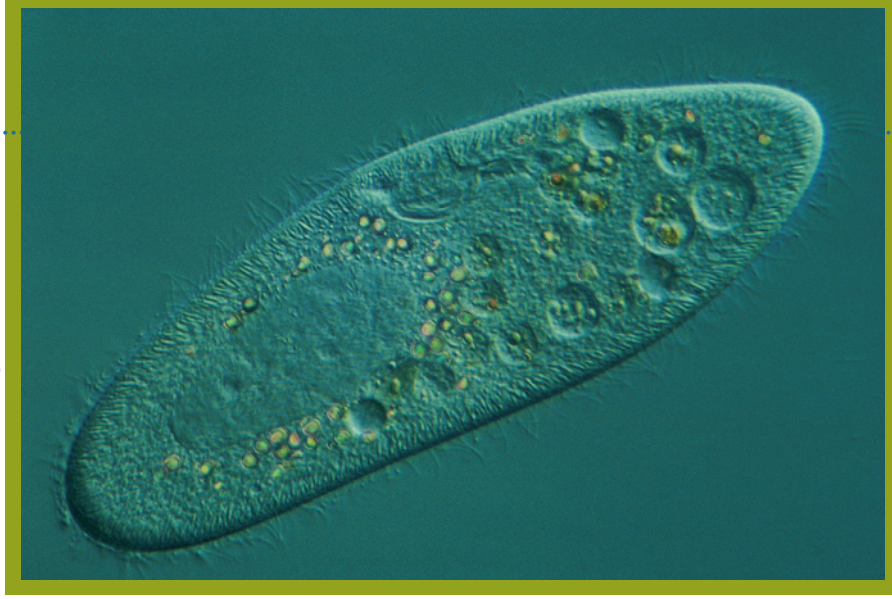


M. I. Walker/Science Source Images

The structures that make up this *Paramecium* cell, and the processes that occur within it, can be explained in chemical terms. All cells contain similar types of macromolecules and undergo similar chemical reactions to acquire energy, grow, communicate, and reproduce.

CHAPTER 1

Introduction to the Chemistry of Life

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Biochemistry is, literally, the study of the chemistry of life. Although it overlaps other disciplines, including cell biology, genetics, immunology, microbiology, pharmacology, and physiology, biochemistry is largely concerned with a limited number of issues:

1. What are the chemical and three-dimensional structures of biological molecules?
2. How do biological molecules interact with one another?
3. How does the cell synthesize and degrade biological molecules?
4. How is energy conserved and used by the cell?
5. What are the mechanisms for organizing biological molecules and coordinating their activities?
6. How is genetic information stored, transmitted, and expressed?

Biochemistry, like other modern sciences, relies on sophisticated instruments to dissect the architecture and operation of systems that are inaccessible to the human senses. In addition to the chemist's tools for separating, quantifying, and otherwise analyzing biological materials, biochemists take advantage of the uniquely biological aspects of their subject by examining the evolutionary histories of organisms, metabolic systems, and individual molecules. In addition to its obvious implications for human health, biochemistry reveals the workings of the natural world, allowing us to understand and appreciate the unique and mysterious condition that we call life. In this introductory chapter, we will review some aspects of chemistry and biology—including the basics of evolution, the different types of cells, and the elementary principles of thermodynamics—to help put biochemistry in context and to introduce some of the themes that recur throughout this book.

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1 The Origin of Life

KEY CONCEPTS

- Biological molecules are constructed from a limited number of elements.
- Certain functional groups and linkages characterize different types of biomolecules.
- During chemical evolution, simple compounds condensed to form more complex molecules and polymers.
- Self-replicating molecules were subject to natural selection.

Certain biochemical features are common to all organisms: the way hereditary information is encoded and expressed, for example, and the way biological molecules are built and broken down for energy. The underlying genetic and biochemical unity of modern organisms implies that they are descended from a single ancestor. Although it is impossible to describe exactly how life first arose, paleontological and laboratory studies have provided some insights about the origin of life.

A Biological Molecules Arose from Inanimate Substances

Living matter consists of a relatively small number of elements (Table 1-1). For example, C, H, O, N, P, Ca, and S account for ~97% of the dry weight of the human body (humans and most other organisms are ~70% water). Living organisms may also contain trace amounts of many other elements, including B, F, Al, Si, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Br, Mo, Cd, I, and W, although not every organism makes use of each of these substances.

The earliest known fossil evidence of life is ~3.5 billion years old (Fig. 1-1). The preceding **prebiotic era**, which began with the formation of the earth ~4.6 billion years ago, left no direct record, but scientists can experimentally duplicate the sorts of chemical reactions that might have given rise to living organisms during that billion-year period.

The atmosphere of the early earth probably consisted of small, simple compounds such as H_2O, N_2, CO_2, and smaller amounts of CH_4 and NH_3. In the 1920s, Alexander Oparin and J. B. S. Haldane independently suggested that ultraviolet radiation from the sun or lightning discharges caused the molecules of the primordial atmosphere to react to form simple **organic** (carbon-containing) **compounds**. This process was replicated in 1953 by Stanley Miller and Harold Urey, who subjected a mixture of H_2O, CH_4, NH_3, and H_2 to an electric discharge for about a week. The resulting solution contained water-soluble organic compounds, including several amino acids (which are components of proteins) and other biochemically significant compounds.

The assumptions behind the Miller–Urey experiment, principally the composition of the gas used as a starting material, have been challenged by some

TABLE 1-1 Most Abundant Elements in the Human Body[a]

Element	Dry Weight (%)
C	61.7
N	11.0
O	9.3
H	5.7
Ca	5.0
P	3.3
K	1.3
S	1.0
Cl	0.7
Na	0.7
Mg	0.3

[a]Calculated from Frieden, E., *Sci. Am.* **227**(1), 54–55 (1972).

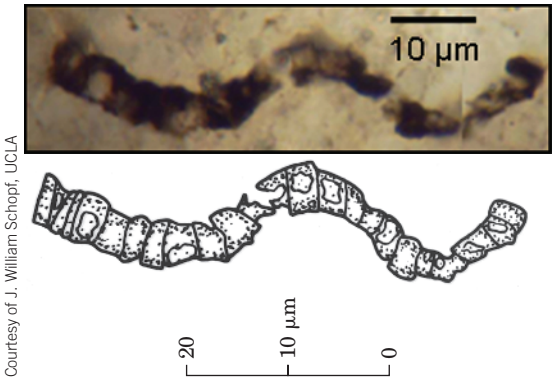
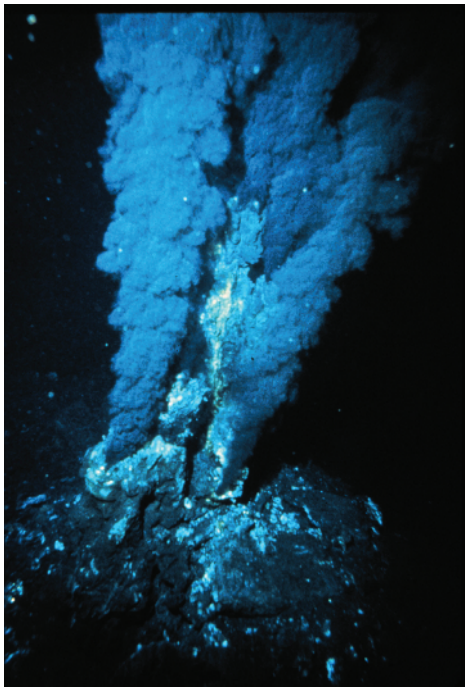


FIG. 1-1 Microfossil of filamentous bacterial cells. This fossil (shown with an interpretive drawing) is from ~3.4-billion-year-old rock from Western Australia.

scientists who have suggested that the first biological molecules were generated in a quite different way: in the dark and under water. Hydrothermal vents in the ocean floor, which emit solutions of metal sulfides at temperatures as high as 400°C (Fig. 1-2), may have provided conditions suitable for the formation of amino acids and other small organic molecules from simple compounds present in seawater.

Whatever their actual origin, the early organic molecules became the precursors of an enormous variety of biological molecules. These can be classified in various ways, depending on their composition and chemical reactivity. A familiarity with organic chemistry is useful for recognizing the **functional groups** (reactive portions) of molecules as well as the **linkages** (bonding arrangements) among them, since these features ultimately determine the biological activity of the molecules. Some of the common functional groups and linkages in biological molecules are shown in Table 1-2.



OAR/National Undersea Research Program (NURP); NOAA

FIG. 1-2 A hydrothermal vent. Such ocean-floor formations are known as "black smokers" because the metal sulfides dissolved in the superheated water they emit precipitate on encountering the much cooler ocean water.

B Complex Self-Replicating Systems Evolved from Simple Molecules

During a period of chemical evolution, the prebiotic era, simple organic molecules condensed to form more complex molecules or combined end-to-end as **polymers** of repeating units. In a **condensation reaction**, the elements of water are lost. The rate of condensation of simple compounds to form a stable polymer must therefore be greater than the rate of **hydrolysis** (splitting by adding the elements of water; Fig. 1-3). In this prebiotic environment, minerals such as clays may have catalyzed polymerization reactions and sequestered the reaction products from water. The size and composition of prebiotic macromolecules would have been limited by the availability of small molecular starting materials, the efficiency with which they could be joined, and their resistance to degradation. The major biological polymers and their individual units **(monomers)** are given in Table 1-3.

Obviously, *combining different monomers and their various functional groups into a single large molecule increases the chemical versatility of that molecule,* allowing it to perform chemical feats beyond the reach of simpler molecules. (This principle of emergent properties can be expressed as "the whole is greater than the sum of its parts.") Separate macromolecules with **complementary arrangements** (reciprocal pairing) of functional groups can associate with each other (Fig. 1-4), giving rise to more complex molecular assemblies with an even greater range of functional possibilities.

Specific pairing between complementary functional groups permits one member of a pair to determine the identity and orientation of the other member. *Such complementarity makes it possible for a macromolecule to* ***replicate****, or copy itself, by directing the assembly of a new molecule from smaller complementary units.* Replication of a simple polymer with intramolecular complementarity is

GATEWAY CONCEPT Functional Groups

Different classes of biological molecules are characterized by different types of functional groups and linkages. A biological molecule may contain multiple functional groups.

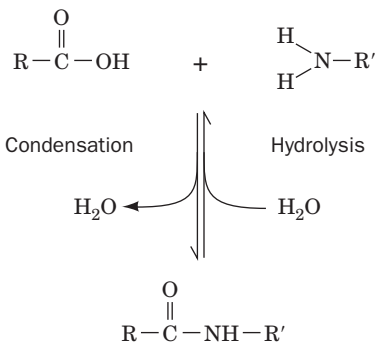


FIG. 1-3 Reaction of a carboxylic acid with an amine. The elements of water are released during condensation. In the reverse process—hydrolysis—water is added to cleave the amide bond. In living systems, condensation reactions are not freely reversible.

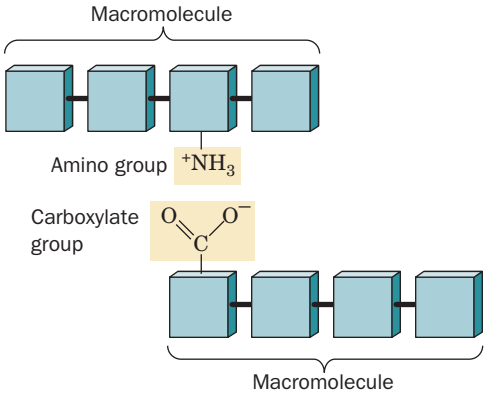
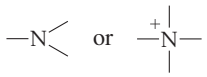
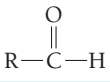
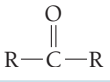
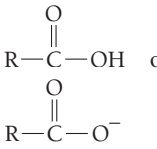
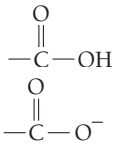
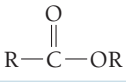
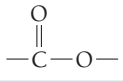
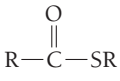
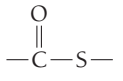
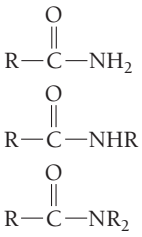
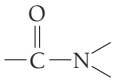
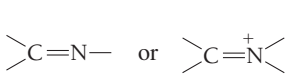
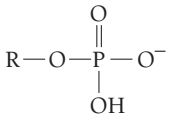
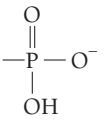
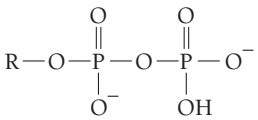
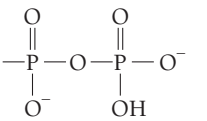
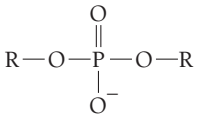
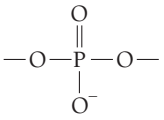


FIG. 1-4 Association of complementary molecules. The positively charged amino group interacts electrostatically with the negatively charged carboxylate group.

TABLE 1-2 Common Functional Groups and Linkages in Biochemistry

Compound Name	Structure[a]	Functional Group or Linkage
Amine[b]	RNH_2 or $R\overset{+}{N}H_3$ R_2NH or $R_2\overset{+}{N}H_2$ R_3N or $R_3\overset{+}{N}H$	 (amino group)
Alcohol	ROH	—OH (hydroxyl group)
Thiol	RSH	—SH (sulfhydryl group)
Ether	ROR	—O— (ether linkage)
Aldehyde		 (carbonyl group)
Ketone		 (carbonyl group)
Carboxylic acid[b]		 (carboxyl group) or (carboxylate group)
Ester		 (ester linkage)  (acyl group)[c]
Thioester		 (thioester linkage)  (acyl group)[c]
Amide		 (amido group)  (acyl group)[c]
Imine (Schiff base)[b]	$R{=}NH$ or $R{=}\overset{+}{N}H_2$ $R{=}NR$ or $R{=}\overset{+}{N}HR$	 (imino group)
Disulfide	R—S—S—R	—S—S— (disulfide linkage)
Phosphate ester[b]		 (phosphoryl group)
Diphosphate ester[b]		 (phosphoanhydride group)
Phosphate diester[b]		 (phosphodiester linkage)

[a]R represents any carbon-containing group. In a molecule with more than one R group, the groups may be the same or different.

[b]Under physiological conditions, these groups are ionized and hence bear a positive or negative charge.

[c]If attached to an atom other than carbon.

? **Cover the Structure column and draw the structure for each compound listed on the left. Do the same for each functional group or linkage.**

TABLE 1-3 Major Biological Polymers and Their Component Monomers

Polymer	Monomer
Protein (polypeptide)	Amino acid
Nucleic acid (polynucleotide)	Nucleotide
Polysaccharide (complex carbohydrate)	Monosaccharide (simple carbohydrate)

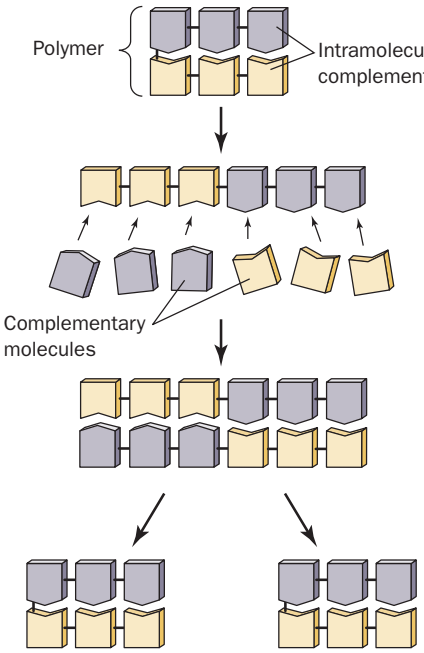


FIG. 1–5 Replication through complementarity. In this simple case, a polymer serves as a template for the assembly of a complementary molecule, which, because of intramolecular complementarity, is an exact copy of the original.

? **Distinguish the covalent bonds from the noncovalent interactions in this polymer.**

illustrated in Fig. 1-5. A similar phenomenon is central to the function of DNA, where the sequence of bases on one strand (e.g., A-C-G-T) absolutely specifies the sequence of bases on the strand to which it is paired (T-G-C-A). When DNA replicates, the two strands separate and direct the synthesis of complementary daughter strands. Complementarity is also the basis for transcribing DNA into RNA and for translating RNA into protein.

A critical moment in chemical evolution was the transition from systems of randomly generated molecules to systems in which molecules were organized and specifically replicated. Once macromolecules gained the ability to self-perpetuate, the primordial environment would have become enriched in molecules that were best able to survive and multiply. The first replicating systems were no doubt somewhat sloppy, with progeny molecules imperfectly complementary to their parents. Over time, **natural selection**, the competitive process by which reproductive preference is given to the better adapted, would have favored molecules that made more accurate copies of themselves.

CHECKPOINT

- Which four elements occur in virtually all biological molecules?
- Summarize the major stages of chemical evolution.
- Practice drawing a simple condensation and hydrolysis reaction.
- Explain why complementarity would have been necessary for the development of self-replicating molecules.

2 Cellular Architecture

KEY CONCEPTS

- Compartmentation of cells promotes efficiency by maintaining high local concentrations of reactants.
- Metabolic pathways evolved to synthesize molecules and generate energy.
- The simplest cells are prokaryotes.
- Eukaryotes are characterized by numerous membrane-bounded organelles, including a nucleus.
- The phylogenetic tree of life includes three domains: bacteria, archaea, and eukarya.
- Evolution occurs as natural selection acts on randomly occurring genetic variations among individuals.

The types of systems described so far would have had to compete with all the other components of the primordial earth for the available resources. A selective advantage would have accrued to a system that was sequestered and protected by boundaries of some sort. How these boundaries first arose, or even what they were made from, is obscure. One theory is that membranous **vesicles** (fluid-filled sacs) first attached to and then enclosed self-replicating systems. These vesicles would have become the first cells.

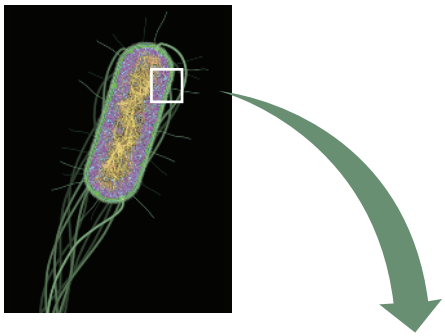
A Cells Carry Out Metabolic Reactions

The advantages of **compartmentation** are several. In addition to receiving some protection from adverse environmental forces, an enclosed system can maintain high local concentrations of components that would otherwise diffuse away. More concentrated substances can react more readily, leading to increased efficiency in polymerization and other types of chemical reactions.

A membrane-bounded compartment that protected its contents would gradually become quite different in composition from its surroundings. Modern cells contain high concentrations of ions, small molecules, and large molecular aggregates that are found only in traces—if at all—outside the cell. For example, a cell of the bacterium ***Escherichia coli* (*E. coli*)** contains millions of molecules, representing some 3000 to 6000 different compounds (**Fig. 1-6**). A typical animal cell may contain 100,000 different types of molecules.

Early cells depended on the environment to supply building materials. As some of the essential components in the prebiotic soup became scarce, natural selection favored organisms that developed **metabolic pathways,** mechanisms for synthesizing the required compounds from simpler but more abundant **precursors**. The first metabolic reactions may have used metal or clay **catalysts** (a catalyst is a substance that promotes a chemical reaction without itself undergoing a net change). In fact, metal ions are still at the heart of many chemical reactions in modern cells. Some catalysts may also have arisen from polymeric molecules that had the appropriate functional groups.

In general, biosynthetic reactions require energy; hence the first cellular reactions also needed an energy source. The eventual depletion of preexisting energy-rich substances in the prebiotic environment would have favored the development of energy-producing metabolic pathways. For example, photosynthesis evolved relatively early to take advantage of a practically inexhaustible energy supply, the sun. However, the accumulation of O_2 generated from H_2O



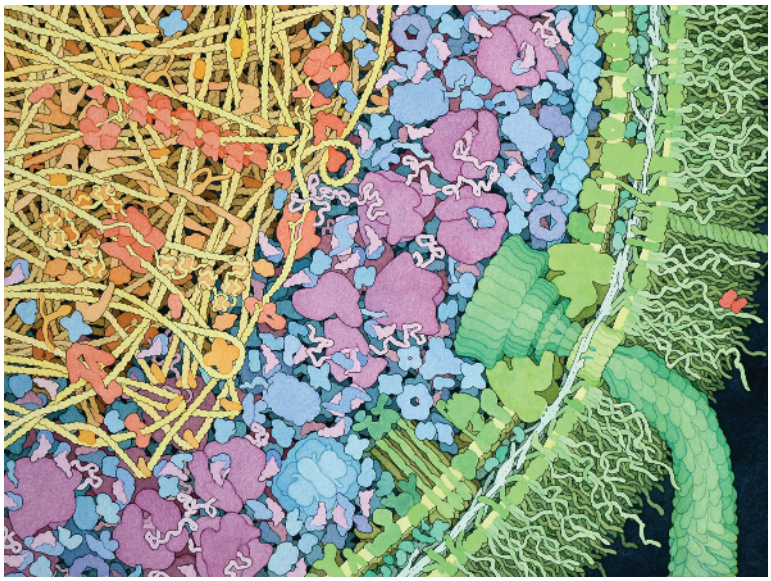


FIG. 1-6 Cross-section through an *E. coli* cell. The cytoplasm is packed with macromolecules. At this magnification (~1,000,000×), individual atoms are too small to resolve. The green structures on the right include the inner and outer membrane components along with a portion of a flagellum. Inside the cell, various proteins are shown in blue, and ribosomes are purple. The gold and orange structures represent DNA and DNA-binding proteins, respectively. In a living cell, the remaining spaces would be crowded with water and small molecules. [From Goodsell, D.S., *The Machinery of Life* (2nd ed.), Springer (2009). Reproduced with permission.]

by photosynthesis (the modern atmosphere is 21% O_2) presented an additional challenge to organisms adapted to life in an oxygen-poor atmosphere. Metabolic refinements eventually permitted organisms not only to avoid oxidative damage but also to use O_2 for oxidative metabolism, a much more efficient form of energy metabolism than anaerobic metabolism. Vestiges of ancient life can be seen in the anaerobic metabolism of certain modern organisms.

Early organisms that developed metabolic strategies to synthesize biological molecules, conserve and utilize energy in a controlled fashion, and replicate within a protective compartment were able to propagate in an ever-widening range of habitats. Adaptation of cells to different external conditions ultimately led to the present diversity of species. Specialization of individual cells also made it possible for groups of differentiated cells to work together in multicellular organisms.

B There Are Two Types of Cells: Prokaryotes and Eukaryotes

All modern organisms are based on the same morphological unit, the cell. There are two major classifications of cells: the **eukaryotes** (Greek: *eu,* good or true + *karyon,* kernel or nut), which have a membrane-enclosed **nucleus** encapsulating their DNA; and the **prokaryotes** (Greek: *pro,* before), which lack a nucleus. *Prokaryotes, comprising the various types of bacteria, have relatively simple structures and are almost all unicellular* (although they may form filaments or colonies of independent cells). *Eukaryotes, which are multicellular as well as unicellular, are vastly more complex than prokaryotes.* (**Viruses** are much simpler entities than cells and are not classified as living because they lack the metabolic apparatus to reproduce outside their host cells.)

Prokaryotes are the most numerous and widespread organisms on the earth. This is because their varied and often highly adaptable metabolisms suit them to an enormous variety of habitats. Prokaryotes range in size from 1 to 10 μm and have one of three basic shapes (**Fig. 1-7**): spheroidal (cocci), rodlike (bacilli), and helically coiled (spirilla). Except for an outer cell membrane, which in most cases is surrounded by a protective cell wall, nearly all prokaryotes lack cellular membranes. However, the prokaryotic **cytoplasm** (cell contents) is by no means a homogeneous soup. Different metabolic functions are carried out in different regions of the cytoplasm (Fig. 1-6). The best characterized prokaryote is *Escherichia coli,* a 2 μm by 1 μm rodlike bacterium that inhabits the mammalian colon.

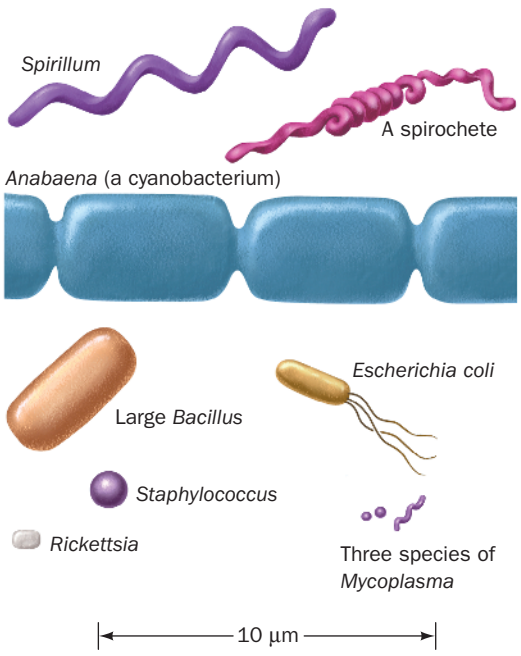


FIG. 1-7 **Scale drawings of some prokaryotic cells.**

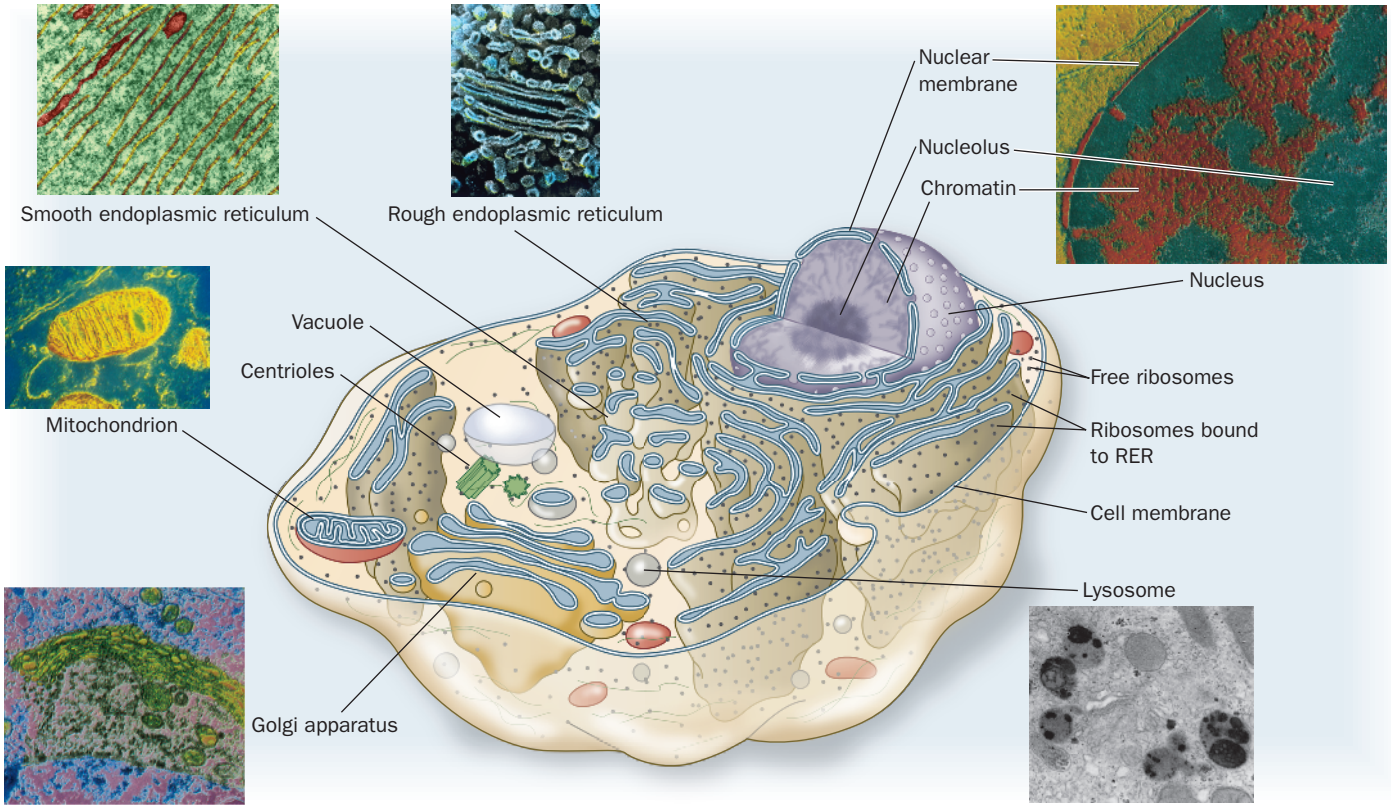


FIG. 1-8 Diagram of a typical animal cell with electron micrographs of its organelles. Membrane-bounded organelles include the nucleus, endoplasmic reticulum, lysosome, peroxisome (not pictured), mitochondrion, vacuole, and Golgi apparatus. The nucleus contains chromatin (a complex of DNA and protein) and the nucleolus (the site of ribosome synthesis). The rough endoplasmic reticulum is studded with ribosomes; the smooth endoplasmic reticulum is not. A pair of centrioles help organize cytoskeletal elements. A typical plant cell differs mainly by the presence of an outer cell wall and chloroplasts in the cytosol. [Smooth endoplasmic reticulum © Dennis Kunkel Microscopy, Inc./Phototake; rough endoplasmic reticulum © Pietro M. Motta & Tomonori Naguro/Photo Researchers, Inc.; nucleus © Tektoff-RM, CNRI/Photo Researchers; mitochondrion © CNRI/Photo Researchers; Golgi apparatus © Secchi-Lecaque/Roussel-UCLAF/CNRI/Photo Researchers; lysosome © Biophoto Associates/Photo Researchers.]

? With the labels covered, name the parts of this eukaryotic cell.

Eukaryotic cells are generally 10 to 100 μm in diameter and thus have a thousand to a million times the volume of typical prokaryotes. It is not size, however, but a profusion of membrane-enclosed **organelles** that best characterizes eukaryotic cells (**Fig. 1-8**). In addition to a nucleus, eukaryotes have an **endoplasmic reticulum**, the site of synthesis of many cellular components, some of which are subsequently modified in the **Golgi apparatus**. The bulk of aerobic metabolism takes place in **mitochondria** in almost all eukaryotes, and photosynthetic cells contain **chloroplasts**, which convert the energy of the sun's rays to chemical energy. Other organelles, such as **lysosomes** and **peroxisomes**, perform specialized functions. **Vacuoles**, which are more prominent in plant than in animal cells, usually function as storage depots. The **cytosol** (the cytoplasm minus its membrane-bounded organelles) is organized by the **cytoskeleton**, an extensive array of filaments that also gives the cell its shape and the ability to move.

The various organelles that compartmentalize eukaryotic cells represent a level of complexity that is largely lacking in prokaryotic cells. Nevertheless, prokaryotes are more efficient than eukaryotes in many respects. Prokaryotes have exploited the advantages of simplicity and miniaturization. Their rapid growth rates permit them to occupy ecological niches in which there may be drastic fluctuations of the available nutrients. In contrast, the complexity of eukaryotes, which renders them larger and more slowly growing than prokaryotes, gives them the competitive advantage in stable environments with limited resources. It is therefore erroneous to consider prokaryotes as evolutionarily primitive compared to eukaryotes. Both types of organisms are well adapted to their respective lifestyles.

C Molecular Data Reveal Three Evolutionary Domains of Organisms

The practice of lumping all prokaryotes in a single category based on what they lack—a nucleus—obscures their metabolic diversity and evolutionary history. Conversely, the remarkable morphological diversity of eukaryotic organisms (consider the anatomical differences among, say, an amoeba, an oak tree, and a human being) masks their fundamental similarity at the cellular level. Traditional taxonomic schemes (**taxonomy** is the science of biological classification), which are based on gross morphology, have proved inadequate to describe the actual relationships between organisms as revealed by their evolutionary history (**phylogeny**).

Biological classification schemes based on reproductive or developmental strategies more accurately reflect evolutionary history than those based solely on adult morphology. However, *phylogenetic relationships are best deduced by comparing polymeric molecules—RNA, DNA, or protein—from different organisms.* For example, analysis of RNA led Carl Woese to group all organisms into three domains (**Fig. 1-9**). The **archaea** (also known as **archaebacteria**) are a group of prokaryotes that are as distantly related to other prokaryotes (the **bacteria**, sometimes called **eubacteria**) as both groups are to eukaryotes (**eukarya**). The archaea include some unusual organisms: the **methanogens** (which produce CH_4), the **halobacteria** (which thrive in concentrated brine solutions), and certain **thermophiles** (which inhabit hot springs). The pattern of branches in Woese's diagram indicates the divergence of different types of organisms (each branch point represents a common ancestor). The three-domain scheme also shows that animals, plants, and fungi constitute only a small portion of all life-forms. Such phylogenetic trees supplement the fossil record, which provides a patchy record of life prior to about 600 million years before the present (multicellular organisms arose about 700–900 million years ago).

It is unlikely that eukaryotes are descended from a single prokaryote, because the differences among eubacteria, archaea, and eukaryotes are so profound. Instead, eukaryotes probably evolved from the association of archaebacterial and eubacterial cells. The eukaryotic genetic material includes features that suggest an archaebacterial origin. In addition, the mitochondria and chloroplasts of modern eukaryotic cells resemble eubacteria in size and shape, and both types of organelles contain their own genetic material and protein synthetic machinery. Evidently, as Lynn Margulis proposed, mitochondria and chloroplasts evolved from free-living eubacteria that formed **symbiotic** (mutually beneficial) relationships with a primordial eukaryotic cell (Box 1-1). In fact, certain eukaryotes that lack mitochondria or chloroplasts permanently harbor symbiotic bacteria.

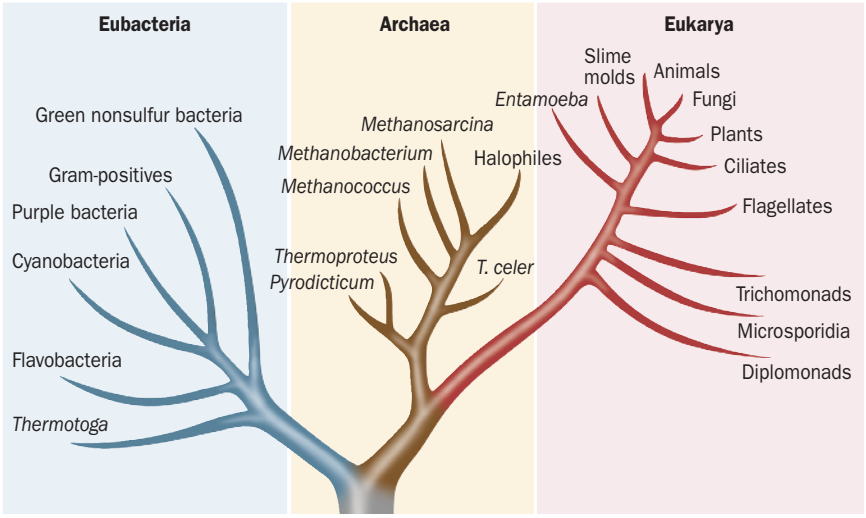


FIG. 1-9 Phylogenetic tree showing the three domains of organisms. The branches indicate the pattern of divergence from a common ancestor. The archaea are prokaryotes, like eubacteria, but share many features with eukaryotes. [After Wheelis, M.L., Kandler, O., and Woese, C.R., *Proc. Natl. Acad. Sci.* **89,** 2931 (1992).]

Box 1-1 Pathways of Discovery Lynn Margulis and the Theory of Endosymbiosis



Lynn Margulis (1938–2011) After growing up in Chicago and enrolling in the University of Chicago at age 16, Lynn Margulis intended to be a writer. Her interest in biology was sparked by a required science course for which she read Gregor Mendel's accounts of his experiments with the genetics of pea plants. Margulis continued her studies at the University of Wisconsin–Madison and at the University of California, Berkeley, earning a doctorate in 1963. Her careful consideration of cellular structures led her to hypothesize that eukaryotic cells originated from a series of endosymbiotic events involving multiple prokaryotes. The term *endo* (Greek: within) refers to an arrangement in which one cell comes to reside inside another. This idea was considered outrageous at the time (1967), but many of Margulis's ideas have since become widely accepted.

Endosymbiosis as an explanation for the origin of mitochondria had been proposed by Ivan Wallin in 1927, who noted the similarity between mitochondria and bacteria in size, shape, and cytological staining. Wallin's hypothesis was rejected as being too fantastic and was ignored until it was taken up again by Margulis. By the 1960s, much more was known about mitochondria (and chloroplasts), including the facts that they contained DNA and reproduced by division. Margulis did not focus all her attention on the origin of individual organelles but instead sought to explain the origin of the entire eukaryotic cell, which also includes centrioles, another possible bacterial relic. Her paper, "On the origin of mitosing cells," was initially rejected by several journals before being accepted by the *Journal of Theoretical Biology*. The notion that a complex eukaryotic cell could arise from a consortium of mutually dependent prokaryotic cells was incompatible with the prevailing view that evolution occurred as a series of small steps. Evolutionary theory of the time had no room for the dramatic amalgamation of cells—and their genetic material—that Margulis had proposed. Nevertheless, the outspoken Margulis persisted, and by the time she published *Symbiosis in Cell Evolution* in 1981, much of the biological community had come on board to agree with her.

Two main tenets of Margulis's theory, that mitochondria are the descendants of oxygen-respiring bacteria and that chloroplasts were originally photosynthetic bacteria, are now almost universally accepted. The idea that the eukaryotic cytoplasm is the remnant of an archaebacterial cell is still questioned by some biologists. Margulis was in the process of collecting evidence to support a fourth idea, that cilia and flagella and some sensory structures such as the light-sensing cells of the eye are descendants of free-living spirochete bacteria. Margulis's original prediction that organelles such as mitochondria could be isolated and cultured has not been fulfilled. However, there is ample evidence for the transfer of genetic material between organelles and the nucleus, consistent with Margulis's theory of endosymbiosis. In fact, current theories of evolution include the movement of genetic material among organisms, as predicted by Margulis, in addition to small random mutations as agents of change.

Perhaps as an extension of her work on bacterial endosymbiosis, Margulis came to recognize that the interactions among many different types of organisms as well as their interactions with their physical environment constitute a single self-regulating system. This notion is part of the Gaia hypothesis proposed by James Lovelock, which views the entire earth as one living entity (Gaia was a Greek earth goddess). However, Margulis had no patience with those who sought to build a modern mythology based on Gaia. She was adamant about the importance of using scientific tools and reasoning to discover the truth and was irritated by the popular belief that humans are the center of life on earth. Margulis understood that human survival depends on our relationships with waste-recycling, water-purifying, and oxygen-producing bacteria, with whom we have been evolving, sometimes endosymbiotically, for billions of years.

Sagan, L., On the origin of mitosing cells, *J. Theor. Biol.* **14,** 255–274 (1967).

D Organisms Continue to Evolve

The natural selection that guided prebiotic evolution continues to direct the evolution of organisms. Richard Dawkins has likened evolution to a blind watchmaker capable of producing intricacy by accident, although such an image fails to convey the vast expanse of time and the incremental, trial-and-error manner in which complex organisms emerge. Small **mutations** (changes in an individual's genetic material) arise at random as the result of chemical damage or inherent errors in the DNA replication process. *A mutation that increases the chances of survival of the individual increases the likelihood that the mutation will be passed on to the next generation.* Beneficial mutations tend to spread rapidly through a population; deleterious changes tend to die along with the organisms that harbor them.

The theory of evolution by natural selection, which was first articulated by Charles Darwin in the 1860s, has been confirmed through observation and experimentation. It is therefore useful to highlight several important—and often misunderstood—principles of evolution:

1. ***Evolution is not directed toward a particular goal.*** It proceeds by random changes that may affect the ability of an organism to reproduce under the prevailing conditions. An organism that is well adapted to its environment may fare better or worse when conditions change.

2. ***Variation among individuals*** allows organisms to adapt to unexpected changes. This is one reason that genetically homogeneous populations (e.g., a corn crop) are so susceptible to a single challenge (e.g., a fungal blight). A more heterogeneous population is more likely to include individuals that can resist the adversity and recover.
3. ***The past determines the future.*** New structures and metabolic functions emerge from preexisting elements. For example, insect wings did not erupt spontaneously but appear to have developed gradually from small heat-exchange structures.
4. ***Evolution is ongoing,*** although it does not proceed exclusively toward complexity. An anthropocentric view places human beings at the pinnacle of an evolutionary scheme, but a quick survey of life's diversity reveals that simpler species have not died out or stopped evolving.

CHECKPOINT

- Explain the selective advantages of compartmentation and metabolic pathways.
- Discuss the differences between prokaryotes and eukaryotes.
- Make a list of the major eukaryotic organelles and their functions.
- Explain why a taxonomy based on molecular sequences is more accurate than one based on morphology.
- Which of the three domains are prokaryotic? Which domain is most similar to eukaryotes?
- Explain how individual variations allow evolution to occur.
- Why is evolutionary change constrained by its past but impossible to predict?

3 Thermodynamics

KEY CONCEPTS

- Energy must be conserved, but it can take different forms.
- In most biochemical systems, enthalpy is equivalent to heat.
- Entropy, a measure of a system's disorder, tends to increase.
- The free energy change for a process is determined by its changes in both enthalpy and entropy.
- A spontaneous process occurs with a decrease in free energy.
- The free energy change for a reaction can be calculated from the temperature and the concentrations and stoichiometry of the reactants and products.
- Biochemists define standard state conditions as a temperature of 25°C, a pressure of 1 atm, and a pH of 7.0.
- Organisms are nonequilibrium, open systems that constantly exchange matter and energy with their surroundings while maintaining homeostasis.
- Enzymes increase the rate at which a reaction approaches equilibrium.

The normal activities of living organisms—moving, growing, reproducing—demand an almost constant input of energy. Even at rest, organisms devote a considerable portion of their biochemical apparatus to the acquisition and utilization of energy. The study of energy and its effects on matter falls under the purview of **thermodynamics** (Greek: *therme,* heat + *dynamis,* power). Although living systems present some practical challenges to thermodynamic analysis, *life obeys the laws of thermodynamics.* Understanding thermodynamics is important not only for describing a particular process—such as a biochemical reaction—in terms that can be quantified, but also for predicting whether that process *can* actually occur; that is, whether the process is **spontaneous**. To begin, we will review the fundamental laws of thermodynamics. We will then turn our attention to free energy and how it relates to chemical reactions. Finally, we will look at how biological systems deal with the laws of thermodynamics.

A The First Law of Thermodynamics States That Energy Is Conserved

In thermodynamics, a **system** is defined as the part of the universe that is of interest, such as a reaction vessel or an organism; the rest of the universe is known as the **surroundings**. The system has a certain amount of **energy, *U.*** *The first law of thermodynamics states that energy is conserved;* it can be neither created nor destroyed. However, when the system undergoes a change, some of its energy can be used to perform work. The energy change of the system is defined as the

difference between the **heat (*q*)** absorbed by the system from the surroundings and **work (*w*)** done by the system on the surroundings:

$$\Delta U = U_{\text{final}} - U_{\text{initial}} = q - w \qquad [1\text{-}1]$$

where the upper case Greek letter Δ (delta) indicates change. Heat is a reflection of random molecular motion, whereas work, which is defined as force times the distance moved under its influence, is associated with organized motion. Force may assume many different forms, including the gravitational force exerted by one mass on another, the expansional force exerted by a gas, the tensional force exerted by a spring or muscle fiber, the electrical force of one charge on another, and the dissipative forces of friction and viscosity. Because energy can be used to perform different kinds of work, it is sometimes useful to speak of energy taking different forms, such as mechanical energy, electrical energy, or chemical energy—all of which are relevant to biological systems.

Most biological processes take place at constant pressure. Under such conditions, the work done by the expansion of a gas (pressure–volume work) is $P\Delta V$. Consequently it is useful to define a new thermodynamic quantity, the **enthalpy** (Greek: *enthalpein,* to warm in), symbolized ***H***:

$$H = U + PV \qquad [1\text{-}2]$$

Then, when the system undergoes a change at constant pressure,

$$\Delta H = \Delta U + P\Delta V = q_P - w + P\Delta V \qquad [1\text{-}3]$$

where q_P is defined as the heat at constant pressure. Since we already know that in this system $w = P\Delta V$,

$$\Delta H = q_P - P\Delta V + P\Delta V = q_P \qquad [1\text{-}4]$$

In other words, the change in enthalpy at constant pressure is equivalent to heat. Moreover, the volume changes in most biochemical reactions are insignificant ($P\Delta V \approx 0$), so the differences between their ΔU and ΔH values are negligible, and hence the energy change for the reacting system is equivalent to its enthalpy change. Enthalpy, like energy, heat, and work, is given units of joules. Some commonly used units and biochemical constants and other conventions are given in Box 1-2.

Thermodynamics is useful for indicating the spontaneity of a process. A **spontaneous process** occurs without the input of additional energy from outside



Box 1-2 Perspectives in Biochemistry Biochemical Conventions

Modern biochemistry generally uses Système International (SI) units, including meters (m), kilograms (kg), and seconds (s) and their derived units, for various thermodynamic and other measurements. The following lists the commonly used biochemical units, some useful biochemical constants, and a few conversion factors.

Units

Energy, heat, work	joule (J)	$kg \cdot m^2 \cdot s^{-2}$ or $C \cdot V$
Electric potential	volt (V)	$J \cdot C^{-1}$

Prefixes for units

mega (M)	10^6	nano (n)	10^{-9}
kilo (k)	10^3	pico (p)	10^{-12}
milli (m)	10^{-3}	femto (f)	10^{-15}
micro (μ)	10^{-6}	atto (a)	10^{-18}

Conversions

angstrom (Å)	10^{-10} m
calorie (cal)	4.184 J
kelvin (K)	degrees Celsius (°C) + 273.15

Constants

Avogadro's number (*N*)	6.0221×10^{23} molecules $\cdot$ mol^{-1}
Coulomb (C)	6.241×10^{18} electron charges
Faraday (*F*)	96,485 C $\cdot$ mol^{-1} or 96,485 J $\cdot$ V^{-1} $\cdot$ mol^{-1}
Gas constant (*R*)	8.3145 J $\cdot$ K^{-1} $\cdot$ mol^{-1}
Boltzmann constant (k_B)	1.3807×10^{-23} J $\cdot$ K^{-1} (*R*/*N*)
Planck's constant (*h*)	6.6261×10^{-34} J $\cdot$ s

Throughout this text, molecular masses of particles are expressed in units of **daltons (D)**, which are defined as l/12th the mass of a ^{12}C atom (1000 D = 1 **kilodalton, kD**). Biochemists also use **molecular weight**, a dimensionless quantity defined as the ratio of the particle mass to l/12th the mass of a ^{12}C atom, which is symbolized M_r (for relative molecular mass).

the system (although keep in mind that thermodynamic spontaneity has nothing to do with how quickly a process occurs). The first law of thermodynamics, however, cannot by itself determine whether a process is spontaneous. Consider two objects of different temperatures that are brought together. Heat flows spontaneously from the warmer object to the cooler one, never vice versa, yet either process would be consistent with the first law of thermodynamics since the aggregate energy of the two objects does not change. Therefore, an additional criterion of spontaneity is needed.

B The Second Law of Thermodynamics States That Entropy Tends to Increase

According to the second law of thermodynamics, spontaneous processes are characterized by the conversion of order to disorder. In this context, disorder is defined as the number of energetically equivalent ways, ***W***, of arranging the components of a system. Note that there are more ways of arranging a disordered system than a more ordered system. To make this concept concrete, consider a system consisting of two bulbs of equal volume, one of which contains molecules of an ideal gas (**Fig. 1-10**). When the stopcock connecting the bulbs is opened, the molecules become randomly but equally distributed between the two bulbs (each gas molecule has a 50% probability of being in the left bulb and hence there are 2^N equivalent ways of randomly distributing them between the two bulbs, where N is the number of gas molecules; note that even when N is as small as 100, 2^N is an astronomically large number). The equal number of gas molecules in each bulb is not the result of any law of motion; it is because the probabilities of all other distributions of the molecules are so overwhelmingly small. Thus, the probability of all the molecules in the system spontaneously rushing into the left bulb (the initial condition, in which $W = 1$) is nil, even though the energy and enthalpy of that arrangement are exactly the same as those of the evenly distributed molecules. By the same token, the mechanical energy (work) of a swimmer jumping into a pool heats the water (increases the random motion of its molecules), but the reverse process, a swimmer being ejected from the water by the organized motion of her surrounding water molecules, has never been observed, even though this process does not violate any law of motion.

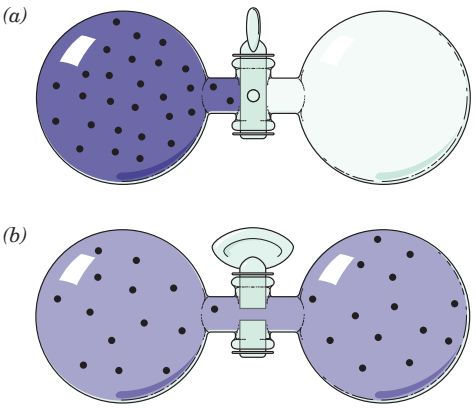


FIG. 1-10 Illustration of entropy. In (*a*), a gas occupies the leftmost of two equal-sized bulbs and hence the entropy is low. When the stopcock is opened (*b*), the entropy increases as the gas molecules diffuse back and forth between the bulbs and eventually become distributed evenly, half in each bulb.

? Does the total heat content of this system change when the stopcock is opened?

Since W is usually inconveniently large, the degree of randomness of a system is better indicated by its **entropy** (Greek: *en,* in + *trope,* turning), symbolized ***S***:

$$S = k_B \ln W \qquad [1\text{-}5]$$

where k_B is the **Boltzmann constant**. The units of S are $J \cdot K^{-1}$ (absolute temperature, in units of kelvins, is a factor because entropy varies with temperature; e.g., a system becomes more disordered as its temperature rises). The most probable arrangement of a system is the one that maximizes W, and hence S. Thus, if a spontaneous process, such as the one shown in Fig. 1-10, has overall energy and enthalpy changes (ΔU and ΔH) of zero, its entropy change (ΔS) must be greater than zero; that is, the number of equivalent ways of arranging the final state must be greater than the number of ways of arranging the initial state. Furthermore, because

$$\Delta S_{system} + \Delta S_{surroundings} = \Delta S_{universe} > 0 \qquad [1\text{-}6]$$

all processes increase the entropy—that is, the disorder—of the universe.

In chemical and biological systems, it is impractical, if not impossible, to determine the entropy of a system by counting all the equivalent arrangements of its components (W). However, there is an entirely equivalent expression for entropy that applies to the constant-temperature conditions typical of biological systems: for a spontaneous process,

$$\Delta S \geq \frac{q}{T} \qquad [1\text{-}7]$$

Thus, the entropy change in a process can be experimentally determined from measurements of heat and temperature.

C The Free Energy Change Determines the Spontaneity of a Process

The spontaneity of a process cannot be predicted from a knowledge of the system's entropy change alone. For example, a mixture of 2 mol of H_2 and 1 mol of O_2, when sparked, reacts (explodes) to form 2 mol of H_2O. Yet two water molecules, each of whose three atoms are constrained to stay together, are more ordered than are the three diatomic molecules from which they formed. Thus, this spontaneous reaction occurs with a decrease in the system's entropy.

What, then, is the thermodynamic criterion for a spontaneous process? Equations 1-4 and 1-7 indicate that at constant temperature and pressure,

$$\Delta S \geq \frac{q_r}{T} = \frac{\Delta H}{T} \qquad [1\text{-}8]$$

Thus,

$$\Delta H - T\Delta S \leq 0 \qquad [1\text{-}9]$$

This is the true criterion for spontaneity as formulated, in 1878, by J. Willard Gibbs. He defined the **Gibbs free energy** (***G,*** usually called just **free energy**) as

$$G = H - TS \qquad [1\text{-}10]$$

The change in free energy for a process is ΔG. Consequently, spontaneous processes at constant temperature and pressure have

$$\boxed{\Delta G = \Delta H - T\Delta S < 0} \qquad [1\text{-}11]$$

Processes in which ΔG is negative are said to be **exergonic** (Greek: *ergon,* work). Processes that are not spontaneous have positive ΔG values ($\Delta G > 0$) and are said to be **endergonic**; they must be driven by the input of free energy. If a process is exergonic, the reverse of that process is endergonic and vice versa. Thus, the ΔG value for a process indicates whether the process can occur spontaneously in the direction written (see Sample Calculation 1-1). Processes at **equilibrium**, those in which the forward and reverse reactions are exactly balanced, are characterized by $\Delta G = 0$. Processes that occur with $\Delta G \approx 0$, so the system, in effect, remains at equilibrium throughout the process, are said to be **reversible**. Processes that occur with $\Delta G \neq 0$ are said to be **irreversible.** An irreversible process with $\Delta G < 0$ is said to be **favorable** or to occur spontaneously, whereas an irreversible process with $\Delta G > 0$ is said to be **unfavorable.**

A process that is accompanied by an increase in enthalpy ($\Delta H > 0$), which opposes the process, can nevertheless proceed spontaneously if the entropy change is sufficiently positive ($\Delta S > 0$; Table 1-4). Conversely, a process that is accompanied by a decrease in entropy ($\Delta S < 0$) can proceed if its enthalpy change is sufficiently negative ($\Delta H < 0$). It is important to emphasize that *a large negative value of* ΔG *does not ensure that a process such as a chemical reaction*

TABLE 1-4 Variation of Reaction Spontaneity (Sign of ΔG) with the Signs of ΔH and ΔS

ΔH	ΔS	$\Delta G = \Delta H - T\Delta S$
−	+	The reaction is both enthalpically favored (exothermic) and entropically favored. It is spontaneous (exergonic) at all temperatures.
−	−	The reaction is enthalpically favored but entropically opposed. It is spontaneous only at temperatures *below* $T = \Delta H/\Delta S$.
+	+	The reaction is enthalpically opposed (endothermic) but entropically favored. It is spontaneous only at temperatures *above* $T = \Delta H/\Delta S$.
+	−	The reaction is both enthalpically and entropically opposed. It is nonspontaneous (endergonic) at all temperatures.

SAMPLE CALCULATION 1-1

The enthalpy and entropy of the initial and final states of a reacting system are shown in the table.

	H (J · mol^{-1})	S (J · K^{-1} · mol^{-1})
Initial state (before reaction)	54,000	22
Final state (after reaction)	60,000	43

a. Calculate the change in enthalpy and change in entropy for the reaction.
b. Calculate the change in free energy for the reaction when the temperature is 4°C. Is the reaction spontaneous?
c. Is the reaction spontaneous at 37°C?

a. $\Delta H = H_{\text{final}} - H_{\text{initial}} = 60{,}000\ \text{J} \cdot \text{mol}^{-1} - 54{,}000\ \text{J} \cdot \text{mol}^{-1} = 6000\ \text{J} \cdot \text{mol}^{-1}$
$\Delta S = S_{\text{final}} - S_{\text{initial}} = \Delta S = 43\ \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1} - 22\ \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$
$= 21\ \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$

b. First, convert temperature from °C to K: 4 + 273 = 277 K. Then use Eq. 1-11.

$$\Delta G = \Delta H - T\Delta S$$
$$\Delta G = (6000\ \text{J} \cdot \text{mol}^{-1}) - (277\ \text{K})(21\ \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1})$$
$$= 6000\ \text{J} \cdot \text{mol}^{-1} - 5820\ \text{J} \cdot \text{mol}^{-1} = 180\ \text{J} \cdot \text{mol}^{-1}$$

The value for ΔG is greater than zero, so this is an endergonic (nonspontaneous) reaction at 4°C.

c. Convert temperature from °C to K: 37 + 273 = 310 K.

$$\Delta G = \Delta H - T\Delta S$$
$$\Delta G = (6000\ \text{J} \cdot \text{mol}^{-1}) - (310\ \text{K})(21\ \text{J} \cdot \text{K} \cdot \text{mol}^{-1})$$
$$= 6000\ \text{J} \cdot \text{mol}^{-1} - 6510\ \text{J} \cdot \text{mol}^{-1} = -510\ \text{J} \cdot \text{mol}^{-1}$$

The value for ΔG is less than zero, so the reaction is spontaneous (exergonic) at 37°C.

WPLS See Sample Calculation Videos.

will proceed at a measurable rate. The rate depends on the detailed mechanism of the reaction, which is independent of ΔG (Section 11-2).

Free energy, as well as energy, enthalpy, and entropy, are **state functions**. In other words, their values depend only on the current state or properties of the system, not on how the system reached that state. Therefore, *thermodynamic measurements can be made by considering only the initial and final states of the system and ignoring all the stepwise changes in enthalpy and entropy that occur in between.* For example, it is impossible to directly measure the energy change for the reaction of glucose with O_2 ***in vivo*** (in a living organism) because of the numerous other simultaneously occurring chemical reactions. However, because ΔG depends on only the initial and final states, the combustion of glucose can be analyzed in any convenient apparatus, using the same starting materials (glucose and O_2) and end products (CO_2 and H_2O) that occur *in vivo.* A system may undergo an irreversible cyclic process that returns it to its initial state and hence, for this system, $\Delta G = 0$. However, this process must be accompanied by an increase in the entropy (disordering) of the surroundings so that for the universe, $\Delta G < 0$.

Note that heat (q) and work (w) are not state functions. This is because, as Eq. 1-1 indicates, they are interchangeable forms of energy and hence the change in both these quantities varies with the pathway taken in changing the state of a system. It is therefore invalid to refer to the heat content or the work content of a system (in the same way that it is invalid to describe the money in your bank account as consisting only of a fixed number of pennies and dimes).

D Free Energy Changes Can Be Calculated from Reactant and Product Concentrations

The entropy (disorder) of a substance increases with its volume. For example, a collection of gas molecules, in occupying all of the volume available to it, maximizes its entropy (assumes its most disordered arrangement). Similarly, dissolved molecules become uniformly distributed throughout their solution volume. Entropy is therefore a function of concentration.

If entropy varies with concentration, so must free energy. Thus, *the free energy change of a chemical reaction depends on the concentrations of both its reacting substances* (*reactants*) *and its reaction products.* This phenomenon has great significance because many biochemical reactions operate spontaneously in either direction depending on the relative concentrations of their reactants and products.

Equilibrium Constants Are Related to ΔG. Only changes in free energy, enthalpy, and entropy (ΔG, ΔH, and ΔS) can be measured, not their absolute values (G, H, and S). To compare these changes for different substances, it is therefore necessary to express their values relative to some **standard state** (likewise, we refer the elevations of geographic locations to sea level, which is arbitrarily assigned the height of zero). We discuss standard state conventions below.

The relationship between the concentration and the free energy of a substance A is approximately

$$\overline{G}_A = \overline{G}^\circ_A + RT \ln [A] \qquad [1\text{-}12]$$

where $\overline{G}_A$ is known as the **partial molar free energy** or the **chemical potential** of A (the bar indicates the quantity per mole), $\overline{G}^\circ_A$ is the partial molar free energy of A in its standard state, R is the gas constant, and [A] is the molar concentration of A. Thus, for the general reaction

$$aA + bB \rightleftharpoons cC + dD$$

the free energy change is

$$\Delta G = c\overline{G}_C + d\overline{G}_D - a\overline{G}_A - b\overline{G}_B \qquad [1\text{-}13]$$

and

$$\Delta G^\circ = c\overline{G}^\circ_C + d\overline{G}^\circ_D - a\overline{G}^\circ_A - b\overline{G}^\circ_B \qquad [1\text{-}14]$$

because free energies are additive and the free energy change of a reaction is the sum of the free energies of the products less those of the reactants. Substituting these relationships into Eq. 1-12 yields

$$\Delta G = \Delta G^\circ + RT \ln \left(\frac{[C]^c [D]^d}{[A]^a [B]^b} \right) \qquad [1\text{-}15]$$

where ΔG° is the free energy change of the reaction when all of its reactants and products are in their standard states (see below). Thus, the expression for the free energy change of a reaction consists of two parts: (1) a constant term whose value depends only on the reaction taking place and (2) a variable term that depends on the concentrations of the reactants and the products, the stoichiometry of the reaction, and the temperature.

For a reaction at equilibrium, there is no *net* change (the rates of the forward and reverse reactions are equal) because the free energy change of the forward reaction exactly balances that of the reverse reaction. Consequently, $\Delta G = 0$, so Eq. 1-15 becomes

$$\boxed{\Delta G^\circ = -RT \ln K_{eq}} \qquad [1\text{-}16]$$

where K_{eq} is the familiar **equilibrium constant** of the reaction:

$$K_{eq} = \frac{[C]_{eq}^{c}[D]_{eq}^{d}}{[A]_{eq}^{a}[B]_{eq}^{b}} = e^{-\Delta G^{\circ}/RT} \qquad [1\text{-}17]$$

The subscript "eq" denotes reactant and product concentrations at equilibrium. (The equilibrium condition is usually clear from the context of the situation, so equilibrium concentrations are usually expressed without this subscript.) *The equilibrium constant of a reaction can therefore be calculated from standard free energy data and vice versa* (see Sample Calculation 1-2). The actual free energy change for a reaction can be calculated from the standard free energy change (ΔG°) and the actual concentrations of the reactants and products (see Sample Calculation 1-3).

SAMPLE CALCULATION 1-3

Using the data provided in Sample Calculation 1-2, what is the actual free energy change for the reaction A → B at 37°C when [A] = 10.0 mM and [B] = 0.100 mM?

Use Equation 1-15 and remember that the units for concentration are moles per liter.

$$\Delta G = \Delta G^{\circ} + RT \ln \frac{[B]}{[A]}$$

$$\begin{aligned}\Delta G &= -15{,}000\ \text{J}\cdot\text{mol}^{-1} + (8.314\ \text{J mol}^{-1}\cdot\text{K}^{-1})(37 + 273\ \text{K})\ \ln(0.0001/0.01) \\ &= -15{,}000\ \text{J}\cdot\text{mol}^{-1} - 11{,}900\ \text{J}\cdot\text{mol}^{-1} \\ &= -26{,}900\ \text{J}\cdot\text{mol}^{-1}\end{aligned}$$

WPLS See Sample Calculation Videos.

SAMPLE CALCULATION 1-2

The standard free energy change for the reaction A → B is $-15.0\ \text{kJ}\cdot\text{mol}^{-1}$. What is the equilibrium constant for the reaction at 25°C?

Since ΔG° is known, Eq. 1-17 can be used to calculate K_{eq}. The absolute temperature is 25 + 273 = 298 K.

$$\begin{aligned}K_{eq} &= e^{-\Delta G^{\circ}/RT} \\ &= e^{-(-15{,}000\ \text{J}\cdot\text{mol}^{-1})/(8314\ \text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1})(298\ \text{K})} \\ &= e^{6.05} \\ &= 426\end{aligned}$$

WPLS See Sample Calculation Videos.

Equations 1-15 through 1-17 indicate that when the reactants in a process are in excess of their equilibrium concentrations, the net reaction will proceed in the forward direction until the excess reactants have been converted to products and equilibrium is attained. Conversely, when products are in excess, the net reaction proceeds in the reverse direction. Thus, as **Le Châtelier's principle** states, *any deviation from equilibrium stimulates a process that tends to restore the system to equilibrium.* In cells, many metabolic reactions are freely reversible ($\Delta G \approx 0$), and the direction of the reaction can shift as reactants and products are added to or removed from the cell. Some metabolic reactions, however, are irreversible; they proceed in only one direction (that with $\Delta G < 0$), which permits the cell to maintain reactant and product concentrations far from their equilibrium values.

***K* Depends on Temperature.** The manner in which the equilibrium constant varies with temperature can be seen by substituting Eq. 1-11 into Eq. 1-16 and rearranging:

$$\ln K_{eq} = \frac{-\Delta H^{\circ}}{R}\left(\frac{1}{T}\right) + \frac{\Delta S^{\circ}}{R} \qquad [1\text{-}18]$$

where H° and S° represent enthalpy and entropy in the standard state. Equation 1-18 has the form $y = mx + b$, the equation for a straight line. A plot of $\ln K_{eq}$ versus $1/T$, known as a **van't Hoff plot**, permits the values of ΔH° and ΔS° (and hence ΔG°) to be determined from measurements of K_{eq} at two (or more) different temperatures. This method is often more practical than directly measuring ΔH and ΔS by calorimetry (which measures the heat, q_P, of a process).

Biochemists Have Defined Standard-State Conventions. According to the convention used in physical chemistry, a solute is in its standard state when the

temperature is 25°C, the pressure is 1 atm, and the solute has an **activity** of 1 (activity of a substance is its concentration corrected for its nonideal behavior at concentrations higher than infinite dilution).

The concentrations of reactants and products in most biochemical reactions are usually so low (on the order of millimolar or less) that their activities are closely approximated by their molar concentrations. Furthermore, because biochemical reactions occur near neutral pH, biochemists have adopted a somewhat different **biochemical standard-state** convention:

1. The activity of pure water is assigned a value of 1, even though its concentration is 55.5 M. This procedure simplifies the free energy expressions for reactions in dilute solutions involving water as a reactant, because the $[H_2O]$ term can then be ignored. In essence, the $[H_2O]$ term is incorporated into the value of the equilibrium constant.
2. The hydrogen ion (H^+) activity is assigned a value of 1 at the physiologically relevant pH of 7. Thus, the biochemical standard state is pH 7.0 (neutral pH, where $[H^+] = 10^{-7}$ M) rather than pH 0 ($[H^+] = 1$ M), the physical chemical standard state, where many biological substances are unstable.
3. The standard state of a substance that can undergo an acid–base reaction is defined in terms of the total concentration of its naturally occurring ion mixture at pH 7. In contrast, the physical chemistry convention refers to a pure species, whether or not it actually exists at pH 0. The advantage of the biochemistry convention is that the total concentration of a substance with multiple ionization states, such as most biological molecules, is usually easier to measure than the concentration of one of its ionic species. *Because the ionic composition of an acid or base varies with pH, however, the standard free energies calculated according to the biochemical convention are valid only at pH 7.*

Under the biochemistry convention, the standard free energy changes of reactions are customarily symbolized by $\Delta G^{\circ\prime}$ to distinguish them from physical chemistry standard free energy changes, ΔG°. If a reaction includes neither H_2O, H^+, nor an ionizable species, then its $\Delta G^{\circ\prime} = \Delta G^\circ$.

GATEWAY CONCEPT The Direction of a Reaction

The free energy change for a reaction, which depends on the reactant and product concentrations as well as the standard free energy change for that reaction, determines whether the process occurs in the forward or reverse direction. Adding products or removing reactants can cause the reaction to proceed in the opposite direction.

E Life Achieves Homeostasis While Obeying the Laws of Thermodynamics

At one time, many scientists believed that life, with its inherent complexity and order, somehow evaded the laws of thermodynamics. However, elaborate measurements on living animals are consistent with the conservation of energy predicted by the first law. Unfortunately, experimental verification of the second law is not practicable, since it requires dismantling an organism to its component molecules, which would result in its irreversible death. Consequently, it is possible to assert only that the entropy of living matter is less than that of the products to which it decays. *Life persists, however, because a system (a living organism) can be ordered at the expense of disordering its surroundings to an even greater extent.* In other words, the total entropy of the system plus its surroundings increases, as required by the second law. Living organisms achieve order by disordering (breaking down) the nutrients they consume. Thus, *the entropy content of food is as important as its energy content.*

Living Organisms Are Open Systems. Classical thermodynamics applies primarily to reversible processes in **isolated systems** (which cannot exchange matter or energy with their surroundings) or in **closed systems** (which can exchange only energy). An isolated system inevitably reaches equilibrium. For example, if

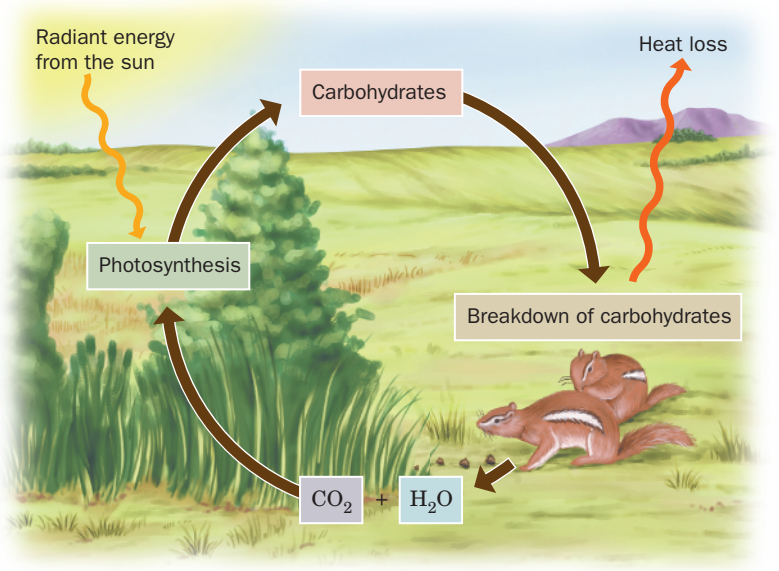


FIG. 1-11 Energy flow in the biosphere. Plants use the sun's radiant energy to synthesize carbohydrates in a process that uses CO_2 and H_2O. Plants or the animals that eat them eventually metabolize the carbohydrates to release their stored free energy and thereby return CO_2 and H_2O to the environment.

its reactants are in excess, the forward reaction will proceed faster than the reverse reaction until equilibrium is attained ($\Delta G = 0$), at which point the forward and reverse reactions exactly balance each other. In contrast, **open systems**, which exchange both matter and energy with their surroundings, can reach equilibrium only after the flow of matter and energy has stopped.

Living organisms, which take up nutrients, release waste products, and generate work and heat, are open systems and therefore can never be at equilibrium. They continuously ingest high-enthalpy, low-entropy nutrients, which they convert to low-enthalpy, high-entropy waste products. The free energy released in this process powers the cellular activities that produce and maintain the high degree of organization characteristic of life. If this process is interrupted, the system ultimately reaches equilibrium, which for living things is synonymous with death. An example of energy flow in an open system is illustrated in Fig. 1-11. Through photosynthesis, plants convert radiant energy from the sun, the primary energy source for life on the earth, to the chemical energy of carbohydrates and other organic substances. The plants, or the animals that eat them, then metabolize these substances to power such functions as the synthesis of biomolecules, the maintenance of intracellular ion concentrations, and cellular movements.

Living Things Maintain a Non-Equilibrium Steady State. Even in a system that is not at equilibrium, matter and energy flow according to the laws of thermodynamics. For example, materials tend to move from areas of high concentration to areas of low concentration. This is why blood takes up O_2 in the lungs, where O_2 is abundant, and releases it to the tissues, where O_2 is scarce.

Living systems are characterized by being in a non-equilibrium **steady state**. This means that all flows in the system are constant so that the system maintains **homeostasis** (does not change with time). An example of metabolic homeostasis is the hormonal maintenance of mammalian blood glucose levels within rigid limits during feast or famine (Section 22-2). Energy flow in the biosphere (Fig. 1-11) is an example of an open system in a non-equilibrium steady state. Slight perturbations from the steady state give rise to changes in flows that restore the system to the steady state (global warming may now be threatening the homeostasis of the biosphere). In all living systems, energy flow is exclusively "downhill" ($\Delta G < 0$). In addition, nature is inherently dissipative, so the recovery

CHECKPOINT

- Summarize the relationship between energy (U), heat (q), and work (w).
- Restate the first and second laws of thermodynamics.
- Use the analogy of a china cabinet to describe a system with low entropy or high entropy.
- Explain why changes in both enthalpy (ΔH) and entropy (ΔS) determine the spontaneity of a process.
- What is the relationship between the rate of a process and its thermodynamic spontaneity?
- What is the free energy change for a reaction at equilibrium?
- Write the equation showing the relationship between $\Delta G°$ and K_{eq}.
- Write the equation showing the relationship between ΔG, $\Delta G°$, and the concentrations of the reactants and products.
- Explain how biochemists define the standard state of a solute. Why do biochemists and chemists use different conventions?
- Explain how organisms avoid reaching equilibrium while maintaining a non-equilibrium steady state.
- How do enzymes affect the rate and free energy change of a reaction?

of free energy from a biochemical process is never total and some energy is always lost to the surroundings.

Enzymes Catalyze Biochemical Reactions. Nearly all the molecular components of an organism can potentially react with one another, and many of these reactions are thermodynamically favored (spontaneous). However, only a subset of all possible reactions actually occur to a significant extent in a living organism. As we shall see (Section 11-2), the rate of a particular reaction depends not on the free energy difference between the initial and final states but on the actual path through which the reactants are transformed to products. Living organisms take advantage of **catalysts**, substances that increase the rate at which the reaction approaches equilibrium without affecting the reaction's ΔG and without themselves undergoing a net change. Biological catalysts are referred to as **enzymes**, most of which are proteins (RNA catalysts are also called **ribozymes**).

Enzymes accelerate biochemical reactions by physically interacting with the reactants and products to provide a more favorable pathway for the transformation of one to the other. Enzymes increase the rates of reactions by increasing the likelihood that the reactants can interact productively. Enzymes cannot, however, promote reactions whose ΔG values are positive.

A multitude of enzymes mediate the flow of energy in every cell. As free energy is harvested, stored, or used to perform cellular work, it may be transferred to other molecules. Although it is tempting to think of free energy as something that is stored in chemical bonds, chemical energy can be transformed into heat, electrical work, osmotic work, or mechanical work, according to the needs of the organism and the biochemical machinery with which it has been equipped through evolution.

Summary

1 The Origin of Life

- A model for the origin of life proposes that organisms ultimately arose from simple organic molecules that polymerized to form more complex molecules capable of replicating themselves.

2 Cellular Architecture

- Compartmentation gave rise to cells that developed metabolic reactions for synthesizing biological molecules and generating energy.
- All cells are either prokaryotic or eukaryotic. Eukaryotic cells contain a variety of membrane-bounded organelles.
- Phylogenetic evidence groups organisms into three domains: archaea, bacteria, and eukarya.
- Natural selection determines the evolution of species.

3 Thermodynamics

- The first law of thermodynamics (energy is conserved) and the second law (spontaneous processes increase the disorder of the universe) apply to biochemical processes. The spontaneity of a process is determined by its free energy change ($\Delta G = \Delta H - T\Delta S$): Spontaneous reactions have $\Delta G < 0$ and nonspontaneous reactions have $\Delta G > 0$.
- The equilibrium constant for a process is related to the standard free energy change for that process.
- Living organisms are open systems that maintain a non-equilibrium steady state (homeostasis).

Key Terms

prebiotic era **2**
organic compound **2**
functional group **3**
linkage **3**
polymer **3**
condensation reaction **3**
hydrolysis **3**
monomer **3**
replication **3**
natural selection **5**
vesicle **6**
compartmentation **6**
metabolic pathways **6**
precursor **6**
catalyst **6**
eukaryote **7**
nucleus **7**
prokaryote **7**
virus **7**
cytoplasm **7**
organelle **8**
endoplasmic reticulum **8**
Golgi apparatus **8**
mitochondrion **8**
chloroplast **8**
lysosome **8**
peroxisome **8**
vacuole **8**
cytosol **8**
cytoskeleton **8**
taxonomy **9**
phylogeny **9**

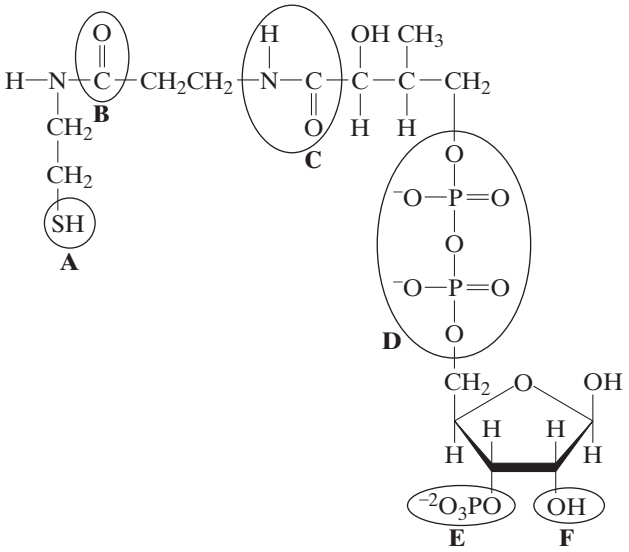
archaea **9**
eubacteria **9**
eukarya **9**
methanogens **9**
halobacteria **9**
thermophiles **9**
symbiosis **9**
mutation **10**
thermodynamics **11**
system **11**
surroundings **11**
U **11**
q **12**
w **12**
H **12**
q_P **12**
D **12**
kD **12**
molecular weight, M_r **12**
spontaneous process **12**
W **13**
S **13**
k_B **13**
G **14**
exergonic **14**
endergonic **14**
equilibrium **14**
reversible process **14**
irreversible process **14**
favorable process **14**
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state function **15**
in vivo **15**
standard state **16**
$\overline{G}_A$ **16**
$\overline{G}_A^\circ$ **16**
equilibrium constant **17**
Le Châtelier's principle **17**
van't Hoff plot **17**
activity **18**
isolated system **18**
closed system **18**
open system **19**
non-equilibrium steady state **19**
homeostasis **19**
enzyme **20**
ribozyme **20**

Problems

EXERCISES

1. Which of the functional groups in Table 1-3 give a molecule a positive charge? Which give a molecule a negative charge?

2. Identify the circled functional groups and linkages in the compound below.



3. Which reactions tend to be characterized by an increase in entropy: condensation or hydrolysis reactions?

4. The bacterium *Thiomargarita namibiensis*—at about 0.1 to 0.3 mm in diameter—is visible to the human eye. How does its size compare to the size of typical prokaryotic cells? How does it compare to the size of typical eukaryotic cells?

5. According to molecular sequence data, to which prokaryotic group are eukaryotes more closely related?

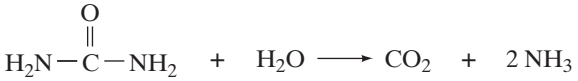
6. (a) Which has greater entropy, liquid water at 0°C or ice at 0°C?

(b) How does the entropy of ice at −5°C differ, if at all, from its entropy at −50°C?

7. Does entropy increase or decrease in the following processes?

(a) $N_2 + 3\,H_2 \rightarrow 2\,NH_3$

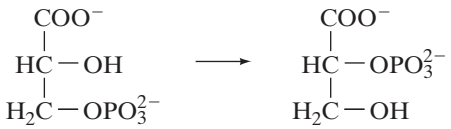
(b)



Urea

(c) 1 M NaCl → 0.5 M NaCl

(d)



3-Phosphoglycerate **2-Phosphoglycerate**

8. Can a process occur if the entropy of the system decreases and the enthalpy increases?

9. Label the following statements true or false:

(a) A reaction is said to be spontaneous when it can proceed in either the forward or reverse direction.

(b) A spontaneous process always happens very quickly.

(c) A nonspontaneous reaction will proceed spontaneously in the reverse direction.

(d) A spontaneous process can occur with a large decrease in entropy.

10. Consider a reaction with $\Delta H = 15$ kJ and $\Delta S = 50\ J \cdot K^{-1}$. Is the reaction spontaneous (a) at 10°C, (b) at 80°C?

11. For the reaction A → B at 298 K, the change in enthalpy is $-7\ kJ \cdot mol^{-1}$ and the change in entropy is $-25\ J \cdot K^{-1} \cdot mol^{-1}$. Is the reaction spontaneous? If not, should the temperature be increased or decreased to make the reaction spontaneous?

12. When the reaction A + B ⇌ C is at equilibrium, the concentrations of reactants are as follows: [A] = 2 mM, [B] = 3 mM, and [C] = 9 mM. What is the standard free energy change for the reaction?

13. Calculate $\Delta G^{\circ\prime}$ for the reaction A + B ⇌ C + D at 25°C when the equilibrium concentrations are [A] = 10 μM, [B] = 15 μM, [C] = 3 μM, and [D] = 5 μM. Is the reaction exergonic or endergonic under standard conditions?

14. Calculate the equilibrium constant for the reaction

$$\text{glucose-1-phosphate} + H_2O \rightarrow \text{glucose} + H_2PO_4^-$$

at pH 7.0 and 25°C ($\Delta G^{\circ\prime} = -20.9\ kJ \cdot mol^{-1}$).

15. $\Delta G^{\circ\prime}$ for the isomerization reaction

$$\text{glucose-1-phosphate (G1P)} \rightleftharpoons \text{glucose-6-phosphate (G6P)}$$

is $-7.1\ kJ \cdot mol^{-1}$. Calculate the equilibrium ratio of [G1P] to [G6P] at 25°C.

CHALLENGE QUESTIONS

16. Why is the cell membrane not an absolute barrier between the cytoplasm and the external environment?

17. Most of the volume of *T. namibiensis* cells (see Problem 4) is occupied by a large central vacuole. Why were scientists surprised to discover a bacterial cell containing a vacuole?

18. A spheroidal bacterium with a diameter of 1 μm contains two molecules of a particular protein. What is the molar concentration of the protein?

19. How many glucose molecules does the cell in Problem 18 contain when its internal glucose concentration is 1.0 mM?

20. For the conversion of reactant A to product B, the change in enthalpy is 7 kJ · mol^{-1} and the change is entropy is 20 J · K^{-1} · mol^{-1}. Above what temperature does the reaction become spontaneous?

21. The equilibrium constant for the reaction Q → R is 25.

(a) If 50 μM of Q is mixed with 50 μM of R, which way will the reaction proceed to generate more Q or more R?

(b) Calculate the equilibrium concentrations of Q and R.

22. At 10°C, K_{eq} for a reaction is 100. At 30°C, $K_{eq} = 10$. Does enthalpy increase or decrease during the reaction?

23. Two biochemical reactions have the same $K_{eq} = 5 \times 10^8$ at temperature $T_1 = 298$ K. However, Reaction 1 has $\Delta H° = -28$ kJ · mol^{-1} and Reaction 2 has $\Delta H° = +28$ kJ · mol^{-1}. The two reactions utilize the same reactants. Your lab partner has proposed that you can get more of the reactants to proceed via Reaction 2 rather than Reaction 1 by lowering the temperature of the reaction. Will this strategy work? Why or why not? How much would the temperature have to be raised or lowered in order to change the value of K_2/K_1 from 1 to 10?

BIOINFORMATICS

Brief Exercises Brief, online bioinformatics homework exercises can be found in WileyPLUS Learning Space.

Exercise 1 The Periodic Table of the Elements and Domains of Life

Exercise 2 Organic Functional Groups and the Three-Dimensional Structure of Vitamin C

MORE TO EXPLORE Look up *methanogen* and *methanotroph*. Where do such organisms occur? Summarize how they obtain matter and energy from their surroundings. Draw a diagram to illustrate the metabolic interdependence of methanogens and methanotrophs.

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