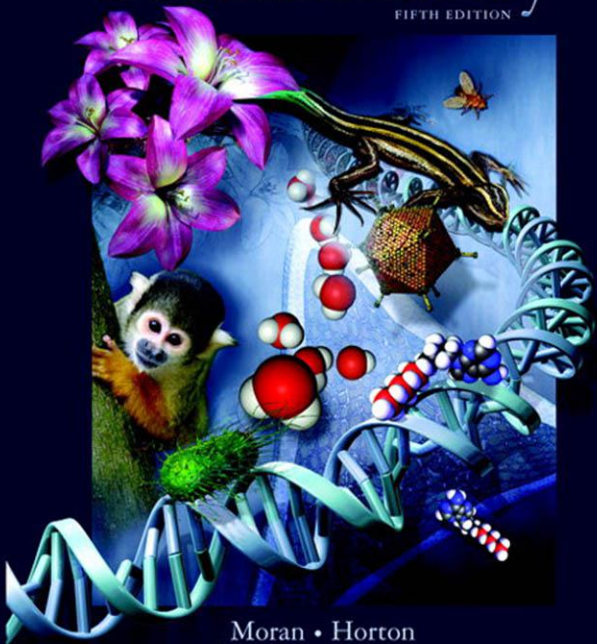


PRINCIPLES OF
Biochemistry
FIFTH EDITION



Moran • Horton
Scrimgeour • Perry

This page intentionally left blank

Principles of Biochemistry

This page intentionally left blank

Principles of Biochemistry

Fifth Edition



Laurence A. Moran

University of Toronto

H. Robert Horton

North Carolina State University

K. Gray Scrimgeour

University of Toronto

Marc D. Perry

University of Toronto

PEARSON

Boston Columbus Indianapolis New York San Francisco Upper Saddle River
Amsterdam Cape Town Dubai London Madrid Milan Munich Paris Montréal Toronto
Delhi Mexico City Sao Paulo Sydney Hong Kong Seoul Singapore Taipei Tokyo

Editor in Chief: Adam Jaworski
Executive Editor: Jeanne Zalesky
Marketing Manager: Erin Gardner
Project Editor: Jennifer Hart
Associate Editor: Jessica Neumann
Editorial Assistant: Lisa Tarabokjia
Marketing Assistant: Nicola Houston
Vice President, Executive Director of Development: Carol Truehart
Developmental Editor: Michael Sypes
Managing Editor, Chemistry and Geosciences: Gina M. Cheselka
Project Manager, Science: Wendy Perez
Senior Technical Art Specialist: Connie Long
Art Studios: Mark Landis Illustrations
/Jonathan Parrish
/2064 Design—Greg Gambino
Image Resource Manager: Maya Melenchuk
Photo Researcher: Eric Schrader
Art Manager: Marilyn Perry
Interior/Cover Designer: Tamara Newnam
Media Project Manager: Shannon Kong
Senior Manufacturing and Operations Manager: Nick Sklitsis
Operations Specialist: Maura Zaldivar
Composition/Full Service: Nesbitt Graphics, Inc.

Cover Illustration: Quade Paul, Echo Medical Media
Cover Image Credit: Monkey adapted from Simone van den Berg/Shutterstock

Credits and acknowledgments borrowed from other sources and reproduced, with permission, in this textbook appear on page 767.

Copyright ©2012, 2006, 2002, 1996 Pearson Education, Inc., All rights reserved. Manufactured in the United States of America. This publication is protected by Copyright and permission should be obtained from the publisher prior to any prohibited reproduction, storage in a retrieval system, or transmission in any form or by any means, electronic, mechanical, photocopying, recording, or likewise. To obtain permission(s) to use material from this work, please submit a written request to Pearson Education, Inc., Permissions Department, 1900 E. Lake Ave., Glenview, IL 60025. For information regarding permissions, call (847) 486-2635.

Many of the designations used by manufacturers and sellers to distinguish their products are claimed as trademarks. Where those designations appear in this book, and the publisher was aware of a trademark claim, the designations have been printed in initial caps or all caps.

Library of Congress Cataloging-in-Publication Data

Principles of biochemistry / H. Robert Horton ... [et al]. — 5th ed.

p. cm.

ISBN 0-321-70733-8

1. Biochemistry. I. Horton, H. Robert, 1935-

QP514.2.P745 2012

612'.015—dc23

2011019987

ISBN 10: 0-321-70733-8

ISBN 13: 978-0-321-70733-8

1 2 3 4 5 6 7 8 9 10—DOW—16 15 14 13 12



www.pearsonhighered.com

*Science should be as simple as possible,
but not simpler.*

– Albert Einstein

This page intentionally left blank

Brief Contents

Part One

Introduction

- 1 Introduction to Biochemistry 1
- 2 Water 28

Part Two

Structure and Function

- 3 Amino Acids and the Primary Structures of Proteins 55
- 4 Proteins: Three-Dimensional Structure and Function 85
- 5 Properties of Enzymes 134
- 6 Mechanisms of Enzymes 162
- 7 Coenzymes and Vitamins 196
- 8 Carbohydrates 227
- 9 Lipids and Membranes 256

Part Three

Metabolism and Bioenergetics

- 10 Introduction to Metabolism 294
- 11 Glycolysis 325
- 12 Gluconeogenesis, the Pentose Phosphate Pathway, and Glycogen Metabolism 355
- 13 The Citric Acid Cycle 385
- 14 Electron Transport and ATP Synthesis 417
- 15 Photosynthesis 443
- 16 Lipid Metabolism 475
- 17 Amino Acid Metabolism 514
- 18 Nucleotide Metabolism 550

Part Four

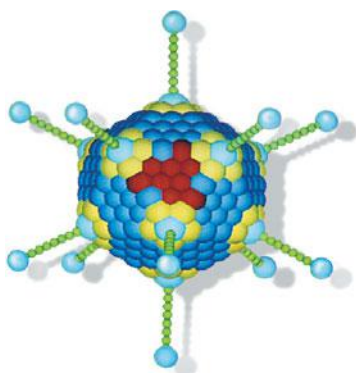
Biological Information Flow

- 19 Nucleic Acids 573
- 20 DNA Replication, Repair, and Recombination 601
- 21 Transcription and RNA Processing 634
- 22 Protein Synthesis 666

Contents

To the Student	xxiii
Preface	xxv
About the Authors	xxxiii

Part One Introduction



1	Introduction to Biochemistry	1
1.1	Biochemistry Is a Modern Science	2
1.2	The Chemical Elements of Life	3
1.3	Many Important Macromolecules Are Polymers	4
	A. Proteins	6
	B. Polysaccharides	6
	C. Nucleic Acids	7
	D. Lipids and Membranes	9
1.4	The Energetics of Life	10
	A. Reaction Rates and Equilibria	11
	B. Thermodynamics	12
	C. Equilibrium Constants and Standard Gibbs Free Energy Changes	13
	D. Gibbs Free Energy and Reaction Rates	14
1.5	Biochemistry and Evolution	15
1.6	The Cell Is the Basic Unit of Life	17
1.7	Prokaryotic Cells: Structural Features	17
1.8	Eukaryotic Cells: Structural Features	18
	A. The Nucleus	20
	B. The Endoplasmic Reticulum and Golgi Apparatus	20
	C. Mitochondria and Chloroplasts	21
	D. Specialized Vesicles	22
	E. The Cytoskeleton	23
1.9	A Picture of the Living Cell	23
1.10	Biochemistry Is Multidisciplinary	26
	Appendix: The Special Terminology of Biochemistry	26
	Selected Readings	27

2	Water	28
2.1	The Water Molecule Is Polar	29
2.2	Hydrogen Bonding in Water	30
	Box 2.1 Extreme Thermophiles	32
2.3	Water Is an Excellent Solvent	32
	A. Ionic and Polar Substances Dissolve in Water	32
	Box 2.2 Blood Plasma and Seawater	33
	B. Cellular Concentrations and Diffusion	34
	C. Osmotic Pressure	34
2.4	Nonpolar Substances Are Insoluble in Water	35



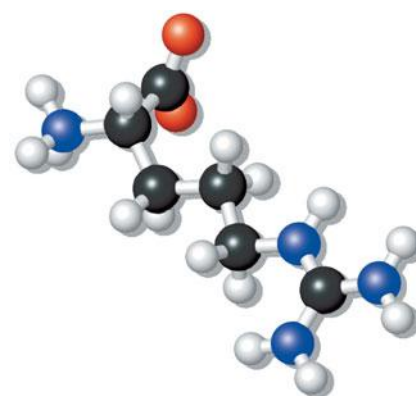
2.5	Noncovalent Interactions	37
	A. Charge–Charge Interactions	37
	B. Hydrogen Bonds	37
	C. Van der Waals Forces	38
	D. Hydrophobic Interactions	39
2.6	Water Is Nucleophilic	39
	Box 2.3 The Concentration of Water	41
2.7	Ionization of Water	41
2.8	The pH Scale	43
	Box 2.4 The Little “p” in pH	44
2.9	Acid Dissociation Constants of Weak Acids	44
	Sample Calculation 2.1 Calculating the pH of Weak Acid Solutions	49
2.10	Buffered Solutions Resist Changes in pH	50
	Sample Calculation 2.2 Buffer Preparation	50
	Summary	52
	Problems	52
	Selected Readings	54

PART TWO

Structure and Function

3 Amino Acids and the Primary Structures of Proteins 55

3.1	General Structure of Amino Acids	56
3.2	Structures of the 20 Common Amino Acids	58
	Box 3.1 Fossil Dating by Amino Acid Racemization	58
	A. Aliphatic R Groups	59
	B. Aromatic R Groups	59
	C. R Groups Containing Sulfur	60
	D. Side Chains with Alcohol Groups	60
	Box 3.2 An Alternative Nomenclature	61
	E. Positively Charged R Groups	61
	F. Negatively Charged R Groups and Their Amide Derivatives	62
	G. The Hydrophobicity of Amino Acid Side Chains	62
3.3	Other Amino Acids and Amino Acid Derivatives	62
3.4	Ionization of Amino Acids	63
	Box 3.3 Common Names of Amino Acids	64
3.5	Peptide Bonds Link Amino Acids in Proteins	67
3.6	Protein Purification Techniques	68
3.7	Analytical Techniques	70
3.8	Amino Acid Composition of Proteins	73
3.9	Determining the Sequence of Amino Acid Residues	74
3.10	Protein Sequencing Strategies	76
3.11	Comparisons of the Primary Structures of Proteins Reveal Evolutionary Relationships	79
	Summary	82
	Problems	82
	Selected Readings	84



4 Proteins: Three-Dimensional Structure and Function 85

4.1	There Are Four Levels of Protein Structure	87
4.2	Methods for Determining Protein Structure	88

4.3 The Conformation of the Peptide Group 91
Box 4.1 Flowering Is Controlled by *Cis/Trans* Switches 93

4.4 The α Helix 94

4.5 β Strands and β Sheets 97

4.6 Loops and Turns 98

4.7 Tertiary Structure of Proteins 99
 A. Supersecondary Structures 100
 B. Domains 101
 C. Domain Structure, Function, and Evolution 102
 D. Intrinsically Disordered Proteins 102

4.8 Quaternary Structure 103

4.9 Protein–Protein Interactions 109

4.10 Protein Denaturation and Renaturation 110

4.11 Protein Folding and Stability 114
 A. The Hydrophobic Effect 114
 B. Hydrogen Bonding 115
Box 4.2 CASP: The Protein Folding Game 116
 C. Van der Waals Interactions and Charge–Charge Interactions 117
 D. Protein Folding Is Assisted by Molecular Chaperones 117

4.12 Collagen, a Fibrous Protein 119
Box 4.3 Stronger Than Steel 121

4.13 Structure of Myoglobin and Hemoglobin 122

4.14 Oxygen Binding to Myoglobin and Hemoglobin 123
 A. Oxygen Binds Reversibly to Heme 123
 B. Oxygen-Binding Curves of Myoglobin and Hemoglobin 124
Box 4.4 Embryonic and Fetal Hemoglobins 126
 C. Hemoglobin Is an Allosteric Protein 127

4.15 Antibodies Bind Specific Antigens 129
 Summary 130
 Problems 131
 Selected Readings 133



5 Properties of Enzymes 134

5.1 The Six Classes of Enzymes 136
Box 5.1 Enzyme Classification Numbers 137

5.2 Kinetic Experiments Reveal Enzyme Properties 138
 A. Chemical Kinetics 138
 B. Enzyme Kinetics 139

5.3 The Michaelis-Menten Equation 140
 A. Derivation of the Michaelis-Menten Equation 141
 B. The Catalytic Constant K_{cat} 143
 C. The Meanings of K_m 144

5.4 Kinetic Constants Indicate Enzyme Activity and Catalytic Proficiency 144

5.5 Measurement of K_m and V_{max} 145
Box 5.2 Hyperbolas Versus Straight Lines 146

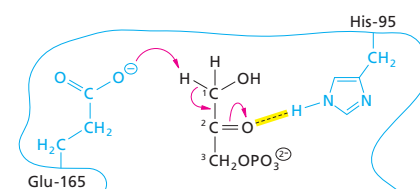
5.6 Kinetics of Multisubstrate Reactions 147

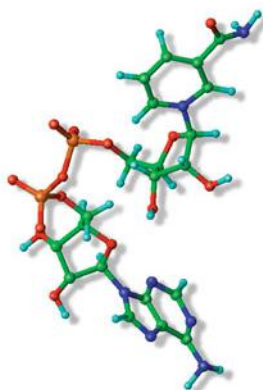
5.7 Reversible Enzyme Inhibition 148
 A. Competitive Inhibition 149
 B. Uncompetitive Inhibition 150

C.	Noncompetitive Inhibition	150
D.	Uses of Enzyme Inhibition	151
5.8	Irreversible Enzyme Inhibition	152
5.9	Regulation of Enzyme Activity	153
A.	Phosphofructokinase Is an Allosteric Enzyme	154
B.	General Properties of Allosteric Enzymes	155
C.	Two Theories of Allosteric Regulation	156
D.	Regulation by Covalent Modification	158
5.10	Multienzyme Complexes and Multifunctional Enzymes	158
	Summary	159
	Problems	159
	Selected Readings	161

6 Mechanisms of Enzymes 162

6.1	The Terminology of Mechanistic Chemistry	162
A.	Nucleophilic Substitutions	163
B.	Cleavage Reactions	163
C.	Oxidation–Reduction Reactions	164
6.2	Catalysts Stabilize Transition States	164
6.3	Chemical Modes of Enzymatic Catalysis	166
A.	Polar Amino Acids Residues in Active Sites	166
	Box 6.1 Site-Directed Mutagenesis Modifies Enzymes	167
B.	Acid–Base Catalysis	168
C.	Covalent Catalysis	169
D.	pH Affects Enzymatic Rates	170
6.4	Diffusion-Controlled Reactions	171
A.	Triose Phosphate Isomerase	172
	Box 6.2 The “Perfect Enzyme”?	174
B.	Superoxide Dismutase	175
6.5	Modes of Enzymatic Catalysis	175
A.	The Proximity Effect	176
B.	Weak Binding of Substrates to Enzymes	178
C.	Induced Fit	179
D.	Transition State Stabilization	180
6.6	Serine Proteases	183
A.	Zymogens Are Inactive Enzyme Precursors	183
	Box 6.3 Kornberg’s Ten Commandments	183
B.	Substrate Specificity of Serine Proteases	184
C.	Serine Proteases Use Both the Chemical and the Binding Modes of Catalysis	185
	Box 6.4 Clean Clothes	186
	Box 6.5 Convergent Evolution	187
6.7	Lysozyme	187
6.8	Arginine Kinase	190
	Summary	192
	Problems	193
	Selected Readings	194





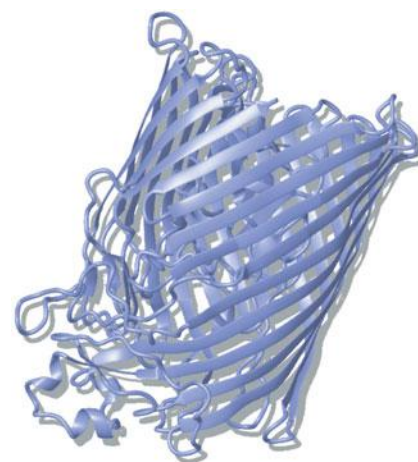
7	Coenzymes and Vitamins	196
7.1	Many Enzymes Require Inorganic Cations	197
7.2	Coenzyme Classification	197
7.3	ATP and Other Nucleotide Cosubstrates	198
	Box 7.1 Missing Vitamins	200
7.4	NAD ⁺ and NADP ⁺	200
	Box 7.2 NAD Binding to Dehydrogenases	203
7.5	FAD and FMN	204
7.6	Coenzyme A and Acyl Carrier Protein	204
7.7	Thiamine Diphosphate	206
7.8	Pyridoxal Phosphate	207
7.9	Vitamin C	209
7.10	Biotin	211
	Box 7.3 One Gene: One Enzyme	212
7.11	Tetrahydrofolate	213
7.12	Cobalamin	215
7.13	Lipoamide	216
7.14	Lipid Vitamins	217
	A. Vitamin A	217
	B. Vitamin D	218
	C. Vitamin E	218
	D. Vitamin K	218
7.15	Ubiquinone	219
	Box 7.4 Rat Poison	220
7.16	Protein Coenzymes	221
7.17	Cytochromes	221
	Box 7.5 Noble Prizes for Vitamins and Coenzymes	223
	Summary	223
	Problems	224
	Selected Readings	226
8	Carbohydrates	227
8.1	Most Monosaccharides Are Chiral Compounds	228
8.2	Cyclization of Aldoses and Ketoses	230
8.3	Conformations of Monosaccharides	234
8.4	Derivatives of Monosaccharides	235
	A. Sugar Phosphates	235
	B. Deoxy Sugars	235
	C. Amino Sugars	235
	D. Sugar Alcohols	236
	E. Sugar Acids	236
8.5	Disaccharides and Other Glycosides	236
	A. Structures of Disaccharides	237
	B. Reducing and Nonreducing Sugars	238
	C. Nucleosides and Other Glycosides	239
	Box 8.1 The Problem with Cats	240
8.6	Polysaccharides	240
	A. Starch and Glycogen	240
	B. Cellulose	243



- C. Chitin **244**
- 8.7 Glycoconjugates **244**
 - A. Proteoglycans **244**
 - Box 8.2** Nodulation Factors Are Lipo-Oligosaccharides **246**
 - B. Peptidoglycans **246**
 - C. Glycoproteins **248**
 - Box 8.3** ABO Blood Group **250**
 - Summary **252**
 - Problems **253**
 - Selected Readings **254**

9 Lipids and Membranes **256**

- 9.1 Structural and Functional Diversity of Lipids **256**
- 9.2 Fatty Acids **256**
 - Box 9.1** Common Names of Fatty Acids **258**
 - Box 9.2** *Trans* Fatty Acids and Margarine **259**
- 9.3 Triacylglycerols **261**
- 9.4 Glycerophospholipids **262**
- 9.5 Sphingolipids **263**
- 9.6 Steroids **266**
- 9.7 Other Biologically Important Lipids **268**
- 9.8 Biological Membranes **269**
 - A. Lipid Bilayers **269**
 - Box 9.3** Gregor Mendel and Gibberellins **270**
 - B. Three Classes of Membrane Proteins **270**
 - Box 9.4** New Lipid Vesicles, or Liposomes **272**
 - Box 9.5** Some Species Have Unusual Lipids in Their Membranes **274**
 - C. The Fluid Mosaic Model of Biological Membranes **274**
- 9.9 Membranes Are Dynamic Structures **275**
- 9.10 Membrane Transport **277**
 - A. Thermodynamics of Membrane Transport **278**
 - B. Pores and Channels **279**
 - C. Passive Transport and Facilitated Diffusion **280**
 - D. Active Transport **282**
 - E. Endocytosis and Exocytosis **283**
- 9.11 Transduction of Extracellular Signals **283**
 - A. Receptors **283**
 - Box 9.6** The Hot Spice of Chili Peppers **284**
 - B. Signal Transducers **285**
 - C. The Adenylyl Cyclase Signaling Pathway **287**
 - D. The Inositol–Phospholipid Signaling Pathway **287**
 - Box 9.7** Bacterial Toxins and G Proteins **290**
 - E. Receptor Tyrosine Kinases **290**
 - Summary **291**
 - Problems **292**
 - Selected Readings **293**





PART THREE

Metabolism and Bioenergetics

10	Introduction to Metabolism	294
10.1	Metabolism Is a Network of Reactions	294
10.2	Metabolic Pathways	297
	A. Pathways Are Sequences of Reactions	297
	B. Metabolism Proceeds by Discrete Steps	297
	C. Metabolic Pathways Are Regulated	297
	D. Evolution of Metabolic Pathways	301
10.3	Major Pathways in Cells	302
10.4	Compartmentation and Interorgan Metabolism	304
10.5	Actual Gibbs Free Energy Change, Not Standard Free Energy Change, Determines the Direction of Metabolic Reactions	306
	Sample Calculation 10.1 Calculating Standard Gibbs Free Energy Change from Energies of Formation	308
10.6	The Free Energy of ATP Hydrolysis	308
10.7	The Metabolic Roles of ATP	311
	A. Phosphoryl Group Transfer	311
	Sample Calculation 10.2 Gibbs Free Energy Change	312
	Box 10.1 The Squiggle	312
	B. Production of ATP by Phosphoryl Group Transfer	314
	C. Nucleotidyl Group Transfer	315
10.8	Thioesters Have High Free Energies of Hydrolysis	316
10.9	Reduced Coenzymes Conserve Energy from Biological Oxidations	316
	A. Gibbs Free Energy Change Is Related to Reduction Potential	317
	B. Electron Transfer from NADH Provides Free Energy	319
	Box 10.2 NAD ⁺ and NADH Differ in Their Ultraviolet Absorption Spectra	321
10.10	Experimental Methods for Studying Metabolism	321
	Summary	322
	Problems	323
	Selected Readings	324

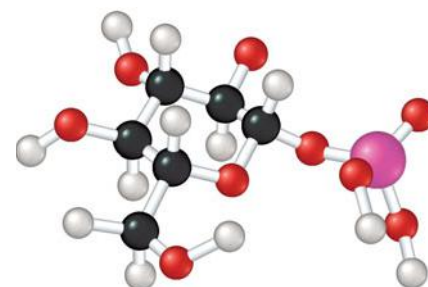


11	Glycolysis	325
11.1	The Enzymatic Reactions of Glycolysis	326
11.2	The Ten Steps of Glycolysis	326
	1. Hexokinase	326
	2. Glucose 6-Phosphate Isomerase	327
	3. Phosphofructokinase-1	330
	4. Aldolase	330
	Box 11.1 A Brief History of the Glycolysis Pathway	331
	5. Triose Phosphate Isomerase	332
	6. Glyceraldehyde 3-Phosphate Dehydrogenase	333
	7. Phosphoglycerate Kinase	335
	Box 11.2 Formation of 2,3-Bisphosphoglycerate in Red Blood Cells	335
	Box 11.3 Arsenate Poisoning	336
	8. Phosphoglycerate Mutase	336
	9. Enolase	338
	10. Pyruvate Kinase	338

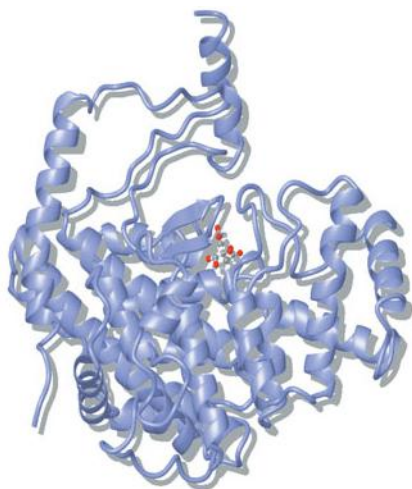
- 11.3 The Fate of Pyruvate **338**
 - A. Metabolism of Pyruvate to Ethanol **339**
 - B. Reduction of Pyruvate to Lactate **340**
 - Box 11.4** The Lactate of the Long-Distance Runner **341**
- 11.4 Free Energy Changes in Glycolysis **341**
- 11.5 Regulation of Glycolysis **343**
 - A. Regulation of Hexose Transporters **344**
 - B. Regulation of Hexokinase **344**
 - Box 11.5** Glucose 6-Phosphate Has a Pivotal Metabolic Role in the Liver **345**
 - C. Regulation of Phosphofructokinase-1 **345**
 - D. Regulation of Pyruvate Kinase **346**
 - E. The Pasteur Effect **347**
- 11.6 Other Sugars Can Enter Glycolysis **347**
 - A. Sucrose Is Cleaved to Monosaccharides **348**
 - B. Fructose Is Converted to Glyceraldehyde 3-Phosphate **348**
 - C. Galactose Is Converted to Glucose 1-Phosphate **349**
 - Box 11.6** A Secret Ingredient **349**
 - D. Mannose Is Converted to Fructose 6-Phosphate **351**
- 11.7 The Entner–Doudoroff Pathway in Bacteria **351**
 - Summary **352**
 - Problems **353**
 - Selected Readings **354**

12 Gluconeogenesis, the Pentose Phosphate Pathway, and Glycogen Metabolism **355**

- 12.1 Gluconeogenesis **356**
 - A. Pyruvate Carboxylase **357**
 - B. Phosphoenolpyruvate Carboxykinase **358**
 - C. Fructose 1,6-*bis*phosphatase **358**
 - Box 12.1** Supermouse **359**
 - D. Glucose 6-Phosphatase **359**
- 12.2 Precursors for Gluconeogenesis **360**
 - A. Lactate **360**
 - B. Amino Acids **360**
 - C. Glycerol **361**
 - D. Propionate and Lactate **361**
 - E. Acetate **362**
 - Box 12.2** Glucose Is Sometimes Converted to Sorbitol **362**
- 12.3 Regulation of Gluconeogenesis **363**
 - Box 12.3** The Evolution of a Complex Enzyme **364**
- 12.4 The Pentose Phosphate Pathway **364**
 - A. Oxidative Stage **366**
 - B. Nonoxidative Stage **364**
 - Box 12.4** Glucose 6-Phosphate Dehydrogenase Deficiency in Humans **367**
 - C. Interconversions Catalyzed by Transketolase and Transaldolase **368**
- 12.5 Glycogen Metabolism **368**
 - A. Glycogen Synthesis **369**
 - B. Glycogen Degradation **370**
- 12.6 Regulation of Glycogen Metabolism in Mammals **372**



A. Regulation of Glycogen Phosphorylase	372
Box 12.5 Head Growth and Tail Growth	373
B. Hormones Regulate Glycogen Metabolism	375
C. Hormones Regulate Gluconeogenesis and Glycolysis	376
12.7 Maintenance of Glucose Levels in Mammals	378
12.8 Glycogen Storage Diseases	381
Summary	382
Problems	382
Selected Readings	383



13 The Citric Acid Cycle 385

Box 13.1 An Egregious Error	386
13.1 Conversion of Pyruvate to Acetyl CoA	387
Sample Calculation 13.1	390
13.2 The Citric Acid Cycle Oxidizes Acetyl CoA	391
Box 13.2 Where Do the Electrons Come From?	392
13.3 The Citric Acid Cycle Enzymes	394
1. Citrate Synthase	394
Box 13.3 Citric Acid	396
2. Aconitase	396
Box 13.4 Three-Point Attachment of Prochiral Substrates to Enzymes	397
3. Isocitrate Dehydrogenase	397
4. The α -Ketoglutarate Dehydrogenase Complex	398
5. Succinyl CoA Synthetase	398
6. Succinate Dehydrogenase Complex	399
Box 13.5 What's in a Name?	399
Box 13.6 On the Accuracy of the World Wide Web	401
7. Fumarase	401
8. Malate Dehydrogenase	401
Box 13.7 Converting One Enzyme into Another	402
13.4 Entry of Pyruvate Into Mitochondria	402
13.5 Reduced Coenzymes Can Fuel the Production of ATP	405
13.6 Regulation of the Citric Acid Cycle	406
13.7 The Citric Acid Cycle Isn't Always a "Cycle"	407
Box 13.8 A Cheap Cancer Drug?	408
13.8 The Glyoxylate Pathway	409
13.9 Evolution of the Citric Acid Cycle	412
Summary	414
Problems	414
Selected Readings	416



14 Electron Transport and ATP Synthesis 417

14.1 Overview of Membrane-associated Electron Transport and ATP Synthesis	418
14.2 The Mitochondrion	418
Box 14.1 An Exception to Every Rule	420
14.3 The Chemiosmotic Theory and the Protonmotive Force	420
A. Historical Background: The Chemiosmotic Theory	420
B. The Protonmotive Force	421

- 14.4 Electron Transport **423**
 - A. Complexes I Through IV **423**
 - B. Cofactors in Electron Transport **425**
- 14.5 Complex I **426**
- 14.6 Complex II **427**
- 14.7 Complex III **428**
- 14.8 Complex IV **431**
- 14.9 Complex V: ATP Synthase **433**
 - Box 14.2** Proton Leaks and Heat Production **435**
- 14.10 Active Transport of ATP, ADP, and P_i Across the Mitochondrial Membrane **435**
- 14.11 The P/O Ratio **436**
- 14.12 NADH Shuttle Mechanisms in Eukaryotes **436**
 - Box 14.3** The High Cost of Living **439**
- 14.13 Other Terminal Electron Acceptors and Donors **439**
- 14.14 Superoxide Anions **440**
 - Summary **441**
 - Problems **441**
 - Selected Readings **442**

15 Photosynthesis **443**

- 15.1 Light-Gathering Pigments **444**
 - A. The Structures of Chlorophylls **444**
 - B. Light Energy **445**
 - C. The Special Pair and Antenna Chlorophylls **446**
 - Box 15.1** Mendel's Seed Color Mutant **447**
 - D. Accessory Pigments **447**
- 15.2 Bacterial Photosystems **448**
 - A. Photosystem II **448**
 - B. Photosystem I **450**
 - C. Coupled Photosystems and Cytochrome *bf* **453**
 - D. Reduction Potentials and Gibbs Free Energy in Photosynthesis **455**
 - E. Photosynthesis Takes Place Within Internal Membranes **457**
 - Box 15.2** Oxygen "Pollution" of Earth's Atmosphere **457**
- 15.3 Plant Photosynthesis **458**
 - A. Chloroplasts **458**
 - B. Plant Photosystems **459**
 - C. Organization of Chloroplast Photosystems **459**
 - Box 15.3** Bacteriorhodopsin **461**
- 15.4 Fixation of CO₂: The Calvin Cycle **461**
 - A. The Calvin Cycle **462**
 - B. Rubisco: Ribulose 1,5-*bis*phosphate Carboxylase-oxygenase **462**
 - C. Oxygenation of Ribulose 1,5-*bis*phosphate **465**
 - Box 15.4** Building a Better Rubisco **466**
 - D. Calvin Cycle: Reduction and Regeneration Stages **466**
- 15.5 Sucrose and Starch Metabolism in Plants **467**
 - Box 15.5** Gregor Mendel's Wrinkled Peas **469**
- 15.6 Additional Carbon Fixation Pathways **469**
 - A. Compartmentalization in Bacteria **469**



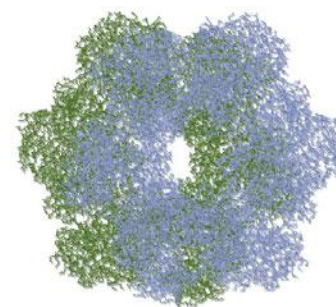
- B. The C₄ Pathway 469
- C. Crassulacean Acid Metabolism (CAM) 471
- Summary 472
- Problems 473
- Selected Readings 474

16 Lipid Metabolism 475

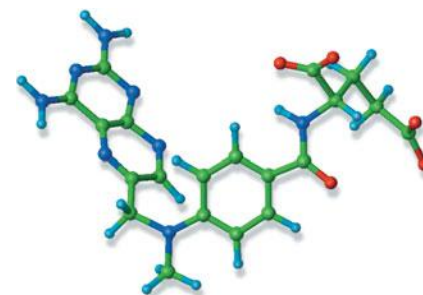
- 16.1 Fatty Acid Synthesis 475
 - A. Synthesis of Malonyl ACP and Acetyl ACP 476
 - B. The Initiation Reaction of Fatty Acid Synthesis 477
 - C. The Elongation Reactions of Fatty Acid Synthesis 477
 - D. Activation of Fatty Acids 479
 - E. Fatty Acid Extension and Desaturation 479
- 16.2 Synthesis of Triacylglycerols and Glycerophospholipids 481
- 16.3 Synthesis of Eicosanoids 483
 - Box 16.1 *sn*-Glycerol 3-Phosphate 484
 - Box 16.2 The Search for a Replacement for Aspirin 486
- 16.4 Synthesis of Ether Lipids 487
- 16.5 Synthesis of Sphingolipids 488
- 16.6 Synthesis of Cholesterol 488
 - A. Stage 1: Acetyl CoA to Isopentenyl Diphosphate 488
 - B. Stage 2: Isopentenyl Diphosphate to Squalene 488
 - C. Stage 3: Squalene to Cholesterol 490
 - D. Other Products of Isoprenoid Metabolism 490
 - Box 16.3 Lysosomal Storage Diseases 492
 - Box 16.4 Regulating Cholesterol Levels 493
- 16.7 Fatty Acid Oxidation 494
 - A. Activation of Fatty Acids 494
 - B. The Reactions of β -Oxidation 494
 - C. Fatty Acid Synthesis and β -Oxidation 497
 - D. Transport of Fatty Acyl CoA into Mitochondria 497
 - Box 16.5 A Trifunctional Enzyme for β -Oxidation 498
 - E. ATP Generation from Fatty Acid Oxidation 498
 - F. β -Oxidation of Odd-Chain and Unsaturated Fatty Acids 499
- 16.8 Eukaryotic Lipids Are Made at a Variety of Sites 501
- 16.9 Lipid Metabolism Is Regulated by Hormones in Mammals 502
- 16.10 Absorption and Mobilization of Fuel Lipids in Mammals 505
 - A. Absorption of Dietary Lipids 505
 - B. Lipoproteins 505
 - Box 16.6 Extra Virgin Olive Oil 506
 - Box 16.7 Lipoprotein Lipase and Coronary Heart Disease 507
 - C. Serum Albumin 508
- 16.11 Ketone Bodies Are Fuel Molecules 508
 - A. Ketone Bodies Are Synthesized in the Liver 509
 - B. Ketone Bodies Are Oxidized in Mitochondria 510
 - Box 16.8 Lipid Metabolism in Diabetes 511
 - Summary 511
 - Problems 511
 - Selected Readings 513



17	Amino Acid Metabolism	514
17.1	The Nitrogen Cycle and Nitrogen Fixation	515
17.2	Assimilation of Ammonia	518
	A. Ammonia Is Incorporated into Glutamate and Glutamine	518
	B. Transamination Reactions	518
17.3	Synthesis of Amino Acids	520
	A. Aspartate and Asparagine	520
	B. Lysine, Methionine, Threonine	520
	C. Alanine, Valine, Leucine, and Isoleucine	521
	Box 17.1 Childhood Acute Lymphoblastic Leukemia Can Be Treated with Asparaginase	522
	D. Glutamate, Glutamine, Arginine, and Proline	523
	E. Serine, Glycine, and Cysteine	523
	F. Phenylalanine, Tyrosine, and Tryptophan	523
	G. Histidine	527
	Box 17.2 Genetically Modified Food	528
	Box 17.3 Essential and Nonessential Amino Acids in Animals	529
17.4	Amino Acids as Metabolic Precursors	529
	A. Products Derived from Glutamate, Glutamine, and Aspartate	529
	B. Products Derived from Serine and Glycine	529
	C. Synthesis of Nitric Oxide from Arginine	530
	D. Synthesis of Lignin from Phenylalanine	531
	E. Melanin Is Made from Tyrosine	531
17.5	Protein Turnover	531
	Box 17.4 Apoptosis—Programmed Cell Death	534
17.6	Amino Acid Catabolism	534
	A. Alanine, Asparagine, Aspartate, Glutamate, and Glutamine	535
	B. Arginine, Histidine, and Proline	535
	C. Glycine and Serine	536
	D. Threonine	537
	E. The Branched Chain Amino Acids	537
	F. Methionine	539
	Box 17.5 Phenylketonuria, a Defect in Tyrosine Formation	540
	G. Cysteine	540
	H. Phenylalanine, Tryptophane, and Tyrosine	541
	I. Lysine	542
17.7	The Urea Cycle Converts Ammonia into Urea	542
	A. Synthesis of Carbamoyl Phosphate	543
	B. The Reactions of the Urea Cycle	543
	Box 17.6 Diseases of Amino Acid Metabolism	544
	C. Ancillary Reactions of the Urea Cycle	547
17.8	Renal Glutamine Metabolism Produces Bicarbonate	547
	Summary	548
	Problems	548
	Selected Readings	549



18	Nucleotide Metabolism	550
18.1	Synthesis of Purine Nucleotides	550
	Box 18.1 Common Names of the Bases	552
18.2	Other Purine Nucleotides Are Synthesized from IMP	554
18.3	Synthesis of Pyrimidine Nucleotides	555



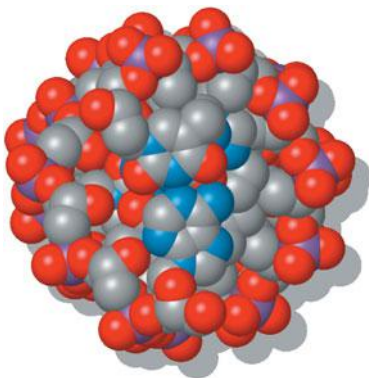
A.	The Pathway for Pyrimidine Synthesis	556
Box 18.2	How Some Enzymes Transfer Ammonia from Glutamate	558
B.	Regulation of Pyrimidine Synthesis	559
18.4	CTP Is Synthesized from UMP	559
18.5	Reduction of Ribonucleotides to Deoxyribonucleotides	560
18.6	Methylation of dUMP Produces dTMP	560
Box 18.3	Free Radicals in the Reduction of Ribonucleotides	562
Box 18.4	Cancer Drugs Inhibit dTTP Synthesis	564
18.7	Modified Nucleotides	564
18.8	Salvage of Purines and Pyrimidines	564
18.9	Purine Catabolism	565
18.10	Pyrimidine Catabolism	568
Box 18.5	Lesch–Nyhan Syndrome and Gout	569
Summary		571
Problems		571
Selected Readings		572

PART FOUR

Biological Information Flow

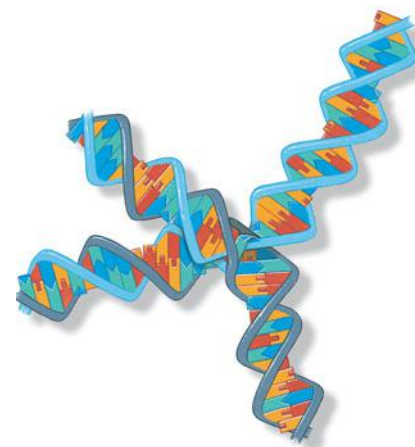
19 Nucleic Acids 573

19.1	Nucleotides Are the Building Blocks of Nucleic Acids	574
A.	Ribose and Deoxyribose	574
B.	Purines and Pyrimidines	574
C.	Nucleosides	575
D.	Nucleotides	577
19.2	DNA Is Double-Stranded	579
A.	Nucleotides Are Joined by 3'–5' Phosphodiester Linkages	580
B.	Two Antiparallel Strands Form a Double Helix	581
C.	Weak Forces Stabilize the Double Helix	583
D.	Conformations of Double-Stranded DNA	585
19.3	DNA Can Be Supercoiled	586
19.4	Cells Contain Several Kinds of RNA	587
Box 19.1	Pulling DNA	588
19.5	Nucleosomes and Chromatin	588
A.	Nucleosomes	588
B.	Higher Levels of Chromatin Structure	590
C.	Bacterial DNA Packaging	590
19.6	Nucleases and Hydrolysis of Nucleic Acids	591
A.	Alkaline Hydrolysis of RNA	591
B.	Hydrolysis of RNA by Ribonuclease A	592
C.	Restriction Endonucleases	593
D.	<i>EcoRI</i> Binds Tightly to DNA	595
19.7	Uses of Restriction Endonucleases	596
A.	Restriction Maps	596
B.	DNA Fingerprints	596
C.	Recombinant DNA	597
Summary		598
Problems		599
Selected Readings		599

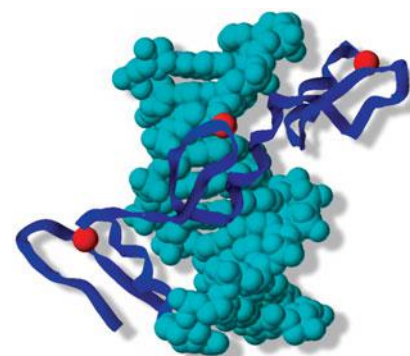


20 DNA Replication, Repair, and Recombination 601

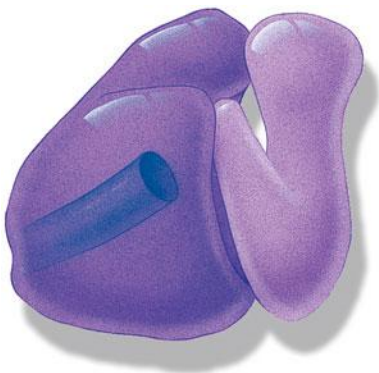
- 20.1 Chromosomal DNA Replication Is Bidirectional **602**
- 20.2 DNA Polymerase **603**
 - A. Chain Elongation Is a Nucleotidyl-Group-Transfer Reaction **604**
 - B. DNA Polymerase III Remains Bound to the Replication Fork **606**
 - C. Proofreading Corrects Polymerization Errors **607**
- 20.3 DNA Polymerase Synthesizes Two Strands Simultaneously **607**
 - A. Lagging Strand Synthesis Is Discontinuous **608**
 - B. Each Okazaki Fragment Begins with an RNA Primer **608**
 - C. Okazaki Fragments Are Joined by the Action of DNA Polymerase I and DNA Ligase **609**
- 20.4 Model of the Replisome **610**
- 20.5 Initiation and Termination of DNA Replication **615**
- 20.6 DNA Replication in Eukaryotes **615**
 - A. The Polymerase Chain Reaction Uses DNA Polymerase to Amplify Selected DNA Sequences **615**
 - B. Sequencing DNA Using Dideoxynucleotides **616**
 - C. Massively Parallel DNA Sequencing by Synthesis **618**
- 20.7 DNA Replication in Eukaryotes **619**
- 20.8 Repair of Damaged DNA **622**
 - A. Repair after Photodimerization: An Example of Direct Repair **622**
 - B. Excision Repair **624**
 - BOX 20.1** The Problem with Methylcytosine **626**
- 20.9 Homologous Recombination **626**
 - A. The Holliday Model of General Recombination **626**
 - B. Recombination in *E. coli* **627**
 - BOX 20.2** Molecular Links Between DNA Repair and Breast Cancer **630**
 - C. Recombination Can Be a Form of Repair **631**
 - Summary **631**
 - Problems **632**
 - Selected Readings **632**

**21 Transcription and RNA Processing 633**

- 21.1 Types of RNA **634**
- 21.2 RNA Polymerase **635**
 - A. RNA Polymerase Is an Oligomeric Protein **635**
 - B. The Chain Elongation Reaction **636**
- 21.3 Transcription Initiation **638**
 - A. Genes Have a 5' → 3' Orientation **638**
 - B. The Transcription Complex Assembles at a Promoter **639**
 - C. The σ sigma Subunit Recognizes the Promoter **640**
 - D. RNA Polymerase Changes Conformation **641**
- 21.4 Transcription Termination **643**
- 21.5 Transcription in Eukaryotes **645**
 - A. Eukaryotic RNA Polymerases **645**
 - B. Eukaryotic Transcription Factors **647**
 - C. The Role of Chromatin in Eukaryotic Transcription **648**
- 21.6 Transcription of Genes Is Regulated **648**
- 21.7 The *lac* Operon, an Example of Negative and Positive Regulation **650**
 - A. *lac* Repressor Blocks Transcription **650**
 - B. The Structure of *lac* Repressor **651**



	C. cAMP Regulatory Protein Activates Transcription	652
21.8	Post-transcriptional Modification of RNA	654
	A. Transfer RNA Processing	654
	B. Ribosomal RNA Processing	655
21.9	Eukaryotic mRNA Processing	655
	A. Eukaryotic mRNA Molecules Have Modified Ends	657
	B. Some Eukaryotic mRNA Precursors Are Spliced	657
	Summary	663
	Problems	663
	Selected Readings	664
22	Protein Synthesis	665
22.1	The Genetic Code	665
22.2	Transfer RNA	668
	A. The Three-Dimensional Structure of tRNA	668
	B. tRNA Anticodons Base-Pair with mRNA Codons	669
22.3	Aminoacyl-tRNA Synthetases	670
	A. The Aminoacyl-tRNA Synthetase Reaction	671
	B. Specificity of Aminoacyl-tRNA Synthetases	671
	C. Proofreading Activity of Aminoacyl-tRNA Synthetases	673
22.4	Ribosomes	673
	A. Ribosomes Are Composed of Both Ribosomal RNA and Protein	674
	B. Ribosomes Contain Two Aminoacyl-tRNA Binding Sites	675
22.5	Initiation of Translation	675
	A. Initiator tRNA	675
	B. Initiation Complexes Assemble Only at Initiation Codons	676
	C. Initiation Factors Help Form the Initiation Complex	677
	D. Translation Initiation in Eukaryotes	679
22.6	Chain Elongation During Protein Synthesis Is a Three-Step Microcycle	679
	A. Elongation Factors Dock an Aminoacyl-tRNA in the A Site	680
	B. Peptidyl Transferase Catalyzes Peptide Bond Formation	681
	C. Translocation Moves the Ribosome by One Codon	682
22.7	Termination of Translation	684
22.8	Protein Synthesis Is Energetically Expensive	684
22.9	Regulation of Protein Synthesis	685
	A. Ribosomal Protein Synthesis Is Coupled to Ribosome Assembly in <i>E. coli</i>	685
	Box 22.1 Some Antibiotics Inhibit Protein Synthesis	686
	B. Globin Synthesis Depends on Heme Availability	687
	C. The <i>E. coli trp</i> Operon Is Regulated by Repression and Attenuation	687
22.10	Post-translational Processing	689
	A. The Signal Hypothesis	691
	B. Glycosylation of Proteins	694
	Summary	694
	Problems	695
	Selected Readings	696
	Solutions	697
	Glossary	751
	Illustration Credits	767
	Index	769



To the Student

Welcome to biochemistry—the study of life at the molecular level. As you venture into this exciting and dynamic discipline, you'll discover many new and wonderful things. You'll learn how some enzymes can catalyze chemical reactions at speeds close to theoretical limits—reactions that would otherwise occur only at imperceptibly low rates. You'll learn about the forces that maintain biomolecular structure and how even some of the weakest of those forces make life possible. You'll also learn how biochemistry has thousands of applications in day-to-day life—in medicine, drug design, nutrition, forensic science, agriculture, and manufacturing. In short, you'll begin a journey of discovery about how biochemistry makes life both possible and better.

Before we begin, we would like to offer a few words of advice:

Don't just memorize facts; instead, understand principles

In this book, we have tried to identify the most important principles of biochemistry. Because the knowledge base of biochemistry is continuously expanding, we must grasp the underlying themes of this science in order to understand it. This textbook is designed to expand on the foundation you have acquired in your chemistry and biology courses and to provide you with a biochemical framework that will allow you to understand new phenomena as you meet them.

Be prepared to learn a new vocabulary

An understanding of biochemical facts requires that you learn a biochemical vocabulary. This vocabulary includes the chemical structures of a number of key molecules. These molecules are grouped into families based on their structures and functions. You will also learn how to distinguish among members of each family and how small molecules combine to form macromolecules such as proteins and nucleic acids.

Test your understanding

True mastery of biochemistry lies with learning how to apply your knowledge and how to solve problems. Each chapter concludes with a set of carefully crafted problems that test your understanding of core principles. Many of these problems are mini case studies that present the problem within the context of a real biochemical puzzle.

For more practice, we are pleased to refer you to *The Study Guide for Principles of Biochemistry* by Scott Leffler and Allen Scism which presents a variety of supplementary questions that you may find helpful. You will also find additional problems on TheChemistryPlace® for *Principles of Biochemistry* (<http://www.chemplace.com>).

Learn to visualize in 3-D

Biochemicals are three-dimensional objects. Understanding what happens in a biochemical reaction at the molecular level requires that you be able to “see” what happens in three dimensions. We present the structures of simple molecules in several different ways in order to illustrate their three-dimensional conformation. In addition to the art in the book, you will find many animations and interactive molecular models on the website. We strongly suggest you look at these movies and do the exercises that accompany them as well as participate in the molecular visualization tutorials.

Feedback

Finally, please let us know of any errors or omissions you encounter as you use this text. Tell us what you would like to see in the next edition. With your help we will continue to evolve this work into an even more useful tool. Our e-mail addresses are at the end of the Preface. Good luck, and enjoy!

This page intentionally left blank

Preface

Given the breadth of coverage and diversity of ways to present topics in biochemistry, we have tried to make the text as modular as possible to allow for greater flexibility and organization. Each large topic resides in its own section. Reaction mechanisms are often separated from the main thread of the text and can be passed over by those who prefer not to cover this level of detail. The text is extensively cross-referenced to make it easier for you to reorganize the chapters and for students to see the interrelationships among various topics and to drill down to deeper levels of understanding.

We built the book explicitly for the beginning student taking a first course in biochemistry with the aim of encouraging students to think critically and to appreciate scientific knowledge for its own sake. Parts One and Two lay a solid foundation of chemical knowledge that will help students understand, rather than merely memorize, the dynamics of metabolic and genetic processes. These sections assume that students have taken prerequisite courses in general and organic chemistry and have acquired a rudimentary knowledge of the organic chemistry of carboxylic acids, amines, alcohols, and aldehydes. Even so, key functional groups and chemical properties of each type of biomolecule are carefully explained as their structures and functions are presented.

We also assume that students have previously taken a course in biology where they have learned about evolution, cell biology, genetics, and the diversity of life on this planet. We offer brief refreshers on these topics wherever possible.

New to this Edition

We are grateful for all the input we received on the first four editions of this text. You'll notice the following improvements in this fifth edition:

- **Key Concept** margin notes are provided throughout to highlight key concepts and principles that students must know.
- **Interest Boxes** have been updated and expanded, with 45% new to the fifth edition. We use interest boxes to explain some topics in more detail, to illustrate certain principles with specific examples, to stimulate students curiosity about science, to show applications of biochemistry, and to explain clinical relevance. We have also added a few interests boxes that warn students about misunderstanding and misapplications of biochemistry. Examples include Blood Plasma and Sea Water; Fossil Dating by Amino Acid Racemization; Embryonic and Fetal Hemoglobins; Clean Clothes; The Perfect Enzyme; Supermouse; The Evolution of a Complex Enzyme; An Egregious Error; Mendels Seed Color Mutant; Oxygen Pollution of Earth's Atmosphere; Extra Virgin Olive Oil; Missing Vitamins; Pulling DNA; and much more.
- New Material has been added throughout, including an improved explanation of early evolution (the Web of Life), more emphasis on protein protein interactions, a new section on intrinsically disordered proteins, and a better description of the distinction between Gibbs free energy changes and reaction rates. We have removed the final chapter on Recombinant DNA Technology and integrated much of that material into earlier chapters. We have added descriptions of a number of new protein structures and integrated them into two major themes: structure-function and multienzyme complexes. The best example is the fatty acid synthase complex in Chapter 16.

In some cases new material was necessary because recent discoveries have changed our view of some reactions and processes. We now know, for example, that older versions of uric acid catabolism were incorrect, the correct pathway is shown in Figure 18.23.

We have been careful not to add extra detail unless it supports and extends the basic concepts and principles that we have established over the past four editions. Similarly, we do not introduce new subjects unless they illustrate new concepts that were not covered in previous editions. The goal is to keep this textbook focused on the fundamentals that students need to know and prevent it from bloating up into an encyclopedia of mostly irrelevant information that detracts from the main pedagogical goals.

- **Selected Readings** after each chapter reflect the most current literature and these have been updated and extended where necessary. We have added over 120 new references and deleted many that are no longer appropriate. Although we have always included references to the pedagogical literature, you will note that we have added quite a few more references of this type. Students now have easy access to these papers and they are often more informative than advanced papers in the purely scientific literature.
- **Art** is an important component of a good textbook. Our art program has been extensively revised, with many new photos to illustrate concepts explained in the text; new and updated ribbon art, and improved versions of many figures. Many of the new photos are designed to attract and/or hold the students attention. They can be powerful memory aids and some of them are used to lighten up the subject in a way that is rarely seen in other textbooks (see page 204). We believe that the look and feel of the book has been much improved, making it more appealing to students without sacrificing any of the rigor and accuracy that has been a hallmark of previous editions.

A focus on principles

There are, in essence, two kinds of biochemistry textbooks: those for reference and those for teaching. It is difficult for one book to be both as it is those same thickets of detail sought by the professional that ensnare the struggling novice on his or her first trip through the forest. This text is unapologetically a text for teaching. It has been designed to foster student understanding and is not an encyclopedia of biochemistry. This book focuses unwaveringly on teaching basic principles and concepts, each principle supported by carefully chosen examples. We really do try to get students to see the forest and not the trees!

Because of this focus, the material in this book can be covered in a two-semester course without having to tell students to skip certain chapters or certain sections. The book is also suitable for a one-semester course that concentrates on certain aspects of biochemistry where some subjects are not covered. Instructors can be confident that the core principles and concepts are explained thoroughly and correctly.

A focus on chemistry

When we first wrote this text, we decided to take the time to explain in chemical terms the principles that we want to emphasize. In fact, one of these principles is to show students that life obeys the fundamental laws of physics and chemistry. To that end, we offer chemical explanations of most biochemical reactions, including mechanisms that tell students how and why things happen.

We are particularly proud of our explanations of oxidation-reduction reactions since these are extremely important in so many contexts. We describe electron movements in the early chapters, explain reduction potentials in Chapter 10 and use this understanding to teach about chemiosmotic theory and protonmotive force in Chapter 14 (Electron Transport and ATP Synthesis). The concept is reinforced in the chapter on photosynthesis.

A focus on biology

While we emphasize chemistry, we also stress the bio in biochemistry. We point out that biochemical systems evolve and that the reactions that occur in some species are variations on a larger theme. In this edition, we increase our emphasis on the similarities of

prokaryotic and eukaryotic systems while we continue to avoid making generalizations about all organisms based on reactions that occur in a few.

The evolutionary, or comparative, approach to teaching biochemistry focuses attention on fundamental concepts. The evolutionary approach differs in many ways from other pedagogical methods such as an emphasis on fuel metabolism. The evolutionary approach usually begins with a description of simple fundamental principles or pathways or processes. These are often the pathways found in bacteria. As the lesson proceeds, the increasing complexity seen in some other species is explained. At the end of a chapter we are ready to describe the unique features of the process found in complex multicellular species, such as humans.

Our approach entails additional changes that distinguish us from other textbooks. When introducing a new chapter, such as lipid metabolism, amino acid metabolism, and nucleotide metabolism, most other textbooks begin by treating the molecules as potential food for humans. We start with the biosynthesis pathways since those are the ones fundamental to all organisms. Then we describe the degradation pathways and end with an explanation of how they relate to fuel metabolism. This biosynthesis first organization applies to all the major components of a cell (proteins, nucleotides, nucleic acids, lipids, amino acids) except carbohydrates where we continue to describe glycolysis ahead of gluconeogenesis. We do, however, emphasize that gluconeogenesis is the original, primitive pathway and glycolysis evolved later.

This has always been the way DNA replication, transcription, and translation have been taught. In this book we extend this successful strategy to all the other topics in biochemistry. The chapter on photosynthesis is an excellent example of how it works in practice.

In some cases the emphasis on evolution can lead to a profound appreciation of how complex systems came to exist. Take the citric acid cycle as an example. Students are often told that such a process cannot be the product of evolution because all the parts are needed before the cycle can function. We explain in Section 13.9 how such a pathway can evolve in a stepwise manner.

A focus on accuracy

We are proud of the fact that this is the most scientifically accurate biochemistry textbook. We have gone to great lengths to ensure that our facts are correct and our explanations of basic concepts reflect the modern consensus among active researchers. Our success is due, in large part, to the dedication of our many reviewers and editors.

The emphasis on accuracy means that we check our reactions and our nomenclature against the IUPAC/IUBMB databases. The result is balanced reactions with correct products and substrates and correct chemical nomenclature. For example, we are one of the very few textbooks that show all of the citric acid cycle reactions correctly. Previous editions of this textbook have always scored highly on the Biochemical Howlers website [bip.cnrs-mrs.fr/bip10/howler.htm] and we feel confident that this edition will achieve a perfect score!

We take the time and effort to accurately describe some difficult concepts such as Gibbs free energy change in a steady-state situation where most reactions are near-equilibrium reactions ($\Delta G = 0$). We present correct definitions of the Central Dogma of Molecular Biology. We don't avoid genuine areas of scientific controversy such as the validity of the Three Domain Hypothesis or the mechanism of lysozyme.

A focus on structure-function

Biochemistry is a three-dimensional science. Our inclusion of the latest computer generated images is intended to clarify the shape and function of molecules and to leave students with an appreciation for the relationship between the structure and function. Many of the protein images in this edition are new; they have been skillfully prepared by Jonathan Parrish of the University of Alberta.

We offer a number of other opportunities. For those students with access to a computer, we have included Protein Data Bank (PDB) reference numbers for the coordinates

from which all protein images were derived. This allows students to further explore the structures on their own. In addition, we have a gallery of prepared PDB files that students can view using Chime or any other molecular viewer; these are posted on the text's TheChemistryPlace® website [chemplace.com] as are animations of key dynamic processes as well as visualization tutorials using Chime.

The emphasis on protein/enzyme structure is a key part of the theme of structure-function that is one of the most important concepts in biochemistry. At various places in this new edition we have added material to emphasize this relationship and to develop it to a greater extent than we have in the past. Some of the most important reactions in the cell, such as the Q-cycle, cannot be properly understood without understanding the structure of the enzyme that catalyzes them. Similarly, understanding the properties of double-stranded DNA is essential to understanding how it serves as the storehouse of biological information.

Walkthrough of features with some visuals

Interests

Biochemistry is at the root of a number of related sciences, including medicine, forensic science, biotechnology, and bioengineering; there are many interesting stories to tell. Throughout the text, you will find boxes that relate biochemistry to other topics. Some of them are intended to be humorous and help students relate to the material.

BOX 8.1 THE PROBLEM WITH CATS

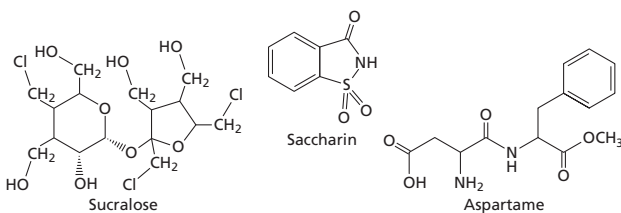
One of the characteristics of sugars is that they taste sweet. You certainly know the taste of sucrose and you probably know that fructose and lactose also taste sweet. So do many of the other sugars and their derivatives, although we don't recommend that you go into a biochemistry lab and start tasting all the carbohydrates in those white plastic bottles on the shelves.

Sweetness is not a physical property of molecules. It's a subjective interaction between a chemical and taste receptors in your mouth. There are five different kinds of taste receptors: sweet, sour, salty, bitter, and umami (umami is like the taste of glutamate in monosodium glutamate). In order to trigger the sweet taste, a molecule like sucrose has to bind to the receptor and initiate a response that eventually makes it to your brain. Sucrose elicits a moderately strong response that serves as the standard for sweetness. The response to fructose is almost twice as strong and the response to lactose is only about one-fifth as strong as that of sucrose. Artificial sweeteners such as saccharin (Sweet'N Low®), sucralose

(Splenda®), and aspartame (NutraSweet®) bind to the sweetness receptor and cause the sensation of sweetness. They are hundreds of times more sweet than sucrose.

The sweetness receptor is encoded by two genes called *Tas1r2* and *Tas1r3*. We don't know how sucrose and the other ligands bind to this receptor even though this is a very active area of research. In the case of sucrose and the artificial sweeteners, how can such different molecules elicit the taste of sweet?

Cats, including lions, tigers and cheetahs, do not have a functional *Tas1r2* gene. It has been converted to a pseudogene because of a 247 bp deletion in exon 3. It's very likely that your pet cat has never experienced the taste of sweetness. That explains a lot about cats.



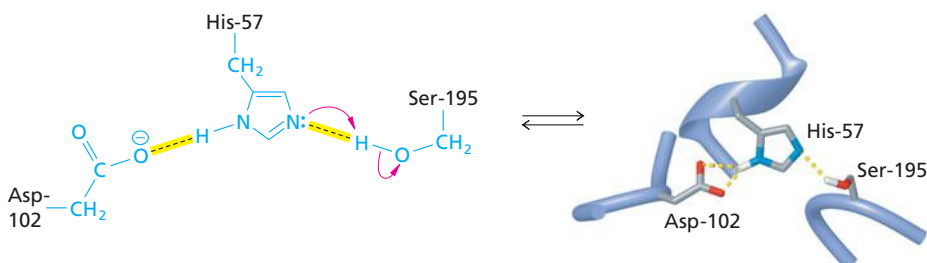
▲ Cats are carnivores. They probably can't taste sweetness.

Key Concepts

To help guide students to the information important in each concept, Key Concept notes have been provided in the margin highlighting this information.

Complete Explanations of the Chemistry

There are thousands of metabolic reactions in a typical organism. You might try to memorize them all but eventually you will run out of memory. What's more, memorization will not help you if you encounter something you haven't seen before. In this book, we show you some of the basic mechanisms of enzyme-catalyzed reactions—an extension of what you learned in organic chemistry. If you understand the mechanism, you'll understand the chemistry. You'll have less to memorize, and you'll retain the information more effectively.



Margin Notes

There is a great deal of detail in biochemistry but we want you to see both the forest and the trees. When we need to cross-reference something discussed earlier in the book, or something that we will come back to later, we put it in the margin. Backward references offer a review of concepts you may have forgotten. Forward references will help you see the big picture.

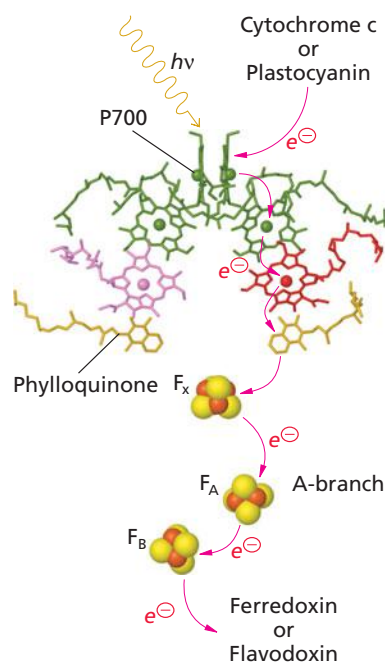
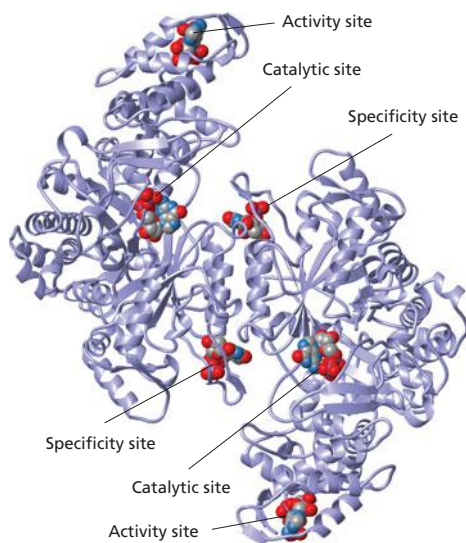
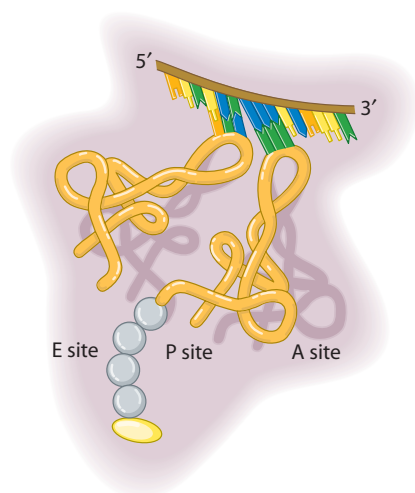
Art

Biochemistry is a three-dimensional science and we have placed a great emphasis on helping you visualize abstract concepts and molecules too small to see. We have tried to make illustrative figures both informative and beautiful.

KEY CONCEPT

The standard Gibbs free energy change (ΔG°) tells us the direction of a reaction when the concentrations of all products and reactants are at 1 M concentration. These conditions will never occur in living cells. Biochemists are only interested in actual Gibbs free energy changes (ΔG), which are usually close to zero. The standard Gibbs free energy change (ΔG°) tells us the relative concentrations of reactants and products when the reaction reaches equilibrium.

The distinction between the normal flow of information and the Central Dogma of Molecular Biology is explained in Section 1.1 and the introduction to Chapter 21.



Sample Calculations

Sample Calculations are included throughout the text to provide a problem solving model and illustrate required calculations.

SAMPLE CALCULATION 10.2 Gibbs Free Energy Change

Q: In a rat hepatocyte, the concentrations of ATP, ADP, and P_i are 3.4 mM, 1.3 mM, and 4.8 mM, respectively. Calculate the Gibbs free energy change for hydrolysis of ATP in this cell. How does this compare to the standard free energy change?

A: The actual Gibbs free energy change is calculated according to Equation 10.10.

$$\Delta G_{\text{reaction}} = \Delta G^{\circ}_{\text{reaction}} + RT \ln \frac{[\text{ADP}][P_i]}{[\text{ATP}]} = \Delta G^{\circ}_{\text{reaction}} + 2.303 RT \log \frac{[\text{ADP}][P_i]}{[\text{ATP}]}$$

When known values and constants are substituted (with concentrations expressed as molar values), assuming pH 7.0 and 25°C.

$$\Delta G = -32000 \text{ J mol}^{-1} + (8.31 \text{ J K}^{-1} \text{ mol}^{-1})(298 \text{ K}) \left[2.303 \log \frac{(1.3 \times 10^{-3})(4.8 \times 10^{-3})}{(3.4 \times 10^{-3})} \right]$$

$$\Delta G = -32000 \text{ J mol}^{-1} + (2480 \text{ J mol}^{-1}) [2.303 \log(1.8 \times 10^{-3})]$$

$$\Delta G = -32000 \text{ J mol}^{-1} - 16000 \text{ J mol}^{-1}$$

$$\Delta G = -48000 \text{ J mol}^{-1} = -48 \text{ kJ mol}^{-1}$$

The actual free energy change is about $1\frac{1}{2}$ times the standard free energy change.

The Organization

We adopt the metabolism-first strategy of organizing the topics in this book. This means we begin with proteins and enzymes then describe carbohydrates and lipids. This is followed by a description of intermediary metabolism and bioenergetics. The structure of nucleic acids follows the chapter on nucleotide metabolism and the information flow chapters are at the back of the book.

While we believe there are significant advantages to teaching the subjects in this order, we recognize that some instructors prefer to teach information flow earlier in the course. We have tried to make the last four chapters on nucleic acids, DNA replication, transcription, and translation less dependant on the earlier chapters but they do discuss aspects of enzymes that rely on Chapters 4, 5 and 6. Instructors may choose to introduce these last four chapters after a description of enzymes if they wish.

This book has a chapter on coenzymes unlike most other biochemistry textbooks. We believe that it is important to put more emphasis on the role of coenzymes (and vitamins) and that's why we have placed this chapter right after the two chapters on enzymes. We know that most instructors prefer to teach the individual coenzymes when specific examples come up in other contexts. We do that as well. This organization allows instructors to refer back to chapter 7 at whatever point they wish.

Student Supplements

The Study Guide for Principles of Biochemistry

by Scott Lefler
(Arizona State University) and
Allen J. Scism
(Central Missouri State University)

No student should be without this helpful resource. Contents include the following:

- carefully constructed drill problems for each chapter, including short-answer, multiple-choice, and challenge problems
- comprehensive, step-by-step solutions and explanations for all problems
- a remedial chapter that reviews the general and organic chemistry that students require for biochemistry—topics are ingeniously presented in the context of a metabolic pathway
- tables of essential data

Chemistry Place for *Principles of Biochemistry*

An online student tool that includes 3-D modules to help visualize biochemistry and MediaLabs to investigate important issues related to its particular chapter. Please visit the site at <http://www.chemplace.com>.

Acknowledgments

We are grateful to our many talented and thoughtful reviewers who have helped shape this book.

Reviewers who helped in the Fifth Edition:

Accuracy Reviewers

Barry Ganong, Mansfield University
Scott Lefler, Arizona State
Kathleen Nolta, University of Michigan

Content Reviewers

Michelle Chang, University of California, Berkeley
Kathleen Comely, Providence College
Ricky Cox, Murray State University
Michel Goldschmidt-Clermont, University of Geneva
Phil Klebba, University of Oklahoma, Norman
Kristi McQuade, Bradley University
Liz Roberts-Kirchoff, University of Detroit, Mercy
Ashley Spies, University of Illinois
Dylan Taatjes, University of Colorado, Boulder
David Tu, Pennsylvania State University
Jeff Wilkinson, Mississippi State University
Lauren Zapanta, University of Pittsburgh

Reviewers who helped in the Fourth Edition:

Accuracy Reviewers

Neil Haave, University of Alberta
David Watt, University of Kentucky

Content Reviewers

Consuelo Alvarez, Longwood University
Marilee Benore Parsons, University of Michigan
Gary J. Blomquist, University of Nevada, Reno
Albert M. Bobst, University of Cincinnati
Kelly Drew, University of Alaska, Fairbanks
Andrew Feig, Indiana University
Giovanni Gadda, Georgia State University
Donna L. Gosnell, Valdosta State University
Charles Hardin, North Carolina State University
Jane E. Hobson, Kwantlen University College
Ramji L. Khandelwal, University of Saskatchewan
Scott Lefler, Arizona State
Kathleen Nolta, University of Michigan

Jeffrey Schineller, Humboldt State University
Richard Shingles, Johns Hopkins University
Michael A. Sypes, Pennsylvania State University
Martin T. Tuck, Ohio University
Julio F. Turrens, University of South Alabama
David Watt, University of Kentucky
James Zimmerman, Clemson University

Thank you to J. David Rawn who's work laid the foundation for this text. We would also like to thank our colleagues who have previously contributed material for particular chapters and whose careful work still inhabits this book:

Roy Baker, University of Toronto
Roger W. Brownsey, University of British Columbia
Willy Kalt, Agriculture Canada
Robert K. Murray, University of Toronto
Ray Ochs, St. John's University
Morgan Ryan, American Scientist
Frances Sharom, University of Guelph
Malcolm Watford, Rutgers, The State University of New Jersey

Putting this book together was a collaborative effort, and we would like to thank various members of the team who have helped give this project life: Jonathan Parrish, Jay McElroy, Lisa Shoemaker, and the artists of Prentice Hall; Lisa Tarabokjia, Editorial Assistant, Jessica Neumann, Associate Editor, Lisa Pierce, Assistant Editor in charge of supplements, Lauren Layn, Media Editor, Erin Gardner, Marketing Manager; and Wendy Perez, Production Editor. We would also like to thank Jeanne Zalesky, our Executive Editor at Prentice Hall.

Finally, we close with an invitation for feedback. Despite our best efforts (and a terrific track record in the previous editions), there are bound to be mistakes in a work of this size. We are committed to making this the best biochemistry text available; please know that all comments are welcome.

Laurence A. Moran
l.moran@utoronto.ca
Marc D. Perry
marc.perry@utoronto.ca

This page intentionally left blank



About the Authors

Laurence A. Moran

After earning his Ph.D. from Princeton University in 1974, Professor Moran spent four years at the Université de Genève in Switzerland. He has been a member of the Department of Biochemistry at the University of Toronto since 1978, specializing in molecular biology and molecular evolution. His research findings on heat-shock genes have been published in many scholarly journals. (l.moran@utoronto.ca)

H. Robert Horton

Dr. Horton, who received his Ph.D. from the University of Missouri in 1962, is William Neal Reynolds Professor Emeritus and Alumni Distinguished Professor Emeritus in the Department of Biochemistry at North Carolina State University, where he served on the faculty for over 30 years. Most of Professor Horton's research was in protein and enzyme mechanisms.

K. Gray Scrimgeour

Professor Scrimgeour received his doctorate from the University of Washington in 1961 and was a faculty member at the University of Toronto for over 30 years. He is the author of *The Chemistry and Control of Enzymatic Reactions* (1977, Academic Press), and his work on enzymatic systems has been published in more than 50 professional journal articles during the past 40 years. From 1984 to 1992, he was editor of the journal *Biochemistry and Cell Biology*. (gray@scrimgeour.ca)

Marc D. Perry

After earning his Ph.D. from the University of Toronto in 1988, Dr. Perry trained at the University of Colorado, where he studied sex determination in the nematode *C. elegans*. In 1994 he returned to the University of Toronto as a faculty member in the Department of Molecular and Medical Genetics. His research has focused on developmental genetics, meiosis, and bioinformatics. In 2008 he joined the Ontario Institute for Cancer Research. (marc.perry@utoronto.ca)

This page intentionally left blank