CHAPTER 1

Life, Cells and Thermodynamics

A variety of complex organic molecules can be found in interstellar gas and dust. The large molecular clouds that give rise to stellar nurseries like those found in this image of the Cederblad 214 nebula (found in the direction of the constellation Cepheus) have been found to contain complex hydrocarbons. These include polycyclic aromatics and many smaller precursor molecules containing carbon, nitrogen, and oxygen that are important constituents of life on Earth. [Photograph by D. Heilman.]

CHAPTER CONTENTS

Life on Earth arose from rather curious beginnings. Approximately 4.5 billion years ago our planet formed from a complex soup of interstellar material orbiting a relatively average, newborn dwarf star. Within that soup were precursors—complex, carbon-rich molecules with a penchant for self-assembly—which would combine and grow in complexity and versatility. This would lead to complex molecular systems that could self-replicate and in the process, iterate: a recipe for evolution. Eventually organisms would emerge capable of highly complex interactions with the environment. Extracting energy from chemical compounds or the sun, they converted this into a bewildering array of complex biomolecules from which life would continue to evolve. The Earth underwent a dramatic transition from a desolate and barren place, to a world utterly teeming with life. Through these origins, organisms on Earth have a common ancestry and therefore share the same chemical makeup; there is a single chemical theme that connects all life on this planet. We have a staggeringly diverse and wonderfully complex array of organisms to inform our understanding of life, but we are also profoundly limited in having only one version of life from which to learn. However, the Earth is not the only place where such biological precursor molecules are found. Curiously, the molecules of life are everywhere. The great cosmic spaces between the stars contain clouds of gas and dust that harbor a myriad of complex organic molecules. Ancient asteroids flung from far away worlds and comets from the outer reaches of the solar system do as well. These may have seeded life on other worlds, including our own. The Earth is but one planet among many worlds in a single solar system; it resides in a galaxy with hundreds of billions of solar systems, in a universe with hundreds of billions of galaxies. The molecules of life are everywhere. Is life then unique to Earth, or a common occurrence throughout the universe? We, who evolved from humble and curious beginnings, stand able to explore these mysteries as well as that of our own origins.

Biochemistry is the study of the chemistry of life, which describes how the properties and interactions of the vast array of biological molecules results in the amazing and diverse living systems on Earth. This chapter will discuss the potential origins of life, and the common biological forms and natural trends that are observed, all of which adhere to the same fundamental principles of chemistry and physics to which you have already been introduced. The precise point at which these systems are considered life is a subject of continuing debate, and care is taken not to apply generalizations or unduly restrict our definitions, as science continues to challenge and expand our understanding. The Earth contains a vast and diverse range of organisms that thrive in the most lush and accommodating of habitats on land and sea, but also in utterly dark, scorching, and forbidding environments where we would least expect to find life. We are continually surprised and delighted by the exotic and profound ways in which life can exist. There is much yet to be discovered both on Earth, and perhaps, on other worlds.

1.1 The Origin of Life

LEARNING OUTCOMES

After reading this section, you will be able to:

Discuss the origins and evolution of biological molecules.

- Describe the general composition of biological molecules.
- Identify the common functional groups found in biochemistry.
- Explain the chemical evolution of complex molecules from simple precursors.
- Discuss the concept of chemical complementarity and its importance in self-replication of biological polymers.

1.1A 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. Miller's analysis showed that the solution contained several amino acids (which are components of proteins) and other biochemically significant compounds. Following Miller's death in 2007, several sealed vials from the original experiment were analyzed using modern techniques, resulting in detection of over 40 different amino acids and amines. Many research groups have performed similar experiments with the benefit of modern technology and have found a multitude of complex molecules including many more amino acids, dipeptides (simple protein chains), complex cyclic hydrocarbons, and the complete palette of nucleotide bases (building blocks of DNA and RNA). Clearly, these precursors to complex biomolecules were more readily available during the formation of the Earth than previously understood.

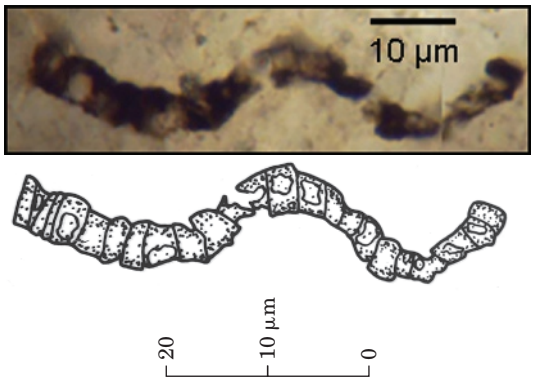
Scientists have also suggested that early biological molecules were generated in quite a different way: in the dark and under water. Hydrothermal vents in the ocean floor, which emit solutions of metal sulfides at temperatures as high as 400 °C (**Fig. 1.2**), may have provided conditions suitable for the formation of amino acids and other small organic molecules from simple compounds present in seawater.

Both of these theories assume a terrestrial origin for early biological molecules, however research indicates that complex biological precursors can also form in the most distant and surprising of places. Nebulae, rich in gas and dust, are ripe with a diverse array of complex carbon compounds. Laboratory experiments conducted by NASA have produced biological precursors under conditions found only in space. Missions that have remotely sampled and analyzed the chemistry of other planets, comets, and asteroids have discovered a wealth of biological precursor molecules. Notably, researchers have found the building blocks of protein and DNA in meteor fragments that are older than the

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).



Courtesy of J. William Schopf, UCLA

FIGURE 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.

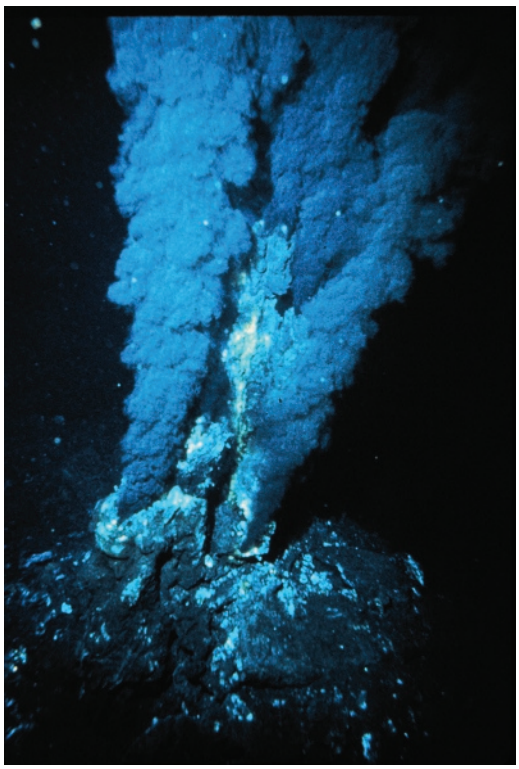


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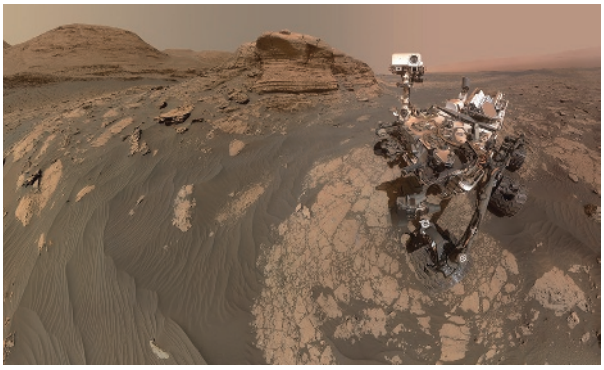
FIGURE 1.2 A hydrothermal vent. Such ocean-floor formations are known as "black smokers" because the metal sulfides dissolved in the superheated water they emit precipitate on encountering the much cooler ocean water.

Perspectives in Biochemistry

BOX 1.1

The Search for Life on Other Worlds



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We on Earth are fortunate to have a wealth of organisms to study and understand life. However, all evidence indicates that life on Earth evolved from a common ancestor and as such, all organisms share the same origin, chemical makeup, and strict dependence on liquid water. Are these the only conditions under which life can form? Is life on Earth unique and are we the sole example in the universe? Many biochemists are preoccupied with such questions and with exploring other possible ways that life may form. The discovery of organisms on Earth that thrive in extreme conditions of temperature, pH, and salinity has changed our understanding of where life might flourish. Organisms such as extreme thermophiles survive in utter darkness where temperatures can exceed 100 °C and with pH values as low as 1.5. Many of these organisms use sulfur instead of oxygen in their metabolism and extract energy from chemical compounds instead of using photosynthesis. From the scorching interiors of volcanic fumaroles to the frozen, arid arctic tundra, organisms have adapted to these hostile environments, serving as a strong indication that we may find life existing under similar conditions on other worlds. Jupiter's moon Io is a world of volcanism, stretched and squeezed by the planet's gravity. Europa, another of Jupiter's moons, is an icy world that is likely to have a subsurface ocean warmed by geothermal energy. It is possible that life could exist on these worlds in our relative backyard where we have, and will continue to, send probes. It is also possible that life may be able to form in solvents other than water, perhaps on the liquid oceans of ethane that exist on Saturn's moon, Titan. Biochemists are studying the types of molecules and chemical strategies for life that might be possible in such a hydrophobic environment.

Exploration of our solar system is now ripe with robotic missions, many of which have the capability to identify complex molecular precursors or conditions under which life could thrive. The NASA Curiosity rover determined that liquid water as well as the chemical building blocks and nutrients needed for supporting life had been present for at least tens of millions of years on Mars. Curiosity's twin, Perseverance followed a number of years later with an enhanced mission to search for signs of ancient life. Deeper into the solar system, probes have been sent to comets and asteroids, representing early steps in studying these distant and ancient bodies. The European Space Agency (ESA) Rosetta mission was the first to orbit a comet nucleus and to land a probe (Philae) on its surface. The Japan Aerospace Exploration Agency (JAXA) successfully sampled the asteroid Ryugu and returned a capsule with material to Earth. Analysis of the material revealed precursor amino acids, complex cyclic aromatic hydrocarbons, and other carbon and nitrogen-containing compounds.

The detection of life on worlds beyond our solar system requires the use of powerful telescopes capable of detecting potentially habitable planets, and the molecular signatures of life, from great distances. NASA's Kepler mission, which surveyed over 500,000 stars in one region of our galaxy, concluded that, on average, nearly every star has at least one planet. Kepler discovered thousands of exoplanets, some of which are rocky planets in habitable zones where liquid water might exist. Missions including the James Webb Space Telescope will assist with follow-up analysis of candidate exoplanet atmospheres with spectroscopic detection of molecules from afar. Evidence gathered so far indicates that the possibility of finding life elsewhere may be much greater than we might have imagined.

age of the solar system (**Box 1.1**). It's possible that the precursor to life on Earth was seeded from space.

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**.

1.1B Complex Self-Replicating Systems Evolved from Simple Molecules

Evolution 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

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 $R_3\overset{+}{N}H$	$-N<$ or $-\overset{+}{N}-$ (amino group)
Alcohol	ROH	—OH (hydroxyl group)
Thiol	RSH	—SH (sulfhydryl group)
Ether	ROR	—O— (ether linkage)
Aldehyde	$R-C(=O)-H$	$-C(=O)-$ (carbonyl group)
Ketone	$R-C(=O)-R$	$-C(=O)-$ (carbonyl group)
Carboxylic acid[b]	$R-C(=O)-OH$ or $R-C(=O)-O^-$	$-C(=O)-OH$ (carboxyl group) or $-C(=O)-O^-$ (carboxylate group)
Ester	$R-C(=O)-OR$	$-C(=O)-O-$ (ester linkage) $R-C(=O)-$ (acyl group)[c]
Thioester	$R-C(=O)-SR$	$-C(=O)-S-$ (thioester linkage) $R-C(=O)-$ (acyl group)[c]
Amide	$R-C(=O)-NH_2$ $R-C(=O)-NHR$ $R-C(=O)-NR_2$	$-C(=O)-N<$ (amido group) $R-C(=O)-$ (acyl group)[c]
Imine (Schiff base)[b]	R=NH or $R=\overset{+}{N}H_2$ R=NR or $R=\overset{+}{N}HR$	$>C=N-$ or $>C=\overset{+}{N}<$ (imino group)
Disulfide	R—S—S—R	—S—S— (disulfide linkage)
Phosphate ester[b]	$R-O-P(=O)(O^-)-OH$	$-P(=O)(O^-)-OH$ (phosphoryl group)
Diphosphate ester[b]	$R-O-P(=O)(O^-)-O-P(=O)(OH)-O^-$	$-P(=O)(O^-)-O-P(=O)(OH)-O^-$ (phosphoanhydride group)
Phosphate diester[b]	$R-O-P(=O)(O^-)-O-R$	$-O-P(=O)(O^-)-O-$ (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.

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

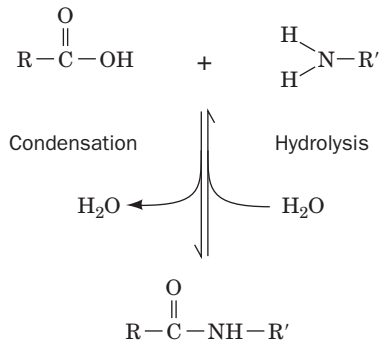


FIGURE 1.3 Reaction of a carboxylic acid with an amine. The elements of water are released during condensation. In the reverse process—hydrolysis—water is added to cleave the amide bond. In living systems, condensation reactions are not freely reversible.

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)

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 one another (**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 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.

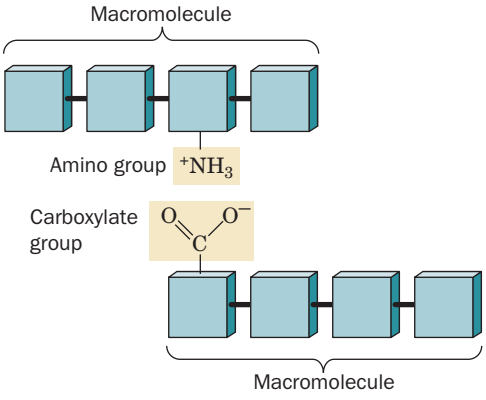


FIGURE 1.4 Association of complementary molecules. The positively-charged amino group interacts electrostatically with the negatively-charged carboxylate group.

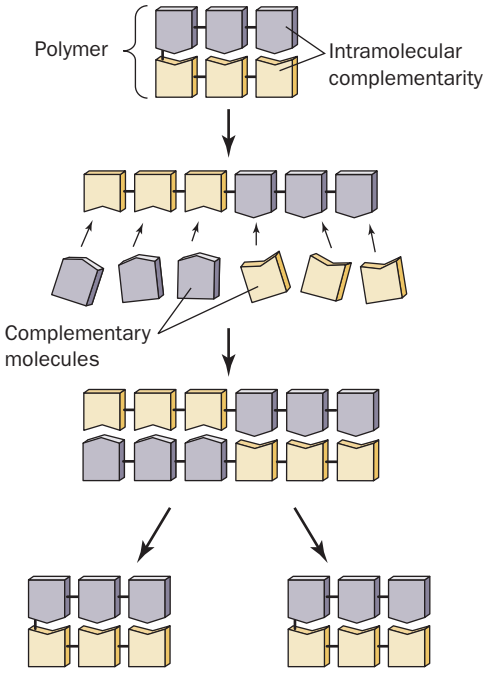


FIGURE 1.5 Replication through complementarity. In this simple case, a polymer serves as a template for the assembly of a complementary molecule, which, because of intramolecular complementarity, is an exact copy of the original.

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

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 parent molecules. Over time, **natural selection**, the competitive evolutionary process by which reproductive preference is given to the better adapted, would have favored molecules that made more accurate copies of themselves.

The "**RNA world**" hypothesis, proposed in 1962 by Alexander Rich, suggests that RNA may have served as the first self-replicating polymer. Like DNA, RNA can also store, transmit, and duplicate genetic information. However, the single-stranded nature of RNA means that this molecule can use complementarity to fold on itself into a great many structures, many having catalytic activity. The ribosome is an excellent example of an ancient catalytic RNA. According to some evolutionary sequence analyses, the ribosome may predate the evolution of the cell itself. Not unlike some modern viruses, early forms of life may have used RNA as their genome. Whether this hypothetical origin for life existed will remain unknown. Regardless, RNA serves as an excellent model system for the study of potential self-replicating systems.

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 that facilitate interactions within and between molecules.

Review Questions

1. Name four elements that occur in virtually all biological molecules.
2. Summarize the major stages of chemical evolution.
3. Describe what happens during a simple condensation and hydrolysis reaction.
4. Explain why complementarity would have been necessary for the development of self-replicating molecules.

1.2 Cellular Architecture

LEARNING OUTCOMES

After reading this section, you will be able to:

Explain how important features of cellular architecture relate to the structure and function of cells.

- Describe the advantages of compartmentation for self-replicating systems.
- Define metabolic pathways and explain the reasoning for their development in organisms.
- Compare the general features of the two major types of cells.
- Describe features of each of the three evolutionary domains of organisms.
- Explain the theory of endosymbiosis and the origin of eukaryotes.
- Outline the four principles of evolution and provide examples of each using modern organisms.

The types of systems described so far would have had to compete for available resources with all of the other components of the primordial Earth. A system that was sequestered and protected by boundaries of some sort would have a selective advantage. 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.

1.2A Cells Carry Out Metabolic Reactions

There are several advantages to **compartmentation**. 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

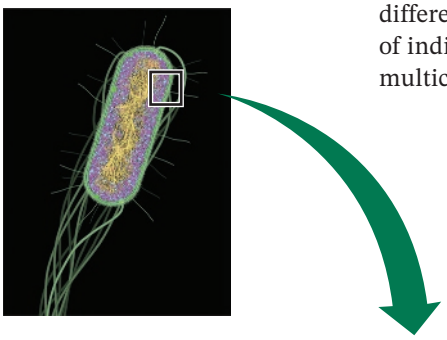
can react more readily, leading to increased efficiency in polymerization and other types of chemical reactions.

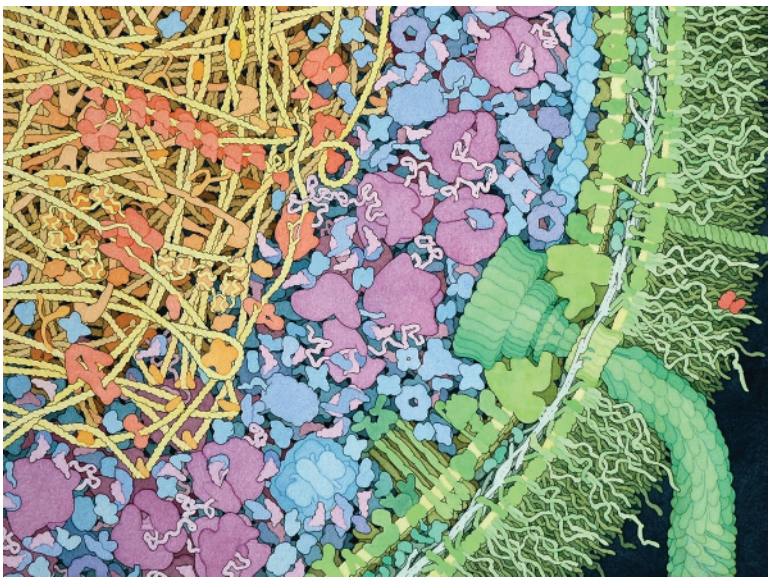
A membrane-bound compartment that protected its contents would gradually become quite different in composition from its surroundings. Modern cells contain high concentrations of ions, small molecules, and large molecular aggregates that are found only in traces—if at all—outside the cell. For example, 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** (substances that promote chemical reactions without 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 with the appropriate functional groups.

In general, biosynthetic reactions require energy; hence the first cellular reactions also would have 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 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.





From Goodsell, D.S., *The Machinery of Life* (2nd ed.), Springer (2009). Reproduced with permission.

FIGURE 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.

1.2B There Are Two Types of Cells: Prokaryotes and Eukaryotes

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 can be multicellular or unicellular, are vastly more complex than prokaryotes.*

Prokaryotes are the most numerous and widespread organisms on the earth. This is because their varied and often highly adaptable metabolisms are well-suited 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.

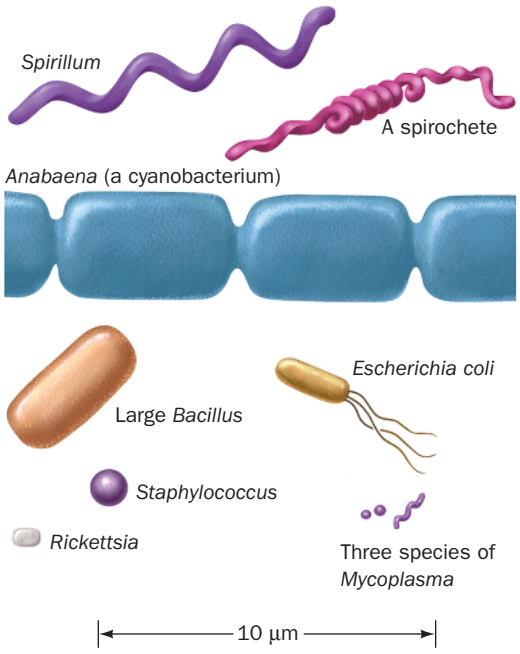


FIGURE 1.7 **Scale drawings of some prokaryotic cells.**

Eukaryotic cells are generally 10 to 100 μm in diameter and thus have a thousand to a million times the volume of typical prokaryotes. However, it is not size, 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-bound 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 renders them larger and more slowly growing than prokaryotes, giving 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.

1.2C Molecular Data Reveal Three Evolutionary Domains of Organisms

Evolution 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

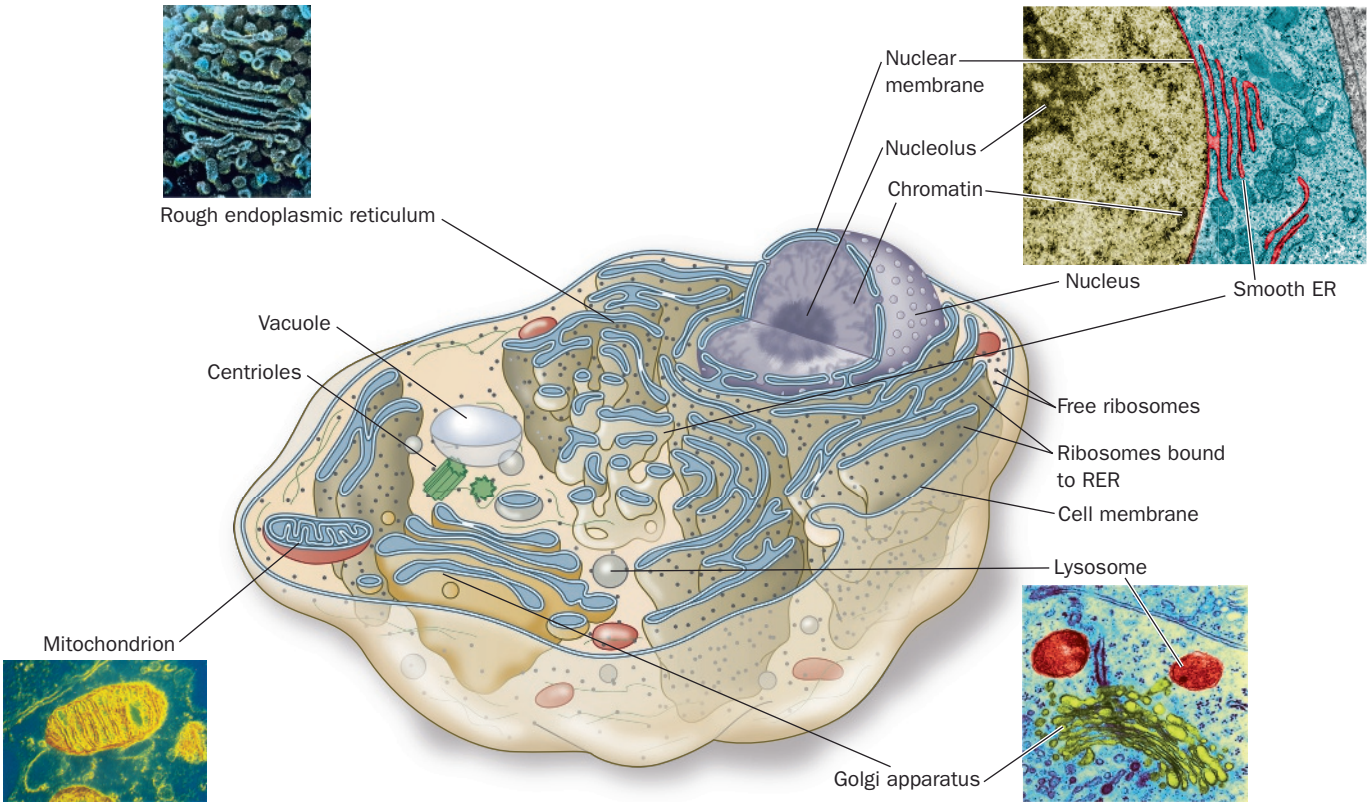


FIGURE 1.8 Diagram of a typical animal cell with electron micrographs of its organelles. Membrane-bound organelles include the nucleus, endoplasmic reticulum, lysosome, peroxisome (not pictured), mitochondrion, vacuole, and Golgi apparatus. The nucleus contains chromatin (a complex of DNA and protein) 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.

[Nucleus and Smooth endoplasmic reticulum JOSE LUIS CALVO MARTIN & JOSE ENRIQUE GARCIA-MAURIÑO MUZQUIZ / Getty Images; rough endoplasmic reticulum Professors Pietro M. Motta & Tomonori Naguro / Science Source; mitochondrion CNRI/Science Source; Golgi apparatus and Lysosome Science Source.]

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

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

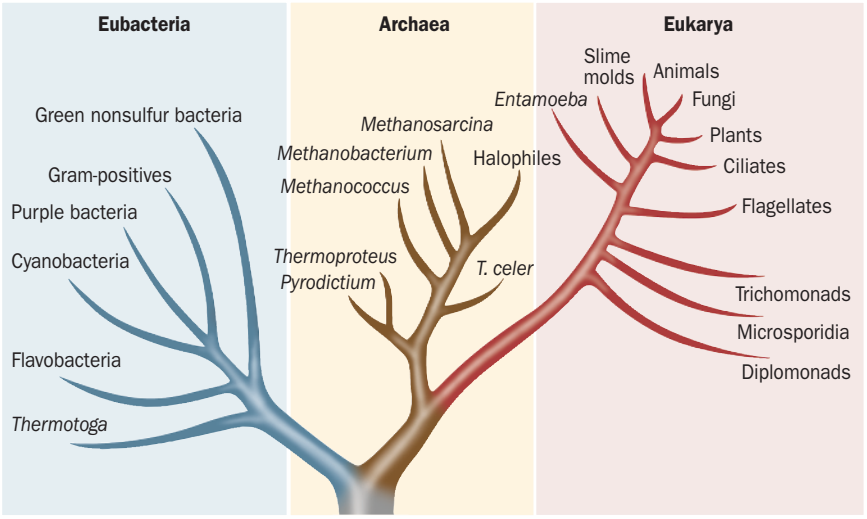


FIGURE 1.9 Phylogenetic tree showing the three domains of organisms. The branches indicate the pattern of divergence from a common ancestor. The archaea are prokaryotes, like eubacteria, but share many features with eukaryotes.

Source: Adapted from Wheelis, M.L., Kandler, O., and Woese, C.R. *Proc. Natl. Acad. Sci.* 89, 2931 (1992).

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, with some unique differences in the genetic code from that of the nucleus. 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 1.2**). In fact, certain eukaryotes that lack mitochondria or chloroplasts permanently harbor symbiotic bacteria.

1.2D Organisms Continue to Evolve

Evolution 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 adverse.
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.

Pathways of Discovery

BOX 1.2

Lynn Margulis and the Theory of Endosymbiosis

Cavan Images/Alamy Stock Photo

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 (in 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; instead, she 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 are now almost universally accepted: (1) mitochondria are the descendants of oxygen-respiring bacteria, and (2) chloroplasts were originally photosynthetic bacteria. The third, 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).

Review Questions

1. Explain the selective advantages of compartmentation and metabolic pathways.
2. Discuss the differences between prokaryotes and eukaryotes.
3. Make a list of the major eukaryotic organelles and their functions.
4. Explain why a taxonomy based on molecular sequences is more accurate than one based on morphology.
5. How are the three evolutionary domains of organisms related to each other?
6. Explain how individual variations allow evolution to occur.
7. Why is evolutionary change constrained by its past but impossible to predict?

1.3 Thermodynamics

LEARNING OUTCOMES

After reading this section, you will be able to:

Distinguish the first and second laws of thermodynamics.

- Relate the concept of enthalpy to the first law of thermodynamics.
- Relate the concept of entropy to the second law of thermodynamics.
- Define free energy and spontaneity and relate the two for any process.
- Explain how the sign of enthalpy or entropy will affect the spontaneity of a process.
- Define state functions and biochemical standard state.
- Calculate the free energy of a chemical reaction under standard and non-standard conditions.
- Explain the non-equilibrium steady state and its relationship to living systems.

The normal activities of living organisms 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. To begin, this section will review the fundamental laws of thermodynamics. It will then turn your 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.

1.3A 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 chemical reaction or an organism; the rest of the universe is known as the surroundings. The system has a certain amount of **energy, *E***. *The first law of thermodynamics states that total energy of the universe is constant and that energy can be neither created nor destroyed during any physical or chemical process.* This means that when the system undergoes a change, some of its energy can be transferred or change form, but it cannot be consumed. For example, the energy stored in chemical bonds can be converted to kinetic energy to perform work. Energy can be used to perform different kinds of work and it is useful to speak of energy in specific forms, such as mechanical energy, electrical energy, or chemical energy—all of which are relevant to living systems.

The change that occurs in the internal energy of a system (ΔE) corresponds to the sum of the heat transferred (q) and work done (w):

$$\Delta E = q + w \tag{1.1}$$

where the upper case Greek letter Δ (delta) indicates change. For many chemical systems, w is defined by pressure-volume work ($w = -P\Delta V$), especially where large amounts of gas are produced, increasing the volume. However, for most biological processes we are not concerned with pressure-volume work as volume changes are typically insignificant.

$$\Delta E = q - P\Delta V = q_v \tag{1.2}$$

In open systems, these processes are typically at constant pressure. Under such conditions q is equivalent to a thermodynamic quantity called **enthalpy** (Greek: *enthalpein*, to warm in), symbolized H, with the following relationship:

$$\Delta E = \Delta H - P\Delta V \tag{1.3}$$

Enthalpy refers to the heat *content* of a system. Since you already know that volume changes in most biological processes are insignificant, you can see that under conditions of constant pressure, the energy change for the reacting system is equivalent to its enthalpy change and thus, q:

$$\begin{aligned} \Delta E &= \Delta H - P\Delta V = q_p + w \\ \Delta E &= \Delta H - 0 = q_p + 0 \\ \Delta E &= \Delta H = q_p \end{aligned} \tag{1.4}$$

Enthalpy, like energy, heat, and work, is given units of joules. Some commonly used units, biochemical constants, and other conventions are given in **Box 1.3**.

Thermodynamics is useful for indicating the **spontaneity** of a process; a determination of whether the process *can* occur (regardless of whether a process *will* occur). A spontaneous process occurs without the input of additional energy from outside the system (although keep in mind that thermodynamic spontaneity has nothing to do with how quickly a process occurs). However, the first law of thermodynamics 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 heat flow in either direction would be consistent with the first law of thermodynamics since the aggregate energy of the two objects would not change. Therefore, heat alone (enthalpy in this case) is not enough to determine spontaneity; an additional thermodynamic parameter is needed.

Perspectives in Biochemistry

BOX 1.3

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 (Da)**, which are defined as 1/12th the mass of a ^{12}C atom (1000 Da = 1 **kDa**). Biochemists also use molecular weight, a dimensionless quantity defined as the ratio of the particle mass to 1/12th the mass of a ^{12}C atom, which is symbolized M_r (for relative molecular mass).

1.3B The Second Law of Thermodynamics States That Entropy Tends to Increase

According to the second law of thermodynamics, spontaneous processes are characterized by the dispersal of energy, in the absence of energy input. In this context, energy dispersal (sometimes referred to less accurately as disorder) is defined as the number of energetically equivalent ways, W, of arranging the components of a 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.

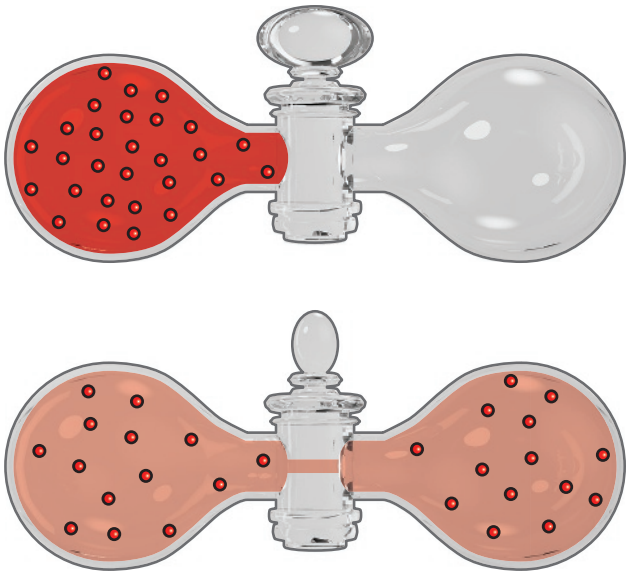


FIGURE 1.10 Illustration of entropy. In (*a*), a gas occupies the leftmost of two equal-sized bulbs and hence the entropy is low. When the stopcock is opened (*b*), the entropy increases as the gas molecules diffuse back and forth between the bulbs and eventually become distributed evenly, half in each bulb.

Question 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:

$$S = k_B \ln W \tag{1.5}$$

where k_B is the **Boltzmann constant** and 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 (ΔE 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

$$\Delta S_{system} + \Delta S_{surroundings} = \Delta S_{universe} > 0 \tag{1.6}$$

all processes increase the entropy 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 expression for entropy applied to the constant-temperature conditions typical of biological systems that is entirely equivalent: for a spontaneous process,

$$\Delta S \geq \frac{q}{T} \tag{1.7}$$

Thus the entropy change in a process can be determined experimentally from measurements of heat and temperature. However, as was the case for enthalpy, the spontaneity of a process cannot be predicted from knowledge of the system's entropy change alone. For example, when sparked, a mixture of 2 mol of H_2 and 1 mol of O_2 reacts (explodes) to form 2 mol of H_2O. Yet two water

molecules, each of which contains three atoms constrained to stay together, have lower entropy (are more ordered) than the three diatomic molecules from which they formed. Thus, this spontaneous reaction occurs with a decrease in the system's entropy. As you will see, prediction of spontaneity requires an understanding of both the enthalpy and entropy of the system.

1.3C The Free Energy Change Determines the Spontaneity of a Process

What, then, is the thermodynamic criterion for a spontaneous process? Equation 1.4 and Equation 1.7 indicate that at constant temperature and pressure,

$$\Delta S \geq \frac{q_p}{T} = \frac{\Delta H}{T} \tag{1.8}$$

Thus,

$$\Delta H - T\Delta S \leq 0 \tag{1.9}$$

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

$$G = H - TS \tag{1.10}$$

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

$$\Delta G = \Delta H - T\Delta S < 0 \tag{1.11}$$

Spontaneous 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**).

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.

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

b. First, convert temperature from °C to K: 4 + 273 = 277 K. Then use Eq. 1.11.

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

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.

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

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

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.

Processes at **equilibrium**, those in which the rates of 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 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 will proceed at a measurable rate. The rate depends on the detailed mechanism of the reaction, which is independent of* ΔG (Section 9.2).

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, $\Delta G < 0$.

When comparing chemical reactions, it is often useful to define a point of reference under defined, standard conditions. For this reason, the standard free energy change ($\Delta G°$) is used, which is determined at room temperature (298 K), constant pressure (1 atm) and 1M for all concentrations of reactants and products. The standard change in free energy is given by:

$$\Delta G° = \Delta H° - T\Delta S° \qquad \textbf{(1.12)}$$

A more practical form of the standard state exists for biochemistry, in which conditions with greater relevance to living systems are used, particularly with regard to the many biochemical reactions that involve proton transfer or include water as a reactant or product. These situations are standardized with pressure at 1 atm, temperature at 298 K, pH at 7.0, H_2O concentration at 55.5 M, and 1 M concentration for all other reactants and products. The pH will be relatively constant (as most biological systems are buffered) and the concentration of solvent will also be constant, so this defines a new standard state, $\Delta G°'$, where the prime indicates the **biochemical standard state**.

1.3D Free Energy Changes Can Be Calculated from Reactant and Product Concentrations

The entropy of a substance increases with its volume. For example, in occupying all of the available volume, a collection of gas molecules maximizes its entropy (assumes its most dispersed

arrangement). Similarly, dissolved molecules become uniformly distributed throughout the volume of a solution. 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 near equilibrium and spontaneously in either direction depending on the relative concentrations of their reactants and products. Note that this **non-standard state** is distinct from the biochemical standard state and would be expected to have a ΔG value close to zero because the reaction is freely reversible.

For the general reaction

$$a\mathrm{A} + b\mathrm{B} \rightleftharpoons c\mathrm{C} + d\mathrm{D}$$

the free energy change is additive and given by subtracting the sum of the free energies of the reactants from the sum of the free energies of the products.

$$\Delta G^{\circ\prime} = cG_C^{\circ\prime} + dG_D^{\circ\prime} - aG_A^{\circ\prime} + bG_B^{\circ\prime} \tag{1.13}$$

The actual free energy change under non-standard conditions is defined by the following relationship:

$$\Delta G = \Delta G^{\circ\prime} + RT \ln Q \tag{1.14}$$

where R is the gas constant (8.314 J/mol K), T is the absolute temperature (in Kelvin), and Q is the mass action ratio of product concentrations to reactant concentrations:

$$Q = \left(\frac{[\mathrm{C}]^c[\mathrm{D}]^d}{[\mathrm{A}]^a[\mathrm{B}]^b}\right) \tag{1.15}$$

Combining Equations 1.14 and 1.15 we derive the following

$$\Delta G = \Delta G^{\circ\prime} + RT \ln \left(\frac{[\mathrm{C}]^c[\mathrm{D}]^d}{[\mathrm{A}]^a[\mathrm{B}]^b}\right) \tag{1.16}$$

where $\Delta G^{\circ\prime}$ is the free energy change of the reaction when all of its reactants and products are in their biochemical standard states. Thus, the expression for the free energy change of a reaction consists of two parts: (1) a constant term with a value that depends only on the reaction taking place under standard conditions 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, $\mathrm{Q} = K_{eq}$ (the equilibrium constant for the reaction) and 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. 1.14 becomes

$$0 = \Delta G^{\circ\prime} + RT \ln K_{eq}$$

and,

$$\Delta G^{\circ\prime} = -RT \ln K_{eq} \tag{1.17}$$

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 ($\Delta G^{\circ\prime}$) and the actual concentrations of the reactants and products (see **Sample Calculation 1.3**).

Sample Calculation 1.2

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

Since ΔG° is known, a rearrangement of Eq. 1.17 can be used to calculate K_{eq}. The absolute temperature is 25 + 273 = 298 K.

$$\begin{aligned} K_{eq} &= e^{-\Delta G^{\circ}/RT} \\ &= e^{-(-15{,}000\ \mathrm{J \cdot mol^{-1}})/(8.314\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}})(298\ \mathrm{K})} \\ &= e^{6.05} \\ &= 426 \end{aligned}$$

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 1.16 and remember that the units for concentration are moles per liter.

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

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

$$= -15{,}000\ \text{J}\cdot\text{mol}^{-1} - 11{,}900\ \text{J}\cdot\text{mol}^{-1}$$

$$= -26{,}900\ \text{J}\cdot\text{mol}^{-1}$$

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. However, some metabolic reactions 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.

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.

***K* Depends on Temperature.** The manner in which the equilibrium constant varies with temperature can be seen by substituting Eq. 1.12 into Eq. 1.17 and rearranging as follows:

$$\ln K_{eq} = \frac{-\Delta H^\circ}{R}\left(\frac{1}{T}\right) + \frac{\Delta S^\circ}{R} \qquad \textbf{(1.18)}$$

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).

1.3E 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 into 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 into 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 its reactants are in excess, the forward reaction will proceed faster than the reverse reaction until equilibrium is attained ($\Delta G = 0$),

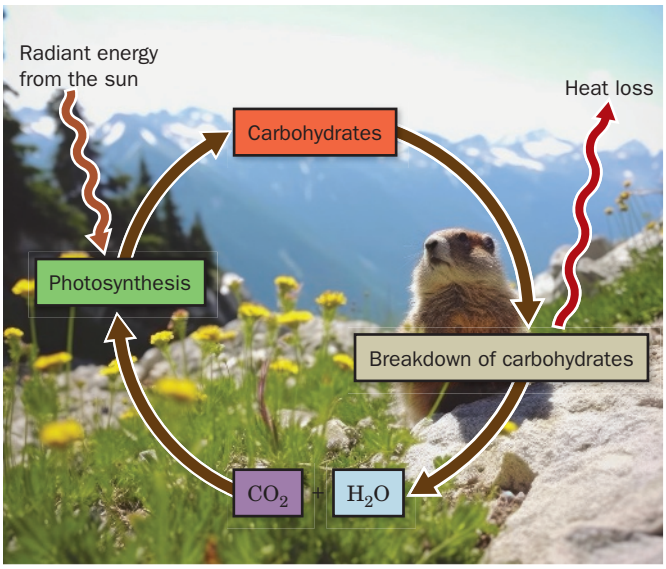


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FIGURE 1.11 Energy flow in the biosphere. Plants use the sun's radiant energy to synthesize carbohydrates in a process that uses CO_2 and H_2O. Plants or the animals that eat them eventually metabolize the carbohydrates to release their stored free energy and thereby return CO_2 and H_2O to the environment.

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. 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, into the chemical energy of carbohydrates and other organic substances. The plants, or the animals that eat them, then metabolize these substances to power functions such 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 *flux* (input and output) in the system is constant so that the system maintains **homeostasis** (does not change with time), yet at concentrations that are typically far from equilibrium. Erwin Schrodinger described this as how "living matter evades the decay to equilibrium" illustrating that for living things, equilibrium is synonymous with death. (Recall that for a process at equilibrium, $\Delta G = 0$ and there is no free energy that can be used to perform work.) For example, reactions between oxygen and methane would ordinarily reach equilibrium at much lower levels, but they coexist at substantial concentrations in the Earth's atmosphere due to steady-state production from biosynthesis. In the biosphere, slight perturbations from the steady state give rise to matter and energy flux that restores the system to the steady state (a situation now being threatened by climate change).

The non-equilibrium steady state is a signature of living systems and a fundamental requirement of any form of life, whether a familiar example from Earth or an exotic and unrecognizable life-form on a distant world. Our understanding of biochemical processes and our technology have both progressed to the point where detection of life on other worlds is now possible. Robotic missions to other worlds within our solar system are capable of searching for the molecular signatures of life, as are powerful telescopes that now have the capability to probe the chemical compositions of exoplanet atmospheres thousands of light years away. Detection of biomolecules and a non-equilibrium steady state may very well be the first step in the discovery of life elsewhere in the universe.

Review Questions

1. Describe the relationship between energy (U), heat (q), and work (w).
2. How does life persist despite the laws of thermodynamics?
3. Use the analogy of a china cabinet to describe a system with low entropy or high entropy.
4. Explain why changes in both enthalpy (ΔH) and entropy (ΔS) determine the spontaneity of a process.
5. What is the relationship between the rate of a process and its thermodynamic spontaneity?
6. What is the free energy change for a reaction at equilibrium?

7. Write the equation showing the relationship between $\Delta G°$ and K_{eq}.
8. Write the equation showing the relationship between ΔG, $\Delta G°$, and the concentrations of the reactants and products.
9. Explain how biochemists define the standard state of a solute. Why do biochemists and chemists use different conventions?
10. Explain how organisms avoid reaching equilibrium while maintaining a non-equilibrium steady state.
11. How do enzymes affect the rate and free energy change of a reaction?

GLOBAL INSIGHT

Contributions of Ancient Civilizations to Biochemistry

In ancient India, the Ayurvedic system of medicine, which dates back over 5,000 years, showcased a profound understanding of the biochemical interactions within the human body. Ayurveda emphasized the balance of bodily humors (doshas) and utilized a variety of herbs and minerals, many of which have been found to contain active biochemical compounds. There is increasing interest that the integration of conventional medicine with traditional, complementary, and alternative medicine may be useful for the prevention and treatment of different types of communicable and chronic diseases related to behaviour and lifestyle

In ancient Egypt, chemistry was a well-developed discipline, as evidenced by the extensive use of natural substances in embalming and medicine. The Egyptians were adept at extracting and utilizing plant-based compounds, minerals, and animal products for therapeutic purposes. Their knowledge of fermentation processes, as seen in the production of beer and bread, also highlights an early understanding of biochemical reactions.

Similarly, ancient Chinese medicine, with its roots in Taoist philosophy, contributed significantly to the understanding of natural compounds and their effects on human health. The use of herbal remedies, acupuncture, and dietary therapy are based on principles that recognize the biochemical balance within the body.

These ancient civilizations laid the foundation for biochemical practices that continue to evolve till date. Their contributions underscore the universality of biochemical principles and highlight the diverse cultural perspectives that have enriched the field.

Summary

1.1 The Origin of Life

- 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.
- 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.

1.2 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-bound organelles.
- Phylogenetic evidence groups organisms into three domains: archaea, bacteria, and eukarya.
- Natural selection determines the evolution of species.

1.3 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

archaea
archaebacteria
bacteria
biochemical standard state
Boltzmann constant
catalyst
chloroplasts
closed system
compartmentation
complementary arrangements
condensation reaction
cytoplasm
cytoskeleton
cytosol
dalton (Da)
endergonic
endoplasmic reticulum (ER)
energy (E)
enthalpy
entropy (S)
equilibrium
Escherichia coli (*E. coli*)
eubacteria
eukarya
eukaryote
exergonic
favorable
free energy (G)
functional group
Gibbs free energy (G)
golgi apparatus
halobacteria
homeostasis
hydrolysis
in vivo
irreversible
isolated system
kDa
Le Châtelier's principle
lysosome
metabolic pathways
methanogen
mitochondria (sing. mitochondrion)
monomer
mutation
natural selection
non-equilibrium steady state
non-standard state
nucleus
open system
organelle
organic compound
peroxisome
phylogeny
polymer
prebiotic era
precursor
prokaryote
replication
reversible
RNA world
spontaneity
state function
symbiosis
system
taxonomy
thermophiles
unfavorable
vacuole
van't Hoff plot
vesicle

Problems

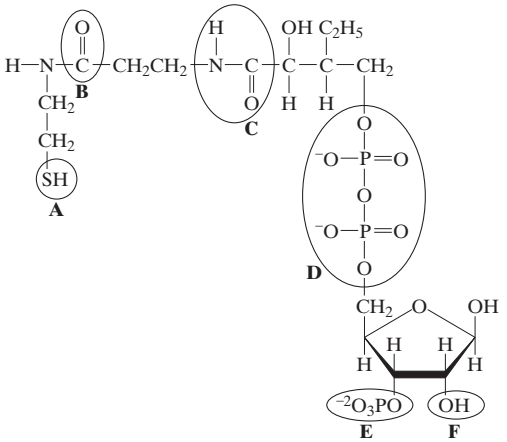
Exercises

1. 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?

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

3. Which of the functional groups in Table 1.2 give a molecule a positive charge? Which give a molecule a negative charge?

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



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

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) $H_2N-C(=O)-NH_2 + H_2O \longrightarrow CO_2 + 2\,NH_3$

Urea

(c) 1 M NaCl ⟶ 0.5 M NaCl

(d) $HC(COO^-)(OH)CH_2OPO_3^{2-} \longrightarrow HC(COO^-)(OPO_3^{2-})CH_2OH$

3-Phosphoglycerate **2-Phosphoglycerate**

8. 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.

9. Can a process occur if the entropy as well as the enthalpy of the system increases?

10. Consider a reaction with $\Delta H = 16$ kJ and $\Delta S = 50$ J · K^{-1}. Is the reaction spontaneous (a) at 70°C, (b) at 5°C?

11. For the reaction A → B at 298 K, the change in enthalpy is −10 kJ · mol^{-1} and the change in entropy is −35 J · K^{-1} · 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] = 4 mM, and [C] = 10 mM. What is the standard free energy change for the reaction?

13. Calculate $\Delta G°'$ for the reaction A + B ⇌ C + D at 25°C when the equilibrium concentrations are [A] = 9 μM, [B] = 15 μM, [C] = 3 μM, and [D] = 6 μM. Is the reaction exergonic or endergonic under standard conditions?

14. $\Delta G°'$ for the isomerization reaction

glucose-1-phosphate (G1P) ⇌ glucose-6-phosphate (G6P)

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

15. Calculate the equilibrium constant for the reaction

glucose-1-phosphate + H_2O → glucose + $H_2PO_4^-$

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

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 1) 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 1.2 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 1.5 mM?

20. For the conversion of reactant A to product B, the change in enthalpy is 8 kJ · mol^{-1} and the change is entropy is 25 J · K^{-1} · mol^{-1}. Above what temperature does the reaction become spontaneous?

21. The equilibrium constant for the reaction Q → R is 15.

(a) If 60 μM of Q is mixed with 60 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. 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?

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

Check Your Understanding

For each of the following spontaneous processes, (1) predict the sign of ΔH and ΔS and use the Gibbs equation (1-11) to determine if the process is enthalpically favored, entropically favored, or both; and (2) comment on the general temperature required to favor a spontaneous process.

24. ice melting on a table top

25. condensation of water droplets on cold glass

26. combustion of propane in a gas grill