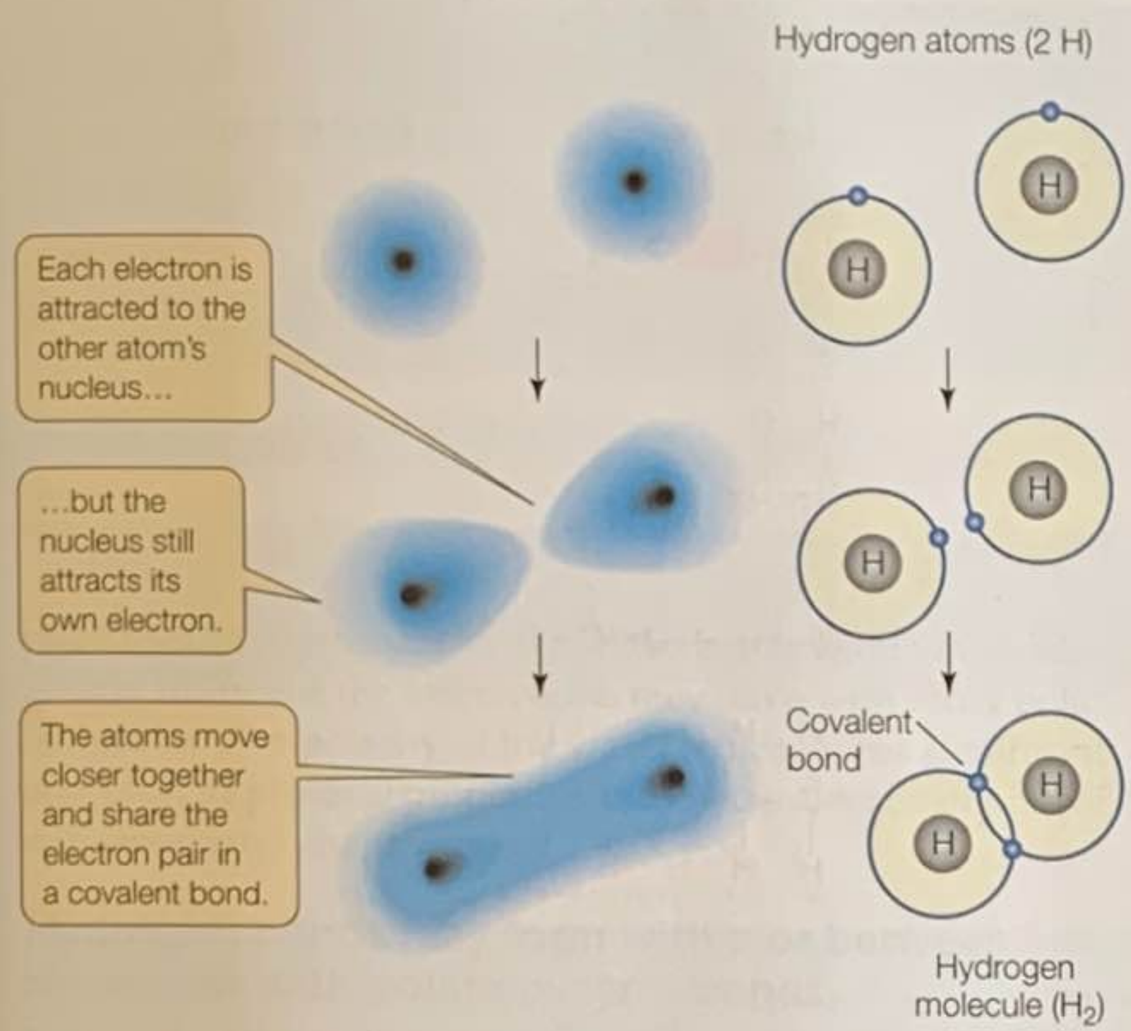


FIGURE 2.2 Electrons Are Shared in Covalent Bonds Two hydrogen atoms can combine to form a hydrogen molecule. A covalent bond forms when the electron shells of the two atoms overlap in an energetically stable manner.

FIGURE 2.3B shows several different ways to represent the molecular structure of methane. **TABLE 2.2** shows the covalent bonding capacities of some biologically important elements.

The properties of molecules are influenced by the characteristics of their covalent bonds. Four important aspects of covalent bonds are orientation, strength and stability, multiple covalent bonds, and the degree of sharing of electrons.

ORIENTATION For a given pair of elements, such as carbon bonded to hydrogen, the length of the covalent bond is always the same. And for a given atom within a molecule, the angle of each covalent bond with respect to the others is generally the same. This is true regardless of the type of larger molecule that contains the atom. For example, the four covalent bonds formed by the carbon atom in methane are always distributed in space so that the bonded hydrogens point to the corners of a regular tetrahedron, with the carbon in the center (see Figure 2.3B). Even when carbon is bonded to four atoms other than hydrogen, this three-dimensional orientation is more or less maintained. As you will see, the orientations of covalent bonds in space give molecules their three-dimensional geometry, and the shapes of molecules contribute to their biological functions.

STRENGTH AND STABILITY Covalent bonds are very strong (see Table 2.1), meaning it takes a lot of energy to break them. At the temperatures at which life exists, the covalent bonds of biological molecules are quite stable, as are their three-dimensional structures. However, this stability does not rule out change, as we will discover.

MULTIPLE COVALENT BONDS As shown in Figure 2.3B, covalent bonds can be represented by lines between the chemical symbols for the linked atoms:

- A *single bond* involves the sharing of a single pair of electrons (for example, H—H or C—H).

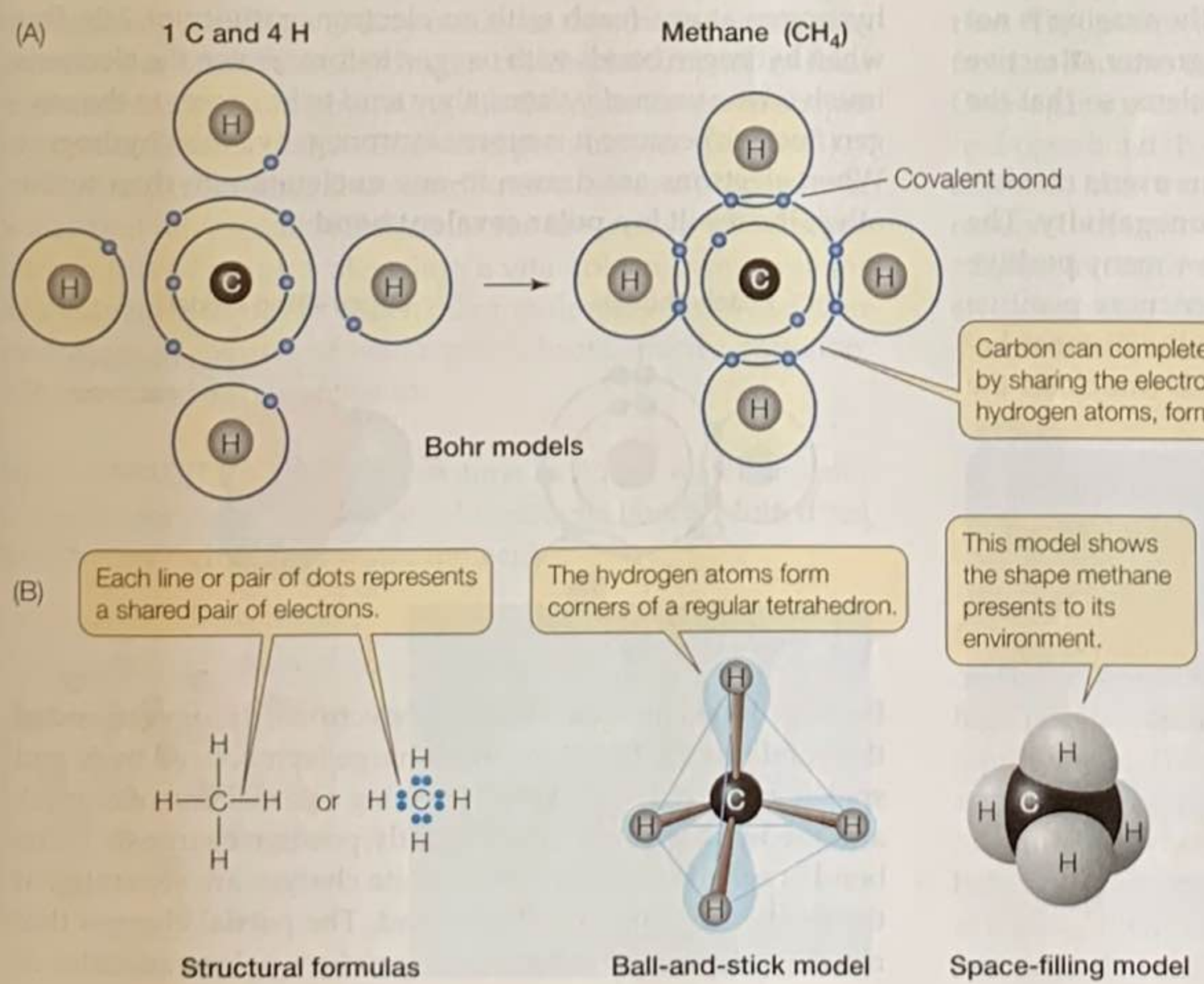


FIGURE 2.3 Covalent Bonding (A) Bohr models showing the formation of covalent bonds in methane, whose molecular formula is CH_4. Electrons are shown in shells around the nuclei. (B) Three additional ways of representing the structure of methane. The ball-and-stick and the space-filling models show the spatial orientations of the bonds. The space-filling model indicates the overall shape and surface of the molecule. In the chapters that follow, different conventions will be used to depict molecules. Bear in mind that these are models to illustrate certain properties and are not the most accurate portrayals of reality.

TABLE 2.1 Chemical Bonds and Interactions

Name	Basis of interaction	Structure	Bond energy[a]
Ionic attraction	Attraction of opposite charges		3–7
Covalent bond	Sharing of electron pairs		50–110
Hydrogen bond	Attraction between H (δ^+) and a strongly electronegative atom		3–7
Hydrophobic interaction	Interaction of nonpolar substances in the presence of polar substances (especially water)		1–2
van der Waals interaction	Interaction of electrons of nonpolar substances		1

[a]Bond energy is the amount of energy (Kcal/mol) needed to separate two bonded or interacting atoms under physiological conditions.

- A *double bond* involves the sharing of four electrons (two pairs; C=C).
- *Triple bonds*—six shared electrons—are rare, but there is one in nitrogen gas (N≡N), which is the major component of the air we breathe.

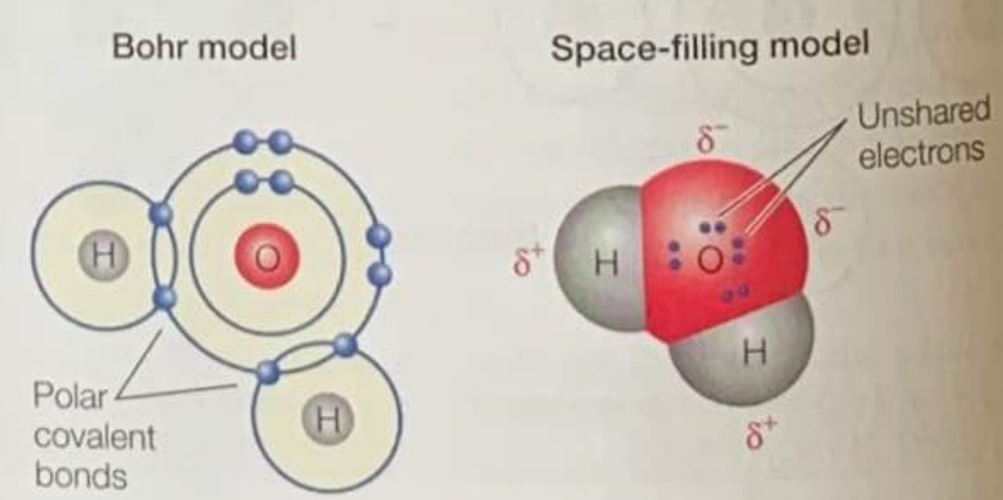
UNEQUAL SHARING OF ELECTRONS If two atoms of the same element are covalently bonded, there is an equal sharing of the pair(s) of electrons in their outermost shells. However, when the two atoms are different elements, the sharing is not necessarily equal. One nucleus may exert a greater attractive force on the electron pair than the other nucleus, so that the pair tends to be closer to that atom.

The attractive force that an atomic nucleus exerts on electrons in a covalent bond is called its **electronegativity**. The electronegativity of a nucleus depends on how many positive charges it has (nuclei with more protons are more positive and thus more attractive to electrons) and on the distance between the electrons in the bond and the nucleus (the closer the electrons, the greater the electronegative pull). **TABLE 2.3** shows the electronegativities of some elements important in biological systems. (Electronegativity is calculated to produce a dimensionless quantity, meaning that it has no unit of measurement such as for length, time, mass, etc.)

TABLE 2.2 Covalent Bonding Capacities of Some Biologically Important Elements

Element	Usual number of covalent bonds
Hydrogen (H)	1
Oxygen (O)	2
Sulfur (S)	2
Nitrogen (N)	3
Carbon (C)	4
Phosphorus (P)	5

If two atoms are 0.5 or less apart in electronegativity, they will share electrons equally in what is called a nonpolar covalent bond. Two oxygen atoms, for example, each with an electronegativity of 3.4, will share electrons equally. So will two hydrogen atoms (each with an electronegativity of 2.2). But when hydrogen bonds with oxygen to form water, the electrons involved are *unequally shared*: they tend to be nearer to the oxygen nucleus because it is more electronegative than hydrogen. When electrons are drawn to one nucleus more than to the other, the result is a **polar covalent bond**:



Because of this unequal sharing of electrons, the oxygen end of the bond has a slightly negative charge (symbolized by δ^- and spoken of as "delta negative," meaning a partial unit of charge), and the hydrogen end has a slightly positive charge (δ^+). The bond is *polar* because these opposite charges are separated at the two ends, or poles, of the bond. The partial charges that result from polar covalent bonds produce polar molecules or

TABLE 2.3 Some Electronegativities

Element	Electronegativity
Oxygen (O)	3.4
Chlorine (Cl)	3.2
Nitrogen (N)	3.0
Carbon (C)	2.6
Phosphorus (P)	2.2
Hydrogen (H)	2.2
Sodium (Na)	0.9
Potassium (K)	0.8

polar regions of large molecules. Polar bonds within molecules greatly influence the interactions they have with other polar molecules. The polarity of the water molecule has significant effects on its physical properties and chemical reactivity, as we will see in later chapters.

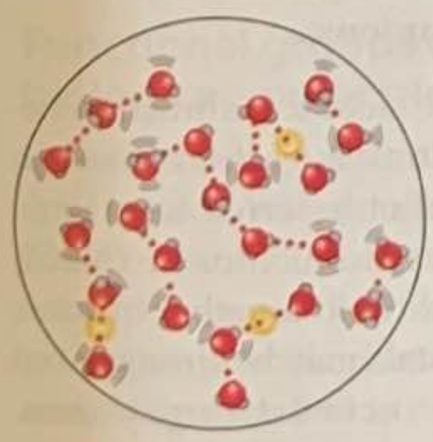
Hydrogen bonds may form within or between molecules with polar covalent bonds

In liquid water, the negatively charged oxygen (δ^-) atom of one water molecule is attracted to the positively charged hydrogen (δ^+) atoms of other water molecules (**FIGURE 2.4A**). The bond resulting from this attraction is called a **hydrogen bond** (see Table 2.1). These bonds are not restricted to water molecules. A hydrogen bond may also form between a strongly electronegative atom and a hydrogen atom that is covalently bonded to another electronegative atom (oxygen or nitrogen), as shown in **FIGURE 2.4B**.

A hydrogen bond is much weaker than a covalent bond (see Table 2.1). Although individual hydrogen bonds are weak, many of them can form within one molecule or between two molecules. In these cases, the hydrogen bonds together have considerable strength and can greatly influence the structure and properties of the substances. Hydrogen bonds play important roles in determining and maintaining the three-dimensional shapes of giant molecules such as DNA and proteins (see Chapter 3).

Hydrogen bonding also contributes to several properties of water that have great significance for life. As we will discuss later in this Concept, water plays a vital role in living systems as a **solvent**: a liquid in which other molecules dissolve. Other important properties of water are its heat capacity, cohesion, adhesion, and surface tension.

HEAT CAPACITY At any given time in liquid water, a water molecule forms an average of 3.4 hydrogen bonds (dotted red lines below) with other water molecules:



Liquid water

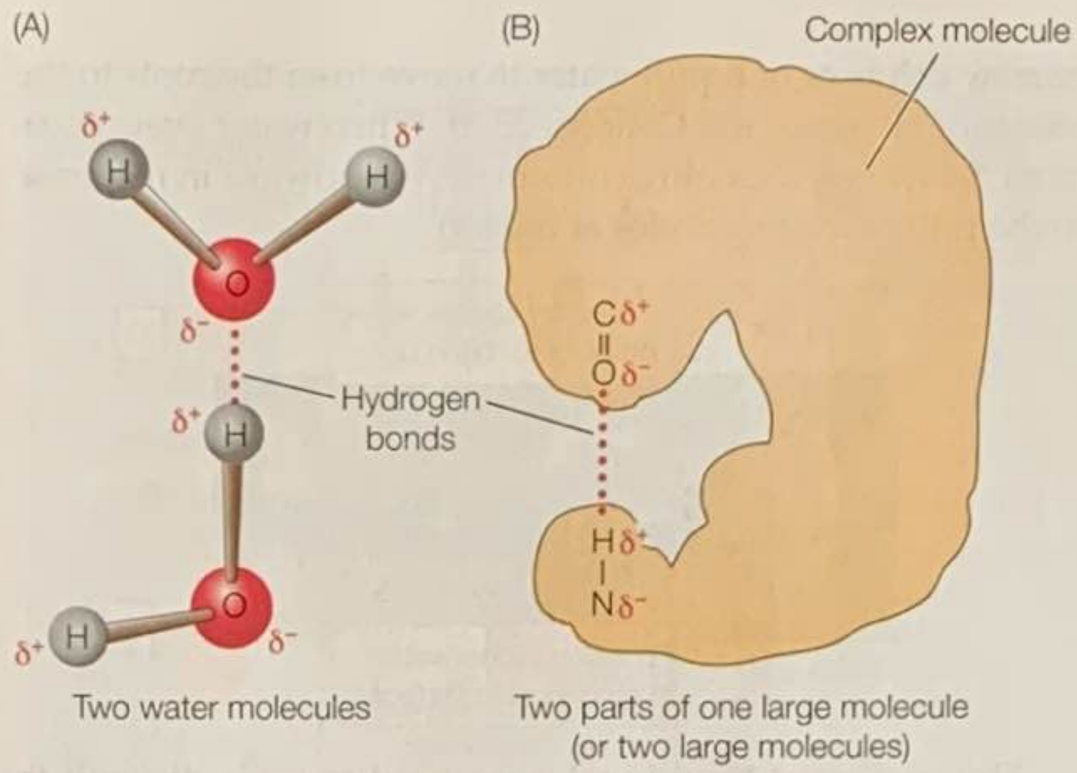


FIGURE 2.4 Hydrogen Bonds Can Form between or within Molecules (A) A hydrogen bond forms between two molecules because of the attraction between an atom with a partial negative charge on one molecule and a hydrogen with a partial positive charge on a second molecule. (B) Hydrogen bonds can form between different parts of the same large molecule.

These multiple hydrogen bonds contribute to the high **heat capacity** of water. Raising the temperature of liquid water takes a lot of heat, because much of the heat energy is used to break the hydrogen bonds that hold the liquid together (indicated by the yellow energy bursts in the liquid water diagram in the previous column). Think of what happens when you apply heat to a pan of water on the stove: it takes a while for the water to begin boiling. The same happens with a living organism—the large amount of water in living tissues shields the organism from fluctuations in environmental temperature.

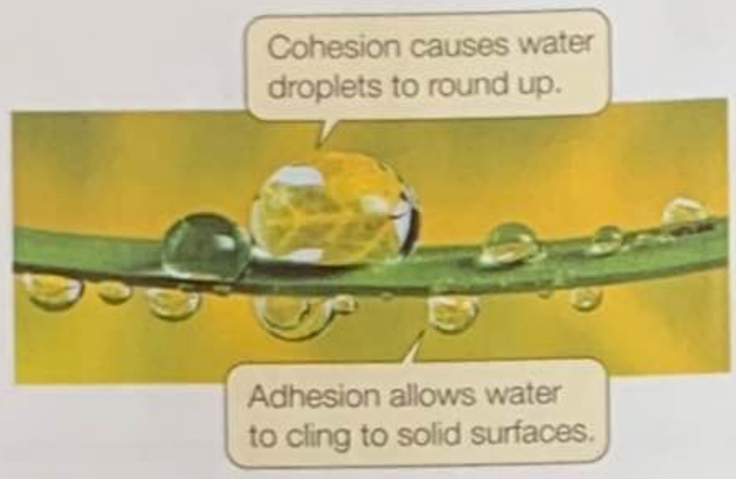
Hydrogen bonding also gives water a high **heat of vaporization**. This means that a lot of heat is required to change water from its liquid to its gaseous state, in the process of evaporation. Once again, much of the heat energy is used to break the many hydrogen bonds between the water molecules. This heat must be absorbed from the environment in contact with the water. Evaporation thus has a cooling effect on the environment—whether a leaf, a forest, or an entire land mass. This effect explains why sweating cools the human body: as sweat evaporates from the skin, it absorbs some of the adjacent body heat.

LINK

Evaporation is important in the physiology of both plants and animals; see **Concepts 25.3 and 29.4**

COHESION, ADHESION, AND SURFACE TENSION The numerous hydrogen bonds that give water a high heat capacity and high heat of vaporization also explain the cohesive strength of liquid water. This cohesive strength, or **cohesion**, is defined as the capacity of water molecules to resist coming apart from one another when placed under tension. Hydrogen bonding between liquid water molecules and the solid surfaces surrounding them also allows for **adhesion** between the water and the solid surfaces. Together, cohesion and adhesion permit

narrow columns of liquid water to move from the roots to the leaves of tall trees (see Concept 25.3). When water evaporates from the leaves, the entire column moves upward in response to the pull of the molecules at the top.



The surface of liquid water exposed to air is difficult to puncture because the water molecules at the surface are hydrogen-bonded to other molecules below them. This **surface tension** permits a container to be filled with water above its rim without overflowing, and it permits spiders to walk on the surface of a pond.

Polar and nonpolar substances: Each interacts best with its own kind

Just as water molecules can interact with one another through hydrogen bonds, any polar molecule can interact with any other polar molecule through the weak (δ^+ to δ^-) attractions of hydrogen bonds. Polar molecules interact with water in this way and are called **hydrophilic** ("water-loving"). In aqueous (watery) solutions, these molecules become separated and surrounded by water molecules (**FIGURE 2.5A**). Thus, water functions as a solvent for polar molecules.

Because they do not have partial charges, nonpolar molecules do not interact with water in this way. Instead, these molecules tend to aggregate with one another. This allows more hydrogen bonds to form between water molecules. Therefore, nonpolar molecules are known as **hydrophobic** ("water-hating"), and the interactions between them are called hydrophobic interactions

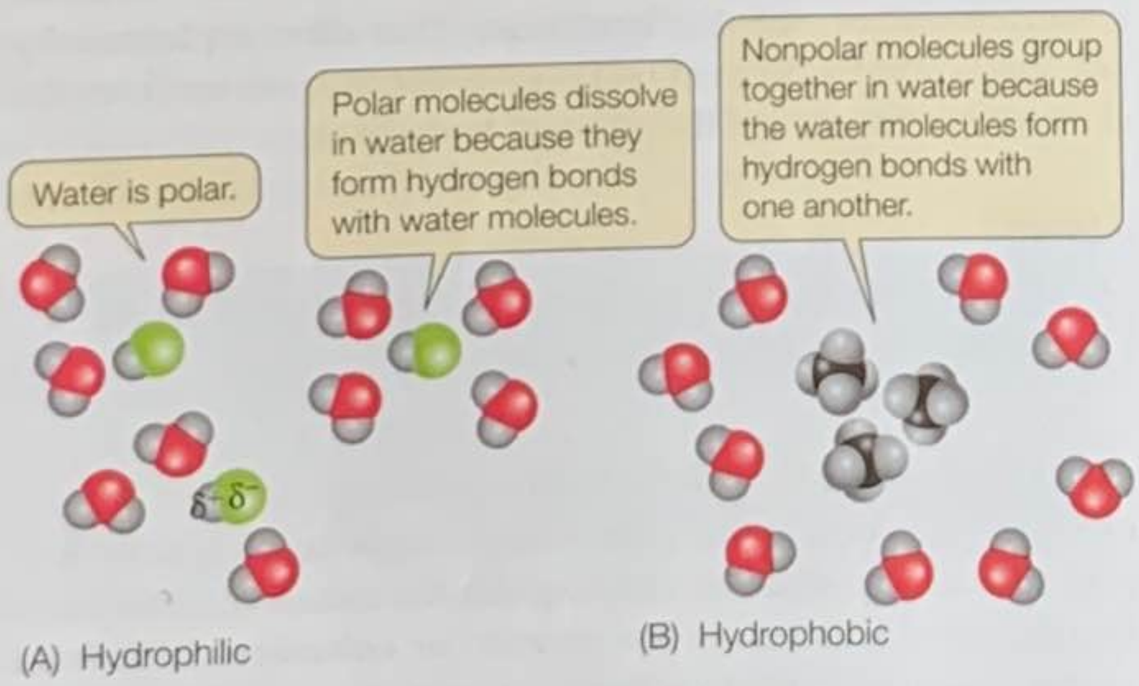


FIGURE 2.5 Hydrophilic and Hydrophobic (A) Molecules with polar covalent bonds are attracted to polar water (they are hydrophilic). (B) Molecules with nonpolar covalent bonds show greater attraction to one another than to water (they are hydrophobic). The color convention in the models shown here (gray, H; red, O; black, C; green, F) is often used.

APPLY THE CONCEPT

Atoms interact and form molecules

The concepts of chemical bonding and electronegativity (see Table 2.2) allow us to predict whether a molecule will be polar or nonpolar, and how it will interact with water. Typically, a difference in electronegativity greater than 0.5 will result in polarity. For each of the bonds below, indicate:

1. Whether the bond is polar or nonpolar
2. If polar, which is the δ^+ end
3. How a molecule with the bond will interact with water (hydrophilic or hydrophobic)

N—H	C—H	C=O	C—N
O—H	C—C	H—H	O—P

(**FIGURE 2.5B**). Hydrophobic substances do not really "hate" water—they can form weak interactions with it, since the electronegativities of the atoms in many nonpolar bonds (e.g., C—H bonds) are not exactly the same. But these interactions are far weaker than the hydrogen bonds between the water molecules, so the nonpolar substances tend to aggregate.

Ionic attractions form between anions and cations

When one interacting atom is much more electronegative than the other (see Table 2.3), a complete transfer of one or more electrons may occur. Consider sodium (11 protons) and chlorine (17 protons). A sodium atom has only one electron in its outermost shell; this condition is unstable. A chlorine atom has seven electrons in its outermost shell—another unstable condition. The most straightforward way for both atoms to achieve stability is to transfer an electron from sodium's outermost shell to that of chlorine (**FIGURE 2.6**). This reaction makes the two atoms more stable because they both have eight electrons in their outer shells. The result is two ions.

An **ion** is an electrically charged particle that forms when an atom gains or loses one or more electrons:

- The sodium ion (Na^+) in our example has a charge of +1 because it has one less electron than it has protons. The outermost electron shell of the sodium ion is stable because it has eight electrons. Positively charged ions are called **cations**.
- The chloride ion (Cl^-) has a charge of –1 because it has one more electron than it has protons. This additional electron gives Cl^- a stable outermost shell with eight electrons. Negatively charged ions are called **anions**.

Ionic attractions form as a result of the electrical attraction between ions bearing opposite charges. Ionic attractions result in stable crystalline structures that are often referred to as ionic compounds or salts. An example is sodium chloride (NaCl; table salt), where cations and anions are held together by ionic attractions. Ionic attractions in salt crystals may be stronger, but attractions between ions in solution, as occur in living systems, are typically weak (see Table 2.1).

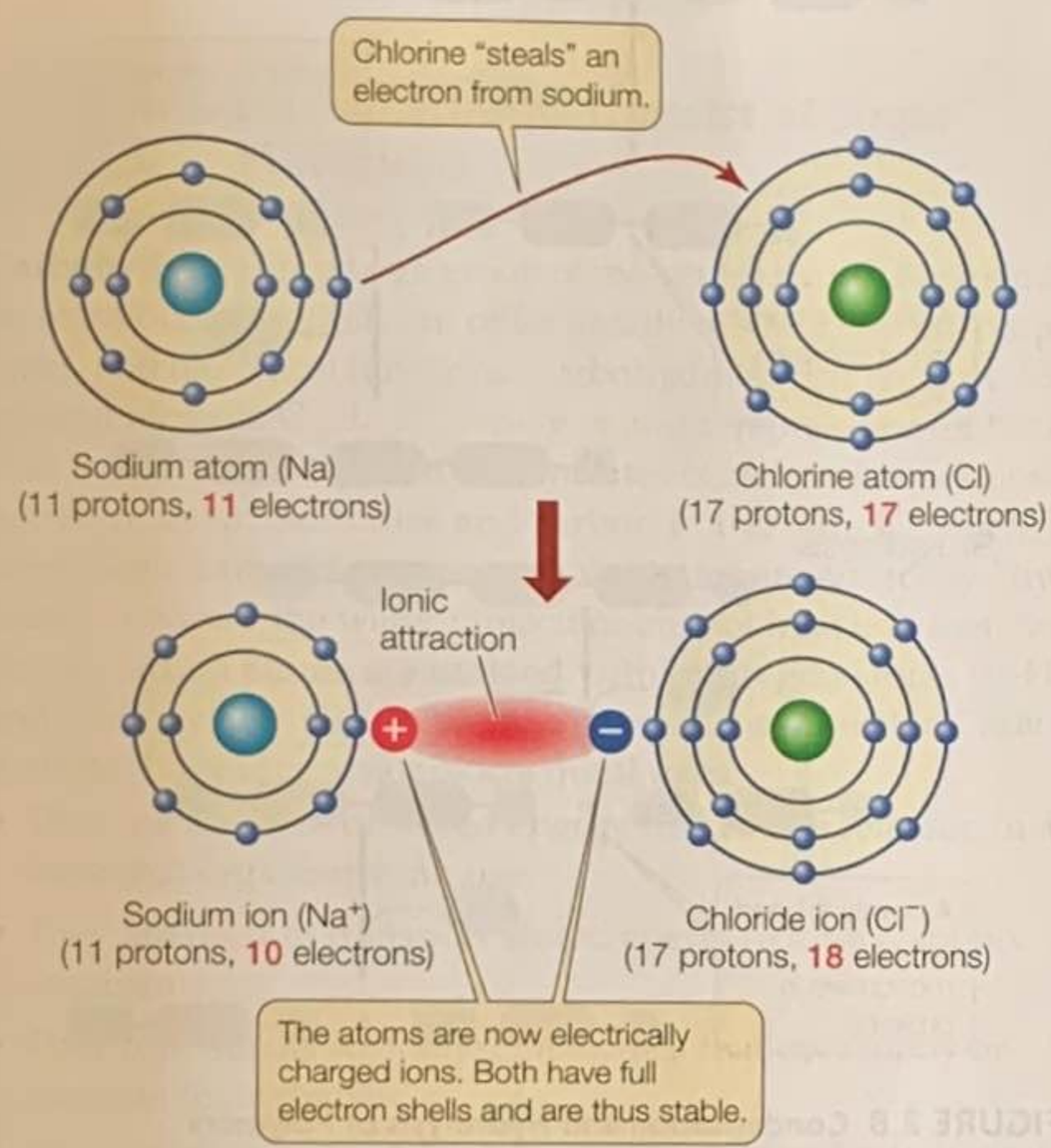
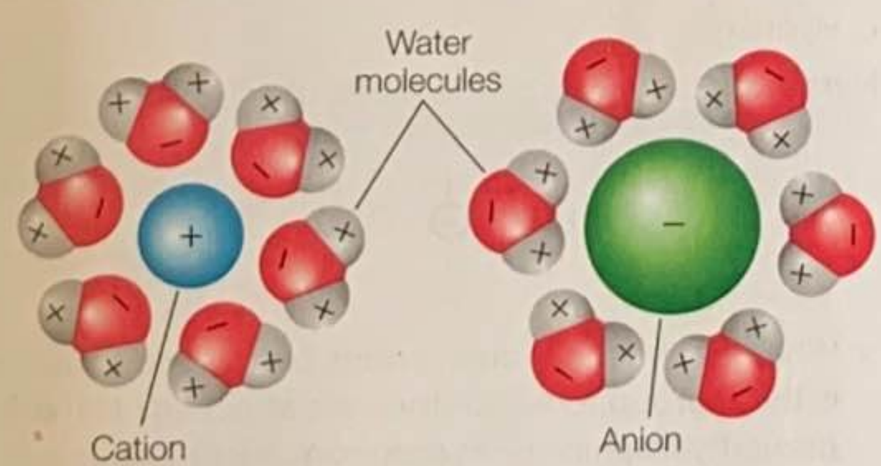


FIGURE 2.6 Ionic Attraction between Sodium and Chlorine When a sodium atom reacts with a chlorine atom, the chlorine fills its outermost shell by "stealing" an electron from the sodium. In so doing, the chlorine atom becomes a negatively charged chloride ion (Cl^-). With one less electron, the sodium atom becomes a positively charged sodium ion (Na^+).

Given that living organisms consist of about 70 percent water, most biological processes occur in the presence of water. Because ionic attractions are weak, salts dissolve in water; the ions separate from one another and become surrounded by water molecules. The water molecules are oriented with their negative poles nearest to the cations and their positive poles nearest to the anions:



Functional groups confer specific properties to biological molecules

Certain small groups of atoms, called **functional groups**, are consistently found together in very different biological molecules. You will encounter several functional groups repeatedly in your study of biology (**FIGURE 2.7**). Each functional group has specific chemical properties (for example, polarity), and when attached to a larger molecule, it gives those properties to the larger molecule. The consistent chemical behavior of functional groups helps us understand the properties of the molecules that contain them.

Functional group	Class of compounds and an example	Properties
Hydroxyl	Alcohols Ethanol	Polar. Hydrogen bonds with water to help dissolve molecules. Enables linkage to other molecules by condensation (see Figure 2.8).
Aldehyde	Aldehydes Acetaldehyde	C=O group is very reactive. Important in building molecules and in energy-releasing reactions.
Keto	Ketones Acetone	C=O group is important in carbohydrates and in energy reactions.
Carboxyl	Carboxylic acids Acetic acid	Acidic. Ionizes in living tissues to form $-COO^-$ and H^+. Enters into condensation reactions by giving up $-OH$. Some carboxylic acids important in energy-releasing reactions.
Amino	Amines Methylamine	Basic. Accepts H^+ in living tissues to form $-NH_3^+$. Enters into condensation reactions by giving up H.
Phosphate	Organic phosphates 3-Phosphoglycerate	Acidic. Enters into condensation reactions by giving up $-OH$. When bonded to another phosphate, hydrolysis releases much energy.
Sulfhydryl	Thiols Mercaptoethanol	By giving up H, two $-SH$ groups can react to form a disulfide bridge, thus stabilizing protein structure.

FIGURE 2.7 Functional Groups Important to Living Systems Highlighted in yellow are the seven functional groups most commonly found in biological molecules. "R" represents the rest of the molecule.

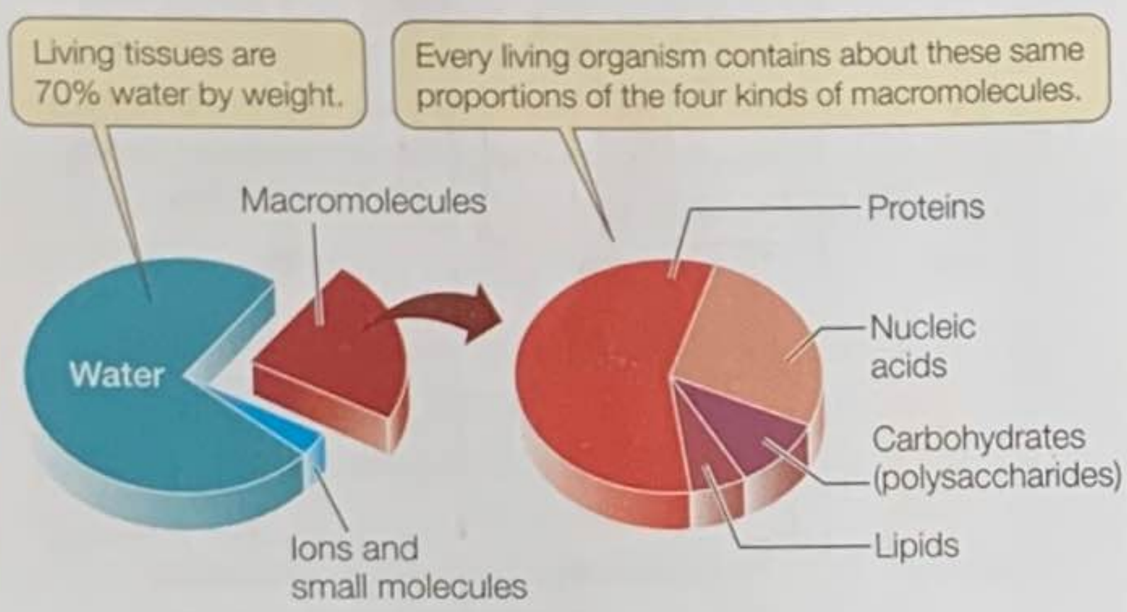
Biological molecules often contain many different functional groups. A single large protein may contain hydrophobic, polar, and charged functional groups. Each group gives a different

specific property to its local site on the protein, and it may interact with another functional group on the same protein or with another molecule. The functional groups thus determine molecular shape and reactivity.

Go to ACTIVITY 2.1 Functional Groups
PoL2e.com/ac2.1

Macromolecules are formed by the polymerization of smaller molecules

Large molecules, called **macromolecules**, are formed by covalent linkages between smaller molecules. Four kinds of macromolecules are characteristic of living things: proteins, carbohydrates, nucleic acids, and lipids.



With the exception of small carbohydrates and lipids, these biological molecules are **polymers** (*poly*, "many"; *mer*, "unit") constructed by the covalent bonding of smaller molecules called **monomers**.

- *Proteins* are formed from different combinations of 20 amino acids, all of which share chemical similarities.
- *Carbohydrates* can be giant molecules, and are formed by linking together chemically similar sugar monomers (monosaccharides) to form polysaccharides.
- *Nucleic acids* are formed from four kinds of nucleotide monomers linked together in long chains.
- *Lipids* also form large structures from a limited set of smaller molecules, but in this case noncovalent forces maintain the interactions between the lipid monomers.

Polymers are formed and broken down by two types of reactions involving water (**FIGURE 2.8**):

- In **condensation**, the removal of water links monomers together.
- In **hydrolysis**, the addition of water breaks a polymer into monomers.

How the macromolecules function and interact with other molecules depends on the properties of the functional groups in their monomers.

Go to ANIMATED TUTORIAL 2.2
Macromolecules: Carbohydrates and Lipids
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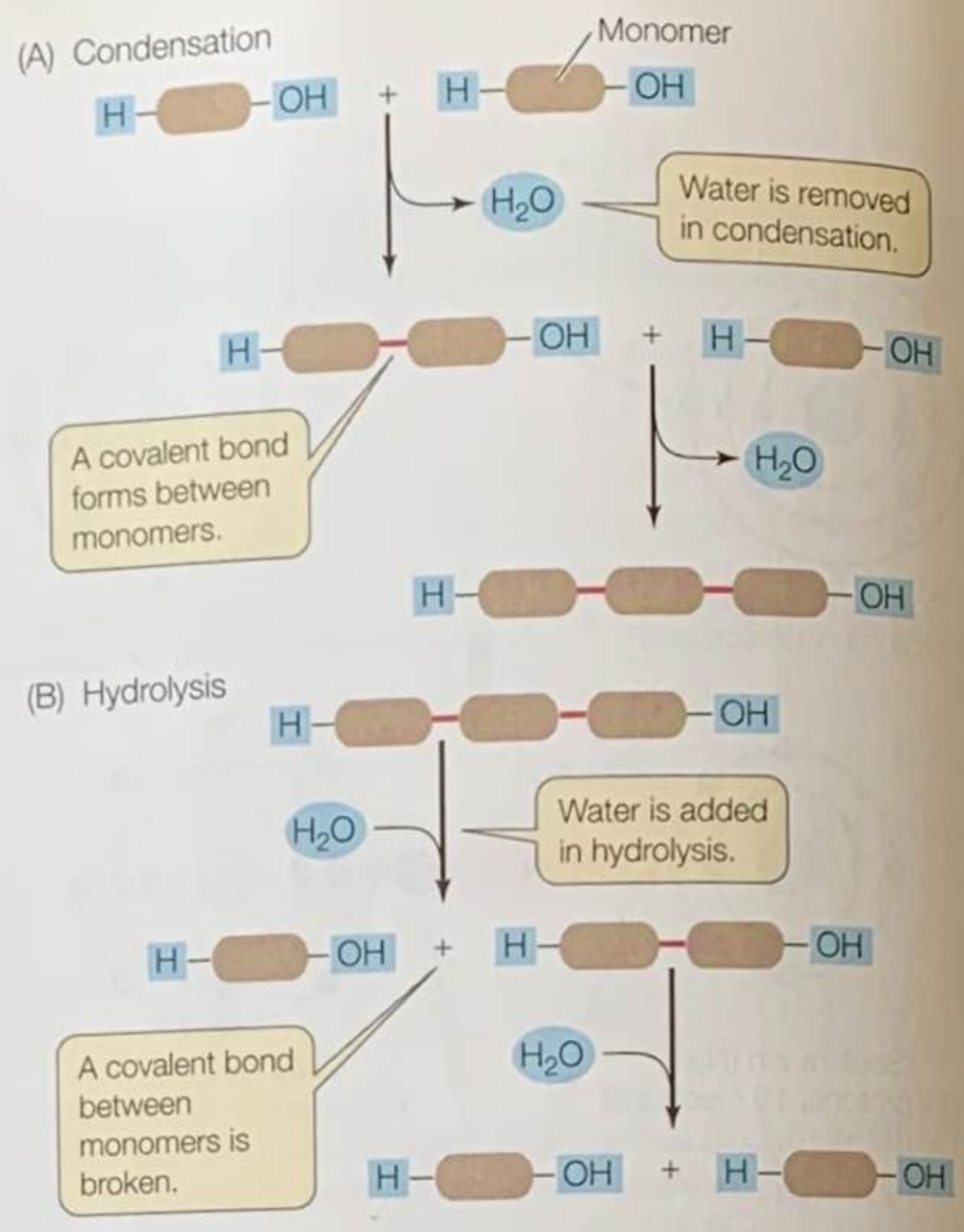


FIGURE 2.8 Condensation and Hydrolysis of Polymers
(A) Condensation reactions link monomers into polymers and produce water. (B) Hydrolysis reactions break polymers into individual monomers and consume water.

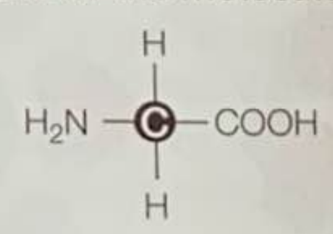
CHECKpoint CONCEPT 2.2

✓ How do differences in electronegativity result in the unequal sharing of electrons in polar molecules?

✓ Some functional groups (see Figure 2.7) can either donate or accept hydrogen bonds with other molecules, acting either as a donor (like the oxygen in a water molecule) or as an acceptor (like the hydrogens in a water molecule). For each of the following, is it an H-bond donor, acceptor, both, or neither?

a. Aldehyde
b. Amino
c. Hydroxyl

✓ Here is the structure of the molecule glycine:



a. What are the functional groups on this molecule? What is the R group to which they are attached? Is the R group hydrophilic or hydrophobic? Explain.
b. Draw two glycine molecules and show how they can be linked by a condensation reaction.

✓ The boiling point (the temperature at which a liquid vaporizes) of water (H_2O) is 100°C, whereas the boiling point of methane (CH_4) is −161°C. Explain this difference in terms of hydrogen bonding between molecules.

We will begin our discussion of the molecules of life with carbohydrates, as they exemplify many of the chemical principles we have outlined so far.

CONCEPT 2.3 Carbohydrates Consist of Sugar Molecules

Carbohydrates are a large group of molecules that all have similar atomic compositions but differ greatly in size, chemical properties, and biological functions. Carbohydrates usually have the general formula $C_mH_{2n}O_n$, where m and n represent numbers. This makes them appear to be hydrates of carbon [associations between water molecules and carbon in the ratio $C_m(H_2O)_n$], hence their name. However, carbohydrates are not really "hydrates" because the water molecules are not intact. Rather, the linked carbon atoms are bonded with hydrogen atoms (—H) and hydroxyl groups (—OH), the components of water. Carbohydrates have four major biochemical roles:

- They are a source of stored energy that can be released in a form that organisms can use.
- They are used to transport stored energy within complex organisms.
- They function as structural molecules that give many organisms their shapes.
- They serve as recognition or signaling molecules that can trigger specific biological responses.

Some carbohydrates are relatively small, such as the simple sugars (for example, glucose) that are the primary energy source for many organisms. Others are large polymers of simple sugars; an example is starch, which is stored in seeds.

Monosaccharides are simple sugars

Monosaccharides (*mono*, "one") are relatively simple molecules with up to seven carbon atoms. They differ in their arrangements of carbon, hydrogen, and oxygen atoms (**FIGURE 2.9**).

Pentoses (*pente*, "five") are five-carbon sugars. Two pentoses are of particular biological importance: the backbones of the nucleic acids RNA and DNA contain ribose and deoxyribose, respectively.

LINK

For a description of the nucleic acids RNA and DNA see Concept 3.1

The hexoses (*hex*, "six") all have the formula $C_6H_{12}O_6$. They include glucose, fructose (so named because it was first found in fruits), mannose, and galactose.

Go to ACTIVITY 2.2 Forms of Glucose
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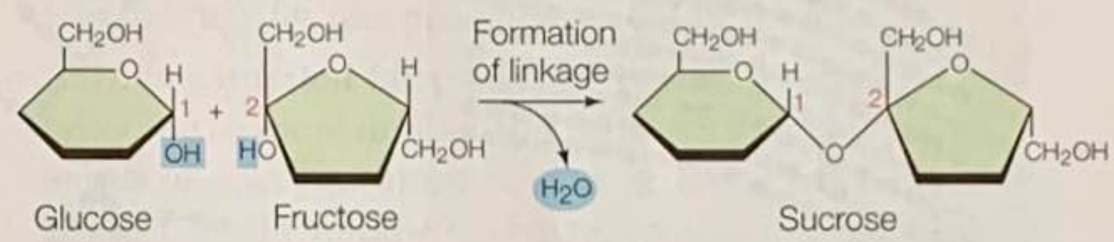
Glycosidic linkages bond monosaccharides

The disaccharides, oligosaccharides, and polysaccharides are all constructed from monosaccharides that are covalently bonded by condensation reactions that form **glycosidic linkages**. A single glycosidic linkage between two monosaccharides forms a **disaccharide**. For example, sucrose—common table sugar—is a major disaccharide formed in plants from a glucose molecule and a fructose molecule (see Figure 2.9 for complete structures):



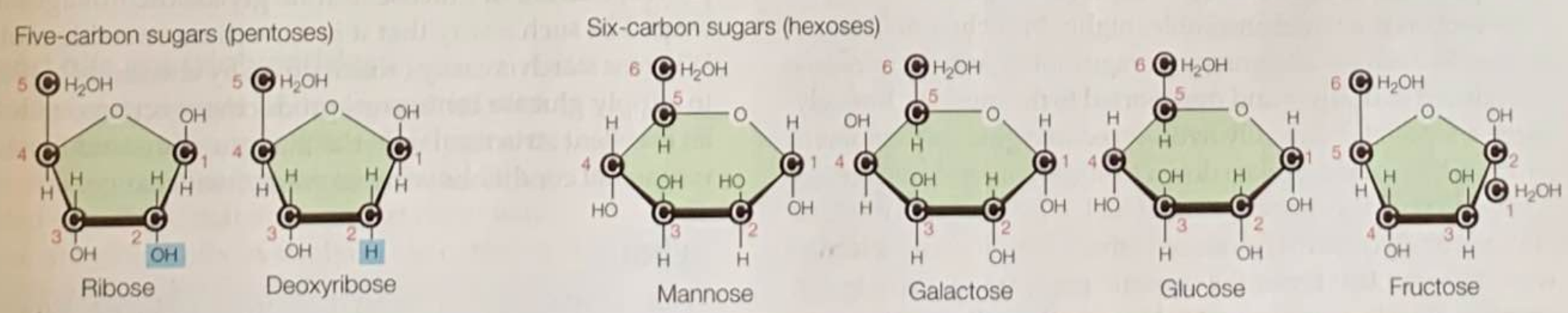
Another disaccharide is maltose, which is formed from two glucose units and is a product of starch digestion. Maltose is an important carbohydrate for making beer.

Oligosaccharides contain several monosaccharides bound together by glycosidic linkages. Many oligosaccharides have additional functional groups, which give them special properties. Oligosaccharides are often covalently bonded to proteins and lipids on the outer surfaces of cells, where they serve as recognition signals. For example, the different human blood groups (the ABO blood types) get their specificity from oligosaccharide chains.

Polysaccharides store energy and provide structural materials

Polysaccharides are large polymers of monosaccharides connected by glycosidic linkages (**FIGURE 2.10**). Polysaccharides are not necessarily linear chains of monomers. Each monomer unit has several sites that are capable of forming glycosidic linkages, and thus branched molecules are possible.

FIGURE 2.9 Monosaccharides Monosaccharides are made up of varying numbers of carbons. Many have the same kind and number of atoms, but the atoms are arranged differently.

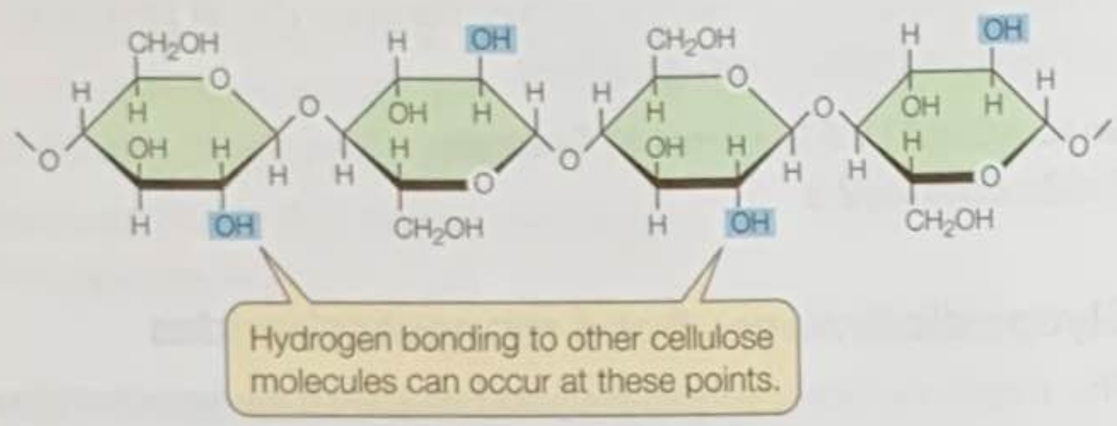


Ribose and deoxyribose each have five carbons, but very different chemical properties and biological roles.

These hexoses all have the formula $C_6H_{12}O_6$, but each has distinct biochemical properties.

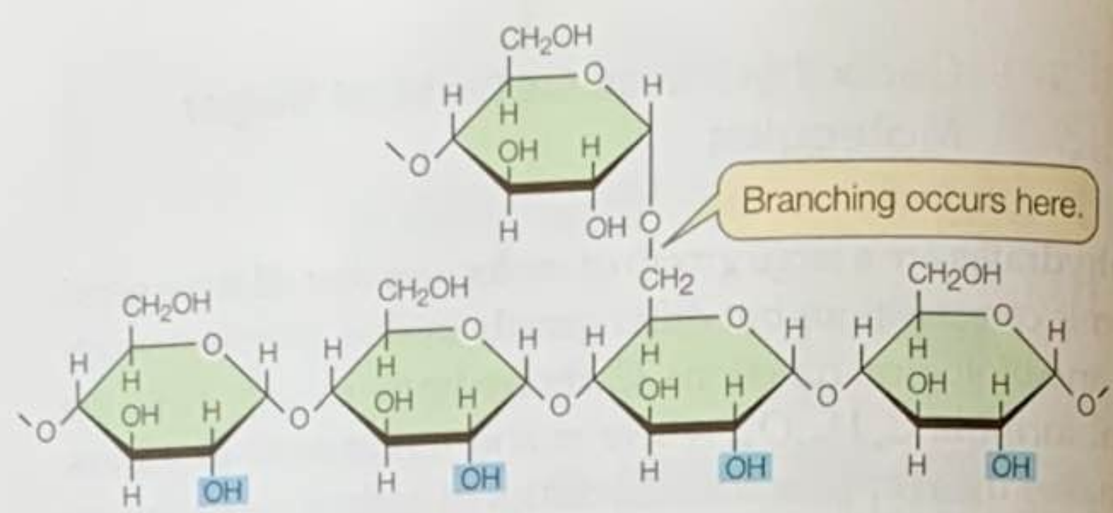
(A) Molecular structure

Cellulose



Cellulose is an unbranched polymer of glucose with linkages that are chemically very stable.

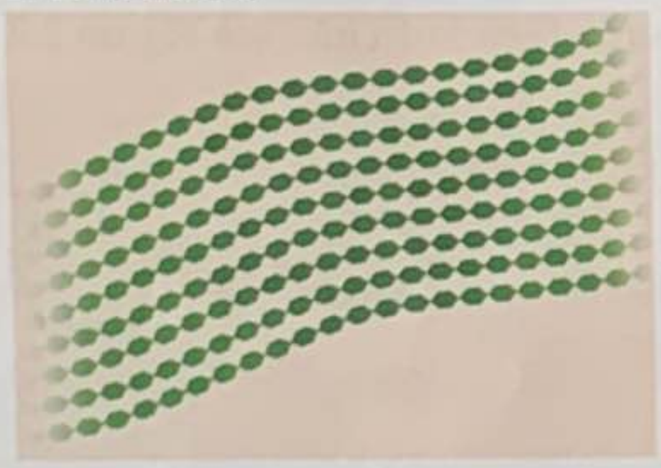
Starch and glycogen



Glycogen and starch are polymers of glucose, with branching at carbon 6 (see Figure 2.9).

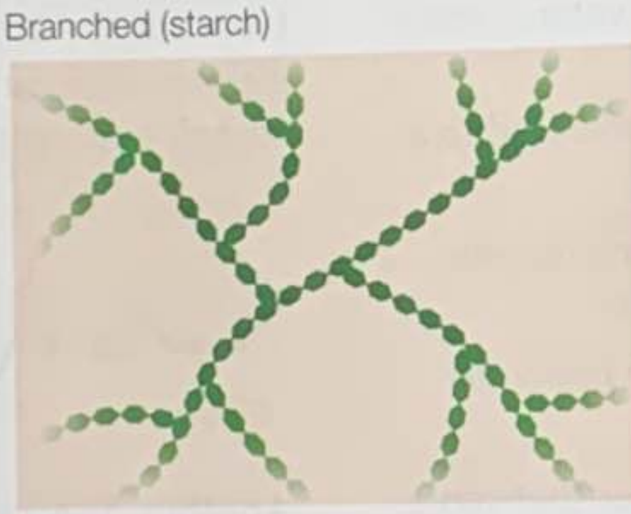
(B) Macromolecular structure

Linear (cellulose)



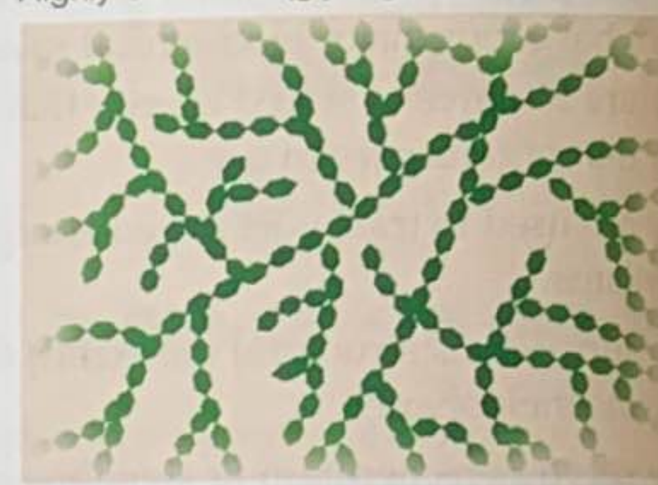
Parallel cellulose molecules form hydrogen bonds, resulting in thin fibrils.

Branched (starch)



Branching limits the number of hydrogen bonds that can form in starch molecules, making starch less compact than cellulose.

Highly branched (glycogen)

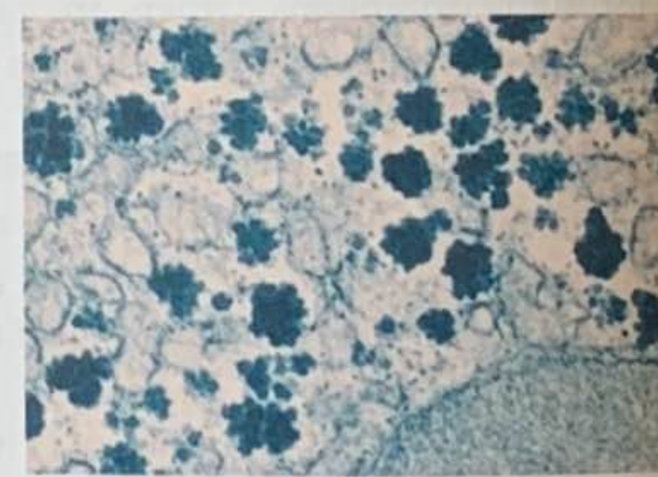


The high amount of branching in glycogen makes its solid deposits more compact than starch.

(C) Polysaccharides in cells

Layers of cellulose fibrils, as seen in this scanning electron micrograph, give plant cell walls great strength. 0.1 μm

Within these potato cells, starch deposits have a granular shape. 15 μm



The dark clumps in this electron micrograph are glycogen deposits in a monkey liver cell. 50 μm

FIGURE 2.10 Polysaccharides Cellulose, starch, and glycogen are all composed of long chains of glucose but with different levels of branching and compaction.

Starches comprise a family of giant molecules that are all polysaccharides of glucose. The different starches can be distinguished by the amount of branching in their polymers. Starch is the principal energy storage compound of plants.

Glycogen is a water-insoluble, highly branched polymer of glucose that is the major energy storage molecule in mammals. It is produced in the liver and transported to the muscles. Both glycogen and starch are readily hydrolyzed into glucose monomers, which in turn can be broken down to liberate their stored energy.

If glucose is the major source of fuel, why store it in the form of starch or glycogen? The reason is that 1,000 glucose molecules would exert 1,000 times the osmotic pressure of a single glycogen molecule, causing water to enter the cells (see Concept 5.2). If it were not for polysaccharides, many organisms would expend a lot of energy expelling excess water from their cells.

As the predominant component of plant cell walls, cellulose is by far the most abundant carbon-containing (organic) compound on Earth. Like starch and glycogen, cellulose is a polysaccharide of glucose, but its glycosidic linkages are arranged in such a way that it is a much more stable molecule. Whereas starch is easily broken down by chemicals or enzymes to supply glucose for energy-producing reactions, cellulose is an excellent structural material that can withstand harsh environmental conditions without substantial change.

LINK

Most animals cannot digest (hydrolyze) cellulose; **Chapter 30** describes adaptations in some animals to use cellulose as an energy source

CHECKpoint CONCEPT 2.3

- ✓ Draw the chemical structure of a disaccharide formed from two glucose monosaccharides.
- ✓ Examine the glucose molecule shown in Figure 2.9. What are the functional groups on the molecule?
- ✓ Notice the large number of hydrogen bonding groups present in the linear structure of cellulose (see Figure 2.10A). Why is this structure so strong?
- ✓ Some sugars have other functional groups in addition to those typically present. Draw the structure of the amino sugar glucosamine, which has an amino group bonded at carbon 2 of glucose. Would this molecule be more or less polar than glucose? Explain why.

We have seen that carbohydrate structure is an example of the monomer–polymer theme in biology. Now we will turn to lipids, which are unusual among the four classes of biological macromolecules in that they are not, strictly speaking, polymers.

CONCEPT 2.4 Lipids Are Hydrophobic Molecules

Lipids—commonly called fats and oils—are hydrocarbons (composed of C and H atoms) that are insoluble in water because of their many nonpolar covalent bonds. As you have seen, nonpolar molecules are hydrophobic and preferentially aggregate together, away from polar water (see Figure 2.5). When nonpolar hydrocarbons are sufficiently close together, weak but additive **van der Waals interactions** (see Table 2.1) hold them together. The huge macromolecular aggregations that can form are not polymers in a strict chemical sense, because the individual lipid molecules are not covalently bonded.

Lipids play several roles in living organisms, including the following:

- They store energy in the C—C and C—H bonds.
- They play important structural roles in cell membranes and on body surfaces, largely because their nonpolar nature makes them essentially insoluble in water.
- Fat in animal bodies serves as thermal insulation.

Fats and oils are triglycerides

The most common units of lipids are **triglycerides**, also known as simple lipids. Triglycerides that are solid at room temperature (around 20°C) are called fats; those that are liquid at room temperature are called oils. A triglyceride contains three fatty acid molecules and one glycerol molecule. **Glycerol** is a small molecule with three hydroxyl (—OH) groups; thus it is an alcohol. A **fatty acid** consists of a long nonpolar hydrocarbon chain attached to the polar carboxyl (—COOH) group, and it is therefore a carboxylic acid. The long hydrocarbon chain is very hydrophobic because of its abundant C—H and C—C bonds.

Synthesis of a triglyceride involves three condensation reactions (**FIGURE 2.11**). The resulting molecule has very little polarity and is extremely hydrophobic. That is why fats and oils do not mix with water but float on top of it in separate globules or layers. The three fatty acids in a single triglyceride molecule need not all have the same hydrocarbon chain length or structure; some may be saturated fatty acids, while others may be unsaturated:

- In a **saturated fatty acid**, all the bonds between the carbon atoms in the hydrocarbon chain are single; there are no double bonds. That is, all the available bonds are saturated with hydrogen atoms (**FIGURE 2.12A**). These fatty acid molecules are relatively rigid and straight, and they pack together tightly, like pencils in a box.
- In an **unsaturated fatty acid**, the hydrocarbon chain contains one or more double bonds. Linoleic acid is an example of a polyunsaturated fatty acid that has two double bonds near the middle of the hydrocarbon chain, causing kinks in the chain (**FIGURE 2.12B**). Such kinks prevent the unsaturated molecules from packing together tightly.

The kinks in fatty acid molecules are important in determining the fluidity and melting point of the lipid. The triglycerides of animal fats tend to have many long-chain saturated fatty acids, which pack tightly together; these fats are usually solid at room temperature and have a high melting point. The triglycerides of plants, such as corn oil, tend to have short or

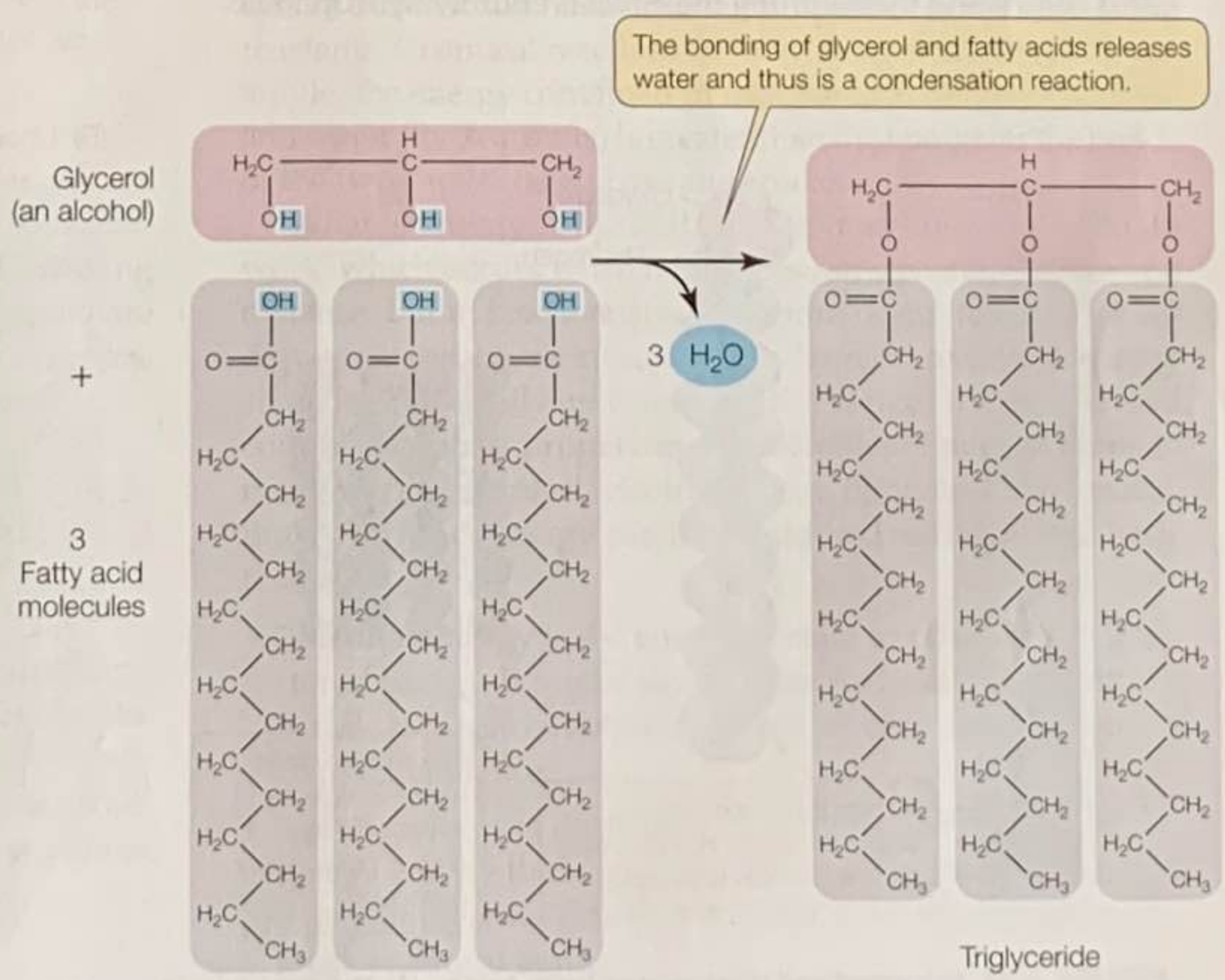


FIGURE 2.11 Synthesis of a Triglyceride In living things, the reaction that forms a triglyceride is more complex than the single step shown here.

unsaturated fatty acids. Because of their kinks, these fatty acids pack together poorly, have low melting points, and are usually liquid at room temperature.

Fats and oils are excellent storehouses for chemical energy. As you will see in Chapter 6, energy is released when these compounds are broken down into smaller molecules. The released energy can be used by an organism for other purposes, such as movement or the synthesis of complex molecules. On a per weight basis, broken-down lipids yield more than twice as much energy as degraded carbohydrates.

Phospholipids form biological membranes

We have mentioned the hydrophobic nature of the many C—C and C—H bonds in a fatty acid. But what about the carboxyl functional group at the end of the molecule? When it ionizes and forms COO^-, it is strongly hydrophilic. So a fatty acid has two opposing chemical properties: a hydrophilic end and a long hydrophobic tail. A molecule that is partly hydrophilic and partly hydrophobic is said to be **amphipathic**.

In triglycerides, a glycerol molecule is bonded to three fatty acid chains and the resulting molecule is entirely hydrophobic. **Phospholipids** are like triglycerides in that they contain fatty acids bound to glycerol. However, in phospholipids, a phosphate-containing compound replaces one of the fatty acids, giving these molecules amphipathic properties (**FIGURE 2.13A**). The phosphate functional group (there are several different kinds in different phospholipids) has a negative electric charge, so this portion of the molecule is hydrophilic, attracting polar water molecules. But the two fatty acids are hydrophobic, so they tend to avoid water and aggregate together or with other hydrophobic substances.

In an aqueous environment, phospholipids line up in such a way that the nonpolar, hydrophobic "tails" pack tightly together and the phosphate-containing "heads" face outward, where they interact with water. The phospholipids thus form a **bilayer**: a sheet two molecules thick, with water excluded from the core (**FIGURE 2.13B**). Although no covalent bonds link individual lipids in these large aggregations, such stable aggregations form readily in aqueous conditions. Biological membranes have this kind of **phospholipid bilayer** structure, and we will devote Chapter 5 to their biological functions.

CHECKpoint CONCEPT 2.4

- ✓ What is the difference between fats and oils?
- ✓ Why are phospholipids amphipathic, and how does this result in a lipid bilayer membrane?
- ✓ If fatty acids are carefully put onto the surface of water, they form a single molecular layer. If the mixture is then shaken vigorously, the fatty acids will form round structures called micelles. Explain these observations.

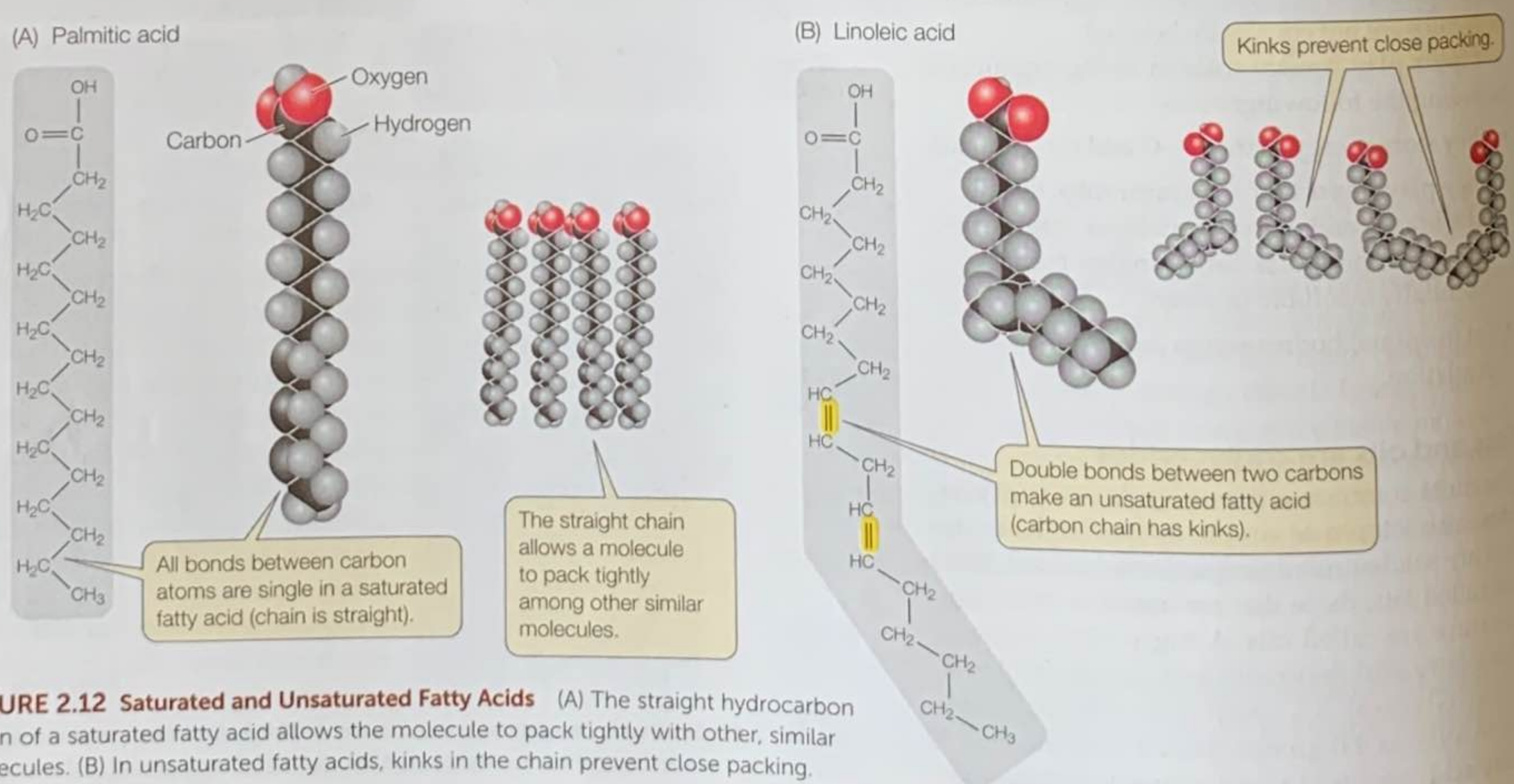


FIGURE 2.12 Saturated and Unsaturated Fatty Acids (A) The straight hydrocarbon chain of a saturated fatty acid allows the molecule to pack tightly with other, similar molecules. (B) In unsaturated fatty acids, kinks in the chain prevent close packing.

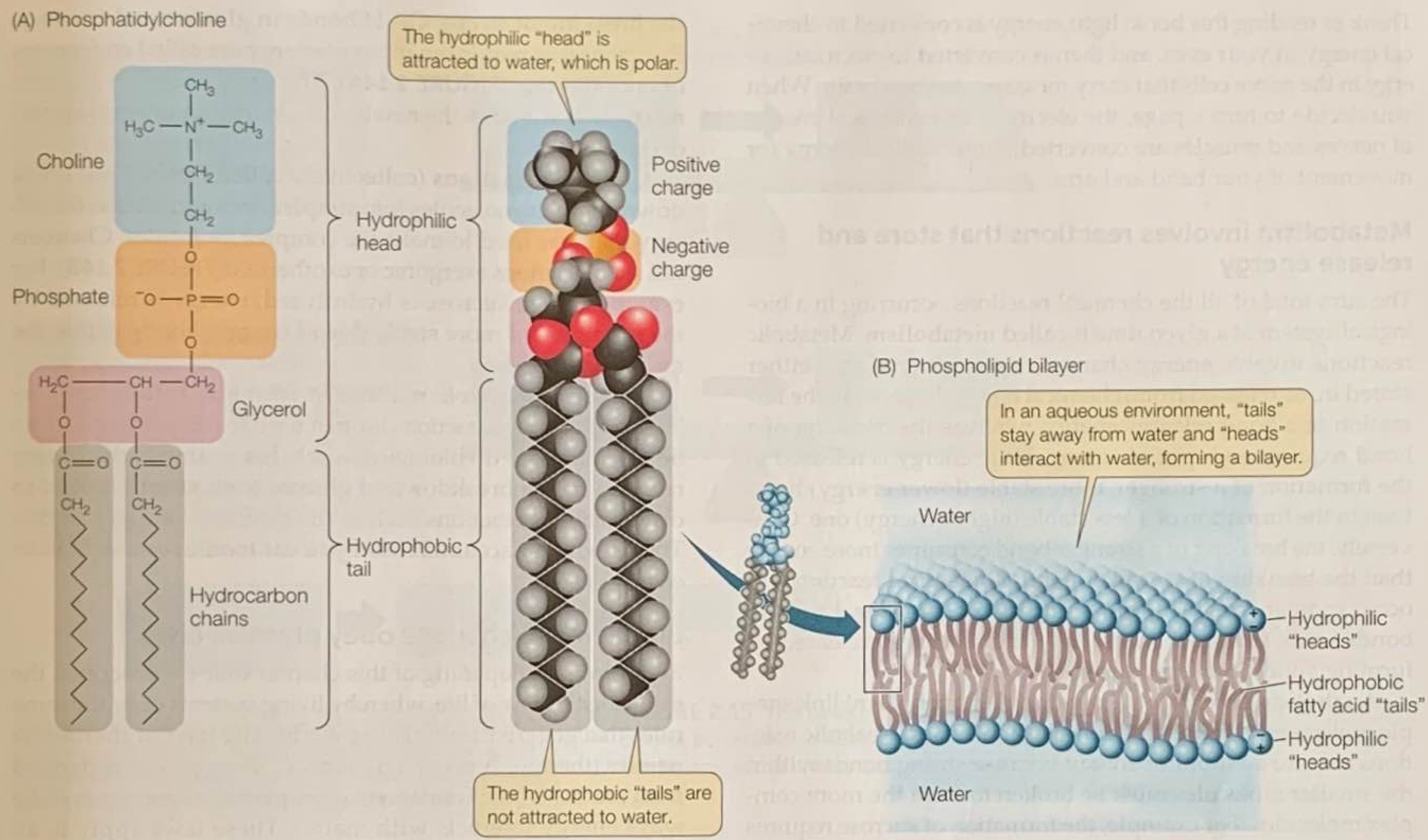


FIGURE 2.13 Phospholipids (A) Phosphatidylcholine (lecithin) is an example of a phospholipid molecule. In other phospholipids, the amino acid serine, the sugar alcohol inositol, or another compound replaces choline. (B) In an aqueous environment, hydrophobic interactions bring the "tails" of phospholipids together in the interior of a bilayer. The hydrophilic "heads" face outward on both sides of the bilayer, where they interact with the surrounding water molecules.

Molecules such as carbohydrates and lipids are not always stable in living systems. Rather, a hallmark of life is its *ability to transform molecules*. This involves making and breaking covalent bonds, as some atoms are removed and others are attached. As part of our introduction to biochemical concepts, we will now turn to these processes of chemical change.

CONCEPT 2.5 Biochemical Changes Involve Energy

A **chemical reaction** occurs when atoms have sufficient energy to combine, or to change their bonding partners. Consider the hydrolysis of the disaccharide sucrose to its component monomers, glucose and fructose (see p. 27 for the chemical structures). We can express this reaction using a chemical equation:

$$\underset{(C_{12}H_{22}O_{11})}{\text{Sucrose}} + H_2O \rightarrow \underset{(C_6H_{12}O_6)}{\text{glucose}} + \underset{(C_6H_{12}O_6)}{\text{fructose}}$$

In this equation, sucrose and water are the **reactants**, and glucose and fructose are the **products**. The reaction proceeds as some bonds in the reactants are broken and new bonds form to make the products. Electrons and protons are transferred from one reactant to the other to form the products. The products of this reaction have different properties from those of the reactants. Chemical reactions involve *changes in energy*; for example, the energy contained in the chemical bonds of sucrose and water (the reactants) is greater than the energy in the bonds of the two products, glucose and fructose.

What is energy? Physicists define it as the capacity to do work, which occurs when a force operates on an object over a distance. But in biochemistry, it is more useful to consider energy as *the capacity for change*. In biochemical reactions, energy changes are usually associated with changes in the chemical composition and properties of molecules. Energy comes in many forms: chemical, electrical, heat, light, and mechanical. But all forms of energy can be considered as one of two basic types:

- **Potential energy** is the energy of state or position—that is, stored energy. It can be stored in many forms: in chemical bonds, as a concentration gradient, or even as an electric charge imbalance.
- **Kinetic energy** is the energy of movement—that is, the type of energy that does work, that makes things change. For example, heat causes molecular motions and can even break chemical bonds.

Potential energy can be converted into kinetic energy and vice versa, and the form that the energy takes can be converted.

Think of reading this book: light energy is converted to chemical energy in your eyes, and then is converted to electrical energy in the nerve cells that carry messages to your brain. When you decide to turn a page, the electrical and chemical energy of nerves and muscles are converted to mechanical energy for movement of your hand and arm.

Metabolism involves reactions that store and release energy

The sum total of all the chemical reactions occurring in a biological system at a given time is called **metabolism**. Metabolic reactions involve energy changes, in which energy is either stored in, or released from, chemical bonds. In general, the formation of a bond releases energy, whereas the breaking of a bond requires an input of energy. More energy is released in the formation of a stronger, more stable (lower energy) bond than in the formation of a less stable (higher energy) one. Conversely, the breaking of a stronger bond consumes more energy than the breaking of a weaker bond. A chemical reaction will occur spontaneously if the total energy consumed by breaking bonds in the reactants is *less than* the total energy released by forming bonds in the products.

Anabolic reactions (collectively called anabolism) link simple molecules to form more complex molecules. Anabolic reactions require an input of energy because strong bonds within the smaller molecules must be broken to form the more complex molecules. For example, the formation of sucrose requires the breaking of strong O—H bonds in glucose and fructose. Reactions that require an input of energy are called endergonic or endothermic (**FIGURE 2.14A**). The energy used in anabolic reactions is stored in the newly formed (higher energy) chemical bonds.

Catabolic reactions (collectively called catabolism) break down complex molecules into simpler ones and release the energy that was used to make the complex molecules. Chemists call such reactions exergonic or exothermic (**FIGURE 2.14B**). For example, when sucrose is hydrolyzed, energy is released by the formation of more stable (lower energy) bonds within the monosaccharides.

Catabolic and anabolic reactions are often linked. The energy released in catabolic reactions is often used to drive anabolic reactions—that is, to do biological work. For example, the energy released by the breakdown of glucose (catabolism) is used to drive anabolic reactions such as the synthesis of triglycerides. That is why fat accumulates if you eat food in excess of your energy needs.

Biochemical changes obey physical laws

Recall from the opening of this chapter that we described the mechanistic view of life, whereby living systems obey the same rules that govern the nonliving world. The **laws of thermodynamics** (thermo, "energy"; dynamics, "change") were derived from studies of the fundamental properties of energy, and the ways energy interacts with matter. These laws apply to all

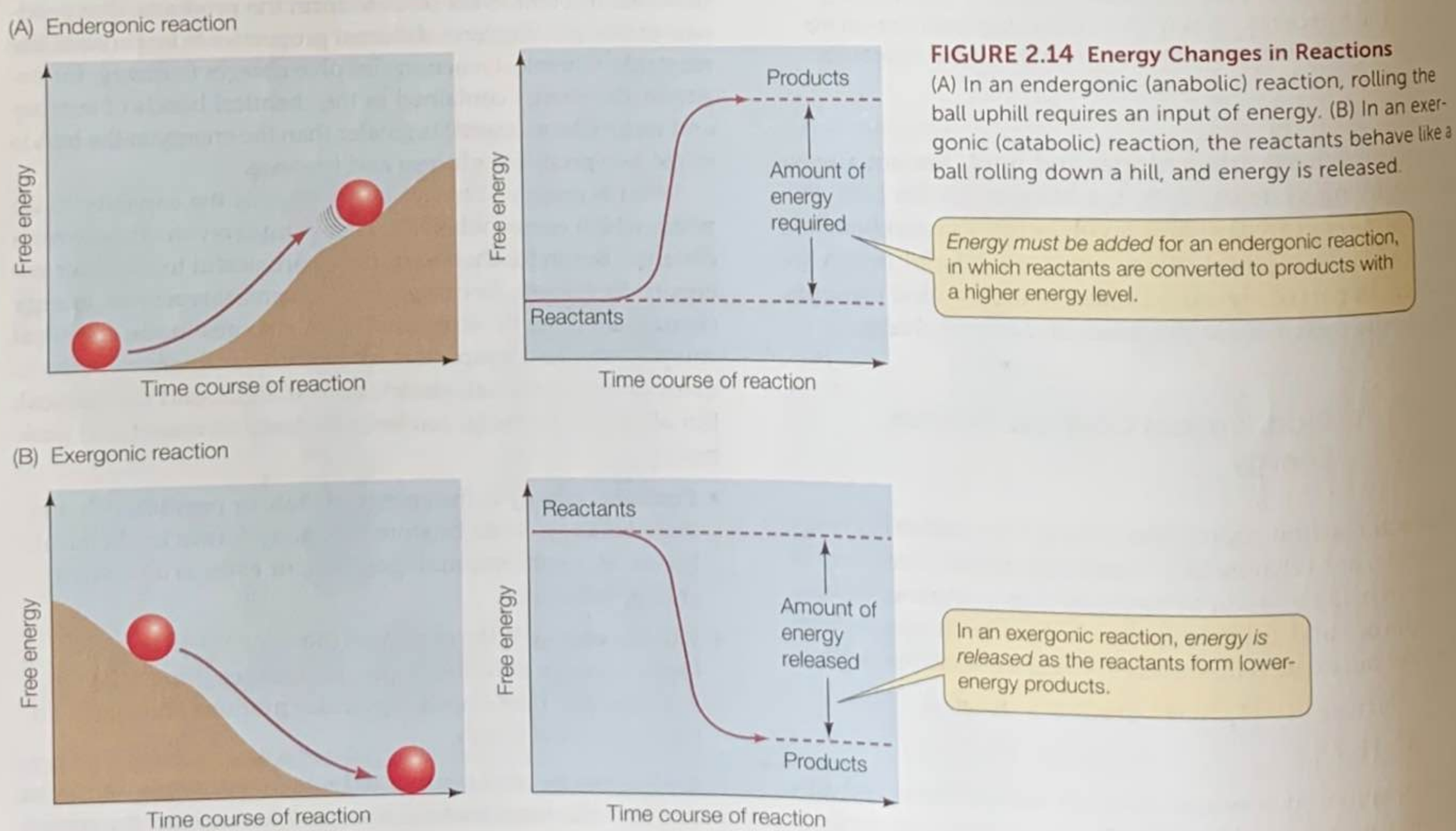
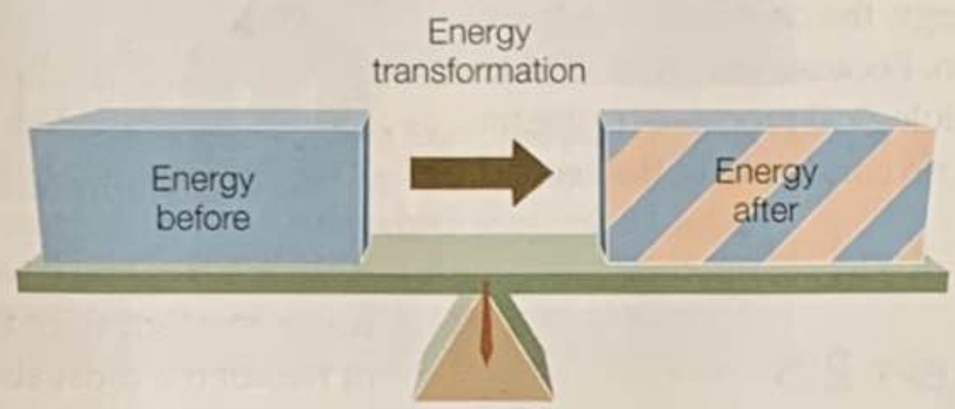


FIGURE 2.14 Energy Changes in Reactions (A) In an endergonic (anabolic) reaction, rolling the ball uphill requires an input of energy. (B) In an exergonic (catabolic) reaction, the reactants behave like a ball rolling down a hill, and energy is released.

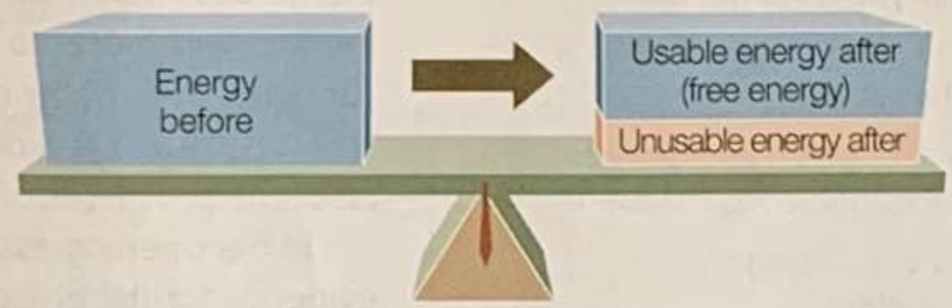
(A)

The First Law of Thermodynamics
The total amount of energy before a transformation equals the total amount after a transformation. No new energy is created, and no energy is lost.



(B)

The Second Law of Thermodynamics
A transformation does not change the total amount of energy within a closed system (one that is not exchanging matter or energy with the surroundings), but after any transformation the amount of energy available to do work (called free energy) is always less than the original amount of energy.



Another statement of the second law is that in a closed system, with repeated energy transformations, free energy decreases and unusable energy (disorder) increases—a phenomenon known as the increase in **entropy**.

FIGURE 2.15 The Laws of Thermodynamics (A) The first law states that energy cannot be created or destroyed. (B) The second law states that after energy transformations, some energy becomes unavailable to do work.

matter and all energy transformations in the universe. Their application to living systems helps us understand how organisms and cells harvest and transform energy to sustain life.

The first law of thermodynamics: Energy is neither created nor destroyed. The first law of thermodynamics states that in any conversion, energy is neither created nor destroyed. Another way of stating this is that the total energy before and after an energy conversion is the same (**FIGURE 2.15A**). [Similarly, matter is also conserved: in the hydrolysis of sucrose (see p. 31), there are 12 carbons, 24 hydrogens, and 12 oxygens on both sides of the equation.]

Although the total amount of energy is conserved, chemical reactions involve changes in the amount of (potential) energy stored in chemical bonds. If energy is released during the reaction, it is available to do work—for example, to drive another chemical reaction. In general, reactions that release energy (catabolic, or exergonic reactions) can occur spontaneously.

The second law of thermodynamics: Useful energy tends to decrease. Although energy cannot be created or destroyed, the second law of thermodynamics implies that when energy is converted from one form to another, some of that energy becomes unavailable for doing work (**FIGURE 2.15B**). In other words, no physical process or chemical reaction is 100 percent efficient; some of the released energy is lost in a form associated with disorder. Think of disorder as a kind of randomness caused by the thermal motion of particles; this energy is so dispersed that it is unusable. **Entropy** is a measure of the disorder in a system.

If a chemical reaction increases entropy, its products are more disordered or random than its reactants. The disorder in a solution of glucose and fructose is greater than that in a solution of sucrose, where the glycosidic bond between the two monosaccharides prevents free movement. Conversely, if there are fewer products and they are more restrained in their movements than the reactants, the disorder is reduced. But this requires an energy input to achieve.

The second law of thermodynamics predicts that, as a result of energy transformations, disorder tends to increase; some energy is always lost to random thermal motion (entropy). Chemical changes, physical changes, and biological processes all tend to increase entropy (see Figure 2.15B), and this tendency gives direction to these processes. Changes in entropy are mathematically related to changes in free energy (the energy available to do work), and thus the second law helps explain why some reactions proceed in one direction rather than another.

How does the second law of thermodynamics apply to organisms? Consider the human body, with its highly organized tissues and organs composed of large, complex molecules. This level of complexity appears to be in conflict with the second law, but for two reasons, it is not. First, the construction of complex molecules also generates disorder. The anabolic reactions needed to construct 1 kg of an animal body require the catabolism of about 10 kg of food. So metabolism creates far more disorder (more energy is lost to entropy) than the amount of order stored in flesh. Second, life requires a constant input of energy

to maintain order. Without this energy, the complex structures of living systems would break down. Because energy is used to generate and maintain order, and biological processes cause an overall increase in entropy, there is no conflict with the second law of thermodynamics.

CHECKpoint CONCEPT 2.5

✓ When you eat a candy bar and then decide to go for a walk, energy transformations take place. Beginning with the food energy in the candy bar, describe the forms of energy used and the changes in energy that occur as you decide to walk and as you do the walking.

✓ What is the difference between anabolism and catabolism? Between endergonic and exergonic reactions?

✓ Predict whether these situations are endergonic or exergonic, and explain your reasoning:

a. The formation of a phospholipid bilayer membrane

b. Turning on a TV set

APPLY THE CONCEPT

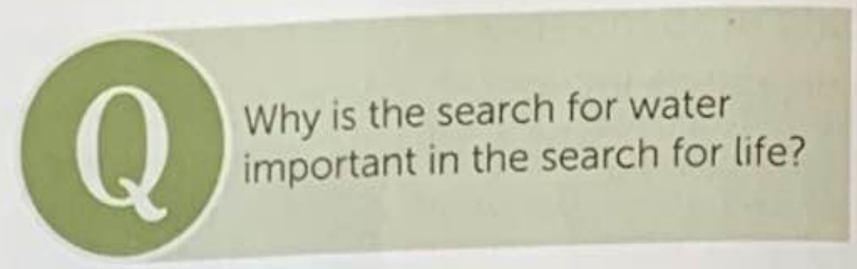
Biochemical changes involve energy

Chemical reactions in living systems involve changes in energy. These can be expressed as changes in available energy, called free energy (designated *G*, for Gibbs—the scientist who first described this parameter). The overall direction of a spontaneous chemical reaction is from higher to lower free energy. In other words, if the $G_{reactants}$ is greater than the $G_{products}$ (negative ΔG; the Greek letter delta stands for "change in" or "difference"), the reaction will be spontaneous; it will tend to go in the direction from reactants to product and release free energy in the process. Reactions where the $G_{reactants}$ is less than the $G_{products}$ (positive ΔG) will occur only if additional free energy is supplied.

The table shows some reactions and the absolute values of their associated free energy changes, $|\Delta G|$ (the vertical lines indicate absolute value).

REACTION	REACTANTS	PRODUCTS	$\|\Delta G\|$
Hydrolysis of sucrose	Sucrose + H_2O	Glucose + fructose	7.0
Triglyceride attachment	Glycerol + fatty acid	Monoglyceride	3.5

1. For each reaction, would you expect ΔG to be positive or negative?
2. Which reactions will be spontaneous? Explain your answer.



Why is the search for water important in the search for life?

ANSWER You have seen throughout this chapter that water is essential for the chemistry of life. Water is composed of two of the most abundant elements (Concept 2.1). Water is a polar molecule (Concept 2.2), which allows biologically important polar molecules such as monosaccharides (Concep 2.3) to dissolve in water. Because they are hydrophobic, lipids interact with water to form important biological structures (Concept 2.4). Water molecules participate directly in the formation and breakdown of polymers (Concept 2.2). In short, all of the processes of life as we know it require water.

In the opening essay of this chapter, we described recent evidence for the presence of water on other bodies in our solar system. Could this water harbor life, now or in the past? One way to investigate this possibility is to study how life on Earth may have originated in an aqueous environment. Geological evidence suggests that Earth was formed about 4.5 billion years ago and that life arose about 3.8 billion years ago. During the time when life originated, there was apparently little oxygen gas (O_2) in the atmosphere. In the 1950s, Stanley Miller and Harold Urey at the University of Chicago set up an experimental "atmosphere" containing various gases thought to be present in Earth's early atmosphere. Among them were ammonia (NH_3), hydrogen (H_2), methane (CH_4), and water vapor (H_2O). Miller and Urey passed an electric spark over the mixture to simulate lightning, providing a source of energy for covalent bond formation. Then they cooled the system so the gases would condense and collect in a watery solution, or "ocean" (**FIGURE 2.16**). Note that water was essential for this experiment as a source of oxygen atoms.

After several days of continuous operation, the system contained numerous complex molecules, including amino acids, the building blocks of proteins. In later experiments the researchers added other gases, such as carbon dioxide (CO_2), nitrogen (N_2), and sulfur dioxide (SO_2). This resulted in the formation of functional groups such as carboxylic acids, fatty acids, and many three- to six-carbon sugars. Taken together, these data suggest a plausible mechanism for the formation of life's chemicals in the aqueous environment of early Earth.

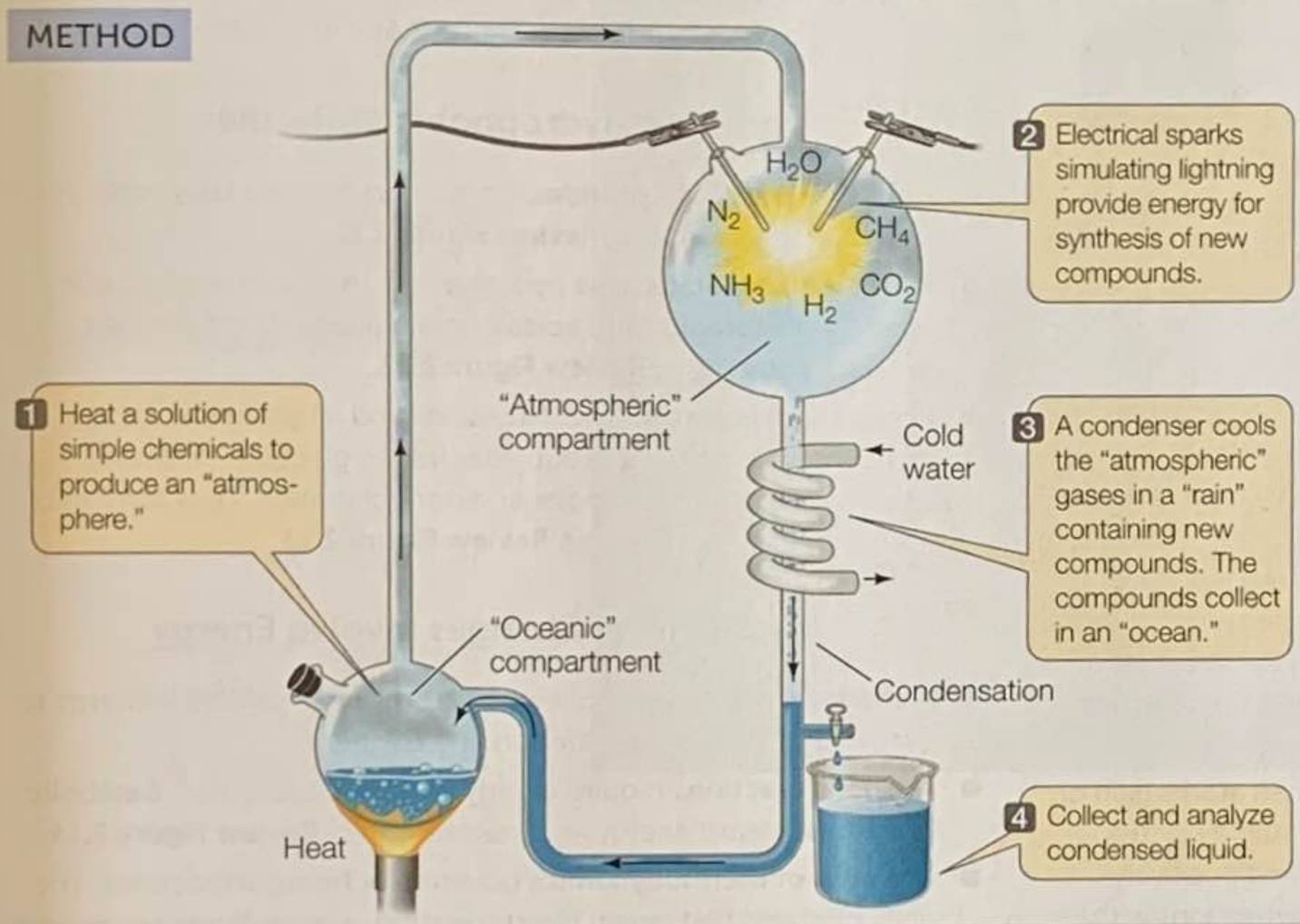
INVESTIGATION

FIGURE 2.16 Miller and Urey Synthesized Prebiotic Molecules in an Experimental Atmosphere With an increased understanding of the atmospheric conditions that existed on primitive Earth, the researchers devised an experiment to see if these conditions could lead to the formation of organic molecules.[a]

HYPOTHESIS

Organic chemical compounds can be generated under conditions similar to those that existed in the atmosphere of primitive Earth.

METHOD



RESULTS

Reactions in the condensed liquid eventually formed organic chemical compounds, including purines, pyrimidines, and amino acids.

CONCLUSION

The chemical building blocks of life could have been generated in the probable atmosphere of early Earth.

ANALYZE THE DATA

The following data show the amount of energy impinging on Earth in different forms.

Source	Energy (cal/[cm^2 × yr])
Total radiation from sun	260,000
Ultraviolet light	199
Wavelength <250 nm	570
Wavelength <200 nm	85
Wavelength <150 nm	3.5
Electric discharges	4
Cosmic rays	0.0015
Radioactivity	0.8
Volcanoes	0.13

A. Only a small fraction of the sun's energy is ultraviolet light (less than 250 nm). What is the rest of the solar energy?

B. The molecules CH_4, H_2O, NH_3, and CO_2 absorb light at wavelengths less than 200 nm. What fraction of total solar radiation is in this range?

C. Instead of electric discharges, what other sources of energy could be used in these experiments?

Go to **LaunchPad** for discussion and relevant links for all **INVESTIGATION** figures.

[a]S. L. Miller and H. C. Urey. 1959. *Science* 130: 245–251.

Go to ANIMATED TUTORIAL 2.3
Synthesis of Prebiotic Molecules
PoL2e.com/at2.3

SUMMARY

CONCEPT 2.1 Atomic Structure Is the Basis for Life's Chemistry

- Matter is composed of atoms. Each **atom** consists of a positively charged **nucleus** made up of **protons** and **neutrons**, surrounded by **electrons** bearing negative charges.
- The number of protons in the nucleus defines an **element**. There are many elements in the universe, but only a few of them (C, H, O, P, N, and S) make up the bulk of living organisms.
- Electrons are distributed in **electron shells** at varying energy levels away from the nucleus. The first shell can have a maximum of 2 electrons; the second shell, 8 electrons; the third shell, 18 electrons; and subsequent shells, 32 electrons. **Review Figure 2.1**

CONCEPT 2.2 Atoms Interact and Form Molecules

- A **chemical bond** is an attractive force that links two atoms together in a molecule. **Review ANIMATED TUTORIAL 2.1**
- A **covalent bond** is a strong bond formed when two atoms share one or more pairs of electrons. **Review Figures 2.2 and 2.3**
- When two atoms of unequal electronegativity bond with each other, a **polar covalent bond** is formed. The two ends, or poles, of the bond have partial charges (δ^+ or δ^-). A **hydrogen bond** is a weak electrical attraction that forms between a δ^+ hydrogen atom in one molecule and a δ^- atom in another molecule (or in another part of a large molecule). Hydrogen bonds are abundant in water. **Review Figure 2.4**
- **Ions** are electrically charged particles that form when atoms gain or lose one or more electrons in order to form more stable electron configurations. **Anions** and **cations** are negatively and positively charged ions, respectively. **Ionic attractions** form when ions with opposite charges attract. **Review Figure 2.6**
- **Functional groups** are covalently bonded groups of atoms that confer specific properties to biological molecules. **Review Figure 2.7**
- **Macromolecules** are formed by polymerization of smaller molecules call **monomers**. **Review Figure 2.8, ANIMATED TUTORIAL 2.2, and ACTIVITY 2.1**

CONCEPT 2.3 Carbohydrates Consist of Sugar Molecules

- **Carbohydrates** contain carbon bonded to hydrogen and oxygen.
- **Monosaccharides** include pentoses (with five carbons) and hexoses (with six carbons). **Review Figure 2.9 and ACTIVITY 2.2**
- Glycosidic linkages are covalent bonds between saccharides. **Disaccharides** such as sucrose each contain two monosaccharides, whereas **polysaccharides** such as starch and cellulose contain long chains of monomers. **Review Figure 2.10**

CONCEPT 2.4 Lipids Are Hydrophobic Molecules

- Fats and oils are **triglycerides**, composed of three **fatty acids** covalently linked to glycerol. **Review Figure 2.11**
- **Saturated fatty acids** have hydrocarbon chains with no double bonds. **Unsaturated fatty acids** contain double bonds in their hydrocarbon chains. **Review Figure 2.12**
- **Phospholipids** contain two fatty acids and a hydrophilic, phosphate-containing polar group attached to glycerol. They are **amphipathic**, with both polar and nonpolar ends. They form into a structural bilayer in water. **Review Figure 2.13**

CONCEPT 2.5 Biochemical Changes Involve Energy

- A **chemical reaction** occurs when atoms have sufficient energy to combine or to change their bonding partners.
- **Anabolic reactions** require energy and are endergonic. **Catabolic reactions** release energy and are exergonic. **Review Figure 2.14**
- The **laws of thermodynamics** govern biochemical reactions. The first law states that in any transformation, energy is neither created nor destroyed. The second law states that useful energy tends to decrease. In other words, **entropy** (disorder) tends to increase. **Review Figure 2.15**

See ANIMATED TUTORIAL 2.3

Go to the Interactive Summary to review key figures, Animated Tutorials, and Activities
PoL2e.com/is2

Go to LaunchPad at **highschool.bfwpub.com/launchpad/pol2e** for additional resources, including LearningCurve Quizzes, Flashcards, and many other study and review resources.

3

Nucleic Acids, Proteins, and Enzymes

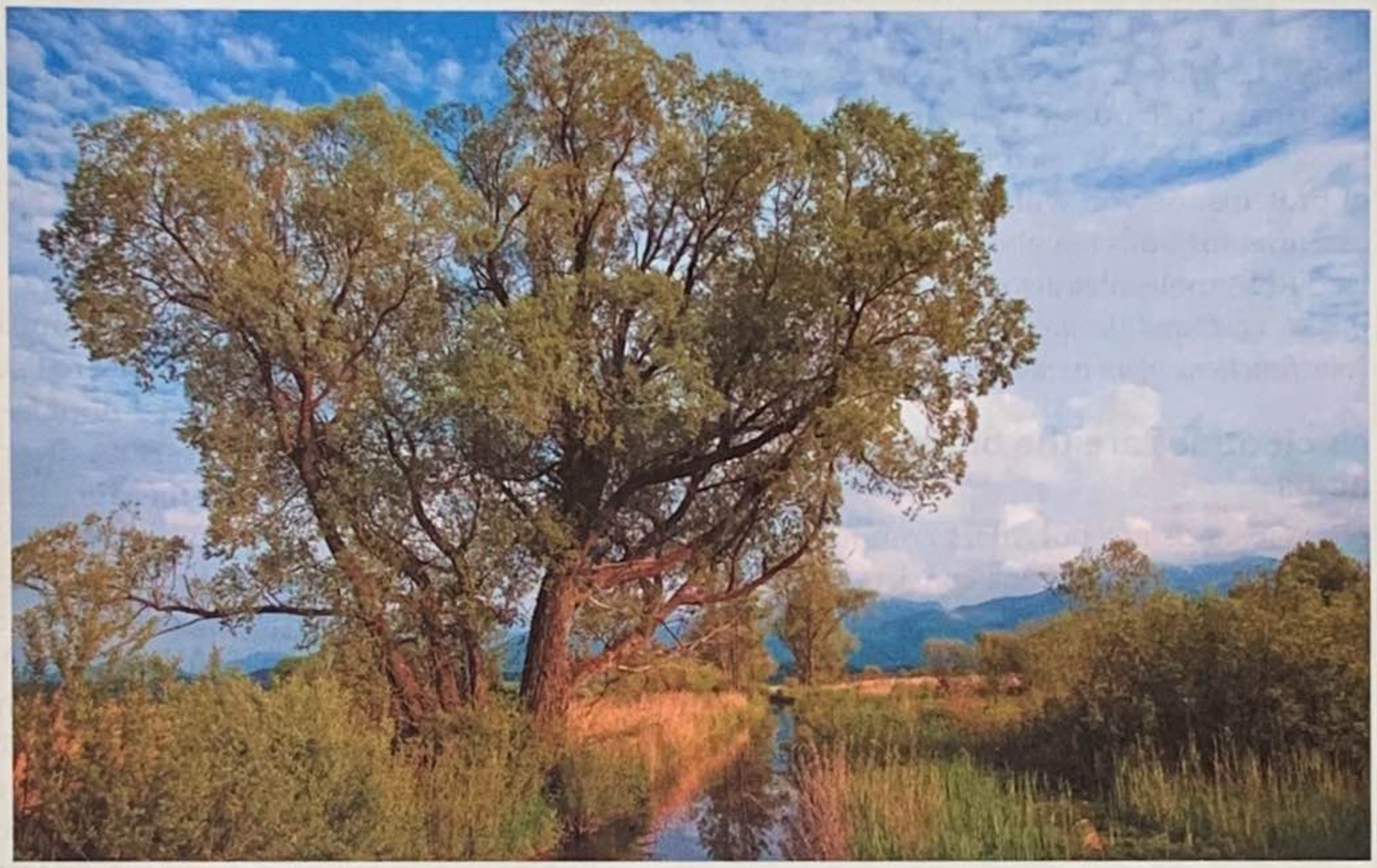
KEY CONCEPTS

3.1 Nucleic Acids Are Informational Macromolecules

3.2 Proteins Are Polymers with Important Structural and Metabolic Roles

3.3 Some Proteins Act as Enzymes to Speed up Biochemical Reactions

3.4 Regulation of Metabolism Occurs by Regulation of Enzymes



The bark of the willow tree (*Salix alba*) was the original source of salicylic acid, later modified to aspirin.

Despite suffering from the "ague," the Reverend Edward Stone went walking in the English countryside. Feverish, tired, with aching muscles and joints, he came across a willow tree. Although apparently unaware that many ancient healers used willow bark extracts to reduce fever, the clergyman knew of the tradition of natural remedies for various diseases. The willow reminded him of the bitter extracts from the bark of South American trees then being sold (at high prices) to treat fevers. Removing some willow bark, Stone sucked on it and found it did indeed taste bitter—and that it relieved his symptoms.

Later he gathered a pound of willow bark and ground it into a powder, which he gave to about 50 people who complained of pain; all said they felt better. Stone reported the results of this "clinical test" in a letter to the Royal Society, England's most respected scientific body. Stone had discovered the main source of salicylic acid, the basis of the most widely used drug in the world. The date of his letter (which still exists) was April 25, 1763.

The chemical structure of salicylic acid (named for *Salix*, the willow genus) was worked out about 70 years later, and soon chemists could synthesize it in the laboratory. Although the compound alleviated pain, its acidity irritated the digestive system. In the late 1890s, the German chemical company Bayer synthesized a milder yet equally effective form, acetylsalicylic acid, which it marketed as aspirin. The new medicine's success launched Bayer to world prominence as a pharmaceutical company, a position it maintains today.

In the 1960s and 1970s, aspirin use declined when two alternative medications, acetaminophen (Tylenol) and ibuprofen (Motrin and Advil), became widely available. But over this same time, clinical studies revealed a new use for aspirin: it is an effective anticoagulant, shown to prevent heart attacks and strokes caused by blood clots. Today many people take a daily low dose of aspirin as a preventive agent against clotting disorders.

Fever, joint pain, headache, blood clots. What do these symptoms have in common? They all are mediated by fatty acid products called prostaglandins and molecules derived from them. Salicylic acid blocks the synthesis of the primary prostaglandin. The biochemical mechanism by which aspirin works was described in 1971. As we will see, an understanding of this mechanism requires an understanding of protein and enzyme function—two subjects of this chapter.

Q How does an understanding of proteins and enzymes help explain how aspirin works?

You will find the answer to this question on page 57.

CONCEPT 3.1 Nucleic Acids Are Informational Macromolecules

Nucleic acids are polymers that store, transmit, and express hereditary (genetic) information. This information is encoded in the sequences of monomers that make up nucleic acids. There are two types of nucleic acids: **DNA** (*d*eoxyribo*n*ucleic *a*cid) and **RNA** (*r*ibo*n*ucleic *a*cid). DNA stores and transmits genetic information. Through RNA intermediates, the information encoded in DNA is used to specify the amino acid sequences of proteins. As you will see later in this chapter, proteins are essential for both metabolism and structure. Certain specialized RNA molecules also play roles in metabolism. Ultimately, *nucleic acids and the proteins encoded by them determine the metabolic functions of an organism.*

Nucleotides are the building blocks of nucleic acids

Nucleic acids are polymers composed of monomers called nucleotides. A **nucleotide** consists of three components: a nitrogen-containing **base**, a pentose sugar, and one to three phosphate groups (**FIGURE 3.1**). Molecules consisting of a pentose sugar and a base—but no phosphate group—are called nucleosides. The nucleotides that make up nucleic acids contain just one phosphate group—they are nucleoside monophosphates.

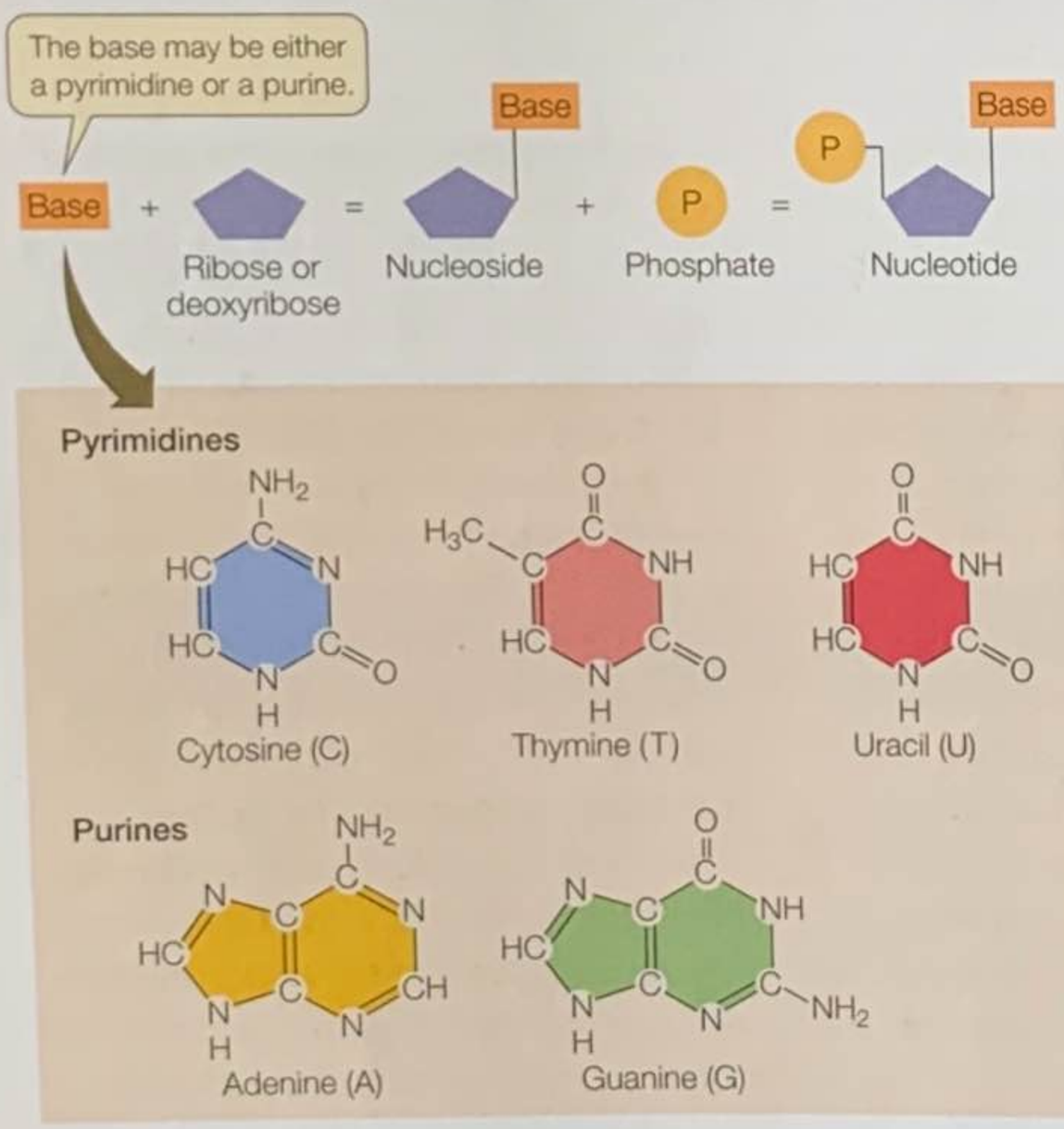


FIGURE 3.1 Nucleotides Have Three Components Nucleotide monomers are the building blocks of DNA and RNA polymers. Nucleotides may have one to three phosphate groups; those in DNA and RNA have one.

Go to ACTIVITY 3.1 Nucleic Acid Building Blocks
PoL2e.com/ac3.1

TABLE 3.1 Distinguishing RNA from DNA

Nucleic acid	Sugar	Bases	Strands
RNA	Ribose	Adenine Cytosine Guanine Uracil	Single
DNA	Deoxyribose	Adenine Cytosine Guanine Thymine	Double

The bases of the nucleic acids take one of two chemical forms: a six-membered single-ring structure called a **pyrimidine**, or a fused double-ring structure called a **purine** (see Figure 3.1). In DNA, the pentose sugar is **deoxyribose**, which differs from the **ribose** found in RNA by the absence of one oxygen atom (see Figure 2.9).

During the formation of a nucleic acid, new nucleotides are added to an existing chain one at a time. The pentose sugar in the last nucleotide of the existing chain and the phosphate on the new nucleotide undergo a condensation reaction (see Figure 2.8) and the resulting linkage is called a **phosphodiester bond**. The phosphate on the new nucleotide is attached to the 5′ (5 prime) carbon atom of its sugar, and the bond occurs between it and the 3′ (3 prime) carbon on the last sugar of the existing chain. Because each nucleotide is added to the 3′ carbon of the last sugar, nucleic acids are said to *grow in the 5′ to 3′ direction* (**FIGURE 3.2**).

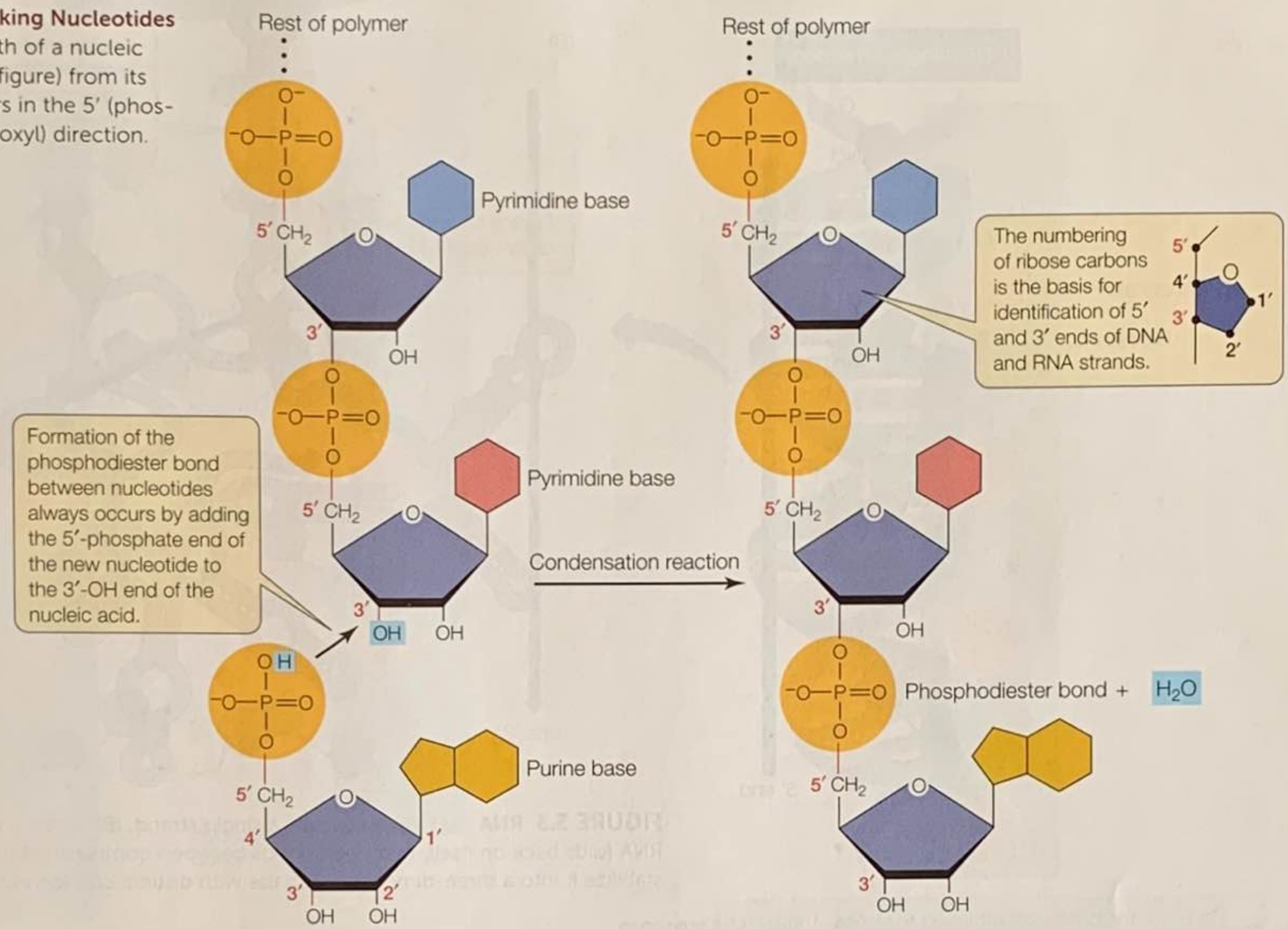
Nucleic acids can be oligonucleotides, with a few to about 20 nucleotide monomers, or longer polynucleotides:

- *Oligonucleotides* include RNA molecules that function as "primers" to begin the duplication of DNA; RNA molecules that regulate the expression of genes; and synthetic DNA molecules used for amplifying and analyzing other, longer nucleotide sequences.
- *Polynucleotides*, more commonly referred to as nucleic acids, include DNA and most RNA. Polynucleotides can be very long, and indeed are the longest polymers in the living world. Some DNA molecules in humans contain hundreds of millions of nucleotides.

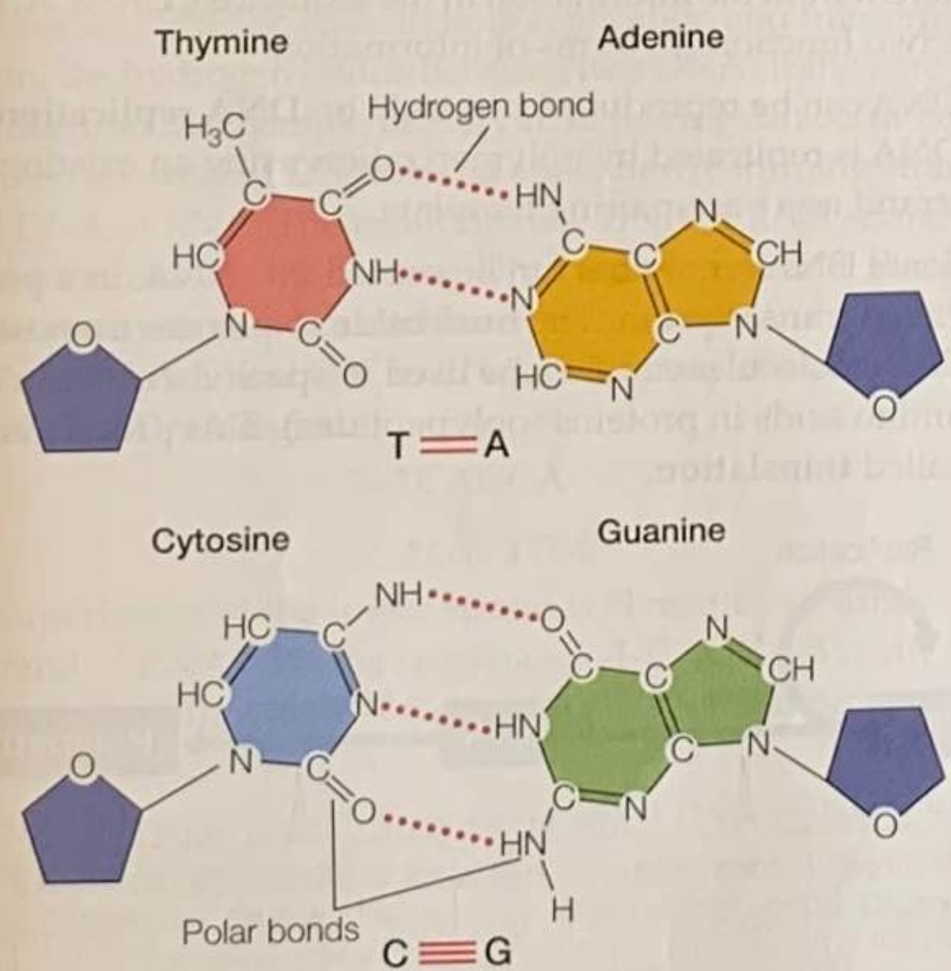
Base pairing occurs in both DNA and RNA

In addition to differing in their sugar groups, DNA and RNA also differ in their bases and general structures (**TABLE 3.1**). Four bases are found in DNA: **adenine** (**A**), **cytosine** (**C**), **guanine** (**G**), and **thymine** (**T**). RNA also contains adenine, cytosine, and guanine, but the fourth base in RNA is **uracil** (**U**) rather than thymine. The lack of a hydroxyl group at the 2′ position of the deoxyribose sugar in DNA makes the structure of DNA less flexible than that of RNA. As we describe below, DNA is composed of two polynucleotide strands whereas RNA is usually single-stranded. However, a long RNA can fold up on itself, forming a variety of structures.

FIGURE 3.2 Linking Nucleotides Together Growth of a nucleic acid (RNA in this figure) from its monomers occurs in the 5′ (phosphate) to 3′ (hydroxyl) direction.



The key to understanding the structure and function of both DNA and RNA is the principle of **complementary base pairing**. In DNA, adenine and thymine always pair (A-T), and cytosine and guanine always pair (C-G):

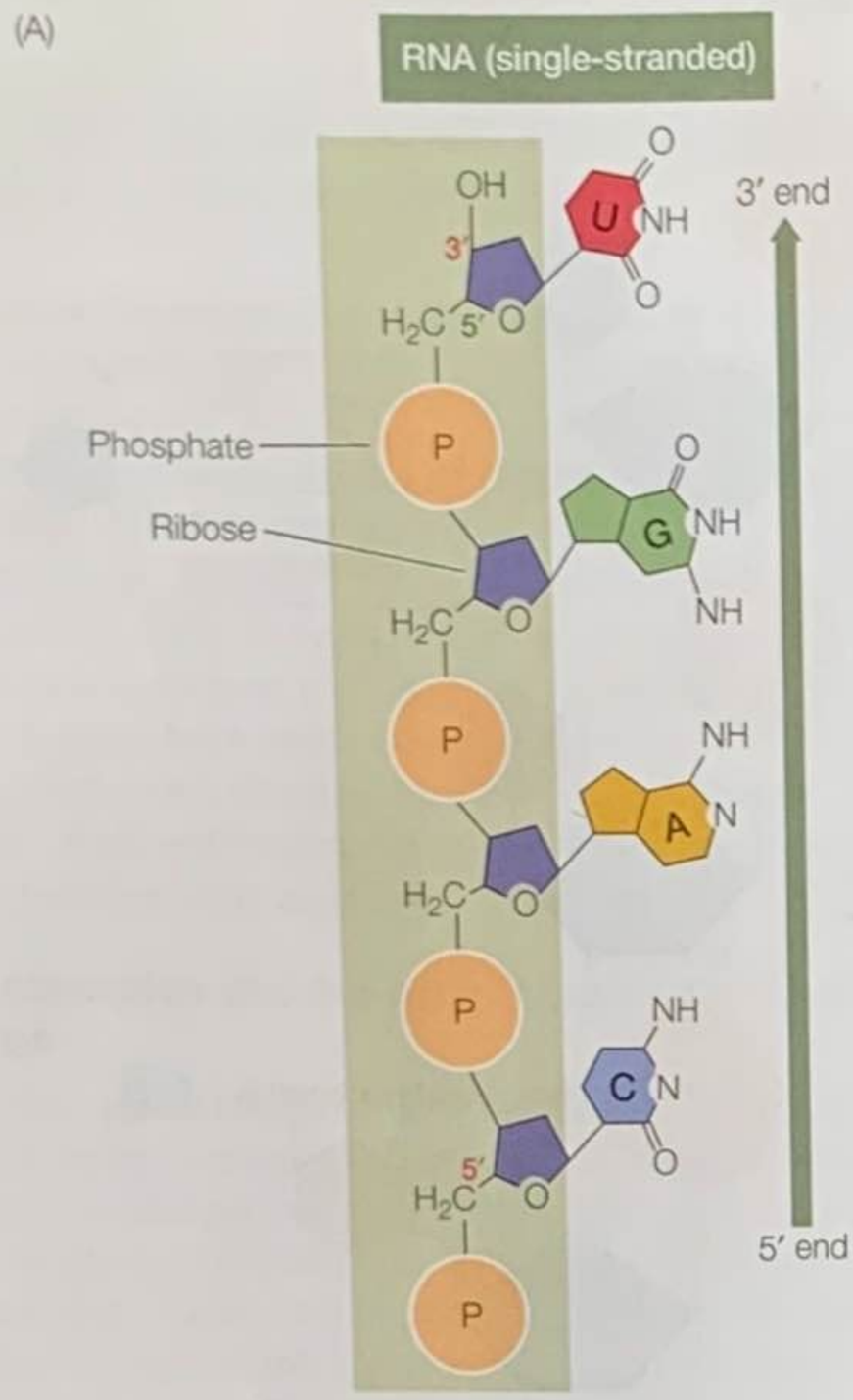


In RNA, the base pairs are A-U and C-G. Base pairs are held together primarily by hydrogen bonds. As you can see, there are polar C=O and N—H covalent bonds in the nucleotide bases (see Concept 2.2 for a discussion of polar covalent bonds). Hydrogen bonds form between the partial negative charge (δ^-) on an oxygen or nitrogen atom of one base, and the partial positive charge (δ^+) on a hydrogen atom of another base. Complementary base pairing occurs because the arrangements of polar bonds in the nucleotide bases favor the pairing of bases as they occur (C with G, and A with U or T).

Individual hydrogen bonds are relatively weak, but there are so many of them in DNA and RNA that collectively they provide a considerable force of attraction. However, this attraction is not as strong as that provided by multiple covalent bonds. This means that base pairs are relatively easy to separate with a modest input of energy. As you will see in Chapters 9 and 10, the breaking and making of hydrogen bonds in nucleic acids is vital to their roles in living systems. Let's now look in a little more detail at the structures of RNA and DNA.

RNA Usually, RNA is single-stranded (**FIGURE 3.3A**). However, many single-stranded RNA molecules fold up into three-dimensional structures, because of hydrogen bonding between nucleotides in separate portions of the molecules (**FIGURE 3.3B**). An RNA strand can also fold back on itself to form a double-stranded helix. This results in a three-dimensional surface for the bonding and recognition of other molecules. It is important to realize that this folding occurs by complementary base pairing, and the structure is thus determined by the particular order of bases in the RNA molecule.

DNA Usually, DNA is double-stranded; that is, it consists of two separate polynucleotide strands of the same length



In RNA, the bases are attached to ribose. The bases in RNA are the purines adenine (A) and guanine (G) and the pyrimidines cytosine (C) and uracil (U).

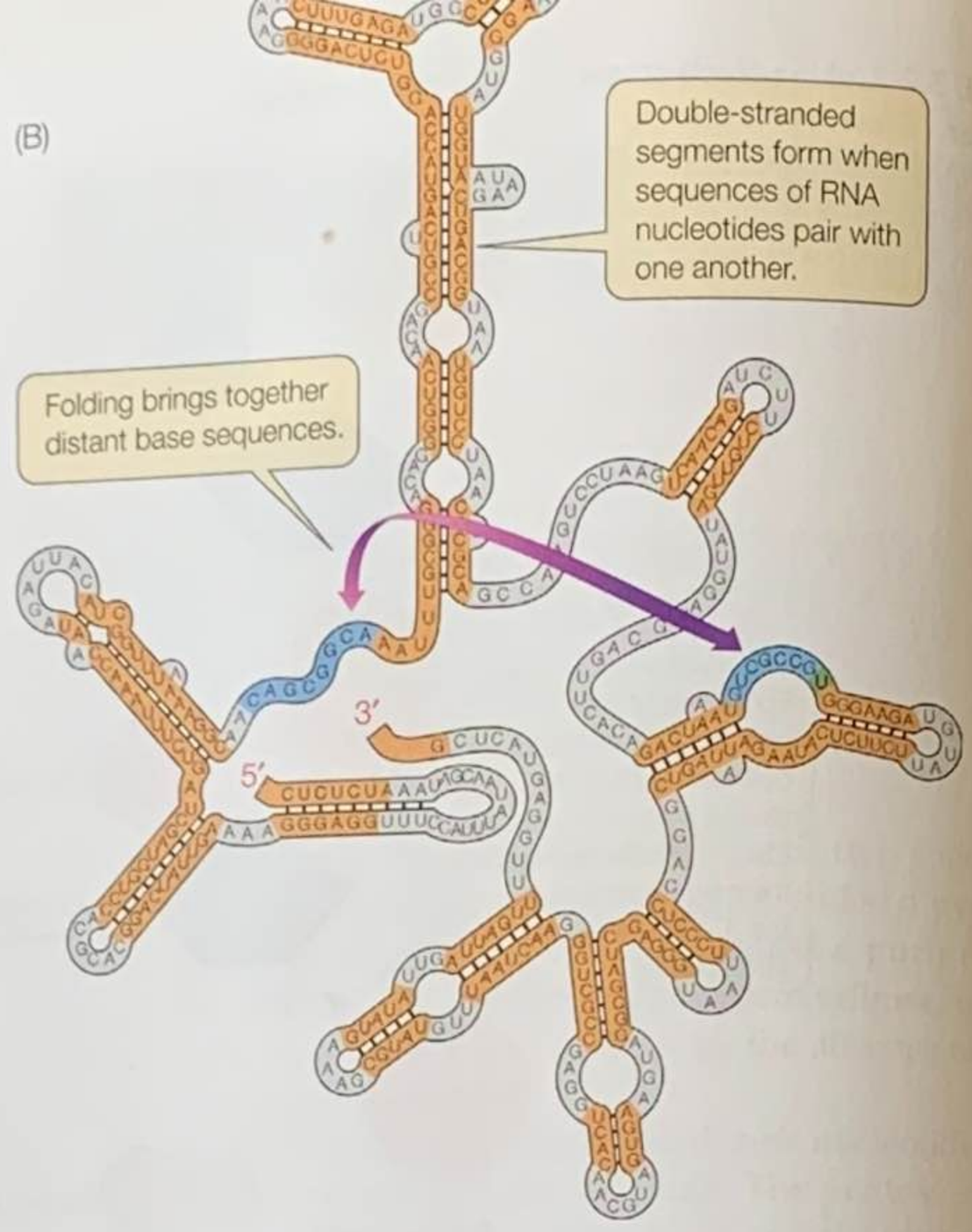
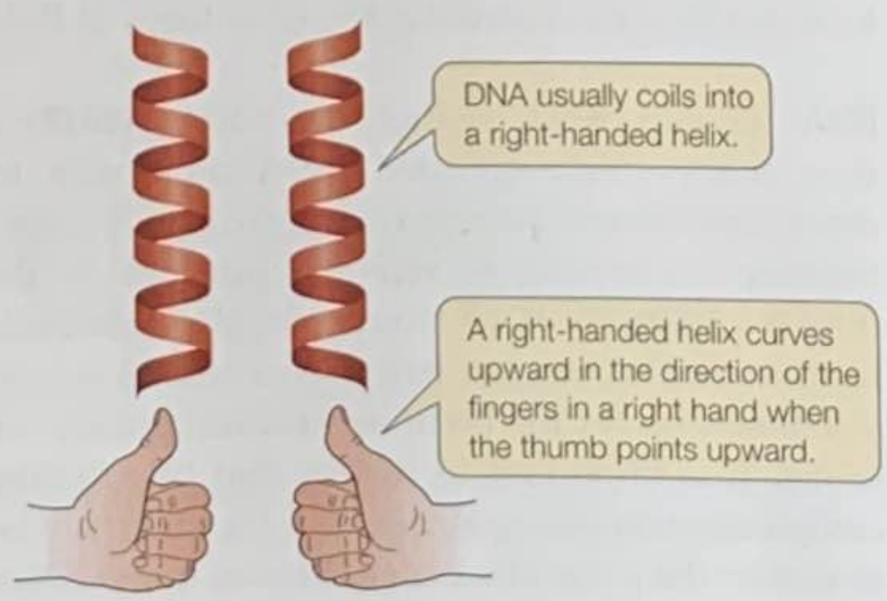


FIGURE 3.3 RNA (A) RNA is usually a single strand. (B) When a single-stranded RNA folds back on itself, hydrogen bonds between complementary sequences can stabilize it into a three-dimensional shape with distinct surface characteristics.

(**FIGURE 3.4A**). The two polynucleotide strands are antiparallel: they run in opposite directions so that their 5′ ends are at opposite ends of the double-stranded molecule. In contrast to RNA's diversity in three-dimensional structure, DNA is remarkably uniform. The A-T and G-C base pairs are about the same size (each is a purine paired with a pyrimidine), and the two polynucleotide strands form a "ladder" that twists into a double helix (**FIGURE 3.4B**). The sugar–phosphate groups form the sides of the ladder, and the bases with their hydrogen bonds form the rungs on the inside. The double helix is almost always right-handed:

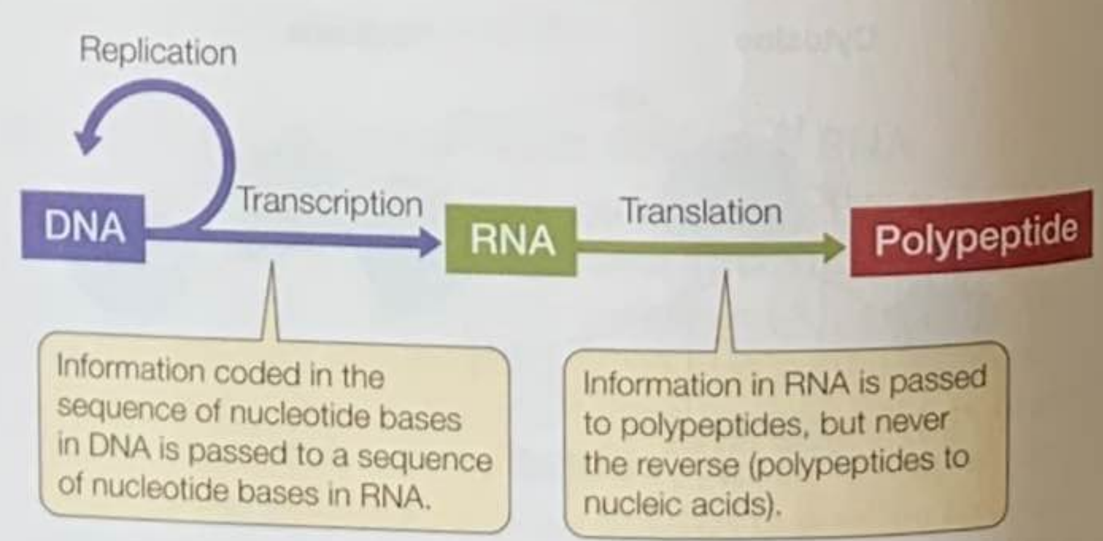


Go to ACTIVITY 3.2 DNA Structure
PoL2e.com/ac3.2

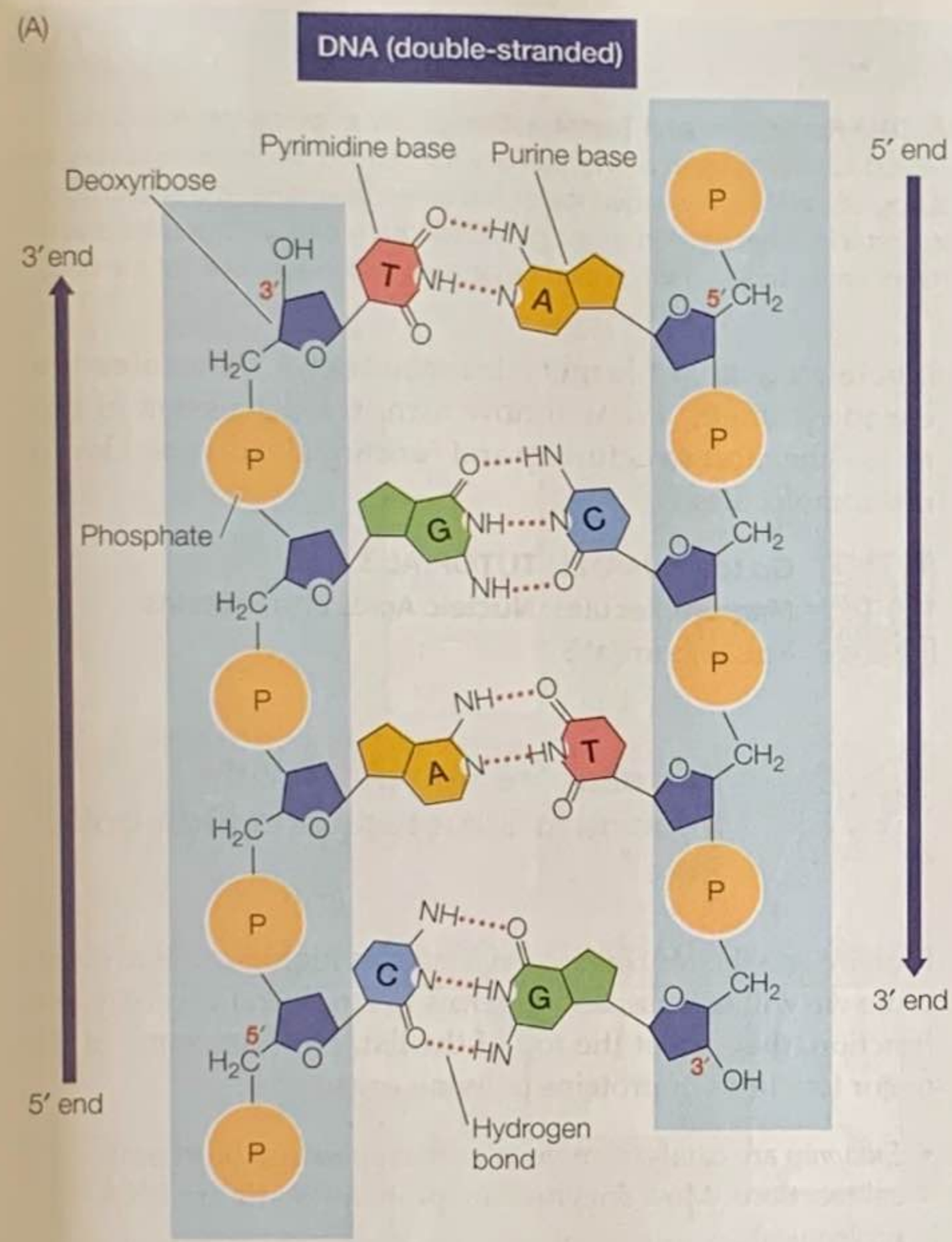
DNA carries information and is expressed through RNA

DNA is a purely informational molecule. The information is encoded in the sequence of bases carried in its strands. For example, the information encoded in the sequence TCAGCA is different from the information in the sequence CCAGCA. DNA has two functions in terms of information:

- DNA can be reproduced precisely by **DNA replication**. DNA is replicated by polymerization using an existing strand as a base-pairing template.
- Some DNA sequences can be copied into RNA, in a process called **transcription**. The nucleotide sequences in most RNA molecules can then be used to specify sequences of amino acids in proteins (polypeptides). This process is called **translation**.



The details of these important processes are described in Chapters 9 and 10, but it is important to realize several things at this point:



In DNA, the bases are attached to deoxyribose, and the base thymine (T) is found instead of uracil. Hydrogen bonds between purines and pyrimidines hold the two strands of DNA together.

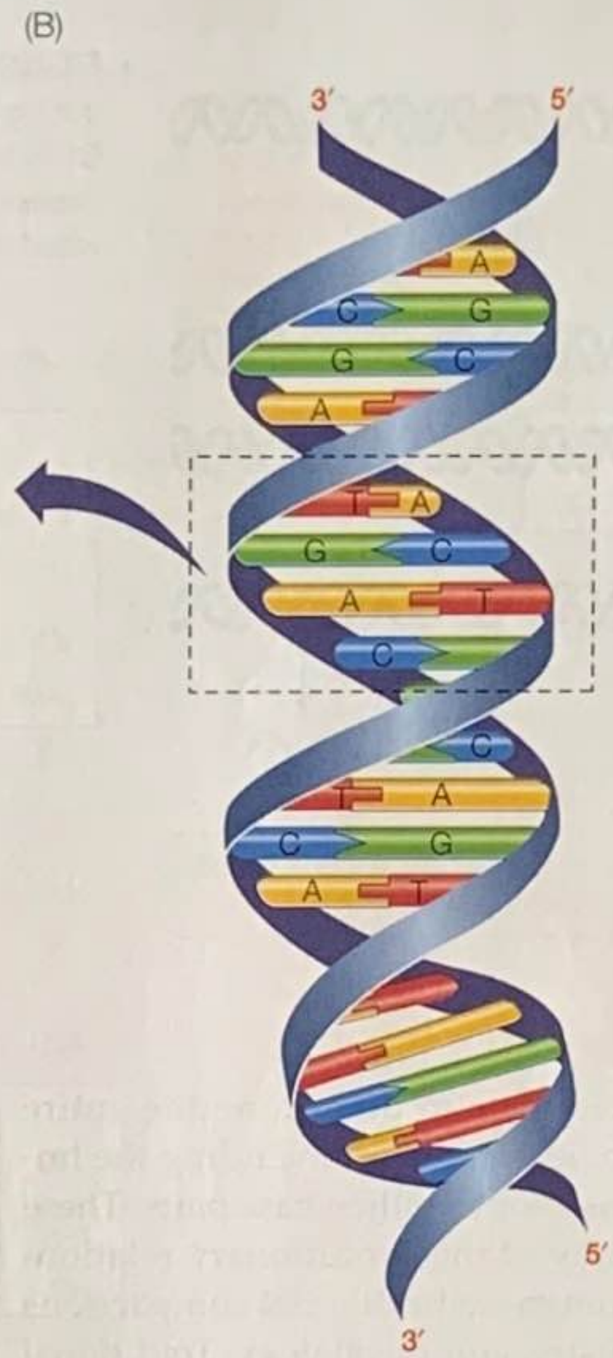


FIGURE 3.4 DNA (A) DNA usually consists of two strands running in opposite directions that are held together by base pairing between purines and pyrimidines opposite one another on the two strands. (B) The two antiparallel strands in a DNA molecule are twisted into a double helix.

- *DNA replication and transcription depend on the base pairing properties of nucleic acids.* In both replication and transcription, the hydrogen bonds between two DNA strands are broken, so that complementary base pairing can occur between an existing DNA strand and a newly forming strand of DNA or RNA. The resulting new DNA or RNA strand is *complementary to* the existing DNA template strand. Recall that the hydrogen-bonded base pairs are A-T and G-C in DNA and A-U and G-C in RNA. Now, consider this double-stranded DNA region:

  5′-TCAGCA-3′

  3′-AGTCGT-5′

  Transcription of the lower strand will result in a single strand of RNA with the sequence 5′-UCAGCA-3′. Can you figure out what RNA sequence the top strand would produce?
- *DNA replication usually involves the entire DNA molecule.* Since DNA holds essential information, it must be replicated completely so that each new cell or new organism receives a complete set of DNA from its parent (**FIGURE 3.5A**).
- *Gene expression is the transcription and translation of specific DNA sequences.* Sequences of DNA that encode specific proteins and are transcribed into RNA are called **genes** (**FIGURE 3.5B**). The complete set of DNA in a living organism is called its **genome**. However, not all of the information in the genome is needed at all times and in all tissues. For example, in humans, the gene that encodes the major protein in hair (keratin) is expressed only in skin cells. The genetic information in the keratin-encoding gene is transcribed into RNA and then translated into the protein keratin. In other tissues such as the muscles, the keratin gene is not transcribed, but other genes are—for example, the genes that encode proteins present in muscles but not in skin.

The DNA base sequence reveals evolutionary relationships

Because DNA carries hereditary information from one generation to the next, a theoretical series of DNA molecules stretches back through the lineage of every organism to the beginning of biological evolution on Earth, about 3.8 billion years ago. The genomes of organisms gradually accumulate changes in their DNA base sequences over evolutionary time. Therefore closely related living species should have more similar base sequences than species that are more distantly related.

Over the past two decades there have been remarkable developments in technologies for determining the order of nucleotides in DNA molecules (DNA sequencing), and in computer technologies to analyze these sequences. These

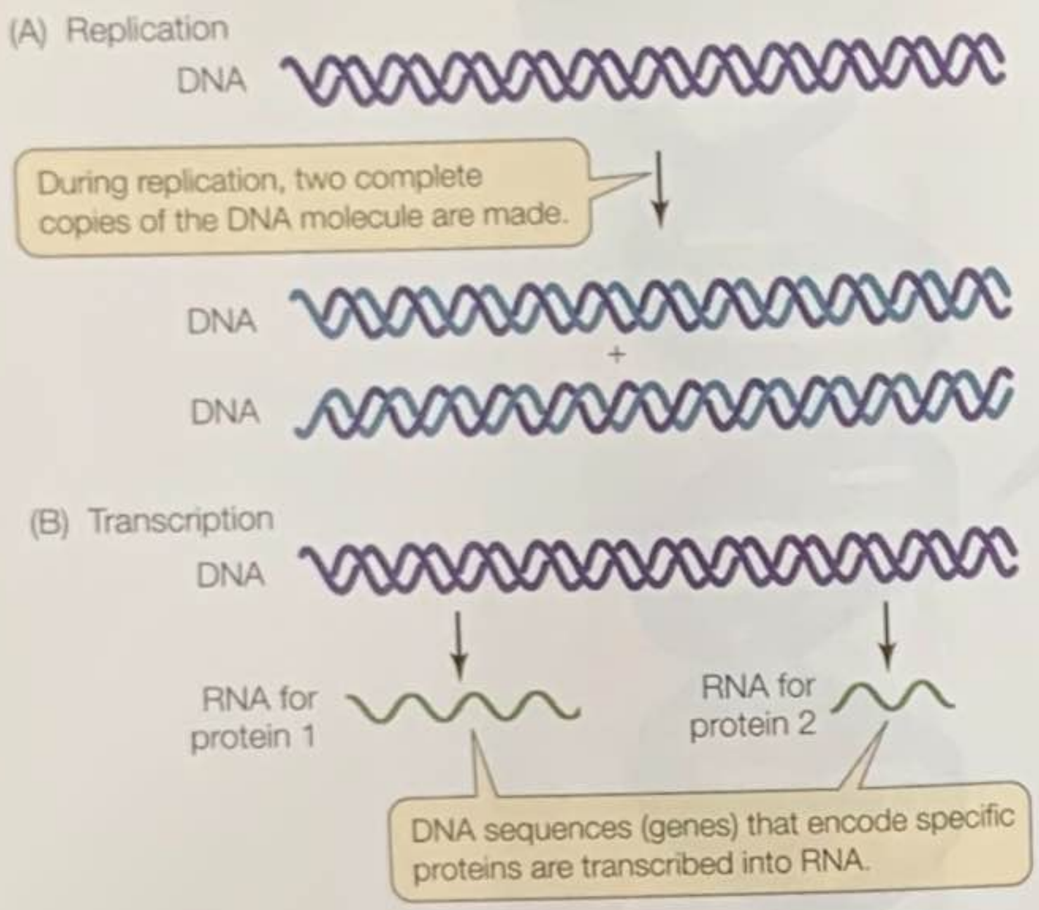


FIGURE 3.5 DNA Replication and Transcription DNA is completely replicated during cell reproduction (A), but it is only partially transcribed (B). In transcription, the DNA code is copied to RNA. The sequence of the latter determines the amino acid sequence of a protein. Transcription of the genes for many different proteins is activated at different times and, in multicellular organisms, in different cells of the body.

advances have enabled scientists to determine the entire DNA base sequences of whole organisms, including the human genome, which contains about 3 billion base pairs. These studies have confirmed many of the evolutionary relationships that were inferred from more traditional comparisons of body structure, biochemistry, and physiology. Traditional comparisons had indicated that the closest living relative of humans (*Homo sapiens*) is the chimpanzee (genus *Pan*). In fact, the chimpanzee genome shares nearly 99 percent of its DNA base sequence with the human genome. Increasingly, scientists turn to DNA analyses to figure out evolutionary relationships when other comparisons are not possible or are not conclusive. For example, DNA studies revealed a close relationship between starlings and mockingbirds that was not expected on the basis of their anatomy or behavior.

LINK

For more on the use of DNA sequences to reconstruct the evolutionary history of life, see **Concept 16.2**

CHECKpoint CONCEPT 3.1

- ✓ List the key differences between DNA and RNA and between purines and pyrimidines.
- ✓ What are the differences between DNA replication and transcription?
- ✓ If one strand of a DNA molecule has the sequence 5′-TTCCGGAT-3′, what is the sequence of the other strand of DNA? If RNA is transcribed from the 5′-TTCCGGAT-3′ strand, what would be its sequence? And if RNA is transcribed from the other DNA strand, what would be its sequence? (Note that it is conventional to write these sequences with the 5′ end on the left.)
- ✓ How can DNA molecules be so diverse when they appear to be structurally similar?

Nucleic acids are largely informational molecules that encode proteins. We will now turn to a discussion of proteins—the most structurally and functionally diverse class of macromolecules.

Go to ANIMATED TUTORIAL 3.1
Macromolecules: Nucleic Acids and Proteins
PoL2e.com/at3.1

CONCEPT 3.2 Proteins Are Polymers with Important Structural and Metabolic Roles

Proteins are the fourth and final type of biological macromolecule we will discuss, and in terms of structural diversity and function, they are at the top of the list. Here are some of the major functions of proteins in living organisms:

- *Enzymes* are catalytic molecules that speed up biochemical reactions. Most enzymes are proteins (some are RNA molecules).
- *Defensive proteins* such as antibodies recognize and respond to substances or particles that invade the organism from the environment.
- *Hormonal and regulatory proteins* such as insulin control physiological processes.
- *Receptor proteins* receive and respond to molecular signals from inside and outside the organism.
- *Storage proteins* store chemical building blocks—amino acids—for later use.
- *Structural proteins* such as collagen provide physical stability and enable movement.
- *Transport proteins* such as hemoglobin carry substances within the organism.
- *Genetic regulatory proteins* (transcription factors) regulate when, how, and to what extent a gene is expressed.

Clearly, the biochemistry of proteins warrants our attention!

Amino acids are the building blocks of proteins

As we noted in Chapter 2, **proteins** are polymers made up of monomers called **amino acids**. As their name suggests, the amino acids all contain two functional groups: the nitrogen-containing amino group and the (acidic) carboxyl group.

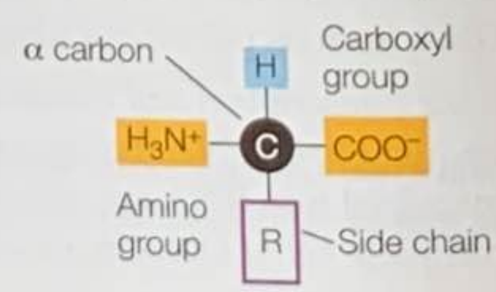
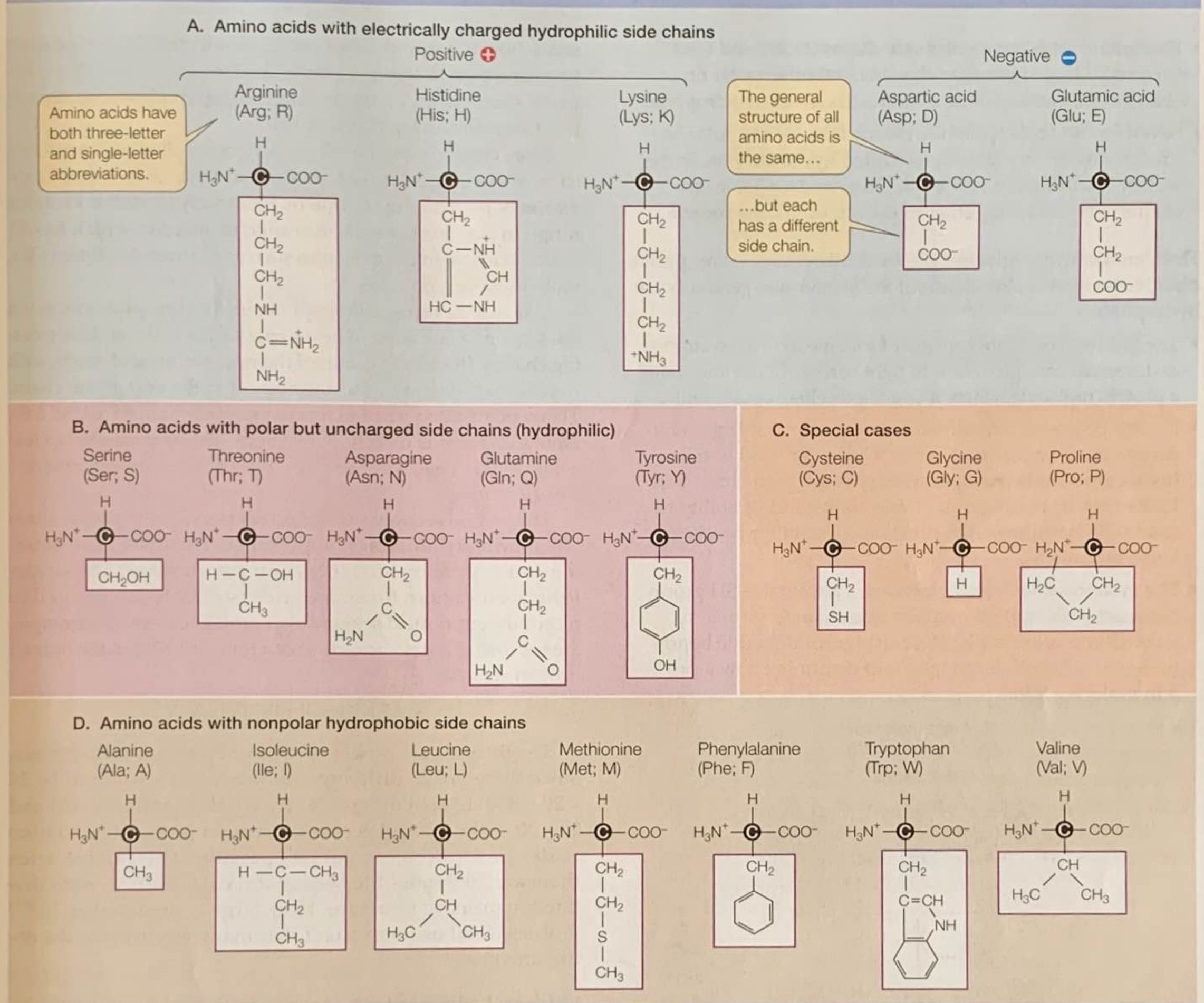


TABLE 3.2 The Twenty Amino Acids in Proteins



The amino and carboxyl groups shown in the diagram are charged. How does this happen? Under the conditions that exist in most living systems, the carboxyl group releases an H^+ (a cation), leaving the rest of the group as an anion:

$$—COOH \rightarrow —COO^- + H^+$$

From your studies of chemistry, you may recognize the carboxyl group as an acid. Conversely, under the same conditions the amino group tends to form a bond with H^+:

$$—NH_2 + H^+ \rightarrow —NH_3^+$$

Your chemistry knowledge should tell you that the amino group is a base.

The central carbon atom of an amino acid—the α (alpha) carbon—has four available electrons for covalent bonding. In all amino acids, two of the electrons are occupied by the two functional groups noted above, and a third is occupied by a hydrogen atom. The fourth bonding electron is shared with a group that differs in each amino acid. This is often referred to as the **R group**, or **side chain**, and is designated by the letter **R**. Each amino acid is identified by its R group.

Go to ACTIVITY 3.3 Features of Amino Acids
PoL2e.com/ac3.3

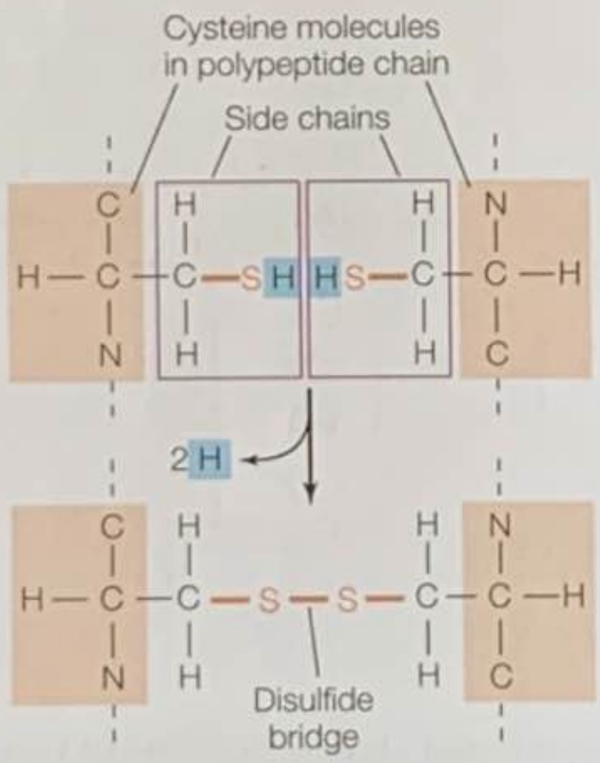
There are hundreds of amino acids known in nature, and many of these occur in plants. But *only 20 amino acids* (listed in **TABLE 3.2**) *occur extensively in the proteins of all organisms*. These 20 amino acids can be grouped according to the properties conferred by their side chains (R groups):

- Five amino acids have electrically charged side chains (+1 or −1), attract water (are hydrophilic), and attract oppositely charged ions of all sorts.

- Five amino acids have polar side chains (δ^+, δ^-) and tend to form hydrogen bonds with water and other polar or charged substances. These amino acids are also hydrophilic.
- Seven amino acids have side chains that are nonpolar hydrocarbons or very slightly modified hydrocarbons. In the watery environment of the cell, these hydrophobic side chains may cluster together in the interior of the protein.

Three amino acids—glycine, proline, and cysteine—are special cases, although the side chains of the former two generally are hydrophobic:

- The glycine side chain consists of a single hydrogen atom and is small enough to fit into tight corners in the interior of a protein molecule, where a larger side chain could not fit.
- Proline possesses a modified amino group that lacks a hydrogen atom and instead forms a covalent bond with the hydrocarbon side chain, resulting in a ring structure. This limits both its hydrogen-bonding ability and its ability to rotate. Thus proline often functions to stabilize bends or loops in proteins.
- The cysteine side chain, which has a terminal —SH group, can react with another cysteine side chain to form a covalent bond called a **disulfide bridge**, or disulfide bond (—S—S—). Disulfide bridges help determine how a protein molecule folds.



In the reaction shown above, the two —SH groups each lose a hydrogen atom (a proton and an electron) and become **oxidized**. The —SH group, which carries the extra electron and proton, is in its **reduced** state.

LINK

In addition to their role in protein structure, oxidation and reduction reactions are important in cellular metabolism; see Concept 6.1

Amino acids are linked together by peptide bonds

Amino acids can form short polymers of 20 or fewer amino acids, called **oligopeptides** or simply **peptides**. These include some hormones and other molecules involved in signaling from one part of an organism to another. Even with their relatively short chains of amino acids, oligopeptides have distinctive three-dimensional structures.

More common are the longer polymers called **polypeptides**, each with a unique sequence of amino acids. A functional protein may be made up of one or more polypeptides. Proteins range in size from small ones such as insulin, which has 51 amino acids, to huge molecules such as the muscle protein titin, with 34,350 amino acids.

Like nucleic acids, oligopeptides and polypeptides form via the sequential addition of new amino acids to the ends of existing chains. The amino group of the new amino acid reacts with the carboxyl group of the amino acid at the end of the chain. This condensation reaction forms a **peptide bond** (FIGURE 3.6). Note that there is directionality here, just as with the nucleic acids. In this case, *polymerization takes place in the amino to carboxyl direction*.

The precise sequence of amino acids in a polypeptide chain is the **primary structure** of a protein. Scientists have determined the primary structures of many proteins. The single-letter abbreviations for amino acids (see Table 3.2) are used to record the amino acid sequences of proteins. Here, for example, are the first 20 amino acids (out of a total of 1,827) in the human protein sucrase:

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The theoretical number of different proteins is enormous. Since there are 20 different amino acids, there could be $20 \times 20 = 400$ distinct dipeptides (two linked amino acids) and $20 \times 20 \times 20 = 8{,}000$ different tripeptides (three linked amino acids). So for even a small polypeptide of 100 amino acids there are 20^{100} possible sequences, each with its own distinctive primary structure. How large is the number 20^{100}? Physicists tell us there aren't that many electrons in the entire universe.

Higher-level protein structure is determined by primary structure

The primary structure of a protein is established by covalent bonds, but higher levels of structure are determined largely by weaker forces, including hydrogen bonds and hydrophobic and hydrophilic interactions. Follow FIGURE 3.7 as we describe how a protein chain becomes a three-dimensional structure.

SECONDARY STRUCTURE A protein's **secondary structure** consists of regular, repeated spatial patterns in different regions of a polypeptide chain. There are two basic types of secondary structure, both determined by hydrogen bonding between the amino acids that make up the primary structure:

- The **α (alpha) helix** is a right-handed coil that turns in the same direction as a standard wood screw (see Figure 3.7B). The R groups extend outward from the peptide backbone of the helix. The coiling results from hydrogen bonds that form between the N—H group on one amino acid and the C=O group on another within the same turn of the helix.

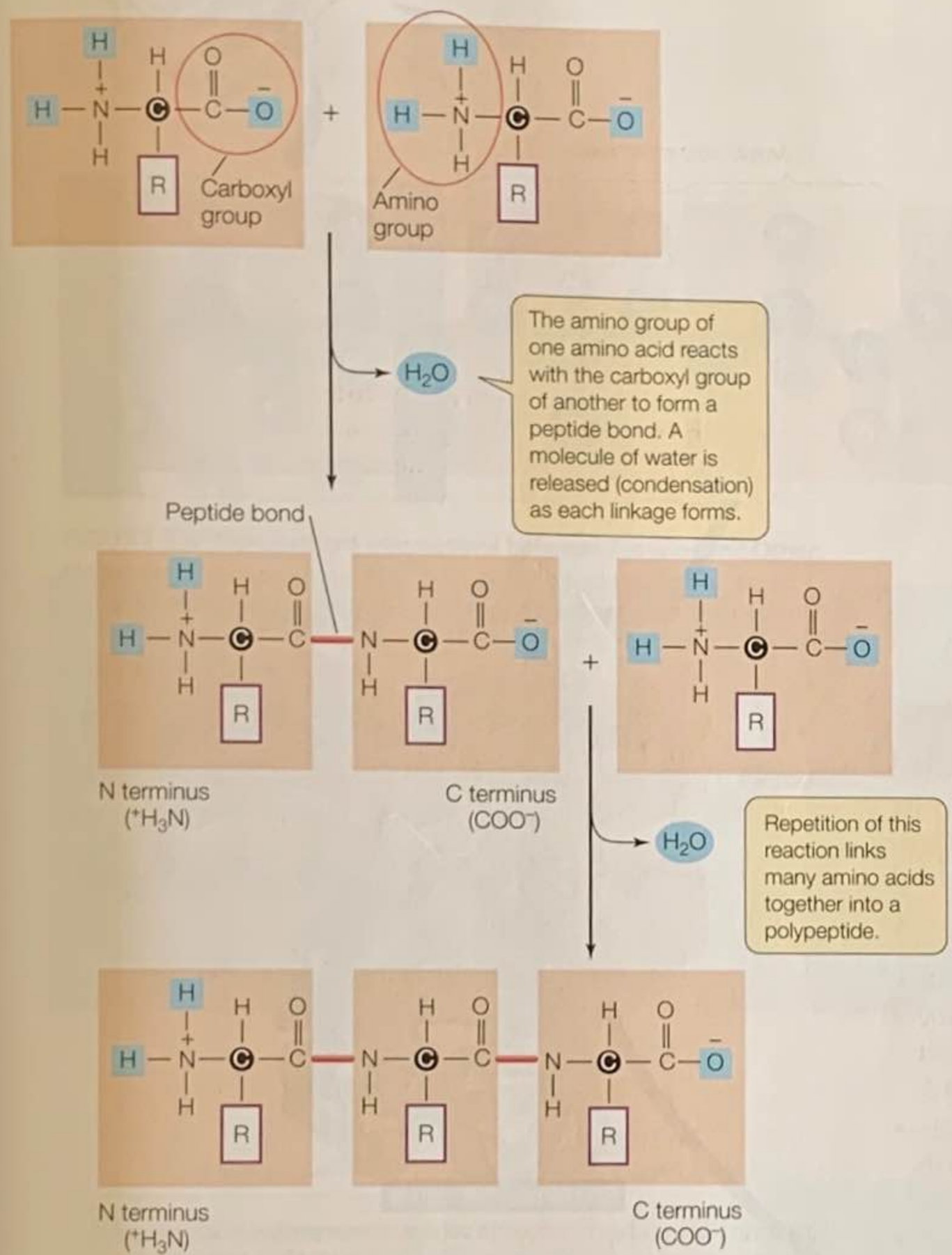


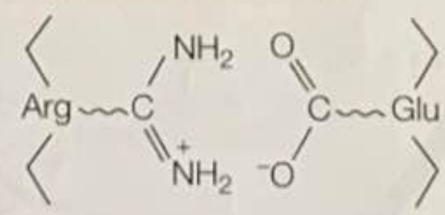
FIGURE 3.6 Formation of a Peptide Bond In living things, the reaction leading to a peptide bond has many intermediate steps, but the reactants and products are the same as those shown in this simplified diagram.

- The β (**beta**) **pleated sheet** is formed from two or more sequences of amino acids that are extended and aligned. The sheet is stabilized by hydrogen bonds between the N—H groups and the C=O groups on the two chains (see Figure 3.7C). A β pleated sheet may form between separate polypeptide chains or between different regions of a single polypeptide chain that is bent back on itself. Many proteins contain both α helices and β pleated sheets in different regions of the same polypeptide chain.

TERTIARY STRUCTURE In many proteins, the polypeptide chain is bent at specific sites and then folded back and forth, resulting in **tertiary structure** (see Figure 3.7D). Tertiary structure results in the polypeptide's definitive three-dimensional shape, including a buried interior as well as a surface that is exposed to the environment. The protein's exposed outer surfaces present functional groups capable of interacting with other molecules in the cell. These molecules might be other proteins or smaller chemical reactants (as in enzymes; see below).

Whereas hydrogen bonding between the N—H and C=O groups within and between chains is responsible for a protein's secondary structure, it is the interactions between R groups—the amino acid side chains—that determine tertiary structure (**FIGURE 3.8**):

- *Covalent disulfide bridges* can form between specific cysteine side chains, holding a folded polypeptide together.
- *Hydrogen bonds* between side chains also stabilize folds in proteins.
- *Hydrophobic side chains* can aggregate together in the interior of a protein, away from water, folding the polypeptide in the process.
- *van der Waals interactions* can stabilize close associations between hydrophobic side chains.
- *Ionic interactions* can form between positively and negatively charged side chains, forming "salt bridges" between amino acids. Ionic interactions can also be buried deep within a protein, away from water. These interactions occur between positively and negatively charged amino acids, for example arginine (which has a positively charged R group) and glutamic acid (which has a negatively charged R group):



LINK

To review the strong and weak interactions that can occur between atoms, see **Concept 2.2**

A complete description of a protein's tertiary structure would specify the location of every atom in the molecule in three-dimensional space, relative to all the other atoms. Many such descriptions are available, including one for the human protein sucrase (**FIGURE 3.9**).

Remember that both secondary and tertiary structure derive from primary structure. If a protein is heated slowly, the heat energy will disrupt only the weaker interactions, causing the secondary and tertiary structure to break down. The protein is then said to be **denatured**. Chemical treatments can also be used to denature proteins. In many cases a denatured protein can return to its normal tertiary structure when it cools or the denaturing

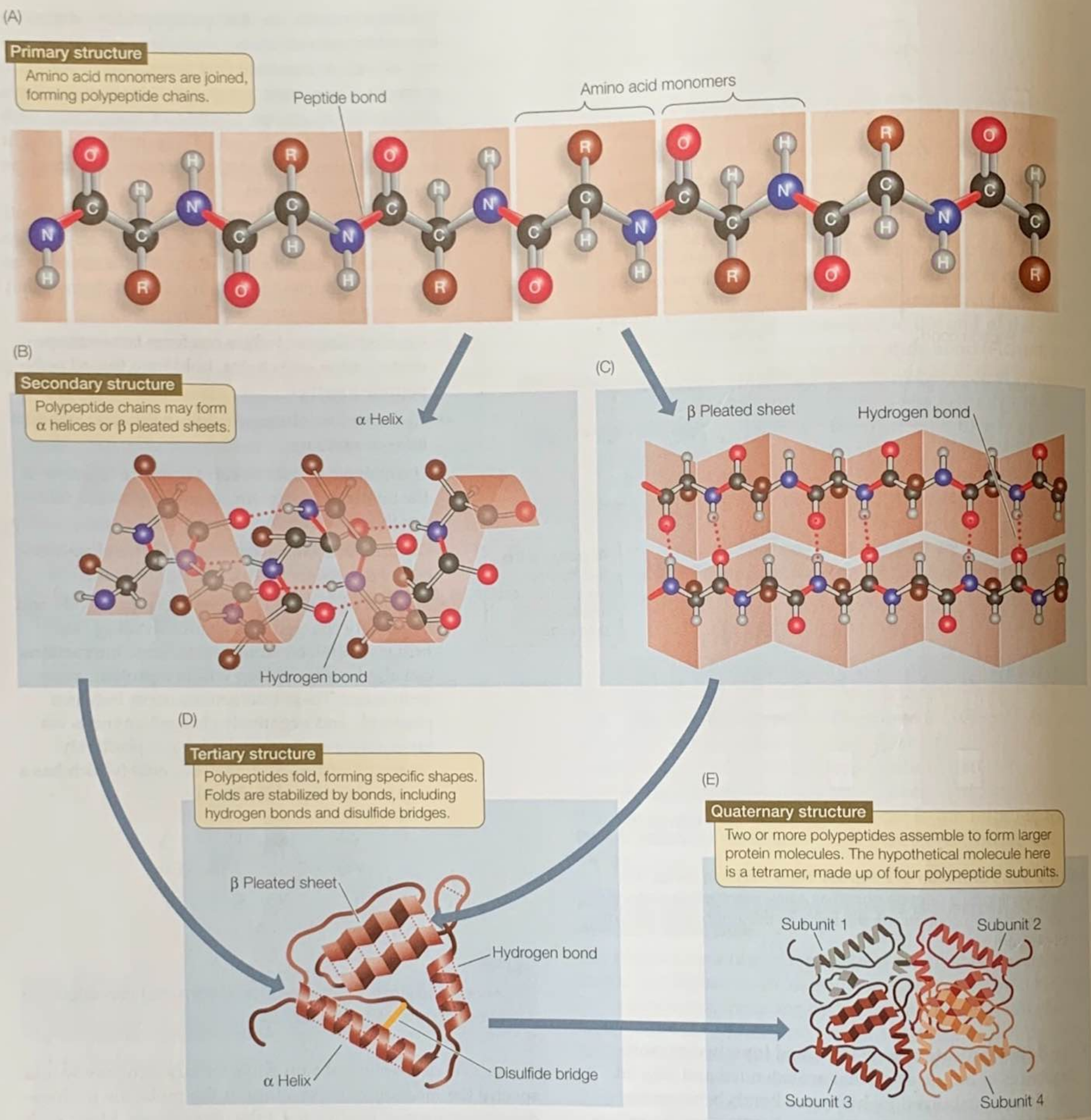


FIGURE 3.7 The Four Levels of Protein Structure The primary structure (A) of a protein determines what its secondary (B and C), tertiary (D), and quaternary (E) structures will be.

chemicals are removed, demonstrating that all the information needed to specify the protein's unique shape is contained in its primary structure. This fact was first shown by biochemist Christian Anfinsen for the protein ribonuclease (**FIGURE 3.10**).

QUATERNARY STRUCTURE Many functional proteins contain two or more polypeptide chains, called subunits, each folded into its own unique tertiary structure. The protein's **quaternary structure** results from the ways in which these

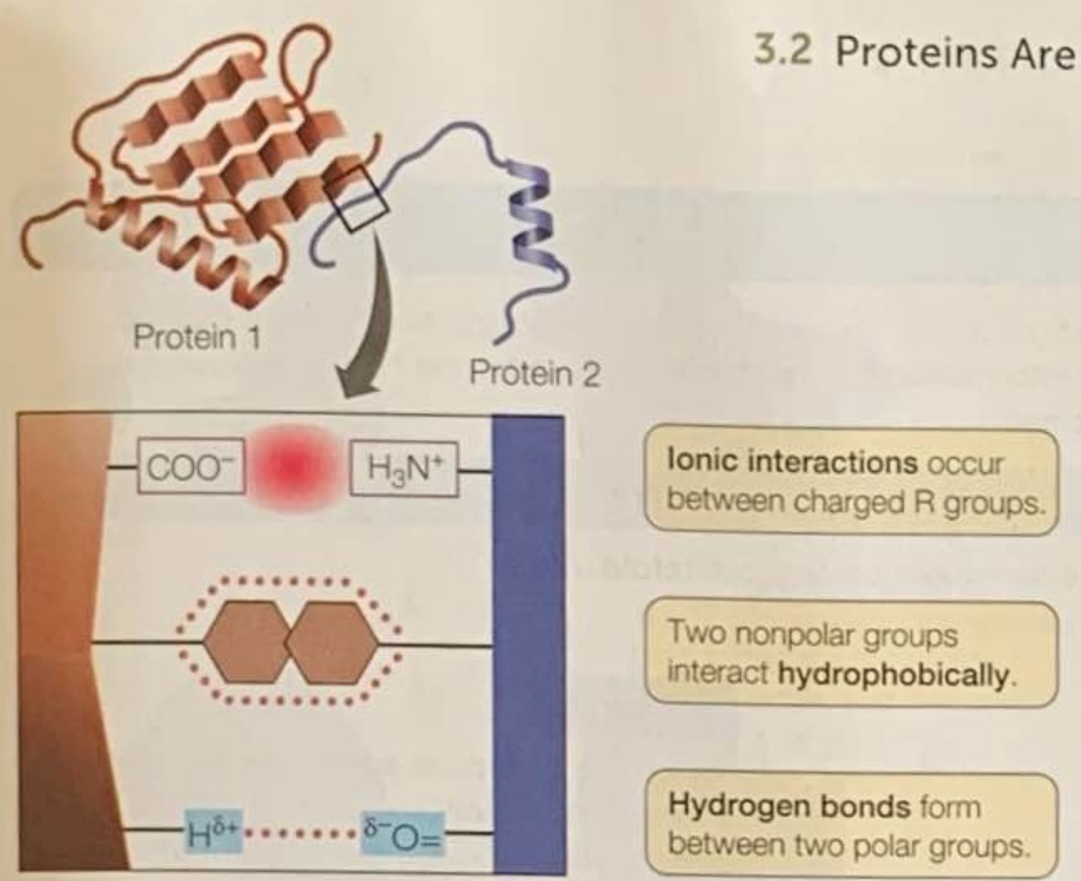
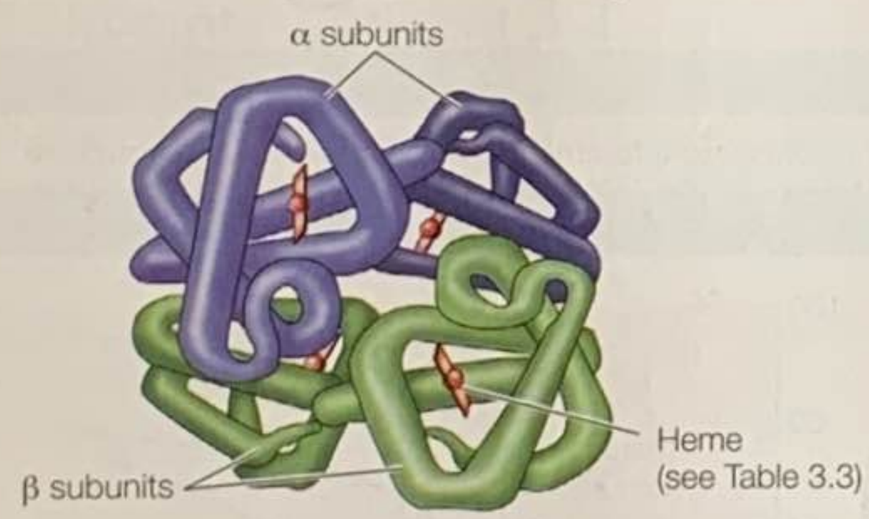


FIGURE 3.8 Noncovalent Interactions between Proteins and Other Molecules Noncovalent interactions allow a protein (brown) to bind tightly to another protein (blue) with specific properties. Noncovalent interactions also allow regions within a single protein to interact with one another.

subunits bind together and interact (see Figure 3.7E). Hemoglobin is an example of a protein with multiple subunits:



Hydrophobic interactions, hydrogen bonds, and ionic interactions all help hold the four subunits together to form a hemoglobin macromolecule. The weak nature of these forces permits small changes in the quaternary structure to aid the protein's function—which is to carry oxygen in red blood cells. As hemoglobin binds one O_2 molecule, the four subunits shift their relative positions slightly, changing the quaternary structure. Ionic interactions are broken, exposing buried side chains that enhance the binding of additional O_2 molecules. The quaternary structure changes again when hemoglobin releases its O_2 molecules to the cells of the body.

Protein structure can change

The environment that surrounds a protein, as well as interactions with other molecules, can change protein structure.

ENVIRONMENT Various conditions can alter the weak, noncovalent interactions that hold proteins together in their secondary, tertiary, and quaternary structures:

- *Increases in temperature* cause more rapid molecular movements and thus can break hydrogen bonds and hydrophobic interactions.

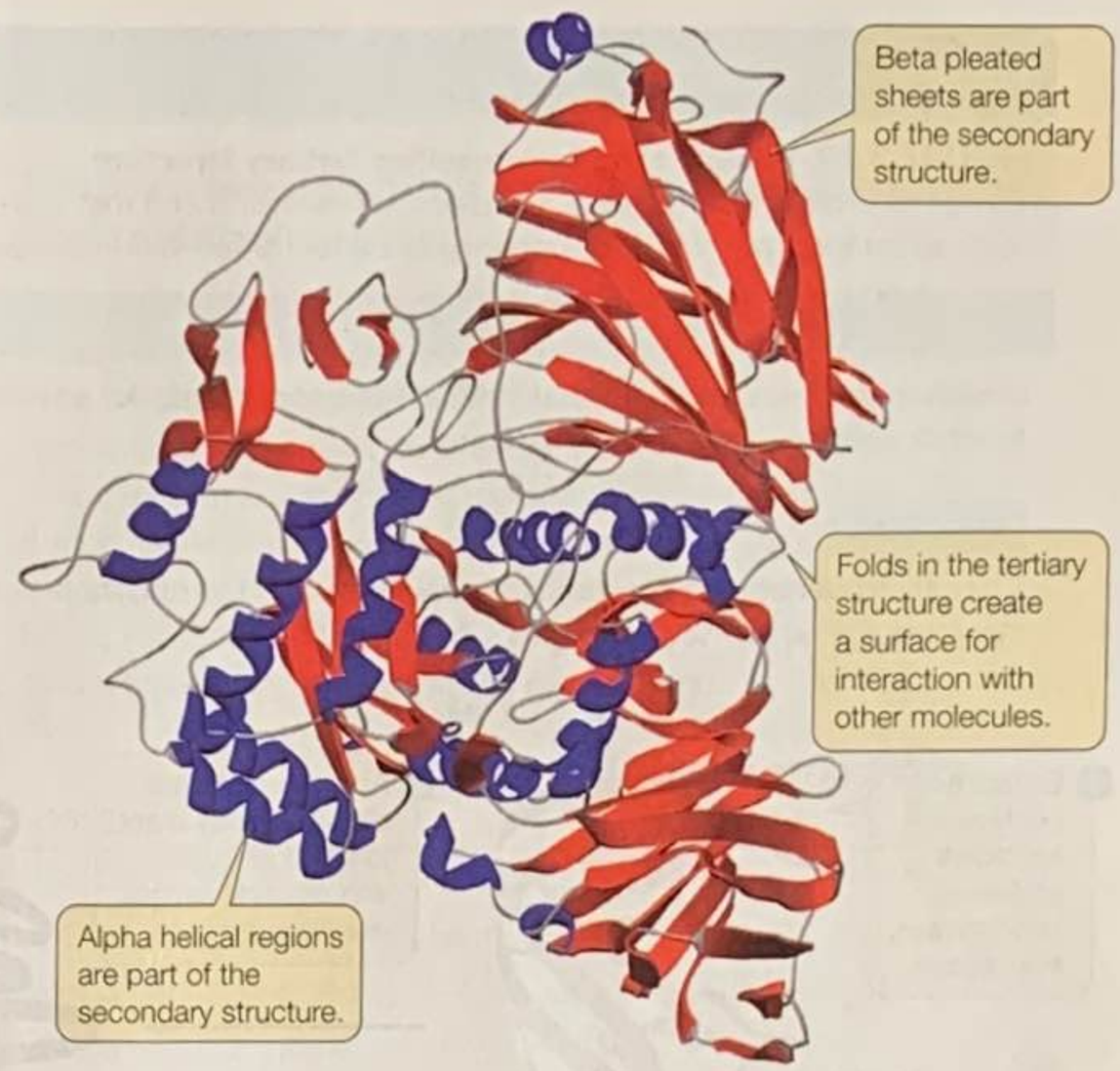


FIGURE 3.9 The Structure of a Protein Sucrase has a specific three-dimensional structure, determined by its primary structure. Sucrase plays a role in digestion in humans.

- *Alterations in the concentration of H^+* (pH) in the solution surrounding the protein can change the patterns of ionization of the exposed carboxyl and amino groups. This can disrupt the patterns of ionic attractions and repulsions.
- *High concentrations of polar substances* such as urea can disrupt the hydrogen bonding that is crucial to protein structure.
- *Nonpolar substances* may also denature a protein in cases where hydrophobic groups are essential for maintaining the protein's structure.

Go to MEDIA CLIP 3.1
Protein Structures in 3D
PoL2e.com/mc3.1

Denaturation can be irreversible when amino acids that were buried in the interior of the protein become exposed at the surface, or vice versa, causing a new structure to form, or causing different molecules to bind to the protein. Boiling an egg denatures its proteins and is, as you know, not reversible.

MOLECULAR INTERACTIONS Proteins do not exist in isolation. Within a living organism, a protein may interact with other proteins, other kinds of macromolecules, or a variety of smaller molecules. These interactions are reminiscent of the interactions that make up quaternary structure (see above). If a polypeptide comes into contact with another molecule, R groups on its surface may form weak interactions (such as hydrogen bonds or ionic interactions) with groups on the surface

INVESTIGATION

FIGURE 3.10 Primary Structure Specifies Tertiary Structure
Using the protein ribonuclease, Christian Anfinsen showed that proteins spontaneously fold into functionally correct three-dimensional configurations.[a] As long as the primary structure is not disrupted, the information for correct folding (under the right conditions) is retained.

HYPOTHESIS

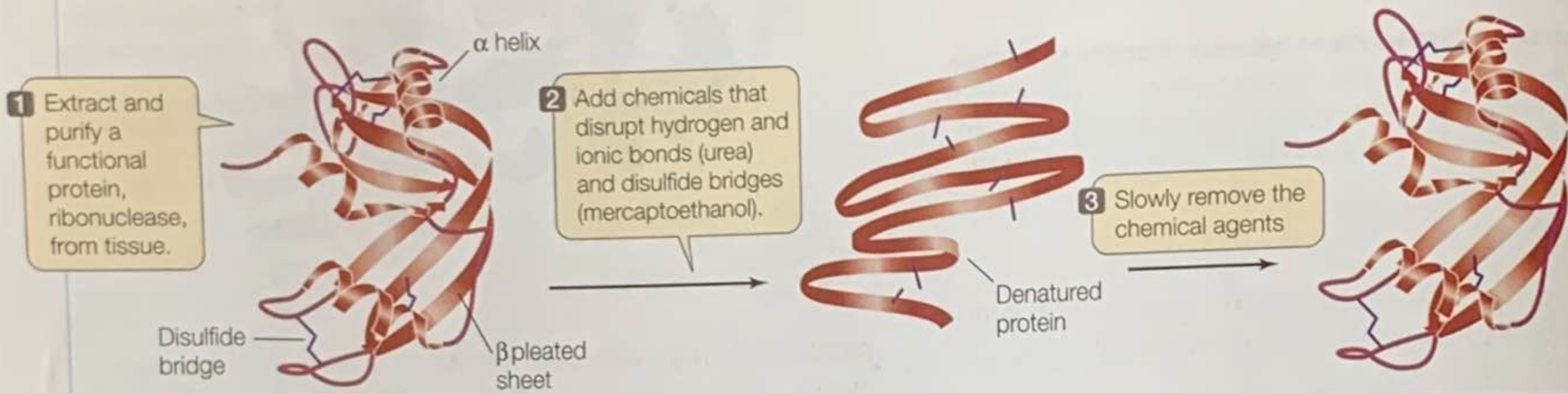
Under controlled conditions that simulate the normal cellular environment, a denatured protein can refold into a functional three-dimensional structure.

METHOD

Chemically denature a functional ribonuclease, so that only its primary structure (i.e., an unfolded polypeptide chain) remains.

RESULTS

When the disruptive agents are removed, three-dimensional structure is restored and the protein once again is functional.



CONCLUSION

In normal cellular conditions, the primary structure of a protein specifies how it folds into a functional, three-dimensional structure.

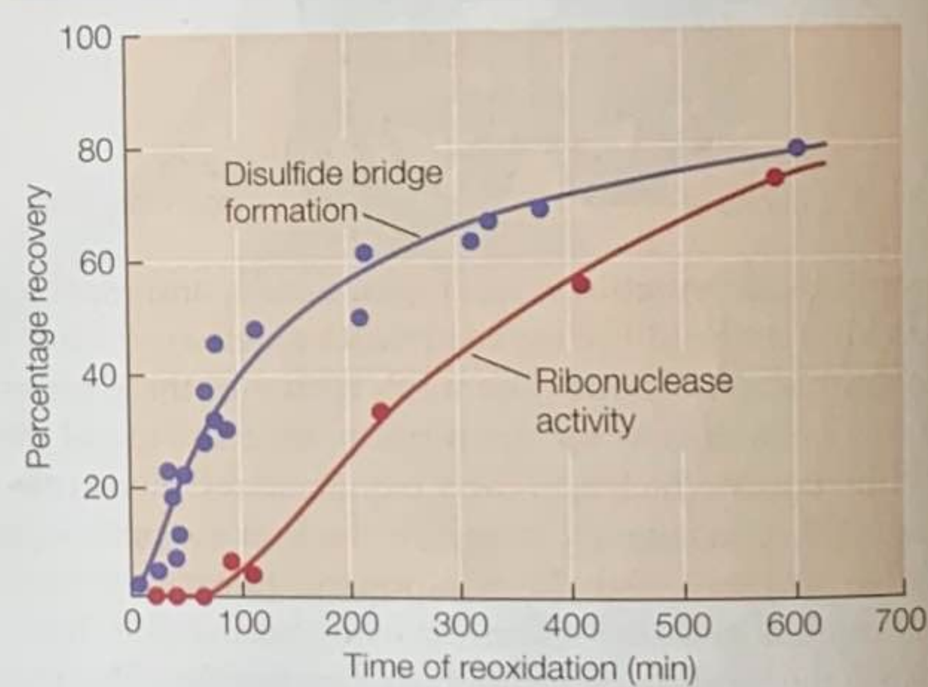
ANALYZE THE DATA

Initially, disulfide bridges (S—S) in ribonuclease were eliminated because the sulfur atoms in cysteine were reduced (—SH). At time 0, reoxidation began and at various times, the amount of disulfide bridge re-formation (blue circles) and the function of ribonuclease (enzyme activity; red circles) were measured by chemical methods. Here are the data:

A. At what time did disulfide bridges begin to form?

B. At what time did enzyme activity begin to appear?

C. Explain the difference between your answers for the times of (A) and (B).



Go to **LaunchPad** for discussion and relevant links for all **INVESTIGATION** figures.

[a]C. B. Anfinsen et al. 1961. *Proceedings of the National Academy of Sciences USA*. 47: 1309–1314.

of the other molecule. This may disrupt some of the interactions between R groups within the polypeptide, causing it to undergo a change in shape (**FIGURE 3.11A**).

The structure of a protein can also be modified by the covalent bonding of a chemical group to the side chain of one or more of its amino acids. The chemical modification of just one amino acid can alter the shape and function of a protein. An example is the addition of a charged phosphate group to a relatively nonpolar R group. This can cause the amino acid to become more hydrophilic and to move to the outer surface of the protein, altering the shape of the protein in the region near the amino acid (**FIGURE 3.11B**).

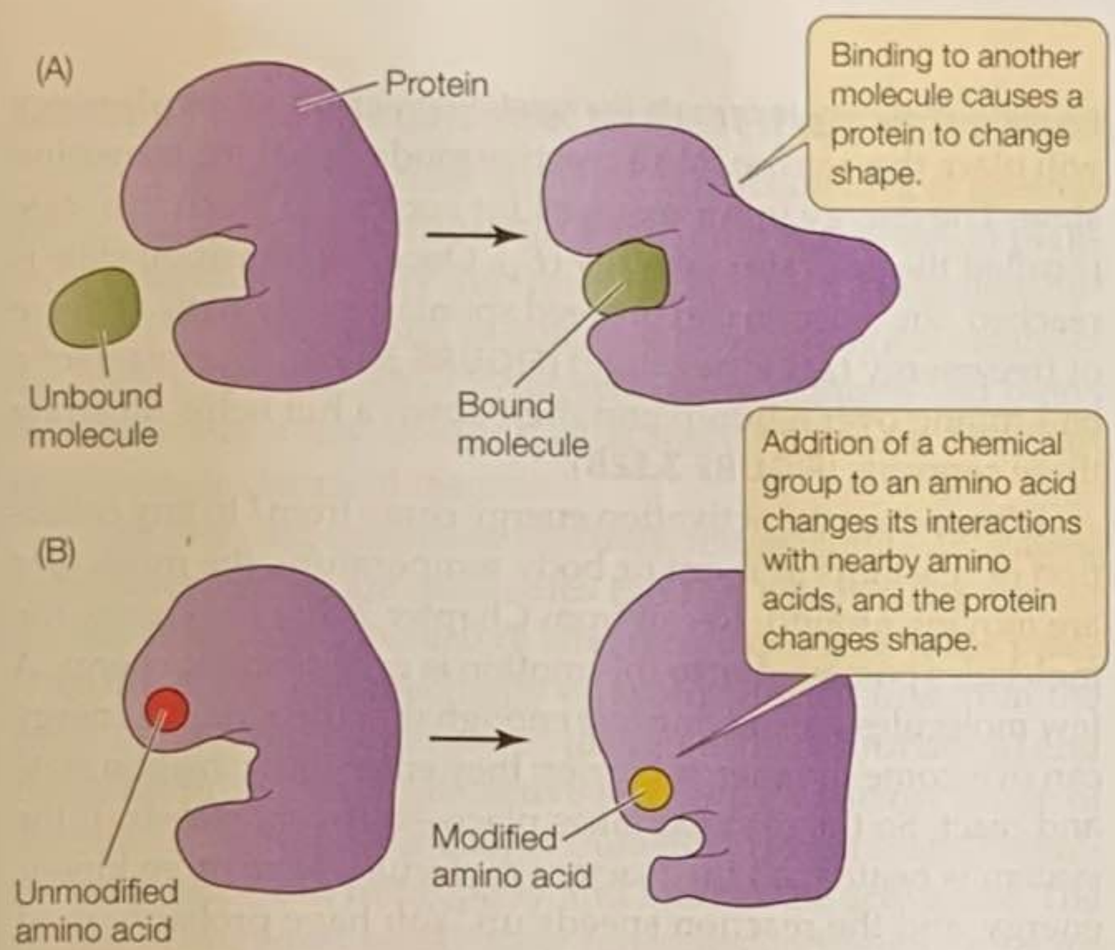


FIGURE 3.11 Protein Structure Can Change Proteins can change their tertiary structure when they bind to other molecules (A) or are modified chemically (B).

CHECKpoint CONCEPT 3.2

- ✓ Sketch the peptide bonding of the two amino acids glycine and leucine (in that order). Now add a third amino acid, alanine, in the position it would have if added within a biological system. What is the directionality of this process?
- ✓ Examine the structure of sucrase (see Figure 3.9). Where in the protein might you expect to find the following amino acids: valine, proline, glutamic acid, and threonine? Explain your answers.
- ✓ Detergents disrupt hydrophobic interactions by coating hydrophobic molecules with a molecule that has a hydrophilic surface. When hemoglobin is treated with a detergent, the four polypeptide chains separate and become random coils. Explain these observations.
- ✓ Several small molecules interact with a protein. The chemical groups on the small molecules interact with specific amino acids as shown in the table below. Fill in the table to show the types of noncovalent interactions that occur between the small molecules and the amino acids.

SMALL MOLECULE CHEMICAL GROUP	AMINO ACID IN PROTEIN	TYPE OF INTERACTION (HYDROGEN BOND; IONIC INTERACTION; HYDROPHOBIC INTERACTION)
$-NH_3^+$	Aspartic acid	
$-CH_3$	Isoleucine	
$-OH$	Glutamine	

We have discussed the remarkable diversity in protein structures. These structures carry functional groups (on exposed amino acid side chains) that can interact with other molecules. In the next section we will see how these interactions can result in catalysis, the speeding up of biochemical reactions.

APPLY THE CONCEPT

Proteins are polymers with important structural and metabolic roles

Biological systems contain "supermolecular complexes" (for example, the ribosome; see Chapter 4), which are composed of individual molecules of RNA and protein that fit together noncovalently. These complexes can be split apart with detergents that disrupt hydrophobic interactions. Based on the concepts discussed in this chapter, fill in the table below to indicate which of the observations are characteristic of RNA, which are characteristic of protein, and which are characteristic of both. Explain your answers.

OBSERVATION	CHARACTERISTIC OF: PROTEIN	RNA
Has three-dimensional (3-D) structure		
3-D structure destroyed by heat		
Monomers connected by N–C bonds		
Contains sulfur atoms		
Contains phosphorus atoms		

CONCEPT 3.3 Some Proteins Act as Enzymes to Speed up Biochemical Reactions

In Chapter 2 we introduced the concepts of biological energetics. We showed that some metabolic reactions are exergonic and some are endergonic, and that biochemistry obeys the laws of thermodynamics (see Figures 2.14 and 2.15). Knowing whether energy is supplied or released in a particular reaction tells us whether the reaction *can* occur in a living system. But it does not tell us *how fast* the reaction will occur.

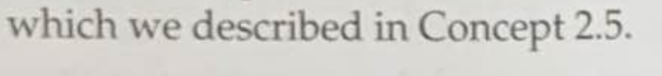
Living systems depend on reactions that occur spontaneously. But without help, most of these reactions would proceed at such slow rates that an organism could not survive. The role of a **catalyst** is to speed up a reaction without itself being permanently altered. A catalyst does not cause a reaction to occur, but it increases the rate of the reaction. This is an important point: *No catalyst makes a reaction occur that would not proceed without it.*

Biological catalysts are called **enzymes**; for example, the synthesis of prostaglandin (see the opening story) is catalyzed by an enzyme (cyclooxygenase). Most enzymes are proteins, but a few important enzymes are RNA molecules called ribozymes. An enzyme can bind the reactants in a chemical reaction and participate in the reaction itself. However, this participation does not permanently change the enzyme. At the end of the reaction, the enzyme is unchanged and available to catalyze additional, similar reactions.

An energy barrier must be overcome to speed up a reaction

An exergonic reaction releases **free energy** (G), which is the amount of energy in a system that is available to do work. For

example, the free energy released in an exergonic reaction can be used by the cell to drive an endergonic reaction, or it can be converted to mechanical energy for movement (see Figure 6.1). But without a catalyst, a reaction will usually take place very slowly. This is because there is an energy barrier between the reactants and the products. Think about the hydrolysis of sucrose, which we described in Concept 2.5.



$$\text{Sucrose} + H_2O \rightarrow \text{glucose} + \text{fructose}$$

In humans, this reaction is part of the process of digestion. The reaction is exergonic, but even if water is abundant, the sucrose molecule will only rarely bind the H atom and the –OH group in the water molecule at the appropriate locations to break the covalent bond between the glucose and fructose—*unless there is an input of energy to initiate the reaction*. Such an input of energy will place the sucrose into a reactive mode called the **transition state**. The energy input required for sucrose to reach this state is called the **activation energy** (E_a). Once the transition state is reached, the reaction can proceed spontaneously with a release of free energy (ΔG is negative) (**FIGURE 3.12A**). The image of a ball rolling over a bump and then down a hill helps illustrate these concepts (**FIGURE 3.12B**).

Where does the activation energy come from? In any collection of reactants at room or body temperature, the molecules are moving around. Recall from Chapter 2 that the energy the molecules possess due to this motion is called kinetic energy. A few molecules are moving fast enough that their kinetic energy can overcome the energy barrier; they enter the transition state and react. So the reaction takes place—but very slowly. If the system is heated, all the reactant molecules have more kinetic energy, and the reaction speeds up. You have probably used this technique in the chemistry laboratory.

Adding enough heat to increase the average kinetic energy of the molecules would not work in a living system, however. Such a nonspecific approach would accelerate all reactions, including destructive ones such as the denaturation of proteins.

An enzyme lowers the activation energy for a reaction by enabling the reactants to come together and react more easily; the reactants need lower amounts of kinetic energy to enter their transition states (**FIGURE 3.13**). In this way, an enzyme can change the rate of a reaction substantially. For example, if a molecule of sucrose just sits in solution, hydrolysis may take hundreds of years. But with the enzyme sucrase present, the same reaction occurs in 1 second! Typically, an enzyme-catalyzed reaction proceeds 10^3 to 10^8 times faster than the uncatalyzed reaction, and the enzyme converts 100 to 1,000 substrate molecules into product per second.

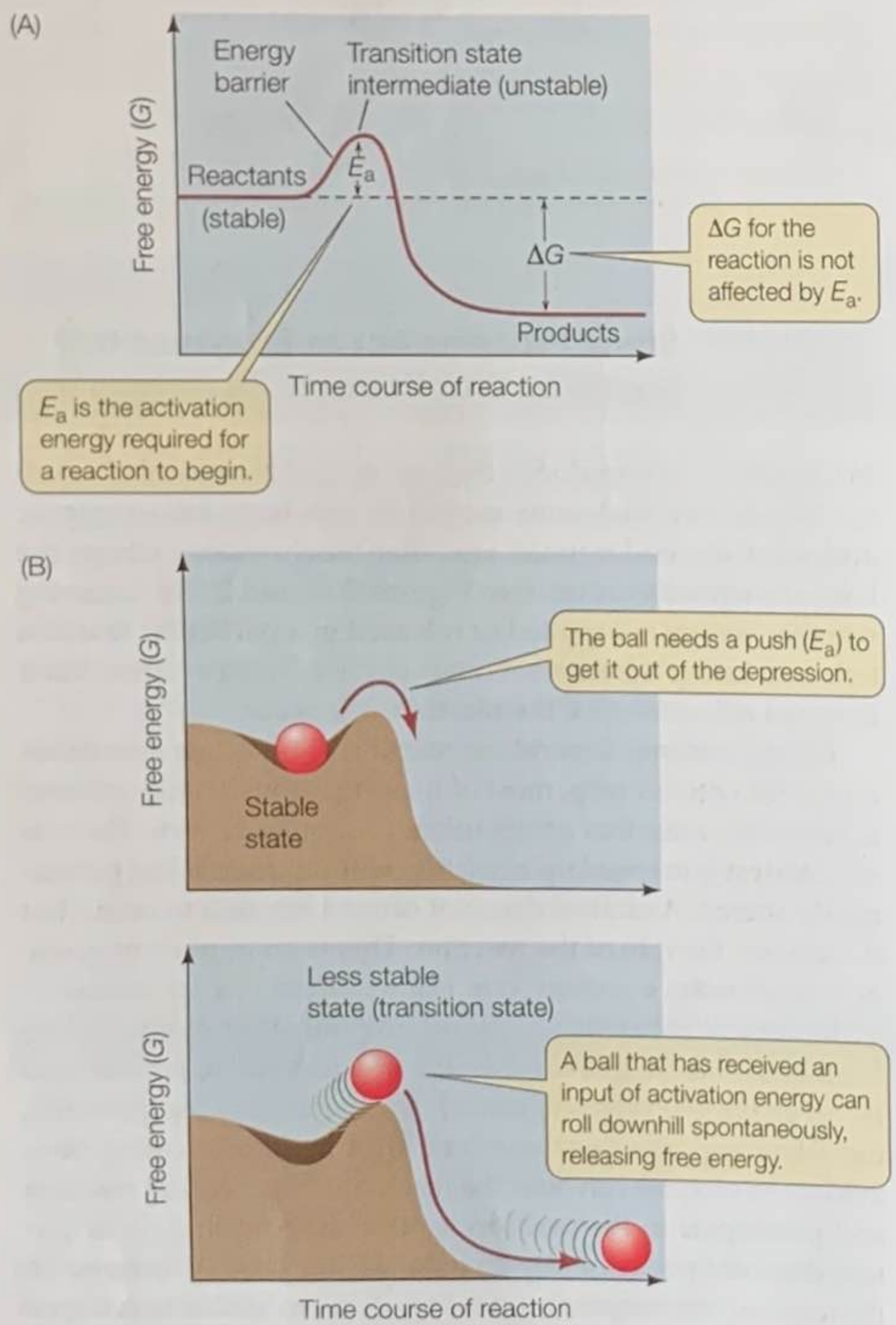


FIGURE 3.12 Activation Energy Initiates Reactions (A) In any chemical reaction, an initial stable state must become less stable before change is possible. (B) A ball on a hillside provides a physical analogy to the biochemical principle graphed in A. Although these graphs show an exergonic reaction, activation energy is needed for endergonic reactions as well.

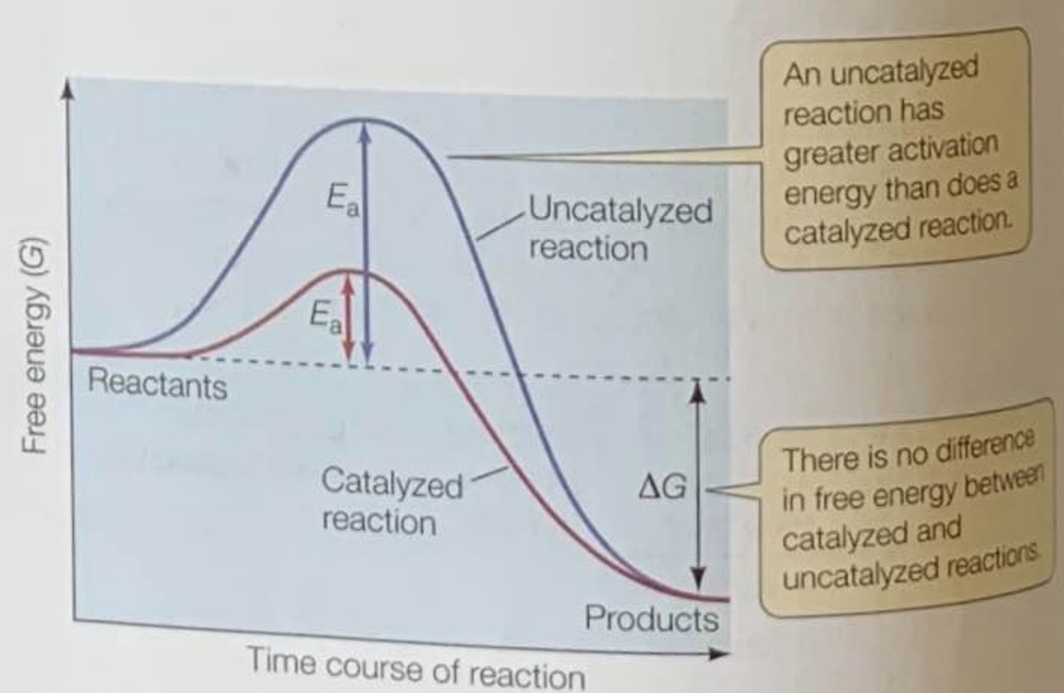


FIGURE 3.13 Enzymes Lower the Energy Barrier The activation energy (E_a) is lower in an enzyme-catalyzed reaction than in an uncatalyzed reaction, but the free energy released is the same with or without catalysis. A lower activation energy means the reaction will take place at a faster rate.

Go to ACTIVITY 3.4 Free Energy Changes
PoL2e.com/ac3.4

Enzymes bind specific reactants at their active sites

Catalysts increase the rates of chemical reactions. Most nonbiological catalysts are nonspecific. For example, powdered platinum catalyzes virtually any reaction in which molecular hydrogen (H_2) is a reactant. In contrast, most biological catalysts are highly specific. An enzyme usually recognizes and binds to only one or a few closely related reactants, and it catalyzes only a single chemical reaction.

In an enzyme-catalyzed reaction, the reactants are called **substrates**. Substrate molecules bind to a particular site on the enzyme, called the **active site**, where catalysis takes place (**FIGURE 3.14**). The specificity of an enzyme results from the exact three-dimensional shape (also called conformation) and chemical properties of its active site. Only a narrow range of substrates, with specific shapes, functional groups, and chemical properties, can fit properly and bind to the active site. The names of enzymes reflect their functions and often end with the suffix "ase." For example, the enzyme sucrase catalyzes the hydrolysis of sucrose, and we write the reaction as follows:

$$\text{Sucrose} + H_2O \xrightarrow{\text{Sucrase}} \text{glucose} + \text{fructose}$$

The binding of a substrate (S) to the active site of an enzyme (E) produces an **enzyme–substrate complex** (**ES**) that is held together by one or more means, such as hydrogen bonding, ionic attraction, or temporary covalent bonding. The enzyme–substrate complex gives rise to product (P) and free enzyme:

$$E + S \rightarrow ES \rightarrow E + P$$

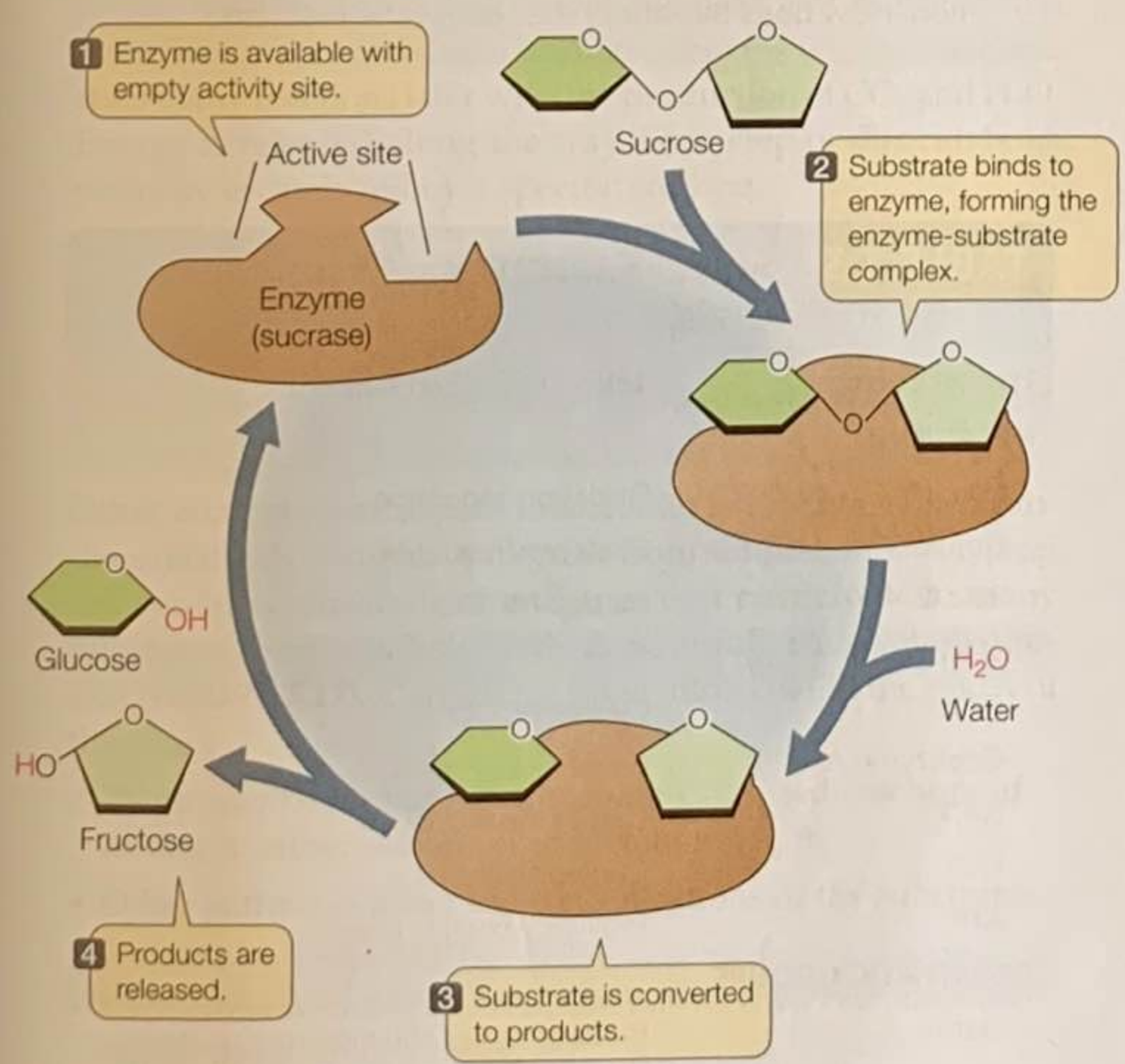
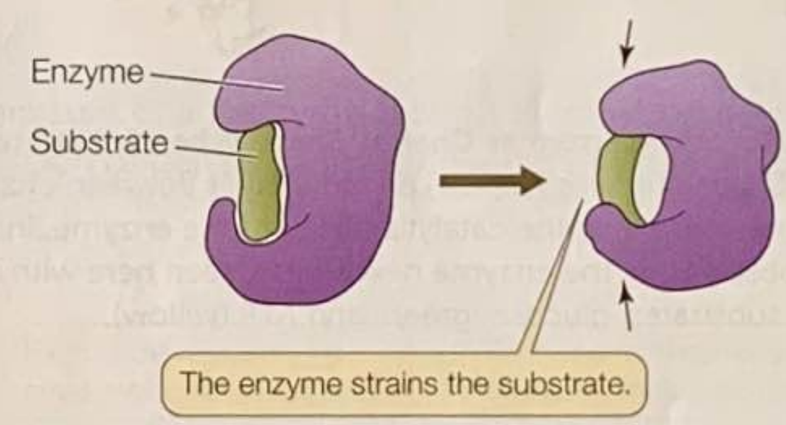


FIGURE 3.14 Enzyme Action Sucrase catalyzes the hydrolysis of sucrose. After the reaction, the enzyme is unchanged and is ready to accept another substrate molecule.

(As we have seen in the case of sucrase, a single enzyme-catalyzed reaction may involve multiple substrates and/or products.) The free enzyme (E) is in the same chemical form at the end of the reaction as at the beginning. While bound to the substrate(s), it may change chemically, but by the end of the reaction it has been restored to its initial form and is ready to catalyze the same reaction again (see Figure 3.14).

HOW ENZYMES WORK During and after the formation of the enzyme–substrate complex, chemical interactions occur. These interactions contribute directly to the breaking of old bonds and the formation of new ones. In catalyzing a reaction, an enzyme may use one or more mechanisms:

- *Inducing strain*: Once the substrate has bound to the active site, the enzyme causes bonds in the substrate to stretch, putting it in an unstable transition state:



- *Substrate orientation:* When free in solution, substrates are moving from place to place randomly while at the same time vibrating, rotating, and tumbling. They only rarely have the proper orientation to react when they collide. The enzyme lowers the activation energy needed to start the reaction, by bringing together specific atoms so that bonds can form.
- *Adding chemical groups:* The side chains (R groups) of an enzyme's amino acids may be directly involved in the reaction. For example, in acid–base catalysis, the acidic or basic side chains of the amino acids in the active site transfer H^+ ions to or from the substrate, destabilizing a covalent bond in the substrate and permitting the bond to break.

The active site is usually only a small part of the enzyme protein. But its three-dimensional structure is so specific that it binds only one or a few related substrates. The binding of the substrate to the active site depends on the same relatively weak forces that maintain the tertiary structure of the enzyme: hydrogen bonds, the attraction and repulsion of charged groups, and hydrophobic interactions. Scientists used to think of substrate binding as being similar to a lock and key fitting together. Actually, for most enzymes and substrates the relationship is more like a baseball and a catcher's mitt: the substrate first binds, and then the active site changes slightly to make the binding tight. **FIGURE 3.15** illustrates this "induced fit" phenomenon. (We introduced the concept of protein structure changes earlier; see Figure 3.11.)

Induced fit at least partly explains why enzymes are so large. The rest of the macromolecule has at least three roles:

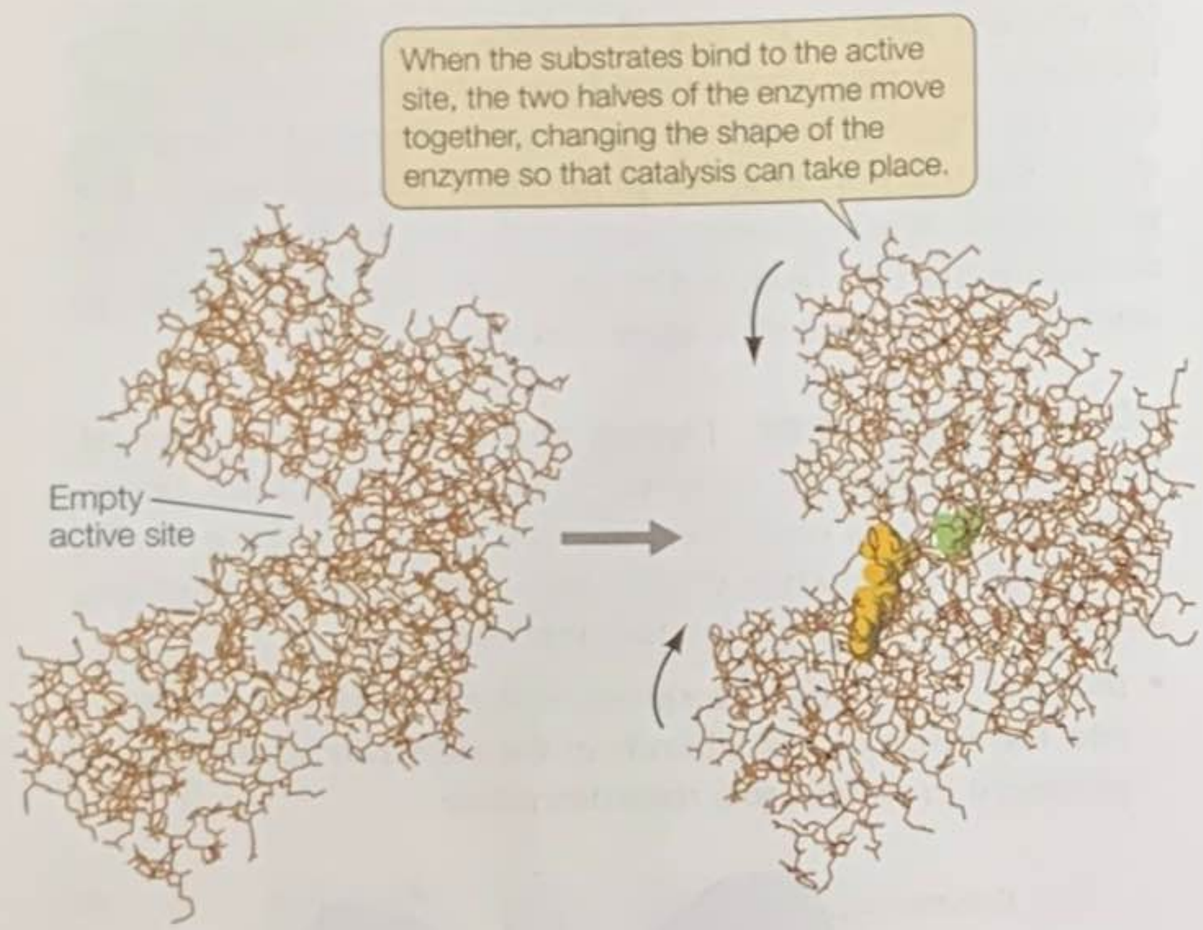


FIGURE 3.15 Some Enzymes Change Shape When Substrate Binds to Them Shape changes result in an induced fit between enzyme and substrate, improving the catalytic ability of the enzyme. Induced fit can be observed in the enzyme hexokinase, seen here with and without its substrates, glucose (green) and ATP (yellow).

- It provides a framework so the amino acids of the active site are properly positioned in relation to the substrate(s).
- It participates in the changes in protein shape and structure that result in induced fit.
- It provides binding sites for regulatory molecules (as we will discuss in Concept 3.4).

NONPROTEIN PARTNERS FOR ENZYMES Some enzymes require ions or other molecules in order to function. These molecules are referred to as **cofactors**, and they can be grouped into three categories (**TABLE 3.3**):

- *Metal ions* such as copper, zinc, and iron bind to certain enzymes and participate in the enzyme-catalyzed reactions. For example, the cofactor zinc binds to the enzyme alcohol dehydrogenase, which catalyzes the breakdown of toxic alcohol.
- A *coenzyme* is a relatively small, carbon-containing (organic) molecule that is required for the action of one or more enzymes. It binds to the active site of the enzyme, adds or removes a chemical group from the substrate, and then separates from the enzyme to participate in other reactions. A coenzyme differs from a substrate in that it can participate in many different reactions with different enzymes.
- *Prosthetic groups* are organic molecules that are permanently bound to their enzymes. An example is a flavin nucleotide, which binds to succinate dehydrogenase, an important enzyme in energy metabolism.

RATE OF REACTION The rate of an uncatalyzed reaction is directly proportional to the concentration of the substrate. The higher the concentration, the more reactions per unit of time. As we have seen, the addition of the appropriate enzyme speeds up the reaction, but it also changes the shape of the plot of rate versus substrate concentration (**FIGURE 3.16**). For a given concentration of enzyme, the rate of the enzyme-catalyzed reaction initially increases as the substrate concentration increases from zero, but then it levels off.

Why does this happen? The concentration of an enzyme is usually much lower than that of its substrate and does not change as substrate concentration changes. When all the enzyme molecules are bound to substrate molecules, the enzyme is working at its maximum rate. Under these conditions the active sites are said to be saturated.

The maximum rate of a catalyzed reaction can be used to measure how efficient the enzyme is—that is, how many molecules of substrate are converted into product by an individual enzyme molecule per unit of time, when there is an excess of substrate present. This turnover number ranges from 1 molecule every second for sucrase to an amazing 40 million molecules per second for the liver enzyme catalase.

CHECKpoint CONCEPT 3.3

- ✓ Explain how the structure of an enzyme makes that enzyme specific.
- ✓ What is activation energy? How does an enzyme lower the activation energy needed to start a reaction?
- ✓ Compare coenzymes with substrates. How do they work together in enzyme catalysis?
- ✓ Compare the state of an enzyme active site at a low substrate concentration and at a high substrate concentration. How does this affect the rate of the reaction?

TABLE 3.3 Some Examples of Enzyme Cofactors

Type of cofactor	Role in catalyzed reactions
METAL IONS	
Iron (Fe^{2+} or Fe^{3+})	Oxidation/reduction
Copper (Cu^{+} or Cu^{2+})	Oxidation/reduction
Zinc (Zn^{2+})	Helps bind NAD
COENZYMES	
Biotin	Carries $-COO^{-}$
Coenzyme A	Carries $-CO-CH_3$
NAD	Carries electrons
FAD	Carries electrons
ATP	Provides/extracts energy
PROSTHETIC GROUPS	
Heme	Binds ions, O_2, and electrons; contains iron cofactor
Flavin	Binds electrons
Retinal	Converts light energy

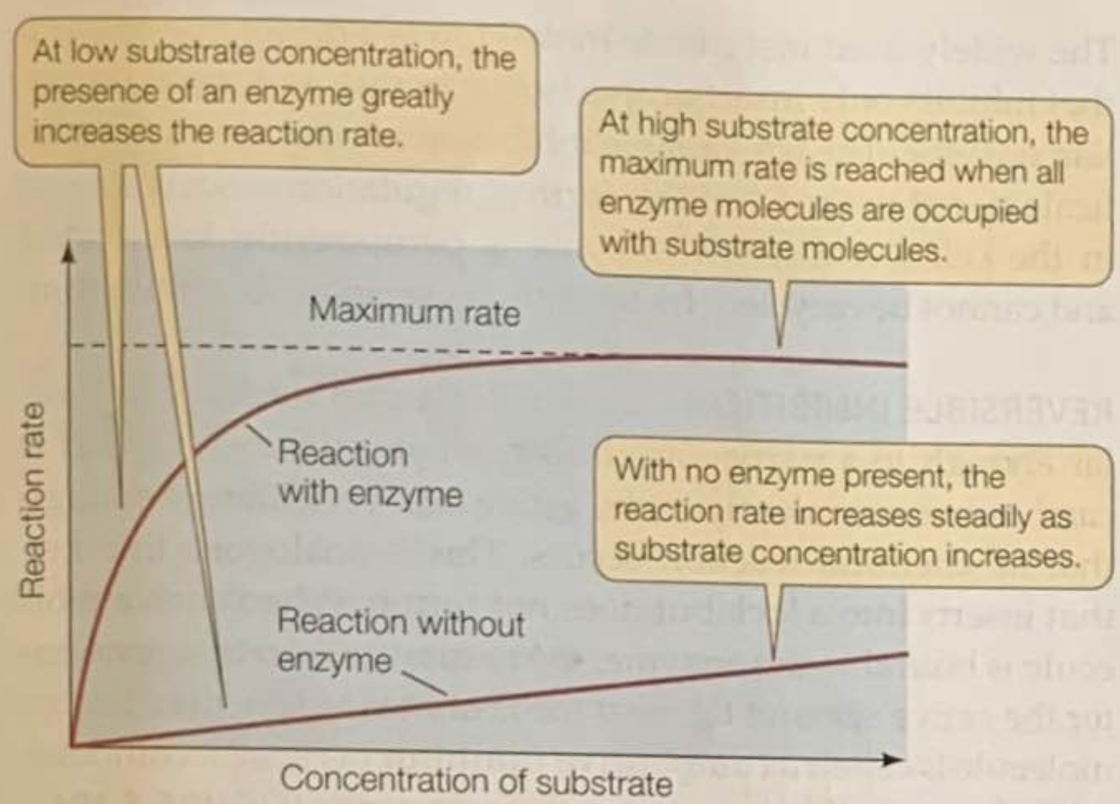


FIGURE 3.16 Catalyzed Reactions Reach a Maximum Rate Because there is usually less enzyme than substrate present, the reaction rate levels off when the enzyme becomes saturated.

Now that you understand more about how enzymes function, let's see how different enzymes work in the metabolism of living organisms.

CONCEPT 3.4 Regulation of Metabolism Occurs by Regulation of Enzymes

The enzyme-catalyzed reactions we have been discussing often operate within **metabolic pathways** in which the product of one reaction is a substrate for the next. For example, the pathway for the catabolism of sucrose begins with sucrase and ends many reactions later with the production of CO_2 and H_2O. Energy is released along the way. Each step of this catabolic pathway is catalyzed by a specific enzyme:

$$\text{Sucrose} + H_2O \xrightarrow{\text{Sucrase}} \text{glucose} + \text{fructose} \longrightarrow$$
$$\xrightarrow{\text{Many enzymes}} CO_2 + H_2O$$

Other enzymes participate in anabolic pathways, which produce relatively complex molecules from simpler ones. A typical cell contains hundreds of enzymes that participate in many interconnecting metabolic pathways, forming a metabolic system (**FIGURE 3.17**). Consider a single molecule in the midst of this map:

- There may be two or more enzyme-catalyzed reactions affecting it: either making it or metabolizing it.
- Other pathways affect the concentrations of the substrates and products of these reactions.
- Each enzyme-catalyzed reaction has its own rate, depending on these concentrations.

Clearly, every component of this complex system is affected by every other component, making it difficult to predict what would happen if one or more components were altered. In the new field of **systems biology**, scientists describe mathematically the components of metabolic systems—the concentrations of all the reactants and the rates of the reactions—and use computer algorithms to make predictions about what would happen if a component of the system were altered (see Concept 1.2, pp. 8–9).

Cells need to maintain stable internal conditions, including constant levels of certain metabolites. In addition, cells need to regulate their metabolic pathways to respond to changes, either within the organism or in its environment. One way a cell can regulate its metabolism is to control the *amount* of an enzyme. For example, the product of a metabolic pathway may be available from the cell's environment in adequate amounts. In this case, it would be energetically wasteful for the cell to continue making large proteins (as most enzymes are) that it doesn't need. For this reason, cells often have the ability to turn off the synthesis of certain enzymes.

LINK

The amount of an enzyme is controlled by regulating the expression of gene(s), a topic covered in **Chapter 11**

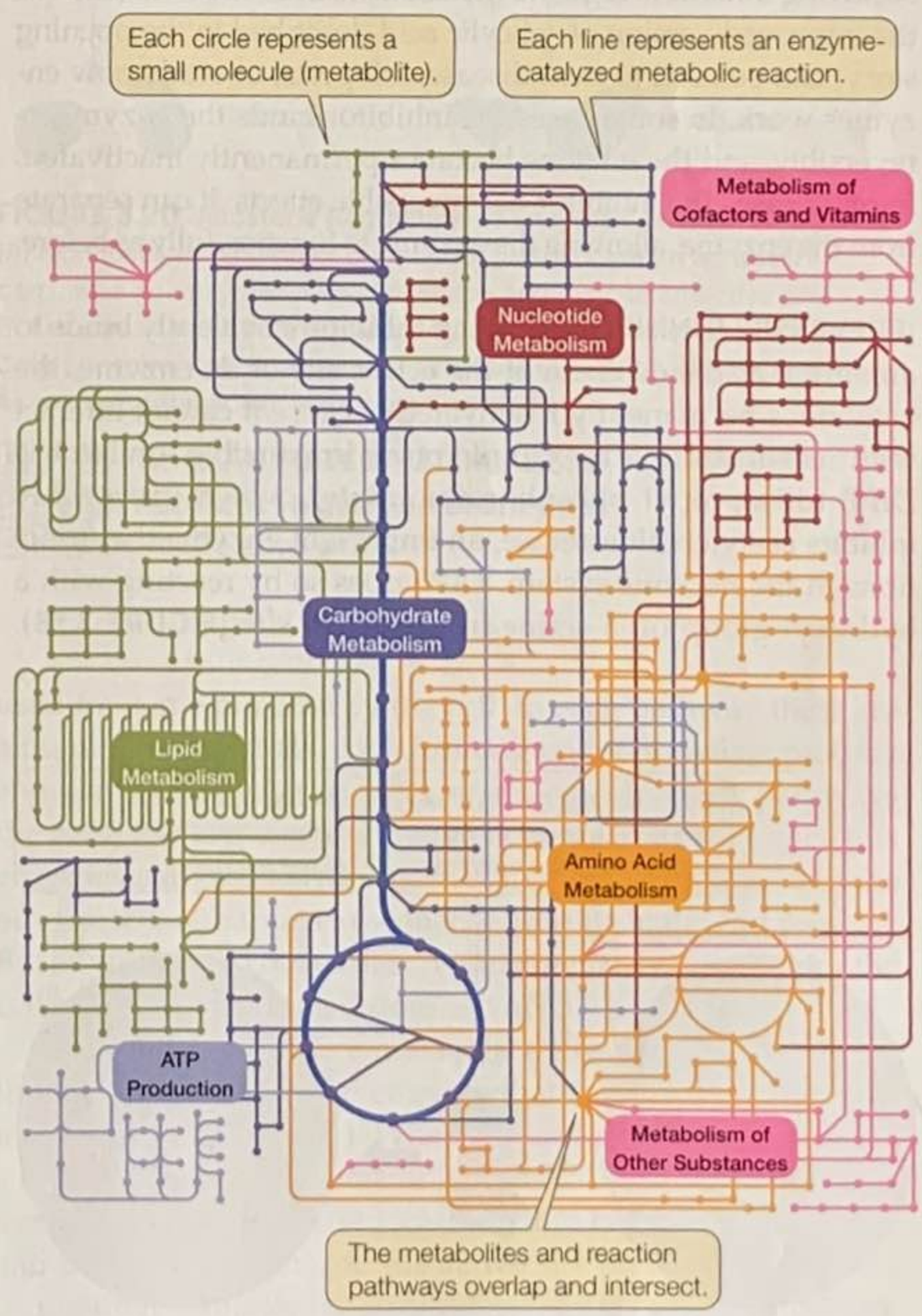


FIGURE 3.17 A Biochemical System The complex interactions of metabolic pathways can be studied using the tools of systems biology. Enzymes are a major element controlling these pathways.

The consequences of *too little* enzyme can be significant. For example, in humans sucrase is important in digestion. In rare cases, infants are born with a congenital sucrase deficiency and the pathway that begins with sucrose is essentially blocked. If these infants ingest foods containing sucrose, the sucrose accumulates rather than being catabolized, and the infant gets diarrhea and stomach cramps. In some cases this leads to slower growth. This deficiency can be treated by limiting sucrose consumption or taking tablets that contain sucrase at every meal.

Cells can also maintain stable internal conditions by regulating the *activity* of enzymes. An enzyme protein may be present continuously, but it may be active or inactive depending on the needs of the cell. Synthesizing and breaking down enzymes takes time, whereas regulating enzyme activity allows cells to fine-tune metabolism relatively quickly in response to changes in the environment. In this section, we will describe how enzyme regulation occurs.

Enzymes can be regulated by inhibitors

Various chemical inhibitors can bind to enzymes, slowing down the rates of the reactions they catalyze. Some inhibitors occur naturally in cells; others can be made in laboratories. Naturally occurring inhibitors regulate metabolism; artificial ones (such as the improved version of salicylic acid described in the opening story) can be used to treat disease, kill pests, or study how enzymes work. In some cases the inhibitor binds the enzyme irreversibly, and the enzyme becomes permanently inactivated. In other cases the inhibitor has reversible effects; it can separate from the enzyme, allowing the enzyme to function fully as before.

IRREVERSIBLE INHIBITION If an inhibitor covalently binds to an amino acid side chain at the active site of an enzyme, the enzyme is permanently inactivated because it cannot interact with its substrate. An example of an irreversible inhibitor is DIPF (diisopropyl phosphorofluoridate), which irreversibly inhibits acetylcholinesterase, an important enzyme that functions in the nervous system. DIPF does so by reacting with a hydroxyl group on a serine in the active site (**FIGURE 3.18**).

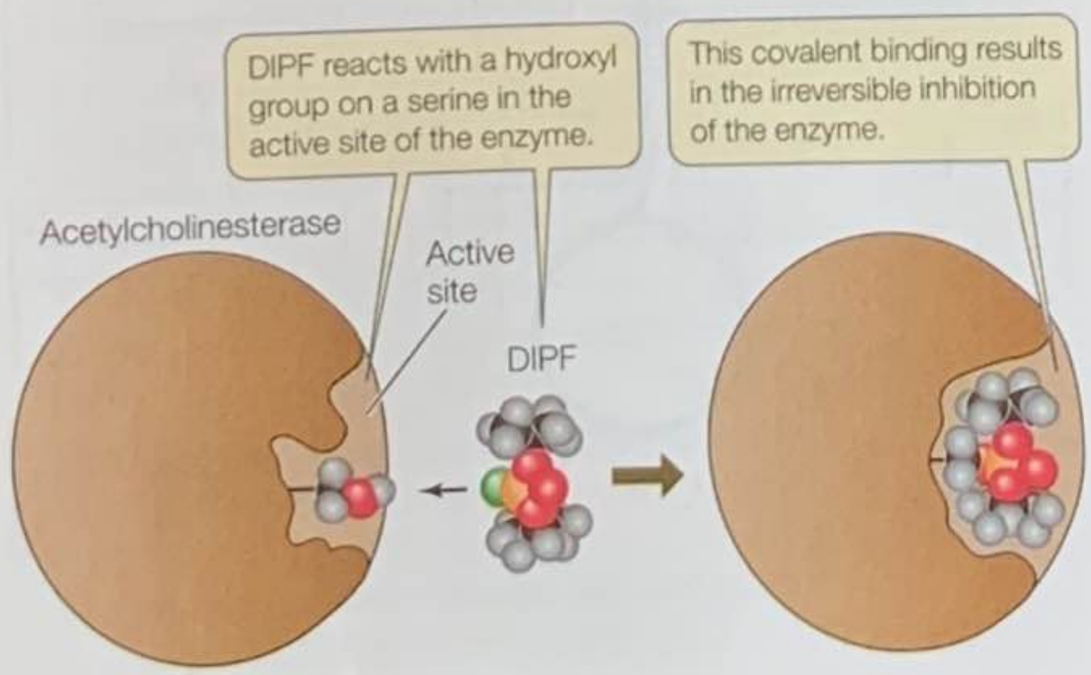


FIGURE 3.18 Irreversible Inhibition DIPF forms a stable covalent bond with the amino acid serine at the active site of the enzyme acetylcholinesterase, thus irreversibly disabling the enzyme.

The widely used insecticide malathion is a derivative of DIPF that inhibits only insect acetylcholinesterase, not the mammalian enzyme. The irreversible inhibition of enzymes is of practical use to humans, but this form of regulation is not common in the cell, because the enzyme is permanently inactivated and cannot be recycled. Instead, cells use reversible inhibition.

REVERSIBLE INHIBITION In some cases, an inhibitor is similar enough to a particular enzyme's natural substrate that it can bind noncovalently to the active site, yet different enough that no chemical reaction occurs. This is analogous to a key that inserts into a lock but does not turn it. When such a molecule is bound to the enzyme, the natural substrate cannot enter the active site and the enzyme is unable to function. Such a molecule is called a **competitive inhibitor** because it competes with the natural substrate for the active site (**FIGURE 3.19A**). Many drugs are competitive inhibitors of enzyme targets. For example, methotrexate is a drug designed with a structure similar to the metabolite dihydrofolate. The latter is converted by an enzyme to a substance essential to cell division. Acting as a competitive inhibitor of the enzyme, methotrexate blocks cell division and is used in cancer therapy. Competitive inhibition is reversible. When the concentration of the competitive inhibitor is reduced, the active site is less likely to be occupied by the inhibitor, and the enzyme regains activity.

A **noncompetitive inhibitor** binds to an enzyme at a site distinct from the active site. This binding causes a change in the shape (the conformation) of the enzyme, altering its activity (**FIGURE 3.19B**). The active site may no longer bind the substrate, or if it does, the rate of product formation may be reduced. Like competitive inhibitors, noncompetitive inhibitors can become unbound, so their effects are reversible.

An allosteric enzyme is regulated by changes in its shape

Noncompetitive inhibition is an example of allostery (*allo*, "different"; *stereos*, "shape"). **Allosteric regulation** occurs when a non-substrate molecule binds or modifies a site other than the active site of an enzyme. The site bound by the non-substrate molecule is called the allosteric site. This binding induces the enzyme to change its conformation, altering the chemical attraction (affinity) of the active site for the substrate. As a result, the rate of the reaction is changed.

An allosteric site may be modified by either noncovalent or covalent binding:

- *Noncovalent binding*: A regulatory molecule may bind noncovalently to an allosteric site, causing the enzyme to change shape. This noncovalent binding is reversible, and may result in the inactivation of an enzyme (see Figure 3.19B) or the activation of a formerly inactive enzyme (**FIGURE 3.20A**).
- *Covalent binding*: Some allosteric sites can be modified by the covalent binding of a molecule or chemical group. For example, an amino acid residue can be covalently modified by the addition of a phosphate group, in a process called phosphorylation (**FIGURE 3.20B**). If this occurs in a hydro-

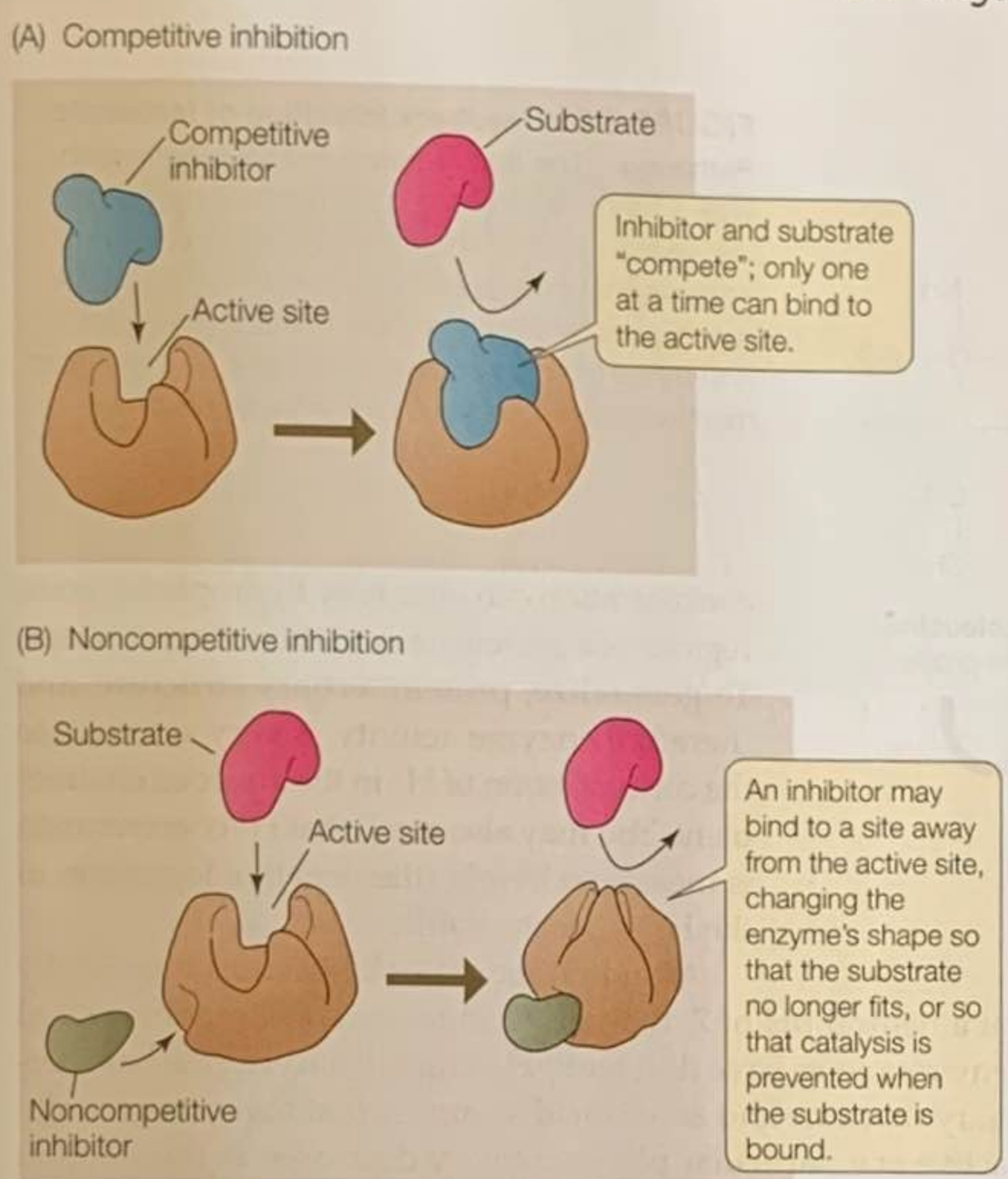


FIGURE 3.19 Reversible Inhibition (A) A competitive inhibitor binds temporarily to the active site of an enzyme. (B) A noncompetitive inhibitor binds temporarily to the enzyme at a site away from the active site. In both cases, the enzyme's function is disabled for only as long as the inhibitor remains bound.

Go to ANIMATED TUTORIAL 3.2
Enzyme Catalysis
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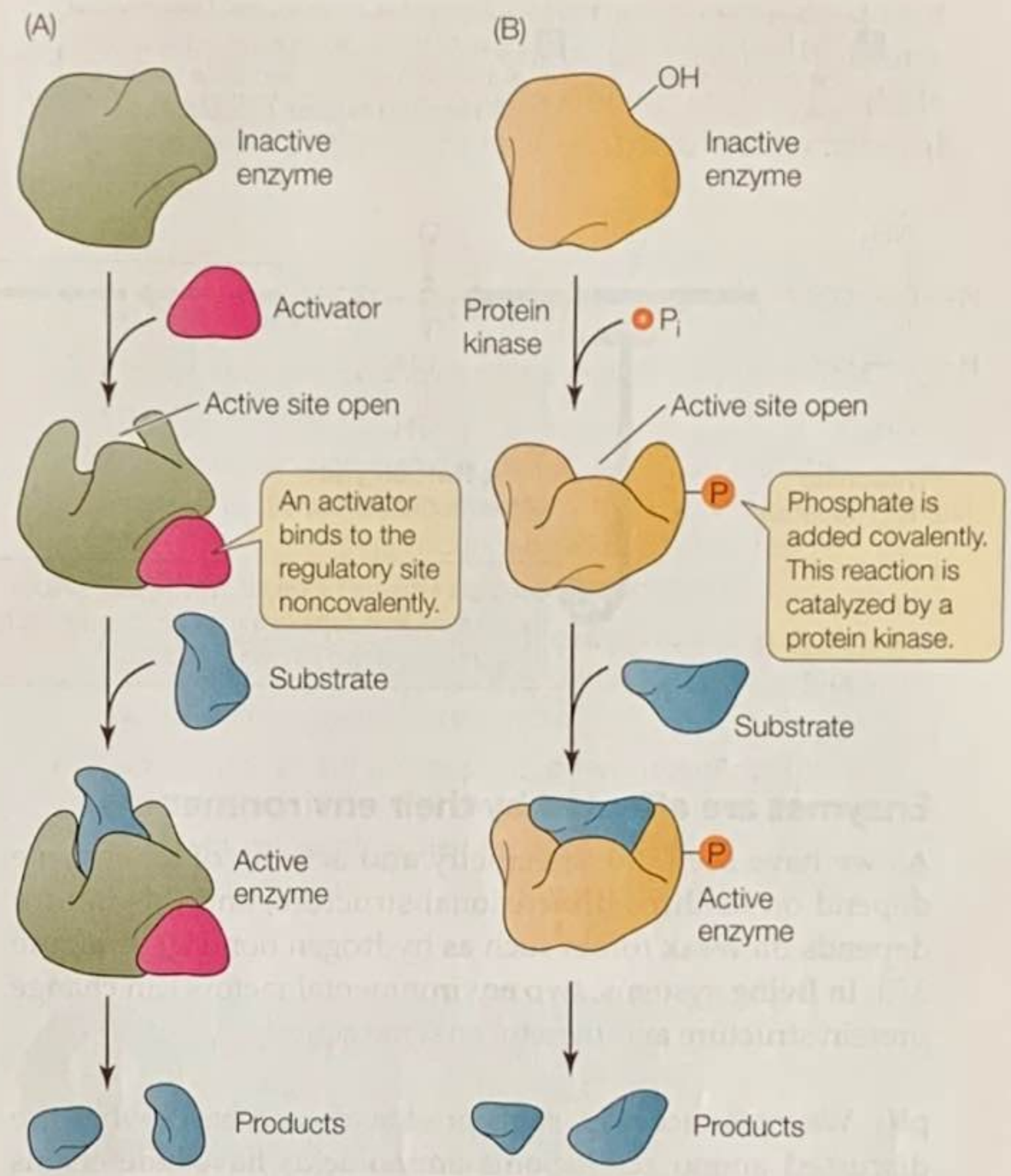

FIGURE 3.20 Allosteric Regulation of Enzyme Activity (A) Noncovalent binding of a regulator (in this case an activator) can cause an enzyme to change shape and expose an active site. B) Enzymes can also be activated by covalent modification, in this case phosphorylation. Note that allosteric regulation can be negative as well, with the active site becoming hidden.

Go to ANIMATED TUTORIAL 3.3
Allosteric Regulation of Enzymes
PoL2e.com/at3.3

phobic region of the enzyme, it makes that region hydrophilic, because phosphate carries a negative charge. The protein twists, and this can expose or hide the active site. Protein phosphorylation is an extremely important mechanism by which cells regulate many different enzymes and other proteins. It is a reversible process: a class of enzymes called protein kinases catalyze the addition of phosphate groups to proteins, whereas protein phosphatases remove phosphate groups from proteins. Humans have hundreds of different protein kinases and phosphatases. We will return to the exact functions of these proteins many times in this book.

LINK

Protein kinases are of particular importance in intracellular signaling pathways (see **Concepts 5.5 and 5.6**) and in the control of cell reproduction (see **Concept 7.3**)

Some metabolic pathways can be controlled by feedback inhibition

A metabolic pathway typically involves a starting material, various intermediate products, and an end product that is used for some purpose by the cell. In each pathway there are a number of reactions, each forming an intermediate product and each catalyzed by a different enzyme. In many pathways the first step is the commitment step, meaning that once this enzyme-catalyzed reaction occurs, the "ball is rolling," and the other reactions happen in sequence, leading to the end product. But as we pointed out earlier, it is energetically wasteful for the cell to make something it does not need.

One way to regulate a metabolic pathway is by having the final product inhibit the enzyme that catalyzes the commitment step (**FIGURE 3.21**). When the end product is present at a high concentration, some of it binds to a site on the commitment step enzyme, thereby causing it to become inactive. The end product may bind to the active site on the enzyme (as a competitive inhibitor) or an allosteric site (as a noncompetitive inhibitor). This mechanism is known as **feedback inhibition** or end-product inhibition. We will describe many other examples of such inhibition in later chapters.

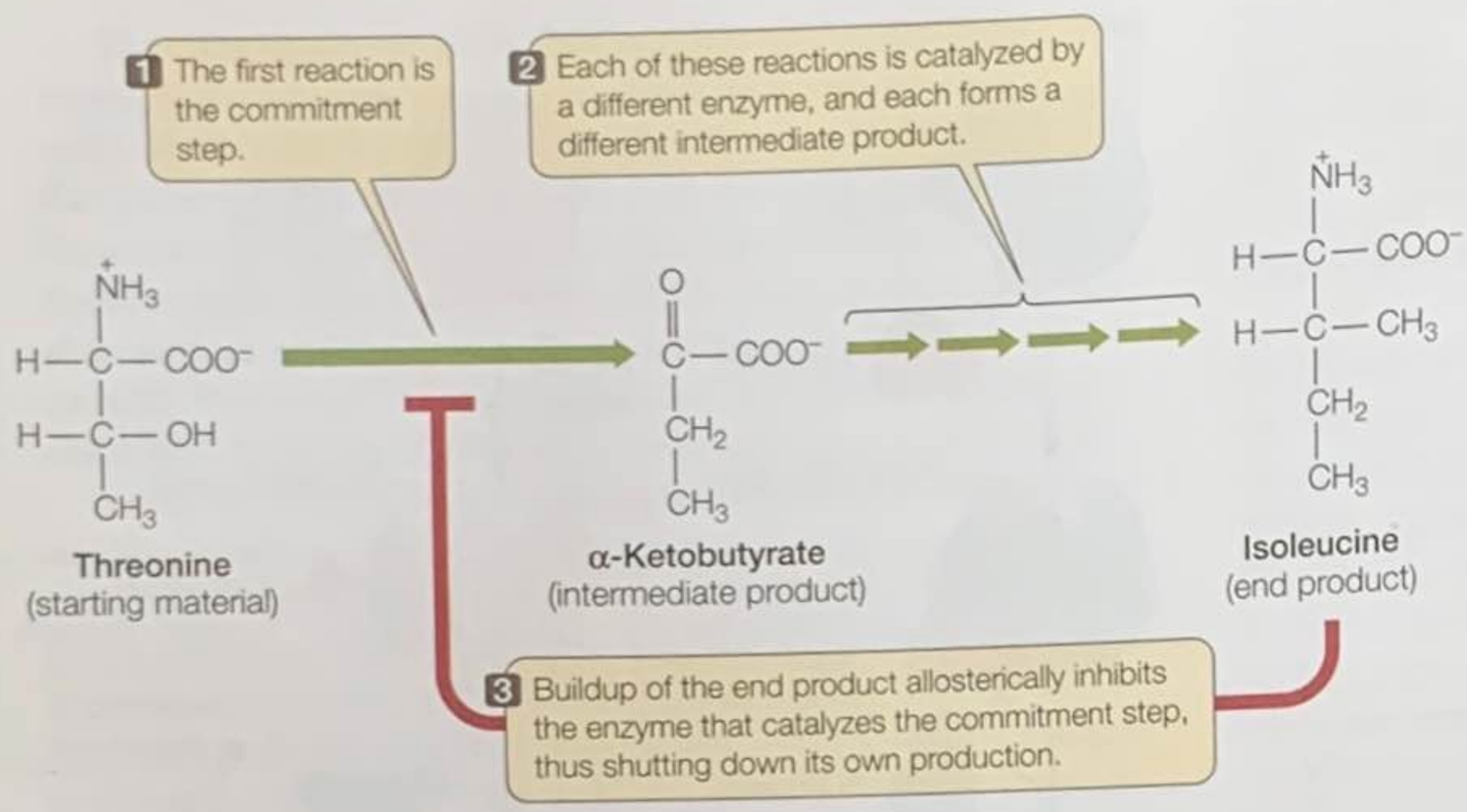

FIGURE 3.21 Feedback Inhibition of Metabolic Pathways The first reaction in a metabolic pathway is referred to as the commitment step. Often the end product of the pathway can inhibit the enzyme that catalyzes the commitment step. The specific pathway shown here is the synthesis of isoleucine from threonine in bacteria. It is typical of many enzyme-catalyzed biosynthetic pathways.

Enzymes are affected by their environment

As we have seen, the specificity and activity of an enzyme depend on its three-dimensional structure, and this in turn depends on weak forces such as hydrogen bonds (see Figure 3.7). In living systems, two environmental factors can change protein structure and thereby enzyme activity.

pH We introduced the concept of acids and bases when we discussed amino acids. Some amino acids have side chains that are acidic or basic (see Table 3.2). That is, they either generate H^+ and become anions, or attract H^+ and become cations. These reactions are often reversible. For example:

$$\text{Glutamic acid—COOH} \rightleftharpoons \text{glutamic acid—COO}^- + H^+$$

The ionic form of this amino acid (right) is far more hydrophilic than the nonionized form (left).

From your studies of chemistry, you may recall the law of mass action or Le Chatelier's principle. In this case the law implies that the higher the H^+ concentration in the solution, the more the reaction will be driven to the left (forming more of the nonionized form of glutamic acid). Therefore changes in the H^+ concentration can alter how hydrophobic some regions of a protein are and thus affect its shape. To generalize, protein tertiary structure, and therefore enzyme activity, is very sensitive to the concentration of H^+ in the aqueous environment. You may also recall that H^+ concentration is measured by pH (the negative logarithm of the H^+ concentration).

Although the water inside cells is generally at a neutral pH of 7, this can change, and different biological environments have different pH values. Each enzyme has a tertiary structure and amino acid sequence that make it optimally active at a particular pH. Its activity decreases as the solution is made more acidic or more basic than this ideal (optimal) pH (**FIGURE 3.22A**). As an example, consider the human digestive system (see Concept 30.4). The pH inside the human stomach is highly acidic, about pH 1.5. Pepsin, an enzyme that is active in the stomach, has a pH optimum near 2. Many enzymes that hydrolyze macromolecules in the intestine, such as proteases, have pH optima in the neutral range. So when food enters the small intestine, a buffer (bicarbonate) is secreted into the intestine to raise the pH to 6.5. This allows the hydrolytic enzymes to be active and digest the food.

TEMPERATURE In general, warming increases the rate of a chemical reaction because a greater proportion of the reactant molecules have enough kinetic energy to provide the activation energy for the reaction. Enzyme-catalyzed reactions are no different (**FIGURE 3.22B**). However, temperatures that are

APPLY THE CONCEPT

Regulation of metabolism occurs by regulation of enzymes

The concept of enzymes as biological catalysts has many applications. In a pile of clothes in your garage, you notice there are bacteria growing on some socks made of this synthetic polymer:

$$[\text{—CO—}(CH_2)_4\text{—CO—NH—}(CH_2)_4\text{—NH—}]_n$$

You make a protein extract from the bacteria and isolate what you think is an enzyme that can cleave the monomers from the polymer. You also synthesize the dipeptide glycine-glycine (see Table 3.2) to test as a possible inhibitor of the enzyme. The table shows the results from several of your experiments.

EXPERIMENT	CONDITION	RATE OF POLYMER CLEAVAGE
1	No enzyme	0.505
2	Enzyme	825.0
3	Enzyme pre-boiled at 100°C	0.520
4	Enzyme + dipeptide	0.495
5	Enzyme + RNA	799.0

1. Explain the results of each experiment.
2. How might the dipeptide work? How would you test your hypothesis?

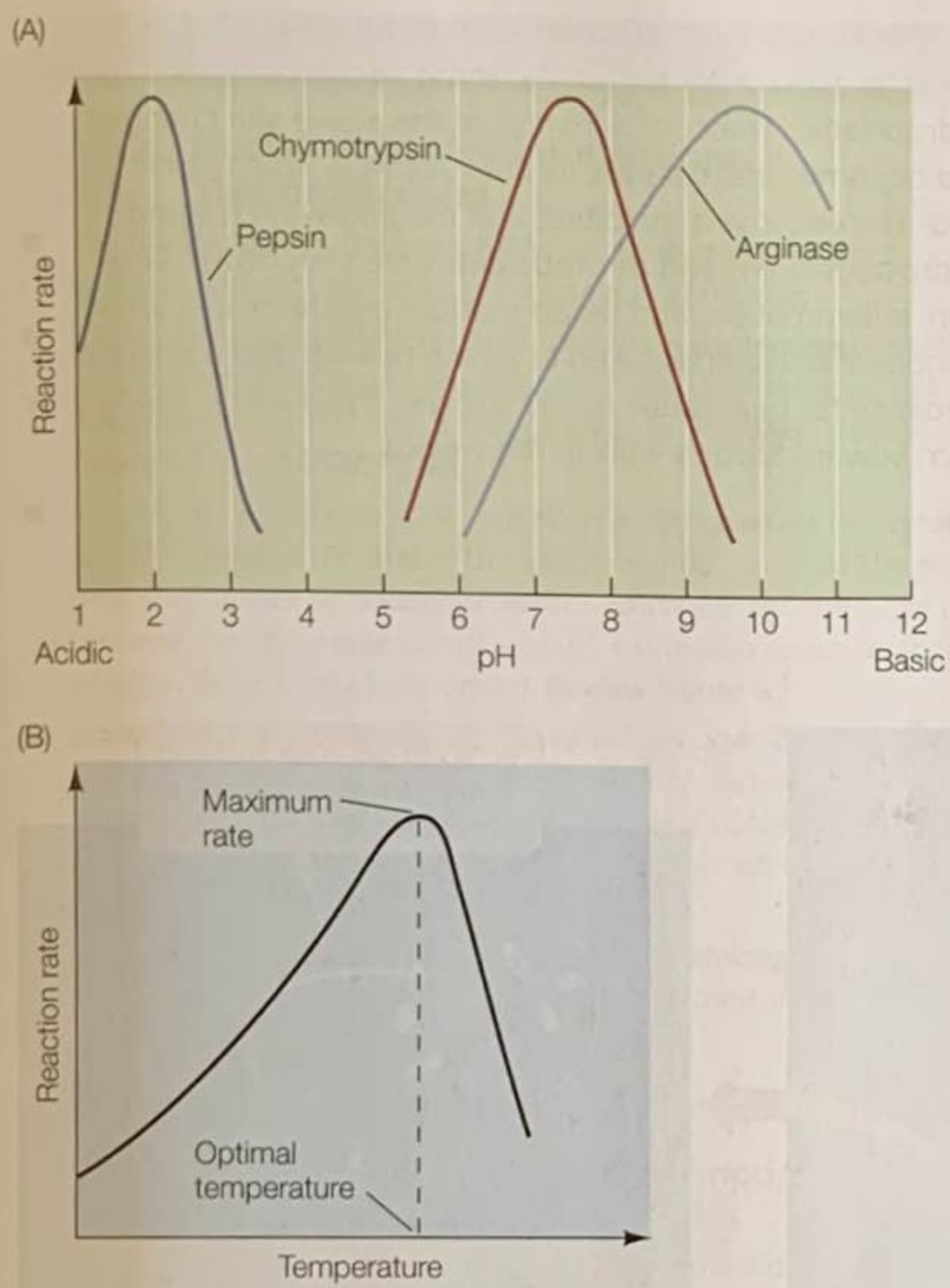

FIGURE 3.22 Enzyme Activity Is Affected by the Environment (A) The activity curve for each enzyme peaks at its optimal pH. For example, pepsin is active in the acidic environment of the stomach, whereas chymotrypsin is active in the neutral environment of the small intestine, and arginase is active in a basic environment. (B) Similarly, there is an optimal temperature for each enzyme. At higher temperatures the enzyme becomes denatured and inactive; this explains why the activity curve falls off abruptly at temperatures that are above optimal.

too high inactivate enzymes, because at high temperatures the polypetides vibrate and twist so rapidly that some of their noncovalent bonds break. When an enzyme's tertiary structure is changed by heat, the enzyme can no longer function. Some enzymes denature at temperatures only slightly above that of the human body, but a few are stable even at the boiling point (or freezing point) of water. All enzymes have an optimal temperature for activity.

Individual organisms adapt to changes in the environment in many ways, one of which is based on groups of enzymes called isozymes, which catalyze the same reaction but have different chemical compositions and physical properties. Different isozymes within a given group may have different optimal temperatures. The rainbow trout, for example, has several isozymes of the enzyme acetylcholinesterase. If a rainbow trout is transferred from warm water to near-freezing water (2°C), the fish produces a different isozyme of acetylcholinesterase. The new isozyme has a lower optimal temperature, allowing the fish's nervous system to perform normally in the colder water.

In general, enzymes adapted to warm temperatures do not denature at those temperatures because their tertiary structures are held together largely by covalent bonds such as disulfide bridges, instead of the more heat-sensitive weak chemical interactions.

CHECKpoint CONCEPT 3.4

- ✓ Explain and give examples of irreversible and reversible enzyme inhibitors.
- ✓ The amino acid glutamic acid (see Table 3.2) is at the active site of an enzyme. Normally the enzyme is active at pH 7. At pH 4 (higher concentration of H^+), the enzyme is inactive. Explain these observations.
- ✓ An enzyme is subject to allosteric regulation. How would you design an inhibitor of the enzyme that was competitive? Noncompetitive? Irreversible?
- ✓ Some organisms thrive at pH 2; other organisms thrive at a temperature of 65°C. Yet mammals cannot tolerate either environment in their tissues. Explain.

Q How does an understanding of proteins and enzymes help explain how aspirin works?

ANSWER The mechanism by which aspirin works exemplifies many of the concepts introduced in this chapter. Robert Vane showed that aspirin binds to a protein with a specific three-dimensional structure (Concept 3.2). This protein is cyclooxygenase, an enzyme (Concept 3.3) that catalyzes the commitment step in a metabolic pathway (Concept 3.4). Aspirin acts as an irreversible inhibitor of cyclooxygenase (Concept 3.4). Follow the description below carefully, as it illustrates these important concepts.

Cyclooxygenase catalyzes the conversion of a fatty acid with 20 carbon atoms, arachidonic acid, to a structure with a ring (thus the "cyclo" in the name of the enzyme). O_2 is a substrate (thus the "oxygen"; **FIGURE 3.23**). The product of

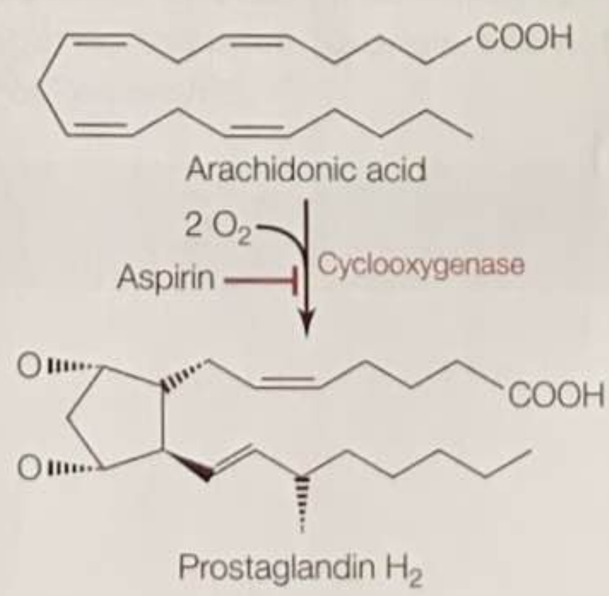

FIGURE 3.23 Aspirin: An Enzyme Inhibitor Aspirin inhibits a key enzyme in the metabolic pathways leading to inflammation and blood clotting.

this reaction (prostaglandin H_2) is the starting material for biochemical pathways that produce two types of molecules:

- prostaglandins, which are involved in inflammation and pain, and
- thromboxanes, which stimulate blood clotting and constriction of blood vessels.

Aspirin binds and reacts with a serine residue within the active site of cyclooxygenase. As a result of this binding, an acetyl group is transferred to the exposed hydroxyl group of the serine residue (**FIGURE 3.24**):

$$\text{(Cyclooxygenase)–serine–OH} \longrightarrow \text{(cyclooxygenase)–serine–O–CH}_2\text{–CH}_3$$

This covalent modification changes the exposed, polar serine to a less polar molecule, and it becomes slightly more hydrophobic. The conformation of the active site changes and becomes inaccessible to the substrate, arachidonic acid. The enzyme is inhibited, and the pathways leading to prostaglandins and thromboxanes are shut down. Less pain, inflammation, and blood clotting are the result. Small wonder that aspirin is taken as a pain reliever and a preventive medicine for heart attacks and strokes. It has come a long way from Edward Stone's walk in the woods

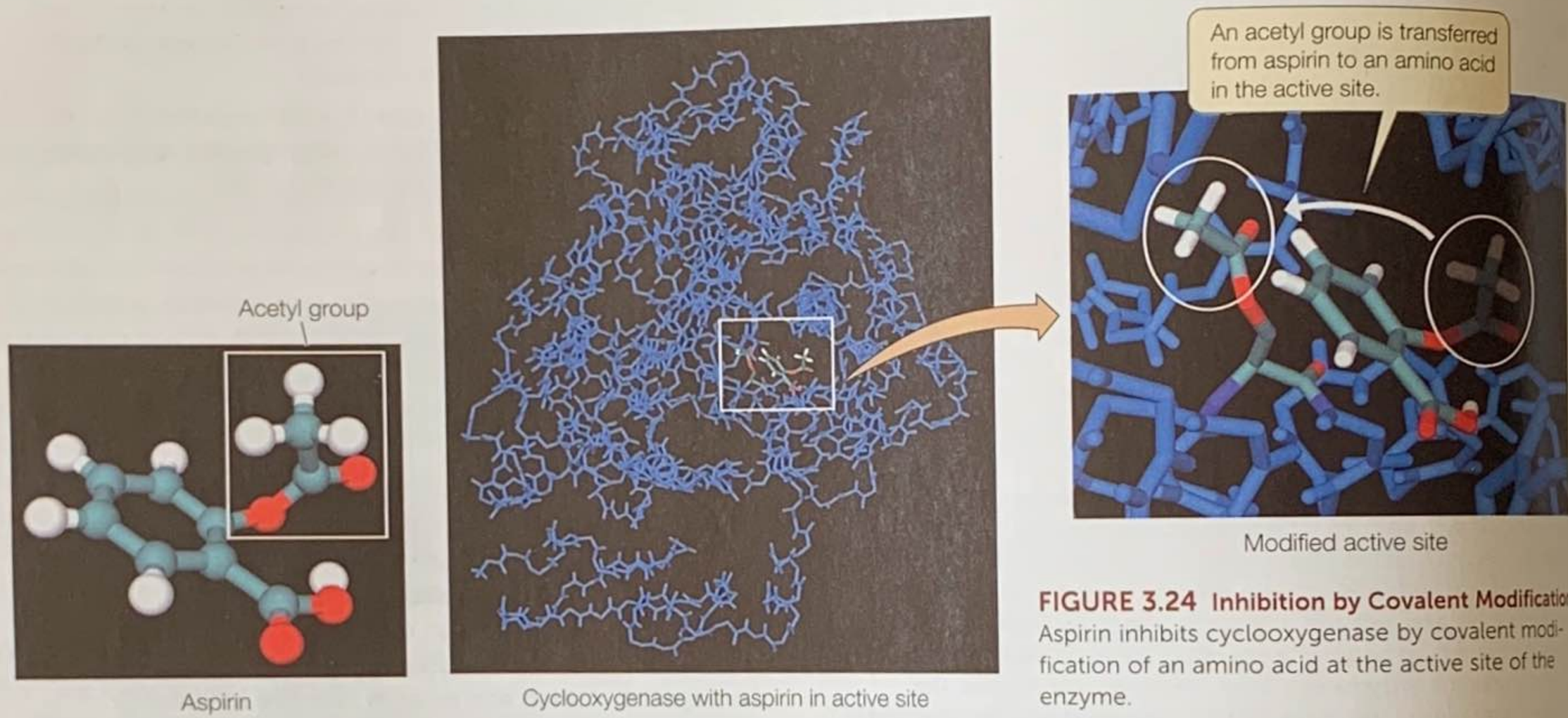

FIGURE 3.24 Inhibition by Covalent Modification Aspirin inhibits cyclooxygenase by covalent modification of an amino acid at the active site of the enzyme.

SUMMARY

CONCEPT 3.1 Nucleic Acids Are Informational Macromolecules

- The **nucleic acids**—**DNA** and **RNA**—are used mainly to store, transmit, and express hereditary (genetic) information.
- Nucleic acids are polymers of nucleotides. A **nucleotide** consists of one to three phosphate groups, a pentose sugar (**ribose** in RNA and **deoxyribose** in DNA), and a nitrogen-containing **base. Review Figure 3.1 and ACTIVITY 3.1**
- In DNA, the nucleotide bases are **adenine** (**A**), **guanine** (**G**), **cytosine** (**C**), and **thymine** (**T**). **Uracil** (**U**) replaces thymine in RNA. The nucleotides are joined by **phosphodiester bonds** between the sugar of one and the phosphate of the next. RNA is usually single-stranded, whereas DNA is double-stranded. **Review Figure 3.2**
- **Complementary base pairing**, based on hydrogen bonds between A and T, A and U, and G and C, occurs in RNA and DNA. In RNA the hydrogen bonds result in a folded molecule; in DNA the hydrogen bonds connect two antiparallel strands into a double helix. **Review Figures 3.3 and 3.4 and ACTIVITY 3.2**
- DNA is expressed as RNA in the process of **transcription**. RNA can then specify the amino acid sequence of a protein in the process of **translation**.

See **ANIMATED TUTORIAL** 3.1

CONCEPT 3.2 Proteins Are Polymers with Important Structural and Metabolic Roles

- The functions of proteins include support, protection, catalysis, transport, defense, regulation, storage, and movement.
- **Amino acids** are the monomers from which polymeric proteins are made by **peptide bonds**. There are 20 different amino acids in proteins, each distinguished by a **side chain** (**R group**) that confers specific properties. **Review Table 3.2 and ACTIVITY 3.3**
- The **primary structure** of a protein is the sequence of amino acids in the polypeptide chain. This chain is folded into a **secondary structure**, which in different parts of the protein may take the form of an **α helix** or a **β pleated sheet**. **Review Figure 3.7**
- **Disulfide bridges** and noncovalent interactions between amino acids cause polypeptide chains to fold into three-dimensional **tertiary structures**. Multiple polypeptides can interact to form **quaternary structures**. A protein's unique shape and chemical structure allow it to bind specifically to other molecules.
- Heat and certain chemicals can result in a protein becoming **denatured**, which involves the loss of tertiary or secondary structure. **Review Figure 3.10**

CONCEPT 3.3 Some Proteins Act as Enzymes to Speed up Biochemical Reactions

- A chemical reaction must overcome an energy barrier to get started. An **enzyme** is a catalyst that affects the rate of a biological reaction by lowering the **activation energy** needed to initiate the reaction. **Review Figure 3.13 and ACTIVITY 3.4**
- A **substrate** binds to the enzyme's **active site**—the site of catalysis—forming an **enzyme–substrate complex**. Enzymes are highly specific for their substrates.
- At the active site, a substrate enters its **transition state**, and the reaction proceeds.
- Substrate binding causes many enzymes to change shape, exposing their active site(s) and allowing catalysis. **Review Figure 3.15**
- Some enzymes require nonprotein "partners" called **cofactors** to carry out catalysis. **Review Table 3.3**
- Substrate concentration affects the rate of an enzyme-catalyzed reaction. At the maximum rate, the enzyme is saturated with substrate. **Review Figure 3.16**

CONCEPT 3.4 Regulation of Metabolism Occurs by Regulation of Enzymes

- Metabolism is organized into pathways in which the product of one reaction is a substrate for the next reaction. A specific enzyme catalyzes each reaction in the pathway.
- Metabolic pathways are integrated into a biochemical system. **Systems biology** is a way to study how biochemical systems behave. **Review Figure 3.17**
- Enzyme activity is subject to regulation. Some inhibitors bind irreversibly to enzymes. Other inhibitors bind reversibly. **Review Figures 3.18 and 3.19 and ANIMATED TUTORIAL 3.2**
- In **allosteric regulation**, a molecule binds to a site on the enzyme other than the active site. This changes the overall structure of the enzyme (including that of its active site) and results in either activation or inhibition of the enzyme's catalytic activity. **Review Figure 3.20 and ANIMATED TUTORIAL 3.3**
- The end product of a metabolic pathway may inhibit an enzyme that catalyzes the "commitment step" of that pathway. This is called **feedback inhibition**. **Review Figure 3.21**
- Environmental pH and temperature affect enzyme activity. **Review Figure 3.22**

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