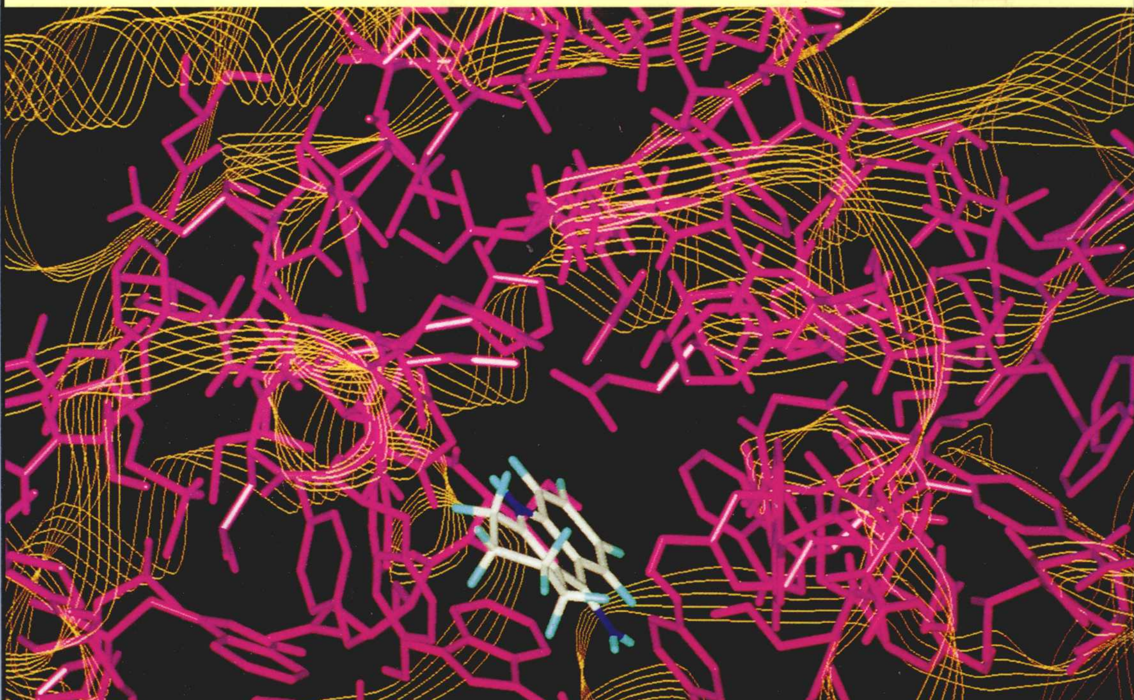
Seyhan Ege

ORGANIC CHEMISTRY

Structure and Reactivity



THIRD EDITION

Organic Chemistry

Structure and Reactivity

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About the cover: Chemists deal every day with questions of structure and reactivity in their work. The picture you see on the cover was generated using molecular modeling programs and computer graphics in the laboratories of the Parke-Davis Pharmaceutical Research Division of Warner-Lambert as part of their ongoing search for more effective medications. The blue and white structure represents a molecule of tacrine (Cognex™), which was recently approved for the treatment of Altzheimer's disease. It is shown docked into the active site of acetylcholinesterase, an enzyme known to be involved in the processes of learning and memory. Scientists, in designing such medications, work with knowledge of the three-dimensional structures (shown in magenta) of the protein molecules that are the enzymes and of the drugs that complex with and inhibit the reactivity of these enzymes. In designing new and more potent drugs, chemists take into account all of the spatial and electronic properties of both the enzyme and of the drug under consideration. Computer modeling is a powerful tool that enables chemists to examine possible structures of drugs and choose the ones most likely to have the right structure and reactivity interactions and, therefore, to be active before starting the extensive experimental work that eventually leads to clinical testing.

The chemistry discussed in this book is aimed at developing the understanding that chemists have of the structure of molecules. The book focuses on how the reactivity of such compounds is determined by their structures and how chemists use such understanding in creating new substances.

Cover image courtesy of Daniel Ortwine, Parke-Davis Pharmaceutical Research, A Division of Warner-Lambert Company.

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PREFACE

The pedagogical aim of *Organic Chemistry: Structure and Reactivity,* Third Edition, is to educate students to think independently about organic chemistry. Students can truly learn organic chemistry only if they are actively involved in developing a practical understanding of the causes of chemical change, rather than trying to master organic chemistry through memorization. In all editions of this book, I have presented organic chemistry by consistently emphasizing important themes and by returning to fundamentals again and again. In this way I have helped students to think as practicing chemists do in predicting reactivity from structure. Students have told me that they have learned an entirely new way of thinking—of analyzing problems, sorting facts, reasoning by analogy, looking for patterns—and that consequently their approach to all of their work has changed.

Like the first two editions, the third edition of *Organic Chemistry: Structure and Reactivity,* has been designed to lead students quickly to the concept that structures of organic compounds determine their chemical reactivity. To that end, the third edition retains the organization of the second edition. The aim is to introduce most of the concepts important to the study of organic chemistry in the first six chapters. The theme of structure and reactivity is apparent immediately, even within the first two chapters of the book, which introduce students to structure and bonding. Here students meet the concepts of connectivity and isomerism, the relationship of structure to physical properties, the structural features of all major functional groups, and orbital models for bonding.

Chapter 3, the first chapter devoted to chemical reactivity, uses the reactions of organic compounds as acids and bases to focus the student's attention on two simple reactions, protonation and deprotonation of organic compounds. Through the practice of solving problems on acidity and basicity, students gain confidence in their ability to predict reactivity as chemists do: by looking at structures of organic compounds and applying fundamental concepts such as atomic and ionic sizes, resonance stabilization of species, and pK_a values. In addition, students learn reactions that are important steps in many of the organic transformations they will study later. Ideas about energy relationships, relative stabilities of species, equilibrium, enthalpy, entropy, and free energy are also introduced here. In addition, mechanisms of organic reactions and their representation by the curved arrow notation are introduced in Chapter 3.

Coverage of the concepts of nucleophile and electrophile in Chapter 4 is built on the chemistry, and the language and symbolism of chemistry, learned in Chapter 3. In Chapter 4, the reactions of chloromethane with hydroxide ion and hydrogen bromide with propene are used to introduce kinetics and ideas about reaction pathways, reactive intermediates, and regioselectivity.

Chapter 5 presents the nomenclature and conformation of both alkanes and cycloalkanes. Stereoisomerism is discussed in Chapter 6. With these first six chapters, students will have mastered the key concepts they will need to understand the chemistry presented to them in the rest of the book. Extensive cross-referencing allows instructors considerable flexibility in choosing the order of subjects to follow. One colleague, for example, has told me that she successfully teaches electrophilic aromatic substitution (Chapter 19) after Chapter 6.

Features of the Third Edition

The features that were introduced in the second edition as aids to learning are retained in this edition.

Emphasis on Process

The third edition is unchanged from the previous editions in its emphasis on an understanding of reactivity rather than on an encyclopedic knowledge of reactions. Students suffer from an overload of different things to remember, and from not learning to think their way toward predicting the outcome of a reaction they have never seen before. Thinking for themselves is a skill that will be valuable to them as graduate students in chemistry, in other sciences with a strong chemical component, and in medicine. A thorough understanding, with an emphasis on mechanism of a few major reactions, enables students to apply the principles they have learned and gives them the confidence to tackle new situations. I would rather teach students who are confident about their abilities than students who are overwhelmed by a mass of undigested material. Once the fundamental thought processes of chemistry have been mastered, teachers find that they can introduce their own favorite reactions to their students.

The length of this book, thus, comes from meticulous explanations and fully detailed mechanisms for selected reactions, mechanisms that were chosen to represent many other reactions of the same type. My experience convinces me that only such an explicit, consistent approach gives students the reinforcement they need to learn a subject they perceive as being difficult.

Does this approach work? Feedback from students has been so positive that it has encouraged me to keep the same approach in this edition as I used in the other two. I particularly cherish reports from faculty at various schools that students using the book receive better scores than before on the standardized ACS examinations at the end of the year and even complain that the examination was too easy! If the book is used as it is intended, students come to enjoy and be challenged by their intellectual competence. To watch this happen is, of course, the ultimate satisfaction for a teacher.

Visualizing the Reaction

As in the first two editions, complete mechanisms are given for each type of reaction. These mechanisms are highlighted in "Visualizing the Reaction" boxes set apart from the text. Students must practice developing their powers of imagination and following a process with the "inner eye," and these complete mechanisms, which feature the judicious use of four colors, enhance the process of visualizing. Acidic or electrophilic sites are highlighted as red atoms, blue shading signifies basic or nucelophilic species, and gray shading emphasizes leaving groups. Color is used to indicate whether the reactive species on one side of an equation are converted into new reactive species after reaction, in order to show students the reversibility of many reactions, especially acid-base reactions.

New Chemistry

The third edition puts earlier emphasis on the concepts of connectivity and of the derivation of structural formulas from molecular formulas than the previous editions did. Some of the chemistry new to the third edition includes the Swern oxidation, further emphasis on the stereochemistry of reactions at carbonyl groups, the chemistry of Danishefsky's diene, fullerene chemistry, the free radical chemistry of fluorochlorocarbons as it relates to the destruction of ozone, and the use of carbohydrates as sources of chiral starting materials.

Use of Biological Examples to Illustrate Chemical Reactions

The first two editions of the book integrated biologically interesting examples of chemistry throughout the text. This edition retains and extends that practice. Biological alkylation reactions appear as early as Chapter 4 as an example of nucleophilic substitution. In Chapter 7, a biological alkylation reaction is used to illustrate the wide range of structures that function as leaving groups. Imine chemistry is exemplified in Chapter 13 by the role of vitamin B_6 in the catalysis of transamination reactions. The problems in the text also emphasize the relationship between chemistry and biology.

Problem-Solving Skills Sections

In working with my students, I have become convinced that encouraging them to analyze problems systematically is the single most important factor in increasing their overall intellectual skills. The Problem-Solving Skills sections, unique among organic chemistry texts, offer students a systematic, questioning approach to solving organic chemistry problems. These sections do not simply provide a way for students to learn to plug data into a prelearned formula; rather, students learn to reason their way to a solution.

- In Chapter 1, students are introduced to the idea that the solution to a problem in chemistry requires a step-by-step analysis of the problem. This analysis takes the form of questions that students pose to themselves in a systematic way.
- In Chapter 4, students are shown how to reason backward in solving problems involving simple syntheses.
- In Chapter 7, students are led through the types of questions that help them to predict the product of a reaction and to transform a given starting material into a desired product. These are complex questions with many types of answers, depending on the particular problem being solved. Not all of the questions are directly applicable to the problem under consideration, but they represent steps in the processes of deciding how to use the data given in the problem.
- The same method of questioning is applied in Chapter 9 to writing mechanisms. To reinforce this practice for students, in most chapters a problem is worked out using the same set of questions.
- The *Study Guide* further reinforces the questioning approach used in the book by applying it to solving some of the problems in and at the end of chapters.

Problems

We try as much as possible to create examination questions using examples from the recent research literature. We tell the students that the problem they are solving is related to real chemistry being performed by chemists doing cutting-edge research on interesting and important problems. That same philosophy is behind the problems in my textbook, of which many are new to this edition. Except for a few routine drill problems, all of them reflect the chemistry that is very much alive in the research literature today.

Concept Maps

Concept maps, which appear in the *Study Guide,* were conceived as a practical way to organize and summarize the material presented in the book, and they present major ideas in outline form. Notes in the margin of the textbook alert students that the concept maps are available. While the concept maps provided can be quite helpful to students, students are encouraged to examine the maps and then create their own, because the process of creating a concept map requires them to give up a purely linear way of thinking about a subject and to explore interrelationships. My students who have used this method to organize their lecture notes and to outline related subjects have found the concept maps not only useful, but fun. Encouraging students to work in this way promotes an active-thinking approach to organic chemistry.

A package of transparency masters containing the complete set of concept maps that appear in the *Study Guide* is available to instructors.

Workbook Exercises

A feature new to the third edition is the introduction into the *Study Guide* of workbook exercises for Chapters 1–9 and 11, 13, 14, 16, and 19. As is also the case for the concept maps, notes in the margin of the textbook alert students to the presence of the exercises in the *Study Guide.* The exercises are intended to encourage students to think about and review concepts learned in earlier chapters in a different context before starting new work. We wish to remind students that although reactions can look very dissimilar, they can usually be understood in terms of mechanistic similarities. We hope also that the workbook exercises will get students actively involved in exploring structural relationships. No answers are provided for the workbook exercises. Students are encouraged to do these exercises with other students and to talk about the issues they raise. The workbook exercises are modeled after the "Problem of the Day" that we often present to our students. In working with these exercises, students have to dissect the information they are given to create their own solutions to problems that deal with structures they have never seen before and for which they have no official answer. If they become comfortable with this process, they achieve the self-confidence that is one important result of their study of organic chemistry.

Use of Four Colors

While four-color printing appears primarily in the "Visualizing the Reaction" boxes, color is also used to enhance figures and to stress, with consistency, various important structural features. For example, in sections where students are just learning to see stereochemistry, green and red shading highlights stereochemical relationships.

In-Text Summaries

Besides the concept maps in the *Study Guide,* two other forms of summary appear in the textbook itself:

- An end-of-chapter *summary* offers a concise review of the major concepts covered in the chapter.
- End-of-chapter *tables* summarize the reactions that appear in the chapter. Organized so as to remind students of how the reactions proceed, they are not made up of general reactions to be memorized, but instead take students briefly through the stages of the reaction again, reminding them of the types of re-

agents needed, reactive intermediates involved, and the stereochemistry of the reaction. These tables are particularly helpful to students when they are used together with the concept maps in the *Study Guide.*

Easy-to-Use Cross-Referencing

The third edition is cross-referenced with page numbers to enable both students and teachers to locate related topics quickly.

Structure and Reactivity as the Basis of a First-Year Course

At the University of Michigan, since 1989, incoming students who have taken chemistry in high school have the opportunity to start college chemistry with a course called "Structure and Reactivity." Each fall, about 700 of the 1100 students in the course have their first experience of college-level chemistry in a new way. "Structure and Reactivity" introduces students to important concepts in chemistry in the context of mechanistic organic chemistry. In teaching this course we emphasize the way chemists think about experimental data and the increasingly sophisticated models they develop to explain and correlate those data. We encourage students to develop skills in reasoning by analogy in the use of quantitative data (such as pK_a values, energies of activation, or rates of reaction) to make qualitative predictions about structure and reactivity relationships in systems new to them. We also try to show students the chemist's unique molecular perspective on phenomena ranging from life to the properties of materials. The lecture courses are accompanied by open-ended investigative laboratory courses in which we try to reinforce the individual problem-solving abilities of our students. Students also have the option of starting with a one-term "Principles" course (which attracts about 1500 students) and continuing with "Structure and Reactivity" in the second term of their first year. "Structure and Reactivity" lasts two terms and meets the organic chemistry requirements of chemistry, biology, chemical engineering, and premedical students at the university.

Feedback from this group of students has been extremely valuable in making clearer to me certain misconceptions about molecular phenomena. I now realize that most students have these misconceptions, but this population of younger students has fewer reservations about articulating them. On the whole, though, I have been gratified by the warm response of large numbers of students to this way of starting chemistry as evidenced by independent evaluations of these courses being carried out as part of our ongoing study of the innovation.

Supplements

Study Guide

Roberta W. Kleinman of Lock Haven University, Pennsylvania, and Marjorie L. C. Carter of Eastern Michigan University are my coauthors for the *Study Guide.* Both of them have given me invaluable help—especially Roberta Kleinman, who, with her skill at the computer, is responsible for transforming the material into camera-ready copy. As in the previous editions, the third edition contains detailed solutions to every problem in the text as well as explanations of the reasoning processes behind the answers for many problems. The answers have been expanded to include many three-dimensional molecular representations. Some problems in this edition are worked out using the questions developed in the Problem-Solving Skills sections of the text to reinforce students' understanding of this approach.

Concept maps, charts summarizing relationships between key ideas in a section or portion of a section, provide an innovative tool for practice and review. Notes in the margin of the text refer students to relevant concept maps in the *Study Guide* and to new workbook exercises, additional review problems that do not have answers in the *Study Guide.*

Transparency Masters

For classroom use by the instructor, a package of *Transparency Masters* contains the complete set of concept maps that appear in the *Study Guide.*

Transparencies

A compete set of *Transparencies* ($8\frac{1}{2} \times 11''$), many of them full color, is available free to college adopters of the textbook. Reproduced from selected figures and chemical structures in the text, the transparencies include spectra, molecular orbitals, space-filling models, stereochemistry, and reaction mechanisms. Special among them are two full-color electron density maps, generated by Roberta Kleinman using the Personal CAChe program, showing the interaction of hydroxide ion with chloromethane and that of hydrogen bromide with propene.

Software

A variety of quality software programs are available by special arrangement. For information and demonstration disks, contact the Marketing Department at D. C. Heath at 1-800-235-3565.

Acknowledgments

Many people have contributed to the third edition of my book. Of all my colleagues at the University of Michigan, Brian Coppola has contributed the most to the evolution of my thinking about how organic chemistry could be taught and, hence, to the development of the book. He is a superb and creative teacher, constantly seeking ways to make students see the linguistic and mechanistic logic and unity of reactions that seem so disparate to their eyes. We have taught the "Structure and Reactivity" course jointly and used the occasion to "examine" the examinations we gave and whether they measured what we intended them to. We conduct an ongoing informal seminar, along with anyone else who wants to join the argument, about the endlessly fascinating subject of how students learn or, unfortunately, do not learn chemistry. He is a vigorous critic of my ideas and, as such, serves me as a consultant. Some of his ideas and innovations have inevitably found their way into the book. His most distinctive contribution is the set of workbook exercises that he created for the *Study Guide.* His participation in the teaching and initiation of the ongoing evaluation of our new courses has been essential to the implementation of the new curriculum at the University of Michigan. I am grateful for his contributions to my teaching and writing.

Suggestions and corrections from colleagues and students who have used the book are particularly valuable. I owe special thanks to Richard Lawton, William Pearson, and John Wiseman, all of the University of Michigan; Jeffrey Moore, the University of Illinois; David Reingold, Juniata College; and David Todd, Worcester Polytechnic Institute. Stanley Winters, Goldenwest College, made many valuable suggestions on both the text and *Study Guide.* Derek Horton, now at American University, guided my

revision of the chapter on carbohydrates with extensive criticism and suggestions, for which I am especially grateful. Anne Sommer, when she was a student in "Structure and Reactivity," used a sharp editorial eye to catch typographical errors and a critical mind to insist on further clarification of certain concepts. She has since helped with the proofreading of the *Study Guide* in its latest version.

Dr. Alex Aisen of the Department of Radiology at the University of Michigan supplied me with information on magnetic resonance imaging and the photograph that appears on page 437 of the text. Torin Dewey, a student of mine who is now doing postdoctoral work at the Massachusetts Institute of Technology, took most of the proton magnetic resonance spectra. Frank Parker and James Windak helped with the spectra illustrating Fourier transform nuclear magnetic resonance and infrared methods.

I very much appreciate the suggestions of the users of the second edition: George B. Clemans, Bowling Green State University; Thomas A. Dix, University of California—Irvine; David Eck, Sonoma State University; James P. Hagen, University of Nebraska—Omaha; Viresh H. Rawal, Ohio State University; Robert Walkup, Texas Tech University; Joseph W. Wilson, University of Kentucky; James K. Wood, University of Nebraska—Omaha.

I am also grateful for the recommendations made by the reviewers for the third edition: Ron Batstone-Cunningham, University of South Dakota; Ronald J. Baumgarten, University of Illinois—Chicago; John R. Grunwell, Miami University; Kenneth Piers, Calvin College; D. S. Wulfman, University of Missouri—Rolla.

Roberta Kleinman and Marjorie Carter contributed substantially to the text as well as to the *Study Guide.* All of the three-dimensional figures in the text were developed by Roberta Kleinman, who combines artistic talent and a knowledge of computer graphics with an interest in how students visualize and learn. She joins me in struggling to see things as the student sees them and not as we, with years of experience, know them to be. She insisted on using Chem3D Plus™ from Cambridge Scientific and Personal CAChe from CAChe Scientific to be sure that the students saw good representations of molecules and not simply an artist's interpretation. I owe a great deal to her critical eye. Marjorie Carter also brings the viewpoint of the students and a questioning mind to the thankless task of proofreading. Many times she has insisted that I try again in drawing structures or explaining my reasoning for greater clarity for the student. She has also prepared the index for all three editions. I value the help of both of these good friends.

Kent Porter Hamann, Editorial Director at D. C. Heath, has guided the book through this revision. I am grateful for her support and encouragement. Karen Wise, Senior Production Editor, and Lyri Merrill, Production Editor, competently and patiently coped with the countless details necessary to make a chemistry book in four colors technically accurate as well as aesthetically pleasing. Without their expertise, the production process would have been much more traumatic. I thank them for their help.

My family and friends by now have become accustomed to the idea that life will never be the way it was "before the book." They continue to encourage me. Without such unquestioning support, my work would not be possible. I thank all of them for their loving care.

Seyhan N. Eğe

BRIEF CONTENTS

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