fourth edition

ORGANIC CHEMISTRY

Francis A. Carey
University of Virginia

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ABOUT THE AUTHOR

Francis A. Carey is a native of Pennsylvania, educated in the public schools of Philadelphia, at Drexel University (B.S. in chemistry, 1959), and at Penn State (Ph.D. 1963). Following postdoctoral work at Harvard and military service, he joined the chemistry faculty of the University of Virginia in 1966.

With his students, Professor Carey has published over 40 research papers in synthetic and mechanistic organic chemistry. He is coauthor (with Richard J. Sundberg) of *Advanced Organic Chemistry,* a two-volume treatment designed for graduate students and advanced undergraduates, and (with Robert C. Atkins) of *Organic Chemistry: A Brief Course,* an introductory text for the one-semester organic course.

Since 1993, Professor Carey has been a member of the Committee of Examiners of the Graduate Record Examination in Chemistry. Not only does he get to participate in writing the Chemistry GRE, but the annual working meetings provide a stimulating environment for sharing ideas about what should (and should not) be taught in college chemistry courses.

Professor Carey's main interest shifted from research to undergraduate education in the early 1980s. He regularly teaches both general chemistry and organic chemistry to classes of over 300 students. He enthusiastically embraces applications of electronic media to chemistry teaching and sees multimedia presentations as the wave of the present.

Frank and his wife Jill, who is a teacher/director of a preschool and a church organist, are the parents of three grown sons and the grandparents of Riyad and Ava.

BRIEF CONTENTS

PREFACE

PHILOSOPHY

From its first edition through this, its fourth, *Organic Chemistry* has been designed to meet the needs of the "mainstream," two-semester, undergraduate organic chemistry course. It has evolved as those needs have changed, but its philosophy remains the same. The overarching theme is that organic chemistry is not only an interesting subject, but also a logical one. It is logical because its topics can be connected in a steady progression from simple to complex. *Our approach has been to reveal the logic of organic chemistry by being selective in the topics we cover, as well as thorough and patient in developing them.*

Teaching at all levels is undergoing rapid change, especially in applying powerful tools that exploit the graphics capability of personal computers. Organic chemistry has always been the most graphical of the chemical sciences and is well positioned to benefit significantly from these tools. Consistent with our philosophy, this edition uses computer graphics to enhance the core material, to make it more visual, and more understandable, but in a way that increases neither the amount of material nor its level.

ORGANIZATION

The central message of chemistry is that the properties of a substance come from its structure. What is less obvious, but very powerful, is the corollary. Someone with training in chemistry can look at the structure of a substance and tell you a lot about its properties. Organic chemistry has always been, and continues to be, the branch of chemistry that best connects structure with properties. This text has a strong bias toward structure, and this edition benefits from the availability of versatile new tools to help us understand that structure.

The text is organized to flow logically and step by step from structure to properties and back again. As the list of chapter titles reveals, the organization is according to functional groups—structural units within a molecule most responsible for a particular property—because that is the approach that permits most students to grasp the material most readily. Students retain the material best, however, if they understand how organic reactions take place. *Thus, reaction mechanisms are stressed early and often, but within a functional group framework.* A closer examination of the chapter titles reveals the close link between a functional group class (Chapter 20, Carboxylic Acid Derivatives) and a reaction type (Nucleophilic Acyl Substitution), for example. It is very satisfying to see students who entered the course believing they needed to memorize everything progress to the point of thinking and reasoning mechanistically.

Some of the important stages in this approach are as follows:

- The first mechanism the students encounter (Chapter 4) describes the conversion of alcohols to alkyl halides. Not only is this a useful functional-group transformation, but its first step proceeds by the simplest mechanism of all—proton transfer. The overall mechanism provides for an early reinforcement of acid-base chemistry and an early introduction to carbocations and nucleophilic substitution.
- Chapter 5 continues the chemistry of alcohols and alkyl halides by showing how they can be used to prepare alkenes by elimination reactions. Here, the students see a second example of the formation of carbocation intermediates from alcohols, but in this case, the carbocation travels a different pathway to a different destination.
- The alkenes prepared in Chapter 5 are studied again in Chapter 6, this time with an eye toward their own chemical reactivity. What the students learned about carbocations in Chapters 4 and 5 serves them well in understanding the mechanisms of the reactions of alkenes in Chapter 6.
- Likewise, the mechanism of nucleophilic addition to the carbonyl group of aldehydes and ketones described in Chapter 17 sets the stage for aldol condensation in Chapter 18, esterification of carboxylic acids in Chapter 19, nucleophilic acyl substitution in Chapter 20, and ester condensation in Chapter 21.

THE SPARTAN INTEGRATION

The third edition of this text broke new ground with its emphasis on *molecular modeling,* including the addition of more than 100 exercises of the model-building type. This, the fourth edition, moves to the next level of modeling. Gwendolyn and Alan Shusterman's 1997 *Journal of Chemical Education* article "Teaching Chemistry with Electron Density Models" described how models showing the results of molecular orbital calculations, especially electrostatic potential maps, could be used effectively in introductory courses. The software used to create the Shustermans' models was Spartan, a product of Wavefunction, Inc.

In a nutshell, the beauty of electrostatic potential maps is their ability to display the charge distribution in a molecule. At the most fundamental level, the forces that govern structure and properties in organic chemistry are the attractions between opposite charges and the repulsions between like charges. We were therefore optimistic that electrostatic potential maps held great promise for helping students make the connection between structure, especially electronic structure, and properties. Even at an early stage we realized that two main considerations had to guide our efforts.

- *An integrated approach was required.* To be effective, Spartan models and the information they provide must be woven into, not added to, the book's core.
- *The level of the coverage had to remain the same.* Spartan is versatile. We used the same software package to develop this edition that is used in research laboratories worldwide. It was essential that we limit ourselves to only those features that clarified a particular point. Organic chemistry is challenging enough. We didn't need to make it more difficult. If we were to err, it would therefore be better to err on the side of caution.

A third consideration surfaced soon after the work began.

- *Student access to Spartan would be essential.* Nothing could help students connect with molecular modeling better than owning the same software used to produce the text or, even better, software that allowed them not only to view models from the text, but also to make their own.

All of this led to a fruitful and stimulating collaboration with Dr. Warren Hehre, a leading theoretical chemist and the founder, president, and CEO of Wavefunction, Inc. Warren was enthusiastic about the project and agreed to actively participate in it. He and Alan Shusterman produced a CD tailored specifically to

NEW IN THIS EDITION

ALL-NEW ILLUSTRATIONS All figures were redrawn to convey visual concepts clearly and forcefully. In addition, the author created a number of new images using the Spartan molecular modeling application. Now students can view electrostatic potential maps to see the charge distribution of a molecule in vivid color. These striking images afford the instructor a powerful means to lead students to a better understanding of organic molecules.

FULL SPARTAN IMAGE INTEGRATION The Spartan-generated images are impressive in their own right, but for teaching purposes they are most effective when they are closely aligned with the text content. Because the author personally generated the images as he wrote this edition, the molecular models are fully integrated with text, and the educational value is maximized. Additionally, icons direct students to specific applications of either the SpartanView or SpartanBuild program, found on the accompanying CD-ROM. Appendix 3 provides a complete guide to the *Learning By Modeling* CD-ROM.

ALL-NEW SPECTRA Chapter 13, Spectroscopy, was heavily revised, with rewritten sections on NMR and with all the NMR spectra generated on a high-field instrument.

IMPROVED SUMMARIES The end-of-chapter summaries are recast into a more open, easier-to-read format, inspired by the popularity of the accompanying summary tables.

NEW DESIGN This edition sports a new look, with an emphasis on neatness, clarity, and color carefully used to heighten interest and to create visual cues for important information.

accompany our text. We call it *Learning By Modeling*. It and *Organic Chemistry* truly complement each other. Many of the problems in *Organic Chemistry* have been written expressly for the model-building software SpartanBuild that forms one part of *Learning By Modeling*. Another tool, SpartanView, lets students inspect more than 250 already constructed models and animations, ranging in size from hydrogen to carboxypeptidase.

We were careful to incorporate Spartan so it would be a true amplifier of the textbook, not just as a stand-alone tool that students might or might not use, depending on the involvement of their instructor. Thus, the content of the CD provides visual, three-dimensional reinforcement of the concepts covered on the printed page. The SpartanView icon invites students to view a molecule or animation as they are reading the text.

Opportunities to use SpartanBuild are similarly correlated to the text with an icon directing students to further explore a concept or solve a modeling-based problem with the software.

In addition to its role as the electronic backbone of the CD component and the integrated learning approach, the Spartan software makes a visible impact on the printed pages of this edition. I used Spartan on my own computer to create many of the figures, providing students with numerous visual explorations of the concepts of charge distribution.

BIOLOGICAL APPLICATIONS AND THEIR INTEGRATION

Comprehensive coverage of the important classes of biomolecules (carbohydrates, lipids, amino acids, peptides, proteins, and nucleic acids) appears in Chapters 25–27. But biological applications are such an important part of organic chemistry that they deserve more attention throughout the course. We were especially alert to opportunities to introduce more biologically oriented material to complement that which had already grown significantly since the first edition. Some specific examples:

- The new boxed essay "Methane and the Biosphere" in Chapter 2 combines elements of organic chemistry, biology, and environmental science to tell the story of where methane comes from and where it goes.
- A new boxed essay, "An Enzyme-Catalyzed Nucleophilic Substitution of an Alkyl Halide," in Chapter 8 makes a direct and simple connection between S_N2 reactions and biochemistry.
- Two new boxed essays, "How Sweet It Is!" in Chapter 25, and "Good Cholesterol? Bad Cholesterol? What's the Difference?" in Chapter 26, cover topics of current interest from an organic chemist's perspective.
- The already-numerous examples of enzyme-catalyzed organic reactions were supplemented by adding biological Baeyer-Villiger oxidations and fumaric acid dehydrogenation.

Chapters 25–27 have benefited substantially from the Spartan connection. We replaced many of the artist-rendered structural drawings of complex biomolecules from earlier editions with accurate models generated from imported crystallographic data. These include:

- maltose, cellobiose, and cellulose in Chapter 25
- triacylglycerols in Chapter 26
- alanylglycine, leucine enkephalin, a pleated β-sheet, an α-helix, carboxypeptidase, myoglobin, DNA, and phenylalanine tRNA in Chapter 27

All of these are included on *Learning By Modeling,* where you can view them as wire, ball-and-spoke, tube, or space-filling models while rotating them in three dimensions.

Both the text and *Learning By Modeling* include other structures of biological interest including:

- a space-filling model of a micelle (Chapter 19)
- electrostatic potential maps of the 20 common amino acids showing just how different the various side chains are (Chapter 27)

SPECTROSCOPY

Because it offers an integrated treatment of nuclear magnetic resonance (NMR), infrared (IR), and ultraviolet-visible (UV-VIS) spectroscopy, and mass spectrometry (MS), Chapter 13 is the longest in the text. It is also the chapter that received the most attention in this edition. All of the sections dealing with NMR were extensively rewritten, all of the NMR spectra were newly recorded on a high-field instrument, and all of the text figures were produced directly from the electronic data files.

Likewise, the IR and UV-VIS sections of Chapter 13 were revised and all of the IR spectra were recorded especially for this text.

After being first presented in Chapter 13, spectroscopy is then integrated into the topics that follow it. The functional-group chapters, 15, 16, 17, 19, 20, 22,

and 24, all contain spectroscopy sections as well as examples and problems based on display spectra.

INTEGRATION OF TOPICS

Too often, in too many courses (and not just in organic chemistry), too many interesting topics never get covered because they are relegated to the end of the text as "special topic chapters" that, unfortunately, fall by the wayside as the end of the term approaches. We have, from the beginning and with each succeeding edition, looked for opportunities to integrate the most important of these "special" topics into the core material. I am pleased with the results. Typically, this integration is accomplished by breaking a topic into its component elements and linking each of those elements to one or more conceptually related core topics.

There is, for example, no end-of-text chapter entitled "Heterocyclic Compounds." Rather, heteroatoms are defined in Chapter 1 and nonaromatic heterocyclic compounds introduced in Chapter 3; heterocyclic aromatic compounds are included in Chapter 11, and their electrophilic and nucleophilic aromatic substitution reactions described in Chapters 12 and 23, respectively. Heterocyclic compounds appear in numerous ways throughout the text and the biological role of two classes of them—the purines and pyrimidines—features prominently in the discussion of nucleic acids in Chapter 27.

The economic impact of synthetic polymers is too great to send them to the end of the book as a separate chapter or to group them with biopolymers. We regard polymers as a natural part of organic chemistry and pay attention to them throughout the text. The preparation of vinyl polymers is described in Chapter 6, polymer stereochemistry in Chapter 7, diene polymers in Chapter 10, Ziegler–Natta catalysis in Chapter 14, and condensation polymers in Chapter 20.

INTEGRATING THE CHEMISTRY CURRICULUM

I always thought that the general chemistry course would be improved if more organic chemists taught it, and have done just that myself for the past nine years. I now see that just as general chemistry can benefit from the perspective that an organic chemist brings to it, so can the teaching and learning of organic chemistry be improved by making the transition from general chemistry to organic smoother. Usually this is more a matter of style and terminology than content—an incremental rather than a radical change. I started making such changes in the third edition and continue here.

I liked, for example, writing the new boxed essay "Laws, Theories, and the Scientific Method" and placing it in Chapter 6. The scientific method is one thing that everyone who takes a college-level chemistry course should be familiar with, but most aren't. It normally appears in Chapter 1 of general chemistry texts, before the students have enough factual knowledge to really understand it, and it's rarely mentioned again. By the time our organic chemistry students get to "Laws, Theories, and the Scientific Method," however, we have told them about the experimental *observations* that led to Markovnikov's *law,* and how our understanding has progressed to the level of a broadly accepted *theory* based on carbocation stability. It makes a nice story. Let's use it.

FEWER TOPICS EQUALS MORE HELP

By being selective in the topics we cover, we can include more material designed to help the student learn.

Solved sample problems: In addition to a generous number of end-of-chapter problems, the text includes more than 450 problems within the chapters themselves. Of these in-chapter problems approximately one-third are multipart exercises that contain a detailed solution to part (a) outlining the reasoning behind the answer.

Summary tables: Annotated summary tables have been a staple of *Organic Chemistry* ever since the first edition and have increased in number to more than 50. Well received by students and faculty alike, they remain one of the text's strengths.

End-of-chapter summaries: Our experience with the summary tables prompted us to recast the narrative part of the end-of-chapter summaries into a more open, easier-to-read format.

SUPPLEMENTS

For the Student

Study Guide and Solutions Manual by Francis A. Carey and Robert C. Atkins. This valuable supplement provides solutions to all problems in the text. More than simply providing answers, most solutions guide the student with the reasoning behind each problem. In addition, each chapter of the *Study Guide and Solutions Manual* concludes with a Self-Test designed to assess the student's mastery of the material.

Online Learning Center

At www.mhhe.com/carey, this comprehensive, exclusive Web site provides a wealth of electronic resources for

instructors and students alike. Content includes tutorials, problem-solving strategies, and assessment exercises for every chapter in the text.

Learning By Modeling CD-ROM

In collaboration with Wavefunction, we have created a cross-function CD-ROM that contains an electronic model-building kit and a rich collection of animations and molecular models that reveal the interplay between electronic structure and reactivity in organic chemistry.

Packaged free with the text, *Learning By Modeling* has two components: SpartanBuild, a user-friendly electronic toolbox that lets you build, examine, and evaluate literally thousands of molecular models; and SpartanView, an application with which you can view and examine more than 250 molecular models and animations discussed in the text. In the textbook, icons point the way to where you can use these state-of-the-art molecular modeling applications to expand your understanding and sharpen your conceptual skills. This edition of the text contains numerous problems that take advantage of these applications. Appendix 3 provides a complete guide to using the CD.

For the Instructor

Overhead Transparencies. These full-color transparencies of illustrations from the text include reproductions of spectra, orbital diagrams, key tables, computer-generated molecular models, and step-by-step reaction mechanisms.

Test Bank. This collection of 1000 multiple-choice questions, prepared by Professor Bruce Osterby of the University of Wisconsin–LaCrosse, is available to adopters in print, Macintosh, or Windows format.

Visual Resource Library. This invaluable lecture aid provides the instructor with all the images from the textbook on a CD-ROM. The PowerPoint format enables easy customization and formatting of the images into the lecture.

The *Online Learning Center,* described in the previous section, has special features for instructors, including quiz capabilities.

Please contact your McGraw-Hill representative for additional information concerning these supplements.

ACKNOWLEDGMENTS

You may have noticed that this preface is almost entirely "we" and "our," not "I" and "my." That is because *Organic Chemistry* is, and always has been, a team effort. From the first edition to this one, the editorial and production staffs at WCB/McGraw-Hill have been committed to creating an accurate, interesting, student-oriented text. Special thanks go to Kent Peterson, Terry Stanton, and Peggy Selle for their professionalism, skill, and cooperative spirit. Linda Davoli not only copy edited the manuscript but offered valuable advice about style and presentation. GTS Graphics had the critical job of converting the copy-edited manuscript to a real book. Our contact there was Heather Stratton; her enthusiasm for the project provided us an unusual amount of freedom to fine-tune the text.

I have already mentioned the vital role played by Warren Hehre and Alan Shusterman in integrating Spartan into this edition. I am grateful for their generosity in giving their time, knowledge, and support to this project. I also thank Dr. Michal Sabat of the University of Virginia for his assistance in my own modeling efforts.

All of the NMR and IR spectra in this edition were recorded at the Department of Chemistry of James Madison University by two undergraduate students, Jeffrey Cross and Karin Hamburger, under the guidance of Thomas Gallaher. We are indebted to them for their help.

Again, as in the three previous editions, Dr. Robert C. Atkins has been indispensable. Bob is the driving force behind the *Study Guide and Solutions Manual* that accompanies this text. He is much more than that, though. He reads and critiques every page of the manuscript and every page of two rounds of proofs. I trust his judgment completely when he suggests how to simplify a point or make it clearer. Most of all, he is a great friend.

This text has benefited from the comments offered by a large number of teachers of organic chemistry who reviewed it at various stages of its development. I appreciate their help. They include

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Finally, I thank my family for their love, help, and encouragement. The "big five" remain the same: my wife Jill, our sons Andy, Bob, and Bill, and daughter-in-law Tasneem. They have been joined by the "little two," our grandchildren Riyad and Ava.

Comments, suggestions, and questions are welcome. Previous editions produced a large number of e-mail messages from students. I found them very helpful and invite you to contact me at: fac6q@unix.mail.virginia.edu.

Francis A. Carey

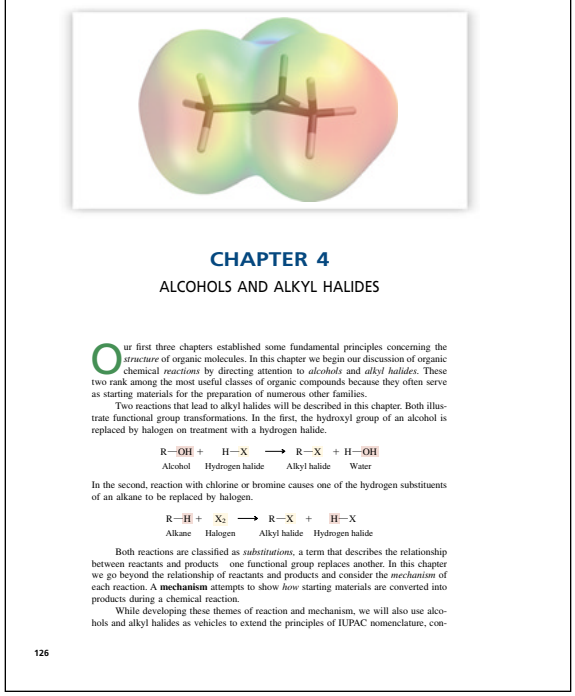
A GUIDE TO USING THIS TEXT

The following pages provide a walk-through of the key features of this text. Every element in this book has a purpose and serves the overall goal of leading students to a true understanding of the processes in organic chemistry.

INTEGRATED TEXT AND VISUALS

With All-new Figures

Because visualization is so important to understanding, illustrations work hand-in-hand with text to convey information. The author generated many of the figures himself as he wrote the text using Spartan software, so that images are fully coordinated with the text.



CHAPTER 4

ALCOHOLS AND ALKYL HALIDES

Our first three chapters established some fundamental principles concerning the *structure* of organic molecules. In this chapter we begin our discussion of organic chemical *reactions* by directing attention to *alcohols* and *alkyl halides*. These two rank among the most useful classes of organic compounds because they often serve as starting materials for the preparation of numerous other families.

Two reactions that lead to alkyl halides will be described in this chapter. Both illustrate functional group transformations. In the first, the hydroxyl group of an alcohol is replaced by halogen on treatment with a hydrogen halide.

$$\underset{\text{Alcohol}}{R{-}OH} + \underset{\text{Hydrogen halide}}{H{-}X} \longrightarrow \underset{\text{Alkyl halide}}{R{-}X} + \underset{\text{Water}}{H{-}OH}$$

In the second, reaction with chlorine or bromine causes one of the hydrogen substituents of an alkane to be replaced by halogen.

$$\underset{\text{Alkane}}{R{-}H} + \underset{\text{Halogen}}{X_2} \longrightarrow \underset{\text{Alkyl halide}}{R{-}X} + \underset{\text{Hydrogen halide}}{H{-}X}$$

Both reactions are classified as *substitutions*, a term that describes the relationship between reactants and products one functional group replaces another. In this chapter we go beyond the relationship of reactants and products and consider the *mechanism* of each reaction. A **mechanism** attempts to show *how* starting materials are converted into products during a chemical reaction.

While developing these themes of reaction and mechanism, we will also use alcohols and alkyl halides as vehicles to extend the principles of IUPAC nomenclature, con-

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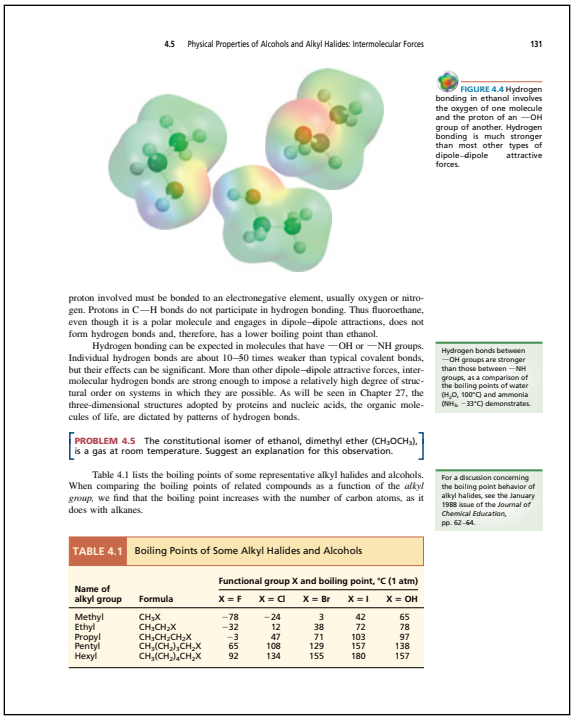


4.5 Physical Properties of Alcohols and Alkyl Halides: Intermolecular Forces 131

FIGURE 4.4 Hydrogen bonding in ethanol involves the oxygen of one molecule and the proton of an —OH group of another. Hydrogen bonding is much stronger than most other types of dipole–dipole attractive forces.

proton involved must be bonded to an electronegative element, usually oxygen or nitrogen. Protons in C—H bonds do not participate in hydrogen bonding. Thus fluoroethane, even though it is a polar molecule and engages in dipole–dipole attractions, does not form hydrogen bonds and, therefore, has a lower boiling point than ethanol.

Hydrogen bonding can be expected in molecules that have —OH or —NH groups. Individual hydrogen bonds are about 10–50 times weaker than typical covalent bonds, but their effects can be significant. More than other dipole–dipole attractive forces, intermolecular hydrogen bonds are strong enough to impose a relatively high degree of structural order on systems in which they are possible. As will be seen in Chapter 27, the three-dimensional structures adopted by proteins and nucleic acids, the organic molecules of life, are dictated by patterns of hydrogen bonds.

Hydrogen bonds between —OH groups are stronger than those between —NH groups, as a comparison of the boiling points of water (H_2O, 100°C) and ammonia (NH_3, −33°C) demonstrates.

PROBLEM 4.5 The constitutional isomer of ethanol, dimethyl ether (CH_3OCH_3), is a gas at room temperature. Suggest an explanation for this observation.

Table 4.1 lists the boiling points of some representative alkyl halides and alcohols. When comparing the boiling points of related compounds as a function of the *alkyl group*, we find that the boiling point increases with the number of carbon atoms, as it does with alkanes.

For a discussion concerning the boiling point behavior of alkyl halides, see the January 1988 issue of the *Journal of Chemical Education*, pp. 62–64.

TABLE 4.1 Boiling Points of Some Alkyl Halides and Alcohols

Name of alkyl group	Formula	Functional group X and boiling point, °C (1 atm)				
		X = F	X = Cl	X = Br	X = I	X = OH
Methyl	CH_3X	−78	−24	3	42	65
Ethyl	CH_3CH_2X	−32	12	38	72	78
Propyl	$CH_3CH_2CH_2X$	−3	47	71	103	97
Pentyl	$CH_3(CH_2)_3CH_2X$	65	108	129	157	138
Hexyl	$CH_3(CH_2)_4CH_2X$	92	134	155	180	157

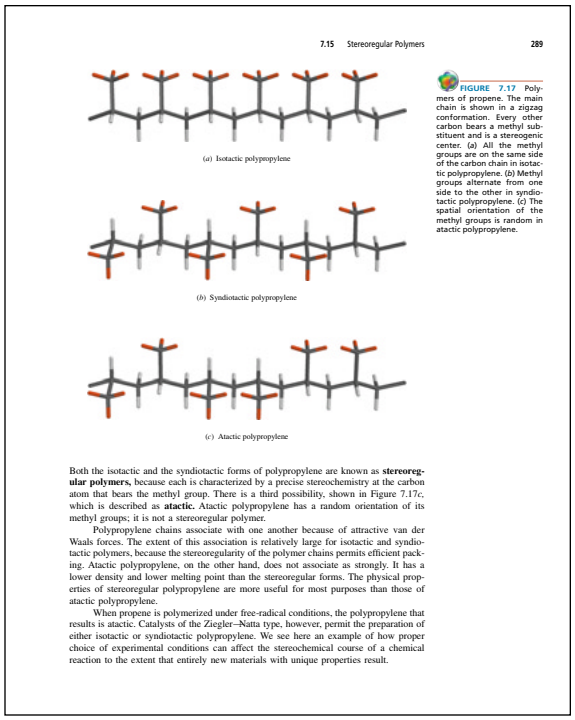
EFFECTIVE ORGANIZATION OF FUNCTIONAL GROUPS

Reaction mechanisms are stressed early and often, but within a functional framework. For example, Chapter 4 is the first chapter to cover a functional group (alcohols and alkyl halides) but it introduces *mechanism* simultaneously.

LEARNING BY MODELING

A Full Correlation

Not only can students view molecular models while using the book, but with the free CD-ROM that accompanies the text, they have access to the software that was used to create the images. With the SpartanView and SpartanBuild software, students can view models from the text and also make their own. The SpartanView icon identifies molecules and animations that can be seen on the CD. Appendix 3 provides a complete tutorial guide to the CD.



7.15 Stereoregular Polymers 289

(*a*) Isotactic polypropylene

(*b*) Syndiotactic polypropylene

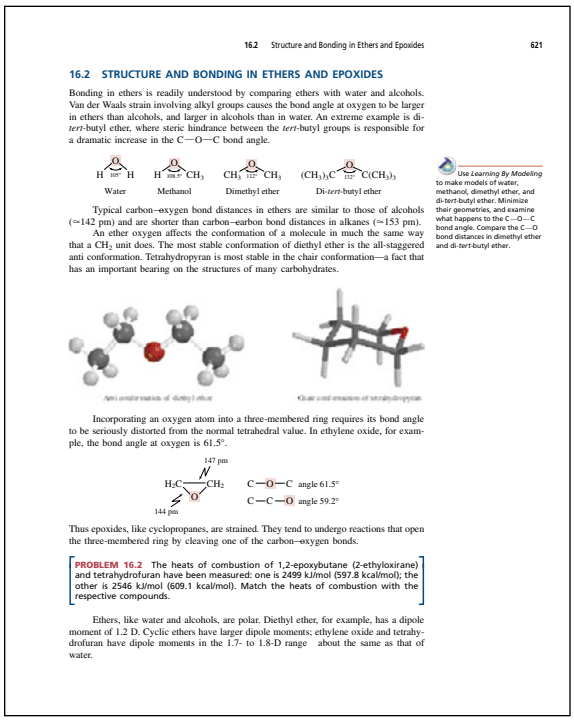
(*c*) Atactic polypropylene

FIGURE 7.17 Polymers of propene. The main chain is shown in a zigzag conformation. Every other carbon bears a methyl substituent and is a stereogenic center. (*a*) All the methyl groups are on the same side of the carbon chain in isotactic polypropylene. (*b*) Methyl groups alternate from one side to the other in syndiotactic polypropylene. (*c*) The spatial orientation of the methyl groups is random in atactic polypropylene.

Both the isotactic and the syndiotactic forms of polypropylene are known as **stereoregular polymers,** because each is characterized by a precise stereochemistry at the carbon atom that bears the methyl group. There is a third possibility, shown in Figure 7.17*c*, which is described as **atactic.** Atactic polypropylene has a random orientation of its methyl groups; it is not a stereoregular polymer.

Polypropylene chains associate with one another because of attractive van der Waals forces. The extent of this association is relatively large for isotactic and syndiotactic polymers, because the stereoregularity of the polymer chains permits efficient packing. Atactic polypropylene, on the other hand, does not associate as strongly. It has a lower density and lower melting point than the stereoregular forms. The physical properties of stereoregular polypropylene are more useful for most purposes than those of atactic polypropylene.

When propene is polymerized under free-radical conditions, the polypropylene that results is atactic. Catalysts of the Ziegler–Natta type, however, permit the preparation of either isotactic or syndiotactic polypropylene. We see here an example of how proper choice of experimental conditions can affect the stereochemical course of a chemical reaction to the extent that entirely new materials with unique properties result.



16.2 Structure and Bonding in Ethers and Epoxides 621

16.2 STRUCTURE AND BONDING IN ETHERS AND EPOXIDES

Bonding in ethers is readily understood by comparing ethers with water and alcohols. Van der Waals strain involving alkyl groups causes the bond angle at oxygen to be larger in ethers than alcohols, and larger in alcohols than in water. An extreme example is di-*tert*-butyl ether, where steric hindrance between the *tert*-butyl groups is responsible for a dramatic increase in the C—O—C bond angle.

Water Methanol Dimethyl ether Di-*tert*-butyl ether

Use *Learning By Modeling* to make models of water, methanol, dimethyl ether, and di-*tert*-butyl ether. Minimize their geometries, and examine what happens to the C—O—C bond angle. Compare the C—O bond distances in dimethyl ether and di-*tert*-butyl ether.

Typical carbon–oxygen bond distances in ethers are similar to those of alcohols (≈142 pm) and are shorter than carbon–carbon bond distances in alkanes (≈153 pm).

An ether oxygen affects the conformation of a molecule in much the same way that a CH_2 unit does. The most stable conformation of diethyl ether is the all-staggered anti conformation. Tetrahydropyran is most stable in the chair conformation—a fact that has an important bearing on the structures of many carbohydrates.

Incorporating an oxygen atom into a three-membered ring requires its bond angle to be seriously distorted from the normal tetrahedral value. In ethylene oxide, for example, the bond angle at oxygen is 61.5°.

147 pm
144 pm
C—O—C angle 61.5°
C—C—O angle 59.2°

Thus epoxides, like cyclopropanes, are strained. They tend to undergo reactions that open the three-membered ring by cleaving one of the carbon–oxygen bonds.

PROBLEM 16.2 The heats of combustion of 1,2-epoxybutane (2-ethyloxirane) and tetrahydrofuran have been measured: one is 2499 kJ/mol (597.8 kcal/mol); the other is 2546 kJ/mol (609.1 kcal/mol). Match the heats of combustion with the respective compounds.

Ethers, like water and alcohols, are polar. Diethyl ether, for example, has a dipole moment of 1.2 D. Cyclic ethers have larger dipole moments; ethylene oxide and tetrahydrofuran have dipole moments in the 1.7- to 1.8-D range about the same as that of water.

LEARNING BY MODELING

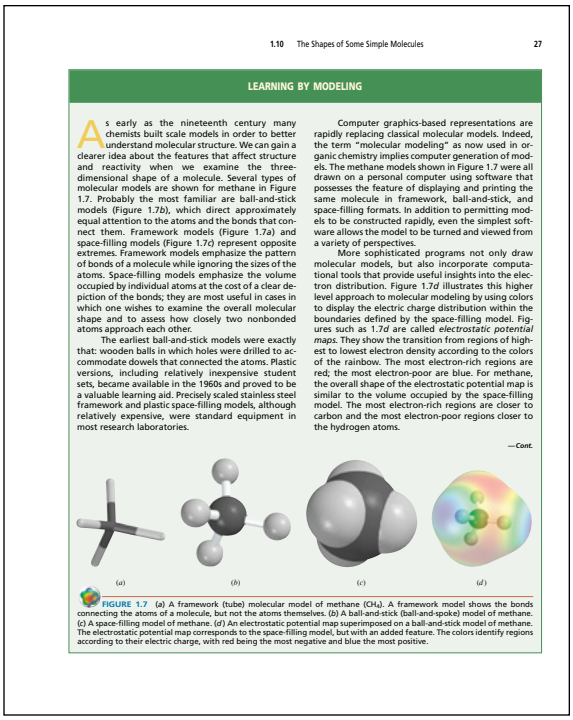
An Active Process

Many of the problems in this edition of the text have been expressly written to involve use of the SpartanBuild software on the *Learning By Modeling* CD-ROM. Students discover the connection between structure and properties by actually building molecules on their own. The SpartanBuild icon directs them when to use this tool.

LEARNING BY MODELING

From Spartan to the Page

New in this edition's figures are molecular models that the author generated using the Spartan modeling application. Electrostatic potential maps give a vivid look at the charge distribution in a molecule, showing the forces that govern structure and properties in organic chemistry.



1.10 The Shapes of Some Simple Molecules 27

LEARNING BY MODELING

As early as the nineteenth century many chemists built scale models in order to better understand molecular structure. We can gain a clearer idea about the features that affect structure and reactivity when we examine the three-dimensional shape of a molecule. Several types of molecular models are shown for methane in Figure 1.7. Probably the most familiar are ball-and-stick models (Figure 1.7*b*), which direct approximately equal attention to the atoms and the bonds that connect them. Framework models (Figure 1.7*a*) and space-filling models (Figure 1.7*c*) represent opposite extremes. Framework models emphasize the pattern of bonds of a molecule while ignoring the sizes of the atoms. Space-filling models emphasize the volume occupied by individual atoms at the cost of a clear depiction of the bonds; they are most useful in cases in which one wishes to examine the overall molecular shape and to assess how closely two nonbonded atoms approach each other.

The earliest ball-and-stick models were exactly that: wooden balls in which holes were drilled to accommodate dowels that connected the atoms. Plastic versions, including relatively inexpensive student sets, became available in the 1960s and proved to be a valuable learning aid. Precisely scaled stainless steel framework and plastic space-filling models, although relatively expensive, were standard equipment in most research laboratories.

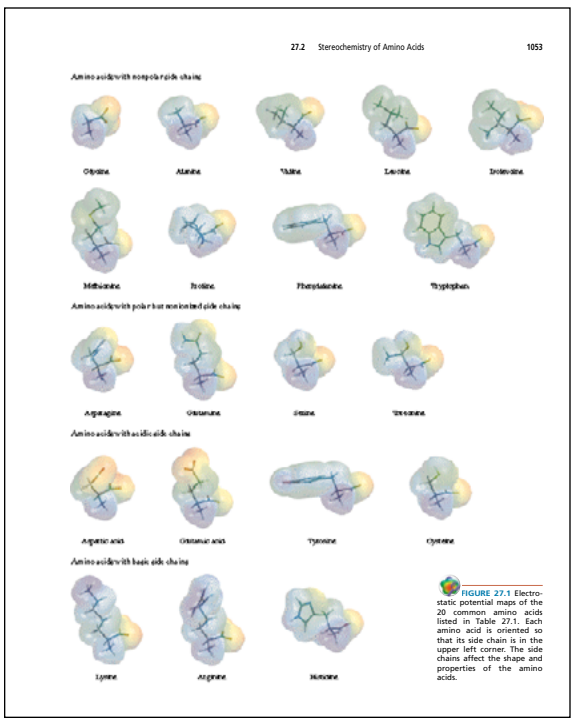
Computer graphics-based representations are rapidly replacing classical molecular models. Indeed, the term "molecular modeling" as now used in organic chemistry implies computer generation of models. The methane models shown in Figure 1.7 were all drawn on a personal computer using software that possesses the feature of displaying and printing the same molecule in framework, ball-and-stick, and space-filling formats. In addition to permitting models to be constructed rapidly, even the simplest software allows the model to be turned and viewed from a variety of perspectives.

More sophisticated programs not only draw molecular models, but also incorporate computational tools that provide useful insights into the electron distribution. Figure 1.7*d* illustrates this higher level approach to molecular modeling by using colors to display the electric charge distribution within the boundaries defined by the space-filling model. Figures such as 1.7*d* are called *electrostatic potential maps*. They show the transition from regions of highest to lowest electron density according to the colors of the rainbow. The most electron-rich regions are red; the most electron-poor are blue. For methane, the overall shape of the electrostatic potential map is similar to the volume occupied by the space-filling model. The most electron-rich regions are closer to carbon and the most electron-poor regions closer to the hydrogen atoms.

—Cont.

(*a*) (*b*) (*c*) (*d*)

FIGURE 1.7 (*a*) A framework (tube) molecular model of methane (CH_4). A framework model shows the bonds connecting the atoms of a molecule, but not the atoms themselves. (*b*) A ball-and-stick (ball-and-spoke) model of methane. (*c*) A space-filling model of methane. (*d*) An electrostatic potential map superimposed on a ball-and-stick model of methane. The electrostatic potential map corresponds to the space-filling model, but with an added feature. The colors identify regions according to their electric charge, with red being the most negative and blue the most positive.



27.2 Stereochemistry of Amino Acids 1053

Amino acids with nonpolar side chains

Glycine Alanine Valine Leucine Isoleucine

Methionine Proline Phenylalanine Tryptophan

Amino acids with polar but nonionized side chains

Asparagine Glutamine Serine Threonine

Amino acids with acidic side chains

Aspartic acid Glutamic acid Tyrosine Cysteine

Amino acids with basic side chains

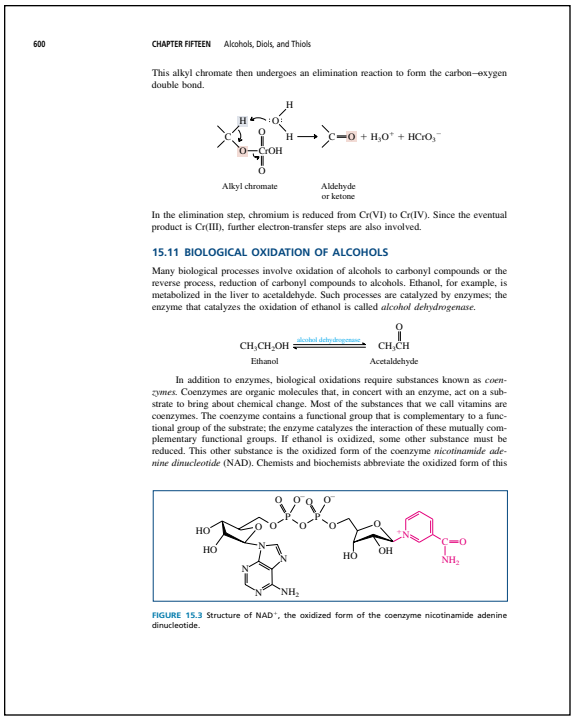
Lysine Arginine Histidine

FIGURE 27.1 Electrostatic potential maps of the 20 common amino acids listed in Table 27.1. Each amino acid is oriented so that its side chain is in the upper left corner. The side chains affect the shape and properties of the amino acids.

LEARNING BY MODELING

Build Biomolecules

In the biological-specific chapters, learning is once again enhanced by the access to Spartan model building. Carbohydrates, lipids, amino acids, peptides, proteins, and nucleic acid benefit from Spartan, and many for this edition were generated from imported crystallographic data. And students can view models of the 20 common amino acids on *Learning By Modeling,* and rotate them in three dimensions, or view them as ball-and-spoke, tube, or space-filling models.


600 CHAPTER FIFTEEN Alcohols, Diols, and Thiols

This alkyl chromate then undergoes an elimination reaction to form the carbon–oxygen double bond.

Alkyl chromate Aldehyde or ketone

In the elimination step, chromium is reduced from Cr(VI) to Cr(IV). Since the eventual product is Cr(III), further electron-transfer steps are also involved.

15.11 BIOLOGICAL OXIDATION OF ALCOHOLS

Many biological processes involve oxidation of alcohols to carbonyl compounds or the reverse process, reduction of carbonyl compounds to alcohols. Ethanol, for example, is metabolized in the liver to acetaldehyde. Such processes are catalyzed by enzymes; the enzyme that catalyzes the oxidation of ethanol is called *alcohol dehydrogenase*.

Ethanol Acetaldehyde

In addition to enzymes, biological oxidations require substances known as *coenzymes*. Coenzymes are organic molecules that, in concert with an enzyme, act on a substrate to bring about chemical change. Most of the substances that we call vitamins are coenzymes. The coenzyme contains a functional group that is complementary to a functional group of the substrate; the enzyme catalyzes the interaction of these mutually complementary functional groups. If ethanol is oxidized, some other substance must be reduced. This other substance is the oxidized form of the coenzyme *nicotinamide adenine dinucleotide* (NAD). Chemists and biochemists abbreviate the oxidized form of this

FIGURE 15.3 Structure of NAD^+, the oxidized form of the coenzyme nicotinamide adenine dinucleotide.

BIOLOGICAL APPLICATIONS THROUGHOUT

While biological topics receive greatest emphasis in Chapters 25–27, they are also introduced throughout the book, reflecting their growing role in the study of organic chemistry. Examples include:

- Biological oxidation of alcohols (p. 600)
- Epoxides in biological processes (p. 637)
- "Methane and the Biosphere" (boxed essay, p. 58)
- A biological dehydrogenation (new, p. 181)
- Figure 19.5, showing a realistic representation of a micelle (p. 744)
- "Chiral drugs" (boxed essay, p. 273)

SPECTROSCOPY

Spectroscopy coverage is up-to-date and thorough in this edition. Chapter 13, "Spectroscopy," features NMR spectra that were newly recorded on a high-field instrument, and all the text figures were produced directly from electronic files. In addition, spectroscopy is integrated into all the functional group chapters that follow 13: Chapters 15, 16, 17, 19, 20, 22, and 24, which contain spectroscopy sections and examples and problems based on displayed spectra.

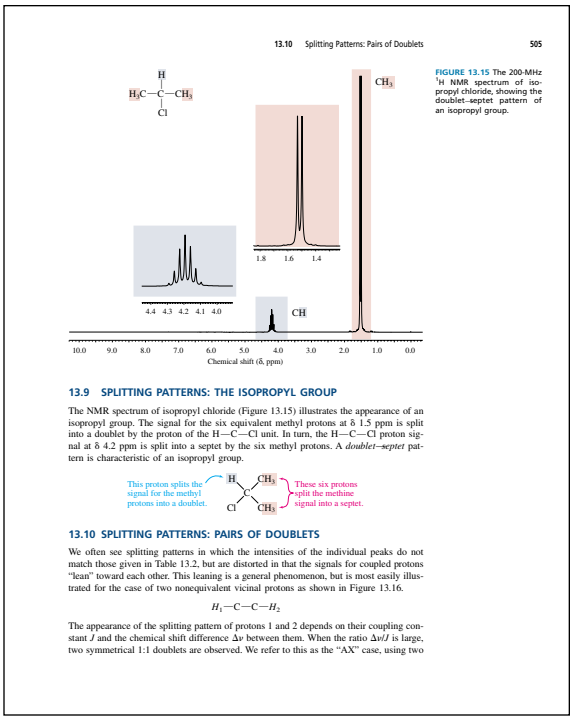

13.10 Splitting Patterns: Pairs of Doublets 505

FIGURE 13.15 The 200-MHz ^{1}H NMR spectrum of isopropyl chloride, showing the doublet–septet pattern of an isopropyl group.

Chemical shift (δ, ppm)

13.9 SPLITTING PATTERNS: THE ISOPROPYL GROUP

The NMR spectrum of isopropyl chloride (Figure 13.15) illustrates the appearance of an isopropyl group. The signal for the six equivalent methyl protons at δ 1.5 ppm is split into a doublet by the proton of the H—C—Cl unit. In turn, the H—C—Cl proton signal at δ 4.2 ppm is split into a septet by the six methyl protons. A *doublet–septet* pattern is characteristic of an isopropyl group.

This proton splits the signal for the methyl protons into a doublet.

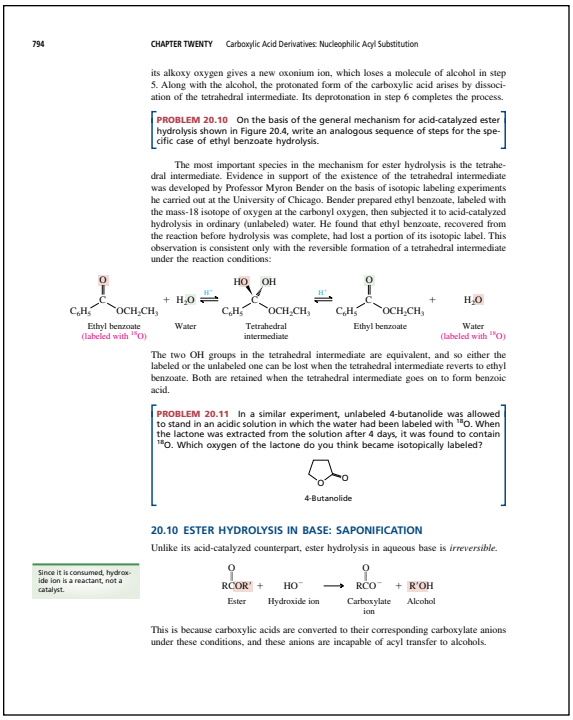
These six protons split the methine signal into a septet.

13.10 SPLITTING PATTERNS: PAIRS OF DOUBLETS

We often see splitting patterns in which the intensities of the individual peaks do not match those given in Table 13.2, but are distorted in that the signals for coupled protons "lean" toward each other. This leaning is a general phenomenon, but is most easily illustrated for the case of two nonequivalent vicinal protons as shown in Figure 13.16.

$$H_1—C—C—H_2$$

The appearance of the splitting pattern of protons 1 and 2 depends on their coupling constant J and the chemical shift difference $\Delta\nu$ between them. When the ratio $\Delta\nu/J$ is large, two symmetrical 1:1 doublets are observed. We refer to this as the "AX" case, using two



794 CHAPTER TWENTY Carboxylic Acid Derivatives: Nucleophilic Acyl Substitution

its alkoxy oxygen gives a new oxonium ion, which loses a molecule of alcohol in step 5. Along with the alcohol, the protonated form of the carboxylic acid arises by dissociation of the tetrahedral intermediate. Its deprotonation in step 6 completes the process.

PROBLEM 20.10 On the basis of the general mechanism for acid-catalyzed ester hydrolysis shown in Figure 20.4, write an analogous sequence of steps for the specific case of ethyl benzoate hydrolysis.

The most important species in the mechanism for ester hydrolysis is the tetrahedral intermediate. Evidence in support of the existence of the tetrahedral intermediate was developed by Professor Myron Bender on the basis of isotopic labeling experiments he carried out at the University of Chicago. Bender prepared ethyl benzoate, labeled with the mass-18 isotope of oxygen at the carbonyl oxygen, then subjected it to acid-catalyzed hydrolysis in ordinary (unlabeled) water. He found that ethyl benzoate, recovered from the reaction before hydrolysis was complete, had lost a portion of its isotopic label. This observation is consistent only with the reversible formation of a tetrahedral intermediate under the reaction conditions:

Ethyl benzoate (labeled with ^{18}O) + Water ⇌ Tetrahedral intermediate ⇌ Ethyl benzoate + Water (labeled with ^{18}O)

The two OH groups in the tetrahedral intermediate are equivalent, and so either the labeled or the unlabeled one can be lost when the tetrahedral intermediate reverts to ethyl benzoate. Both are retained when the tetrahedral intermediate goes on to form benzoic acid.

PROBLEM 20.11 In a similar experiment, unlabeled 4-butanolide was allowed to stand in an acidic solution in which the water had been labeled with ^{18}O. When the lactone was extracted from the solution after 4 days, it was found to contain ^{18}O. Which oxygen of the lactone do you think became isotopically labeled?

4-Butanolide

20.10 ESTER HYDROLYSIS IN BASE: SAPONIFICATION

Unlike its acid-catalyzed counterpart, ester hydrolysis in aqueous base is *irreversible*.

Since it is consumed, hydroxide ion is a reactant, not a catalyst.

Ester + Hydroxide ion → Carboxylate ion + Alcohol

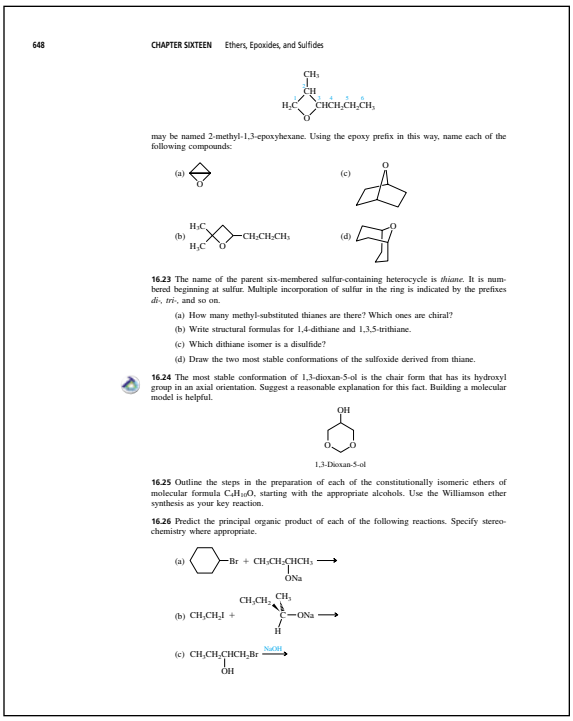
This is because carboxylic acids are converted to their corresponding carboxylate anions under these conditions, and these anions are incapable of acyl transfer to alcohols.

PROBLEM SOLVING—BY EXAMPLE

Problem-solving strategies and skills are emphasized throughout. Understanding of topics is continually reinforced by problems that appear within topic sections. For many problems, sample solutions are given.

. . . AND MORE PROBLEMS

Every chapter ends with a comprehensive bank of problems that give students liberal opportunity to master skills by working problems. And now many of the problems are written expressly for use with the software on the *Learning By Modeling* CD-ROM. Both within the chapters and at the end, these problems are flagged with the Spartan-Build icon.



648 CHAPTER SIXTEEN Ethers, Epoxides, and Sulfides

may be named 2-methyl-1,3-epoxyhexane. Using the epoxy prefix in this way, name each of the following compounds:

(a) (c) (b) (d)

16.23 The name of the parent six-membered sulfur-containing heterocycle is *thiane*. It is numbered beginning at sulfur. Multiple incorporation of sulfur in the ring is indicated by the prefixes *di-*, *tri-*, and so on.

(a) How many methyl-substituted thianes are there? Which ones are chiral?

(b) Write structural formulas for 1,4-dithiane and 1,3,5-trithiane.

(c) Which dithiane isomer is a disulfide?

(d) Draw the two most stable conformations of the sulfoxide derived from thiane.

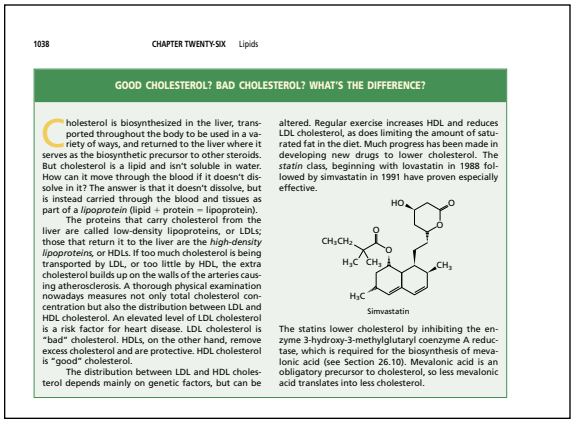
16.24 The most stable conformation of 1,3-dioxan-5-ol is the chair form that has its hydroxyl group in an axial orientation. Suggest a reasonable explanation for this fact. Building a molecular model is helpful.

1,3-Dioxan-5-ol

16.25 Outline the steps in the preparation of each of the constitutionally isomeric ethers of molecular formula $C_4H_{10}O$, starting with the appropriate alcohols. Use the Williamson ether synthesis as your key reaction.

16.26 Predict the principal organic product of each of the following reactions. Specify stereochemistry where appropriate.

(a) (b) (c)


1038 CHAPTER TWENTY-SIX Lipids

GOOD CHOLESTEROL? BAD CHOLESTEROL? WHAT'S THE DIFFERENCE?

Cholesterol is biosynthesized in the liver, transported throughout the body to be used in a variety of ways, and returned to the liver where it serves as the biosynthetic precursor to other steroids. But cholesterol is a lipid and isn't soluble in water. How can it move through the blood if it doesn't dissolve in it? The answer is that it doesn't dissolve, but is instead carried through the blood and tissues as part of a *lipoprotein* (lipid + protein = lipoprotein).

The proteins that carry cholesterol from the liver are called low-density lipoproteins, or LDLs; those that return it to the liver are the *high-density lipoproteins*, or HDLs. If too much cholesterol is being transported by LDL, or too little by HDL, the extra cholesterol builds up on the walls of the arteries causing atherosclerosis. A thorough physical examination nowadays measures not only total cholesterol concentration but also the distribution between LDL and HDL cholesterol. An elevated level of LDL cholesterol is a risk factor for heart disease. LDL cholesterol is "bad" cholesterol. HDLs, on the other hand, remove excess cholesterol and are protective. HDL cholesterol is "good" cholesterol.

The distribution between LDL and HDL cholesterol depends mainly on genetic factors, but can be altered. Regular exercise increases HDL and reduces LDL cholesterol, as does limiting the amount of saturated fat in the diet. Much progress has been made in developing new drugs to lower cholesterol. The *statin* class, beginning with lovastatin in 1988 followed by simvastatin in 1991 have proven especially effective.

Simvastatin

The statins lower cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is required for the biosynthesis of mevalonic acid (see Section 26.10). Mevalonic acid is an obligatory precursor to cholesterol, so less mevalonic acid translates into less cholesterol.

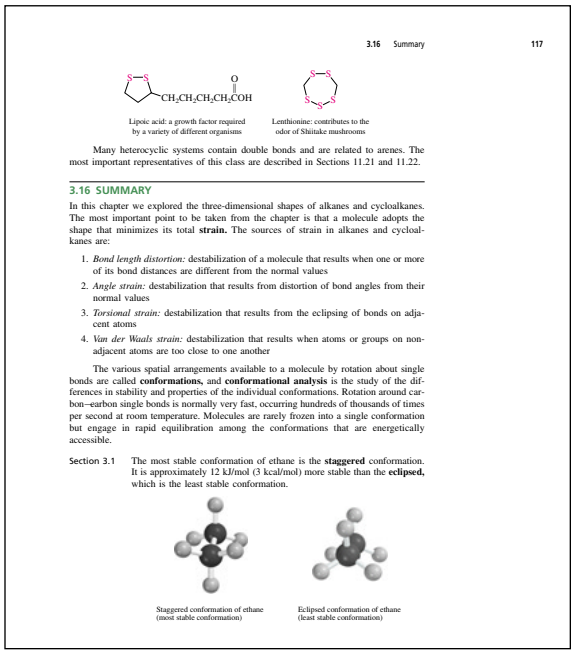
INSTRUCTIVE BOXED ESSAYS

The essays in the book aren't just for decoration; they help students think and learn by relating concepts to biological, environmental, and other real-world applications. Examples include:

- "Methane and the Biosphere"
- "An Enzyme-Catalyzed Nucleophilic Substitution of an Alkyl Halide"
- "Good Cholesterol? Bad Cholesterol? What's the Difference?"

THE SUMMARY

Summaries ending each chapter are crafted to allow students to check their knowledge and revisit chapter content in a study-friendly format. Learning is reinforced through concise narrative and through Summary Tables that students find valuable.


3.16 Summary 117

Lipoic acid: a growth factor required by a variety of different organisms

Lenthionine: contributes to the odor of Shiitake mushrooms

Many heterocyclic systems contain double bonds and are related to arenes. The most important representatives of this class are described in Sections 11.21 and 11.22.

3.16 SUMMARY

In this chapter we explored the three-dimensional shapes of alkanes and cycloalkanes. The most important point to be taken from the chapter is that a molecule adopts the shape that minimizes its total **strain.** The sources of strain in alkanes and cycloalkanes are:

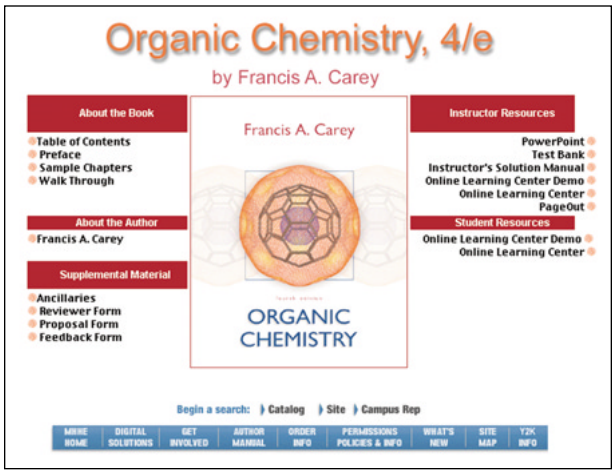
1. *Bond length distortion:* destabilization of a molecule that results when one or more of its bond distances are different from the normal values
2. *Angle strain:* destabilization that results from distortion of bond angles from their normal values
3. *Torsional strain:* destabilization that results from the eclipsing of bonds on adjacent atoms
4. *Van der Waals strain:* destabilization that results when atoms or groups on nonadjacent atoms are too close to one another

The various spatial arrangements available to a molecule by rotation about single bonds are called **conformations,** and **conformational analysis** is the study of the differences in stability and properties of the individual conformations. Rotation around carbon–carbon single bonds is normally very fast, occurring hundreds of thousands of times per second at room temperature. Molecules are rarely frozen into a single conformation but engage in rapid equilibration among the conformations that are energetically accessible.

Section 3.1 The most stable conformation of ethane is the **staggered** conformation. It is approximately 12 kJ/mol (3 kcal/mol) more stable than the **eclipsed,** which is the least stable conformation.

Staggered conformation of ethane (most stable conformation)

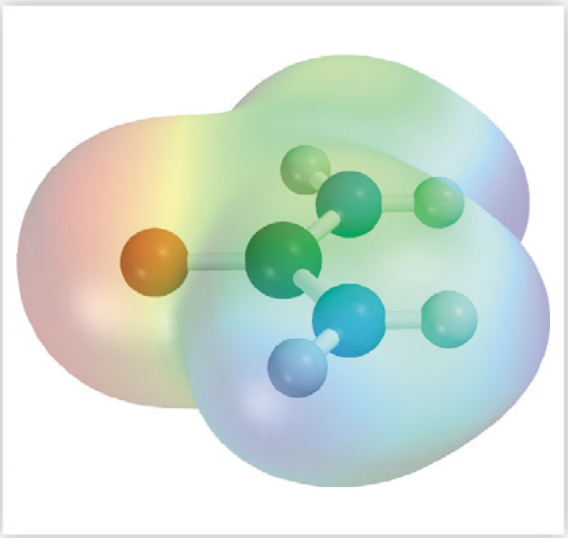
Eclipsed conformation of ethane (least stable conformation)



ONLINE LEARNING CENTER

The exclusive Carey Online Learning Center, at www.mhhe.com/carey, is a rich resource that provides additional support for the fourth edition of *Organic Chemistry,* offering tutorials, practice problems, and assessment exercises for every chapter in the text.

The tutorial materials provide a short overview of the chapter content, drawing attention to key concepts. The Learning Center also provides access to review materials for these concepts, using multimedia images, movies, etc.—including Chime images—to enhance and facilitate learning. Practice problems and assessment exercises provide instant feedback, to pinpoint the topics on which a student needs to spend more time.



INTRODUCTION

At the root of all science is our own unquenchable curiosity about ourselves and our world. We marvel, as our ancestors did thousands of years ago, when fireflies light up a summer evening. The colors and smells of nature bring subtle messages of infinite variety. Blindfolded, we know whether we are in a pine forest or near the seashore. We marvel. And we wonder. How does the firefly produce light? What are the substances that characterize the fragrance of the pine forest? What happens when the green leaves of summer are replaced by the red, orange, and gold of fall?

THE ORIGINS OF ORGANIC CHEMISTRY

As one of the tools that fostered an increased understanding of our world, the science of chemistry—the study of matter and the changes it undergoes—developed slowly until near the end of the eighteenth century. About that time, in connection with his studies of combustion the French nobleman Antoine Laurent Lavoisier provided the clues that showed how chemical compositions could be determined by identifying and measuring the amounts of water, carbon dioxide, and other materials produced when various substances were burned in air. By the time of Lavoisier's studies, two branches of chemistry were becoming recognized. One branch was concerned with matter obtained from natural or living sources and was called *organic chemistry.* The other branch dealt with substances derived from nonliving matter—minerals and the like. It was called *inorganic chemistry.* Combustion analysis soon established that the compounds derived from natural sources contained carbon, and eventually a new definition of organic chemistry emerged: **organic chemistry is the study of carbon compounds.** This is the definition we still use today.

BERZELIUS, WÖHLER, AND VITALISM

As the eighteenth century gave way to the nineteenth, Jöns Jacob Berzelius emerged as one of the leading scientists of his generation. Berzelius, whose training was in medicine, had wide-ranging interests and made numerous contributions in diverse areas of

chemistry. It was he who in 1807 coined the term "organic chemistry" for the study of compounds derived from natural sources. Berzelius, like almost everyone else at the time, subscribed to the doctrine known as **vitalism.** Vitalism held that living systems possessed a "vital force" which was absent in nonliving systems. Compounds derived from natural sources (organic) were thought to be fundamentally different from inorganic compounds; it was believed inorganic compounds could be synthesized in the laboratory, but organic compounds could not—at least not from inorganic materials.

In 1823, Friedrich Wöhler, fresh from completing his medical studies in Germany, traveled to Stockholm to study under Berzelius. A year later Wöhler accepted a position teaching chemistry and conducting research in Berlin. He went on to have a distinguished career, spending most of it at the University of Göttingen, but is best remembered for a brief paper he published in 1828. Wöhler noted that when he evaporated an aqueous solution of ammonium cyanate, he obtained "colorless, clear crystals often more than an inch long," which were not ammonium cyanate but were instead urea.

The article "Wöhler and the Vital Force" in the March 1957 issue of the *Journal of Chemical Education* (pp. 141–142) describes how Wöhler's experiment affected the doctrine of vitalism. A more recent account of the significance of Wöhler's work appears in the September 1996 issue of the same journal (pp. 883–886).

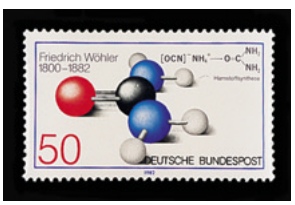
$$\underset{\text{Ammonium cyanate (an inorganic compound)}}{NH_4{}^{+}{}^{-}OCN} \longrightarrow \underset{\text{Urea (an organic compound)}}{O{=}C(NH_2)_2}$$

The transformation observed by Wöhler was one in which an *inorganic* salt, ammonium cyanate, was converted to urea, a known *organic* substance earlier isolated from urine. This experiment is now recognized as a scientific milestone, the first step toward overturning the philosophy of vitalism. Although Wöhler's synthesis of an organic compound in the laboratory from inorganic starting materials struck at the foundation of vitalist dogma, vitalism was not displaced overnight. Wöhler made no extravagant claims concerning the relationship of his discovery to vitalist theory, but the die was cast, and over the next generation organic chemistry outgrew vitalism.

What particularly seemed to excite Wöhler and his mentor Berzelius about this experiment had very little to do with vitalism. Berzelius was interested in cases in which two clearly different materials had the same elemental composition, and he invented the term **isomerism** to define it. The fact that an inorganic compound (ammonium cyanate) of molecular formula CH_4N_2O could be transformed into an organic compound (urea) of the same molecular formula had an important bearing on the concept of isomerism.

Lavoisier as portrayed on a 1943 French postage stamp.

A 1979 Swedish stamp honoring Berzelius.



This German stamp depicts a molecular model of urea and was issued in 1982 to commemorate the hundredth anniversary of Wöhler's death. The computer graphic that opened this introductory chapter is also a model of urea.

THE STRUCTURAL THEORY

It is from the concept of isomerism that we can trace the origins of the **structural theory**—the idea that a precise arrangement of atoms uniquely defines a substance. Ammonium cyanate and urea are different compounds because they have different structures. To some degree the structural theory was an idea whose time had come. Three scientists stand out, however, in being credited with independently proposing the elements of the structural theory. These scientists are August Kekulé, Archibald S. Couper, and Alexander M. Butlerov.

It is somehow fitting that August Kekulé's early training at the university in Giessen was as a student of architecture. Kekulé's contribution to chemistry lies in his description of the architecture of molecules. Two themes recur throughout Kekulé's work: critical evaluation of experimental information and a gift for visualizing molecules as particular assemblies of atoms. The essential features of Kekulé's theory, developed and presented while he taught at Heidelberg in 1858, were that carbon normally formed four bonds and had the capacity to bond to other carbons so as to form long chains. Isomers were possible because the same elemental composition (say, the CH_4N_2O molecular formula common to both ammonium cyanate and urea) accommodates more than one pattern of atoms and bonds.

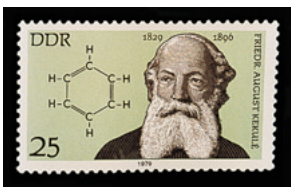
Shortly thereafter, but independently of Kekulé, Archibald S. Couper, a Scot working in the laboratory of Charles-Adolphe Wurtz at the École de Medicine in Paris, and Alexander Butlerov, a Russian chemist at the University of Kazan, proposed similar theories.

The University of Kazan was home to a number of prominent nineteenth-century organic chemists. Their contributions are recognized in two articles published in the January and February 1994 issues of the *Journal of Chemical Education* (pp. 39–42 and 93–98).

ELECTRONIC THEORIES OF STRUCTURE AND REACTIVITY

In the late nineteenth and early twentieth centuries, major discoveries about the nature of atoms placed theories of molecular structure and bonding on a more secure foundation. Structural ideas progressed from simply identifying atomic connections to attempting to understand the bonding forces. In 1916, Gilbert N. Lewis of the University of California at Berkeley described covalent bonding in terms of shared electron pairs. Linus Pauling at the California Institute of Technology subsequently elaborated a more sophisticated bonding scheme based on Lewis' ideas and a concept called **resonance,** which he borrowed from the quantum mechanical treatments of theoretical physics.

Once chemists gained an appreciation of the fundamental principles of bonding, a logical next step became the understanding of how chemical reactions occurred. Most



A 1968 German stamp combines a drawing of the structure of benzene with a portrait of Kekulé.

Linus Pauling is portrayed on this 1977 Volta stamp. The chemical formulas depict the two resonance forms of benzene, and the explosion in the background symbolizes Pauling's efforts to limit the testing of nuclear weapons.

The discoverer of penicillin, Sir Alexander Fleming, has appeared on two stamps. This 1981 Hungarian issue includes both a likeness of Fleming and a structural formula for penicillin.

notable among the early workers in this area were two British organic chemists, Sir Robert Robinson and Sir Christopher Ingold. Both held a number of teaching positions, with Robinson spending most of his career at Oxford while Ingold was at University College, London.

Robinson, who was primarily interested in the chemistry of natural products, had a keen mind and a penetrating grasp of theory. He was able to take the basic elements of Lewis' structural theories and apply them to chemical transformations by suggesting that chemical change can be understood by focusing on electrons. In effect, Robinson analyzed organic reactions by looking at the electrons and understood that atoms moved because they were carried along by the transfer of electrons. Ingold applied the quantitative methods of physical chemistry to the study of organic reactions so as to better understand the sequence of events, the **mechanism,** by which an organic substance is converted to a product under a given set of conditions.

Our current understanding of elementary reaction mechanisms is quite good. Most of the fundamental reactions of organic chemistry have been scrutinized to the degree that we have a relatively clear picture of the intermediates that occur during the passage of starting materials to products. Extension of the principles of mechanism to reactions that occur in living systems, on the other hand, is an area in which a large number of important questions remain to be answered.

THE INFLUENCE OF ORGANIC CHEMISTRY

Many organic compounds were known to and used by ancient cultures. Almost every known human society has manufactured and used beverages containing ethyl alcohol and has observed the formation of acetic acid when wine was transformed into vinegar. Early Chinese civilizations (2500–3000 BC) extensively used natural materials for treating illnesses and prepared a drug known as *ma huang* from herbal extracts. This drug was a stimulant and elevated blood pressure. We now know that it contains ephedrine, an organic compound similar in structure and physiological activity to adrenaline, a hormone secreted by the adrenal gland. Almost all drugs prescribed today for the treatment of disease are organic compounds—some are derived from natural sources; many others are the products of synthetic organic chemistry.

As early as 2500 BC in India, indigo was used to dye cloth a deep blue. The early Phoenicians discovered that a purple dye of great value, Tyrian purple, could be extracted from a Mediterranean sea snail. The beauty of the color and its scarcity made purple the color of royalty. The availability of dyestuffs underwent an abrupt change in 1856 when William Henry Perkin, an 18-year-old student, accidentally discovered a simple way to prepare a deep-purple dye, which he called *mauveine,* from extracts of coal tar. This led to a search for other synthetic dyes and forged a permanent link between industry and chemical research.

Many countries have celebrated their chemical industry on postage stamps. The stamp shown was issued in 1971 by Argentina.

The synthetic fiber industry as we know it began in 1928 when E. I. Du Pont de Nemours & Company lured Professor Wallace H. Carothers from Harvard University to direct their research department. In a few years Carothers and his associates had produced *nylon,* the first synthetic fiber, and *neoprene,* a rubber substitute. Synthetic fibers and elastomers are both products of important contemporary industries, with an economic influence far beyond anything imaginable in the middle 1920s.

COMPUTERS AND ORGANIC CHEMISTRY

A familiar arrangement of the sciences places chemistry between physics, which is highly mathematical, and biology, which is highly descriptive. Among chemistry's subdisci-

plines, organic chemistry is less mathematical than descriptive in that it emphasizes the qualitative aspects of molecular structure, reactions, and synthesis. The earliest applications of computers to chemistry took advantage of the "number crunching" power of mainframes to analyze data and to perform calculations concerned with the more quantitative aspects of bonding theory. More recently, organic chemists have found the graphics capabilities of minicomputers, workstations, and personal computers to be well suited to visualizing a molecule as a three-dimensional object and assessing its ability to interact with another molecule. Given a biomolecule of known structure, a protein, for example, and a drug that acts on it, molecular-modeling software can evaluate the various ways in which the two may fit together. Such studies can provide information on the mechanism of drug action and guide the development of new drugs of greater efficacy.

The influence of computers on the practice of organic chemistry is a significant recent development and will be revisited numerous times in the chapters that follow.

A DNA double helix as pictured on a 1964 postage stamp issued by Israel.

CHALLENGES AND OPPORTUNITIES

A major contributor to the growth of organic chemistry during this century has been the accessibility of cheap starting materials. Petroleum and natural gas provide the building blocks for the construction of larger molecules. From petrochemicals comes a dazzling array of materials that enrich our lives: many drugs, plastics, synthetic fibers, films, and elastomers are made from the organic chemicals obtained from petroleum. As we enter an age of inadequate and shrinking supplies, the use to which we put petroleum looms large in determining the kind of society we will have. Alternative sources of energy, especially for transportation, will allow a greater fraction of the limited petroleum available to be converted to petrochemicals instead of being burned in automobile engines. At a more fundamental level, scientists in the chemical industry are trying to devise ways to use carbon dioxide as a carbon source in the production of building block molecules.

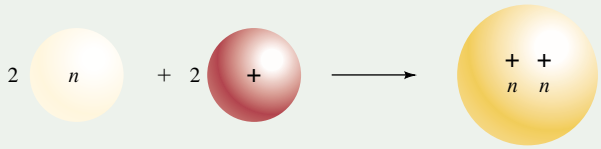
Many of the most important processes in the chemical industry are carried out in the presence of **catalysts.** Catalysts increase the rate of a particular chemical reaction but are not consumed during it. In searching for new catalysts, we can learn a great deal from **biochemistry,** the study of the chemical reactions that take place in living organisms. All these fundamental reactions are catalyzed by enzymes. Rate enhancements of several millionfold are common when one compares an enzyme-catalyzed reaction with the same reaction performed in its absence. Many diseases are the result of specific enzyme deficiencies that interfere with normal metabolism. In the final analysis, effective treatment of diseases requires an understanding of biological processes at the molecular level—what the substrate is, what the product is, and the mechanism by which substrate is transformed to product. Enormous advances have been made in understanding biological processes. Because of the complexity of living systems, however, we have only scratched the surface of this fascinating field of study.

Spectacular strides have been made in genetics during the past few years. Although generally considered a branch of biology, genetics is increasingly being studied at the molecular level by scientists trained as chemists. Gene-splicing techniques and methods for determining the precise molecular structure of DNA are just two of the tools driving the next scientific revolution.

You are studying organic chemistry at a time of its greatest influence on our daily lives, at a time when it can be considered a mature science, when the challenging questions to which this knowledge can be applied have never been more important.

WHERE DID THE CARBON COME FROM?

According to the "big-bang" theory, the universe began expanding about 12 billion years ago when an incredibly dense (10^{96} g·cm^{-3}), incredibly hot (10^{32} K) ball containing all the matter in the universe exploded. No particles more massive than protons or neutrons existed until about 100 s after the big bang. By then, the temperature had dropped to about 10^9 K, low enough to permit the protons and neutrons to combine to form helium nuclei.

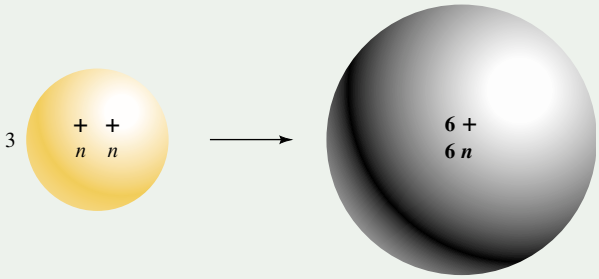


Two neutrons Two protons Helium nucleus

Conditions favorable for the formation of helium nuclei lasted for only a few hours, and the universe continued to expand without much "chemistry" taking place for approximately a million years.

As the universe expanded, it cooled, and the positively charged protons and helium nuclei combined with electrons to give hydrogen and helium atoms. Together, hydrogen and helium account for 99% of the mass of the universe and 99.9% of its atoms. Hydrogen is the most abundant element; 88.6% of the atoms in the universe are hydrogen, and 11.3% are helium.

Some regions of space have higher concentrations of matter than others, high enough so that the expansion and cooling that followed the big bang is locally reversed. Gravitational attraction causes the "matter clouds" to collapse and their temperature to increase. After the big bang, the nuclear fusion of hydrogen to helium took place when the temperature dropped to 10^9 K. The same nuclear fusion begins when gravitational attraction heats matter clouds to 10^7 K and the ball of gas becomes a star. The star expands, reaching a more or less steady state at which hydrogen is consumed and heat is evolved. The size of the star remains relatively constant, but its core becomes enriched in helium. After about 10% of the hydrogen is consumed, the amount of heat produced is insufficient to maintain the star's size, and it begins to contract. As the star contracts the temperature of the helium-rich core increases, and helium nuclei fuse to form carbon.



Three helium nuclei Nucleus of ^{12}C

Fusion of a nucleus of ^{12}C with one of helium gives ^{16}O. Eventually the helium, too, becomes depleted, and gravitational attraction causes the core to contract and its temperature to increase to the point at which various fusion reactions give yet heavier nuclei.

Sometimes a star explodes in a supernova, casting debris into interstellar space. This debris includes the elements formed during the life of the star, and these elements find their way into new stars formed when a cloud of matter collapses in on itself. Our own sun is believed to be a "second generation" star, one formed not only from hydrogen and helium, but containing the elements formed in earlier stars as well.

According to one theory, earth and the other planets were formed almost 5 billion years ago from the gas (the solar nebula) that trailed behind the sun as it rotated. Being remote from the sun's core, the matter in the nebula was cooler than that in the interior and contracted, accumulating heavier elements and becoming the series of planets that now circle the sun.

Oxygen is the most abundant element on earth. The earth's crust is rich in carbonate and silicate rocks, the oceans are almost entirely water, and oxygen constitutes almost one fifth of the air we breathe. Carbon ranks only fourteenth among the elements in natural abundance, but is second to oxygen in its abundance in the human body. It is the chemical properties of carbon that make it uniquely suitable as the raw material for the building blocks of life. Let's find out more about those chemical properties.