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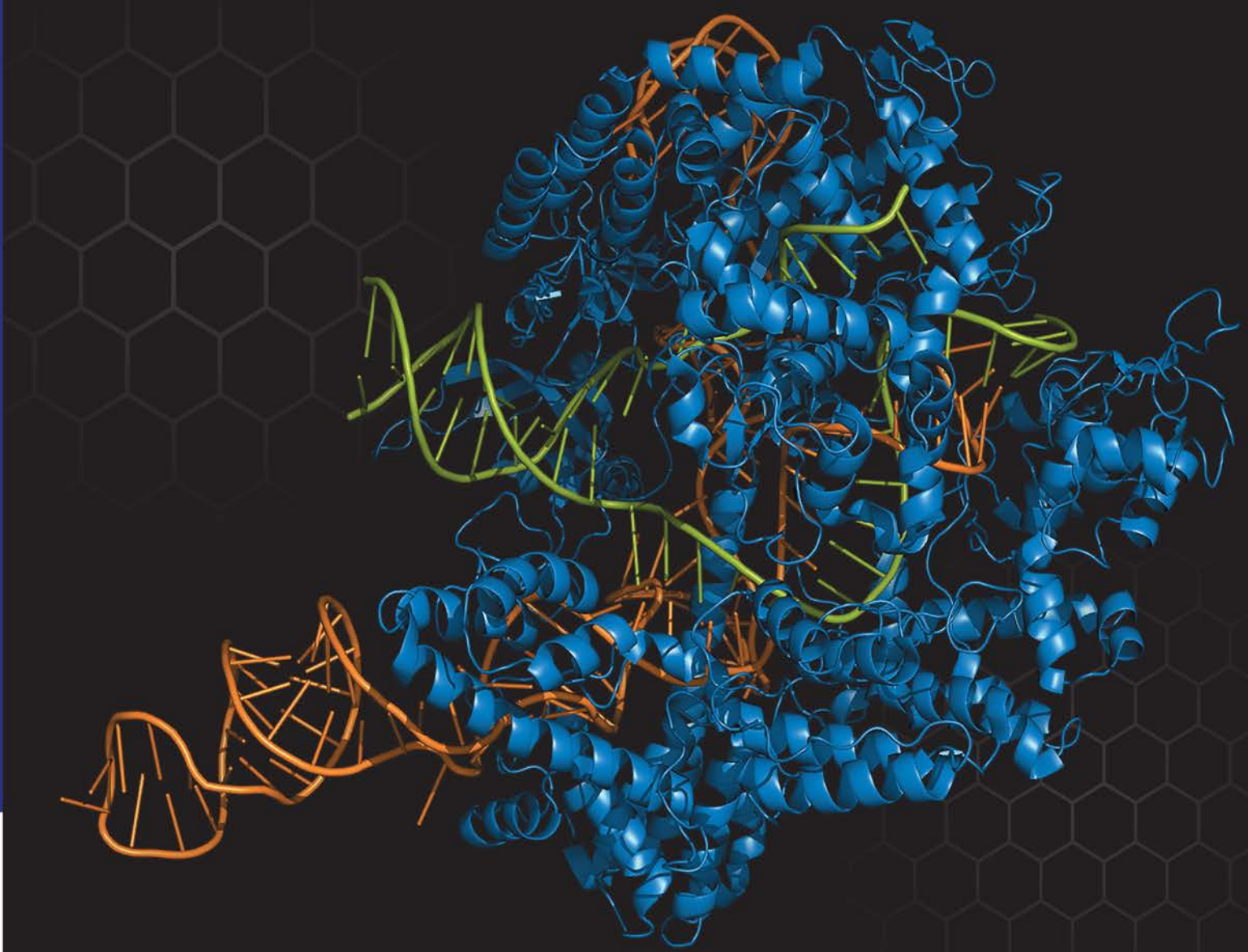
Reginald H. Garrett
Charles M. Grisham

biochemistry

seventh edition



biochemistry

SEVENTH EDITION

Reginald H. Garrett | Charles M. Grisham

University of Virginia

With molecular graphic images

by Michal Sabat and Tina Chai, University of Virginia

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***Biochemistry*, Seventh Edition**
Reginald H. Garrett, Charles M. Grisham

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Dedication

To our grandchildren Jackson, Bella, Reggie, Ricky, Charlotte Mayberry, Ann Clara, and Kathleen Elizabeth, and to the generations to follow...

About the Authors

Reginald H. Garrett was educated in the Baltimore city public schools and at the Johns Hopkins University, where he earned his Ph.D. in biology in 1968. Since then, he has been at the University of Virginia, where he is a Professor Emeritus of Biology. He is the author of previous editions of *Biochemistry* as well as *Principles of Biochemistry* (Cengage, Brooks/Cole) and numerous papers and review articles on the biochemical, genetic, and molecular biological aspects of inorganic nitrogen metabolism. His research interests focused on the pathway of nitrate assimilation in filamentous fungi. His investigations contributed substantially to our understanding of the enzymology, genetics, and regulation of this major pathway of biological nitrogen acquisition. More recently, he has collaborated in systems approaches to the metabolic basis of nutrition-related diseases. His research has been supported by the National Institutes of Health, the National Science Foundation, and private industry. He is a former Fulbright Scholar at the Universität für Bodenkultur in Vienna, Austria and served as Visiting Scholar at the University of Cambridge on two separate occasions. During the second, he was the Thomas Jefferson Visiting Fellow in Downing College. In 2003, he was Professeur Invité at the Université Paul Sabatier/Toulouse III and the Centre National de la Recherche Scientifique, Institute for Pharmacology and Structural Biology in France. He taught biochemistry at the University of Virginia for 46 years. He is a member of the American Society for Biochemistry and Molecular Biology.

Charles M. Grisham was born and raised in Minneapolis, Minnesota, and educated at Benilde High School. He received his B.S. in chemistry from the Illinois Institute of Technology in 1969 and his Ph.D. in chemistry from the University of Minnesota in 1973. Following a postdoctoral appointment at the Institute for Cancer Research in Philadelphia, he joined the faculty of the University of Virginia, where he is Professor of Chemistry. He is the author of previous editions of *Biochemistry* and *Principles of Biochemistry* (Cengage, Brooks/Cole) and numerous papers and review articles on active transport of sodium, potassium, and calcium in mammalian systems, on protein kinase C, and on the applications of NMR and EPR spectroscopy to the study of biological systems. He also authored *Interactive Biochemistry CD-ROM and Workbook*, a tutorial CD for students. His work has been supported by the National Institutes of Health, the National Science Foundation, the Muscular Dystrophy Association of America, the Research Corporation, the American Heart Association, and the American Chemical Society. He is a Research Career Development Awardee of the National Institutes of Health, and in 1983 and 1984 he was a Visiting Scientist at the Aarhus University Institute of Physiology Denmark. In 1999, he was Knapp Professor of Chemistry at the University of San Diego. He has taught biochemistry, introductory chemistry, and physical chemistry at the University of Virginia for 48 years. He is a member of the American Society for Biochemistry and Molecular Biology.

Gene Runion

Reginald H. Garrett and Charles M. Grisham

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Careers in Chemistry

PSAFE (Protein Structure and Function Exploration)

A Resource for Biochemistry Students and Instructors

The Protein Structure and Function Exploration (PSAFE) project* http://psafeonline.net at the University of Virginia was created as a semester-long project for biochemistry students to explore structure−function relationships in macromolecules and to research and write about their findings. Students doing the PSAFE project use the molecular-document capability of the ICM Browser (from Molsoft LLC) to accomplish their goals. In this exercise, each student progresses through tutorials about the basics of biomolecular structure to individual in-depth analysis of a chosen macromolecule and how it achieves its function. The project culminates in each student creating an interactive graphical display and accompanying narrative describing the chosen macromolecule's structure-function relationships, together with relevant references. These student creations are reviewed and edited before posting to an archival website (http://psafeonline.net). The PSAFE archive contains descriptions of well over 1300 different proteins and nucleic acids and is available to anyone with an interest in exploring structure-function relationships in *macromolecules*. This semester-long research and writing project has been added to the Biochemistry 7e, online course to provide students with the opportunity to explore the structure and function of an assigned protein. The project culminates in the composition of an interactive narrative describing the macromolecule's structure and function.

*Magnotti, E., Moy, J., Sleppy, R., Carey, A., Firdyiwek, Y., Garrett, R. H., and Grisham, C., 2019. "Developing and Implementing a Free Online Protein Structure and Function Exploration Project to Teach Undergraduate Students Macromolecular Structure−Function Relationships." *Journal of Chemical Education* **96**:729–733.

Laboratory Techniques in Biochemistry

All of our knowledge of biochemistry is the outcome of experiments. For the most part, this text presents biochemical knowledge as established fact, but students should never lose sight of the obligatory connection between scientific knowledge and its validation by observation and analysis. The path of discovery by experimental research is often indirect, tortuous, and confounding before the truth is realized. Laboratory techniques lie at the heart of scientific inquiry, and many techniques of biochemistry are presented within these pages to foster a deeper understanding of the biochemical principles and concepts that they reveal.

Recombinant DNA Techniques

Restriction endonuclease digestion of DNA *Section 10.6d*
Restriction mapping *Section 10.6e–f*
DNA sequencing *Section 11.1*
Nucleic acid hybridization *Section 11.3*
Chemical synthesis of nucleic acids *Section 11.6*
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Reporter gene constructs *Section 12.3b*
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Probing the Function of Biomolecules

Green fluorescent protein *Section 4.4*
Plotting enzyme kinetic data *Section 13.3j*
Enzyme inhibition *Section 13.4*
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RNAi *Section 12.4*
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Techniques Relevant to Clinical Biochemistry

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"Knockout" mice *Section 28.7*

Isolation/Purification of Macromolecules

Ion exchange chromatography *Section 5.2*
Protein purification protocols *Section 5.2*
Dialysis and ultrafiltration *Section 5.2*
Size exclusion chromatography *Section 5.2*
SDS-polyacrylamide gel electrophoresis *Section 5.2*
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Two-dimensional gel electrophoresis *Section 5.2*
Hydrophobic interaction chromatography *Section 5.2*
High-performance liquid chromatography *Section 5.2*
Affinity chromatography *Section 5.2*
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Fractionation of cell extracts by centrifugation *Section 5.2*
Proteomic analysis by multidimensional protein identification technology *Section 5.8b*

Analyzing the Physical and Chemical Properties of Biomolecules

Titration of weak acids *Section 2.2b*
Preparation of buffers *Section 2.3*
Measurement of standard reduction potentials *Section 3.6*
Edman degradation *Section 4.3*
Nuclear magnetic resonance (NMR) *Sections 4.5 and 6.4*
Estimation of protein concentration *Section 5.2*
Amino acid analysis *Section 4.6*
Amino acid sequence determination *Section 5.3*
Mass spectrometry of proteins *Section 5.3i*
Solid-phase peptide synthesis *Section 5.5*
Cryo-Electron Microscopy *Section 6.4*
Membrane lipid phase transitions *Section 9.4b*
Nucleic acid hydrolysis *Section 10.6*
DNA sequencing *Section 11.1*
Single-molecule DNA sequencing *Section 11.1e,f*
Density gradient (isopycnic) centrifugation *Section 11.3*

Preface

Biochemistry

Scientific understanding of the molecular nature of life is growing at an astounding rate. Significantly, society is the prime beneficiary of this increased understanding. Cures for diseases, better public health, remedies for environmental pollution, and the development of cheaper and safer natural products are just a few practical benefits of this knowledge. In addition, this expansion of information fuels, in the words of Thomas Jefferson, "the illimitable freedom of the human mind." Scientists can use the tools of biochemistry and molecular biology to explore all aspects of an organism—from basic questions about its chemical composition, through inquiries into the complexities of its metabolism, differentiation, and development, to analysis of its evolution, and even its behavior. New procedures based on the results of these explorations lie at the heart of the many modern medical miracles. Biochemistry is a science whose boundaries now encompass all aspects of biology, from molecules to cells, to organisms, to ecology, and to all aspects of health care. This seventh edition of *Biochemistry* embodies and reflects the expanse of this knowledge. We hope that this new edition will encourage students to ask questions of their own and to push the boundaries of their curiosity about science.

Making Connections

As the explication of natural phenomena rests more and more on biochemistry, its inclusion in undergraduate and graduate curricula in biology, chemistry, and the health sciences becomes imperative. The challenge to authors and instructors is a formidable one: how to familiarize students with the essential features of modern biochemistry in an introductory course or textbook. Fortunately, the increased scope of knowledge allows scientists to make generalizations connecting the biochemical properties of living systems with the character of their constituent molecules. As a consequence, these generalizations, validated by numerous examples, emerge in time as principles of biochemistry, principles that are useful in discerning and describing new relationships between diverse biomolecular functions and in predicting the mechanisms underlying newly discovered biomolecular processes. Nevertheless, it is increasingly apparent that students must develop skills in inquiry-based learning, so that beyond this first encounter with biochemical principles and concepts students are equipped to explore science on their own. Much of the design of this new edition is meant to foster the development of such skills.

We are both biochemists, but one of us spent his career in a biology department, and the other in a chemistry department. Undoubtedly, we each view biochemistry through the lens of our respective disciplines. We believe, however, that our collaboration on this textbook represents a melding of our perspectives that will provide new dimensions of appreciation and understanding for all students.

Our Audience

This biochemistry textbook is designed to communicate the fundamental principles upon which all life is based to students encountering biochemistry for the first time. We aim to bring an appreciation of biochemistry to a broad audience that includes undergraduates majoring in the life sciences, physical sciences, or premedical programs as well as medical students and graduate students in the various health sciences for whom biochemistry is an important route to understanding human physiology. To make this subject matter more relevant and interesting to all readers, we emphasize, where appropriate, the biochemistry of humans.

Objectives and Building on Previous Editions

We carry forward the clarity of purpose found in previous editions; namely, to illuminate for students the principles governing the structure, function, and interactions of biological molecules. At the same time, this new edition has been revised to reflect tremendous developments in biochemistry. Significantly, emphasis is placed on the interrelationships of ideas so that students can begin to appreciate the overarching questions of biochemistry.

New Features

New Textbook Features

- **Think-Pair-Share Problems** in every chapter encourage students to work collaboratively to further their understanding of biochemistry concepts.
- **Careers in Chemistry** showcase various career paths that students can take after studying biochemistry. By seeing a diverse, inclusive, and equitable chemical community, all students know that they have a future in chemistry-related careers.
- **Over 160 New and Revised Exercises** were added to the book and online course to keep the content current.
- **Step-by-Step Solutions** were added to examples to help students master the approach to complicated problems.
- **Recent Developments in Biochemistry:** A number of *Deeper Look* and *Critical Developments in Biochemistry* boxes were added to address the latest developments in biochemistry such as the human proteome, NMR and Cryo-EM, AlfaFold, and CRISPR-Cas9.

New to the Online Course and Resources

- **MCAT Essays and Practice Problems** accompanied by detailed answer explanations, written by members of medical school admissions and advisors, have been added to the online course in OWLv2 to prepare students for the biochemistry section of the MCAT exam.
- **Hints and Targeted Feedback.** Over fifty percent of problems in OWLv2 now come with targeted feedback on common errors that students make. The targeted feedback explains why the student's answer is incorrect and guides them toward a correct solution.
- **Laddered Assessments.** Conceptual mastery modules are combined with more traditional homework questions into one structured learning path, organized by topic at the chapter level.
- **Over 300 New Problems** were added to the online course.
- **PSAFE: Protein Structure and Function Exploration Project.** Students research a protein and use protein-modeling software to practice biochemistry actively in this research and writing semester-long project.
- **Protein Structure and Function Exploration Library of Proteins and Nucleic Acids** is an online resource (http://www.psafeonline.net/) of over 1300 protein and nucleic acid animations and interactive views, sorted by proteins and chapters in this textbook.

New to this Edition

Chapter 3 A new Deeper Look box called "Why Nature Chose Phosphates."

Chapter 4 A new Deeper Look box called "Why Nature Chose Selenium," and a revised Critical Developments in Biochemistry box on the incorporation of unnatural amino acids into proteins.

Chapter 5 A new exercise on determining amino-acid sequence from mass spectrometry data. Efforts to describe the human proteome are introduced in a new Deeper Look box: "The Human Proteome Project and the Human Protein Atlas."

Chapter 6 A new Critical Developments in Biochemistry box on the X-ray crystallography of proteins and a revised Deeper Look feature on metamorphic proteins, which exist as an ensemble of structures of similar energies and stabilities. New Critical Developments in Biochemistry boxes on the Protein Data Bank (PDB) and "NMR and Cryo-EM — Revolutionary Methods that Probe Protein Structure and Dynamics" (including cryo-EM structure of the 2P spike protein mutant related to development of COVID-19 vaccines). New coverage of AlphaFold, artificial intelligence software that accurately predicts the three-dimensional structures of proteins based solely on their amino acid sequences.

Chapter 8 A new Human Biochemistry box on the development of vaccines for COVID-19 that employ lipid nanoparticles and make RNA vaccines practical and effective.

Chapter 9 New coverage of monotopic, bitopic, and polytopic membrane proteins and a section called "Dynamic Exchange of Lipids and Proteins with Membrane Domains."

Chapter 10 An updated introduction to the many roles of small RNAs in the regulation of gene expression: miRNAs and the long, noncoding RNAs (lincRNAs).

Chapter 11 Completion of the complete nucleotide sequence determination for the human genome in 2022. Focus on the rapidly growing science of bioinformatics: the study of the nature and organization of biological information, including functional genomics and proteomics. New principles emerging about the higher order structural organization of chromosomes, chromosome territories, and chromosome dynamics. Synthetic chromosomes, DNA as a data storage medium.

Chapter 12 Genome engineering with CRISPR-Cas9, CRISPR-Cas9 in gene-editing and base-editing. A new section on human gene therapy, rewriting the human genome.

Chapter 14 A new Critical Developments in Biochemistry box on Nobel laureate Frances Arnold and her pioneering work on the directed evolution of enzymes.

Chapter 17 Metabolites at the center of life, metabolomics as the driver of all the other –omics.

Chapter 18 The newly-discovered protein kinase activity of protein kinase M2 (PK M2), its stimulation by SAICAR (an intermediate in the purine biosynthetic pathway), and its role in tumor proliferation.

Chapter 20 The new molecular structures of the supercomplexes that carry out electron transport and oxidative phosphorylation, including the new structure of Complex I and insights regarding its mechanism of action.

Chapter 22 A new Human Biochemistry box called "Metformin — A Diabetes Drug with Multiple Actions," and a Critical Developments in Biochemistry feature describing how the consumption of ATP promotes and supports the metabolism of cancer cells.

Chapter 25 Synthesis of cysteine in humans by a reverse transsulfurylation pathway. A new Human Biochemistry box on amino acid metabolism and cancer.

Chapter 26 Figure describing the purinosome metabolon that synthesizes purines on a PRPP platform.

Chapter 27 New molecular graphic of mTORC1, the master integrator of information about nutrient status and a global regulator of biosynthesis. A new section on AMPK inhibition of mTORC1 through reversible phosphorylation. A new section on SIRT1, mTORC1, AMPK, caloric restriction, and metabolic syndrome.

Chapter 28 New discussion and figure illustrating that DNA polymerases are immobilized within replication factories. New figure showing the structural organization of eukaryotic DNA replicons.

Chapter 29 Updated discussion of eukaryotic gene regulatory sequences such as promoters, enhancers, insulators, and silencers.

Chapter 30 Pyrrolysine as the twenty-second amino acid. New art illustrating the richly detailed events in eukaryotic translation initiation.

Chapter 31 New structures of the SecY channel and the SecA ATPase, and cryo-EM structures of co-translational and post-translational states of the Sec61 translocon complex. New cryo-EM structures of a cullin-RING-UBE2D ubiquitin ligation assembly.

Chapter 32 New cryo-EM structure of the neurotensin receptor-arrestin2 complex. New section on ion channels that respond to physical stimuli (including temperature, voltage, pH, redox status, and mechanical phenomena) rather than chemical signals.

Features

- **Clarity of Instruction** This edition was re-organized for increased clarity and readability. Many of the lengthier figure legends were shortened and more information was included directly within illustrations. These changes will help the more visual reader.
- **Visual Instruction** The richness of the Protein Data Bank (**www.pdb.org**) and availability of molecular graphics software has been exploited to enliven this text. Over 1100 images of prominent proteins and nucleic acids involved with essential biological functions illustrate and inform the subject matter and were prepared especially for this book.
- **Essential Questions Organization** Each chapter in this book is framed around an Essential Question that invites students to become actively engaged in their learning and encourages curiosity and imagination about the subject matter. For example, the Essential Question of Chapter 3 asks, "What are the laws and principles of thermodynamics that allow us to describe the flows and interchanges of heat, energy, and matter in biochemical systems?" The section heads then pose Key Questions that serve as organizing principles for a lecture such as, "What is the daily human requirement for ATP?" The subheadings are designed to be concept statements that respond to the section headings.
- **Foundational Biochemistry** At the end of each chapter, this feature provides a comprehensive list of the principal facts and concepts that a student should understand after reading each chapter. Presented as short statements or descriptive phrases, the items in the Foundational Biochemistry list serve as guides to students of the knowledge they have acquired from the chapter and as checklists the students can review in assessing their learning.
- **End-of-Chapter Problems** More than 700 end-of-chapter problems are provided. They serve as meaningful exercises that help students develop problem-solving skills useful in achieving their learning goals. Some problems require students to employ calculations to find mathematical answers to relevant structural or functional questions. Other questions address conceptual problems whose answers require application and integration of ideas and concepts introduced in the chapter.
- **Think-Pair-Share** problems encourage students to work collaboratively to further their understanding.
- **Further Readings** sections at the end of each chapter make it easy for students to find up-to-date additional information about each topic.

- **Critical Developments in Biochemistry** essays emphasize recent and historical advances in the field.
- **Human Biochemistry** essays emphasize the central role of basic biochemistry in medicine and the health sciences. These essays often present clinically important issues such as diet, diabetes, and cardiovascular health.
- **A Deeper Look** essays expand on the text, highlighting selected topics or experimental observations.
- **Laboratory Techniques** The experimental nature of biochemistry is highlighted, and a list of laboratory techniques found in this book can be seen on page xxxi.

Instructor and Student Resources

Instructor and student resources are available online.

Instructor resources include:

- Solution and Answer Guide
- Test Bank
- Transition Guide from the Sixth Edition to the Seventh Edition
- Lecture Note PowerPoint slides
- Image Library slides
- Guide to Teaching Online
- Educator's Guide

Acknowledgments

We are indebted to the many experts in biochemistry and molecular biology who carefully reviewed this book at several stages for their outstanding and invaluable advice on how to construct an effective textbook.

Reviewers for the 7th edition

Bobby Burkes, Grambling State University

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Brent Znosko, Saint Louis University

Lisa Zuraw, The Citadel

We also wish to gratefully acknowledge many other people who assisted and encouraged us in this endeavor. Roxanne Wang, our Product Manager for Upper-Level Chemistry, has brought enthusiasm and an unwavering emphasis on student learning as the fundamental purpose of our collective enterprise. Meaghan Ford, the Senior Content Manager for this edition, has kept us focused on the matters at hand, the urgencies

of the schedule, and limits of scale in a textbook's dimensions. She is truly a colleague in these endeavors, as is Mona Zeftel, our Learning Designer, whose focus on student learning and student perceptions provided crucial guiderails for us in keeping the education of students uppermost as we created this new edition. We also applaud the unsung but absolutely indispensable contributions by Maria Lokshin, Ph.D., our Development Editor. Maria's editorial grace was precise and immensely helpful. Her writing skills and scientific acumen made this textbook eminently more readable. The contribution of new supplementary end-of-chapter problems by Koen Vercruysse of East Tennessee State University is gratefully acknowledged and appreciated. This book's design and layout is the creative result of work by Chris Doughman. If this book has visual appeal, it is due to Katy Gabel and John Rich, Project Managers at Lumina Datamatics and their colleagues. The beautiful illustrations that not only decorate this text but also explain its contents are a testament to a number of important collaborators. Many colleagues provided original art and graphic images for this book, particularly Professor Jane Richardson of Duke University. We acknowledge with pleasure the scientific and artistic contributions of Michal Sabat of the University of Virginia. Michal was the creator of most of the PyMOL-based molecular graphics in this book. Much of the visual appeal that you will find in these pages gives testimony to his fine craftsmanship and his unflagging dedication to our purpose. Tina Chai, B.S. (Chemistry) graduate of the University of Virginia, his successor and our Molecular Graphics Design specialist, carried his work further. Elizabeth Magnotti, B.S. (Chemistry) graduate of the University of Virginia, and Ph.D., Emory University, pioneered the development of the PSAFE project, a multi-faceted task requiring scientific knowledge and a sense of its importance. Yitna Firdyiwek was instrumental in the creation of the PSAFE archive site. Celeste Costa, a current University of Virginia student, prepared content and tutorial videos for the current PSAFE course. We want to acknowledge P. Kelley, of Philander Smith College who audited the content for accuracy, Michael Cascio, of Duquesne University who is writing hints and targeted feedback for new questions for the online course, and Rochelle Williams, of the ARC Network, who advised on inclusivity and diversity for this edition. We owe a special thank you to Rosemary Jurbala Grisham, much loved spouse of Charles and wonderfully tolerant friend of Reg. Also to be acknowledged with love and pride are Georgia Cobb Garrett, spouse of Reg, and our children, Jeffrey, Randal, and Robert Garrett, David and Andrew Grisham, and Emily Grisham Cooke.

We hope this seventh edition of our textbook has captured the growing sense of wonder and imagination that researchers, teachers, and students share as they explore the ever-changing world of biochemistry.

"Imagination is more important than knowledge. For while knowledge defines all we currently know and understand, imagination points to all we might yet discover and create."

—Albert Einstein

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Charlottesville, VA

Charles M. Grisham

Ivy, VA

December 2022

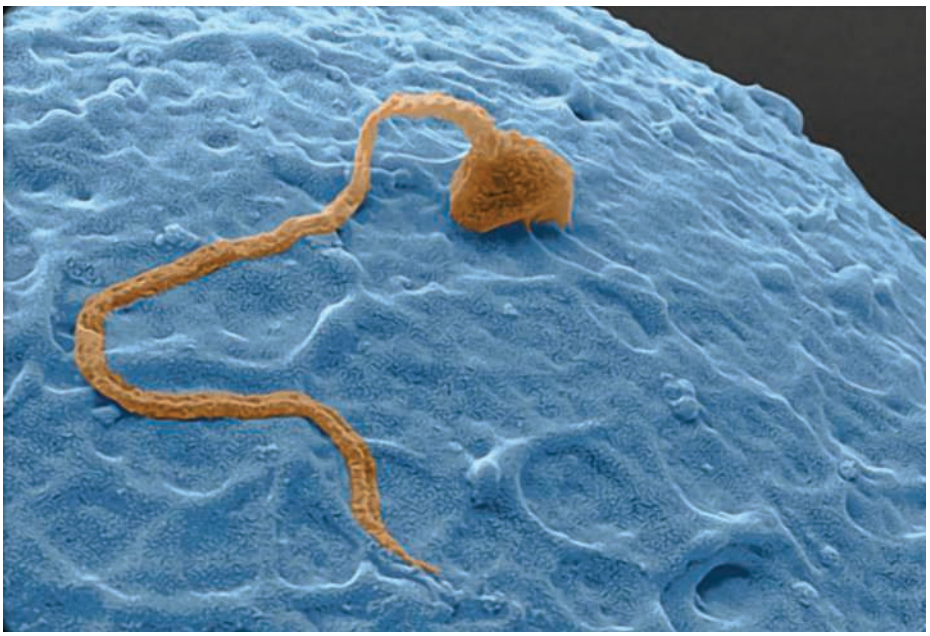
The Facts of Life: Chemistry Is the Logic of Biological Phenomena

1

Part I
Molecular Components of Cells

"…everything that living things do can be understood in terms of the jigglings and wigglings of atoms."

Richard P. Feynman. Lectures on Physics, Addison-Wesley, 1963



Marmaduke St. John/Alamy

◀ A sperm fertilizing an egg.

Essential Question

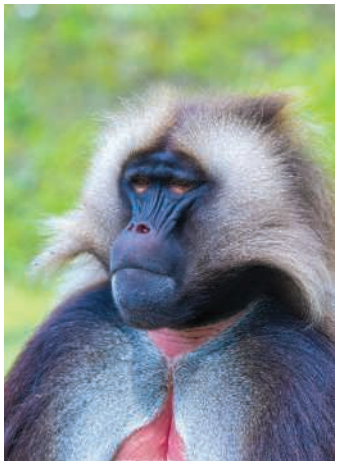
Molecules are lifeless. Yet the properties of living things derive from the properties of molecules. **Despite the spectacular diversity of life, the elaborate structure of biological molecules, and the complexity of vital mechanisms, are life functions ultimately interpretable in chemical terms?**

Key Questions

Molecules are lifeless. Yet, in appropriate complexity and number, molecules compose living things. These living systems are distinct from the inanimate world because they have certain extraordinary properties. They can grow, move, perform the incredible chemistry of metabolism, respond to stimuli from the environment, and, most significantly, replicate themselves with exceptional fidelity. The chemistry of the living cell resembles the chemistry of organic reactions. Indeed, cellular constituents, or **biomolecules**, must conform to the chemical and physical principles that govern all matter. Despite the spectacular diversity of life, the intricacy of biological structures, and the complexity of vital mechanisms, life functions are interpretable in chemical terms. *Chemistry is the logic of biological phenomena. Living organisms are self-sustaining systems of chemical reactions.*

1.1 What Are the Distinctive Properties of Living Systems?

The most obvious quality of **living organisms** is that they are *complicated and highly organized* (Figure 1.1). For example, organisms large enough to be seen with the naked eye are composed of many **cells**, typically of many types. In turn, these cells possess subcellular structures, called **organelles**, which are complex assemblies of very large polymeric molecules, called **macromolecules**. These macromolecules show an exquisite



(a) **(b)**

Figure 1.1 **(a)** Gelada (*Theropithecus gelada*), a baboon native to the Ethiopian highlands. **(b)** Tropical orchid (*Masdevallia norops*), Ecuador.

degree of organization in their intricate three-dimensional architecture, even though they are composed of simple sets of chemical building blocks, such as sugars and amino acids. Indeed, the complex three-dimensional structure of a macromolecule, known as its **conformation**, is a consequence of interactions between the monomeric units, according to their individual chemical properties.

Biological structures serve functional purposes. That is, biological structures play a role in the organism's existence. From parts of organisms, such as limbs and organs, down to the chemical agents of metabolism, such as enzymes and metabolic intermediates, a biological purpose can be given for each component. In biology, it is always meaningful to seek the purpose of observed structures, organizations, or patterns; that is, to ask what functional role they serve within the organism.

Living systems are actively engaged in energy transformations. Maintenance of the highly organized structure and activity of living systems depends on their ability to extract energy from the environment. The ultimate source of energy is the sun. Solar energy flows from photosynthetic organisms (organisms able to capture light energy by the process of photosynthesis) through food chains to herbivores and ultimately to carnivorous predators at the apex of the food pyramid. The biosphere is thus a system through which energy flows. Organisms capture some of this energy, be it from photosynthesis or the metabolism of food, by forming special energized biomolecules. **ATP** and **NADPH** are the two most prominent examples (Figure 1.2). (Commonly used abbreviations such as ATP and NADPH are defined on the inside back cover of this book.) ATP and NADPH are energized biomolecules because they represent chemically useful forms of stored energy. When these molecules react with other molecules in the cell, the energy released can be used to drive energetically unfavorable processes. That is, ATP, NADPH, and related compounds are the power sources that drive the energy-requiring activities of the cell, including biosynthesis, movement, osmotic work against concentration gradients, and, in special instances, light emission (bioluminescence). *The living state is characterized by the flow of energy through the organism*. Only upon death does an organism reach equilibrium with its inanimate environment. At the expense of energy flow, the organism can maintain its intricate order and activity far removed from equilibrium with its surroundings, yet exist in a state of apparent constancy over time. This state of apparent constancy, or so-called **steady state**, is actually a very dynamic condition: Energy and material are consumed by the organism to maintain its stability and order. In contrast, inanimate matter, as exemplified by the universe in totality, is moving to a condition of increasing disorder or, in thermodynamic terms, maximum **entropy**.

Entropy A thermodynamic term used to designate that amount of energy in a system that is unavailable to do work.

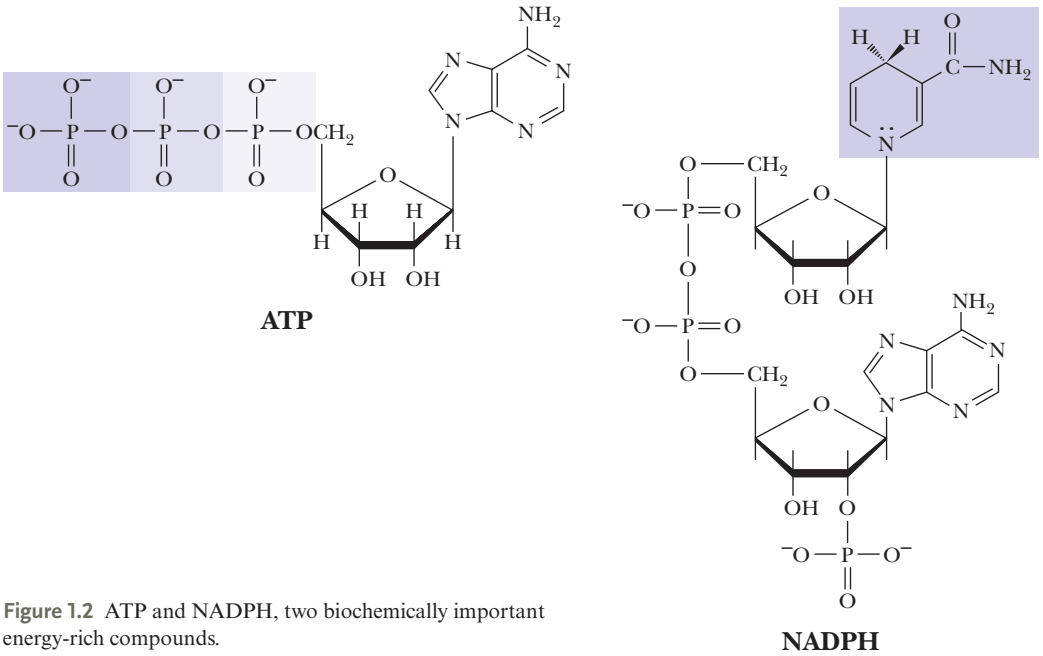


Figure 1.2 ATP and NADPH, two biochemically important energy-rich compounds.

Living systems have a remarkable capacity for self-replication. Generation after generation, organisms reproduce virtually identical copies of themselves. This self-replication can proceed by a variety of mechanisms, ranging from simple division in bacteria to sexual reproduction in plants and animals; but in every case, it is characterized by an astounding degree of fidelity (Figure 1.3). Indeed, if the accuracy of self-replication

Randal H. Garrett

Figure 1.3 Organisms resemble their parents. Orangutan with infant.

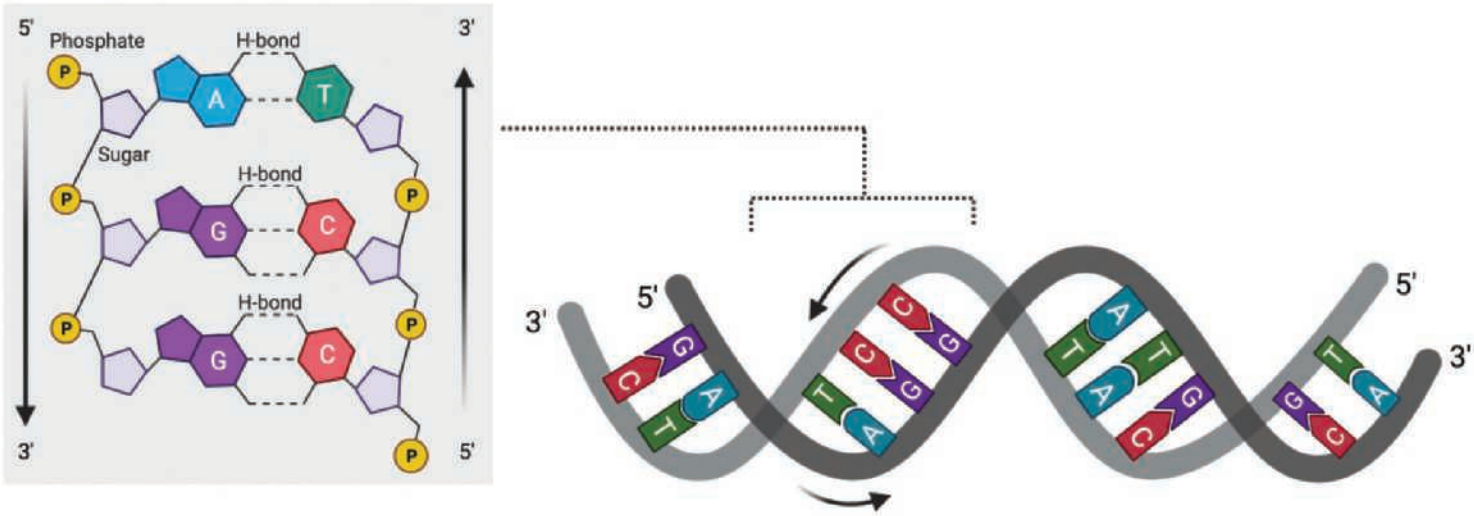


Figure 1.4 The DNA double helix. Two complementary polynucleotide chains run in opposite directions and pair through hydrogen bonding between their nitrogenous bases, A with T and C with G. Note that everywhere there is an A in one strand, the other has a T; everywhere there is a C in one strand, there is a G in the other. These complementary nucleotide sequences give rise to structural complementarity.

were significantly greater, the evolution of organisms would be hampered. This is so because evolution depends upon natural selection operating on individual organisms that vary slightly in their fitness for the environment. The fidelity of self-replication resides ultimately in the chemical nature of the genetic material. This substance is **deoxyribonucleic acid**, abbreviated as **DNA**. It consists of a pair of polymeric chains built using four different monomers known as deoxynucleotides. These four deoxynucleotide building blocks are symbolized by the letters A, C, G, and T. Information is encoded in each polynucleotide strand in the form of the precise sequence of A, C, G, and T deoxynucleotides along its length, much as this sentence contains information as encoded in the letters of the words that compose it. The two deoxynucleotide chains are **structurally complementary** to one another (Figure 1.4) in that everywhere there is an A in one strand, the other has a T, and everywhere there is a C in one strand, there is a G in the other. DNA can generate two identical copies of itself in a rigorously executed polymerization process whereby each chain is copied precisely, using the information provided by its complementary strand. This process ensures a faithful reproduction of the information written by the original polynucleotide strands. In contrast, the molecules of the inanimate world lack this capacity to replicate. A crude mechanism of replication must have existed at life's origin.

In biochemistry and molecular biology, **structurally complementary** means that two structures align and fit together like pieces of a puzzle.

1.2 | What Kinds of Molecules Are Biomolecules?

The elemental composition of living matter differs markedly from the relative abundance of elements in the earth's crust. Hydrogen (H), oxygen (O), carbon (C), and nitrogen (N) constitute more than 99% of the atoms in the human body, with most of the H and O occurring as water, H_2O. Oxygen, silicon (Si), aluminum (Al), and iron (Fe) are the most abundant atoms in the earth's crust, with hydrogen, carbon, and nitrogen being relatively rare (less than 0.2% each). Nitrogen as dinitrogen (N_2) is the predominant gas in the atmosphere, and carbon dioxide (CO_2) is present at a level of 0.04%, a small but critical amount. What property unites hydrogen, oxygen, carbon, and nitrogen and renders these atoms so suitable to the chemistry of life? It is their ability to form covalent bonds by electron-pair sharing. Furthermore, hydrogen, carbon, nitrogen, and oxygen are among the lightest elements of

the periodic table capable of forming such bonds (Figure 1.5). Because the strength of covalent bonds is inversely proportional to the atomic weights of the atoms involved, hydrogen, carbon, nitrogen, and oxygen form the strongest covalent bonds. Two other covalent bond-forming elements, phosphorus (as phosphate [$-OPO_3^{2-}$] derivatives) and sulfur, also play important roles in biomolecules.

1.2a Biomolecules Are Carbon Compounds

All biomolecules contain carbon. The prevalence of carbon is due to its unparalleled versatility in forming stable covalent bonds through electron-pair sharing. Carbon can form up to four such bonds by sharing each of the four electrons in its outer shell with electrons contributed by other atoms. Atoms commonly found in covalent linkage to carbon are carbon itself, hydrogen, oxygen, and nitrogen. Hydrogen can form one such bond by contributing its single electron to the formation of an electron pair. Oxygen, with two unpaired electrons in its outer shell, can participate in two covalent bonds, and nitrogen, which has three unshared electrons, can form three such covalent bonds. Furthermore, carbon, nitrogen, and oxygen can share two electron pairs to form double bonds with one another within biomolecules, a property that enhances their chemical versatility. Carbon and nitrogen can even share three electron pairs to form triple bonds.

Two properties of carbon covalent bonds merit particular attention. One is the ability of carbon to form covalent bonds with itself. The other is the tetrahedral nature of the four covalent bonds when carbon atoms form only single bonds. Together these properties hold the potential for an incredible variety of linear, branched, and cyclic carbon compounds. This diversity is multiplied further by the possibilities for including nitrogen, oxygen, and hydrogen atoms in these compounds (Figure 1.6). We can therefore envision the ability of carbon to generate complex structures in three dimensions. These structures, by virtue of appropriately included nitrogen, oxygen, and hydrogen atoms, can display unique chemistries suitable to the living state. Thus, we may ask, is there any pattern or underlying organization that brings order to this astounding potentiality?

Atoms	e^- pairing	Covalent bond	Bond energy (kJ/mol)
H· + H·	H:H	H—H	436
·C· + H·	·C:H	–C—H	414
·C· + ·C·	·C:C·	–C—C–	343
·C· + ·N:	·C:N:	–C—N<	292
·C· + ·O:	·C:O:	–C—O–	351
·C· + ·C·	C::C	>C=C<	615
·C· + ·N:	C::N:	>C=N–	615
·C· + ·O:	C::O:	>C=O	686
·O: + ·O:	·O:O·	–O—O–	142
·O: + ·O:	O::O:	O=O	402
·N: + ·N:	:N:::N:	N≡N	946
·N: + H·	:N:H	>N—H	393
·O: + H·	·O:H	–O—H	460

Figure 1.5 Covalent bond formation by e^- pair sharing. The energy necessary to break a bond is given in kJ/mol.

1.3 What Is the Structural Organization of Complex Biomolecules?

Examination of the chemical composition of cells reveals a dazzling variety of organic compounds covering chemical dimensions such as length and mass (Table 1.1). When biomolecules are classified based on size and chemical properties, an organizational pattern emerges. The biomolecules are built according to a structural hierarchy: Simple molecules are the units for building complex structures.

The molecular constituents of living matter do not reflect randomly the infinite possibilities for combining carbon, hydrogen, oxygen, and nitrogen atoms. Instead, only a limited set of the many possibilities is found, and these collections share certain properties essential to the living state. The most prominent aspect of biomolecular organization is that simple molecules are the building blocks for polymers that contain thousands or even millions of atoms, structures so large that we refer to them as **macromolecules**. What properties do these biomolecules possess that make them so appropriate for the condition of life?

Macro - prefix from the Greek "makros" meaning large or long.

1.3a Metabolites Are Used to Form the Building Blocks of Macromolecules

The major precursors for the formation of biomolecules are water, carbon dioxide, and three inorganic nitrogen compounds—ammonium (NH_4^+), nitrate (NO_3^-), and dinitrogen (N_2). Metabolic processes transform these inorganic precursors through ever

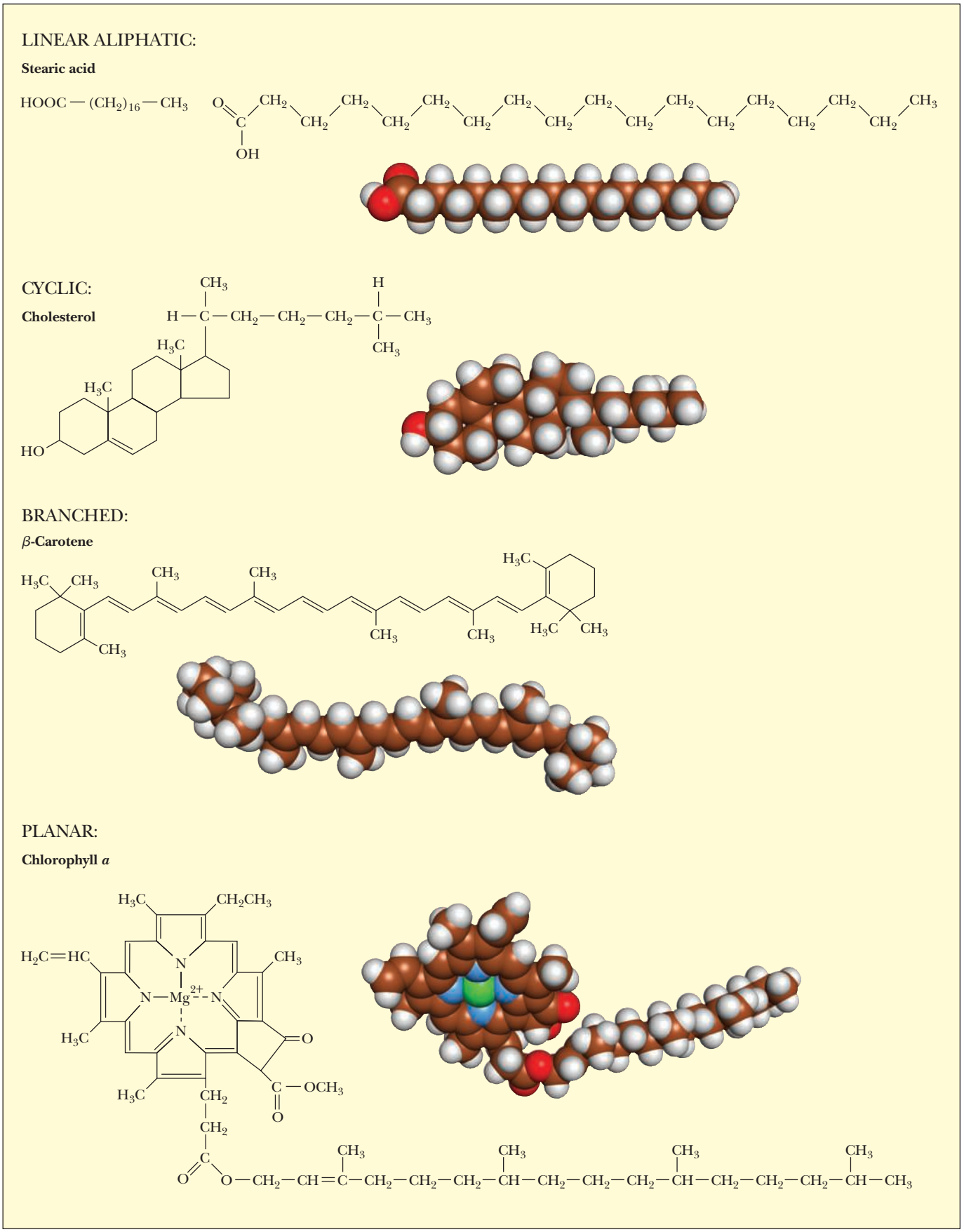


Figure 1.6 Examples of the versatility of C—C bonds to build complex structures: linear, cyclic, branched, and planar.

Table 1.1 Biomolecular Dimensions

The dimensions of mass* and length for biomolecules are given typically in daltons and nanometers,† respectively. One dalton (Da) is approximately equal to the mass of one hydrogen atom, 1.66×10^{-24} g. One nanometer (nm) is 10^{-9} m, or 10 Å (angstroms).

Biomolecule	Length (long dimension, nm)	Mass	
		Daltons	Picograms
Water	0.3	18	
Alanine	0.5	89	
Glucose	0.7	180	
Phospholipid	3.5	750	
Ribonuclease (a small protein)	4	12,600	
Immunoglobulin G (IgG)	14	150,000	
Myosin (a large muscle protein)	160	470,000	
Ribosome (bacterial)	18	2,520,000	
Bacteriophage ϕX174 (a very small bacterial virus)	25	4,700,000	
Pyruvate dehydrogenase complex (a multienzyme complex)	60	7,000,000	
Tobacco mosaic virus (a plant virus)	300	40,000,000	6.68×10^{-5}
Mitochondrion (liver)	1500		1.5
Escherichia coli cell	2000		2
Chloroplast (spinach leaf)	8000		60
Liver cell	20,000		8000

*Molecular mass is expressed in units of daltons (Da) or kilodaltons (kDa) in this book; alternatively, the dimensionless term *molecular weight*, symbolized by M_r, and defined as the ratio of the mass of a molecule to 1 dalton of mass, is used.

†Prefixes used for powers of 10 are as follows:

10^6	mega	M	10^{-3}	milli	m
10^3	kilo	k	10^{-6}	micro	μ
10^{-1}	deci	d	10^{-9}	nano	n
10^{-2}	centi	c	10^{-12}	pico	p
			10^{-15}	femto	f

more complex levels of biomolecular order (Figure 1.7). In the first step, precursors are converted to **metabolites**, simple organic compounds that are intermediates in cellular energy transformation and the biosynthesis of various sets of **building blocks**: amino acids, sugars, nucleotides, fatty acids, and glycerol. Through the covalent linkage of these building blocks, **macromolecules** are constructed: proteins, polysaccharides, polynucleotides (DNA and RNA), and lipids. (Strictly speaking, lipids contain relatively few building blocks and are therefore not really polymeric like other macromolecules; however, lipids are important contributors to higher levels of complexity.) Interactions among macromolecules lead to the next level of structural organization, **supramolecular complexes**. Here, various members of one or more of the classes of macromolecules come together to form specific assemblies that serve important subcellular functions. Examples of these supramolecular assemblies are multifunctional enzyme complexes, ribosomes, chromosomes, and cytoskeletal elements. For example, a eukaryotic ribosome contains four different RNA molecules and at least 70 unique proteins. Ribosomes are the supramolecular complexes where proteins are synthesized. These supramolecular assemblies are an interesting contrast to their components because their structural integrity is maintained by noncovalent forces, not covalent bonds. These noncovalent forces include hydrogen bonds, ionic attractions, van der Waals forces, and hydrophobic interactions between macromolecules. Such forces maintain these supramolecular assemblies in a highly ordered functional state. Although noncovalent forces are weak (less than 40 kJ/mol), they are numerous in these assemblies and thus can collectively maintain the essential architecture of the supramolecular complex under conditions of temperature, pH, and ionic strength that are consistent with cell life.

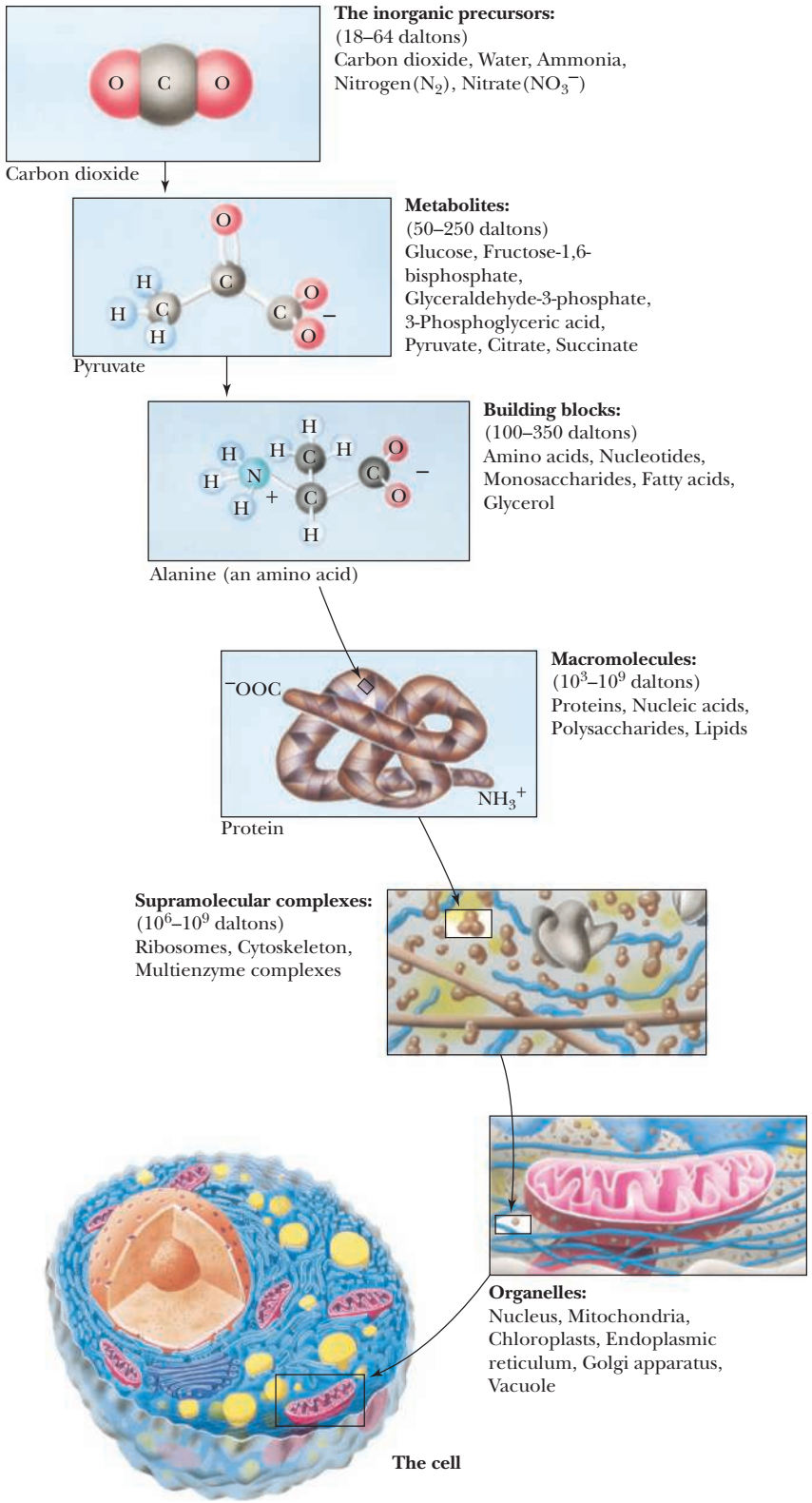


Figure 1.7 Molecular organization in the cell is a hierarchy.

1.3b Organelles Represent a Higher Order in Biomolecular Organization

The next higher rung in the hierarchical ladder is occupied by the organelles. Organelles are found only in **eukaryotic cells**, that is, the cells of higher organisms (eukaryotic cells are described in Section 1.5). Organelles are subcellular structures dedicated to a specific purpose. Several kinds, such as mitochondria and chloroplasts, evolved from bacteria that entered the cytoplasm of early eukaryotic cells.

Careers in Chemistry

Michelle Nguyen

Michelle Nguyen is a Vietnamese American immigrant who earned her BS at Ohio State University and decided to stay local to work at Nationwide Children's Hospital in their Compliance and Integrity Office. She considers her work as a Conflict of Interests Administrator to be a mixture of science and law since her responsibilities include mitigating biases within clinical and research programs to protect the integrity of the research. Maintaining scientific impartiality is a crucial step to ensuring overall patient safety.

Nguyen credits her biochemistry education as a fundamental component of her understanding of the research being done and a necessary element to interacting with the doctors and researchers about their work.

Nguyen found her career path after initially pursuing another career in pharmaceuticals but realized that she was truly passionate about life sciences and a major in Biology. Her advice to students still finding their way is to not fear the road less traveled because you might find it more meaningful for you in the end.

Other organelles include the nucleus, endoplasmic reticulum, Golgi apparatus, and vacuoles as well as other relatively small cellular inclusions, such as peroxisomes, lysosomes, and chromoplasts. The **nucleus** is the repository of genetic information contained within the linear sequences of nucleotides in the DNA of chromosomes. **Mitochondria** capture the energy released during aerobic metabolism and use it to produce ATP. **Chloroplasts** endow cells with the ability to carry out photosynthesis, capturing light energy and transforming it into metabolically useful chemical forms.

1.3c Membranes Are Supramolecular Assemblies That Define the Boundaries of Cells

Membranes define the boundaries of cells and organelles. As such, they are not easily classified as supramolecular assemblies or organelles, although they share the properties of both. Membranes resemble supramolecular complexes in their construction because they are complexes of proteins and lipids maintained by noncovalent forces. **Hydrophobic interactions** are particularly important in maintaining membrane structure. Hydrophobic interactions arise because water molecules prefer to interact with each other rather than nonpolar substances. The presence of nonpolar molecules lessens the range of opportunities for water–water interaction by forcing water molecules into ordered arrays around the nonpolar groups. Such ordering can be minimized if the individual nonpolar molecules redistribute from a dispersed state in the water into an aggregated organic phase surrounded by water. The spontaneous assembly of membranes in the aqueous environment, where life arose and exists, is the natural result of the hydrophobic ("water-fearing") character of lipids and proteins. Hydrophobic interactions are the creative means of membrane formation and the driving force that presumably established the boundary of the first cell. The membranes of organelles, such as nuclei, mitochondria, and chloroplasts, differ from one another, with each having a characteristic protein and lipid composition tailored to the organelle's function. The formation of these discrete compartments in the cell allows these cells to carry out unique functions.

1.3d The Unit of Life Is the Cell

The cell is characterized as the unit of life, the smallest entity capable of displaying the attributes associated uniquely with the living state: growth, metabolism, stimulus response, and replication. In previous discussions, we explicitly narrowed the infinity of chemical complexity potentially available to organic life and we previewed an organizational arrangement, moving from simple to complex, that provides insights into the functional and structural plan of the cell. Nevertheless, these features do not explain the living characteristics of cells. Can we find other themes represented within biomolecules that are explicitly chemical yet anticipate or illuminate the living condition?