

Advanced Organic Chemistry

FIFTH
EDITION

Part A: Structure and Mechanisms

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PART B: Reactions and Synthesis

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Part A: Structure and Mechanisms

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Preface

This Fifth Edition marks the beginning of the fourth decade that *Advanced Organic Chemistry* has been available. As with the previous editions, the goal of this text is to allow students to build on the foundation of introductory organic chemistry and attain a level of knowledge and understanding that will permit them to comprehend much of the material that appears in the contemporary chemical literature. There have been major developments in organic chemistry in recent years, and these have had a major influence in shaping this new edition to make it more useful to students, instructors, and other readers.

The expanding application of computational chemistry is reflected by amplified discussion of this area, especially density function theory (DFT) calculations in Chapter 1. Examples of computational studies are included in subsequent chapters that deal with specific structures, reactions and properties. Chapter 2 discusses the principles of both configuration and conformation, which were previously treated in two separate chapters. The current emphasis on enantioselectivity, including development of many enantioselective catalysts, prompted the expansion of the section on stereoselective reactions to include examples of enantioselective reactions. Chapter 3, which covers the application of thermodynamics and kinetics to organic chemistry, has been reorganized to place emphasis on structural effects on stability and reactivity. This chapter lays the groundwork for later chapters by considering stability effects on carbocations, carbanions, radicals, and carbonyl compounds.

Chapters 4 to 7 review the basic substitution, addition, and elimination mechanisms, as well as the fundamental chemistry of carbonyl compounds, including enols and enolates. A section on the control of regiochemistry and stereochemistry of aldol reactions has been added to introduce the basic concepts of this important area. A more complete treatment, with emphasis on synthetic applications, is given in Chapter 2 of Part B.

Chapter 8 deals with aromaticity and Chapter 9 with aromatic substitution, emphasizing electrophilic aromatic substitution. Chapter 10 deals with concerted pericyclic reactions, with the aromaticity of transition structures as a major theme. This part of the text should help students solidify their appreciation of aromatic stabilization as a fundamental concept in the chemistry of conjugated systems. Chapter 10 also considers

the important area of stereoselectivity of concerted pericyclic reactions. Instructors may want to consider dealing with these three chapters directly after Chapter 3, and we believe that is feasible.

Chapters 11 and 12 deal, respectively, with free radicals and with photochemistry and, accordingly, with the chemistry of molecules with unpaired electrons. The latter chapter has been substantially updated to reflect the new level of understanding that has come from ultrafast spectroscopy and computational studies.

As in the previous editions, a significant amount of specific information is provided in tables and schemes. These data and examples serve to illustrate the issues that have been addressed in the text. Instructors who want to achieve a broad coverage, but without the level of detail found in the tables and schemes, may choose to advise students to focus on the main text. In most cases, the essential points are clear from the information and examples given in the text itself.

We have made an effort to reduce the duplication between Parts A and B. In general, the discussion of basic mechanisms in Part B has been reduced by cross-referencing the corresponding discussion in Part A. We have expanded the discussion of specific reactions in Part A, especially in the area of enantioselectivity and enantioselective catalysts.

We have made more extensive use of abbreviations than in the earlier editions. In particular, EWG and ERG are used throughout both Parts A and B to designate electron-withdrawing and electron-releasing substituents, respectively. The intent is that the use of these terms will help students generalize the effect of certain substituents such as C=O, C≡N, NO₂, and RSO₂ as electron withdrawing and R (alkyl) and RO (alkoxy) as electron releasing. Correct use of this shorthand depends on a solid understanding of the interplay between polar and resonance effects in overall substituent effects. This matter is discussed in detail in Chapter 3 and many common functional groups are classified.

Several areas have been treated as “Topics”. Some of the Topics discuss areas that are still in a formative stage, such as the efforts to develop DFT parameters as quantitative reactivity indices. Others, such as the role of carbocations in gasoline production, have practical implications.

We have also abstracted information from several published computational studies to present three-dimensional images of reactants, intermediates, transition structures, and products. This material, including exercises, is available at the publishers web site, and students who want to see how the output of computations can be applied may want to study it. The visual images may help toward an appreciation of some of the subtle effects observed in enantioselective and other stereoselective reactions. As in previous editions, each chapter has a number of problems drawn from the literature. A new feature is solutions to these problems, which are also provided at the publisher’s website at springer.com/carey-sundberg

Our goal is to present a broad and fairly detailed view of the core area of organic reactivity. We have approached this goal by extensive use of both the primary and review literature and the sources are referenced. Our hope is that the reader who works through these chapters, problems, topics, and computational studies either in an organized course or by self-study will be able to critically evaluate and use the current literature in organic chemistry in the range of fields in which is applied, including the pharmaceutical industry, agricultural chemicals, consumer products, petroleum chemistry, and biotechnology. The companion volume, Part B, deals extensively with organic synthesis and provides many more examples of specific reactions.

Acknowledgment and Personal Statement

The revision and updating of *Advanced Organic Chemistry* that appears as the Fifth Edition spanned the period September 2002 through December 2006. Each chapter was reworked and updated and some reorganization was done, as described in the Prefaces to Parts A and B. This period began at the point of conversion of library resources to electronic form. Our university library terminated paper subscriptions to the journals of the American Chemical Society and other journals that are available electronically as of the end of 2002. Shortly thereafter, an excavation mishap at an adjacent construction project led to structural damage and closure of our departmental library. It remained closed through June 2007, but thanks to the efforts of Carol Hunter, Beth Blanton-Kent, Christine Wiedman, Robert Burnett, and Wynne Stuart, I was able to maintain access to a few key print journals including the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Organic Letters*, *Tetrahedron*, and *Tetrahedron Letters*. These circumstances largely completed an evolution in the source for specific examples and data. In the earlier editions, these were primarily the result of direct print encounter or search of printed *Chemical Abstracts* indices. The current edition relies mainly on electronic keyword and structure searches. Neither the former nor the latter method is entirely systematic or comprehensive, so there is a considerable element of circumstance in the inclusion of specific material. There is no intent that specific examples reflect either priority of discovery or relative importance. Rather, they are interesting examples that illustrate the point in question.

Several reviewers provided many helpful corrections and suggestions, collated by Kenneth Howell and the editorial staff of Springer. Several colleagues provided valuable contributions. Carl Trindle offered suggestions and material from his course on computational chemistry. Jim Marshall reviewed and provided helpful comments on several sections. Michal Sabat, director of the Molecular Structure Laboratory, provided a number of the graphic images. My co-author, Francis A. Carey, retired in 2000 to devote his full attention to his text, *Organic Chemistry*, but continued to provide valuable comments and insights during the preparation of this edition. Various users of prior editions have provided error lists, and, hopefully, these corrections have

been made. Shirley Fuller and Cindy Knight provided assistance with many aspects of the preparation of the manuscript.

This Fifth Edition is supplemented by the *Digital Resource* that is available at springer.com/carey-sundberg. The *Digital Resource* summarizes the results of several computational studies and presents three-dimensional images, comments, and exercises based on the results. These were developed with financial support from the Teaching Technology Initiative of the University of Virginia. Technical support was provided by Michal Sabat, William Rourk, Jeffrey Hollier, and David Newman. Several students made major contributions to this effort. Sara Higgins Fitzgerald and Victoria Landry created the prototypes of many of the sites. Scott Geyer developed the dynamic representations using IRC computations. Tanmaya Patel created several sites and developed the measurement tool. I also gratefully acknowledge the cooperation of the original authors of these studies in making their output available. *Problem Responses* have been provided and I want to acknowledge the assistance of R. Bruce Martin, David Metcalf, and Daniel McCauley in helping work out some of the specific kinetic problems and in providing the attendant graphs.

It is my hope that the text, problems, and other material will assist new students to develop a knowledge and appreciation of structure, mechanism, reactions, and synthesis in organic chemistry. It is gratifying to know that some 200,000 students have used earlier editions, hopefully to their benefit.

Richard J. Sundberg
Charlottesville, Virginia
March 2007

Introduction

This volume is intended for students who have completed the equivalent of a two-semester introductory course in organic chemistry and wish to expand their understanding of *structure and reaction mechanisms* in organic chemistry. The text assumes basic knowledge of physical and inorganic chemistry at the advanced undergraduate level.

Chapter 1 begins by reviewing the familiar Lewis approach to structure and bonding. Lewis's concept of electron pair bonds, as extended by adding the ideas of hybridization and resonance, plus fundamental atomic properties such as electronegativity and polarizability provide a solid foundation for *qualitative* descriptions of trends in reactivity. In polar reactions, for example, the molecular properties of acidity, basicity, nucleophilicity, and electrophilicity can all be related to information embodied in Lewis structures. The chapter continues with the more *quantitative* descriptions of molecular structure and properties that are obtained by quantum mechanical calculations. Hückel, semiempirical, and *ab initio* molecular orbital (MO) calculations, as well as density functional theory (DFT) are described and illustrated with examples. This material is presented at a level sufficient for students to recognize the various methods and their ranges of application. Computational methods can often provide insight into reaction mechanisms by describing the structural features of intermediates and transition structures. Another powerful aspect of computational methods is their ability to represent electron density. Various methods of describing electron density, including graphical representations, are outlined in this chapter and applied throughout the remainder of the text. Chapter 2 explores the two structural levels of stereochemistry—*configuration* and *conformation*. Molecular conformation is important in its own right, but can also influence reactivity. The structural relationships between stereoisomers and the origin and consequences of molecular chirality are discussed. After reviewing the classical approach to resolving racemic mixtures, modern methods for chromatographic separation and kinetic resolution are described. The chapter also explores how stereochemistry affects reactivity with examples of *diastereoselective* and *enantioselective* reactions, especially those involving addition to carbonyl groups. Much of today's work in organic chemistry focuses on enantioselective reagents and catalysts. The enantioselectivity of these reagents usually involves rather small and sometimes subtle differences in intermolecular interactions. Several of the best-understood enantioselective

reactions, including hydrogenation, epoxidation of allylic alcohols, and dihydroxylation of alkenes are discussed. Chapter 3 provides examples of structure-stability relationships derived from both experimental thermodynamics and computation. Most of the chapter is about the effects of substituents on reaction rates and equilibria, how they are measured, and what they tell us about reaction mechanisms. The electronic character of the common functional groups is explored, as well as substituent effects on the stability of carbocations, carbanions, radicals, and carbonyl addition intermediates. Other topics in this chapter include the Hammett equation and related linear free-energy relationships, catalysis, and solvent effects. Understanding how thermodynamic and kinetic factors combine to influence reactivity and developing a sense of structural effects on the energy of reactants, intermediates and transition structures render the outcome of organic reactions more predictable.

Chapters 4 to 7 relate the patterns of addition, elimination, and substitution reactions to the general principles developed in Chapters 1 to 3. A relatively small number of reaction types account for a wide range of both simple and complex reactions. The fundamental properties of carbocations, carbanions, and carbonyl compounds determine the outcome of these reactions. Considerable information about reactivity trends and stereoselectivity is presented, some of it in tables and schemes. Although this material may seem overwhelming if viewed as individual pieces of information, taken in the context of the general principles it fills in details and provides a basis for recognizing the relative magnitude of various structural changes on reactivity. The student should strive to develop a sufficiently broad perspective to generate an intuitive sense of the effect of particular changes in structure.

Chapter 4 begins the discussion of specific reaction types with an examination of *nucleophilic substitution*. Key structural, kinetic, and stereochemical features of substitution reactions are described and related to reaction mechanisms. The limiting mechanisms S_N1 and S_N2 are presented, as are the “merged” and “borderline” variants. The relationship between stereochemistry and mechanism is explored and specific examples are given. Inversion is a virtually universal characteristic of the S_N2 mechanism, whereas stereochemistry becomes much more dependent on the specific circumstances for borderline and S_N1 mechanisms. The properties of carbocations, their role in nucleophilic substitution, carbocation rearrangements, and the existence and relative stability of bridged (nonclassical) carbocations are considered. The importance of carbocations in many substitution reactions requires knowledge of their structure and reactivity and the effect of substituents on stability. A fundamental characteristic of carbocations is the tendency to rearrange to more stable structures. We consider the mechanism of carbocation rearrangements, including the role of bridged ions. The case of nonclassical carbocations, in which the bridged structure is the most stable form, is also discussed.

Chapter 5 considers the relationship between mechanism and regio- and stereoselectivity. The reactivity patterns of electrophiles such as protic acids, halogens, sulfur and selenium electrophiles, mercuric ion, and borane and its derivatives are explored and compared. These reactions differ in the extent to which they proceed through discrete carbocations or bridged intermediates and this distinction can explain variations in regio- and stereochemistry. This chapter also describes the E1, E2, and E1cb mechanisms for elimination and the idea that these represent specific cases within a continuum of mechanisms. The concept of the variable mechanism can explain trends in reactivity and regiochemistry in elimination reactions. Chapter 6 focuses on the fundamental properties and reactivity of *carbon nucleophiles*, including

organometallic reagents, enolates, enols, and enamines. The mechanism of the aldol addition is discussed. The acidity of hydrocarbons and functionalized molecules is considered. Chapter 7 discusses the fundamental reactions of carbonyl groups. The reactions considered include hydration, acetal formation, condensation with nitrogen nucleophiles, and the range of substitution reactions that interconvert carboxylic acid derivatives. The relative stability and reactivity of the carboxylic acid derivatives is summarized and illustrated. The relationships described in Chapters 6 and 7 provide the broad reactivity pattern of carbonyl compounds, which has been extensively developed and is the basis of a rich synthetic methodology.

Chapter 8 discusses the concept of *aromaticity* and explores the range of its applicability, including annulenes, cyclic cations and anions, polycyclic hydrocarbons, and heterocyclic aromatic compounds. The criteria of aromaticity and some of the methods for its evaluation are illustrated. We also consider the *antiaromaticity* of cyclobutadiene and related molecules. Chapter 9 explores the mechanisms of *aromatic substitution* with an emphasis on electrophilic aromatic substitution. The general mechanism is reviewed and the details of some of the more common reactions such as nitration, halogenation, Friedel-Crafts alkylation, and acylation are explored. Patterns of position and reactant selectivity are examined. Recent experimental and computational studies that elucidate the role of aromatic radical cations generated by electron transfer in electrophilic aromatic substitution are included, and the mechanisms for nucleophilic aromatic substitution are summarized. Chapter 10 deals with *concerted pericyclic reactions*, including *cycloaddition*, *electrocyclic reactions*, and *sigmatropic rearrangements*. This chapter looks at how *orbital symmetry* influences reactivity and introduces the idea of aromaticity in transition structures. These reactions provide interesting examples of how stereochemistry and reactivity are determined by the structure of the transition state. The role of Lewis acids in accelerating Diels-Alder reactions and the use of chiral auxiliaries and catalysts to achieve enantioselectivity are explored.

Chapter 11 deals with *free radicals* and their reactions. Fundamental structural concepts such as substituent effects on bond dissociation enthalpies (BDE) and radical stability are key to understanding the mechanisms of radical reactions. The patterns of stability and reactivity are illustrated by discussion of some of the absolute rate data that are available for free radical reactions. The reaction types that are discussed include halogenation and oxygenation, as well as addition reactions of hydrogen halides, carbon radicals, and thiols. Group transfer reactions, rearrangements, and fragmentations are also discussed.

Chapter 12 ventures into the realm of *photochemistry*, where structural concepts are applied to following the path from initial excitation to the final reaction product. Although this discussion involves comparison with some familiar intermediates, especially radicals, and offers mechanisms to account for the reactions, photochemistry introduces some new concepts of *reaction dynamics*. The excited states in photochemical reactions traverse energy surfaces that have small barriers relative to most thermal reactions. Because several excited states can be involved, the mechanism of conversion between excited states is an important topic. The nature of *conical intersections*, the transition points between excited state energy surfaces is examined.

Fundamental concepts of structure and its relationship to reactivity within the context of organic chemistry are introduced in the first three chapters, and thereafter the student should try to relate the structure and reactivity of the intermediates and transition structures to these concepts. Critical consideration of bonding, stereochemistry, and substituent effects should come into play in examining each of the basic

reactions. Computational studies frequently serve to focus on particular aspects of the reaction mechanism. Many specific reactions are cited, both in the text and in schemes and tables. The purpose of this specific information is to illustrate the broad patterns of reactivity. As students study this material, the goal should be to look for the underlying relationships in the broad reactivity patterns. Organic reactions occur by a combination of a relatively few reaction types—substitution, addition, elimination, and rearrangement. Reagents can generally be classified as electrophilic, nucleophilic, or radical in character. By focusing on the fundamental character of reactants and reagents, students can develop a familiarity with organic reactivity and organize the vast amount of specific information on reactions.

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