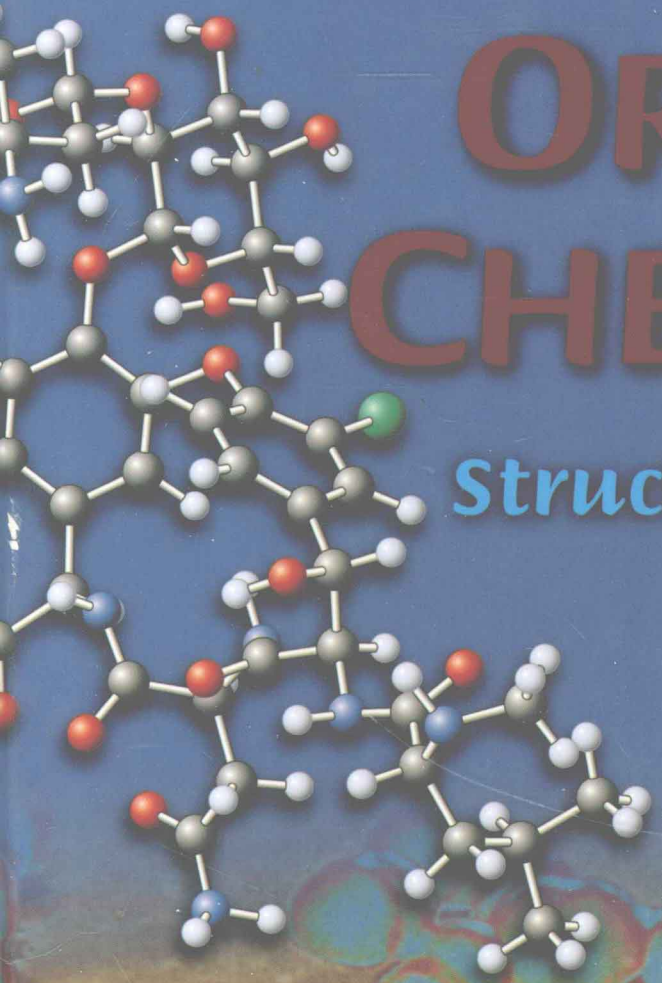
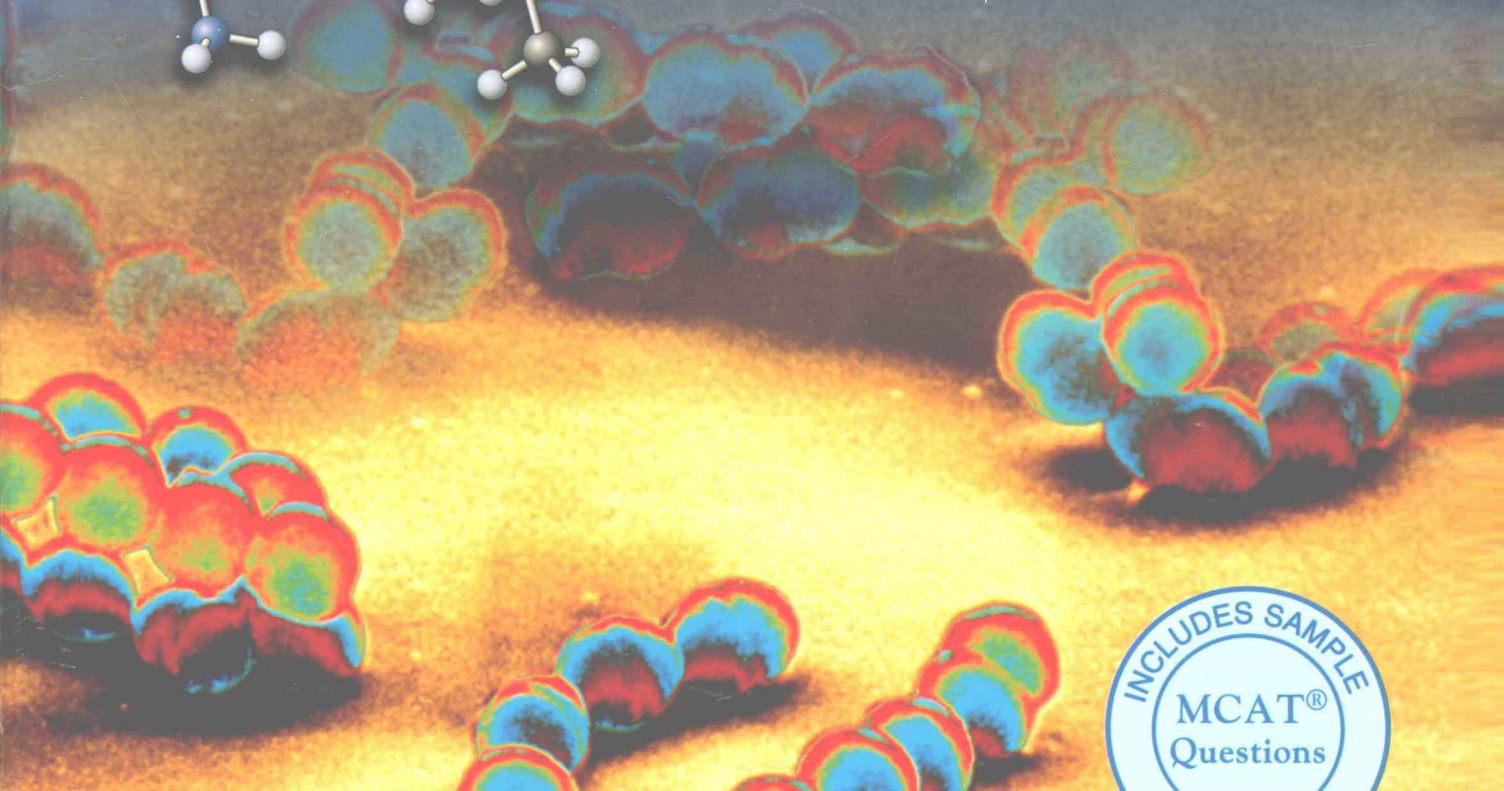
K. PETER C. VOLLHARDT NEIL E. SCHORE

ORGANIC CHEMISTRY

Structure and Function

FOURTH EDITION





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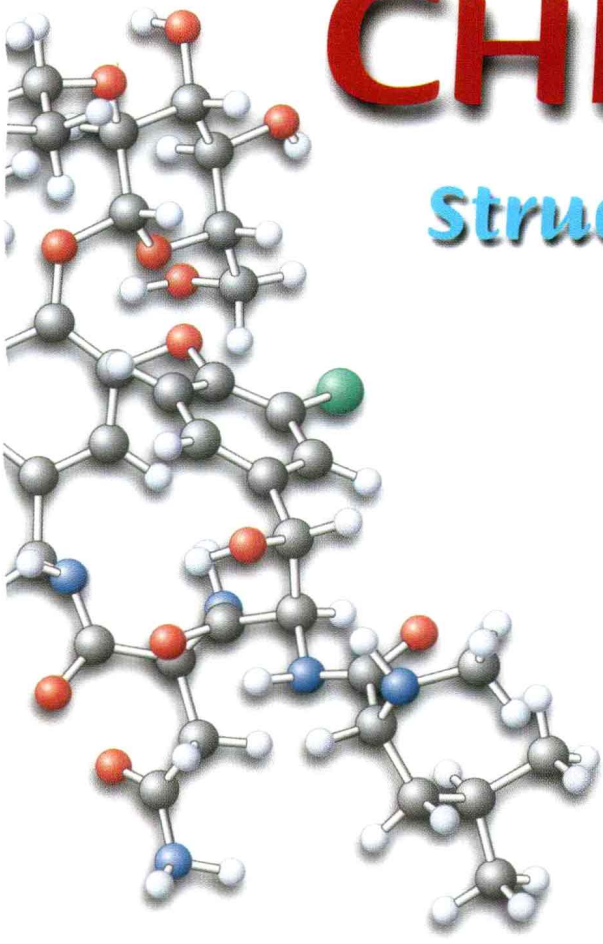

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New York

ABOUT THE COVER

Hailed as the last line of defense against bacteria, vancomycin is one of the most successful antibiotics clinically used today against drug-resistant bacteria. First discovered by Eli Lilly and Company in 1956, this important natural product possesses a novel and challenging molecular architecture that withstood the attempts of synthetic chemists to construct it in the laboratory for many years. Recently, however, improved synthetic strategies and tactics led to its total synthesis independently by the groups of K. C. Nicolaou at The Scripps Research Institute and the University of California, San Diego (who provided the idea for the cover picture, based on that of *Angewandte Chemie International Edition* **1999**, *38,* issue 15), David A. Evans at Harvard University, and Dale L. Boger at The Scripps Research Institute. The front cover shows the molecule of vancomycin (as a ball-and-stick model), hovering over a picture of *Streptococcus pyogenes,* recent strains of which have shown dangerous drug resistance. The model of vancomycin wraps around to the back, on which we also depict the molecules of erythromycin and penicillin, two of the most celebrated antibiotics of all time. Synthetic strategies used to construct complex molecules, such as these three antibiotics, are discussed in Chapter 8 and subsequently throughout the text. The biological and medicinal context of organic molecules is addressed in many Chemical Highlights, such as Chemical Highlight 20-2, which specifically discusses the antibiotics on the cover, in the general text, and in numerous problems.

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Preface

A User's Guide to *Organic Chemistry: Structure and Function*

Over the previous editions of *Organic Chemistry: Structure and Function,* we have tried to provide a logical framework for students to learn and understand the material. This framework is the idea that understanding the structure of an organic molecule can lead to understanding how that molecule functions in a chemical reaction. Our goal has been to help students make sense of the potentially overwhelming multitude of facts presented in the course and fit them into a cohesive picture of contemporary organic chemistry. We have continued this theme in the present edition by reinforcing its practical application to problem solving and by cutting back on extraneous details, emphasizing instead the major ideas of reactivity, mechanisms, and applications.

Accessible for Students

Review and Extension of General Chemistry Concepts

The first five chapters of the book focus on the general principles of bonding, reactivity, and stereochemistry that enable students to understand the connections between structure and function. Thus, Chapter 1 reviews the fundamentals of how structure affects bonding, laying the groundwork for later examinations of functional groups. Chapter 2 discusses the basics of polar reactions, comparing the properties of acids and bases with those of nucleophiles and electrophiles, while also presenting initial ideas of reaction kinetics and thermodynamics.

2-2 Acids and Bases; Electrophiles and Nucleophiles
Let us turn to a fundamental application of thermodynamics: the chemistry of acids and bases. This section reviews the way in which acids and bases interact and how we quantify this process. We shall see that acid-base reactions provide a model for the reactivity of organic molecules possessing polar covalent bonds.

Developing the Basic Tools for Understanding Function

We provide an overview of the major functional groups of organic chemistry in Chapter 2. Chapter 2 also describes the nonreactive backbone of common organic molecules, as illustrated by the properties and behavior of the alkanes. Chapter 3 introduces the idea of bond-dissociation energies, illustrated by the radical halogenation of alkanes. Chapter 4 presents the first cyclic molecules, the cycloalkanes. Finally, to prepare students for learning the mechanisms of substitution and elimination reactions of haloalkanes (Chapters 6 and 7) and the addition reactions of alkenes (Chapter 12), in Chapter 5 we cover stereochemistry.

Innovative Pedagogy for Solving Problems

WORKING WITH THE CONCEPTS Before we go into the details of this problem, let us dissect it along the lines of taking an inventory:

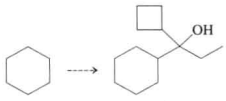
1. What topological/connectivity changes are taking place? *Answer:* The six-membered ring stays intact, but the functionality has migrated from a secondary to a tertiary carbon.
2. What is the change in molecular formula? *Answer:* We start with $C_7H_{14}O$ and wind up with $C_7H_{13}Br$. The net change is that OH is being replaced by Br; no carbons are added or subtracted from the starting material.
3. What thoughts come to mind when considering the functional group and the reagent to which it is exposed? *Answer:* We have an alcohol that is treated with HBr, a strong acid. The hydroxy function will be protonated, turning it into a good leaving group, and hence we have to consider substitution and elimination as possible reaction pathways.
4. The answer to point 1 (rearrangement) and consideration of point 3 (alcohol and acid) strongly implicate an acid-catalyzed rearrangement via a carbocation.

New to this edition are worked-out solutions to in-chapter exercises, called **Working with the Concepts.** These solutions, two per chapter, emphasize the reasoning students need to apply in attacking problems, arranging the steps logically and carefully so students can see the pitfalls and avoid them. The exercises chosen are typical homework or test problems, so students get a feel for solving complex problems rather than artificially simplified situations.

Special categories of end-of-chapter problems, introduced in the preceding edition, have been retained in this one:

8-19. Tertiary alcohols are important additives in some industrial processes utilizing Lewis acidic metal compounds (Sections 2-2 and 6-4) as catalysts. The alcohol provides the metal with a sterically protecting and hydrophobic environment (see Figure 8-3; see also Chemical Highlight 8-1), which ensures solubility in organic solvents, longer lifetimes, and selectivity in substrate activation. Preparation of these tertiary alcohols typically follows the synthetic principles outlined in Section 8-9.

Starting from cyclohexane and using any other building blocks containing four or fewer carbons, in addition to any necessary reagents, formulate a synthesis of tertiary alcohol A.



A

- We have doubled the number of **Chapter Integration Problems**, which feature worked-out step-by-step solutions involving several concepts from within chapters and from among several chapters. As before, we place particular emphasis on problem analysis, deductive reasoning, and logical conclusions.
- **Team Problems** encourage discussion and collaborative learning among students. They can be assigned as regular homework but can also be worked on by groups of students in a library, study hall, or dormitory room, where free exchange of ideas and information can take place.
- For students planning careers in medicine or related fields, **Preprofessional Problems** have a multiple-choice format typical of problems on the MCAT®, GRE, and DAT. In addition, a selection of actual test passages and questions from past MCAT® exams appears in an appendix.

Help in Seeing the Big Picture

IN SUMMARY In Brønsted-Lowry terms, acids are proton donors and bases are proton acceptors. Acid-base interactions are governed by equilibria, which are quantitatively described by an acidity constant K_a. Removal of a proton from an acid generates its conjugate base; attachment of a proton to a base forms its conjugate acid. Lewis bases donate an electron pair to form a covalent bond with Lewis acids, a process depicted by a curved arrow pointing from the lone pair of the base toward the acid. Electrophiles and nucleophiles are species in organic chemistry that interact very much like acids and bases. The carbon–halogen bond in the haloalkane is its functional group. It contains an electrophilic carbon atom, which reacts with nucleophiles in a process called nucleophilic substitution.

Because students are presented with so many facts to learn about the structure and function of the various families of organic compounds, it is easy for them to lose sight of the important concepts in the course. In this edition, we have highlighted a short summary at the end of most sections in the book, emphasizing the main ideas for students to remember.

THE BIG PICTURE

Alkanes lack functional groups, so they do not undergo the kinds of electrophile–nucleophile reactions typical of functionalized molecules. In fact, alkanes are pretty unreactive. However, under appropriate conditions, they undergo homolytic bond cleavage to form radicals, which are reactive species containing odd numbers of electrons. This is another situation in which the *structure* of a class of compounds determines their *function*. Unlike heterolytic processes, which normally proceed via movement of *pairs* of electrons to form or break bonds, homolytic chemistry utilizes the splitting of covalent bonds to give unpaired *single* electrons, as well as their combination to give new bonds.

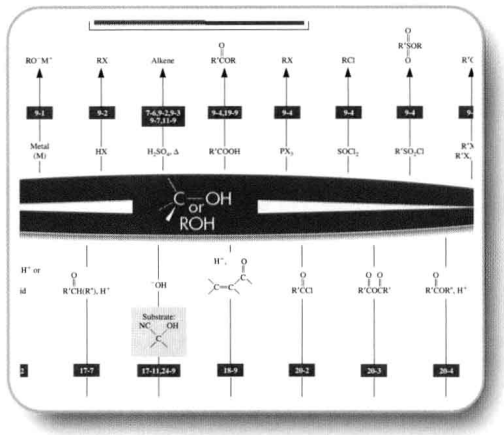
Although in organic chemistry radical reactions are not encountered as frequently as those of polar functional groups, they play prominent roles in biological, environmental, and industrial chemistry. The halogenation of alkanes, a radical process in which hydrogen is replaced by halogen, forms the haloalkane functional group. Examination of halogenation allows us to learn about a number of features common to most transformations, including the way information about a reaction mechanism may be obtained from experimental observations, the relationship between thermodynamics and kinetics, and notions of reactivity and selectivity. The products of halogenation, the haloalkanes, are the starting compounds for a wide variety of reactions, as we will see in Chapters 6–9.

Before we examine other classes of compounds and their properties, we need to learn more about the structures and, in particular, the geometric shapes of organic molecules. In Chapter 4 we discuss compounds that contain atoms in rings, and in Chapter 5 we study additional forms of isomerism. The ideas we introduce are a necessary background as we begin a systematic study of polar reactions of haloalkanes and alcohols in the chapters that follow.

In addition, the end of each chapter has a short section, called **The Big Picture,** that reinforces the connections between topics and fits the material into the overall presentation of the course. These sections are not summaries, but serve as road maps to indicate where we've been and where we're going. They often reinforce the themes stated in the chapter opening introductions, which help set the context for the material in the chapter.

We have retained the **Reaction Summary Road Maps,** also at the ends of some chapters, that summarize the reactions for preparation and applications of each major functional group. However, we have

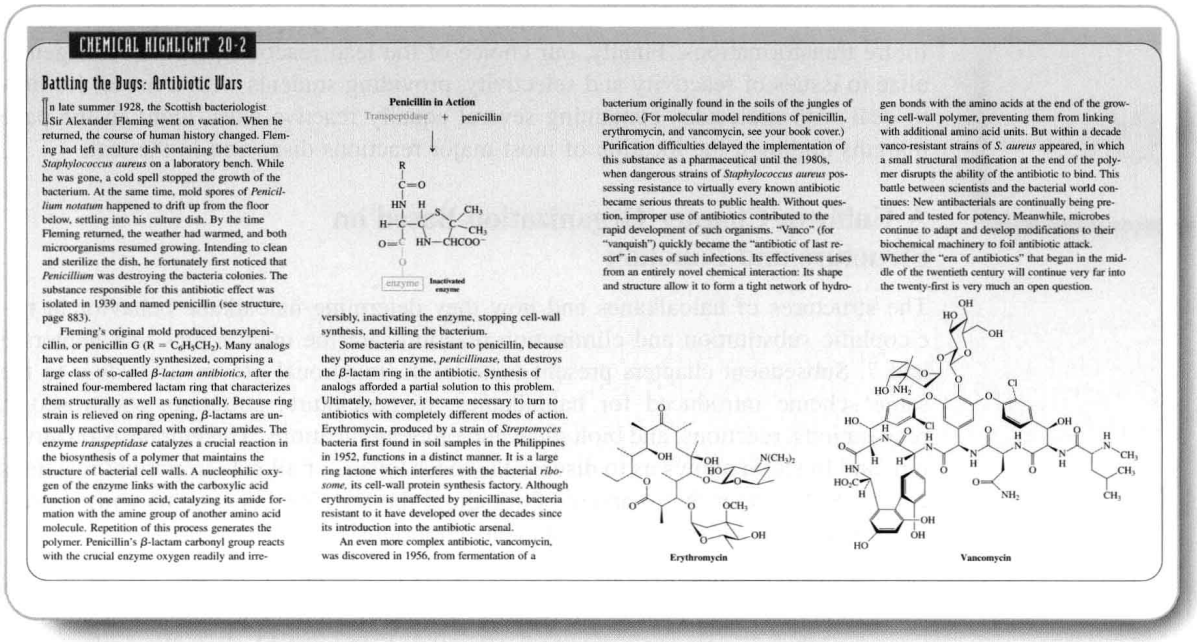
simplified these maps to make them more useful for students. As before, the **Preparation maps** indicate the possible origins of a functionality—that is, the precursor functional groups. The **Reaction maps** show what each functional group does. Reaction arrows in both maps are labeled with particular reagents and start from or end at specific reactants or products. The reaction arrows are also labeled with section numbers indicating where the transformation is discussed in the text.



Real Chemistry by Practicing Chemists

An Emphasis on Practical Applications

Every chapter of this text features discussions of biological, medical, and industrial applications of organic chemistry, many of them new to this edition. Some of these applications are found in the text discussion, others in the exercises, and still others



CHEMICAL HIGHLIGHT 20-2

Battling the Bugs: Antibiotic Wars

In late summer 1928, the Scottish bacteriologist Sir Alexander Fleming went on vacation. When he returned, the course of human history changed. Fleming had left a culture dish containing the bacterium *Staphylococcus aureus* on a laboratory bench. While he was gone, a cold spell stopped the growth of the bacterium. At the same time, mold spores of *Penicillium notatum* happened to drift up from the floor below, settling into his culture dish. By the time Fleming returned, the weather had warmed, and both microorganisms resumed growing. Intending to clean and sterilize the dish, he fortunately first noticed that *Penicillium* was destroying the bacteria colonies. The substance responsible for this antibiotic effect was isolated in 1939 and named penicillin (see structure, page 883).

Fleming's original mold produced benzylpenicillin, or penicillin G (R = $C_6H_5CH_2$). Many analogs have been subsequently synthesized, comprising a large class of so-called *β-lactam antibiotics*, after the strained four-membered lactam ring that characterizes them structurally as well as functionally. Because ring strain is relieved on ring opening, β-lactams are unusually reactive compared with ordinary amides. The enzyme *transpeptidase* catalyzes a crucial reaction in the biosynthesis of a polymer that maintains the structure of bacterial cell walls. A nucleophilic oxygen of the enzyme links with the carboxylic acid function of one amino acid, catalyzing its amide formation with the amine group of another amino acid molecule. Repetition of this process generates the polymer. Penicillin's β-lactam carbonyl group reacts with the crucial enzyme oxygen readily and irreversibly, inactivating the enzyme, stopping cell-wall synthesis, and killing the bacterium.

Penicillin in Action

Transpeptidase + penicillin

enzyme — Inactivated enzyme

Some bacteria are resistant to penicillin, because they produce an enzyme, *penicillinase*, that destroys the β-lactam ring in the antibiotic. Synthesis of analogs afforded a partial solution to this problem. Ultimately, however, it became necessary to turn to antibiotics with completely different modes of action. Erythromycin, produced by a strain of *Streptomyces* bacteria first found in soil samples in the Philippines in 1952, functions in a distinct manner. It is a large ring lactone which interferes with the bacterial *ribosome*, its cell-wall protein synthesis factory. Although erythromycin is unaffected by penicillinase, bacteria resistant to it have developed over the decades since its introduction into the antibiotic arsenal.

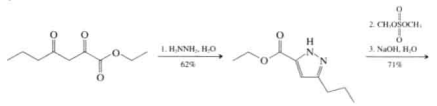
An even more complex antibiotic, vancomycin, was discovered in 1956, from fermentation of a bacterium originally found in the soils of the jungles of Borneo. (For molecular model renditions of penicillin, erythromycin, and vancomycin, see your book cover.) Purification difficulties delayed the implementation of this substance as a pharmaceutical until the 1980s, when dangerous strains of *Staphylococcus aureus* possessing resistance to virtually every known antibiotic became serious threats to public health. Without question, improper use of antibiotics contributed to the rapid development of such organisms. "Vanco" (for "vanquish") quickly became the "antibiotic of last resort" in cases of such infections. Its effectiveness arises from an entirely novel chemical interaction: Its shape and structure allow it to form a tight network of hydrogen bonds with the amino acids at the end of the growing cell-wall polymer, preventing them from linking with additional amino acid units. But within a decade vanco-resistant strains of *S. aureus* appeared, in which a small structural modification at the end of the polymer disrupts the ability of the antibiotic to bind. This battle between scientists and the bacterial world continues: New antibacterials are continually being prepared and tested for potency. Meanwhile, microbes continue to adapt and develop modifications to their biochemical machinery to foil antibiotic attack. Whether the "era of antibiotics" that began in the middle of the twentieth century will continue very far into the twenty-first is very much an open question.

Erythromycin

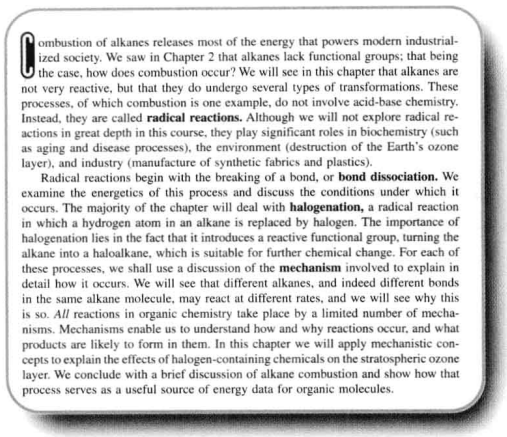
Vancomycin

in the **Chemical Highlight** boxes. Topics range from new families of antibiotics to fight drug-resistant bacteria (Chapter 20) to organic polymers that conduct electricity (Chapter 14) to some recent advances in the chemistry of fused hydrocarbon rings (Chapter 15). Updated applications include synthetic chlorine compounds and the stratospheric ozone layer (Chapter 3), chiral substances in nature (Chapter 5), and carbohydrate-derived sugar substitutes (Chapter 24).

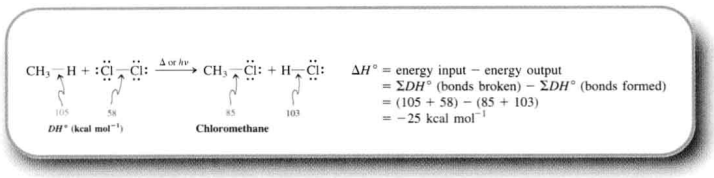
25-23. Viagra (sildenafil citrate, see Chapter Opening) was introduced in 1998 as an effective way to treat male erectile dysfunction (MED). It was discovered accidentally during clinical trials of the compound as a treatment for coronary heart disease and works by enhancing the production of nitric oxide (NO) in erectile tissue, ultimately leading to vasodilation (see Chemical Highlight 26-1). The route by which Viagra was made originally in the research laboratory is shown below.

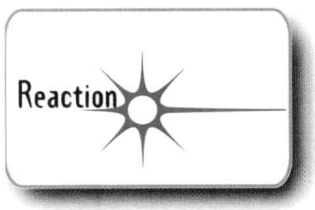


A major application of organic chemistry, stressed throughout the text, is the synthesis of new products and materials. We emphasize the development of a good synthetic strategy and the


Combustion of alkanes releases most of the energy that powers modern industrialized society. We saw in Chapter 2 that alkanes lack functional groups; that being the case, how does combustion occur? We will see in this chapter that alkanes are not very reactive, but that they do undergo several types of transformations. These processes, of which combustion is one example, do not involve acid-base chemistry. Instead, they are called **radical reactions.** Although we will not explore radical reactions in great depth in this course, they play significant roles in biochemistry (such as aging and disease processes), the environment (destruction of the Earth's ozone layer), and industry (manufacture of synthetic fabrics and plastics).

Radical reactions begin with the breaking of a bond, or **bond dissociation.** We examine the energetics of this process and discuss the conditions under which it occurs. The majority of the chapter will deal with **halogenation,** a radical reaction in which a hydrogen atom in an alkane is replaced by halogen. The importance of halogenation lies in the fact that it introduces a reactive functional group, turning the alkane into a haloalkane, which is suitable for further chemical change. For each of these processes, we shall use a discussion of the **mechanism** involved to explain in detail how it occurs. We will see that different alkanes, and indeed different bonds in the same alkane molecule, may react at different rates, and we will see why this is so. *All* reactions in organic chemistry take place by a limited number of mechanisms. Mechanisms enable us to understand how and why reactions occur, and what products are likely to form in them. In this chapter we will apply mechanistic concepts to explain the effects of halogen-containing chemicals on the stratospheric ozone layer. We conclude with a brief discussion of alkane combustion and show how that process serves as a useful source of energy data for organic molecules.





avoidance of pitfalls, illustrating these ideas with many Working with the Concepts and Integration Problems. Specific syntheses of biological and medicinal importance are discussed in many chapters.

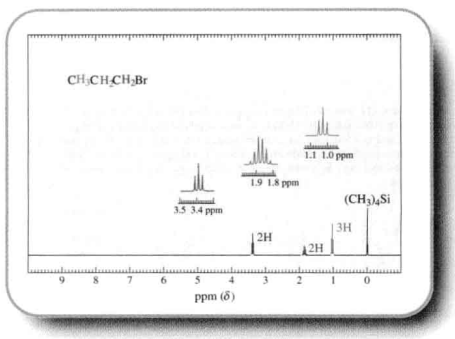
Early Introduction of Reactions

The payoff for learning how structure affects function comes in understanding organic reactions. In this edition, we have revised Chapter 2 to place more emphasis on polar reactions, stressing their importance throughout the course. However, as in previous editions, the first reaction we discuss in detail is the radical halogenation of methane, presented in Chapter 3. This sequence enables us to introduce the concepts of bond-dissociation energy and the stability of radicals in the context of the simplest organic bonds, C—H and C—C. Because the halogenation of methane does not include ionic species, we can analyze the overall process, as well as the individual steps, from the point of view of thermodynamics and potential energy diagrams, giving students new tools for judging the feasibility of all future transformations. Finally, our choice of the lead reaction permits us to generalize to issues of reactivity and selectivity, providing students with a model for how to deal with molecules containing several equally reactive sites. Icons in the page margins highlight the location of most major reactions discussed in the text.

A Uniform Chapter Organization Based on Structure and Function

The structures of haloalkanes and how they determine haloalkane behavior in nucleophilic substitution and elimination reactions are the main topics of Chapters 6 and 7. Subsequent chapters present material on functional groups according to the same scheme introduced for haloalkanes: nomenclature, structure, spectroscopy, preparations, reactions, and biological and other applications. The emphasis on structure and function allows us to discuss the mechanisms of all new important reactions concurrently, rather than scattered throughout the text. We believe this unified presentation of mechanisms benefits students enormously.

We treat alcohols early (Chapters 8 and 9), because understanding their chemistry leads to appreciating their central role in synthesis. Similarly, we present carbocations (and their rearrangements; see Section 9-3) before the Markovnikov rule (Chapter 12); alkenes (Chapter 12) before conjugated polyenes (Chapter 14); and conjugated polyenes before aromatic systems (Chapter 15). The coverage of spectroscopy in the first half of the text (Chapters 10 and 11), after students have learned some of the basic functional groups, continues the theme of how structure affects function. This organization allows students to apply spectroscopic techniques in the context of later functional groups.



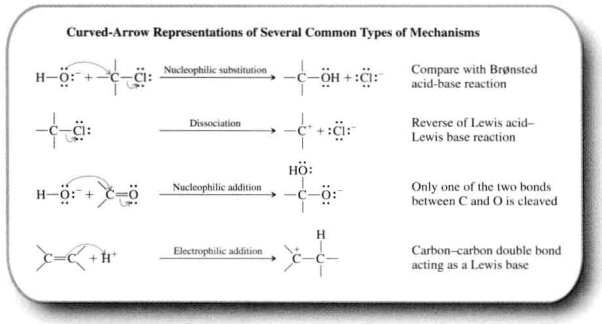
Updated Presentation of Spectroscopy

We integrate spectroscopy into relevant chapters, but nevertheless in a modular manner that allows the instructor to introduce it at any stage of the course. We have thoroughly revised the treatment of NMR spectroscopy (Chapter 10) with 300-MHz spectra, instead of the older

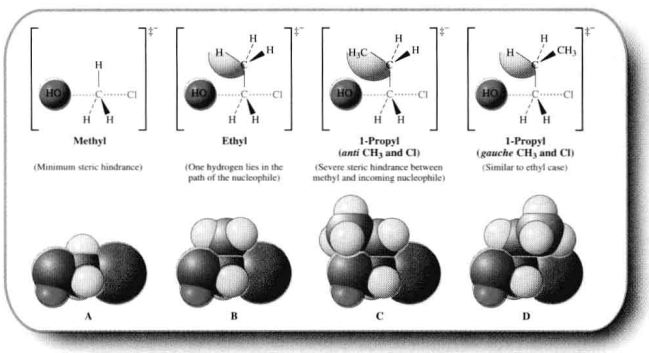
90-MHz spectra, and we present new 300-MHz spectra in all subsequent chapters. As before, we place NMR and IR spectroscopy at the end of the first half of the book, so students have attained some familiarity with the functional groups used to explain the spectroscopic methods and can then learn the spectroscopic characteristics of all other types of compounds as they are introduced. We cover UV-visible spectroscopy in the context of delocalized pi systems (Chapter 14) and mass spectroscopy after the treatment of carbonyl compounds (in order to explain α-cleavage and the McLafferty rearrangement, Chapter 20). Several text discussions and problems unify the application of spectroscopic techniques in structure determination.

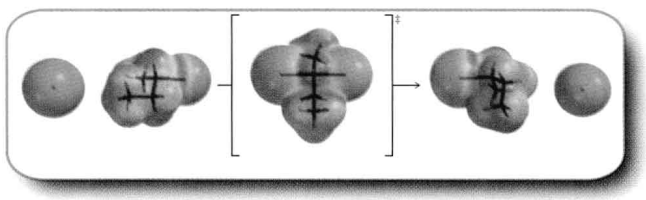
Visualizing Organic Chemistry

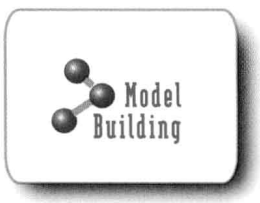
This edition continues our emphasis on mechanisms as a way of understanding why and how reactions occur. In response to comments from users, we have increased our use of electron-pushing arrows, introduced it earlier in Section 2-2, and reinforced it again in Section 6-3 and all subsequent chapters.



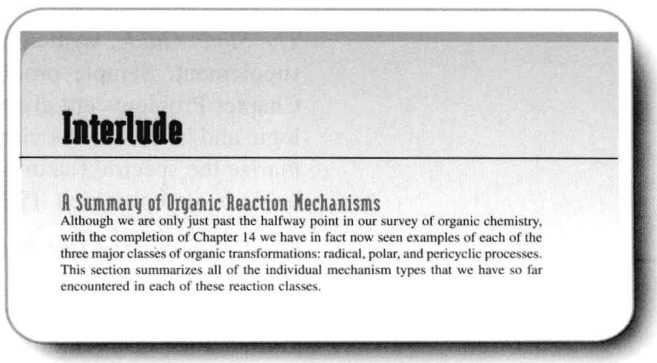
We have also retained the use of computer-generated ball-and-stick and space-filling models. As in the previous edition, icons in the page margins indicate where model-building by students would be especially helpful for visualizing three-dimensional structures and dynamics. In this edition, we have added electrostatic potential maps of many species, helping students see how their electron distribution affects their behavior with other species. Once again, structure determines function.





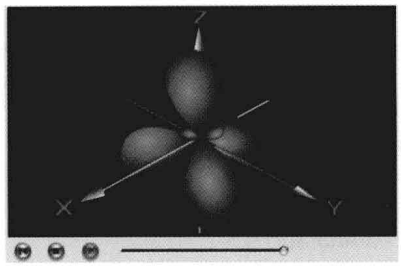


We continue to use icons in the page margins to highlight the location of important mechanisms. In this edition, we have also included marginal Media Link Icons to indicate those mechanisms that have been animated on the W. H. Freeman Web site. To emphasize to students the relatively few types of mechanisms that drive the majority of organic reactions, we summarize the mechanisms in an Interlude following Chapter 14.

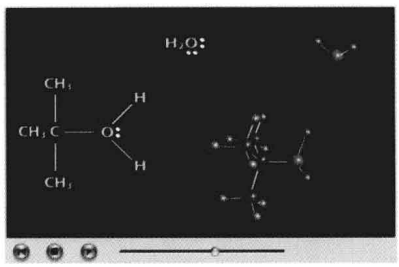


Supplements

The Web site found at **www.whfreeman.com/vollhardtschore4e** is a multimedia learning tool developed by W. H. Freeman and Company in conjunction with Sumanas, Inc. (some of the animations and Animated Mechanisms were storyboarded from the VisChem project created by Roy Tasker and the University of Western Sydney). All the features of the Web site function within the context of the book's coverage. Two features of this interactive Web site are integrated with the textbook using media icons and descriptive text.



- **Animations:** These Web accessible animations allow students to view motion, three dimensions, atomic and molecular interactions, and chemical reactions at a microscopic level. Topics focus on orbitals and hybridization.



- **Animated Mechanisms:** More than 25 animations that allow students to view molecular interactions as structural formulas and as ball-and-stick models. Topics include chemical reactivity and structures and bonding.

Other features of the Web site include:

- **Molecule Database:** 120 CHIME Molecular Models sorted by molecule type—structures mentioned in the book and depicted as three-dimensional animations with multiple-display options.
- **Online Quizzing:** 15–20 randomized multiple-choice questions per chapter, with assessment and feedback. Stores scores, so instructor can access them at a later date.
- **Nomenclature Exercises:** 19 drop and drag exercises designed for rote memorization.
- **Reaction Exercises:** 16 drop and drag exercises designed for memorization.
- **Tools:** Interactive periodic table and calculators in a Flash format.

The Study Guide, written by Neil Schore, provides a direct link from the text to the supplement. Sample problems are worked out, and the solutions to the End-of-Chapter Problems are given. Keys to the Chapter sections point out pitfalls of faulty logic and help students visualize the solution steps for various exercises. Tables summarize the spectral features associated with each functional group. A glossary of key terms is also provided. ISBN 0-7167-9759-3

The Computerized Test Bank, by Charles M. Garner and Kevin G. Pinney of Baylor University, is available on a dual platform CD-ROM. Instructors can easily change and add questions as well as import their own electronic drawings. A print option is available for instructors who prefer a hard copy Test Bank.

The Maruzen Molecular Structure Model Set is available for student purchase. This essential tool can be used to present orbitals, single, double, and triple bonds, and locations of atoms. ISBN 0-7167-4822-3

Laboratory Manuals

Jerry R. Mohrig, *Carleton College*
Christina Noring Hammond, *Vassar College*
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Modern Projects and Experiments in Organic Chemistry helps instructors turn their organic chemistry laboratories into places of discovery and critical thinking. In addition to traditional experiments, the manual offers a variety of inquiry-based experiments and multi-week projects, giving students a better understanding of how lab work is actually accomplished. Instead of simply following directions, students learn how to investigate the experimental process itself. The only difference between the two versions of the manual is that each is tailored to specific laboratory equipment. They are identical in content.

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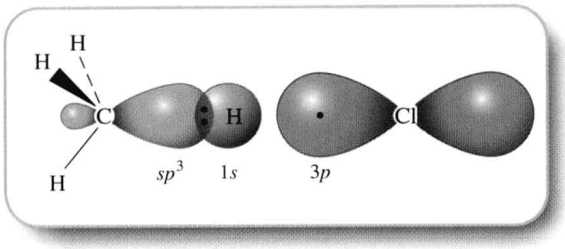
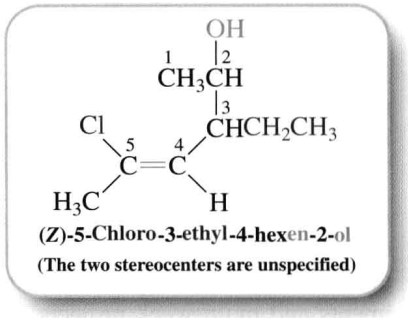
Key to the Functional Use of Color

We use color consistently and functionally to help students master basic principles, including nomenclature, orbitals, sequence rules in stereochemistry, the relation of spectral lines to functional groups, topological changes in molecular transformations, and the reactivity of functional groups. Color is suspended in exercises, chapter reviews, and problems. In this edition, we have carefully reevaluated the application of color in reaction schemes and simplified its use.

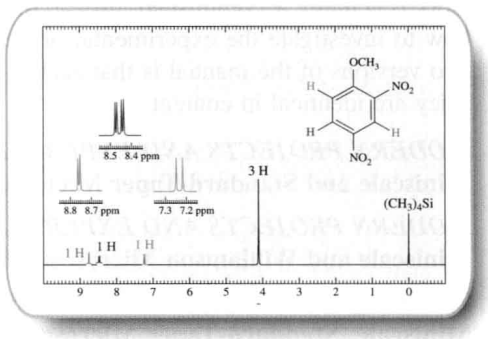


For example, wherever possible, *s* orbitals are shown in red, 2*p* orbitals in blue, sp^n hybrids in purple, and 3*p* orbitals in green.

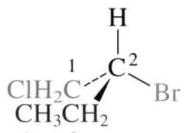
Color shows the relation of the names of organic molecules to their structures. In the illustration shown at the right, which is from Chapter 11, the functional groups that give the molecule its unique chemical behavior and other substituents are clearly differentiated from the stem.



Color is used to associate spectral features with certain molecular units. For example, in the spectrum at the right the three colors show how the three nonequivalent hydrogens give rise to three distinct "peaks"—an observation that will help the students to identify a molecule when they know its spectrum.



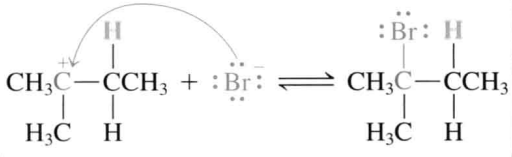
Remember the use of color to denote group priorities:
a **Highest—red**
b **Second highest—blue**
c **Third highest—green**
d **Lowest—black**



Optically active
2R

Color offers clues to a molecule's stereochemistry, or the arrangement of its atoms in space. The student will see in Chapter 5 that substituents in three dimensions can be assigned a priority according to certain "sequence rules," and this assignment has been indicated, in diminishing order of priority, by red, blue, green, and black.

STEP 4. Trapping by bromide



Most important, color frequently shows how the functional groups transform in the reaction mechanism. Electron-rich, or "nucleophilic," parts are shown in red; electron-deficient, or "electrophilic," fragments are blue; and radicals and leaving groups are green. Red arrows in these transformations indicate the movements of electrons.

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