

Bettelheim · Brown · March



INTRODUCTION TO
**ORGANIC &
BIOCHEMISTRY**

fourth edition

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FREDERICK A. BETTELHEIM

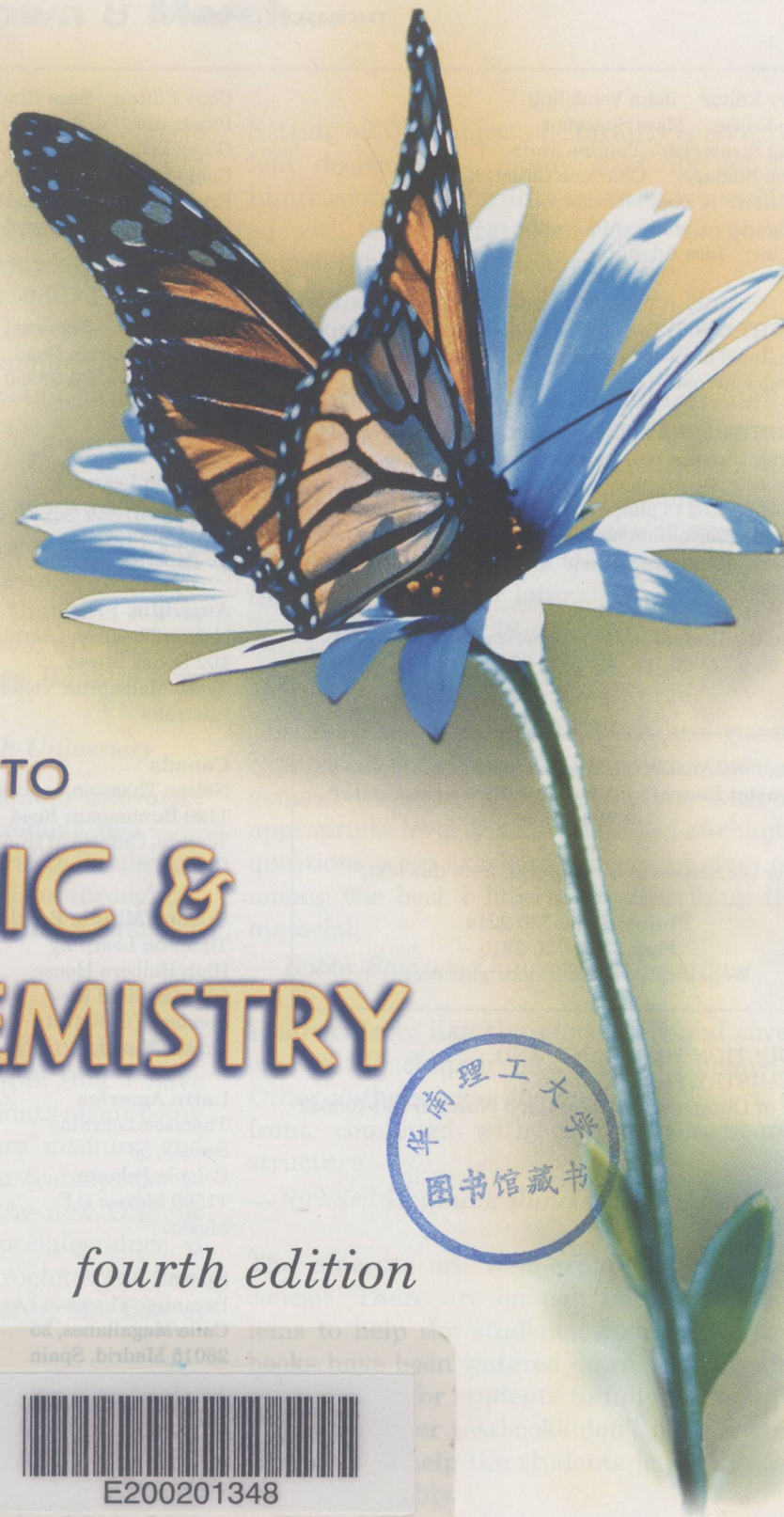
Adelphi University

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BIOCHEMISTRY**



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Here's What Your Colleagues Are Saying About Bettelheim, Brown & March...

The main reason I continue to choose Bettelheim for my course is the readability of the text. The large number of medical application boxes is also extremely important in showing the relevancy of the material to [the students'] future careers in allied health. Another strong feature of the text is the large number of worked example problems and an extremely good collection of end-of-chapter problems.

— *Eric Johnson, Ball State University*

The key strength of this text is its readability. Students actually read this textbook! The writing style and level of presentation are appropriate for the audience that this text is aimed at. The boxes, I believe, are another strength of the book. The Test Bank is very good, as are the illustrations.

— *Steve Socol, Southern Utah University*

Breaking up the Organic chapters into more and shorter chapters is an excellent idea The separate chapter on Chirality is also an excellent idea . . . the applications throughout the text are very good and bring a practical aspect to the subject.

— *Jack Hefley, Blinn College*

This text has one of the lowest incidences of factual and typographical errors that I have seen. Students have no complaints about being able to understand the authors' meaning and message. Text is also well-illustrated; color is used effectively I like the new Organic presentation very much, especially since it does allow the individual instructor some flexibility without drastically altering the flow of the text.

— *Larry McGahey, The College of St. Scholastica*

The clarity of the writing and the style of presentation are the real strengths of this textbook. Students find it easy to read and to understand.

— *James Yuan, Old Dominion University*

Setting off the subject of Chirality is an excellent decision . . . many students get the impression that chirality is strongly associated with carbohydrates and only marginally transferable to other biomolecules.

— *William Scovell, Bowling Green State University*

The authors do a good job of addressing the chemistry of the various functional groups that are important in biochemistry The excellent discussions of reactions in the organic section can only make it easier for students to understand the metabolic reactions they encounter later.

— *David Reinhold, Western Michigan University*

The chapters dealing with DNA and genetic expression are excellent. They were written in general terms, not too descriptive, with an appropriate level of detail. The end-of-chapter questions were excellent. These chapters are among the best I have seen describing this material.

— *Bobby Stanton, University of Georgia*

I particularly like the placement and coverage of the chapter on Nuclear Chemistry. Other authors seem inclined to include it up front, combined with chapters on atomic structure.

— *Richard Hoffman, Illinois Central College*

The concepts are well explained, clear and concise. There are enough homework problems to help the students. Some other textbooks have been watered down so much that it is difficult for students to fully understand concepts. Other textbooks don't have enough problems to help the students learn the concepts thoroughly.

— *Jennifer Tan, Ohlone College*

*This text is dedicated to
the living memory of Jerry March
(1929 – 1997)*

ABOUT THE AUTHORS

Frederick A. Bettelheim

Frederick A. Bettelheim is a Distinguished University Research Professor at Adelphi University, and a Visiting Scientist at the National Eye Institute. He has coauthored every edition of *Introduction to General, Organic & Biochemistry* and several laboratory manuals, including *Laboratory Experiments for General, Organic & Biochemistry* and *Experiments for Introduction to Organic Chemistry*. He is the author of *Experimental Physical Chemistry* and coauthor of numerous monographs and research articles. Professor Bettelheim received his Ph.D. from the University of California, Davis, and his areas of specialization have included the biochemistry of proteins and carbohydrates and the physical chemistry of polymers. He was Fulbright Professor at the Weizman Institute, Israel, and Visiting Professor at the University of Uppsala, Sweden, at Technion, Israel, and at the University of Florida. He is keynote lecturer at the 16th International Conference on Chemical Education, August 2000, in Budapest, Hungary, where his lecture topic is Modern Trends in Teaching Chemistry to Nurses and Other Health-Related Professionals.

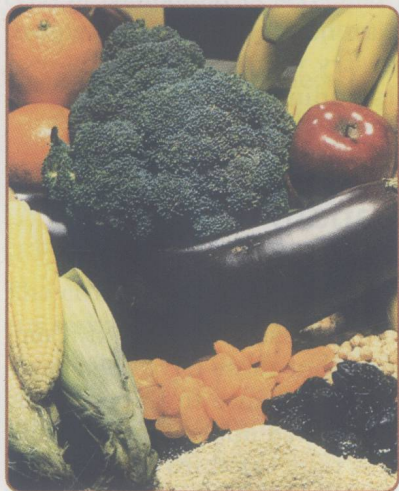
William H. Brown

William H. Brown, a new coauthor for the sixth edition of *Introduction to General, Organic & Biochemistry*, is Professor of Chemistry at Beloit College, where he has twice been named Teacher of the Year. He is also the author of two best-selling undergraduate texts, *Introduction to Organic Chemistry*, Second Edition, and *Organic Chemistry*, Second Edition. His regular teaching responsibilities include organic chemistry, advanced organic chemistry, and special topics in pharmacology and drug synthesis. He is the leader of a team revising the organic chemistry material appearing in the upcoming *Encyclopaedia Britannica CD-ROM*. Professor Brown received his Ph.D. from Columbia University under the direction of Gilbert Stork and did postdoctoral work at the California Institute of Technology and the University of Arizona.

Jerry March

Jerry March (d. 1997) was the coauthor of *Introduction to General, Organic & Biochemistry* for its first five editions. He was the sole author of the best-selling *Advanced Organic Chemistry* text, now in its fifth edition, which has been translated into many languages including Russian and Japanese. He was a member of the Physical Organic Chemistry Commission of the International Union of Pure and Applied Chemistry, and as such was instrumental in the development of several nomenclature systems. Professor March received his Ph.D. at Pennsylvania State University and was Professor of Chemistry at Adelphi University, specializing in organic chemistry.

PREFACE



(Charles D. Winters)

In me are hidden constellations.

Once I managed to sight one
through the lens of equations
that could be solved only
approximately. Still
with that imperfect rule
I taught others the electrons
lobed motions. . . .
I work this wild chemical
garden with one old tool.

Let me show others new ways to see.

Roald Hoffmann: Gaps and Verges

It is the dream of every educator to convey the subject for all to see, to elicit excitement in learning, to discover in wonderment, and through the discovery to let the self be discovered. In writing this Preface for the fourth edition of our textbook, it is tempting to recall the excitement and elation that greeted the first edition 10 years ago. We had a book that was novel in its coverage and its pedagogy that made concepts relevant by frequent examples of their applications. Throughout the years, the cutting edge of this presentation was acknowledged and rewarded by the adoption of this book by our colleagues for their courses. The ideas originated and developed in our book became the standard and were incorporated into many textbooks.

Now it is time to provide a new look: we brighten an old gem, polish its surface, turn its edges toward the Sun, and let it glitter. We hope that in this new edition we have managed to achieve the most comprehensive treatment of the subject of chemistry in a clearcut presentation for the edification and enjoyment of our students.

This fourth edition intends to be even more readable and understandable than earlier editions, and we have forged a greater unity of the two domains of the text: organic and biochemistry. Chemistry, especially biochemistry, is a fast-developing discipline, and we include new, relevant material in the text. We have done this not only by upgrading information, but also by enlarging the scope of the book in the text and in the boxes containing medical and other applications of chemical principles. At the same time, we are aware of the need to keep the book to a manageable size and proportion. Approximately 25 percent of the problems are new, and we have increased the number of more challenging, thought-provoking problems (marked by asterisks).

Audience

As were the previous editions, this book is intended for nonchemistry majors, mainly those entering health science and related fields (such as nursing, medical technology, physical therapy, and nutrition). It also can be used by students in environmental studies. In its entirety, it can be used for one term or a two-quarter section) course in chemistry.

We assume that the students using the book have a one- or two-semester general chemistry background. We start by reviewing funda-



(Charles D. Winters)

mentals of general chemistry before progressing to organic and biochemistry, including acid-base chemistry. The two parts of the book are integrated by keeping a unified view of chemistry. We introduce concepts slowly at the beginning, increasing the tempo and the level of sophistication as we go on.

While teaching the chemistry of the human body is our ultimate goal, we try to show that each subsection of chemistry is important in its own right, besides being required for future understanding.

Boxes (Medical and Other Applications of Chemical Principles)

The boxes contain applications of the principles discussed in the text. Comments from users of the earlier editions indicate that these have been especially well-received, providing a much requested relevance to the text. The large number of boxes deal mainly with health-related applications, including ones related to the environment. Some boxes from the third edition have been dropped, and a few others have been incorporated into the text or other boxes.

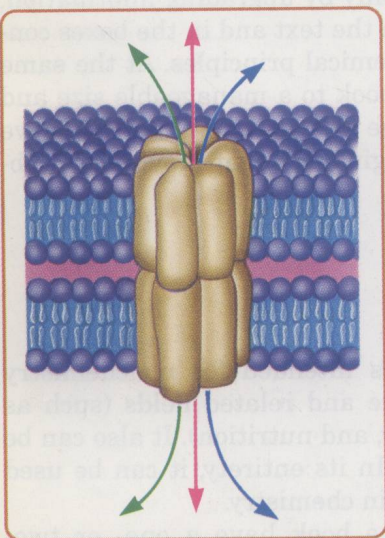
Numerous new boxes dealing with diverse topics such as chiral drugs, toxicity and drug dosage, transport across cell membranes, protein conformation-dependent diseases, and tumor suppressor genes, among others, have been added. Many boxes have been enlarged and updated. For example, boxes on nitric oxide, anti-inflammatory drugs, Alzheimer's disease, laser surgery, and AIDS now contain recent information.

The presence of boxes allows a considerable degree of flexibility. If an instructor wants to assign only the main text, the boxes do not interrupt continuity, and the essential material will be covered. However, most instructors will probably wish to assign at least some of the boxes, since they enhance the core material. In our experience, students are eager to read the relevant boxes without assignments and they do so with discrimination. From such a large number of boxes, the instructor can select those that best fit the particular needs of the course and of the students. **Problems are provided at the end of each chapter for nearly all of the boxes.**

Metabolism: Color Code

The biological functions of chemical compounds are explained in each of the biochemistry chapters and in many of the organic chapters. Emphasis is placed on chemistry rather than on physiology. We have received much positive feedback regarding the way in which we have organized the topic of metabolism (Chapters 17, 18, and 19). We have maintained this organization.

First we introduce the common metabolic pathway through which all food will be utilized (citric acid cycle; oxidative phosphorylation), and only after that do we discuss the specific pathways leading to the common pathway. We find this a useful pedagogic device, and it enables us to sum up the caloric values of each type of food because their utilization through the common pathway has already been learned. Finally, we separate the catabolic pathways from the anabolic pathways by treating them in different chapters, emphasizing the different ways the body breaks down and builds up different molecules.



The topic of metabolism is a difficult one for most students. We have tried to explain it as clearly as possible. As in the previous edition, we enhance the clarity of presentation by the use of a color code for the most important biological compounds discussed in Chapters 17, 18, and 19. Each type of compound is screened in a specific color, which remains the same throughout the three chapters. These colors are as follows:

- ATP and other nucleoside triphosphates
- ADP and other nucleoside diphosphates
- The oxidized coenzymes NAD^+ and FAD
- The reduced coenzymes NADH and FADH_2
- Acetyl coenzyme A



The circled numbers in the figures showing the steps involved in the various metabolism pathway are always in yellow.

In addition to this main use of a color code, other figures in various parts of the book are color-coded, so that the same color is used for the same entity throughout. For example, in Chapter 13, enzymes are always shown in blue and substrates in orange in all the figures that show enzyme-substrate interactions.

Features

One of the main features of this book, as in earlier editions, is the **number of applications of chemical concepts presented in the boxes**. Another important feature is the **Glossary**, which is now separate from the Index. The definition of each term is given along with the number of the section in which the term appears. Another feature is the list of **Key Terms** at the end of each chapter, with notation of the section number in which the term is introduced. Some chapters list **Key Reactions** after the Key Terms. Many students find these lists to be helpful study tools.

Other features are the **Summary** at the end of each chapter and the substantial number of **Margin Notes**. In this sixth edition, we have added **Margin Definitions** to complement nearby text. Another new feature includes **Conceptual Problems** at the end of every chapter, which provide a balance of conceptual understanding and reinforcement of critical skills. Here is a summary of the new features:

New Feature	Location	Benefit
Margin definitions	Throughout text	Helps student learn terminology; avoids cluttering narrative with definitions
Molecular artwork	Throughout text	Helps student visualize molecular properties and reactions
Conceptual Problems	At end of each chapter	Helps student frame the problems in the proper conceptual framework; avoids rote problem-solving
Key Reactions	At end of most Organic chapters	Provides convenient reference
Glossary separate from Index; terms identified by section number	At end of text, precedes Index	Allows for more terms to be defined and thus improves student comprehension of terminology



(James King-Holmes / Science Photo Library / Photo Researchers, Inc.)

Style

Feedback from colleagues and students alike indicates that the style of the book, which addresses the students directly in simple and clear phrasing, is one of its major assets. We continue to make special efforts to provide clear and concise writing. Our hope is that this facilitates the understanding and absorption of difficult concepts.

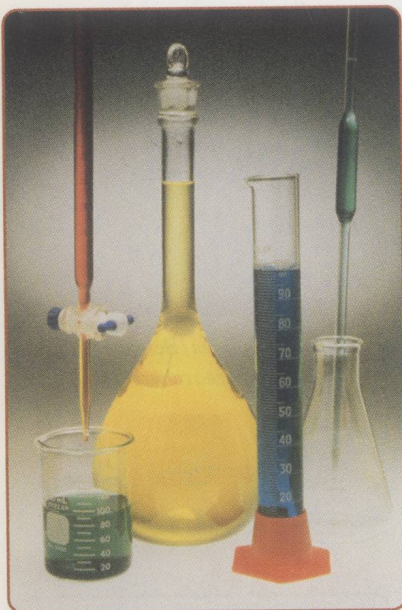
Problems

About 25 percent of the problems in this edition are new. The number of starred problems, which represent the more challenging, thought-provoking questions, has been increased. The end-of-chapter problems are grouped and given subheads in order of topic coverage. In the last group, headed "Additional Problems," problems are not arranged in any specific order. The answers to all the in-text problems and to the odd-numbered end-of-chapter problems are given at the end of the book. Answers to the even-numbered problems are included in the Instructor's Manual.

Ancillaries

An Introduction to General, Organic & Biochemistry, a more complete version of this text, is available to those instructors who include the general chemistry chapters. Both the full version and the modified texts are accompanied by a number of ancillary publications.

- **Student CD-ROM** New to this edition, this high-quality interactive CD-ROM, created by William Vining at the University of Massachusetts, features tutorials in general chemistry, practice in visualizing organic molecules, and some biochemistry animations.
- **Web Site** An interactive Web site containing, among other things, extra practice exercises, teaching and learning tips correlated to each chapter, and PowerPoint™ presentations.
- **Study Guide** by William Scovell, Bowling Green State University. Includes reviews of chapter objectives, important terms and comparisons, focused reviews of concepts, and self-tests.
- **Instructor's Manual** by text authors contains suggested course outlines and answers to the even-numbered problems.
- **Test Bank** by Peter Krieger of Palm Beach Community College and Shawn Farrell of Colorado State University contains more than 1600 multiple-choice questions—more than twice as many questions as in the last edition.
- **ExaMaster™ Computerized Test Bank** is the software version of the printed test bank. Instructors can create thousands of questions in the multiple-choice format. A command reformats a multiple-choice question into a short-answer question. New problems can be added and existing problems modified, and graphics can be incorporated. ExaMaster™ has grade-book capabilities for recording and graphing students' grades.
- Approximately 150 **Overhead Transparencies** in full color are available. Figures and tables are taken from the text.
- **Laboratory Experiments for General, Organic & Biochemistry, 4/e**, by Frederick A. Bettelheim and Joseph M. Landesberg.



(Charles D. Winters)

Fifty-two experiments—including a new one on analysis of drinking water and one on the law of definite proportions—illustrate important concepts and principles in general, organic, and biochemistry. Many experiments have been revised to miniscale the use of chemicals for environmental concerns and economic reasons. The large number of experiments allows sufficient flexibility for the instructor.

- **Instructor's Manual** to accompany Laboratory Experiments. This manual will help instructors in grading the answers to the questions and in assessing the range of experimental results obtained by students.
- **Chemistry 2001 Instructor CD-ROM** provides imagery from the text. Available as a presentation tool, this CD-ROM can be used in conjunction with commercial presentation packages, such as PowerPoint™, Persuasion™, and Podium™, as well as the Lecture-Active™ presentation software. Available in both Macintosh® and Windows™ platforms.
- **Flash Cards** by H. Akers, Lamar University, comprise 200 bi-directional flash cards that offer drills on important reactions, terms, structures, and classifications.

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(Charles D. Winters)

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Frederick A. Bettelheim

William H. Brown

June 2000

REVISION SUMMARY

The major organizational changes are in the organic and biochemistry chapters. The order of chapters has been changed to:

1. Provide more logical order in pedagogy.
2. Emphasize the shift in importance of biochemical topics and the tremendous developments in some fields of biochemistry.
3. Help solidify the connection between organic and biochemistry. The logical order emphasizes the presentation of a topic (e.g., proteins), first emphasizing the structure, the chemistry, and biological properties, before discussion of interactions.

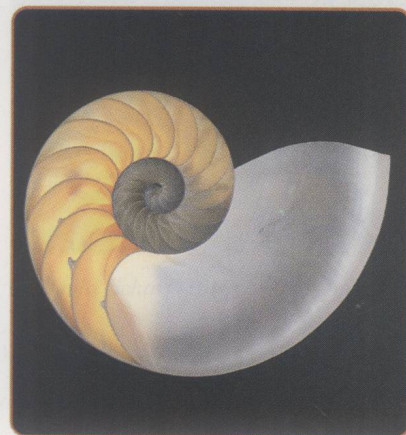
In general, every chapter has been updated to reflect advances in the disciplines and professions involving chemistry. Every chapter has about four new **Conceptual Problems** and 25 percent new problems overall. Every chapter has **Margin Definitions** of those terms that were not defined in the text. Throughout the text, particularly in the organic chapters, we have added ball-and-stick and space-filling **molecular models** to encourage students to think of molecules as three-dimensional objects.

Below is a short outline of the overall features of the presentation. Please read the rest of the Preface for more details.

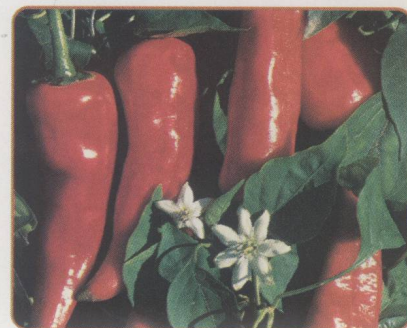
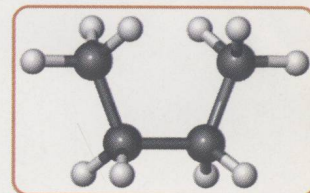
Feature	Benefit
Greater integration of general, organic, and biochemistry	Student acquires a unified view of chemistry.
Logical presentation of structures first, followed by metabolism	All factors in metabolism are established before their interactions are treated.
Ample illustrations of principles in boxes, more than any competing text	Generates interest when students see applications to every principle.
Unique, extensive coverage of the discipline, such as chemical communication and immunochemistry	Students advancing to health professions will apply this knowledge in various procedures and administering of drugs.
Challenging problems identified by asterisks	Gives instructor flexibility in assigning problems and avoids rote problem-solving.
Many new photographs and molecular models	Helps students visualize difficult topics.

Organic Chemistry

Reviewers have commented that the reorganization of the organic chemistry material allows for **greater flexibility** in presentation. Also, the separation of some topics makes each less intimidating to the student. These chapters do retain their concentration on the structure, properties, and reactions of only those **functional groups** necessary to lay a foundation for the coverage of biochemistry that follows. We consider the progress from general to organic to biochemistry to be an ascent and, in the organic chapters, we concentrate on the classes of organic compounds and reactions that have physiological activity of one sort or another and have **biological importance**.



(Charles D. Winters)



(Connie Brown)

The organic section begins with **Chapter 1, Organic Chemistry**. This short chapter concentrates on the structure of organic compounds and an introduction to the concept of functional groups: the hydroxyl group of alcohols, the amino group of amines, the carbonyl group of aldehydes and ketones, and the carboxyl group of carboxylic acids.

Chapter 2, Alkanes and Cycloalkanes, concentrates on the structure of these two classes of saturated hydrocarbons and further develops an appreciation of molecular shapes through the study of conformations of alkanes and cycloalkanes, and cis-trans isomerism in cycloalkanes.

Chapter 3, Alkenes and Alkynes, introduces students to one aspect of the molecular logic of living systems—namely, that in building large molecules (in this case, terpenes), small subunits (in this case, isoprene units) are strung together by a series of enzyme-catalyzed reactions. Chapter 3 also introduces students to organic reactions, with concentration on the acid-catalyzed hydration of alkenes. It is only in this chapter that reaction mechanisms are discussed—namely, carbocation intermediates in alkene addition reactions. **We limit our discussion of mechanisms deliberately**; in the relatively brief portion of the text devoted to organic chemistry, students have little time to learn anything substantial about them. Chapter 3 closes with a brief overview of polymerization of ethylene and substituted ethylenes, including the structure and properties of both low-density and high-density polyethylenes.

Chapter 4 is devoted to the structure, nomenclature, and important reactions of **Alcohols, Ethers, and Thiols**. Then follows **Chapter 5**, which concentrates on the structure of **Benzene and Its Derivatives**, as well as the acidity of phenols.

Chapter 6, unique to this text, is an early introduction to **Chirality** and the significance of chirality in the biological world. It has been common in the past to introduce chirality within the context of carbohydrates or amino acids, but the subject of chirality is broader than this. Furthermore, chirality is an additional demonstration of the importance of viewing molecules as three-dimensional objects. The R,S system for assigning configuration to a stereocenter is developed in a simple and direct manner. It is our belief that a greater understanding of molecular shape facilitates the mastery of molecular behavior, knowledge that these students will apply both in this course and in their profession. *Note:* This chapter can be moved up closer to Chapter 10, Carbohydrates, if desired.

Chapter 7 concentrates on the most important chemical property of **Amines**—namely, their basicity. **Chapters 8 and 9** are devoted to the chemistry of **Aldehydes and Ketones** and **Carboxylic Acids and Their Derivatives**. Included in Chapter 9 is an overview of step-growth polymerization and the structure of representative polyamides, polyesters, and polycarbonates.

Bioorganic chemistry is emphasized throughout the organic chapters in 30 boxes and in problems. There are numerous references to *The Merck Index* (Susan Budavari, Editor, 12th Edition, Merck Research Laboratories, 1996). At no point are students required to access this valuable resource. Rather, these new references are given for those who wish to learn more about the chemistry and biochemistry of organic compounds mentioned in the text.

New to these chapters are a large number of ball-and-stick and space-filling **molecular models**. Their purpose is to assist students in visualizing the three-dimensional nature of organic molecules. All models have been prepared using CambridgeSoft Corporation ChemDraw and Chem3D software.

An end-of-chapter summary of **Key Reactions** highlights each new reaction presented in the organic chapters and keys each to the section where it is discussed.

Biochemistry

The logical order emphasizes the presentation of a topic first in separate chapters—(e.g., Carbohydrates and Lipids), discussing the structure, chemistry, and biological properties—and the interrelationship with other groups of compounds in later chapters on metabolism, nutrition, immunochemistry, and so on.

The Nucleic Acids and Protein Synthesis chapter from the third edition has been separated into two chapters to properly represent the exploding information available in this field. A new chapter on Immunochemistry has been created to pull together the essential information in this rapidly developing field, which is so important in the health sciences. The Nutrition chapter has been moved to follow immediately after Metabolism (Chapters 17 to 19) in order to emphasize the connection between the two topics. More details follow:

In **Chapter 10, Carbohydrates**, we make the distinction between the R,S system and the D,L system of configuration, offer extra treatment of chair conformations, and add new boxes on Glucose Assay and Blood Types.

In **Chapter 11, Lipids**, we have added topics, including phosphatidyl inositol as a signaling agent, COX enzymes in prostaglandin production, and thromboxanes. There is a new box on transport across cell membranes and new material in Box 11J, Action of Anti-Inflammatory Drugs.

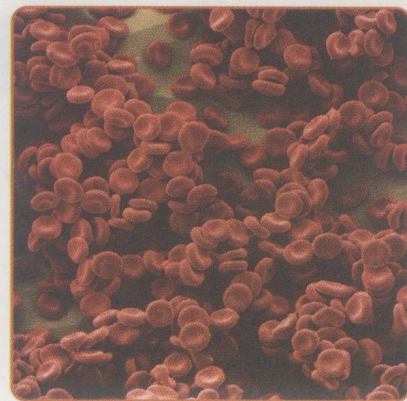
There is an abundance of new topics in **Chapter 12, Proteins**, including fetal hemoglobin; classification of glycoproteins on the basis of the carbohydrate-protein linkage; hydroxyurea, a new treatment of sickle cell disease, protein conformation-dependent diseases (mad cow, Jacob-Kreutzfeld, prion); the power of quaternary structure in mechanical stress and strain, and laser surgery (denaturation by physical means).

In **Chapter 13, Enzymes**, we examine enzymes of thermophilic bacteria and PCR technique, the pH environment of *Helicobacter*, a detailed 3D map of the active site of pyruvate kinase, and protein modification (phosphorylation) and enzyme activity.

A major rewriting of **Chapter 14, Chemical Communication: Neurotransmitters and Hormones** combines discussion of neurotransmitters and hormones and treats them from the point of view of the chemical nature of the messenger. New emphasis is placed on the trinity of mode of transmission, receptor/ligand/secondary messengers, and the fact that most drugs in use affect chemical communications in one way or another and that drugs may act as (a) agonists or (b) antagonists of receptors, (c) influencing the release of chemical messengers, (d) influencing the decomposition of chemical messengers. Other covered topics include ligand-gated ion channel, signal transduction-G-protein-adenylate cyclase cascade, amino acid neurotransmitters and NMDA receptor, P-protein, and steroid hormone action. New boxes on calcium as secondary messenger and breast cancer and tamoxifen have been added, and the box on nitric oxide has been completely revised.

In **Chapter 15, Nucleotides, Nucleic Acids and Heredity**, we have updated our treatment of polymerase factories and PCR techniques and added new boxes on telomerase and immortality and on apoptosis (programmed cell death). In **Chapter 16, Gene Expression and Protein Synthesis**, we introduce ribozymes, update the discussion of signaling for transcription, present the 3D structure of ribosomes, and add a new box on tumor suppressor genes.

In **Chapter 17, Bioenergetics**, we have revised the discussion of oxidative phosphorylation, present structural details of proton translocating ATPase, and examine superoxide dismutase. In **Chapter 18, Specific Catabolic Pathways**, we detail the pentose phosphate pathway and



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examine ubiquitin and cystic fibrosis. The role of RubisCo enzyme in photosynthesis is included in **Chapter 19, Biosynthetic Pathways**.

In **Chapter 20, Nutrition and Digestion**, we have condensed the presentation of RDA and other information on vitamins and minerals in table form, cited the new Dietary Reference Intakes (a set of dietary recommendations new to the field of nutrition), and added a new box on dieting. **Chapter 21, Immunochemistry** is an entirely **new chapter** that will help prepare students for further work and study in health fields. Topics include location of the immune system, antigens and antigen presentation, immunoglobulins, T cells and their responses, control of immune response, and cytokines. There are boxes on myasthenia gravis, antibodies and cancer therapies, immunization, and mobilization of leukocytes. The final chapter, **Chapter 22, Body Fluids**, presents new problems, and updated information in all boxes.

A final note on organization and coverage:

This new edition has a total of three more chapters than the third edition, yet the amount of material is basically the same in order to ease the burden of teaching. The new organization of the organic and biochemistry chapters has been carefully planned to permit greater flexibility in coverage.