BIOCHEMISTRY

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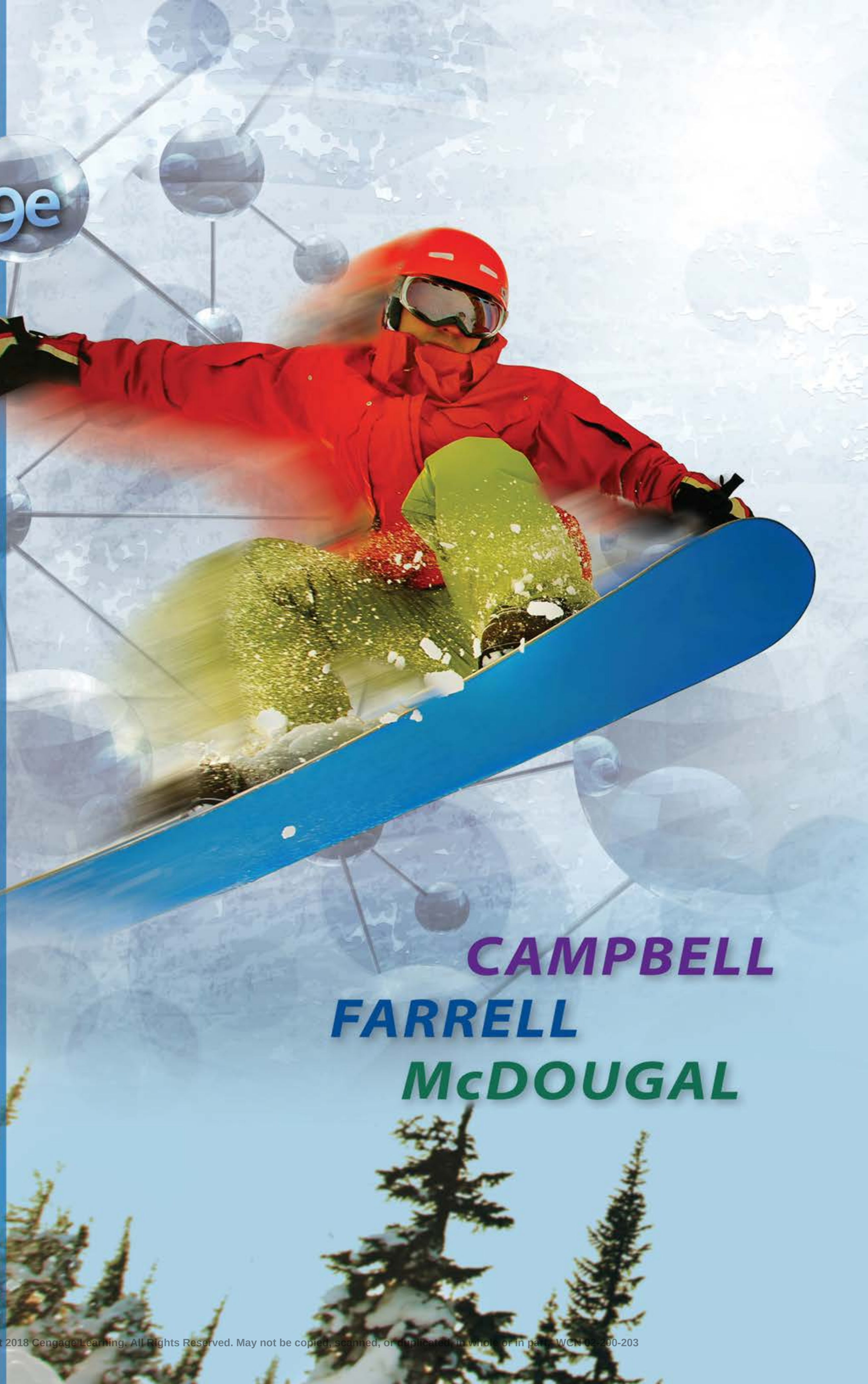

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BIOCHEMISTRY

BIOCHEMISTRY

9TH EDITION

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Mount Holyoke College

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***Biochemistry*, Ninth Edition**
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This book is dedicated to the memory of Mary Campbell, who was passionately involved in its creation. Her avid interest in writing and devotion to student engagement led to the publication of the first eight highly successful editions of this textbook.

—Mary K. Campbell

To the returning adult students in my classes, especially those with children and a full-time job . . . my applause.

—Shawn O. Farrell

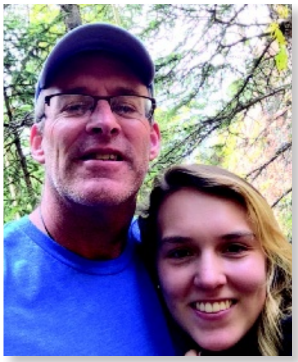
My recognition and appreciation go to those who saw the potential in me that has taken so many years to develop, and to those students who are on the path to fulfilling their dreams.

—Owen M. McDougal

About the Authors

Mary K. Campbell

Mary K. Campbell was a professor emeritus of chemistry at Mount Holyoke College, where she taught for 36 years. Mary received her PhD from Indiana University and did postdoctoral work in biophysical chemistry at Johns Hopkins University. Her area of interest included researching the physical chemistry of biomolecules, specifically, spectroscopic studies of protein–nucleic acid interactions.



Shawn O. Farrell

Shawn O. Farrell grew up in northern California and received a B.S. degree in biochemistry from the University of California, Davis, where he studied carbohydrate metabolism. He completed his Ph.D. in biochemistry at Michigan State University, where he studied fatty acid metabolism. For 18 years, Shawn worked at Colorado State University teaching undergraduate biochemistry lecture and laboratory courses. Because of his interest in biochemical education, Shawn has written a number of scientific journal articles about teaching biochemistry. He is the coauthor (with Lynn E. Taylor) of *Experiments in Biochemistry: A Hands-On Approach*. Shawn became interested in biochemistry while in college because it coincided with his passion for bicycle racing. An active outdoorsman, Shawn raced competitively for 17 years and now officiates at bicycle races around the world. He was the technical director of USA Cycling, the national governing body of bicycle racing in the United States for 11 years before returning to teaching at CSU in Pueblo, Colorado. He is also an avid fly fisherman, a third-degree black belt in Tae Kwon Do, and a first-degree black belt in combat hapkido. Shawn has also written articles on fly fishing for *Salmon Trout Steelheader* magazine. His other passions are music and foreign languages. He is fluent in Spanish and French and is currently learning to play the guitar.

On his fiftieth birthday, he had his first downhill skiing lesson and now cannot get enough of it. Never tired of education, he visited CSU again, this time from the other side of the podium, and earned his Master of Business Administration in 2008.

Owen M. McDougal

Owen M. McDougal is a professor of chemistry and biochemistry at Boise State University. He is a native of upstate New York where he earned chemistry degrees at State University of New York at Morrisville (AS) and Oswego (BS). His love of the outdoors motivated him to travel west for graduate school and pursue a PhD at the University of Utah in the laboratory of C. Dale Poulter. His work to elucidate the three-dimensional structures of neuropeptides by nuclear magnetic resonance spectroscopy involved the application of physical chemistry to address problems in biological systems. Graduate studies in the heart of the Wasatch Mountains in Utah led to his lifelong enthusiasm for mountain biking and telemark skiing. In this capacity, Owen tested his skills at competitive mountain bike racing and pursued what resulted in a ten-year stint on the National Ski Patrol. Upon completion of his PhD, Owen sought an academic environment that allowed him to share his passion for science with students in small classes. He taught general, organic, and biological chemistry at Southern Oregon University, which allowed him to hone his instructional skills. Looking to advance his love for writing, Owen shifted to a faculty position in the research intensive environment at Boise State University, where he investigates the bioactivity of marine and terrestrial natural products, including studies of food chemistry, nutraceutical products, and specialty chemicals. Owen lives in Boise, Idaho, with wife Lynette, daughters McKenzie and Riley, dog Tater, cat Melody, tortoise Touché, and rabbit Bixby.

Brief Contents

Contents

Preface

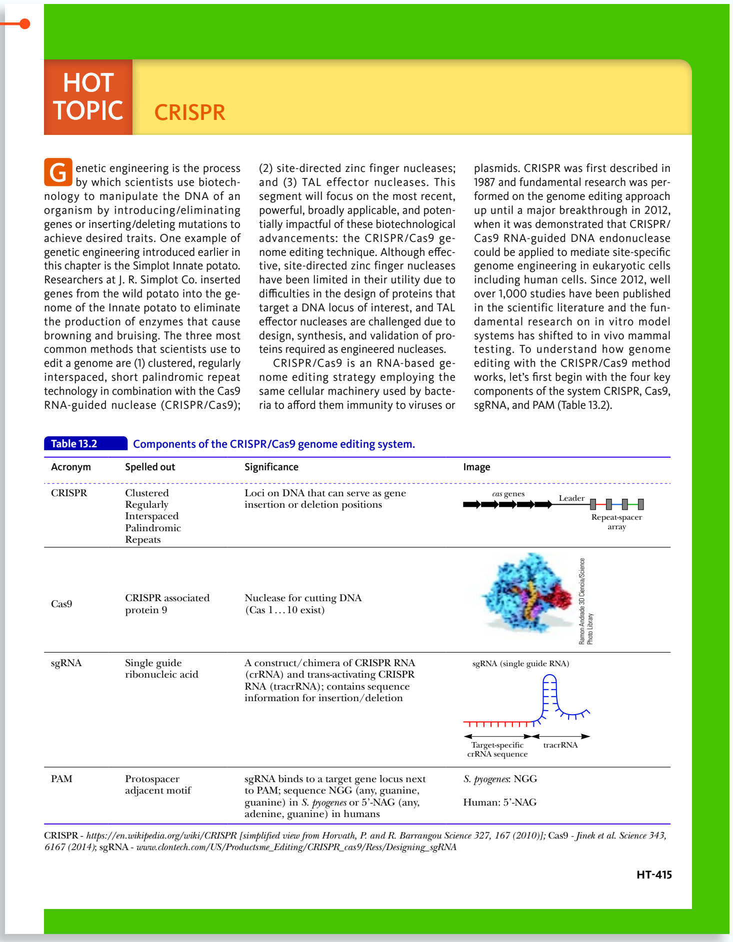
This text is intended for students in any field of science or engineering who want a one-semester introduction to biochemistry but who do not intend to be biochemistry majors. Our main goal in writing this book is to make biochemistry as clear and applied as possible and to familiarize science students with the major aspects of biochemistry. For students of biology, chemistry, physics, geology, nutrition, sports physiology, and agriculture, biochemistry impacts greatly on the content of their fields, especially in the areas of medicine and biotechnology. For engineers, studying biochemistry is especially important for those who hope to enter a career in biomedical engineering or some form of biotechnology.

Students who will use this text are at an intermediate level in their studies. A beginning biology course, general chemistry, and at least one semester of organic chemistry are assumed as preparation.

What's New

All textbooks evolve to meet the interests and needs of students and instructors and to include the most current information. Several changes mark this edition.

Biochemistry Hot Topics These articles are now conveniently located within the relevant chapters. They highlight new breakthroughs and topics in the area of biochemistry such as CRISPR, Alzheimer's disease, epigenetics, brown fat, and more!



HOT TOPIC CRISPR

Genetic engineering is the process by which scientists use biotechnology to manipulate the DNA of an organism by introducing/eliminating genes or inserting/deleting mutations to achieve desired traits. One example of genetic engineering introduced earlier in this chapter is the Simplot Innate potato. Researchers at J. R. Simplot Co. inserted genes from the wild potato into the genome of the Innate potato to eliminate the production of enzymes that cause browning and bruising. The three most common methods that scientists use to edit a genome are (1) clustered, regularly interspaced, short palindromic repeat technology in combination with the Cas9 RNA-guided nuclease (CRISPR/Cas9); (2) site-directed zinc finger nucleases; and (3) TAL effector nucleases. This segment will focus on the most recent, powerful, broadly applicable, and potentially impactful of these biotechnological advancements: the CRISPR/Cas9 genome editing technique. Although effective, site-directed zinc finger nucleases have been limited in their utility due to difficulties in the design of proteins that target a DNA locus of interest, and TAL effector nucleases are challenged due to design, synthesis, and validation of proteins required as engineered nucleases.

CRISPR/Cas9 is an RNA-based genome editing strategy employing the same cellular machinery used by bacteria to afford them immunity to viruses or plasmids. CRISPR was first described in 1987 and fundamental research was performed on the genome editing approach up until a major breakthrough in 2012, when it was demonstrated that CRISPR/Cas9 RNA-guided DNA endonuclease could be applied to mediate site-specific genome engineering in eukaryotic cells including human cells. Since 2012, well over 1,000 studies have been published in the scientific literature and the fundamental research on in vitro model systems has shifted to in vivo mammal testing. To understand how genome editing with the CRISPR/Cas9 method works, let's first begin with the four key components of the system CRISPR, Cas9, sgRNA, and PAM (Table 13.2).

Table 13.2 Components of the CRISPR/Cas9 genome editing system.

Acronym	Spelled out	Significance	Image
CRISPR	Clustered Regularly Interspaced Palindromic Repeats	Loci on DNA that can serve as gene insertion or deletion positions	*cas* genes; Leader; Repeat-spacer array
Cas9	CRISPR associated protein 9	Nuclease for cutting DNA (Cas 1…10 exist)	Ramon Andrade 3D Ciencia/Science Photo Library
sgRNA	Single guide ribonucleic acid	A construct/chimera of CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA); contains sequence information for insertion/deletion	sgRNA (single guide RNA); Target-specific crRNA sequence; tracrRNA
PAM	Protospacer adjacent motif	sgRNA binds to a target gene locus next to PAM; sequence NGG (any, guanine, guanine) in *S. pyogenes* or 5'-NAG (any, adenine, guanine) in humans	*S. pyogenes*: NGG Human: 5'-NAG

CRISPR - *https://en.wikipedia.org/wiki/CRISPR [simplified view from Horvath, P. and R. Barrangou Science 327, 167 (2010)];* Cas9 - *Jinek et al. Science 343, 6167 (2014)*; sgRNA - *www.clontech.com/US/Productsme_Editing/CRISPR_cas9/Ress/Designing_sgRNA*

HT-415

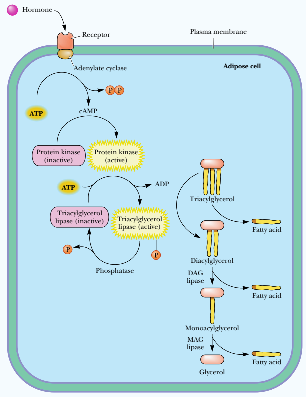
Updated Coverage Each chapter in the text has been updated with the current developments and scientific findings in the biochemistry field.

New Design and Updated Art Illustrations throughout the text have been redrawn for improved consistency. In conjunction with the book's updated art program, a more contemporary design and color palette have been utilized.

Further Reading An annotated bibliography is now provided in the Further Reading section at the end of each chapter, making these resources more easily accessible to the student.

Table of Changes by Chapter

Chapter 1	Added summary of major types of biomolecules
Chapter 3	Expanded Biochemical Connection on oxytocin and its social effects, added four new Review Exercises
Chapter 4	Updated Biochemical Connection on prion diseases, added Hot Topic about aging
Chapter 6	Updated Biochemical Connection on enzyme markers for diseases
Chapter 7	Added new Hot Topic on Alzheimer's disease, added four new Review Exercises
Chapter 8	Added expanded Hot Topic on happiness and depression, added two new Review Exercises
Chapter 9	Added Hot Topic on breast cancer, added material on long noncoding RNA, added new section on medical applications of RNA, deleted Biochemical Connection on synthetic genome
Chapter 10	Added brief mention of replication termination
Chapter 11	Added new Hot Topic on epigenetics, deleted Biochemical Connections box about CREB, deleted Biochemical Connections about epigenetics and cancer
Chapter 13	Added new Hot Topic on clustered, regularly interspaced, short palindromic repeat technology in combination with the Cas9 RNA-guided nuclease (CRISPR/Cas9) method of genetic engineering, example of CRISPR/Cas9 to engineer Innate potato
Chapter 14	Updated content on vaccine development for Ebola and advances in stem cell research
Chapter 16	New research findings that correlate the use of artificial sweeteners to gut microbiome, suggesting the reason diet products may not result in weight loss
Chapter 17	Updated content associated with biofuels
Chapter 19	New information on the use of the compound 1080 (sodium fluoroacetate) for control of mammal populations in New Zealand
Chapter 20	Added a new Hot Topic on brown fat to include recent research developments demonstrating the benefits of brown adipose tissue to maintenance of healthy metabolism
Chapter 24	Added updated Hot Topic on G-protein–coupled receptors to include recent research on the biased agonism or functional selectivity model associated with opioid receptors



Proven Features

Visual Impact Ideal for visual learners, this book's state-of-the-art approach helps students visualize key processes and understand important topics.

Biochemical Connections The Biochemical Connections highlight special topics of particular interest to students. Topics frequently have clinical implications, such as cancer, AIDS, and nutrition. These essays help students make the connection between biochemistry and the real-world. They are flowed in with the narrative and are placed exactly where they need to be read in each chapter. And although they have a different presentation than the rest of the narrative, they are meant to be read with the narrative and should not be skipped. They are like crescendos in classical music—the change in tempo from the usual narrative to the unique visual presentation and voice of the Biochemical Connections prevents the student's level of interest from dipping—students are always engaged. See a full listing of Biochemical Connections boxes in the Table of Contents.

12B BIOCHEMICAL CONNECTIONS
Neurology
Protein Synthesis Makes Memories

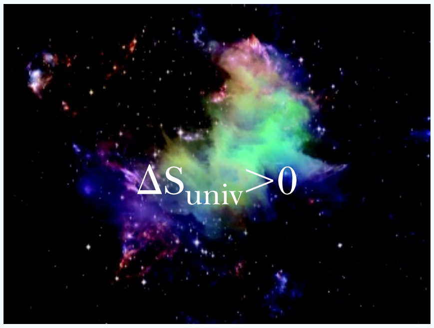
Apply Your Knowledge The Apply Your Knowledge boxes are interspersed within chapters and are designed to provide students with problem-solving experience. The topics chosen are areas of study where students usually have the most difficulty. Solutions and problem-solving strategies are included, giving examples of the problem-solving approach for specific material.

2.1 APPLY YOUR KNOWLEDGE
pH Calculations

Marginal Glossary No flipping back and forth to read full definitions of key terms. Terms are defined in the margins.

titration an experiment in which a measured amount of base is added to an acid

Early Inclusion of Thermodynamics Select material on thermodynamics appears early in the text. Chapter 1 includes sections on energy and change, spontaneity in biochemical reactions, and life and thermodynamics. Also, Chapter 4 contains an extended section on protein-folding dynamics. We feel it is critical that students understand the driving force of biological processes and see that so much of biology (protein folding, protein–protein interactions, small molecule binding, etc.) is driven by the favorable disordering of water molecules.



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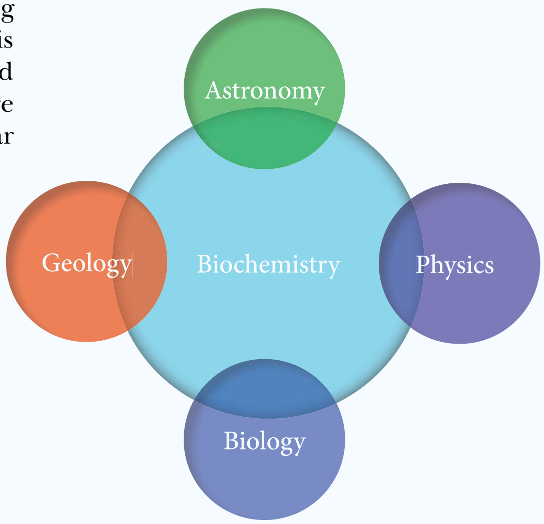
Summaries and Questions Each chapter closes with a concise summary, a broad selection of questions, and an annotated bibliography that suggests sources for further reading. The Review Exercises fall into four categories: **RECALL**, **REFLECT AND APPLY**, **BIOCHEMICAL CONNECTIONS**, and **MATHEMATICAL**. The **RECALL** questions are designed for students to quickly assess their mastery of the material, and the **REFLECT AND APPLY** questions are for students to work through more thought-provoking questions. **BIOCHEMICAL CONNECTIONS** questions test students on the **BIOCHEMICAL CONNECTIONS** essays in that chapter. The **MATHEMATICAL** questions are quantitative in nature and focus on calculations.

Organization

Because biochemistry is a multidisciplinary science, the first task in presenting it to students of widely varying backgrounds is to put it in context. The text is organized into four categories. The first provides the necessary background and connects biochemistry to other sciences. The next focuses on the structure and dynamics of important cellular components. This is followed by molecular biology and then intermediary metabolism.

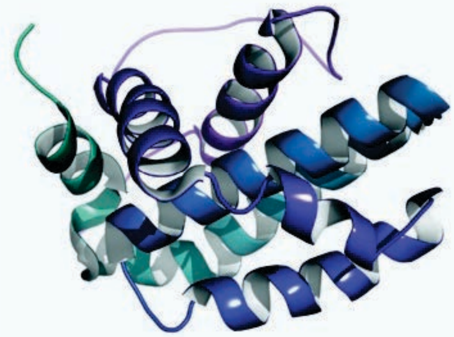


Chapters 1 & 2: Background and Connections

- Relationship between biochemistry and other sciences, particularly concerning the origins of life
- Organic functional groups in the context of biochemistry
- Link between biochemistry and biology, especially the distinction between prokaryotes and eukaryotes and the role of organelles in eukaryotes
- Biochemical view of buffers, solvent properties of water, and other familiar general chemistry topics

Chapters 3-8: Structure and Dynamics of Cellular Components

- Amino acids, peptides, the structure and action of proteins, including enzyme catalysis
- Thermodynamics, hydrophobic interactions
- Techniques for isolating and studying proteins
- Enzyme kinetics and mechanisms
- Structure of membranes and their lipid components



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Chapters 9-14: Molecular Biology

- Replication of DNA
- Transcription and gene regulation
- Biosynthesis of nucleic acids
- Translation of the genetic message and protein synthesis
- Biotechnology techniques
- Viruses, cancer, and immunology

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Chapters 15-24: Intermediary Metabolism

- Thermodynamic concepts applied specifically to biochemical topics such as coupled reactions
- Connection between metabolism and electron transfer (oxidation–reduction) reactions
- Coenzymes
- Overview of the metabolic pathways: glycolysis
- Glycogen metabolism, gluconeogenesis, and the pentose phosphate pathway
- Citric acid cycle, electron transport chain, and oxidative phosphorylation
- Catabolic and anabolic aspects of lipid metabolism
- Photosynthesis and carbohydrate metabolism
- Plant origin of antimalarials
- Metabolism of nitrogen-containing compounds such as amino acids, porphyrins, and nucleobases
- Integrated look at metabolism, including a treatment of hormones and second messengers
- Nutrition
- Immune system

Some topics such as enzymes and the biosynthesis of nucleic acids are split into two chapters to give students ample time to fully understand the concepts involved. Some are discussed several times, such as the control of carbohydrate metabolism. Subsequent discussions make use of and build on information students have already learned. It is particularly useful to return to a topic after students have had time to assimilate and reflect on it.

This text gives an overview of important topics of interest to biochemists and shows how the remarkable recent progress of biochemistry impinges on other sciences. The length is intended to provide instructors with a choice of favorite topics without being overwhelming for the limited amount of time available in one semester.

Alternative Teaching Options

The order in which individual chapters are covered can be changed to suit the needs of specific groups of students. Although we prefer an early discussion of thermodynamics, the portions of Chapters 1 and 4 that deal with thermodynamics can be covered at the beginning of Chapter 15. All of the molecular biology chapters (Chapters 9 through 14) can precede metabolism or can follow it, depending on the instructor's choice. The order in which the material on molecular biology is treated can be varied according to the preference of the instructor.

Alternate Editions

Loose-Leaf Edition for Biochemistry 9e
ISBN: 978-1-305-96195-1
A loose-leaf (unbound, three-hole-punched) version of *Biochemistry 9e,* which can be inserted in a binder, is also available.

Acknowledgments

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Supporting Materials

Please visit **http://www.cengage.com/chemistry/campbell/biochemistry9e** for information about student and instructor resources for this text.

A Final Note from Shawn Farrell

I cannot adequately convey how impossible this project would have been without my wonderful family, who put up with a husband and father who became a hermit in the back office. I would also like to thank David Hall, book representative, for starting me down this path, and the late John Vondeling for giving me an opportunity to expand into other types of books and projects.

I met Mary Campbell in the mid-1990s when I was asked to collaborate on the fourth edition of this textbook with her. She was a fascinating individual and a visionary in this field. She believed that biochemistry should be accessible not only to the hard-core chemistry and biochemistry majors, but also to the wide range of majors that embrace biochemistry. Such was her inspiration for this one-semester text. She was very generous with her time and helped me immensely during the process of writing our first edition together. She also had a rapier wit and was a hoot to hang out with at science conventions. Her sudden passing in May 2014 was a shock to us all, and she will be sorely missed.

A Final Note from Owen McDougal

I wish to thank my wife Lynette for her patience and support, may the road rise to meet you…, my children McKenzie and Riley for reminding me where my priorities belong, and my parents Bob and Bobbie for unconditional support and inspiration to be all I can be.

Chapter Outline

1

Biochemistry and the Organization of Cells

1-1 Basic Themes

Biochemistry and Life

▶ ***How does biochemistry describe life processes?***

Living organisms, such as humans, and even the individual cells of which they are composed, are enormously complex and diverse. Nevertheless, certain unifying features are common to all living things from the simplest bacterium to the human being. They all use the same types of *biomolecules,* and they all use energy. As a result, organisms can be studied via the methods of chemistry and physics.

Biochemistry can be defined in many ways. From the name, it is clear it is the chemistry of life. It combines biology and chemistry, and any given instructor may have more of a biology focus, a chemistry focus, or anything in between.

Disciplines that appear to be unrelated to biochemistry can provide answers to important biochemical questions. For example, the magnetic resonance imaging (MRI) tests that play an important role in the health sciences originated with physicists, became a vital tool for chemists, and currently play a large role in biochemical research. The field of biochemistry draws on many disciplines, and its multidisciplinary nature allows it to use results from many sciences to answer questions about the *molecular nature of life processes.* Important applications of this kind of knowledge are made in medically related fields; an understanding of health and disease at the molecular level leads to more effective treatment of illnesses of many kinds.

The activities within a cell are similar to the transportation system of a city. The cars, buses, and taxis correspond to the molecules involved in reactions (or series of reactions) within a cell. The routes traveled by vehicles likewise can be compared to the reactions that occur in the life of the cell. Note particularly that many vehicles travel more than one route—for instance, cars and taxis can go almost anywhere—whereas other, more specialized modes of transportation, such as subways and streetcars, are confined to single paths. Similarly, some molecules play multiple roles, whereas others take part only in specific series of reactions. Also, *the routes operate simultaneously,* and we shall see that this is true of the many reactions within a cell.

To continue the comparison, the transportation system of a large city has more kinds of transportation than does a smaller one. Although a small city may have only cars, buses, and taxis, a large city may have all of these plus others, such as streetcars or subways. Analogously, some reactions are found in all cells, and others are found only in specific kinds of cells. Also, more structural features are found in the larger, more complex cells of larger organisms than in the simpler cells of organisms such as bacteria.

An inevitable consequence of this complexity is the large quantity of terminology that is needed to describe it; learning considerable new vocabulary is an essential part of the study of biochemistry. You will also see many cross-references in this book, which reflect the many connections among the processes that take place in the cell.

Origin of Life on Earth

The fundamental similarity of cells of all types makes speculating on the origins of life a worthwhile question. How did the components of our bodies come to be and to do the things that they do? What are the molecules of life? Even the structures of comparatively small biomolecules consist of several parts. Large biomolecules, such as proteins and nucleic acids, have complex structures, and living cells are enormously more complex. Even so, *both molecules and cells must have arisen ultimately from very simple molecules,* such as water, methane, carbon dioxide, ammonia, nitrogen, and hydrogen (Figure 1.1). In turn, these simple molecules must have arisen from atoms.

▶ *How did living things originate?*

The way in which the Universe itself, and the atoms of which it is composed, came to be is a topic of great interest to astrophysicists as well as other scientists. Simple molecules were formed by combining atoms, and reactions of simple molecules led in turn to more complex molecules. The molecules that play a role in living cells today are the same molecules as those encountered in organic chemistry; they simply operate in a different context.

1-2 Chemical Foundations of Biochemistry

organic chemistry the study of compounds of carbon, especially of carbon and hydrogen and their derivatives

Organic chemistry is the study of compounds of carbon and hydrogen and their derivatives. Because the cellular apparatus of living organisms is made up of carbon compounds, biomolecules are part of the subject matter of organic chemistry. Additionally, many carbon compounds are not found in any organism, and many topics of importance to organic chemistry have little connection with living things. We are going to concentrate on the aspects of organic chemistry that we need in order to understand what goes on in living cells.

The small molecules found in the cell can usually be lumped into four basic classes. We will see these over and over again during our study of biochemistry. They are the basic building blocks of life.

Amino Acids

The simplest compounds are the amino acids. They get their name from the fact that they all contain an amino group and a carboxyl group, as shown in Figure 1.2. Under physiological conditions both the carboxyl group and amino group are ionized (-COO^- and –NH_3^+, respectively). Amino acids can be shown in various ways, including a structural formula or a ball and stick formula. Amino acids have a basic structure where a central carbon atom is bonded to a carboxyl group, an amino group, a hydrogen, and a variable group, called

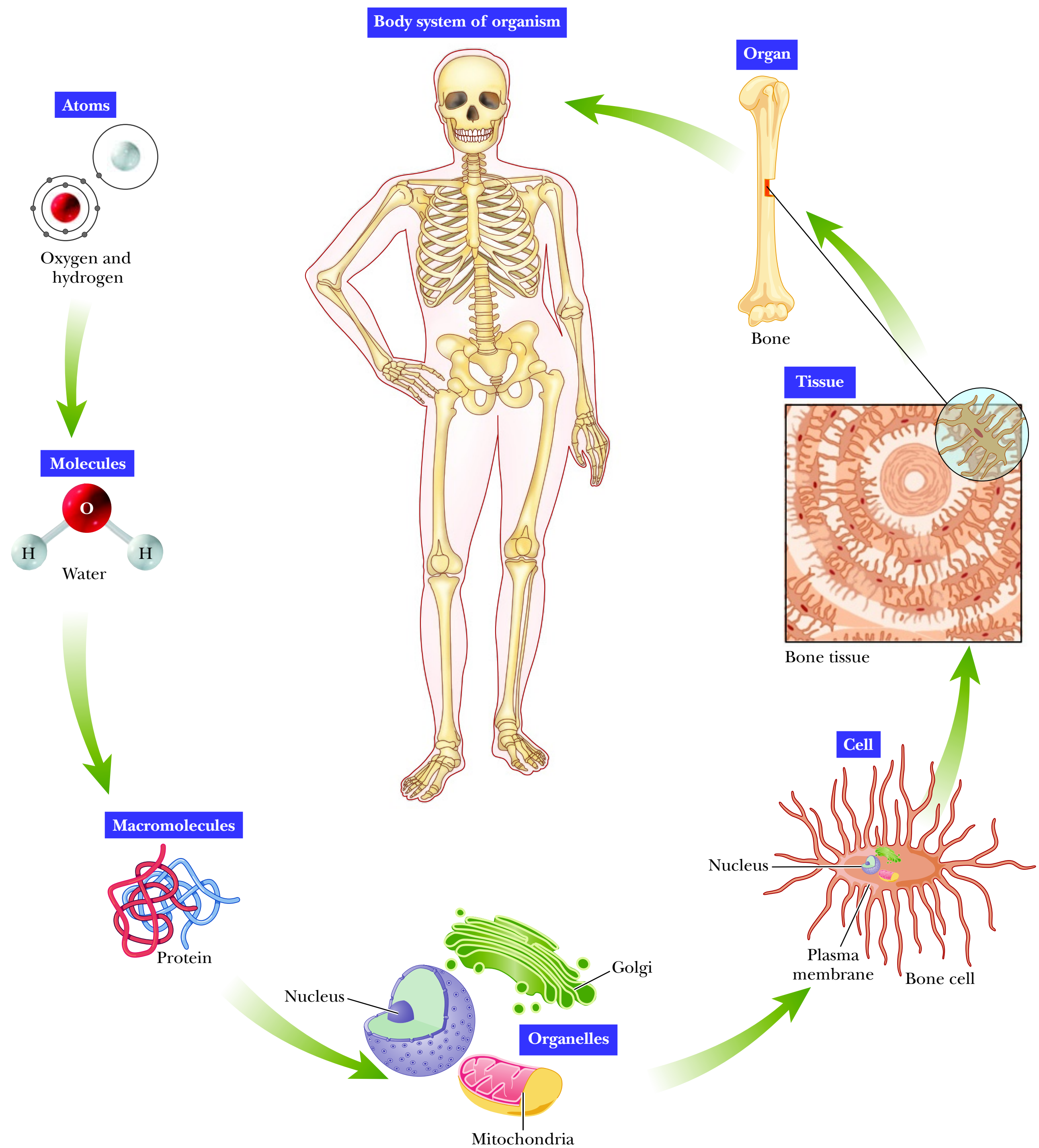


Figure 1.1 **Levels of structural organization in the human body.** Note the hierarchy from simple to complex.

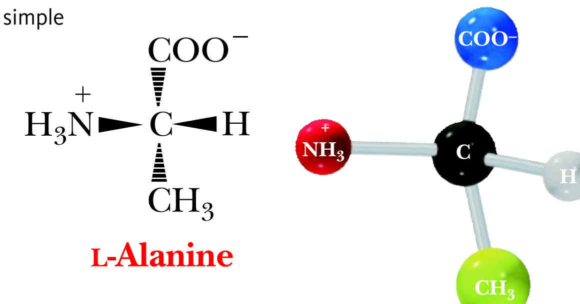


Figure 1.2 **Basic structure of the amino acid, alanine.**

the R group. It is the difference between the R groups that makes each amino acid unique.

Carbohydrates

Carbohydrates are compounds made up of carbon, hydrogen, and oxygen, with a general formula of $(CH_2O)_n$, where n is at least 3. The simplest forms are called monosaccharides, or sugars. The most common

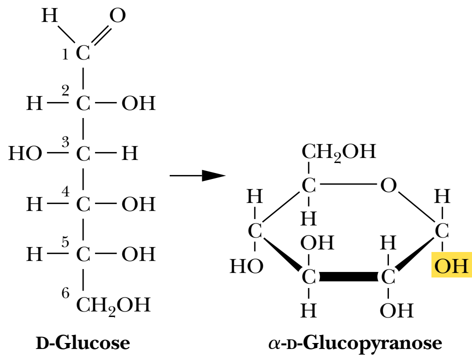


Figure 1.3 Straight chain and cyclic depictions of glucose, the most common monosaccharide.

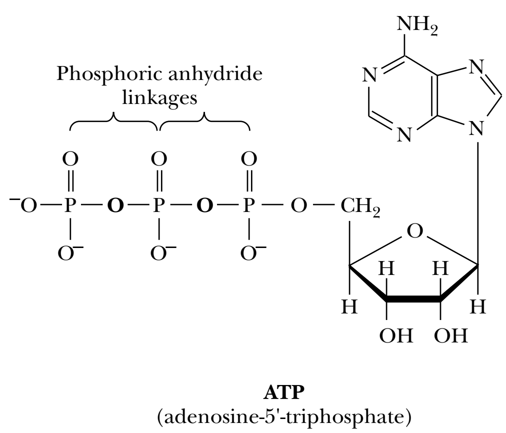


Figure 1.4 The structure of ATP, an important nucleotide in energy production.

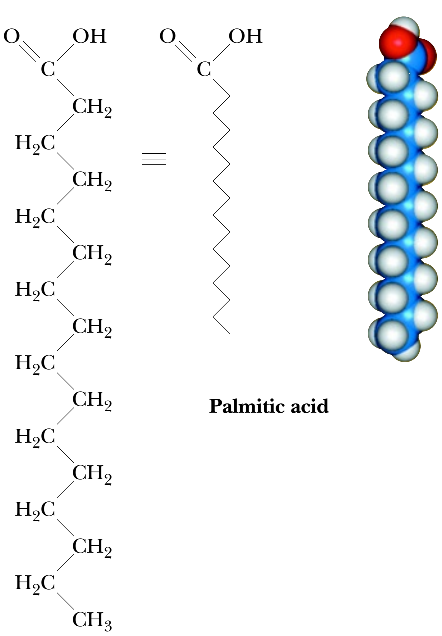


Figure 1.5 The simple lipid palmitic acid, shown with a structural formula, an abbreviated formula, and a space-filling model.

functional groups groups of atoms that give rise to the characteristic reactions of organic compounds

monosaccharide is glucose, which has the formula $C_6H_{12}O_6$, as shown in Figure 1.3. For convenience, sugars are often drawn as a straight chain, but in solution they form cyclic structures. Simple sugars often make up much larger polymers and are used for energy storage and structural components.

Nucleotides

Nucleotides are the basic unit of the hereditary materials DNA and RNA. They also form the molecular currency of the cell, adenosine triphosphate (ATP). A nucleotide is composed of a five-carbon sugar, a nitrogen-containing ring, and one or more phosphate groups. The important nucleotide, ATP, is shown in Figure 1.4. It is composed of the nitrogenous base adenine, the sugar ribose, and three phosphates.

Lipids

The fourth major group of biochemicals consists of lipids. They are the most diverse and cannot be shown with a simple structure common to all lipids. However, they all have the common trait that they are poorly soluble in water. This is because most of their structure is composed of long chains of hydrocarbons. A simple lipid is palmitic acid, which has 16 carbons. There are several ways to depict such a lipid, as shown in Figure 1.5.

Another important lipid you have heard of is cholesterol, shown in Figure 1.6. It differs considerably in its structure from palmitic acid, but is still very insoluble in water due to the chains of carbon and the fact that it has only a single oxygen molecule in it.

▶ *Can a chemist make the molecules of life in a laboratory?*

Until the early part of the 19th century, there was a widely held belief in "vital forces," forces presumably unique to living things. This belief included the idea that the compounds found in living organisms could not be produced in the laboratory. German chemist Friedrich Wöhler performed the critical experiment that disproved this belief in 1828. Wöhler synthesized urea, a well-known waste product of animal metabolism, from ammonium cyanate, a compound obtained from mineral (i.e., nonliving) sources.

$$NH_4OCN \rightarrow H_2NCONH_2$$

Ammonium cyanate → Urea

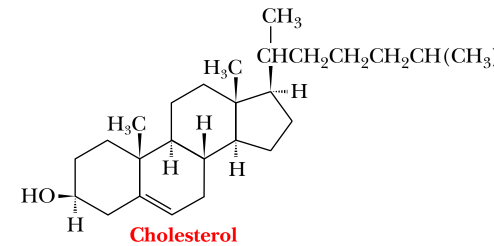
It has subsequently been shown that any compound that occurs in a living organism can be synthesized in the laboratory, although in many cases the synthesis represents a considerable challenge to even the most skilled organic chemist.

The reactions of biomolecules can be described by the methods of organic chemistry, which requires the classification of compounds according to their **functional groups**. *The reactions of molecules are based on the reactions of their respective functional groups.*

Functional Groups Important in Biochemistry

Table 1.1 lists some biologically important functional groups. Note that most of these functional groups contain oxygen and nitrogen, which are among the most electronegative elements. As a result, many of these functional groups are polar, and their polar nature plays a crucial role in their reactivity. Some groups that are vitally important to organic chemists are missing from the table because molecules containing these groups, such as alkyl halides and acyl chlorides, do not have any particular applicability in biochemistry. Conversely, carbon-containing derivatives of phosphoric acid are mentioned infrequently in beginning courses on organic chemistry, but esters and anhydrides of phosphoric acid (Figure 1.7) are of vital importance in biochemistry. ATP, a molecule that is the energy currency of the cell, contains both ester and anhydride linkages involving phosphoric acid.

Important classes of biomolecules have characteristic functional groups that determine their reactions. We shall discuss the reactions of the functional groups when we consider the compounds in which they occur.



Cholesterol

Figure 1.6 The structure of cholesterol, an important lipid in biological membranes.

Table 1.1 Functional Groups of Biochemical Importance

Class of Compound	General Structure	Characteristic Functional Group	Name of Functional Group	Example
Alkenes	$RCH{=}CH_2$ $RCH{=}CHR$ $R_2C{=}CHR$ $R_2C{=}CR_2$	$C{=}C$	**Double bond**	$CH_2{=}CH_2$
Alcohols	ROH	—OH	**Hydroxyl group**	CH_3CH_2OH
Ethers	ROR	—O—	**Ether group**	CH_3OCH_3
Amines	RNH_2 R_2NH R_3N	$-N<$	**Amino group**	CH_3NH_2
Thiols	RSH	—SH	**Sulfhydryl group**	CH_3SH
Aldehydes	$R{-}C({=}O){-}H$	$-C({=}O)-$	**Carbonyl group**	$CH_3C({=}O)H$
Ketones	$R{-}C({=}O){-}R$	$-C({=}O)-$	**Carbonyl group**	$CH_3C({=}O)CH_3$
Carboxylic acids	$R{-}C({=}O){-}OH$	$-C({=}O){-}OH$	**Carboxyl group**	$CH_3C({=}O)OH$
Esters	$R{-}C({=}O){-}OR$	$-C({=}O){-}OR$	**Ester group**	$CH_3C({=}O)OCH_3$
Amides	$R{-}C({=}O){-}NR_2$ $R{-}C({=}O){-}NHR$ $R{-}C({=}O){-}NH_2$	$-C({=}O){-}N<$	**Amide group**	$CH_3C({=}O)N(CH_3)_2$
Phosphoric acid esters	$R{-}O{-}P({=}O)(OH){-}OH$	$-O{-}P({=}O)(OH){-}OH$	**Phosphoric ester group**	$CH_3{-}O{-}P({=}O)(OH){-}OH$
Phosphoric acid anhydrides	$R{-}O{-}P({=}O)(OH){-}O{-}P({=}O)(OH){-}OH$	$-P({=}O)(OH){-}O{-}P({=}O)(OH)-$	**Phosphoric anhydride group**	$HO{-}P({=}O)(OH){-}O{-}P({=}O)(OH){-}OH$

1 Reaction of phosphoric acid with a hydroxyl group to form an ester, which contains a P-O-R linkage. Phosphoric acid is shown in its nonionized form in this figure. Space-filling models of phosphoric acid and its methyl ester are shown. The red spheres represent oxygen; the white, hydrogen; the green, carbon; and the orange, phosphorus.

2 Reaction of two molecules of phosphoric acid to form an anhydride, which contains a P-O-P linkage. A space-filling model of the anhydride of phosphoric acid is shown.

3 The structure of ATP (adenosine triphosphate), showing two anhydride linkages and one ester.

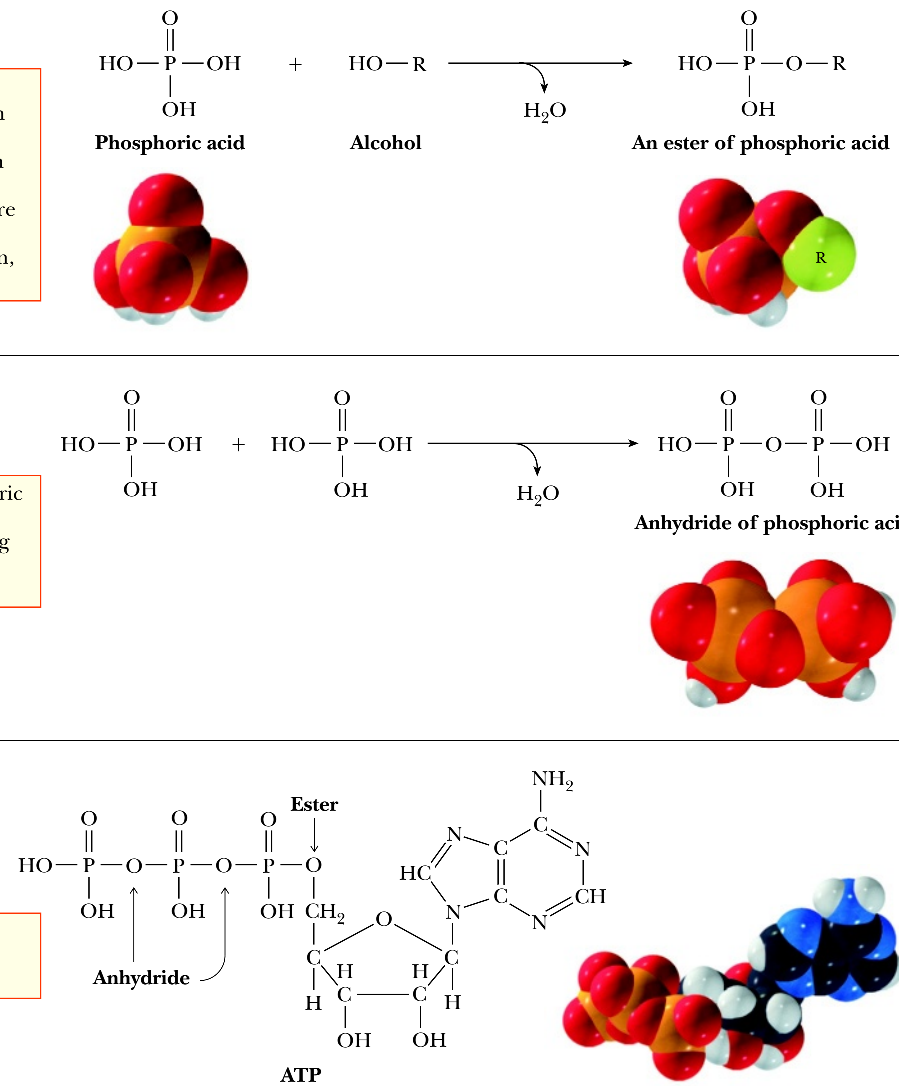


Figure 1.7 ATP and the reactions for its formation.

1-3 The Beginnings of Biology

The Earth and Its Age

Although humans in general and science fiction writers in particular are fascinated by the idea of life on other planets, to date, we are aware of only one planet that unequivocally supports life: our own. The Earth and its waters are universally understood to be the source and mainstay of life as we know it. A natural first question is how the Earth, along with the Universe of which it is a part, came to be.

▶ ***How and when did the Earth come to be?***

Currently, the most widely accepted cosmological theory for the origin of the Universe is the *big bang*, a cataclysmic explosion. According to big-bang cosmology, all the matter in the Universe was originally confined to a comparatively small volume of space. As a result of a tremendous explosion, this "primordial fireball" started to expand with great force. Immediately after the big bang, the Universe was extremely hot, on the order of 15 billion

(15×10^9) K. (Note that Kelvin temperatures are written without a degree symbol.) The average temperature of the Universe has been decreasing ever since as a result of expansion, and the lower temperatures have permitted the formation of stars and planets. In its earliest stages, the Universe had a fairly simple composition. Hydrogen, helium, and some lithium (the three smallest and simplest elements on the periodic table) were present, having been formed in the original big-bang explosion. The rest of the chemical elements are thought to have been formed in three ways: (1) by thermonuclear reactions that normally take place in stars, (2) in explosions of stars, and (3) by the action of cosmic rays outside the stars since the formation of the galaxy. The process by which the elements are formed in stars is a topic of interest to chemists as well as to astrophysicists. For our purposes, note that the most abundant isotopes of biologically important elements such as carbon, oxygen, nitrogen, phosphorus, and sulfur have *particularly stable nuclei.* These elements were produced by nuclear reactions in first-generation stars, the original stars produced after the beginning of the Universe (Table 1.2). Many first-generation stars were destroyed by explosions called *supernovas,* and their stellar material was recycled to produce second-generation stars, such as our own Sun, along with our solar system. Radioactive dating, which uses the decay of unstable nuclei, indicates that the age of the Earth (and the rest of the solar system) is 4 billion to 5 billion $(4 \times 10^9$ to $5 \times 10^9)$ years. The atmosphere of the early Earth was very different from the one we live in, and it probably went through several stages before reaching its current composition. The most important difference is that, according to most theories of the origins of the Earth, very little or no free oxygen (O_2) existed in the early stages (Figure 1.8). The early Earth was constantly irradiated with ultraviolet light from the Sun because there was no ozone (O_3) layer in the atmosphere to block it. Under these conditions, the chemical reactions that produced simple biomolecules took place.

The gases usually postulated to have been present in the atmosphere of the early Earth include NH_3, H_2S, CO, CO_2, CH_4, N_2, H_2, and (in both liquid and vapor forms) H_2O. However, there is less agreement on the relative amounts of these components, from which biomolecules ultimately arose. Many of the earlier theories of the origin of life postulated CH_4 as

Table 1.2 Abundance of Important Elements Relative to Carbon*

Element	Abundance in Organisms	Abundance in Universe
Hydrogen	80–250	10,000,000
Carbon	1,000	1,000
Nitrogen	60–300	1,600
Oxygen	500–800	5,000
Sodium	10–20	12
Magnesium	2–8	200
Phosphorus	8–50	3
Sulfur	4–20	80
Potassium	6–40	0.6
Calcium	25–50	10
Manganese	0.25–0.8	1.6
Iron	0.25–0.8	100
Zinc	0.1–0.4	0.12

*Each abundance is given as the number of atoms relative to a thousand atoms of carbon.

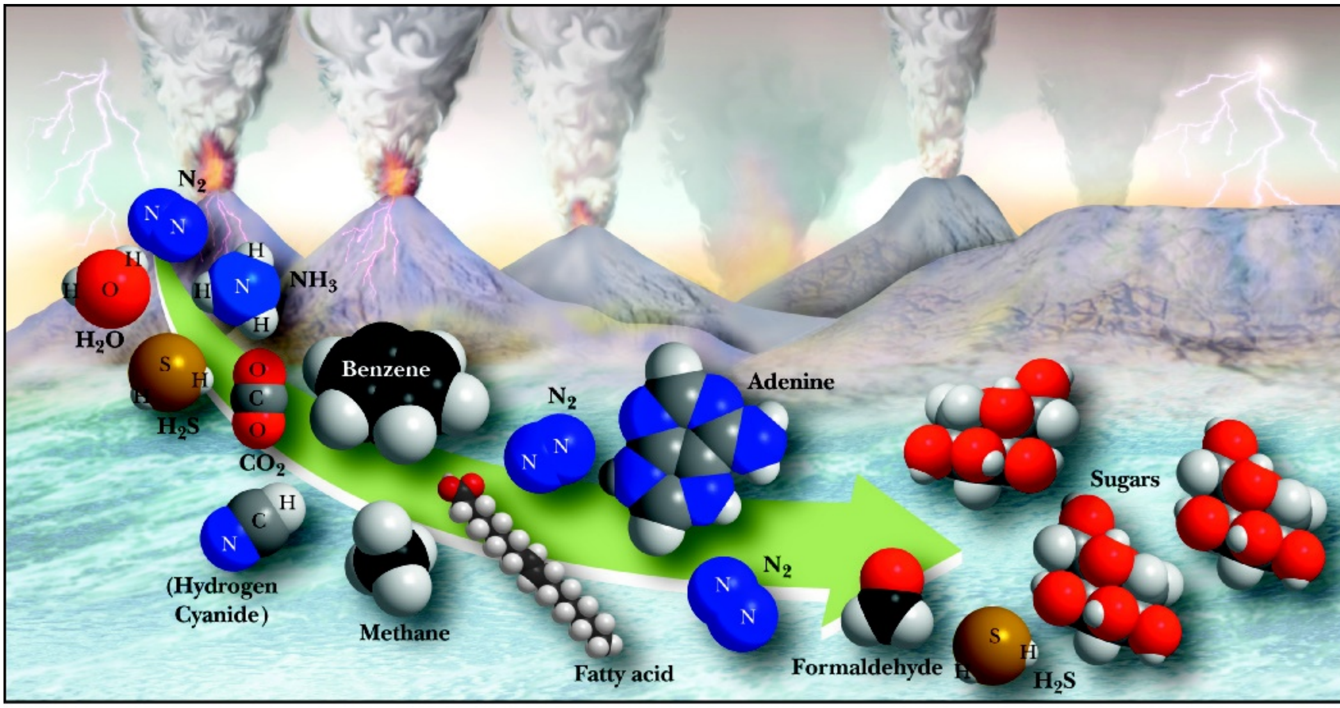


Figure 1.8 Formation of biomolecules on the early Earth. Conditions on early Earth would have been inhospitable for most of today's life. Very little or no oxygen (O_2) existed. Volcanoes erupted, spewing gases, and violent thunderstorms produced torrential rainfall that covered the Earth. The green arrow indicates the formation of biomolecules from simple precursors.

the carbon source, but more recent studies have shown that appreciable amounts of CO_2 must have existed in the atmosphere at least 3.8 billion (3.8×10^9) years ago.

This conclusion is based on geological evidence: The earliest known rocks are 3.8 billion years old, and they are carbonates, which arise from CO_2. Any NH_3 originally present must have dissolved in the oceans, leaving N_2 in the atmosphere as the nitrogen source required for the formation of proteins and nucleic acids.

Biomolecules

▶ ***How were biomolecules likely to have formed on the early Earth?***

Experiments have been performed in which the simple compounds of the early atmosphere were allowed to react under the varied sets of conditions that might have been present on the early Earth. The results of such experiments indicate that these simple compounds react *abiotically* or, as the word indicates (*a,* "not," and *bios,* "life"), in the absence of life, to give rise to biologically important compounds such as the components of proteins and nucleic acids. Of historic interest is the well-known Miller–Urey experiment. In each trial, an electric discharge, simulating lightning, is passed through a closed system that contains H_2, CH_4, and NH_3, in addition to H_2O. Simple organic molecules, such as formaldehyde (HCHO) and hydrogen cyanide (HCN), are typical products of such reactions, as are amino acids, the building blocks of proteins. According to one theory, reactions such as these took place in the Earth's early oceans; other researchers postulate that such reactions occurred on the surfaces of clay particles that were present on the early Earth. It is certainly true that mineral substances similar to clay can serve as catalysts in many types of reactions. Recent theories of the origin of life focus on RNA, not proteins, as the first genetic molecules. Proteins are thought to have developed later in the evolution of the earliest cells. This point does not diminish the importance of this first experiment on abiotic synthesis of biomolecules.

Recent experiments have shown it is possible to synthesize nucleotides from simple molecules by a pathway that includes a precursor that is neither a sugar nor a nucleobase, but a fragment consisting of a sugar and a part of a base. This fragment, 2-aminooxazole, is highly volatile and can vaporize and condense so as to give rise to pockets of pure material in reasonably large amounts. In turn, phosphates released by volcanic action can react with the 2-aminooxazole to produce nucleotides (Figure 1.9). The products include nucleotides that are not part of present-day RNA, but intense ultraviolet light, which was present on the early Earth, destroyed those nucleotides, leaving those found in RNA today.

Living cells today are assemblages that include very large molecules, such as proteins, nucleic acids, and polysaccharides. These molecules are larger by

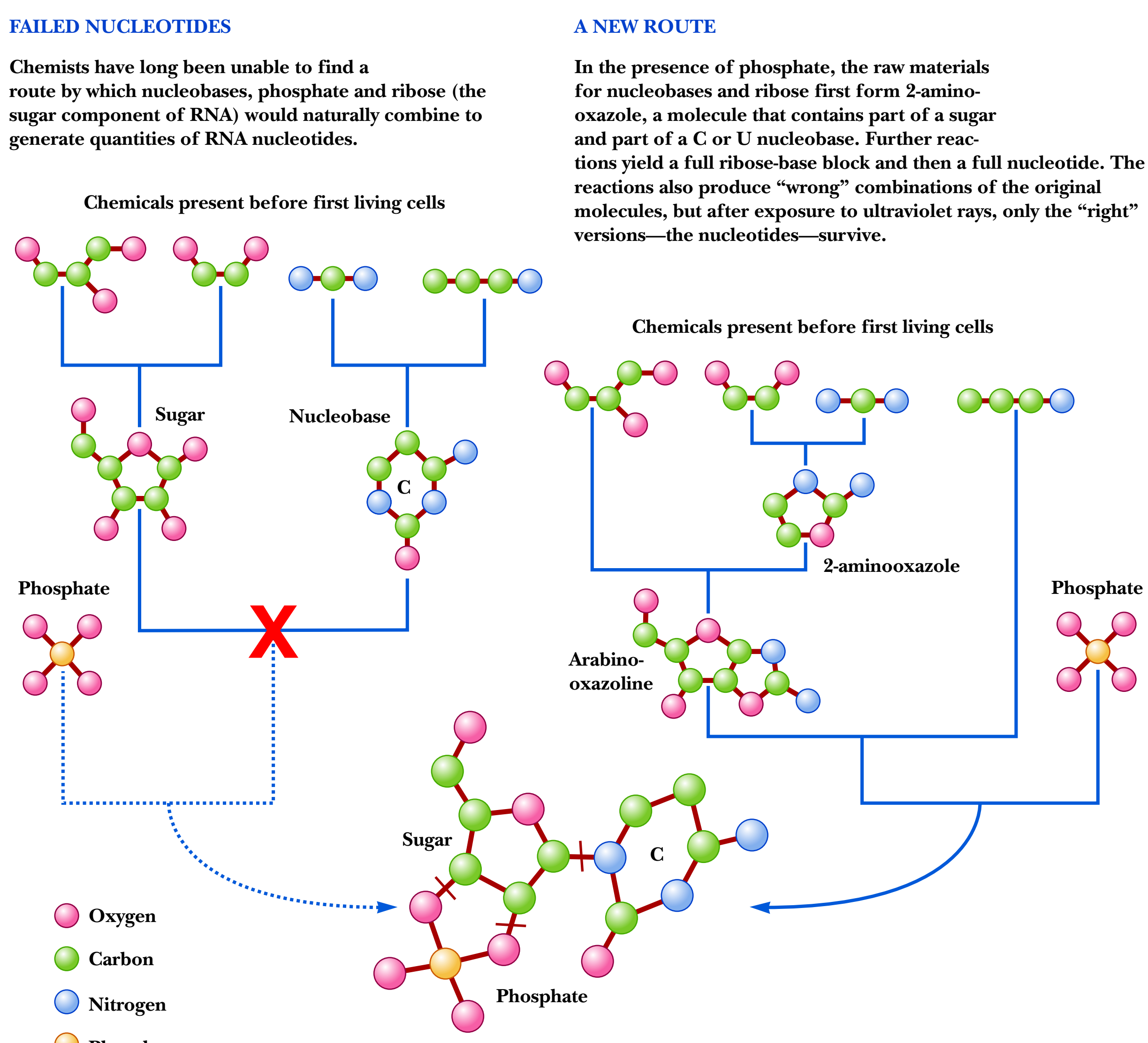


Figure 1.9 Abiotic synthesis of nucleotides. The volatile compound 2-aminooxazole is a key intermediate that eventually gives rise to nucleotides. *(Copyright © Andrew Swift)*