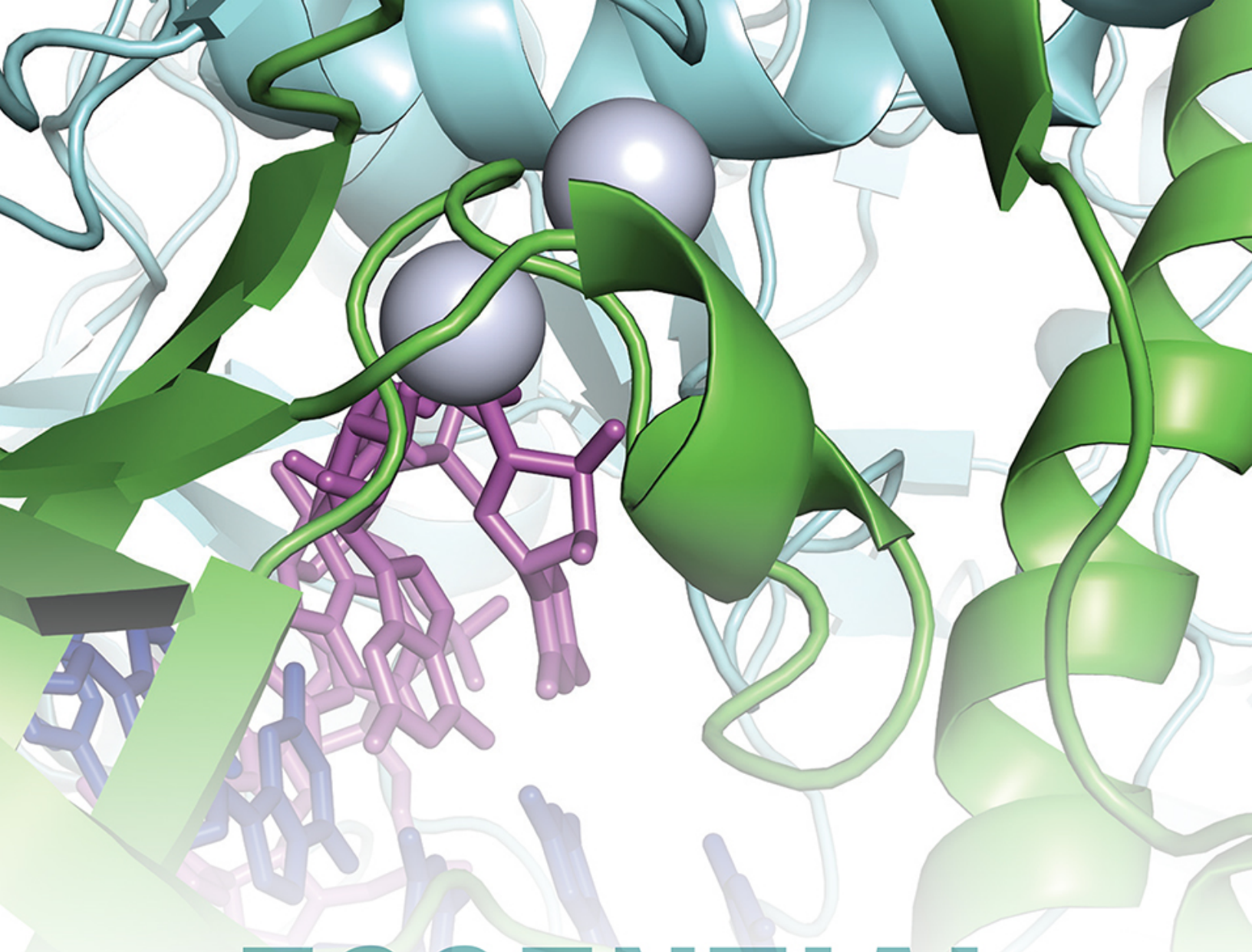


ESSENTIAL BIOCHEMISTRY

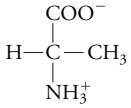
FOURTH EDITION

CHARLOTTE W. PRATT • KATHLEEN CORNELY

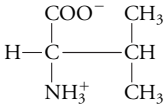
WILEY

AMINO ACID STRUCTURES AND ABBREVIATIONS

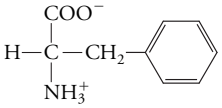
Hydrophobic amino acids



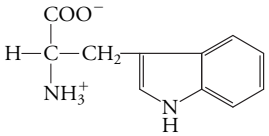
Alanine (Ala, A)



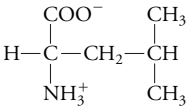
Valine (Val, V)



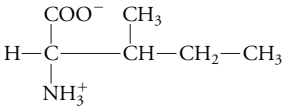
Phenylalanine (Phe, F)



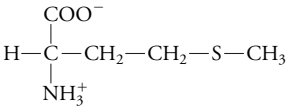
Tryptophan (Trp, W)



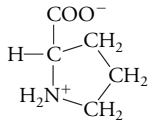
Leucine (Leu, L)



Isoleucine (Ile, I)

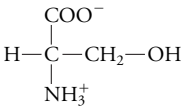


Methionine (Met, M)

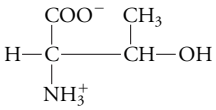


Proline (Pro, P)

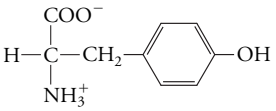
Polar amino acids



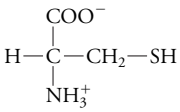
Serine (Ser, S)



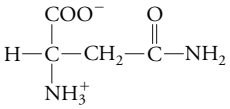
Threonine (Thr, T)



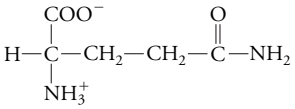
Tyrosine (Tyr, Y)



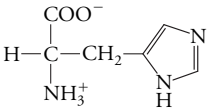
Cysteine (Cys, C)



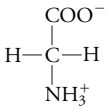
Asparagine (Asn, N)



Glutamine (Gln, Q)

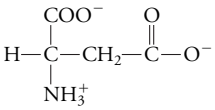


Histidine (His, H)

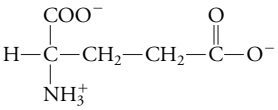


Glycine (Gly, G)

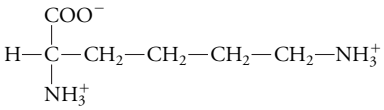
Charged amino acids



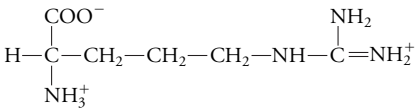
Aspartate (Asp, D)



Glutamate (Glu, E)



Lysine (Lys, K)



Arginine (Arg, R)

Essential Biochemistry

Fourth Edition

CHARLOTTE W. PRATT
Seattle Pacific University

KATHLEEN CORNELY
Providence College

WILEY

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This book was typeset by Aptara and printed and bound by Quad Graphics Versailles. The cover was printed by Quad Graphics Versailles.

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About the Authors

CHARLOTTE PRATT received a B.S. in biology from the University of Notre Dame and a Ph.D. in biochemistry from Duke University. She is a protein chemist who has conducted research in blood coagulation and inflammation at the University of North Carolina at Chapel Hill. She is currently Associate Professor in the Biology Department at Seattle Pacific University. Her interests include molecular evolution, enzyme action, and the relationship between metabolic processes and disease. She has written numerous research and review articles, has worked as a textbook editor, and is a co-author, with Donald Voet and Judith G. Voet, of *Fundamentals of Biochemistry*, published by John Wiley & Sons, Inc.

KATHLEEN CORNELY holds a B.S. in chemistry from Bowling Green (Ohio) State University, an M.S. in biochemistry from Indiana University, and a Ph.D. in nutritional biochemistry from Cornell University. She currently serves as a Professor in the Department of Chemistry and Biochemistry at Providence College where she has focused on expanding the use of case studies and guided inquiry across a broad spectrum of classes. Her interest in active pedagogy has led to her involvement in national programs including Project Kaleidoscope, the POGIL Project, and the Howard Hughes Medical Institute SEA PHAGES program, which has also fueled her current experimental research in phage genomics. She has been a member of the editorial board of *Biochemistry and Molecular Biology Education* and has served for several years as coordinator of the undergraduate poster competition at the annual meeting of the American Society for Biochemistry and Molecular Biology.

Brief Contents

Contents

Preface

Several years ago, we set out to write a short biochemistry textbook that combined succinct, clear chapters with extensive problem sets. We believed that students would benefit from a modern approach involving broad but not overwhelming coverage of biochemical facts, focusing on the chemistry behind biology, and providing students with practical knowledge and problem-solving opportunities. Our experience in the classroom continues to remind us that effective learning also requires students to become as fully engaged with the material as possible. To that end, we have embraced a strategy of posing questions and suggesting study activities throughout each chapter, so that students will not simply read and memorize but will explore and discover on their own—a truer reflection of how biochemists approach their work in the laboratory or clinic.

As always, we view our textbook as a guidebook for students, providing a solid foundation in biochemistry, presenting complete, up-to-date information, and showing the practical aspects of biochemistry as it applies to human health, nutrition, and disease. We hope that students will develop a sense of familiarity and comfort as they encounter new material, explore it, and test their understanding through problem solving.

New to This Edition

Many details in the text and illustration program have been updated, with virtually no section left untouched. Some significant changes are worth mentioning: Chapter 3 includes an updated discussion of genomics and a completely new presentation of DNA sequencing technologies and the use of CRISPR-Cas to edit genes. Other new items include a discussion of archaeal lipids, details on the GLUT membrane transport protein, a box on exosomes, new illustrations of respiratory cilia and bacterial peptidoglycan, new molecular graphics of mitochondrial respiratory complexes, an updated presentation of the ribonucleotide reductase mechanism, and more information on the microbiome, cancer, and obesity. Descriptions of DNA replication and transcription have been extensively modified, with numerous new diagrams to present a more realistic picture of these processes. The histone code and readers, writers, and erasers are explained. New details on RNA splicing and protein translocation round out the revised text.

Eight health-related topics that were previously confined to short boxes have been updated and expanded to **Clinical Connection** sections to give them the appropriate attention: 2.5 Acid–Base Balance in Humans, 4.5 Protein Misfolding and Disease, 5.2 Hemoglobin Variants, 6.5 Blood Coagulation, 7.4 Drug Development, 13.5 Disorders of Carbohydrate Metabolism, 19.4 Cancer Metabolism, and 20.4 Cancer as a Genetic Disease.

With the same goal of making it easy for students to navigate complex topics, some material within sections has been reorganized, and several new sections of text now focus on key content areas: 14.3 Thermodynamics of the Citric Acid Cycle, 17.1 Lipid Transport, 18.5 Nucleotide Metabolism, 20.5 DNA Packaging, 21.1 Initiating Transcription, and 22.1 tRNA and the Genetic Code.

Above all, the focus of the fourth edition is ease of use, particularly for students and instructors taking advantage of new ways to assess student understanding. New **Learning Objectives** at the start of every section are based on verbs, giving students an indication of what they need to be able to *do,* not just *know.* **Before You Go On** study hints at end of each section reinforce the activities that support learning. The **end-of-chapter problem sets** have been refreshed, with a total of 1,624 problems (averaging 74 per chapter, an increase of 18% over the previous edition). Problems are grouped by section and offered in pairs, with the answers to odd-numbered problems provided in an appendix.

Traditional Pedagogical Strengths

- "Do You Remember?" **review questions** start each chapter, to help students tie new topics to what they have already studied.
- **Figure Questions** that accompany key tables and figures prompt students to inspect information more closely.
- **Key sentences** summarizing main points are printed in italics to assist with quick visual identification.
- **Tools and Techniques Sections** appear at the end of Chapters 2, 3, and 4, to showcase practical aspects of biochemistry and provide an overview of experimental techniques that students will encounter in their reading or laboratory experience.
- **Metabolism overview figures** introduced in Chapter 12 and revisited in subsequent chapters help students place individual metabolic pathways into a broader context.
- Chapter **Summaries**, organized by major section headings, highlight important concepts to guide students to the most important points within each section.
- **Key terms** are in boldface. Their definitions are also included in the **Glossary**.
- An annotated list of **Selected Readings** for each chapter includes recent short papers, mostly reviews, that students are likely to find useful as sources of additional information.

Organization

We have chosen to focus on aspects of biochemistry that tend to receive little coverage in other courses or present a challenge to many students. Thus, in this textbook, we devote proportionately more space to topics such as acid–base chemistry, enzyme mechanisms, enzyme kinetics, oxidation–reduction reactions, oxidative phosphorylation, photosynthesis, and the enzymology of DNA replication, transcription, and translation. At the same time, we appreciate that students can become overwhelmed with information. To counteract this tendency, we have intentionally left out some details, particularly in the chapters on metabolic pathways, in order to emphasize some general themes, such as the stepwise nature of pathways, their evolution, and their regulation.

The 22 chapters of *Essential Biochemistry* are relatively short, so that students can spend less time reading and more time extending their learning through active problem-solving. Most of the problems require some analysis rather than simple recall of facts. Many problems based on research data provide students a glimpse of the "real world" of science and medicine.

Although each chapter of *Essential Biochemistry*, *Fourth Edition* is designed to be self-contained so that it can be covered at any point in the syllabus, the 22 chapters are organized into four parts that span the major themes of biochemistry, including some chemistry background, structure–function relationships, the transformation of matter and energy, and how genetic information is stored and made accessible.

Part 1 of the textbook includes an introductory chapter and a chapter on water. Students with extensive exposure to chemistry can use this material for review. For students with little previous experience, these two chapters provide the chemistry background they will need to appreciate the molecular structures and metabolic reactions they will encounter later.

Part 2 begins with a chapter on the genetic basis of macromolecular structure and function (Chapter 3, From Genes to Proteins). This is followed by chapters on protein structure (Chapter 4) and protein function (Chapter 5), with coverage of myoglobin and hemoglobin, and cytoskeletal and motor proteins. An explanation of how enzymes work (Chapter 6) precedes a discussion of enzyme kinetics (Chapter 7), an arrangement that allows students to grasp the importance of enzymes and to focus on the chemistry of enzyme-catalyzed reactions before delving into the more quantitative aspects of enzyme kinetics. A chapter on lipid chemistry (Chapter 8, Lipids and Membranes) is followed by two chapters that discuss critical biological functions of membranes (Chapter 9, Membrane Transport, and Chapter 10, Signaling). The section ends with a chapter on carbohydrate chemistry (Chapter 11), completing the survey of molecular structure and function.

Part 3 begins with an introduction to metabolism that provides an overview of fuel acquisition, storage, and mobilization as well as the thermodynamics of metabolic reactions (Chapter 12). This is followed, in traditional fashion, by chapters on glucose and glycogen metabolism (Chapter 13); the citric acid cycle (Chapter 14); electron transport and oxidative phosphorylation (Chapter 15); the light and dark reactions of photosynthesis (Chapter 16); lipid catabolism and biosynthesis (Chapter 17); and pathways involving nitrogen-containing compounds, including the synthesis and degradation of amino acids, the synthesis and degradation of nucleotides, and the nitrogen cycle (Chapter 18). The final chapter of Part 2 explores the integration of mammalian metabolism, with extensive discussions of hormonal control of metabolic pathways, disorders of fuel metabolism, and cancer (Chapter 19).

Part 4, the management of genetic information, includes three chapters, covering DNA replication and repair (Chapter 20), transcription (Chapter 21), and protein synthesis (Chapter 22). Because these topics are typically also covered in other courses, Chapters 20–22 emphasize the relevant biochemical details, such as topoisomerase action, nucleosome structure, mechanisms of polymerases and other enzymes, structures of accessory proteins, proofreading strategies, and chaperone-assisted protein folding.

The WileyPLUS Advantage

WileyPLUS is a research-based online environment for effective teaching and learning. WileyPLUS is packed with interactive study tools and resources, including the complete online textbook.

NEW Ten **Guided Tours** cover the major topics of the course. These multi-part tutorials explain biochemistry in time and space. Interactive questions at the end of each tour reinforce learning.

NEW **Assignable End-of-Chapter Questions,** over 20 per chapter, can be assigned to students through WileyPLUS.

NEW Twenty-four **Sample Calculation Videos** walk students through each step of the sample calculations.

NEW **Brief Bioinformatics Exercises** crafted by Rakesh Mogul at California State Polytechnic University, Pomona, provide detailed instructions for novices to access and use bioinformatics databases and software tools. Each of the 57 exercises includes multiple-choice questions to help students gauge their success in learning from these resources.

NEW **Do You Remember Practice Quizzes** help students prepare for new material by reinforcing relevant topics from previous chapters.

NEW **Concept Check Questions** for each section allow students to test their knowledge.

NEW **Discussion Questions** are thought-provoking questions that serve as a point of departure for student discussion and engagement with content.

NEW Twenty-three **Animated Process Diagrams** bring multi-step figures to life.

NEW **ORION Biology and Chemistry Refresher** offers ORIONS's diagnostics and adaptive practice for foundational topics, to support Biochemistry students who come to the course with differing levels of background knowledge.

UPDATED **Bioinformatics Projects,** written by Paul Craig at Rochester Institute of Technology, provide guidance

for 12 extended explorations of online databases, with questions, many open-ended, for students to learn on their own.

Additional Instructor Resources in WileyPLUS

- PowerPoint Art Slides.
- Exercise Questions with immediate descriptive feedback updated for the fourth edition by Rachel Milner, University of Alberta; Adrienne Wright, University of Alberta; and Mary Peek, Georgia Institute of Technology.
- Test Bank Questions by Scott Lefler, Arizona State University.
- Practice and Pre-Lecture Questions by Steven Vik, Southern Methodist University, and Mary Peek, Georgia Institute of Technology.
- PowerPoint Lecture Slides with Answer Slides by Mary Peek, Georgia Institute of Technology.
- Personal Response System ("Clicker") Questions by Gail Grabner, University of Texas at Austin, and Mary Peek, Georgia Institute of Technology.

Acknowledgments

We would like to thank everyone who helped develop *Essential Biochemistry, Fourth Edition,* including Biochemistry Editor Joan Kalkut, Product Designer Sean Hickey, Associate Development Editor Laura Rama, Senior Production Editor Elizabeth Swain, Senior Designer Tom Nery, and Senior Photo Editor Billy Ray.

We also thank all the reviewers who provided essential feedback on manuscript and media, corrected errors, and made valuable suggestions for improvements that have been so important in the writing and development of *Essential Biochemistry, Fourth Edition*.

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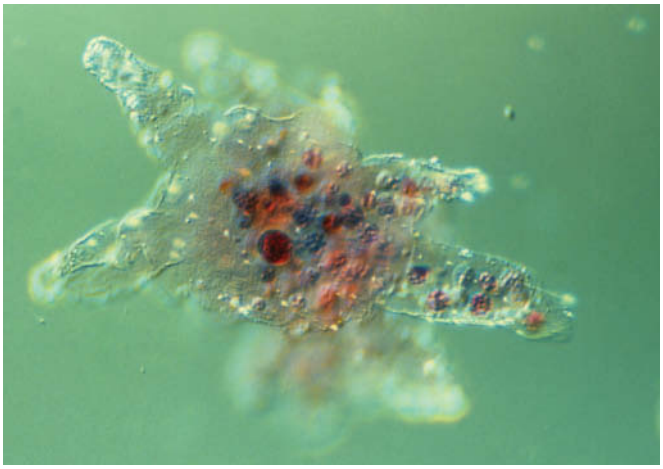
CHAPTER 1

The Chemical Basis of Life



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While no one has yet succeeded in reproducing all of a cell's chemical reactions in a test tube, it is possible to identify and quantify the thousands of molecules present in a cell, such as this amoeba. Understanding the structures and functions of those molecules is key to understanding how cells live, move, grow, and reproduce.

This first chapter offers a preview of the study of biochemistry, broken down into three sections that reflect how topics in this book are organized. First come brief descriptions of the four major types of small biological molecules and their polymeric forms. Next is a summary of the thermodynamics that apply to metabolic reactions. Finally, there is a discussion of the origin of self-replicating life-forms and their evolution into modern cells. These short discussions introduce some of the key players and major themes of biochemistry and provide a foundation for the topics that will be encountered in subsequent chapters.

1.1 What Is Biochemistry?

LEARNING OBJECTIVE

Recognize the main themes of biochemistry.

Biochemistry is the scientific discipline that seeks to explain life at the molecular level. It uses the tools and terminology of chemistry to describe the various attributes of living organisms. Biochemistry offers answers to such fundamental questions as "What are we made of?" and "How do we work?" Biochemistry is also a practical science: It generates powerful techniques that underlie advances in other fields, such as genetics, cell biology, and immunology; it offers insights into the treatment of diseases such as cancer and diabetes; and it improves the efficiency of industries such as wastewater treatment, food production, and drug manufacturing.

Some aspects of biochemistry can be approached by studying individual molecules isolated from cells. A thorough understanding of each molecule's physical structure and chemical reactivity helps lead to an understanding of how molecules cooperate and combine to form larger functional units and, ultimately, the intact organism (Fig. 1.1). But just as a clock completely disassembled no longer resembles a clock, information about a multitude of biological molecules does not necessarily reveal how an organism lives. Biochemists therefore investigate how organisms behave under different conditions or when a particular molecule is modified or absent. In addition, they collect vast amounts of information about molecular structures and functions—information that is stored and analyzed by computer, a field of study known as **bioinformatics.** A biochemist's laboratory is as likely to hold racks of test tubes as flasks of bacteria or computers.

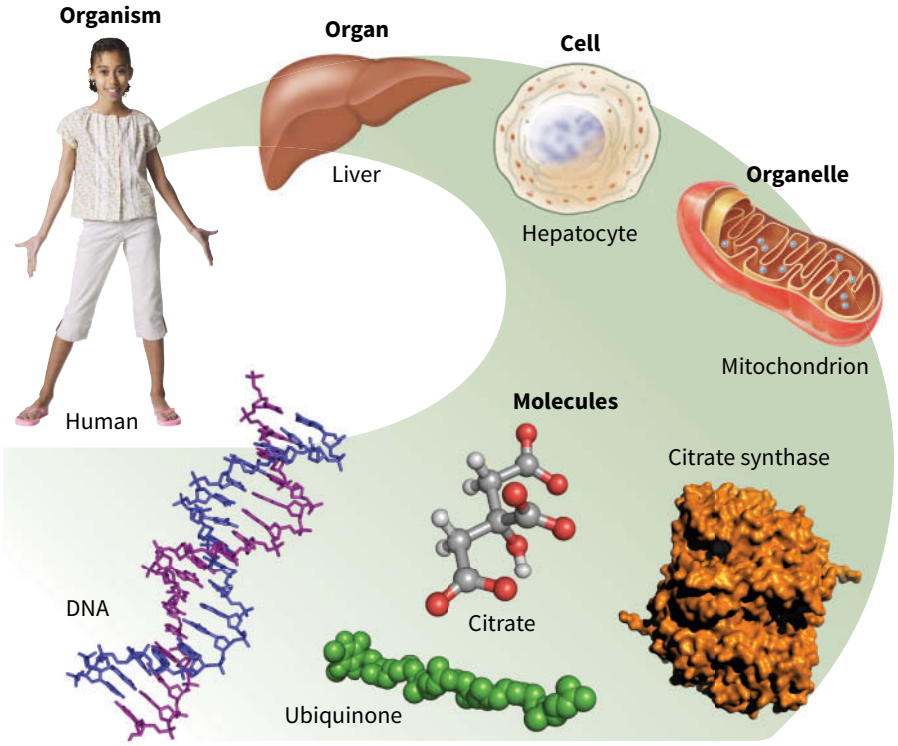


FIGURE 1.1 Levels of organization in a living organism. Biochemistry focuses on the structures and functions of molecules. Interactions between molecules give rise to higher-order structures (for example, organelles), which may themselves be components of larger entities, leading ultimately to the entire organism. [Photodisc/Rubberball/Getty Images]

Chapters 3 through 22 of this book are divided into three groups that roughly correspond to three major themes of biochemistry:

1. *Living organisms are made of macromolecules*. Some molecules are responsible for the physical shapes of cells. Others carry out various activities in the cell. (For convenience, we often use cell interchangeably with organism since the simplest living entity is a single cell.) In all cases, the structure of a molecule is intimately linked to its function. Understanding a molecule's structural characteristics is therefore an important key to understanding its functional significance.
2. *Organisms acquire, transform, store, and use energy.* The ability of a cell to carry out metabolic reactions—to synthesize its constituents and to move, grow, and reproduce—requires the input of energy. A cell must extract this energy from the environment and spend it or store it in a manageable form.
3. *Biological information is transmitted from generation to generation.* Modern human beings look much like they did 100,000 years ago. Certain bacteria have persisted for millions, if not billions, of years. In all organisms, the genetic information that specifies a cell's structural composition and functional capacity must be safely maintained and transmitted each time the cell divides.

Several other themes run throughout biochemistry, and we will highlight these where appropriate.

4. *Cells maintain a state of homeostasis.* Even within its own lifetime, a cell may dramatically alter its shape or metabolic activities, but it does so within certain limits. And in order to remain in a steady, non-equilibrium state—**homeostasis**—the cell must recognize changing internal and external conditions and regulate its activities.
5. *Organisms evolve.* Over long periods of time, the genetic composition of a population of organisms changes. Examining the molecular makeup of living organisms allows biochemists to identify the genetic features that distinguish groups of organisms and to trace their evolutionary history.
6. *Diseases can be explained at the biochemical level.* Identifying the molecular defects that underlie human diseases, or investigating the pathways that allow one organism to infect another, is the first step in diagnosing, treating, preventing, or curing a host of ailments.

1.2 Biological Molecules

Even the simplest organisms contain a staggering number of different molecules, yet this number represents only an infinitesimal portion of all the molecules that are chemically possible. For one thing, *only a small subset of the known elements are found in living systems* (Fig. 1.2). The most abundant of these are C, N, O, and H, followed by Ca, P, K, S, Cl, Na, and Mg. Certain **trace elements** are also present in very small quantities.

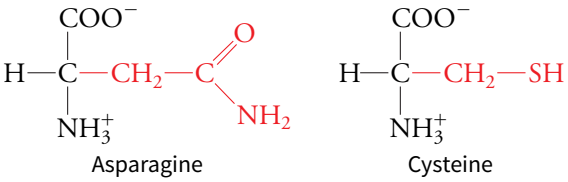
Virtually all the molecules in a living organism contain carbon, so biochemistry can be considered to be a branch of organic chemistry. In addition, biological molecules are constructed from H, N, O, P, and S. Most of these molecules belong to one of a few structural classes, which are described below.

Similarly, *the chemical reactivity of biomolecules is limited relative to the reactivity of all chemical compounds*. A few of the functional groups and intramolecular linkages that are common in biochemistry are listed in Table 1.1. Familiarity with these functional groups is essential for understanding the behavior of the different types of biological molecules we will encounter throughout this book.

Cells contain four major types of biomolecules

Most of the cell's small molecules can be divided into four classes. Although each class contains many members, *they are united under a single structural or functional definition*. Identifying a particular molecule's class may help predict its chemical properties and possibly its role in the cell.

1. Amino Acids Among the simplest compounds are the **amino acids,** so named because they contain an amino group (—NH_2) and a carboxylic acid group (—COOH). Under physiological conditions, these groups are actually ionized to —NH_3^+ and —COO^-. The common amino acid alanine—like other small molecules—can be depicted in different ways, for example, by a structural formula, a ball-and-stick model, or a space-filling model (Fig. 1.3). Other amino acids resemble alanine in basic structure, but instead of a methyl group (—CH_3), they have another group—called a side chain or R group—that may also contain N, O, or S; for example,



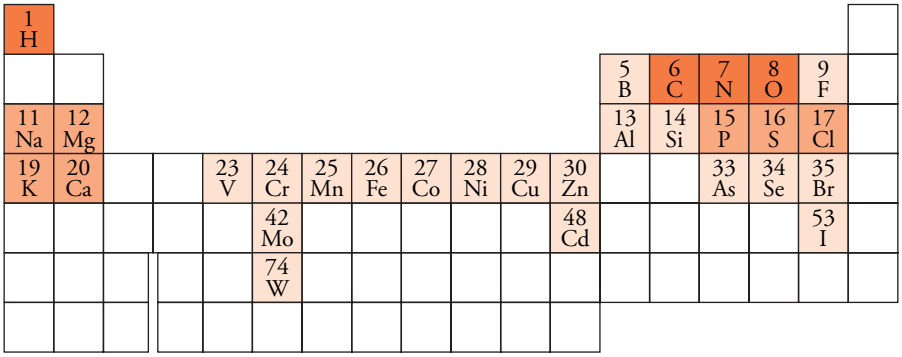


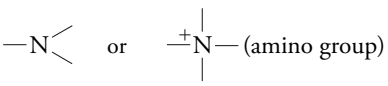
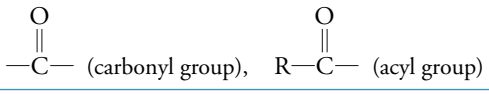
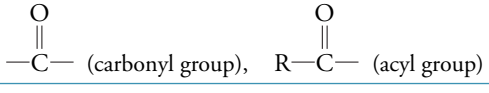
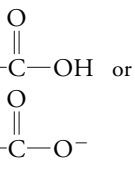
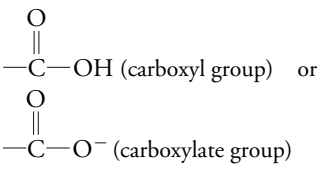
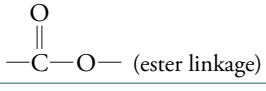
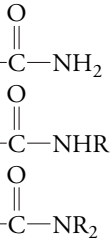
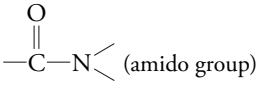
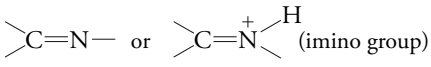
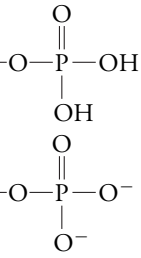
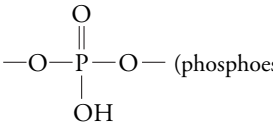
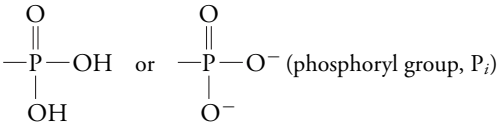
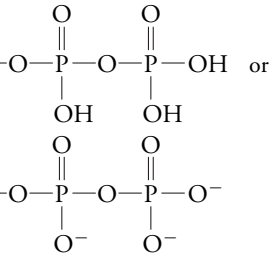
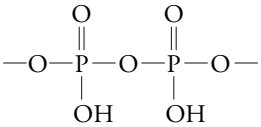
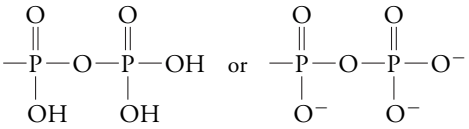
FIGURE 1.2 Elements found in biological systems. The most abundant elements are most darkly shaded; trace elements are most lightly shaded. Not every organism contains every trace element. Biological molecules primarily contain H, C, N, O, P, and S.

LEARNING OBJECTIVES

Identify the major classes of biological molecules.

- List the elements found in biological molecules.
- Draw and name the common functional groups in biological molecules.
- Draw and name the common linkages in biological molecules.
- Distinguish the main structural features of carbohydrates, amino acids, nucleotides, and lipids.
- Identify the monomers and linkages in polysaccharides, polypeptides, and nucleic acids.
- Summarize the biological functions of the major classes of biological molecules.

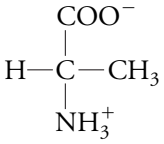
TABLE 1.1 Common Functional Groups and Linkages in Biochemistry

COMPOUND NAME	STRUCTURE[a]	FUNCTIONAL GROUP
Amine[b]	RNH_2 or RNH_3^+ R_2NH or $R_2NH_2^+$ R_3N or R_3NH^+	 (amino group)
Alcohol	ROH	—OH (hydroxyl group)
Thiol	RSH	—SH (sulfhydryl group)
Ether	ROR	—O— (ether linkage)
Aldehyde		 (carbonyl group), (acyl group)
Ketone		 (carbonyl group), (acyl group)
Carboxylic acid[b] (Carboxylate)		 (carboxyl group) or (carboxylate group)
Ester		 (ester linkage)
Amide		 (amido group)
Imine[b]	R=NH or $R=NH_2^+$ R=NR or $R=NHR^+$	 (imino group)
Phosphoric acid ester[b]		 (phosphoester linkage)  (phosphoryl group, P_i)
Diphosphoric acid ester[b]		 (phosphoanhydride linkage)  (diphosphoryl group, pyrophosphoryl group, PP_i)

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

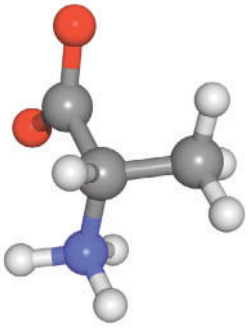
[b] Under physiological conditions, these groups are ionized and hence bear a positive or negative charge.

Q Cover the Structure column and draw the structure for each compound listed on the left. Do the same for each functional group.



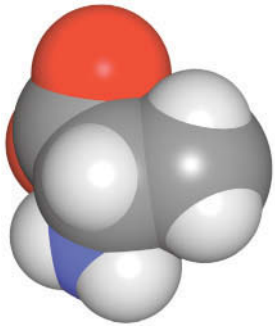
(a)

In a structural formula, some bonds, such as the C—O and N—H bonds, are implied. Around the central carbon, the horizontal bonds extend slightly above the plane of the page, and the vertical bonds extend slightly behind it.



(b)

The atoms are color-coded by convention: C gray, N blue, O red, and H white. A ball-and-stick representation reveals the identities of the atoms and their positions in space.



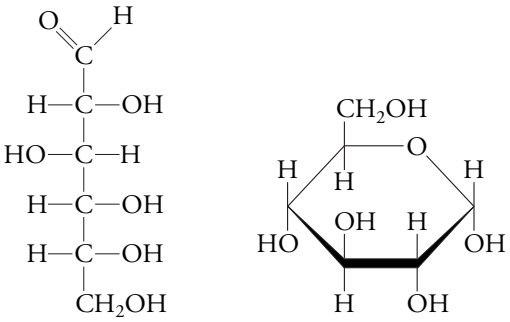
(c)

In a space-filling model, each atom is presented as a sphere whose radius (the van der Waals radius) corresponds to the distance of closest approach by another atom.

FIGURE 1.3 **Representations of alanine.** The structural formula (a) indicates all the atoms and the major bonds. Because the central carbon atom has tetrahedral geometry, its four bonds do not lie flat in the plane of the paper. This tetrahedral arrangement is more accurately depicted in the ball-and-stick model (b), although the relative sizes and electrical charges of atoms are not shown. A space-filling model (c) best represents the actual shape of the molecule but may obscure some of its atoms and linkages.

2. Carbohydrates

Simple **carbohydrates** (also called **monosaccharides** or just sugars) have the formula $(CH_2O)_n$, where n is ≥ 3. Glucose, a monosaccharide with six carbon atoms, has the formula $C_6H_{12}O_6$. It is sometimes convenient to draw it as a ladder-like chain (*left*); however, glucose forms a cyclic structure in solution (*right*):

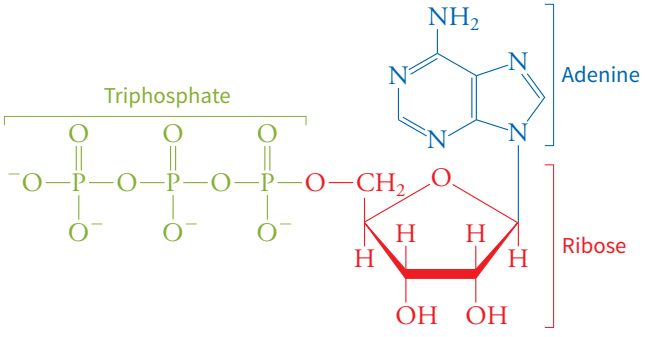


Glucose

In the representation of the cyclic structure, the darker bonds project in front of the page and the lighter bonds project behind it. In many monosaccharides, one or more hydroxyl groups are replaced by other groups, but the ring structure and multiple —OH groups of these molecules allow them to be easily recognized as carbohydrates.

3. Nucleotides

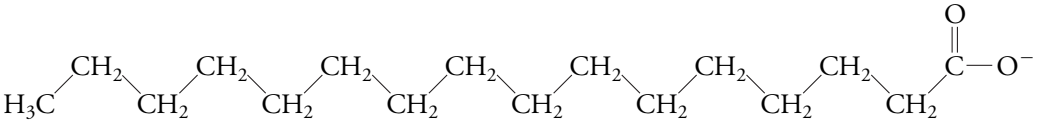
A five-carbon sugar, a nitrogen-containing ring, and one or more phosphate groups are the components of **nucleotides.** For example, adenosine triphosphate (ATP) contains the nitrogenous group adenine linked to the monosaccharide ribose, to which a triphosphate group is also attached:



Adenosine triphosphate (ATP)

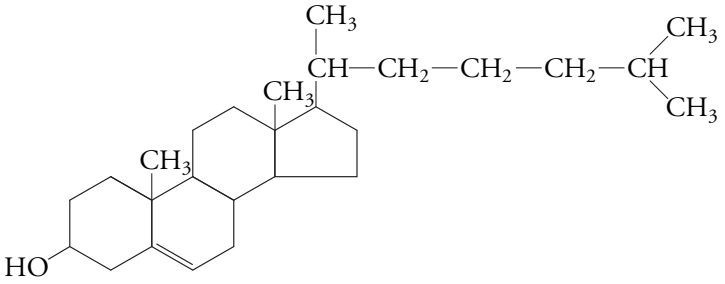
The most common nucleotides are mono-, di-, and triphosphates containing the nitrogenous ring compounds (or "bases") adenine, cytosine, guanine, thymine, or uracil (abbreviated A, C, G, T, and U).

4. Lipids The fourth major group of biomolecules consists of the **lipids.** These compounds cannot be described by a single structural formula since they are a diverse collection of molecules. However, they all tend to be poorly soluble in water because the bulk of their structure is hydrocarbon-like. For example, palmitic acid consists of a highly insoluble chain of 15 carbons attached to a carboxylic acid group, which is ionized under physiological conditions. The anionic lipid is therefore called palmitate.



Palmitate

Cholesterol, although it differs significantly in structure from palmitate, is also poorly soluble in water because of its hydrocarbon-like composition.



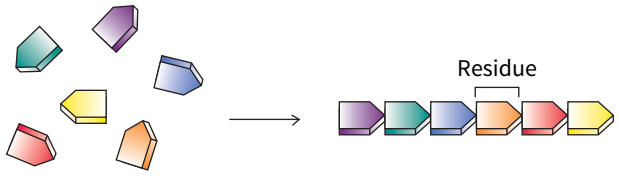
Cholesterol

Cells also contain a few other small molecules that cannot be easily classified into the groups above or that are constructed from molecules belonging to more than one group.

There are three major kinds of biological polymers

In addition to small molecules consisting of relatively few atoms, organisms contain macromolecules that may consist of thousands of atoms. Such huge molecules are not synthesized in one piece but are built from smaller units. This is a universal feature of nature: *A few kinds of building blocks can be combined in different ways to produce a wide variety of larger structures*. This is advantageous for a cell, which can get by with a limited array of raw materials. In addition, the very act of chemically linking individual units **(monomers)** into longer strings **(polymers)** is a way of encoding information (the sequence of the monomeric units) in a stable form. Biochemists use certain units of measure to describe both large and small molecules (**Box 1.A**).

Amino acids, monosaccharides, and nucleotides each form polymeric structures with widely varying properties. In most cases, the individual monomers become covalently linked in head-to-tail fashion:



Box 1.A Units Used in Biochemistry

Biochemists follow certain conventions when quantifying objects on a molecular scale. For example, the mass of a molecule can be expressed in atomic mass units; however, the masses of biological molecules—especially very large ones—are typically given without units. Here it is understood that the mass is expressed relative to one-twelfth the mass of an atom of the common carbon isotope ^{12}C (12.011 atomic mass units). Occasionally, units of daltons (D) are used (1 dalton = 1 atomic mass unit), often with the prefix kilo, k (kD). This is useful for macromolecules such as proteins, many of which have masses in the range from 20,000 (20 kD) to over 1,000,000 (1000 kD).

The standard metric prefixes are also necessary for expressing the minute concentrations of biomolecules in living cells. Concentrations are usually given as moles per liter (mol · L^{-1} or M), with the appropriate prefix such as m, μ, or n:

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}		

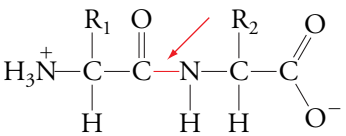
For example, the concentration of the sugar glucose in human blood is about 5 mM, but many intracellular molecules are present at concentrations of μM or less.

Distances are customarily expressed in angstroms, Å (1 Å = 10^{-10} m) or in nanometers, nm (1 nm = 10^{-9} m). For example, the distance between the centers of carbon atoms in a C—C bond is about 1.5 Å, and the diameter of a DNA molecule is about 20 Å.

Q The diameter of a typical spherical bacterial cell is about 1 μm. What is the cell's volume?

The linkage between monomeric units is characteristic of each type of polymer. The monomers are called **residues** after they have been incorporated into the polymer. Strictly speaking, lipids do not form polymers, although they do tend to aggregate to form larger structures such as cell membranes.

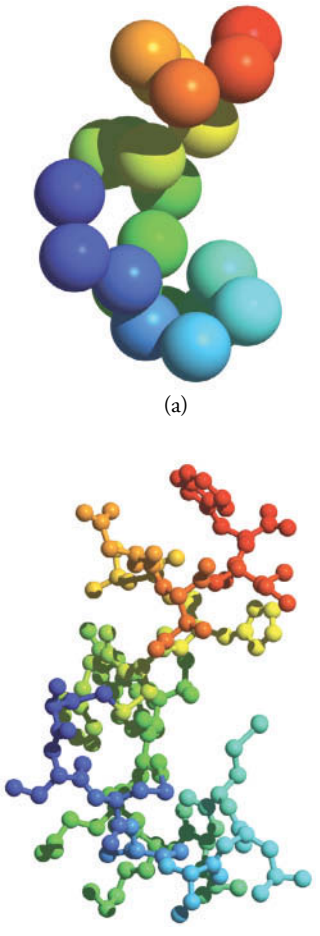
1. Proteins Polymers of amino acids are called **polypeptides** or **proteins.** Twenty different amino acids serve as building blocks for proteins, which may contain many hundreds of amino acid residues. The amino acid residues are linked to each other by amide bonds called **peptide bonds.** A peptide bond (*arrow*) links the two residues in a dipeptide (the side chains of the amino acids are represented by R_1 and R_2).



Because the side chains of the 20 amino acids have different sizes, shapes, and chemical properties, the exact **conformation** (three-dimensional shape) of the polypeptide chain depends on its amino acid composition and sequence. For example, the small polypeptide endothelin, with 21 residues, assumes a compact shape in which the polymer bends and folds to accommodate the functional groups of its amino acid residues (Fig. 1.4).

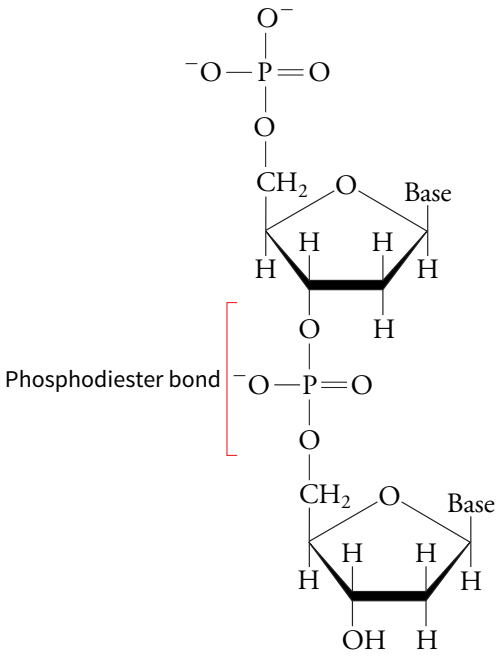
The 20 different amino acids can be combined in almost any order and in almost any proportion to produce myriad polypeptides, all of which have unique three-dimensional shapes. This property makes proteins as a class the most structurally variable and therefore the most functionally versatile of all the biopolymers. Accordingly, *proteins perform a wide variety of tasks in the cell, such as mediating chemical reactions and providing structural support.*

2. Nucleic Acids Polymers of nucleotides are termed **polynucleotides** or **nucleic acids,** better known as DNA and RNA. Unlike polypeptides, with 20 different amino acids available for polymerization, each nucleic acid is made from just four different nucleotides. For example, the residues in RNA contain the bases adenine, cytosine, guanine, and uracil, whereas the residues in DNA contain adenine, cytosine, guanine, and thymine. Polymerization involves the phosphate and sugar groups of the nucleotides, which become linked by **phosphodiester bonds.**



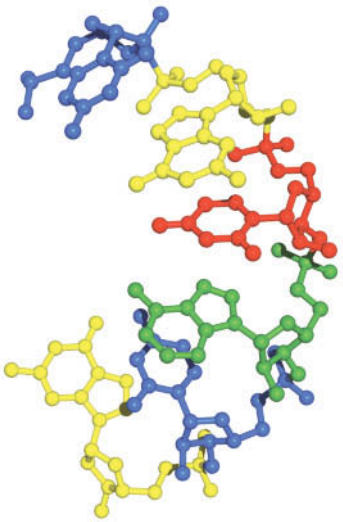
(a) (b)

FIGURE 1.4 Structure of human endothelin. The 21 amino acid residues of this polypeptide, shaded from blue to red, form a compact structure. In (a), each amino acid residue is represented by a sphere. The ball-and-stick model (b) shows all the atoms except hydrogen. [Structure (pdb 1EDN) determined by B. A. Wallace and R. W. Jones.]



CGUACG

(a)



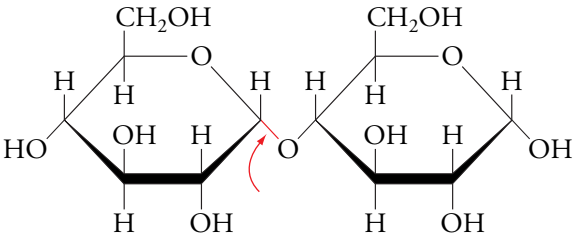
(b)

FIGURE 1.5 Structure of a nucleic acid. (a) Sequence of nucleotide residues, using one-letter abbreviations. (b) Ball-and-stick model of the polynucleotide, showing all atoms except hydrogen (this structure is a six-residue segment of RNA). [Structure (pdb ARF0108) determined by R. Biswas, S. N. Mitra, and M. Sundaralingam.]

In part because nucleotides are much less variable in structure and chemistry than amino acids, nucleic acids tend to have more regular structures than proteins. *This is in keeping with their primary role as carriers of genetic information, which is contained in their sequence of nucleotide residues rather than in their three-dimensional shape* (Fig. 1.5). Nevertheless, many nucleic acids do bend and fold into compact globular shapes, as proteins do.

3. Polysaccharides

Polysaccharides usually contain only one or a few different types of monosaccharide residues, so even though a cell may synthesize dozens of different kinds of monosaccharides, most of its polysaccharides are homogeneous polymers. This tends to limit their potential for carrying genetic information in the sequence of their residues (as nucleic acids do) or for adopting a large variety of shapes and mediating chemical reactions (as proteins do). On the other hand, *polysaccharides perform essential cell functions by serving as fuel-storage molecules and by providing structural support.* For example, plants link the monosaccharide glucose, which is a fuel for virtually all cells, into the polysaccharide starch for long-term storage. The glucose residues are linked by **glycosidic bonds** (the bond is shown in red in this disaccharide):



Glucose monomers are also the building blocks for cellulose, the extended polymer that helps make plant cell walls rigid (Fig. 1.6). The starch and cellulose polymers differ in the arrangement of the glycosidic bonds between glucose residues.

The brief descriptions of biological polymers given above are generalizations, meant to convey some appreciation for the possible structures and functions of these macromolecules. *Exceptions to the generalizations abound.* For example, some small polysaccharides encode information that allows cells bearing the molecules on their surfaces to recognize each other. Likewise, some nucleic acids perform structural roles, for example, by serving as scaffolding in ribosomes, the small particles where protein synthesis takes place. Under certain conditions,

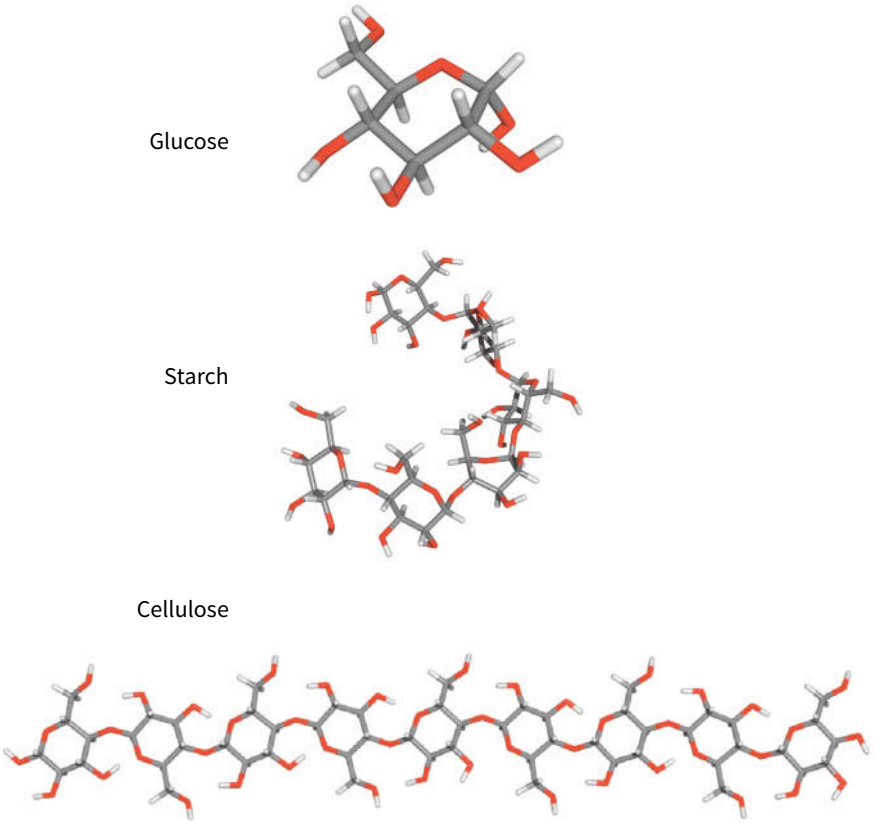


FIGURE 1.6 **Glucose and its polymers.** Both starch and cellulose are polysaccharides containing glucose residues. They differ in the type of chemical linkage between the monosaccharide units. Starch molecules have a loose helical conformation, whereas cellulose molecules are extended and relatively stiff.

proteins are called on as fuel-storage molecules. A summary of the major and minor functions of proteins, polysaccharides, and nucleic acids is presented in Table 1.2.

BEFORE GOING ON

- List the six most abundant elements in biological molecules.
- Name the common functional groups and linkages shown in Table 1.1.
- Give the structural or functional definitions for amino acids, monosaccharides, nucleotides, and lipids.
- Describe the advantage of building a polymer from monomers.
- Give the structural definitions and major functions of proteins, polysaccharides, and nucleic acids.
- Name the linkage in each type of polymer.
- List the major functions of proteins, polysaccharides, and nucleic acids.

TABLE 1.2 **Functions of Biopolymers**

BIOPOLYMER	ENCODE INFORMATION	CARRY OUT METABOLIC REACTIONS	STORE ENERGY	SUPPORT CELLULAR STRUCTURES
Proteins	—	✔	✓	✔
Nucleic acids	✔	✓	—	✓
Polysaccharides	✓	—	✔	✔

✔ major function
✓ minor function

LEARNING OBJECTIVES

Explain how enthalpy, entropy, and free energy apply to biological systems.

- Define enthalpy, entropy, and free energy.
- Write the equation that links changes in enthalpy, entropy, and free energy.
- Relate changes in enthalpy and entropy to the spontaneity of a process.
- Describe the energy flow that makes living systems thermodynamically possible.

1.3 Energy and Metabolism

Assembling small molecules into polymeric macromolecules requires energy. And unless the monomeric units are readily available, a cell must synthesize the monomers, which also requires energy. In fact, *cells require energy for all the functions of living, growing, and reproducing.*

It is useful to describe the energy in biological systems using the terminology of thermodynamics (the study of heat and power). An organism, like any chemical system, is subject to the laws of thermodynamics. According to the first law of thermodynamics, energy cannot be created or destroyed. However, it can be transformed. For example, the energy of a river flowing over a dam can be harnessed as electricity, which can then be used to produce heat or perform mechanical work. Cells can be considered to be very small machines that use chemical energy to drive metabolic reactions, which may also produce heat or carry out mechanical work.

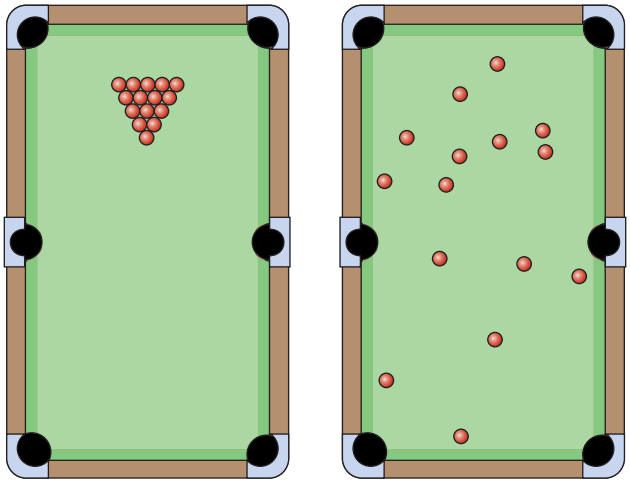
Enthalpy and entropy are components of free energy

The energy relevant to biochemical systems is called the Gibbs free energy (after the scientist who defined it) or just **free energy.** It is abbreviated ***G*** and has units of joules per mol ($J \cdot mol^{-1}$). Free energy has two components: enthalpy and entropy. ***Enthalpy*** (abbreviated ***H***, with units of $J \cdot mol^{-1}$) *is taken to be equivalent to the heat content of the system.* ***Entropy*** (abbreviated ***S***, with units of $J \cdot K^{-1} \cdot mol^{-1}$) *is a measure of how the energy is dispersed within that system.* Entropy can therefore be considered to be a measure of the system's disorder or randomness, because the more ways a system's components can be arranged, the more dispersed its energy. For example, consider a pool table at the start of a game when all 15 balls are arranged in one neat triangle (a state of high order or low entropy). After play has begun, the balls are scattered across the table, which is now in a state of disorder and high entropy (Fig. 1.7).

Free energy, enthalpy, and entropy are related by the equation

$$G = H - TS \qquad \textbf{[1.1]}$$

where T represents temperature in Kelvin (equivalent to degrees Celsius plus 273). Temperature is a coefficient of the entropy term because entropy varies with temperature; the entropy of a substance increases when it is warmed because more thermal energy has been dispersed



(a) (b)

FIGURE 1.7 Illustration of entropy. Entropy is a measure of the dispersal of energy in a system, so it reflects the system's randomness or disorder. (a) Entropy is low when all the balls are arranged in a single area of the pool table. (b) Entropy is high after the balls have been scattered, because there are now a large number of different possible arrangements of the balls on the table.

Q Compare the entropy of a ball of yarn before and after a cat has played with it.

within it. The enthalpy of a chemical system can be measured, although with some difficulty, but it is next to impossible to measure a system's entropy because this would require counting all the possible arrangements of its components or all the ways its energy could be spread out among them. Therefore, it is more practical to deal with *changes* in these quantities (change is indicated by the Greek letter delta, Δ) so that

$$\Delta G = \Delta H - T\Delta S \qquad \textbf{[1.2]}$$

Biochemists can measure how the free energy, enthalpy, and entropy of a system differ before and after a chemical reaction. For example, **exothermic reactions** are accompanied by the release of heat to the surroundings ($H_{final} - H_{initial} = \Delta H < 0$), whereas **endothermic reactions** absorb heat from the surroundings ($\Delta H > 0$). Similarly, the entropy change, $S_{final} - S_{initial} = \Delta S$, can be positive or negative. When ΔH and ΔS for a process are known, Equation 1.2 can be used to calculate the value of ΔG at a given temperature (see Sample Calculation 1.1).

SAMPLE CALCULATION 1.1

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Problem

Use the information below to calculate the change in enthalpy and the change in entropy for the reaction A → B.

	Enthalpy ($kJ \cdot mol^{-1}$)	Entropy ($J \cdot K^{-1} \cdot mol^{-1}$)
A	60	22
B	75	97

Solution

$$\begin{aligned}\Delta H &= H_B - H_A \\ &= 75\ kJ \cdot mol^{-1} - 60\ kJ \cdot mol^{-1} \\ &= 15\ kJ \cdot mol^{-1} \\ &= 15{,}000\ J \cdot mol^{-1}\end{aligned}$$

$$\begin{aligned}\Delta S &= S_B - S_A \\ &= 97\ J \cdot K^{-1} \cdot mol^{-1} \\ &\quad - 22\ J \cdot K^{-1} \cdot mol^{-1} \\ &= 75\ J \cdot K^{-1} \cdot mol^{-1}\end{aligned}$$

ΔG is less than zero for a spontaneous process

A china cup dropped from a great height will break, but the pieces will never reassemble themselves to restore the cup. The thermodynamic explanation is that the broken pieces have less free energy than the intact cup. *In order for a process to occur, the overall change in free energy (**ΔG**) must be negative.* For a chemical reaction, this means that the free energy of the products must be less than the free energy of the reactants:

$$\Delta G = G_{products} - G_{reactants} < 0 \qquad \textbf{[1.3]}$$

When ΔG is less than zero, the reaction is said to be **spontaneous** or **exergonic.** A **nonspontaneous** or **endergonic** reaction has a free energy change greater than zero; in this case, the reverse reaction is spontaneous.

A → B	B → A
$\Delta G > 0$	$\Delta G < 0$
Nonspontaneous	Spontaneous

Note that thermodynamic spontaneity does not indicate how *fast* a reaction occurs, only whether it will occur as written. (The rate of a reaction depends on other factors, such as the concentrations of the reacting molecules, the temperature, and the presence of a catalyst.) When a reaction, such as A → B, is at equilibrium, the rate of the forward reaction is equal to the rate of the reverse reaction, so there is no net change in the system. In this situation, $\Delta G = 0$.

A quick examination of Equation 1.2 reveals that *a reaction that occurs with a decrease in enthalpy and an increase in entropy is spontaneous at all temperatures because* ΔG *is always less than zero.* These results are consistent with everyday experience. For example, heat moves spontaneously from a hot object to a cool object, and items that are neatly arranged tend to become disordered, never the other way around. (This is a manifestation of the second law of thermodynamics, which states that energy tends to spread out.) Accordingly, reactions in which the enthalpy increases and entropy decreases do not occur. If enthalpy and entropy both increase or both decrease during a reaction, the value of ΔG then depends on the temperature, which governs whether the $T\Delta S$ term of Equation 1.2 is greater than or less than the ΔH term. This means that a large increase in entropy can offset an unfavorable (positive) change in enthalpy. Conversely, the release of a large amount of heat ($\Delta H < 0$) during a reaction can offset an unfavorable decrease in entropy (see Sample Calculation 1.2).

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SAMPLE CALCULATION 1.2

Problem

Use the information given in Sample Calculation 1.1 to determine whether the reaction A → B is spontaneous at 25°C.

Solution

Substitute the values for ΔH and ΔS, calculated in Sample Calculation 1.1, into Equation 1.2. To express the temperature in Kelvin, add 273 to the temperature in degrees Celsius: 273 + 25 = 298 K.

$$\begin{aligned}\Delta G &= \Delta H - T\Delta S \\ &= 15{,}000\ \text{J} \cdot \text{mol}^{-1} - 298\ \text{K}\ (75\ \text{J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}) \\ &= 15{,}000 - 22{,}400\ \text{J} \cdot \text{mol}^{-1} \\ &= -7400\ \text{J} \cdot \text{mol}^{-1} \\ &= -7.4\ \text{kJ} \cdot \text{mol}^{-1}\end{aligned}$$

Because ΔG is less than zero, the reaction is spontaneous. Even though the change in enthalpy is unfavorable, the large increase in entropy makes ΔG favorable.

Life is thermodynamically possible

In order to exist, life must be thermodynamically spontaneous. Does this hold at the molecular level? When analyzed in a test tube (***in vitro,*** literally "in glass"), many of a cell's metabolic reactions have free energy changes that are less than zero, but some reactions do not. Nevertheless, the nonspontaneous reactions are able to proceed ***in vivo*** (in a living organism) because they occur in concert with other reactions that are thermodynamically favorable. Consider two reactions *in vitro,* one nonspontaneous ($\Delta G > 0$) and one spontaneous ($\Delta G < 0$):

$$\begin{aligned}&\text{A} \rightarrow \text{B} \qquad \Delta G = +15\ \text{kJ} \cdot \text{mol}^{-1} \quad \text{(nonspontaneous)} \\ &\text{B} \rightarrow \text{C} \qquad \Delta G = -20\ \text{kJ} \cdot \text{mol}^{-1} \quad \text{(spontaneous)}\end{aligned}$$

When the reactions are combined, their ΔG values are added, so the overall process has a negative change in free energy:

$$\begin{aligned}\text{A} + \text{B} \rightarrow \text{B} + \text{C} \qquad &\Delta G = (15\ \text{kJ} \cdot \text{mol}^{-1}) + (-20\ \text{kJ} \cdot \text{mol}^{-1}) \\ \text{A} \rightarrow \text{C} \qquad &\Delta G = -5\ \text{kJ} \cdot \text{mol}^{-1}\end{aligned}$$

This phenomenon is shown graphically in **Figure 1.8**. In effect, the unfavorable "uphill" reaction A → B is pulled along by the more favorable "downhill" reaction B → C.

Cells couple unfavorable metabolic processes with favorable ones so that the net change in free energy is negative. Note that it is permissible to add ΔG values because the free energy, G,