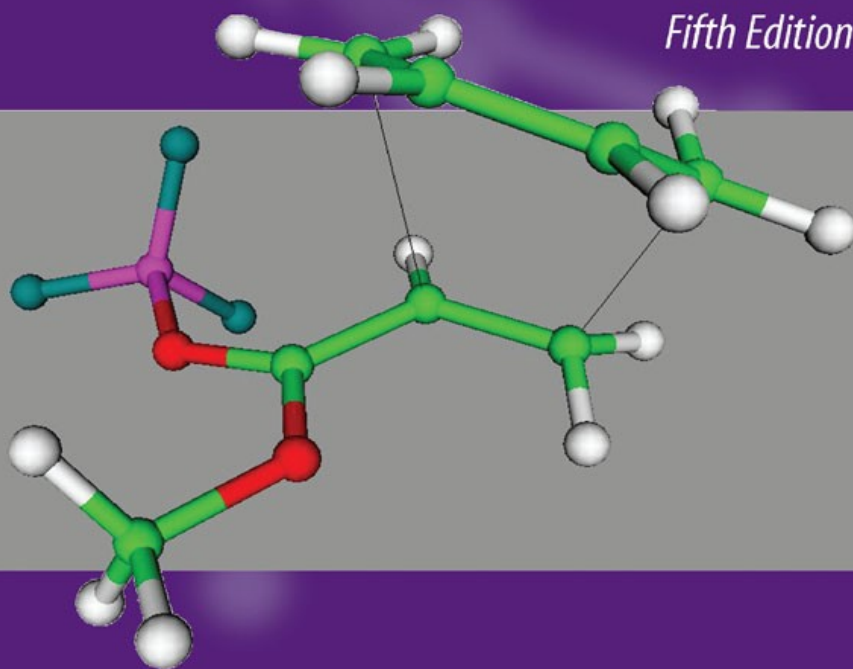


Advanced Organic Chemistry

Part A: Structure and Mechanisms

Fifth Edition



Francis A. Carey
Richard J. Sundberg

 Springer

Advanced Organic Chemistry

FIFTH
EDITION

Part A: Structure and Mechanisms

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PART A: Structure and Mechanisms

PART B: Reactions and Synthesis

Advanced Organic Chemistry

FIFTH
EDITION

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 Rourke, 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 $E1c_b$ 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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Chemical Bonding and Molecular Structure

Introduction

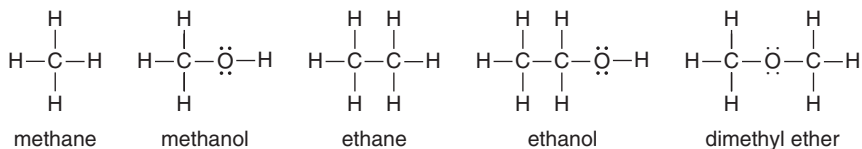
In this chapter we consider *molecular structure* and the concepts of *chemical bonding* that are used to interpret molecular structure. We will also begin to see how information about molecular structure and ideas about bonds can be used to interpret and predict physical properties and chemical reactivity. *Structural formulas* are a key tool for describing both structure and reactivity. At a minimum, they indicate *molecular constitution* by specifying the *connectivity* among the atoms in the molecule. Structural formulas also give a rough indication of electron distribution by representing electron pairs in bonds by lines and unshared electrons as dots, although the latter are usually omitted in printed structures. The reader is undoubtedly familiar with structural formulas for molecules such as those shown in Scheme 1.1.

In quantitative terms, molecular structure specifies the relative position of all atoms in a molecule. These data provide the bond lengths and bond angles. There are a number of experimental means for precise determination of molecular structure, primarily based on spectroscopic and diffraction methods, and structural data are available for thousands of molecules. Structural information and interpretation is also provided by *computational chemistry*. In later sections of this chapter, we describe how molecular orbital theory and density functional theory can be applied to the calculation of molecular structure and properties.

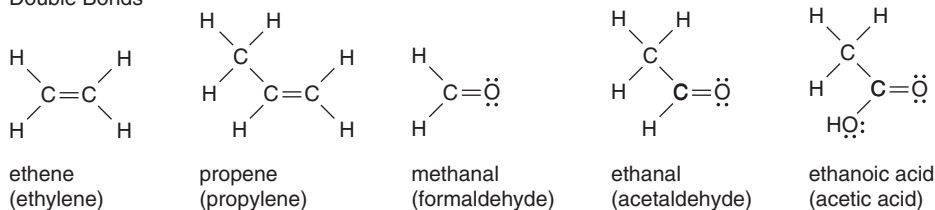
The *distribution of electrons* is another element of molecular structure that is very important for understanding chemical reactivity. It is considerably more difficult to obtain experimental data on *electron density*, but fortunately, in recent years the rapid development of both structural theory and computational methods has allowed such calculations. We make use of computational electron density data in describing molecular structure, properties, and reactivity. In this chapter, we focus on the minimum energy structure of individual molecules. In Chapter 2, we consider other elements of molecular geometry, including dynamic processes involving *conformation*, that is, the variation of molecular shape as a result of bond rotation. In Chapter 3, we discuss

Scheme 1.1. Lewis Structures of Simple Molecules

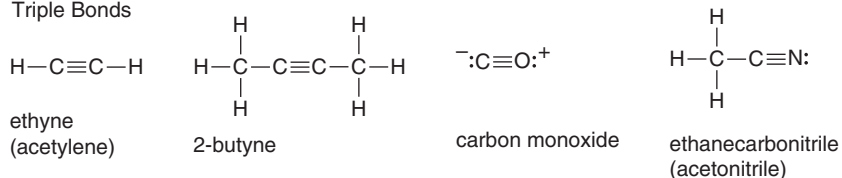
Single Bonds



Double Bonds



Triple Bonds



how structure effects the energy of *transition structures* and *intermediates* in chemical reactions. The principal goal of this chapter is to discuss the concepts that chemists use to develop relationships between molecular structure and reactivity. These relationships have their foundation in the fundamental physical aspects of molecular structure, that is, nuclear position and electron density distribution. Structural concepts help us see, understand, and apply these relationships.

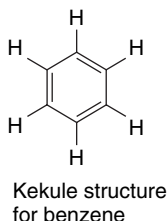
1.1. Description of Molecular Structure Using Valence Bond Concepts

Introductory courses in organic chemistry usually rely primarily on the valence bond description of molecular structure. Valence bond theory was the first structural theory applied to the empirical information about organic chemistry. During the second half of the nineteenth century, correct structural formulas were deduced for a wide variety of organic compounds. The concept of “valence” was recognized. That is, carbon almost always formed four bonds, nitrogen three, oxygen two, and the halogens one. From this information, chemists developed structural formulas such as those in Scheme 1.1. Kekule’s structure for benzene, published in 1865, was a highlight of this period. The concept of *functional groups* was also developed. It was recognized that structural entities such as hydroxy ($-\text{OH}$), amino ($-\text{NH}_2$), carbonyl ($\text{C}=\text{O}$), and

carboxy (CO₂H) groups each had characteristic reactivity that was largely independent of the hydrocarbon portion of the molecule.

 SECTION 1.1

 Description of Molecular
Structure Using Valence
Bond Concepts



These structural formulas were developed without detailed understanding of the nature of the *chemical bond* that is represented by the lines in the formulas. There was a key advance in the understanding of the origin of chemical bonds in 1916, when G.N. Lewis introduced the concept of electron-pair bonds and the “rule of 8” or *octet rule*, as we now know it. Lewis postulated that chemical bonds were the result of sharing of electron pairs by nuclei and that for the second-row atoms, boron through neon, the most stable structures have eight valence shell electrons.¹ Molecules with more than eight electrons at any atom are very unstable and usually dissociate, while those with fewer than eight electrons at any atom are usually highly reactive toward electron donors. The concept of bonds as electron pairs gave a fuller meaning to the traditional structural formulas, since the lines then specifically represent single, double, and triple bonds. The dots represent unshared electrons. Facility with Lewis structures as a tool for accounting for electrons, bonds, and charges is one of the fundamental skills developed in introductory organic chemistry.

Lewis structures, however, convey relatively little information about the details of molecular structure. We need other concepts to deduce information about relative atomic positions and, especially, electron distribution. *Valence bond theory* provides one approach to deeper understanding of molecular structure. Valence bond (VB) theory has its theoretical foundation in quantum mechanics calculations that demonstrated that electrons hold nuclei together, that is, form bonds, when shared by two nuclei. This fact was established in 1927 by calculations on the hydrogen molecule.² The results showed that an energy minimum occurs at a certain internuclear distance if the electrons are free to associate with either nucleus. Electron density accumulates between the two nuclei. This can be depicted as an electron density map for the hydrogen molecule, as shown in Figure 1.1a. The area of space occupied by electrons is referred to as an *orbital*. A fundamental concept of VB theory is that there is a concentration of electron density between atoms that are bonded to one another. Figure 1.1b shows that there is *electron density depletion* relative to spherical atoms outside of the hydrogen nuclei. Nonbonding electrons are also described by orbitals, which are typically more diffuse than bonding ones. The mathematical formulation of molecular structure by VB theory is also possible. Here, we emphasize qualitative concepts that provide insight into the relationship between molecular structure and properties and reactivity.

¹ G. N. Lewis, *J. Am. Chem. Soc.*, **38**, 762 (1916).

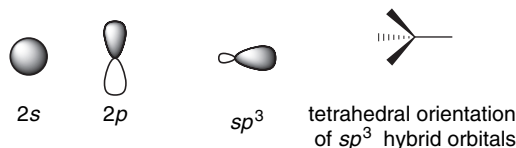
² W. Heitler and F. London, *Z. Phys.*, **44**, 455 (1927).



(b)

1.1.1. Hybridization

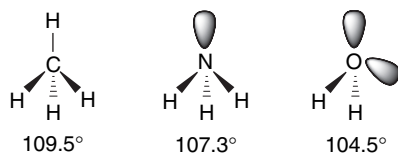
Qualitative application of VB theory to molecules containing second-row elements such as carbon, nitrogen, and oxygen involves the concept of *hybridization*, which was developed by Linus Pauling.³ The atomic orbitals of the second-row elements include the spherically symmetric $2s$ and the three $2p$ orbitals, which are oriented perpendicularly to one another. The combination of these atomic orbitals is equivalent to four sp^3 orbitals directed toward the corners of a tetrahedron. These are called *sp^3 hybrid orbitals*. In methane, for example, these orbitals overlap with hydrogen $1s$ orbitals to form σ bonds.



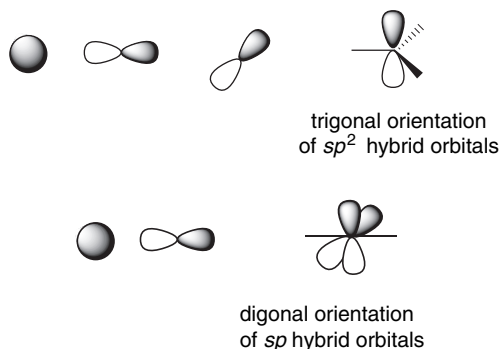
The valence bond description of methane, ammonia, and water predicts tetrahedral geometry. In methane, where the carbon valence is four, all the hybrid orbitals are involved in bonds to hydrogen. In ammonia and water, respectively, one and two nonbonding (unshared) pairs of electrons occupy the remaining orbitals. While methane

3. L. Pauling, *J. Am. Chem. Soc.*, **53**, 1367 (1931).

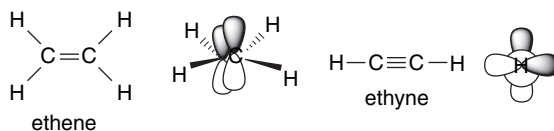
is perfectly tetrahedral, the bond angles in ammonia and water are somewhat reduced. This suggests that the electron-electron repulsions between unshared pairs are greater than for electrons in bonds to hydrogen. In other words, the unshared pairs occupy somewhat larger orbitals. This is reasonable, since these electrons are not attracted by hydrogen nuclei.



The hybridization concept can be readily applied to molecules with double and triple bonds, such as those shown in Scheme 1.1. Second-row elements are described as having sp^2 or sp orbitals, resulting from hybridization of the s orbital with two or one p orbitals, respectively. The double and triple bonds are conceived as arising from the overlap of the unhybridized p orbitals on adjacent atoms. These bonds have a nodal plane and are called π bonds. Because the overlap is not as effective as for sp^3 orbitals, these bonds are somewhat weaker than σ bonds.



The prototypical hydrocarbon examples of sp^2 and sp hybridization are ethene and ethyne, respectively. The total electron density between the carbon atoms in these molecules is the sum from the π and σ bonds. For ethene, the electron density is somewhat elliptical, because the π component is not cylindrically symmetrical. For ethyne, the combination of the two π bonds restores cylindrical symmetry. The electron density contours for ethene are depicted in Figure 1.2, which shows the highest density near the nuclei, but with net accumulation of electron density between the carbon and hydrogen atoms.



The hybridization concept also encompasses empty antibonding orbitals, which are designated by an asterisk (*). These orbitals have nodes between the bound atoms. As discussed in Section 1.1.8, σ^* and π^* orbitals can interact with filled orbitals and contribute to the ground state structure of the molecule. These empty orbitals are also

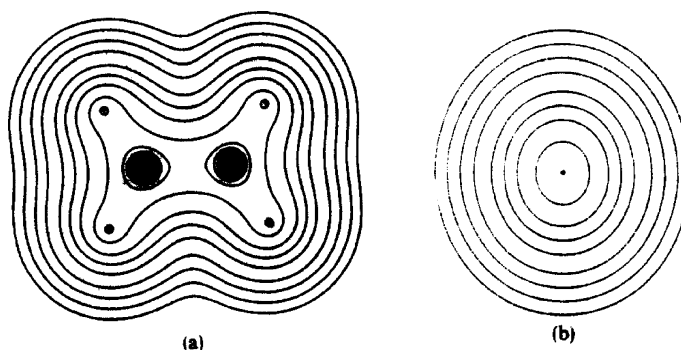
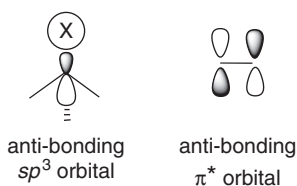
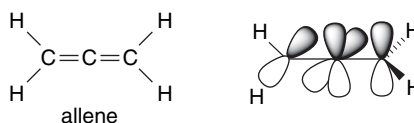


Fig. 1.2. (a) Contour map of electron density in the plane of the ethene molecule. (b) Contour map of electron density perpendicular to the plane of the ethene molecule at the midpoint of the C=C bond. Reproduced with permission from R. F. W. Bader, T. T. Nguyen-Dang, and Y. Tal, *Rep. Prog. Phys.*, **44**, 893 (1981).

of importance in terms of reactivity, particularly with electron-donating *nucleophilic* reagents, since it is the empty antibonding orbitals that interact most strongly with approaching nucleophiles.



The hybridization concept indicates some additional aspects of molecular structure. The tetrahedral, trigonal, and digonal natures of sp^3 , sp^2 , and sp carbon atoms provide an approximation of bond angles. The idea that π bonds are formed by the overlap of p orbitals puts some geometrical constraints on structure. Ethene, for example, is planar to maximize p -orbital overlap. Allene, on the other hand, must have the terminal CH_2 groups rotated by 90° to accommodate two π bonds at the central sp carbon.



It is important to remember that hybridization is a *description* of the observed molecular geometry and electron density. Hybridization does not *cause* a molecule to have a particular shape. Rather, the molecule adopts a particular shape because it maximizes bonding interactions and minimizes electron-electron and other repulsive interactions. We use the hybridization concept to recognize similarities in structure that have their origin in fundamental forces within the molecules. The concept of hybridization helps us to see how molecular structure is influenced by the number of ligands and electrons at a particular atom.

It is worth noting at this point that a particular hybridization scheme *does not provide a unique description of molecular structure*. The same fundamental conclusions about geometry and electron density are reached if ethene and ethyne are described in terms of sp^3 hybridization. In this approach, the double bond in ethene is thought of as arising from two overlapping sp^3 orbitals. The two bonds are equivalent and are called *bent bonds*. This bonding arrangement also predicts a planar geometry and elliptical electron distribution, and in fact, this description is mathematically equivalent to the sp^2 hybridization description. Similarly, ethyne can be thought of as arising by the sharing of three sp^3 hybrid orbitals. The fundamental point is that there is a single real molecular structure defined by atomic positions and electron density. Orbitals partition the electron density in specific ways, and it is the *sum of the orbital contributions that describes the structure*.



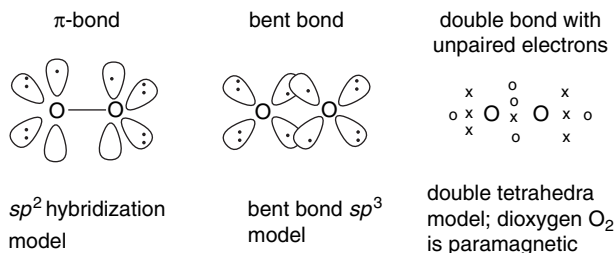
1.1.2. The Origin of Electron-Electron Repulsion

We have already assumed that electron pairs, whether in bonds or as nonbonding pairs, repel other electron pairs. This is manifested in the tetrahedral and trigonal geometry of tetravalent and trivalent carbon compounds. These geometries correspond to maximum separation of the electron-pair bonds. Part of this repulsion is electrostatic, but there is another important factor. The *Pauli exclusion principle* states that only two electrons can occupy the same point in space and that they must have opposite spin quantum numbers. Equivalent orbitals therefore maintain maximum separation, as found in the sp^3 , sp^2 , and sp hybridization for tetra-, tri-, and divalent compounds of the second-row elements. The combination of Pauli exclusion and electrostatic repulsion leads to the *valence shell electron-pair repulsion rule* (VSEPR), which states that bonds and unshared electron pairs assume the orientation that permits maximum separation.

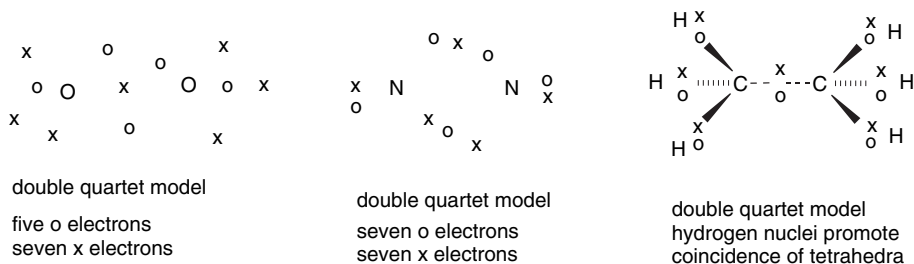
An important illustration of the importance of the Pauli exclusion principle is seen in the O_2 molecule. If we were to describe O_2 using either the sp^2 hybridization or bent bond model, we would expect a double bond with all the electrons paired. In fact, O_2 is *paramagnetic*, with two unpaired electrons, and yet it does have a double bond. If we ask how electrons would be distributed to maintain maximum separation, we arrive at two tetrahedral arrays, with the tetrahedra offset by the maximum amount.⁴ Electronic spin can be represented as x and o. The structure still has four bonding electrons between the oxygen atoms, that is, a double bond. It also obeys the octet rule for each oxygen and correctly predicts that two of the electrons are unpaired.

⁴. J. W. Linnett, *The Electronic Structure of Molecules*, Methren Co. LTD, London, 1964, pp. 37–42;
R. J. Gillespie and P. L. A. Popelier, *Chemical Bonding and Molecular Geometry*, Oxford University
Press, New York, 2001, pp 102–103.

This structure minimizes electron-electron repulsions and obeys the Pauli principle by maximizing the separation of electrons having the same spin.



A similar representation of N_2 with offset of the tetrahedral of electrons correctly describes the molecule as having a triple bond, but it is diamagnetic, since there are equal numbers of electrons of each spin. For ethane, all the electrons are bonding and are attracted toward the hydrogen nuclei, and the tetrahedra of electrons of opposite spin both occupy a region of space directed toward a hydrogen nucleus.



For most of the molecules and reactions we want to consider, the Pauling hybridization scheme provides an effective structural framework, and we use VB theory to describe most of the reactions and properties of organic compounds. However, we have to keep in mind that it is *neither a unique nor a complete description of electron density*, and we will find cases where we need to invoke additional ideas. In particular, we discuss *molecular orbital theory* and *density functional theory*, which are other ways of describing molecular structure and electron distribution.

1.1.3. Electronegativity and Polarity

The VB concept of electron-pair bonds recognizes that the sharing of electrons by the nuclei of two different elements is unequal. Pauling defined the concept of unequal sharing in terms of *electronegativity*,⁵ defining the term as “the power of an atom in a molecule to attract electrons to itself.” Electronegativity depends on the number of protons in the nucleus and is therefore closely associated with position in the periodic table. The metals on the left of the periodic table are the least electronegative elements, whereas the halogens on the right have the highest electronegativity in each row. Electronegativity decreases going down the periodic table for both metals and nonmetals.

The physical origin of these electronegativity trends is *nuclear screening*. As the atomic number increases from lithium to fluorine, the nuclear charge increases, as does

⁵ L. Pauling, *J. Am. Chem. Soc.*, **54**, 3570 (1932).

the number of electrons. Each successive electron “feels” a larger nuclear charge. This charge is partially screened by the additional electron density as the shell is filled. However, the screening, on average, is less effective for each electron that is added. As a result, an electron in fluorine is subject to a greater effective nuclear charge than one in an atom on the left in the periodic table. As each successive shell is filled, the electrons in the valence shell “feel” the effective nuclear charge as screened by the filled inner shells. This screening is more effective as successive shells are filled and the outer valence shell electrons are held less tightly going down the periodic table. As we discuss later, the “size” of an atom also changes in response to the nuclear charge. Going across the periodic table in any row, the atoms become *smaller* as the shell is filled because of the higher effective nuclear charge. Pauling devised a numerical scale for electronegativity, based on empirical interpretation of energies of bonds and relating specifically to electron sharing in covalent bonds, that has remained in use for many years. Several approaches have been designed to define electronegativity in terms of other atomic properties. Allred and Rochow defined electronegativity in terms of the electrostatic attraction by the effective nuclear charge Z_{eff} ⁶:

$$\chi_{\text{AR}} = \frac{0.3590Z_{\text{eff}}}{r^2} + 0.744 \quad (1.1)$$

where r is the covalent radius in Å. This definition is based on the concept of nuclear screening described above. Another definition of electronegativity is based explicitly on the relation between the number of valence shell electrons, n , and the effective atomic radius r :⁷

$$V = n/r \quad (1.2)$$

As we will see shortly, covalent and atomic radii are not absolutely measurable quantities and require definition.

Mulliken found that there is a relationship between *ionization potential* (IP) and *electron affinity* (EA) and defined electronegativity χ as the average of those terms:⁸

$$\chi_{\text{abs}} = \frac{\text{IP} + \text{EA}}{2} \quad (1.3)$$

This formulation, which turns out to have a theoretical justification in density functional theory, is sometimes referred to as *absolute electronegativity* and is expressed in units of eV.

A more recent formulation of electronegativity, derived from the basic principles of atomic structure, has led to a *spectroscopic scale for electronegativity*.⁹ In this formulation, the electronegativity is defined as the average energy of a valence electron in an atom. The lower the average energy, the greater the electron-attracting power (electronegativity) of the atom. The formulation is

$$\chi_{\text{spec}} = \frac{(a\text{IP}_s + b\text{IP}_p)}{a + b} \quad (1.4)$$

⁶ A. L. Allred and E. G. Rochow, *J. Inorg. Nucl. Chem.*, **5**, 264 (1958).

⁷ Y.-R. Luo and S. W. Benson, *Acc. Chem. Res.*, **25**, 375 (1992).

⁸ R. S. Mulliken, *J. Chem. Phys.*, **2**, 782 (1934); R. S. Mulliken, *J. Chem. Phys.*, **3**, 573 (1935).

⁹ L. C. Allen, *J. Am. Chem. Soc.*, **111**, 9003 (1989); L. C. Allen, *Int. J. Quantum Chem.*, **49**, 253 (1994); J. B. Mann, T. L. Meek, and L. C. Allen, *J. Am. Chem. Soc.*, **122**, 2780 (2000).

where IP_s and IP_p are the ionization potentials of the s and p electrons and a and b are the number of s and p electrons, respectively.

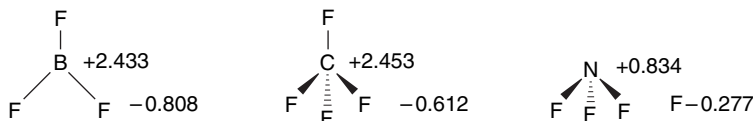
The values on this scale correlate well with the Pauling and Allred-Rochow scales. One feature of this scale is that the IP values can be measured accurately so that electronegativity becomes an *experimentally measured* quantity. When the same concepts are applied to atoms in molecules, the atom undergoes an electronegativity adjustment that can be related to the energy of its orbitals (as expressed by molecular orbital theory). The average adjusted energy of an electron is called the *energy index* (EI). The EI values of two bound atoms provide a measure of bond polarity called the *bond polarity index*¹⁰ (BPI), formulated as

$$BPI_{AB} = (EI_A - EI_A^{\text{ref}}) - (EI_B - EI_B^{\text{ref}}) \quad (1.5)$$

where EI^{ref} are parameters of A–A and B–B bonds.

These approaches, along with several others, give electronegativity scales that are in good relative agreement in assessing the electron-attracting power of the elements. Each scale is based on fundamental atomic properties. However, they are in different units and therefore not directly comparable. Table 1.1 gives the values assigned by some of the electronegativity scales. The numerical values are scaled to the original Pauling range. At this point, we wish to emphasize the broad consistency of the values, not the differences. We use the *order of the electronegativity of the elements* in a qualitative way, primarily when discussing *bond polarity*. It should be noted, however, that the concept of electronegativity has evolved from an empirical scale to one with specific physical meaning. We pursue the relationship between these scales further in Topic 1.5.3.

The most obvious consequence of differential electronegativity is that covalent bonds between different elements are *polar*. Each atom bears a partial charge reflecting the relative electronegativity of the two elements sharing the bond. These charges can be estimated, and the values found for BF_3 , CF_4 , and NF_3 are shown below.¹¹ Note that the negative charge on fluorine becomes smaller as the electronegativity of the central atom increases.



The individual polar bonds contribute to the polarity of the overall molecule. The overall molecular polarity is expressed as the dipole moment. For the three molecules shown, the overall molecular dipole moment is 0 for BF_3 (planar) and CF_4 (tetrahedral), because of the symmetry of the molecules, but NF_3 has a dipole moment of 0.235 D, since the molecule is pyramidal.¹²

¹⁰ L. C. Allen, D. A. Egolf, E. T. Knight, and C. Liang, *J. Phys. Chem.*, **94**, 5603 (1990); L. C. Allen, *Can. J. Chem.*, **70**, 631 (1992).

¹¹ R. J. Gillespie and P. L. A. Popelier, *Chemical Bonding and Molecular Geometry*, Oxford University Press, New York, 2001, p. 47.

¹² Dipole moments are frequently expressed in Debye (D) units; $1\text{ D} = 3.335641 \times 10^{-30}\text{ C m}$ in SI units.

Table 1.1. Electronegativity Scales^a

Atom	Original Pauling ^b	Modified Pauling ^c	Allred-Rochow ^d	Luo-Benson ^e	Mulliken ^f	Allen ^g
H	2.1	2.20	2.20		2.17	2.30
Li	1.0	0.98	0.97	0.93	0.91	0.91
Be	1.5	1.57	1.47	1.39	1.45	1.58
B	2.0	2.04	2.01	1.93	1.88	2.05
C	2.5	2.55	2.50	2.45	2.45	2.54
N	3.0	3.04	3.07	2.96	2.93	3.07
O	3.5	3.44	3.50	3.45	3.61	3.61
F	4.0	3.98	4.10	4.07	4.14	4.19
Na	0.9	0.93	1.01	0.90	0.86	0.87
Mg	1.2	1.31	1.23	1.20	1.21	1.29
Al	1.5	1.61	1.47	1.50	1.62	1.61
Si	1.8	1.90	1.74	1.84	2.12	1.92
P	2.1	2.19	2.06	2.23	2.46	2.25
S	2.5	2.58	2.44	2.65	2.64	2.59
Cl	3.0	3.16	2.83	3.09	3.05	2.87
Ge	1.8	2.01	2.02	1.79	2.14	1.99
As	2.0	2.18	2.20	2.11	2.25	2.21
Se	2.4	2.55	2.48	2.43	2.46	2.42
Br	2.8	2.96	2.74	2.77	2.83	2.69
Sn	1.8	1.96	1.72	1.64	2.12	1.82
I	2.5	2.66	2.21	2.47	2.57	2.36

a. All numerical values are scaled to the original Pauling scale.

b. L. Pauling, *The Nature of the Chemical Bond*, 3rd Edition, Cornell University Press, Ithaca, NY, 1960.

c. A. L. Allred, *J. Inorg. Nucl. Chem.*, **17**, 215 (1961).

d. A. L. Allred and E.G. Rochow, *J. Inorg. Nucl. Chem.*, **5**, 264 (1958).

e. Y. R. Luo and S.W. Benson, *Acc. Chem. Res.*, **25**, 375 (1992).

f. D. Bergman and J. Hinze, *Angew. Chem. Int. Ed. Engl.*, **35**, 150 (1996).

g. L. C. Allen, *Int. J. Quantum Chem.*, **49**, 253 (1994).

1.1.4. Electronegativity Equalization

The concept of *electronegativity equalization* was introduced by R. T. Sanderson.¹³ The idea is implicit in the concept of a molecule as consisting of nuclei embedded in an electronic cloud and leads to the conclusion that the electron density will reach an equilibrium state in which there is no net force on the electrons. The idea of electronegativity equalization finds a theoretical foundation in *density functional theory* (see Section 1.3). Several numerical schemes have been developed for the assignment of charges based on the idea that electronegativity equalization must be achieved. Sanderson's initial approach averaged all atoms of a single element, e.g., carbon, in a molecule and did not distinguish among them. This limitation was addressed by Hercules and co-workers,¹⁴ who assigned electronegativity values called SR' values to specific groups within a molecule. For example, the methyl and ethyl groups, respectively, were derived from the number of C and H atoms in the group:

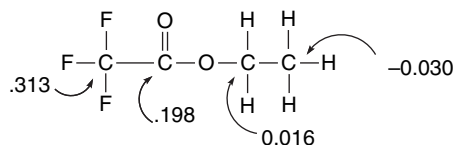
$$SR'_{CH_3} = (SR_C \times SR_H^3)^{1/4} \quad (1.6)$$

$$SR'_{C_2H_5} = [(SR_C \times SR_H^2)(SR_C \times SR_H^3)^{1/4}]^{1/4} \quad (1.7)$$

¹³. R. T. Sanderson, *Chemical Bonds and Bond Energies*, Academic Press, New York, 1976;
R. T. Sanderson, *Polar Covalence*, Academic Press, New York, 1983.

¹⁴. J. C. Carver, R. C. Gray, and D. M. Hercules, *J. Am. Chem. Soc.*, **96**, 6851 (1974).

This approach was extended by M. Sastry to a variety of organic compounds.¹⁵ For example, the charges calculated for the carbon atoms in $\text{CF}_3\text{CO}_2\text{C}_2\text{H}_5$ are as shown below. We see that the carbon of the methyl group carries a small negative charge, whereas the carbons bound to more electronegative elements are positive.



The calculated charge on carbon for a number of organic molecules showed good correlation with the core atomic binding energies, as measured by X-ray photoemission spectroscopy. We discuss other methods of assigning charges to atoms based on computational chemistry in Section 1.4. We also find that all these methods are in some sense arbitrary divisions of molecules. The concept of electronegativity equalization is important, however. It tells us that electron density shifts in response to bonding between atoms of different electronegativity. This is the basis of *polar substituent effects*. Furthermore, as the data above for ethyl trifluoroacetate suggest, a highly electronegative substituent induces a net positive charge on carbon, as in the CF_3 and $\text{C}=\text{O}$ carbons in ethyl trifluoroacetate. Electronegativity differences are the origin of *polar bonds*, but electronegativity equalization suggests that there will also be an *inductive effect*, that is, the propagation of changes in electron distribution to adjacent atoms.

1.1.5. Differential Electronegativity of Carbon Atoms

Although carbon is assigned a single numerical value in the Pauling electronegativity scale, its effective electronegativity depends on its hybridization. The qualitative relationship is that carbon electronegativity toward other bound atoms increases with the extent of s character in the bond, i.e., $sp^3 < sp^2 < sp$. Based on the atomic radii approach, the carbon atoms in methane, benzene, ethene, and ethyne have electronegativity in the ratio 1:1.08:1.15:1.28. A scale based on bond polarity measures gives values of 2.14, 2.34, and 2.52 for sp^3 , sp^2 , and sp carbons, respectively.¹⁶ A scale based on NMR coupling constants gives values of 1.07 for methyl, 1.61 for ethenyl, and 3.37 for ethynyl.¹⁷ If we use the density functional theory definition of electronegativity (see Topic 1.5.1) the values assigned to methyl, ethyl, ethenyl, and ethynyl are 5.12, 4.42, 5.18, and 8.21, respectively.¹⁸ Note that by this measure methyl is significantly more electronegative than ethyl. With an *atoms in molecules* approach (see Section 1.4.3), the numbers assigned are methyl 6.84; ethenyl 7.10, and ethynyl 8.23.¹⁹ Table 1.2 converts each of these scales to a relative scale with methyl equal to 1. Note that the various definitions *do not* reach a numerical consensus on the relative electronegativity of sp^3 , sp^2 , and sp carbon, although the order is consistent. We are

¹⁵ M. Sastry, *J. Electron Spectros.*, **85**, 167 (1997).

¹⁶ N. Inamoto and S. Masuda, *Chem. Lett.*, 1003, 1007 (1982).

¹⁷ S. Marriott, W. F. Reynolds, R. W. Taft, and R. D. Topsom, *J. Org. Chem.*, **49**, 959 (1984).

¹⁸ F. De Proft, W. Langenaeker, and P. Geerlings, *J. Phys. Chem.*, **97**, 1826, (1995).

¹⁹ S. Hati and D. Datta, *J. Comput. Chem.*, **13**, 912 (1992).

Table 1.2. Ratio of Electronegativity for Carbon of Different Hybridization

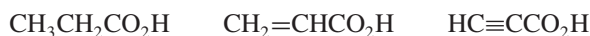
Comparison	Methyl	Ethenyl	Ethynyl
Atomic radii	1.0	1.15	1.28
Bond polarity	1.0	1.09	1.18
NMR coupling	1.0	1.50	3.15
Density function theory	1.0	1.01	1.60
Atoms in molecules	1.0	1.04	1.20

SECTION 1.1

Description of Molecular
Structure Using Valence
Bond Concepts

not so concerned with the precise number, but rather with the trend of increasing electronegativity $sp^3 < sp^2 < sp$. It is also important to note that the range of carbon electronegativities is close to that of hydrogen. While sp^3 carbon and hydrogen are similar in electronegativity, sp^2 and sp carbon are more electronegative than hydrogen.

If we compare the pK_a values of propanoic acid (4.87), propenoic acid (4.25), and propynoic acid (1.84), we get some indication that the hybridization of carbon does exert a substantial polar effect. The acidity increases with the electronegativity of the carbon group.



Orbitals of different hybridization on the same carbon are also thought of as having different electronegativities. For example, in strained hydrocarbons such as cyclopropane the C–H bonds are more acidic than normal. This is attributed to the additional s character of the C–H bonds, which compensates for the added p character of the strained C–C bonds.²⁰

It is also possible to assign electronegativity values to groups. For alkyl groups the numbers are: CH_3 , 2.52; C_2H_5 , 2.46; $(\text{CH}_3)_2\text{CH}$, 2.41; $(\text{CH}_3)_3\text{C}$, 2.38; C_6H_5 , 2.55, $\text{CH}_2=\text{CH}$, 2.55; $\text{HC}\equiv\text{C}$, 2.79.²¹ The order is in accord with the general trend that *more-substituted alkyl groups are slightly better electron donors than methyl groups*. The increased electronegativity of sp^2 and sp carbons is also evident. These values are based on bond energy data by a relationship first explored by Pauling and subsequently developed by many other investigators. The original Pauling expression is

$$D[A-B] = 1/2(D[A-A] + D[B-B]) + 23(\Delta\chi)^2 \quad (1.8)$$

where $\Delta\chi$ is the difference in electronegativity of A and B.

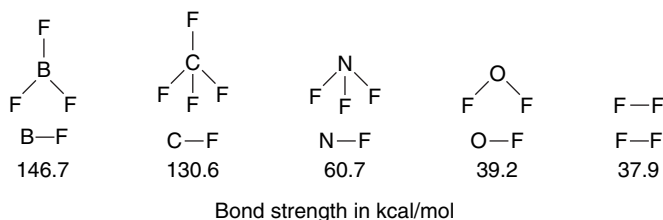
Thus the bond strength (in kcal/mol) can be approximated as the average of the two corresponding homonuclear bonds and an increment that increases with the difference in electronegativity. For any bond, application of this equation suggests a “covalent” and “polar” term. The results for the series CH_3F , CH_3OH , CH_3NH_2 , and CH_3CH_3 is shown below.

²⁰. J. N. Shoolery, *J. Chem. Phys.*, **31**, 1427 (1959); N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 1471 (1959); K. B. Wiberg, R. F. W. Bader, and C. D. H. Lau, *J. Am. Chem. Soc.*, **109**, 1001 (1987).

²¹. N. Matsunaga, D. W. Rogers, and A. A. Zavitsas, *J. Org., Chem.*, **68**, 3158 (2003).

	D(A – A)	χ	$(\Delta\chi)^2$	Covalent	Polar	% Covalent	% Polar
CH ₃	89.8	2.525					
–F	38.0	3.938	1.189	63.90	27.35	70	30
–OH	56.1	3.500	0.987	72.95	22.70	76	24
–NH ₂	61.1	3.071	0.749	75.45	17.23	81	19
–CH ₃	89.8	2.525	0.000	89.8	0.0	100	0

An important qualitative result emerges from these numbers. *Bond strength is increased by electronegativity differences.* This is illustrated, for example, by the strength of the bonds of fluorine with the other second-row elements.



1.1.6. Polarizability, Hardness, and Softness

The interaction of valence shell electrons with the nucleus and intervening filled shells also affects the *polarizability* of the valence shell electrons. Polarizability can be described in terms of *hardness* and *softness*. A relatively large atom or ion with a small effective nuclear charge is relatively easily distorted (polarized) by an external charge and is called *soft*. A more compact electron distribution resulting from a higher net nuclear charge and less effective screening is called *hard*. The hard-soft-acid-base (HSAB) theory of stability and reactivity, introduced by Pearson,²² has been extensively applied to qualitative reactivity trends,²³ and has been theoretically justified.²⁴ The qualitative expression of HSAB is that hard-hard and soft-soft reaction partners are preferred to hard-soft combinations. As for electronegativity, numerical scales of hardness and softness have been devised. One definition, like the Mulliken definition of absolute electronegativity, is based on ionization potential and electron affinity:

$$\text{Hardness} = \eta = \frac{1}{2}(\text{IP} - \text{EA}) \quad \text{and} \quad \text{Softness} = \sigma = 1/\eta \sim 2(\text{IP} - \text{EA}) \quad (1.9)$$

Hardness increases with electronegativity and with positive charge. Thus, for the halogens the order is $\text{F}^- > \text{Cl}^- > \text{Br}^- > \text{I}^-$, and for second-row anions, $\text{F}^- > \text{HO}^- > \text{H}_2\text{N}^- > \text{H}_3\text{C}^-$. For cations, hardness decreases with size and increases with positive charge, so that $\text{H}^+ > \text{Li}^+ > \text{Na}^+ > \text{K}^+$. The proton, lacking any electrons, is infinitely hard. In solution it does not exist as an independent entity but contributes to the hardness of some protonated species. Metal ion hardness increases with oxidation state as the electron cloud contracts with the removal of each successive electron. All these as

²² R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967); R. G. Pearson, *J. Chem. Educ.*, **45**, 581, 643 (1968).

²³ R. G. Pearson, *Inorg. Chim. Acta*, **240**, 93 (1995).

²⁴ P. K. Chattaraj, H. Lee, and R. G. Parr, *J. Am. Chem. Soc.*, **113**, 1855 (1991).

well as other hardness/softness relationships are consistent with the idea that hardness and softness are manifestations of the influence of nuclear charge on polarizability.

For polyatomic molecules and ions, hardness and softness are closely related to the HOMO and LUMO energies, which are analogous to the IP and EA values for atoms. The larger the HOMO-LUMO gap, the greater the hardness. Numerically, hardness is approximately equal to half the energy gap, as defined above for atoms. In general, chemical reactivity increases as LUMO energies are lower and HOMO energies are higher. The implication is that softer chemical species, those with smaller HOMO-LUMO gaps, tend to be more reactive than harder ones. In qualitative terms, this can be described as the ability of nucleophiles or bases to donate electrons more readily to electrophiles or acids and begin the process of bond formation. Interactions between harder chemical entities are more likely to be dominated by electrostatic interactions. Table 1.3 gives hardness values for some atoms and small molecules and ions. Note some of the trends for cations and anions. The smaller Li^+ , Mg^{2+} , and Na^+ ions are harder than the heavier ions such as Cu^+ , Hg^{2+} , and Pd^{2+} . The hydride ion is quite hard, second only to fluoride. The increasing hardness in the series $\text{CH}_3^- < \text{NH}_2^- < \text{OH}^- < \text{F}^-$ is of considerable importance and, in particular, correlates with nucleophilicity, which is in the order $\text{CH}_3^- > \text{NH}_2^- > \text{OH}^- > \text{F}^-$.

Figure 1.3 shows the IP-EA gap (2η) for several neutral atoms and radicals. Note that there is a correlation with electronegativity and position in the periodic table. The halogen anions and radicals become progressively softer from fluorine to iodine. Across the second row, softness decreases from carbon to fluorine. The cyanide ion is a relatively soft species.

The HSAB theory provides a useful precept for understanding Lewis acid-base interactions in that hard acids prefer hard bases and soft acids prefer soft bases. The principle can be applied to chemical equilibria in the form of the *principle of maximum hardness*,²⁵ which states that “molecules arrange themselves so as to

Table 1.3. Hardness of Some Atoms, Acids, and Bases^a

Atom	η	Cations	η	Anions	η
H	6.4	H^+		H^-	6.8
Li	2.4	Li^+	35.1	F^-	7.0
C	5.0	Mg^{2+}	32.5	Cl^-	4.7
N	7.3	Na^+	21.1	Br^-	4.2
O	6.1	Ca^{2+}	19.7	I^-	3.7
F	7.0	Al^{3+}	45.8	CH_3^-	4.0
Na	2.3	Cu^+	6.3	NH_2^-	5.3
Si	3.4	Cu^{2+}	8.3	OH^-	5.6
P	4.9	Fe^{2+}	7.3	SH^-	4.1
S	4.1	Fe^{3+}	13.1	CN^-	5.3
Cl	4.7	Hg^{2+}	7.7		
		Pb^{2+}	8.5		
		Pd^{2+}	6.8		

a. From R. G. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, **105**, 7512 (1983).

²⁵ R. G. Pearson, *Acc. Chem. Res.*, **26**, 250 (1993); R. G. Parr and Z. Zhou, *Acc. Chem. Res.*, **26**, 256 (1993); R. G. Pearson, *J. Org. Chem.*, **54**, 1423 (1989); R. G. Parr and J. L. Gazquez, *J. Phys. Chem.*, **97**, 3939 (1993).

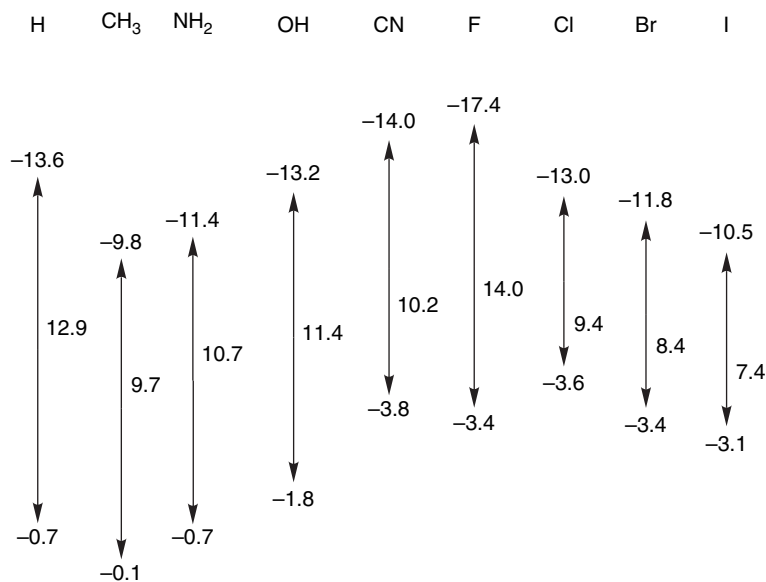
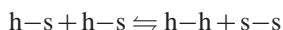


Fig. 1.3. Ionization (IP) and electron affinity (EA) gaps in eV for neutral atoms and radicals. Adapted from R. G. Pearson, *J. Am. Chem. Soc.*, **110**, 7684 (1988).

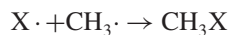
be as hard as possible.” Expressed in terms of reaction energetics, ΔE is usually negative for



The hard-hard interactions are dominated by electrostatic attraction, whereas soft-soft interactions are dominated by mutual polarization.²⁶ Electronegativity and hardness determine the extent of electron transfer between two molecular fragments in a reaction. This can be approximated numerically by the expression

$$\Delta N = \frac{\chi_x - \chi_y}{2(\eta_x + \eta_y)} \quad (1.10)$$

where χ is absolute electronegativity and η is hardness for the reacting species. For example, we can calculate the degree of electron transfer for each of the four halogen atoms reacting with the methyl radical to form the corresponding methyl halide.



$X \cdot$	χ_x	η_x	ΔN	$\eta_{\text{CH}_3\text{X}}$
$\text{F} \cdot$	10.4	7.0	0.23	9.4
$\text{Cl} \cdot$	8.3	4.7	0.17	7.5
$\text{Br} \cdot$	7.6	4.2	0.14	5.8
$\text{I} \cdot$	6.8	3.7	0.10	4.7

²⁶ R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); T. L. Ho, *Hard and Soft Acids and Bases in Organic Chemistry*, Academic Press, New York, 1977; W. B. Jensen, *The Lewis Acid-Base Concept*, Wiley-Interscience, New York, 1980, Chap. 8.

According to this analysis, the C–X bond is successively both more polar and harder in the order $I < Br < Cl < F$. This result is in agreement with both the properties and reactivities of the methyl halides. When bonds are compared, reacting pairs of greater hardness result in a larger net charge transfer, which adds an increment to the exothermicity of bond formation. That is, bonds formed between two hard atoms or groups are stronger than those between two soft atoms or groups.²⁷ This is an example of a general relationship that recognizes that there is an increment to bond strength resulting from added ionic character.²⁸

Polarizability measures the response of an ion or molecule to an electric field and is expressed in units of volume, typically 10^{-24} cm^3 or $\text{\AA}^3$. Polarizability increases with atomic or ionic radius; it depends on the effectiveness of nuclear screening and increases as each valence shell is filled. Table 1.4 gives the polarizability values for the second-row atoms and some ions, molecules, and hydrocarbons. Methane is the least polarizable hydrocarbon and polarity increases with size. Polarizability is also affected by hybridization, with ethane > ethene > ethyne and propane > propene > propyne.

It should be noted that polarizability is *directional*, as illustrated in Scheme 1.2 for the methyl halides and halogenated benzenes.

Polarizability is related to the *refractive index* (n) of organic molecules, which was one of the first physical properties to be carefully studied and related to molecular structure.²⁹ As early as the 1880s, it was recognized that the value of the refractive index can be calculated as the sum of atomic components. Values for various groups were established and revised.³⁰ It was noted that some compounds, in particular compounds with conjugated bonds, had higher (“exalted”) polarizability. Polarizability is also directly related to the dipole moment *induced by an electric field*. The greater the polarizability of a molecule, the larger the induced dipole.

Table 1.4. Polarizability of Some Atoms, Ions, and Molecules^a

Atoms		Ions		Molecules		Hydrocarbons	
H	0.67			H ₂ O	1.45	CH ₄	2.59
Li	24.3			N ₂	1.74	C ₂ H ₆	4.47
Be	5.6			CO	1.95	CH ₂ =CH ₂	4.25
B	3.0			NH ₃	2.81	HC≡CH	3.93
C	1.8			CO ₂	2.91	C ₃ H ₈	6.29
N	1.1			BF ₃	3.31	CH ₃ CH=CH ₂	6.26
O	0.8					CH ₃ C≡CH	6.18
F	0.06	F [−]	1.2			<i>n</i> -C ₄ H ₁₀	8.20
Ne	1.4	Na ⁺	0.9			<i>i</i> -C ₄ H ₁₀	8.14
Cl	2.2	Cl [−]	3			<i>n</i> -C ₅ H ₁₂	9.99
Ar	3.6	K ⁺	2.3			Neopentane	10.20
Br	3.1	Br [−]	4.5			<i>n</i> -C ₆ H ₁₄	11.9
Kr	4.8					Cyclohexane	10.9
I	5.3	I [−]	7			C ₆ H ₆	10.3
Xe	6.9						

a. T. M. Miller, in *Handbook of Chemistry and Physics*, 83rd Edition, pp. 10-163–10-177, 2002.

b. A. Dalgarno, *Adv. Phys. Org. Chem.*, **11**, 281 (1962), as quoted by R. J. W. Le Fevre, *Adv. Phys. Org. Chem.*, **3**, 1 (1965).

²⁷. P. K. Chattaraj, A. Cedillo, R. G. Parr, and E.M. Arnett, *J. Org. Chem.*, **60**, 4707 (1995).

²⁸. P. R. Reddy, T. V. R. Rao, and R. Viswanath, *J. Am. Chem. Soc.*, **111**, 2914 (1989).

²⁹. R. J. W. Le Fevre, *Adv. Phys. Org. Chem.*, **3**, 1 (1965).

³⁰. K. von Auwers, *Chem. Ber.*, **68**, 1635 (1935); A. I. Vogel, *J. Chem. Soc.*, 1842 (1948); J. W. Brühl, *Liebigs Ann.Chem.*, **235**, 1 (1986); J. W. Brühl, *Liebigs Ann.Chem.*, **236**, 233 (1986).

Scheme 1.2. Molecular Polarizability^a

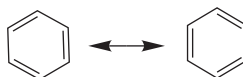
x		1.026	.411	.499	.657
y		1.026	.411	.499	.657
z		1.026	.509	.656	.872
x		1.12	1.255	1.301	1.588
y		.736	.821	.892	.996
z		1.12	1.478	1.683	1.971

a. From R J. W. Le Fevre, *Adv. Phys. Org. Chem.*, **3**, 1 (1965).

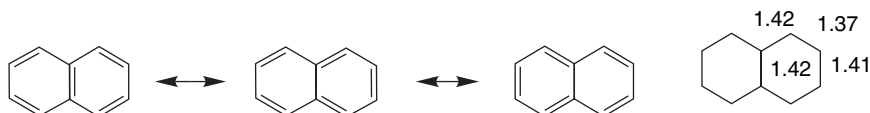
The concepts of electronegativity, polarizability, hardness, and softness are all interrelated. For the kind of qualitative applications we make in discussing reactivity, the concept that initial interactions between reacting molecules can be dominated by either partial electron transfer and bond formation (soft reactants) or by electrostatic interaction (hard reactants) is an important generalization.

1.1.7. Resonance and Conjugation

Qualitative application of VB theory makes use of the concept of *resonance* to relate structural formulas to the description of molecular structure and electron distribution. The case of benzene is a familiar and striking example. Two equivalent Lewis structures can be drawn, but the actual structure is the average of these two *resonance structures*. The double-headed arrow is used to specify a resonance relationship.



What structural information does this symbolism convey? Resonance structures imply that the true molecular structure is a weighted average of the individual structures. In the case of benzene, since the two structures are equivalent, each contributes equally. The *resonance hybrid* structure for benzene indicates hexagonal geometry and that the bond lengths are intermediate between a double and a single bond, since a bond order of 1.5 results from the average of the two structures. The actual structure of benzene is in accord with these expectations. It is perfectly hexagonal in shape and the carbon-carbon bond length is 1.40 Å. On the other hand, naphthalene, with three neutral resonance structures, shows bond length variation in accord with the predicted 1.67 and 1.33 bond orders.



Another important property of benzene is its thermodynamic stability, which is greater than expected for either of the two resonance structures. It is much more stable than noncyclic polyenes of similar structure, such as 1,3,5-hexatriene. What is the origin of this additional stability, which is often called *resonance stabilization* or *resonance energy*? The resonance structures imply that the π electron density in benzene is equally distributed between the sets of adjacent carbon atoms. This is not the case in acyclic polyenes. The electrons are evenly spread over the benzene ring, but in the polyene they are more concentrated between alternating pairs of carbon atoms. Average electron-electron repulsion is reduced in benzene. The difference in energy is called the *delocalization energy*. The resonance structures for benzene describe a particularly favorable bonding arrangement that leads to greater thermodynamic stability. In keeping with our emphasis on structural theory as a means of describing molecular properties, resonance *describes, but does not cause*, the extra stability.

Figure 1.4 shows electron density contours for benzene and 1,3,5-hexatriene. Note that the contours show completely uniform electron density distribution in benzene, but significant concentration between atoms 1,2; 3,4; and 5,6 in hexatriene, as was argued qualitatively above.

Resonance is a very useful concept and can be applied to many other molecules. Resonance is associated with delocalization of electrons and is a feature of *conjugated systems*, which have alternating double bonds that permit overlap between adjacent π bonds. This permits delocalization of electron density and usually leads to stabilization of the molecule. We will give some additional examples shortly.

We can summarize the applicability of the concept of resonance as follows:

1. When alternative Lewis structures can be written for a molecule and they differ only in the assignment of electrons among the nuclei, with nuclear positions being constant, then the molecule is not completely represented by a single Lewis structure, but has weighted properties of all the alternative Lewis structures.
2. Resonance structures are restricted to the maximum number of valence electrons that is appropriate for each atom: two for hydrogen and eight for second-row elements.

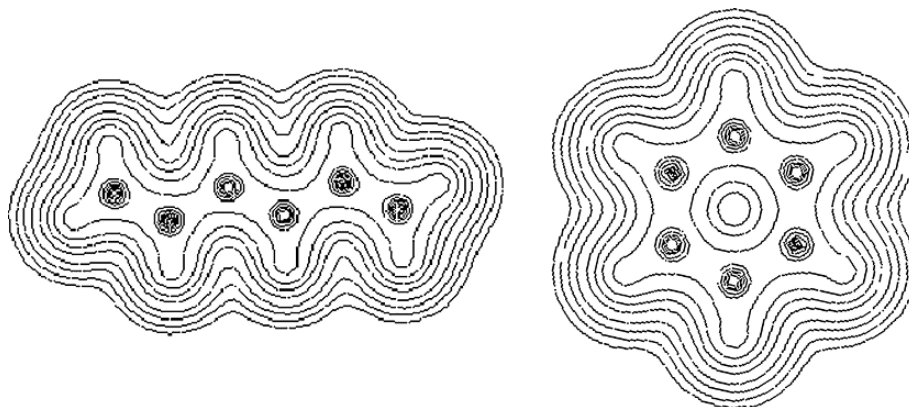
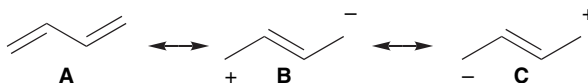


Fig. 1.4. Contour maps of electron density for 1,3,5-hexatriene and benzene in the planes of the molecules. Electron density was calculated at the HF/6-311G level. Electron density plots were created by applying the AIM2000 program; F.Biegler-Koenig, J.Shoenbohm and D.Dayles, *J. Compt. Chem.*, **22**, 545-559 (2001).

3. The more stable Lewis structures make the largest contribution to the weighted composite structure. Structures that have the following features are more stable and make the largest contribution: (a) maximum number of bonds, (b) minimum separation of opposite charges, and (c) charge distribution that is consistent with relative electronegativity.

Resonance structures are used to convey the structural and electron distribution consequences of conjugation and delocalization. Let us look specifically at 1,3-butadiene, 1,3,5-hexatriene, prop-2-enal (acrolein), methoxyethene (methyl vinyl ether), and ethenamine (vinylamine) to illustrate how resonance can help us understand electron distribution and reactivity. The hybridization picture for 1,3-butadiene suggests that there can be overlap of the p orbitals. Thermodynamic analysis (see Section 3.1.2.3) indicates that there is a net stabilization of about 3–4 kcal/mol, relative to two isolated double bonds. The electron density profile in Figure 1.5 shows some enhancement of π -electron density between C(2) and C(3).

Resonance structures portray increased electron density between C(2) and C(3), but only in structures that have fewer bonds and unfavorable charge separation.



In the diagram above there are two identical structures having opposite charge distributions and there is no net separation of charge. The importance of resonance structures to the composite structure increases with the stability of the individual structures, so structures B and C are less important than A, as they have separation of charge and only one rather than two π bonds. By applying resonance criteria 3a and 3b, we conclude that these two structures contribute less stabilization to butadiene than the two equivalent benzene resonance structures. Therefore, we expect the enhancement of electron density between C(2) and C(3) to be small.

For propenal (acrolein), one uncharged and two charged structures analogous to 1,3-butadiene can be drawn. In this case, the two charged structures are not equivalent.

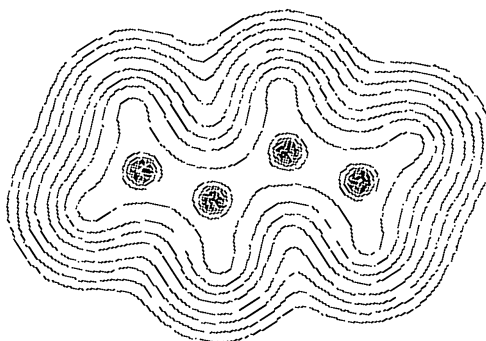
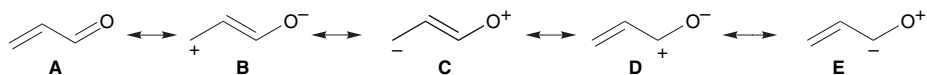
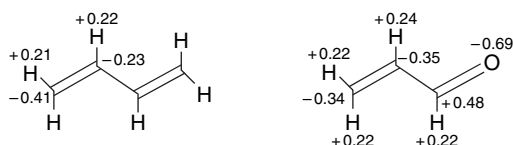


Fig. 1.5. Contour map of electron density for 1,3-butadiene in the plane of the molecule. Electron density was calculated at the HF/6-311G level. Electron density plots were created by applying the AIM2000 program; F.Biegler-Koenig, J.Shoenbohm and D.Dayles, *J. Comput. Chem.*, **22**, 545-559 (2001).

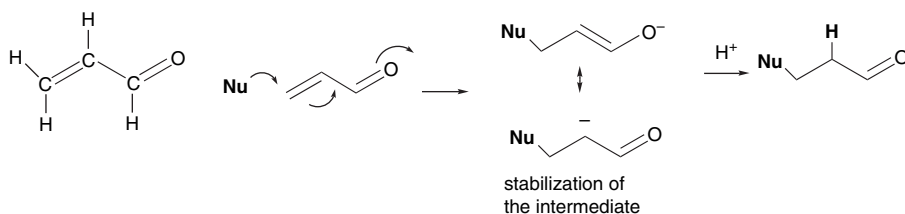
Structure **B** is a better structure than **C** because it places the negative charge on a more electronegative element, oxygen (resonance criteria 3c). Structure **D** accounts for the polarity of the C=O bond. The real molecular structure should then reflect the character of **A** > **B** ~ **D** > **C** ~ **E**. The composite structure can be qualitatively depicted by indicating weak partial bonding between C(1) and C(2) and partial positive charges at C(1) and C(3).



The electronic distributions for butadiene and propenal have been calculated using molecular orbital methods and are shown below.³¹ Butadiene shows significantly greater negative charge at the terminal carbons. In propenal there is a large charge distortion at the carbonyl group and a decrease in the electron density at the terminal carbon C(3).

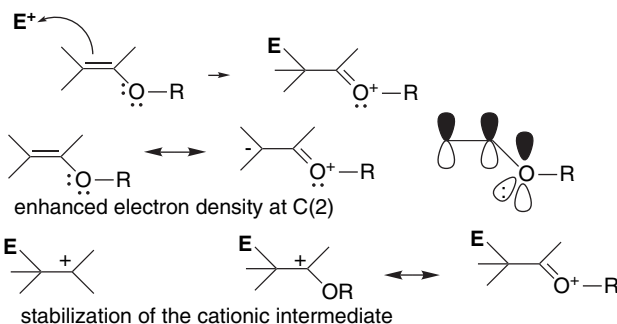


The chemical reactivity of propenal is representative of α, β -unsaturated carbonyl compounds. The conjugation between a carbon-carbon double bond and a carbonyl group leads to characteristic reactivity, which includes reduced reactivity of the carbon-carbon double bond toward electrophiles and enhanced susceptibility to the addition of nucleophilic reagents at the β carbon. The anion formed by addition is a delocalized enolate, with the negative charge shared by oxygen and carbon. The topic of nucleophilic addition to enals and enones is considered further in Section 2.6, Part B.



Methoxyethene (methyl vinyl ether) is the prototype of another important class of compounds, the *vinyl ethers*, which have an alkoxy substituent attached directly to a double bond. Such compounds have important applications in synthesis, and the characteristic reactivity is toward electrophilic attack at the β -carbon.

³¹. M. A. McAllister and T. T. Tidwell, *J. Org. Chem.*, **59**, 4506 (1994).



Why does an alkoxy group enhance reactivity and direct the electrophile to the β position? A resonance structure can be drawn that shows an oxygen unshared pair in conjugation with the double bond. More importantly, the same conjugation strongly stabilizes the cation formed by electrophilic attack. This conjugation provides an additional covalent bond in the intermediate and is strongly stabilizing (resonance criterion 3a). Taking the ethyl cation for comparison, there is a stabilization of nearly 30 kcal, according to PM3 MO semiempirical computations (see Section 1.2.2).³² Stabilization relative to the methyl cation is as follows:

CH_3^+	CH_3CH_2^+	$\text{CH}_3\text{CH}=\text{O}^+\text{R}$	$\text{CH}_3\text{CH}=\text{N}^+\text{H}_2$
0	29.0 kcal/mol	57.6 kcal/mol	80.2 kcal/mol

Vinyl amines (also called enamines) are even more reactive than vinyl ethers toward electrophiles. The qualitative nature of the conjugation is the same as in vinyl ethers, both for the neutral vinyl amine and for the cationic intermediate. However, nitrogen is an even better electron donor than oxygen, so the stabilizing effect is stronger. The stabilization for the cation is calculated to be around 80 kcal/mol relative to the methyl cation.

These molecules, propenal, methoxyethene, and etheneamine, show how we can apply VB theory and resonance to questions of reactivity. We looked at how structure and conjugation affect *electron density* and *bond formation* in both the reactant and the intermediate. When VB theory indicates that the particular disposition of function groups will change the electron distribution relative to an unsubstituted molecule, we can expect to see those differences reflected in altered reactivity. For propenal, the *electron withdrawal* by the formyl group causes decreased reactivity toward electrophiles and increased reactivity toward nucleophiles. For methoxyethene and ethenamine, the *electron release* of the substituents is reflected by increased reactivity toward electrophiles with strong *selectivity* for the β -carbon.

1.1.8. Hyperconjugation

All the examples of resonance cited in the previous section dealt with conjugation through π bonds. VB theory also incorporates the concept of hyperconjugation, which is the idea that there can be electronic interactions between σ and σ^* bonds and between σ and π^* bonds. In alkenes such as propene or 2-methylpropene, the electron-releasing effect of the methyl substituents can be represented by hyperconjugated

³² A. M. El-Nahas and T. Clark, *J. Org. Chem.*, **60**, 8023 (1995).

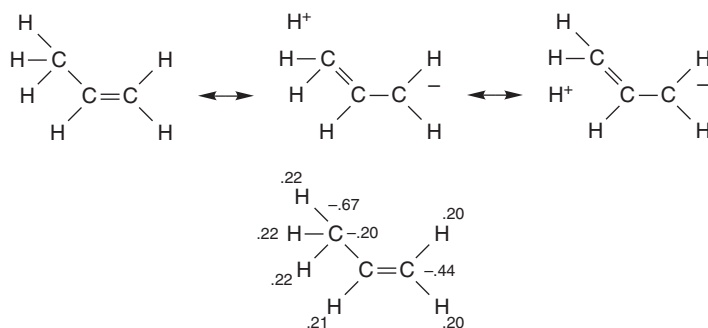
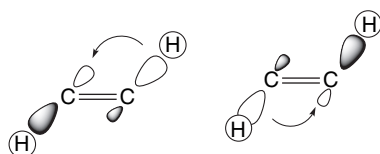


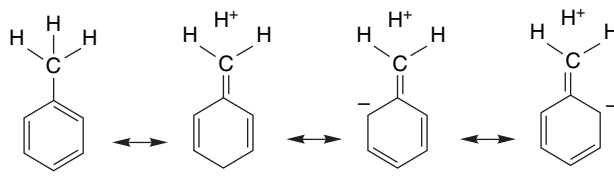
Fig. 1.6. Electron density distribution for propene.

(no-bond) resonance structures. The implication of these resonance structures is that some electron density is transferred from the C–H σ bond to the empty π^* orbital. This is in accord with the calculated electron density distribution for propene shown in Figure 1.6. Carbon-1, which is negatively charged in the resonance structure, has a higher electron density than carbon-2, even though the latter carries the methyl substituent.

There is also hyperconjugation *across* the double bond. Indeed, this interaction may be even stronger because the double bond is shorter than a corresponding single bond, permitting better orbital overlap.³³ Because these resonance structures show equivalent compensating charge transfer, there is no net charge separation, but structural features, such as bond length, and spectroscopic properties are affected.



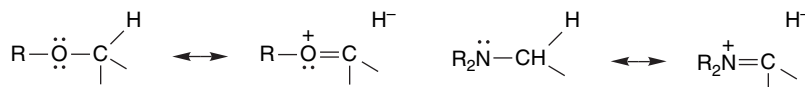
Hyperconjugation also can describe the electron-releasing effect of alkyl groups on aromatic rings.



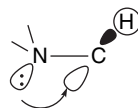
While part of the electron-releasing effect of alkyl groups toward double bonds and aromatic rings can be attributed to the electronegativity difference between sp^3 and sp^2 carbon, the fact that the β -carbon of alkenes and the *ortho* and *para* positions of aromatic rings are selectively affected indicates a resonance component.

³³. I. V. Alabugin and T. A. Zeidan, *J. Am. Chem. Soc.*, **124**, 3175 (2002).

Heteroatoms with unshared electron pairs can also interact with adjacent σ^* bonds. For example, oxygen and nitrogen substituents substantially weaken an adjacent (geminal) C–H bond.



This interaction is readily apparent in spectroscopic properties of amines. The C–H bond that is antiperiplanar to a nitrogen unshared electron pair is lengthened and weakened.³⁴ Absorptions for C–H bonds that are *anti* to nitrogen nonbonded pairs are shifted in both IR and NMR spectra. The C–H vibration is at higher frequency (lower bond energy) and the ^1H signal is at higher field (increased electron density), as implied by the resonance structures. There is a *stereoelectronic* component in hyperconjugation. The optimal alignment is for the σ C–H bond that donates electrons to be aligned with the σ^* orbital. The heteroatom bond-weakening effect is at a maximum when the electron pair is antiperiplanar to the C–H bond, since this is the optimal alignment for the overlap of the n and σ^* orbitals (see Topic 1.2 for further discussion).



Population of σ^* orbital
weakens anti C–H bond

1.1.9. Covalent and van der Waals Radii of Atoms

Covalent and van der Waals radii are other fundamental properties of atoms in molecules that are influenced by nuclear charge and electron distribution. A glance at a molecular model or graphic suggests that most atoms have several different dimensions. There is the distance between each bound atom and also a dimension in any direction in which the atom is not bonded to another atom. The former distance, divided between the two bonded atoms, is called the *covalent radius*. The nonbonded dimension of an atom or group in a molecule is called the *van der Waals radius*. This is the distance at which nonbonded atoms begin to experience mutual repulsion. Just short of this distance, the interatomic forces are weakly attractive and are referred to as *dispersion* or *London* forces and are attributed to mutual *polarization* of atoms.

There are several definitions and values assigned to covalent radii. Pauling created an early scale using bond lengths in simple homonuclear compounds as the starting point. An extended version of this scale is listed as “covalent” in Table 1.5. A related, but more comprehensive, approach is to examine structural data to determine covalent radii that best correlate with observed bond distances. This approach was developed by Slater.³⁵ An extensive tabulation of bond lengths derived from structural data was published in 1987.³⁶ These values are labeled “structural” in Table 1.5. A set of

³⁴ A. Pross, L. Radom, and N. V. Riggs, *J. Am. Chem. Soc.*, **102**, 2253 (1980).

³⁵ J. C. Slater, *J. Chem. Phys.*, **39**, 3199 (1964); J. C. Slater, *Quantum Theory of Molecules and Solids*, McGraw-Hill, New York, 1965, Vol. 2.

³⁶ F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Opren and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, Supplement S1–S19 (1987).

Table 1.5. Covalent Radii in Å

	Covalent ^a	Structural ^b	Alcock ^c	Carbon ^d
H	0.37	0.25	0.30	0.327
Li	1.34	1.45		1.219
Be	0.90	1.05	1.06	0.911
B	0.82	0.85	0.83	0.793
C (sp^3)	0.77	0.70	0.77	0.766
C (sp^2)	0.67			
C (sp)	0.60			
N	0.75	0.65	0.70	0.699
O	0.73	0.60	0.66	0.658
F	0.71	0.50	0.62	0.633
Al	1.18	1.25	1.18	1.199
Si	1.11	1.10	1.09	1.123
P	1.06	1.00	1.09	1.110
S	1.02	1.00	1.05	1.071
Cl	0.99	1.00	1.02	1.039
Se	1.19	1.15	1.20	1.201
Br	1.14	1.15	1.20	1.201
I	1.33	1.4	1.40	1.397

a. L. E. Sutton, ed., *Tables of Interatomic Distances and Configuration in Molecules and Ions*, Suppl., 1956–1959, Chemical Society Special Publication No. 18, 1965.

b. J. C. Slater, *J. Chem. Phys.*, **39**, 3199 (1964).

c. N. W. Alcock, *Bonding and Structure*, Ellis Horwood, Chichester, 1990.

d. C. H. Suresh and N. Koga, *J. Phys. Chem. A*, **105**, 5940 (2001).

SECTION 1.1
Description of Molecular
Structure Using Valence
Bond Concepts

numbers that may be particularly appropriate for organic compounds was introduced by Alcock, who examined carbon compounds and subtracted the carbon covalent radii to obtain the covalent radii of the bound atoms.³⁷ This definition was subsequently applied to a larger number of compounds using computational bond length data.³⁸ These values are listed as “carbon” in Table 1.5. The covalent radii given for sp^3 , sp^2 , and sp carbon are half of the corresponding C–C bond lengths of 1.55, 1.34, and 1.20 Å. Note that the covalent radii shorten somewhat going to the right in the periodic table. This trend reflects the greater nuclear charge and the harder character of the atoms on the right and is caused by the same electronic shielding effect that leads to decreased polarizability, as discussed in Section 1.1.6. Covalent radii, of course, increase going down the periodic table.

Van der Waals radii also require definition. There is no point at which an atom ends; rather the electron density simply decreases to an infinitesimal value as the distance from the nucleus increases. There are several approaches to assigning van der Waals radii. A set of numbers originally suggested by Pauling was refined and extended by Bondi.³⁹ These values were developed from nonbonded contacts in crystal structures and other experimental measures of minimum intermolecular contact. A new set of data of this type, derived from a much larger structural database, was compiled somewhat more recently.⁴⁰ The latter values were derived from a search of nearly 30,000 crystal structures. Table 1.6 gives both sets of radii.

³⁷. N. W. Alcock, *Bonding and Structure*, Ellis Horwood, Chichester, 1990.

³⁸. C. H. Suresh and N. Koga, *J. Phys. Chem. A*, **105**, 5940 (2001).

³⁹. A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).

⁴⁰. R. S. Rowland and R. Taylor, *J. Phys. Chem.*, **100**, 7384 (1996).

Table 1.6. Van der Waals Radii in Å

	Bondi ^a	Structural ^b
H	1.20	1.09
C	1.70	1.75
N	1.55	1.61
O	1.52	1.56
F	1.47	1.44
S	1.80	1.79
Cl	1.75	1.74
Br	1.85	1.85
I	1.98	2.00

a. A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).b. R. S. Rowland and R. Taylor, *J. Phys. Chem.*, **100**, 7384 (1996).

Van der Waals dimensions are especially significant in attempts to specify the “size” of molecules, for example, in computational programs that attempt to “fit” molecules into biological receptor sites. In the next chapter, we discuss the effects of van der Waals interactions on molecular shape (conformation). These effects can be quantified by various *force fields* that compute the repulsive energy that molecules experience as *nonbonded repulsion*.

1.2. Molecular Orbital Theory and Methods

Molecular orbital (MO) theory is an alternative way of describing molecular structure and electron density. The fundamental premise of MO theory is that the orbitals used to describe the molecule are not necessarily associated with particular bonds between the atoms but can encompass all the atoms of the molecule. The properties of the molecule are described by the sum of the contributions of all orbitals having electrons. There are also empty orbitals, which are usually at positive (i.e., antibonding) energies. The theoretical foundation of MO theory lies in quantum mechanics and, in particular, the Schrödinger equation, which relates the total energy of the molecule to a wave function describing the electronic configuration:

$$E = \int \psi H \psi d\tau \quad \text{when} \quad \int \psi^2 d\tau = 1 \quad (1.11)$$

where H is a Hamiltonian operator.

The individual MOs are described as linear combinations of the atomic orbitals $\{\varphi_x\}$ (LCAO):

$$\psi_p = c_{1p}\varphi_1 + c_{2p}\varphi_2 + c_{3p}\varphi_3 \dots c_{np}\varphi_n \quad (1.12)$$

The atomic orbitals that are used constitute the *basis set* and a minimum basis set for compounds of second-row elements is made up of the $2s$, $2p_x$, $2p_y$, and $2p_z$ orbitals of each atom, along with the $1s$ orbitals of the hydrogen atoms. In MO calculations, an initial molecular structure and a set of approximate MOs are chosen and the molecular energy is calculated. Iterative cycles of calculation of a self-consistent electrical field (SCF) and geometry optimization are then repeated until a minimization

Stereochemistry, Conformation, and Stereoselectivity

Introduction

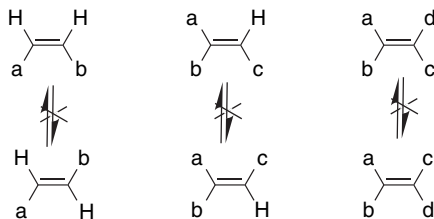
In the discussion of the structural features of carbon compounds in the Chapter 1, we emphasized some fundamental principles of molecular geometry. Except in strained rings, sp^3 carbon is nearly tetrahedral in shape. Double bonds involving sp^2 carbon are trigonal and planar and have a large barrier to rotation. The sp hybridization, e.g., in alkynes, leads to a linear (digonal) geometry. *Stereochemistry* in its broadest sense describes how the atoms of a molecule are arranged in three-dimensional space. In particular, *stereoisomers* are molecules that have identical connectivity (constitution) but differ in three-dimensional structure. Stereoisomers differ from one another in *configuration* at one or more atoms. *Conformations* are the various shapes that are available to molecules by single-bond rotations and other changes that do not involve bond breaking. Usually, conformational processes have relatively low energy requirements. The stereochemical features of a molecule, both configuration and conformation, can influence its reactivity. After discussing configuration and conformation, we consider *stereoselectivity*, the preference of a reaction for a particular stereoisomeric product.

2.1. Configuration

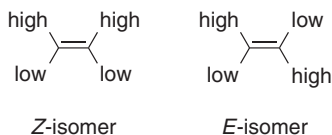
2.1.1. Configuration at Double Bonds

The sp^2 hybridization in the carbon atoms in a double bond and the resulting π bond favor a planar arrangement of the two carbon atoms and the four immediate

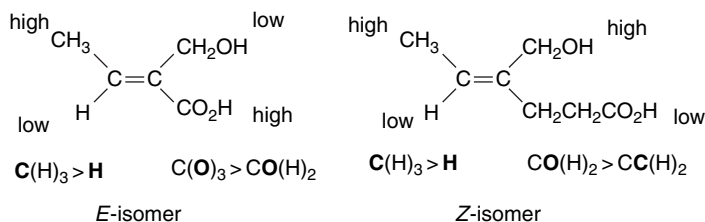
ligand atoms. When the substituents at the two carbons are nonidentical, two structurally distinct molecules exist.



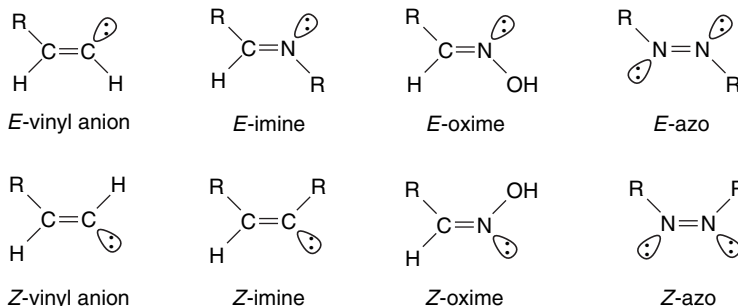
Owing to the high barrier to rotation in most alkenes (> 50 kcal/mol), these structures are not easily interconverted and the compounds exist as two isomers (stereoisomers) having different physical and chemical properties. There are two common ways of naming such compounds. If there is only one substituent at each carbon, the compounds can be called *cis* and *trans*. The isomer with both substituents on the same side of the double bond is the *cis* isomer, whereas the one with substituents on opposite sides is the *trans* isomer. If there is more than one substituent at either carbon, these designations can become ambiguous. There is an unambiguous system that can be applied to all compounds, no matter how many or how complex the substituents might be: the isomers are designated *Z* (for together) or *E* (for opposite). This system is based on the *Cahn-Ingold-Prelog priority rules*, which assign priority in the order of decreasing atomic number. If two substituent atoms have the same atomic number (e.g., two carbon substituents), the atomic numbers of successive atoms in the groups are compared until a difference is found. Multiple bonds, such as in a carbonyl group, are counted as two (or three for a triple bond) atoms. It is the *first difference* that determines priority. When priority has been assigned, the isomer with the higher-priority groups at each carbon on the same side of the double bond is called the *Z*-isomer. The isomer with the higher-priority substituents on opposite sides is the *E*-isomer.



Example 2.1

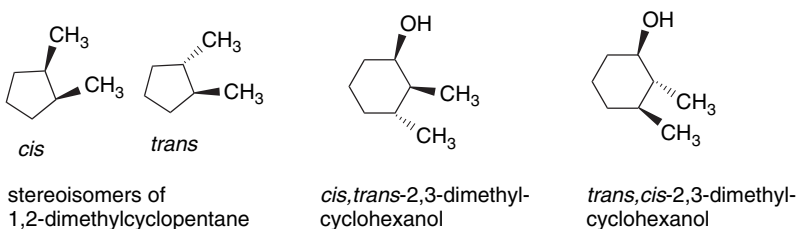


Certain atoms have an unshared electron pair rather than a substituent. Electron pairs are assigned the lowest priority in the Cahn-Ingold-Prelog convention, so assignment the *Z*- or *E*-configuration to compounds such as imines and oximes follows the same rules with R or H >:.

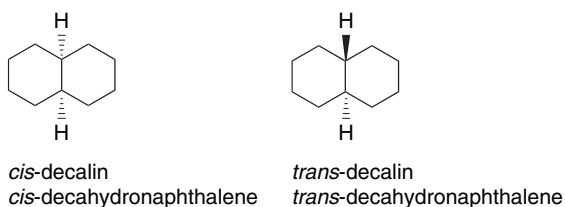


2.1.2. Configuration of Cyclic Compounds

Just as substituents can be on the same or opposite side of a double bond, they can be on the same or opposite side in cyclic compounds. The two arrangements are different *configurations* and cannot be interchanged without breaking and reforming at least one bond. Here the terms *cis* (for the same side) and *trans* (for the opposite side) are unambiguous and have been adopted as the designation of configuration. The stereochemistry is specified *relative to the group that takes precedence in the naming of the molecule*, as illustrated for 2,3-dimethylcyclohexanol.

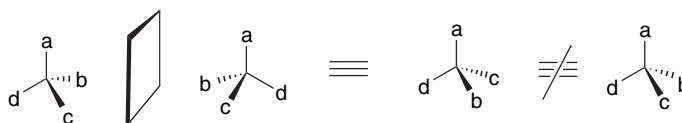


Stereoisomers also arise when two rings share a common bond. In the *cis* isomer both branches of the fused ring are on the same side. In the *trans* isomer they are on opposite sides.



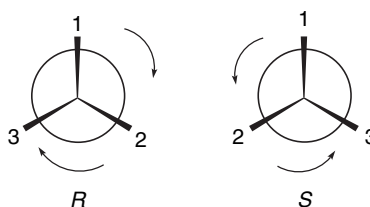
2.1.3. Configuration at Tetrahedral Atoms

Carbon and other atoms with sp^3 hybridization have approximately tetrahedral geometry. With the exception of small deviations in bond angles, each of the substituents is in a geometrically equivalent position. Nevertheless, there is an important stereochemical feature associated with tetrahedral centers. If all four substituents are different, they can be arranged in two different ways. The two different arrangements are mirror images of one another, but they cannot be superimposed.

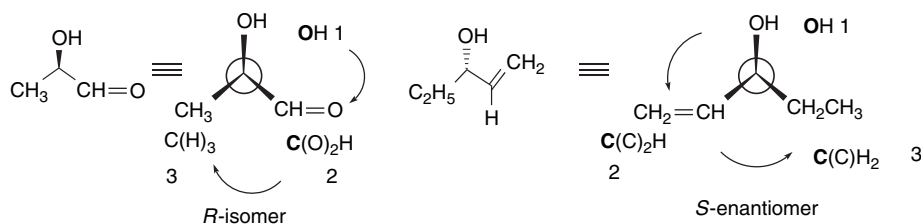


Any object that cannot be superimposed on its mirror image is called *chiral*, that is, it has the property of being right-handed or left-handed. Molecules (or other objects) that are not chiral are described as being *achiral*, which is the opposite of chiral. Tetrahedral atoms with four nonidentical substituents, then, give rise to two stereoisomers. Such atoms are called *stereogenic centers*, sometimes shortened to *stereocenters*. An older term applied specifically to carbon is *asymmetric carbon*.

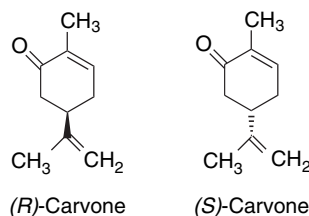
The chirality (or handedness) at stereogenic centers is specified by application of the Cahn-Ingold-Prelog priority rules, as described for double bonds. The four nonidentical ligand atoms are assigned a decreasing priority $1 > 2 > 3 > 4$. The molecule is then viewed opposite from the lowest-priority group, that is, the group is placed behind the stereocenter and away from the viewer. Two arrangements are possible for the other three substituents. The groups can decrease in priority in either a clockwise or a counterclockwise direction. The clockwise direction configuration is assigned *R* (for *rectus*) and the counterclockwise direction is assigned *S* (for *sinistre*).



Example 2.2



The two nonsuperimposable mirror image molecules are called an *enantiomeric pair* and each is the *enantiomer* of the other. The separated enantiomers have identical properties with respect to achiral environments. They have the same solubility, physical, and spectroscopic properties and the same chemical reactivity toward achiral reagents. However, they have different properties in chiral environments. The enantiomers react at different rates toward chiral reagents and respond differently to chiral catalysts. Usually enantiomers cause differing physiological responses, since biological receptors are chiral. For example, the odor of the *R*- (spearmint oil) and *S*- (caraway seed oil) enantiomers of carvone are quite different.



The activity of enantiomeric forms of pharmaceuticals is often distinctly different.

Enantiomers also differ in a specific physical property, namely the rotation of plane polarized light. The two enantiomers rotate the light in equal, but opposite directions. The property of rotating plane polarized light is called *optical activity*, and the magnitude of rotation can be measured by instruments called polarimeters. The observed rotation, known as α , depends on the conditions of measurement, including concentration, path length, solvent, and the wavelength of the light used. The rotation that is characteristic of an enantiomer is called the *specific rotation* and is symbolized by $[\alpha]_{\lambda}$, where the subscript designates the wavelength of the light. The observed rotation α at any wavelength is related to $[\alpha]_{\lambda}$ by the equation

$$[\alpha]_{\lambda} = \frac{100\alpha}{cl} \quad (2.1)$$

where c is the concentration in g/100 mL and l is the path length in decimeters.

Depending on how it was obtained, a sample of a chiral compound can contain only one enantiomer or it can be a mixture of both. Enantiomerically pure materials are referred to as *homochiral* or *enantiopure*. The 1:1 mixture of enantiomers has zero net rotation (because the rotations caused by the two enantiomers precisely cancel each other) and is called a *racemic mixture* or *racemate*. A racemic mixture has its own characteristic properties in the solid state. It differs in melting point and solubility from the pure enantiomers, owing to the fact that the racemic mixture can adopt a different crystalline structure from that of the pure enantiomers. For example, Figure 2.1 shows the differing intermolecular hydrogen-bonding and crystal-packing arrangements in (+/−) and (−) 2,5-diazabicyclo[2.2.2]octa-3,6-dione.¹

The composition of a mixture of enantiomers is given by the *enantiomeric excess*, abbreviated e.e., which is the percentage excess of the major enantiomer over the minor enantiomer:

$$\text{e.e.} = \% \text{ Major} - \% \text{ Minor} \quad (2.2)$$

¹. M.-J. Birenne, J. Gabard, M. Leclercq, J.-M. Lehn, M. Cesario, C. Pascard, M. Cheve, and G. Dutruc-Rosset, *Tetrahedron Lett.*, **35**, 8157 (1994).

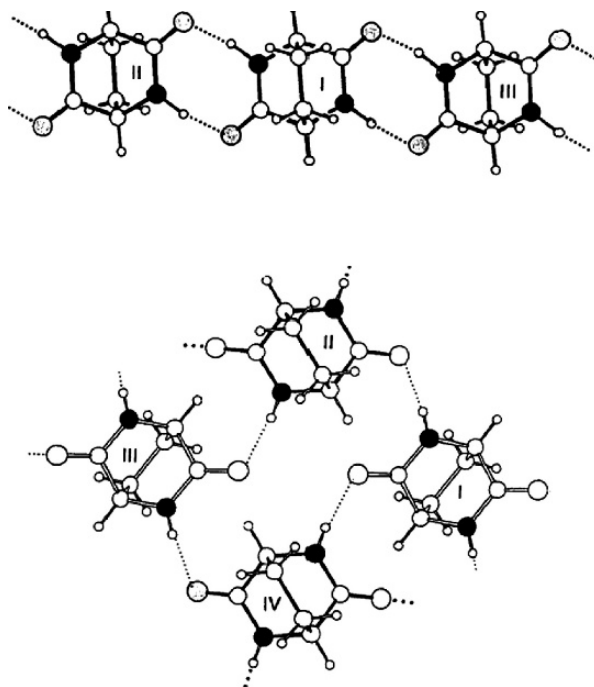


Fig. 2.1. Alternative hydrogen-bonding and crystal-packing arrangements for racemic (top) and (–) (bottom) forms of 2,5-diazabicyclo[2.2.2]octane-3,6-dione. Reproduced from *Tetrahedron Lett.*, **35**, 8157 (1994), by permission of Elsevier.

Alternatively, e.e. can be expressed in terms of the mole fraction of each enantiomer:

$$\text{e.e.} = (\text{Mole fraction}_{\text{major}} - \text{Mole fraction}_{\text{minor}}) \times 100 \quad (2.3)$$

The *optical purity*, an older term, is numerically identical. It represents the observed rotation, relative to the rotation of the pure enantiomer. Since the two enantiomers cancel each other out, the observed rotation is the product of (% Major – % Minor) $\times$ $[\alpha]_{\lambda}$. If $[\alpha]_{\lambda}$ is known, measurement of α allows the optical purity and enantiomeric excess to be determined:

$$\text{e.e.} = \frac{\alpha_{\text{obs}} \times 100}{[\alpha]_{\lambda}} \quad (2.4)$$

There are several other ways of measuring e.e., including NMR spectroscopy, chromatography, and capillary electrophoresis (see Topic 2.1).

Measurement of rotation as a function of wavelength is useful in structural studies aimed at determining the configuration of a chiral molecule. This technique is called *optical rotatory dispersion* (ORD),² and the resulting plot of rotation against wavelength is called an ORD curve. The shape of the ORD curve is determined by the

² P. Crabbe, *Top. Stereochem.* **1**, 93 (1967); C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill, New York, 1960; P. Crabbe, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden Day, San Francisco, 1965; E. Charney, *The Molecular Basis of Optical Activity. Optical Rotatory Dispersion and Circular Dichroism*, Wiley, New York, 1979.

configuration of the molecule and its absorption spectrum. In many cases, the ORD curve can be used to determine the configuration of a molecule by comparison with similar molecules of known configuration. Figure 2.2 shows the UV, ORD, and CD spectra of an enantiomerically pure sulfonium ion salt.³

Chiral substances also show differential absorption of circularly polarized light. This is called *circular dichroism* (CD) and is quantitatively expressed as the molecular ellipticity θ , where ϵ_L and ϵ_R are the extinction coefficients of left and right circularly polarized light:

$$\theta = 3330(\epsilon_L - \epsilon_R) \quad (2.5)$$

Molecular ellipticity is analogous to specific rotation in that two enantiomers have exactly opposite values at every wavelength. Two enantiomers also show CD spectra having opposite signs. A compound with several absorption bands may show both positive and negative bands. Figure 2.3 illustrates the CD curves for both enantiomers of 2-amino-1-phenyl-1-propanone.⁴

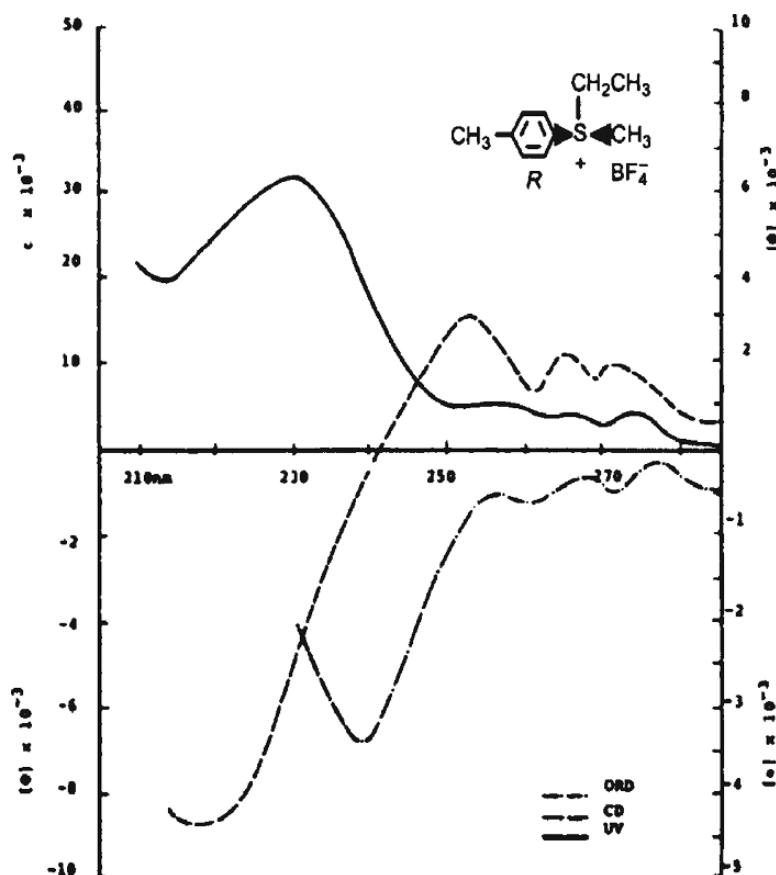


Fig. 2.2. UV absorption, ORD, and CD curves of (*R*)-ethyl methyl *p*-tolyl sulfonium tetrafluoroborate. Reproduced from *J. Org. Chem.*, **41**, 3099 (1976), by permission of the American Chemical Society.

³. K. K. Andersen, R. L. Caret, and D. L. Ladd, *J. Org. Chem.*, **41**, 3096 (1976).

⁴. J.-P. Wolf and H. Pfander, *Helv. Chim. Acta*, **69**, 1498 (1986).

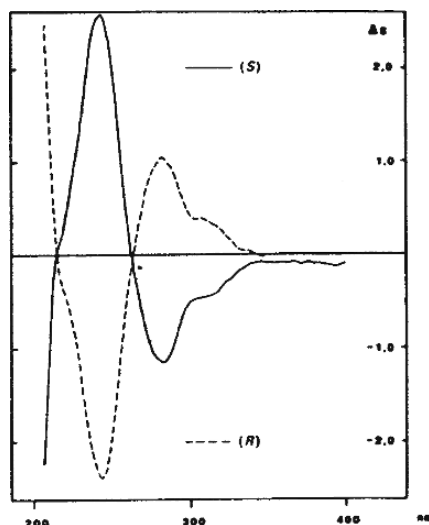


Fig. 2.3. CD spectra of (S)- and (R)-2-amino-1-phenyl-1-propanone hydrochloride. Reproduced from *Helv. Chim. Acta*, **69**, 1498 (1986), by permission of Wiley-VCH.

2.1.4. Molecules with Multiple Stereogenic Centers

Molecules can have several stereogenic centers, including double bonds with *Z* or *E* configurations and asymmetrically substituted tetrahedral atoms. The maximum number of stereoisomers that can be generated from n stereogenic centers is 2^n . There are several ways of representing molecules with multiple stereogenic centers. At the present time, the most common method in organic chemistry is to depict the molecule in an extended conformation with the longest chain aligned horizontally. The substituents then point in or out and up or down at each tetrahedral site of substitution, as represented by wedged and dashed bonds. The four possible stereoisomers of 2,3,4-trihydroxybutanal are shown in this way in Figure 2.4. The configuration at each center is specified as *R* or *S*. The isomers can also be characterized as *syn* or *anti*. Two

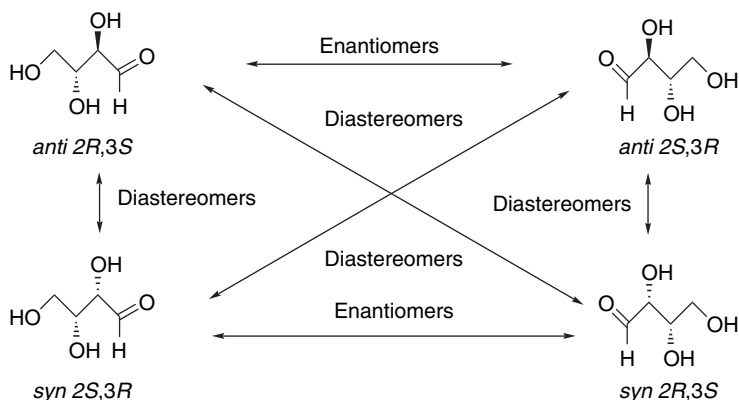
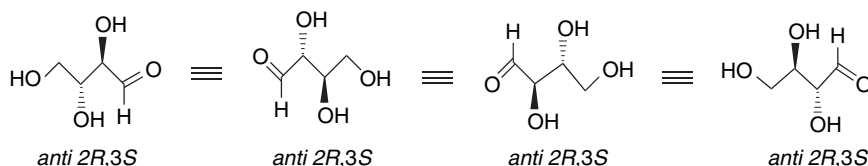


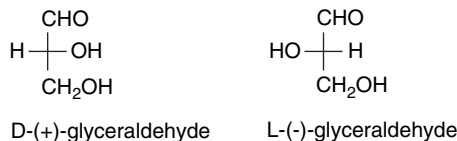
Fig. 2.4. Extended chain representation of all stereoisomers of 2,3,4-trihydroxybutanal.

adjacent substituents pointed in the same direction (in or out) are *syn*, whereas those pointed in opposite directions are *anti*.

For molecules with more than one stereogenic center, the *enantiomeric pair must have the opposite configuration at each center*. The two enantiomeric relationships are shown in Figure 2.4. There are four other pairings that do not fulfill this requirement, but the structures are still stereoisomeric. Molecules that are stereoisomeric but are not enantiomeric are called *diastereomers*, and four of these relationships are pointed out in Figure 2.4. Molecules that are diastereomeric have the same *constitution* (connectivity) but differ in *configuration* at one or more of the stereogenic centers. The positions in two diastereomers that have different configurations are called *epimeric*. For example, the *anti-2R,3R* and *syn-2R,3S* stereoisomers have the same configuration at C(2), but are epimeric at C(3). There is nothing unique about the way in which the molecules in Figure 2.4 are positioned, except for the conventional depiction of the extended chain horizontally. For example, the three other representations below also depict the *anti-2R,3S* stereoisomer.



Another means of representing molecules with several stereocenters is by *Fischer projection formulas*. The main chain of the molecule is aligned vertically, with (by convention) the most oxidized end of the chain at the top. The substituents that are shown horizontally project toward the viewer. Thus the vertical carbon-carbon bonds point away from the viewer at all carbon atoms. Fischer projection formulas represent a *completely eclipsed conformation* of the vertical chain. Because the horizontal bonds project from the plane of the paper, any reorientation of the structures must not change this feature. *Fischer projection formulas may be reoriented only in the plane of the paper*. Fischer projection formulas use an alternative system for specifying chirality. The chirality of the highest-numbered chiral center (the one most distant from the oxidized terminus, that is, the one closest to the bottom in the conventional orientation), is specified as D or L, depending on whether it is like the D- or L-enantiomer of glyceraldehyde, which is the reference compound. In the conventional orientation, D-substituents are to the right and L-substituents are to the left.



The *relative configuration* of adjacent substituents in a Fischer projection formula are designated *erythro* if they are on the same side and *threo* if they are on the opposite side. The stereochemistry of adjacent stereocenters can also be usefully represented

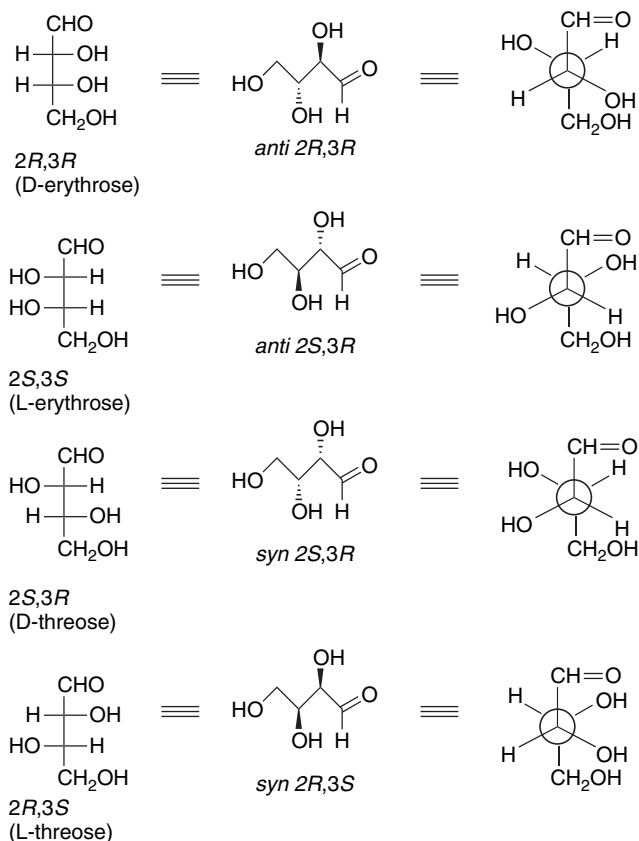


Fig. 2.5. Fischer, extended, and Newman projection representations of the stereoisomers of 2,3,4-trihydroxybutanal.

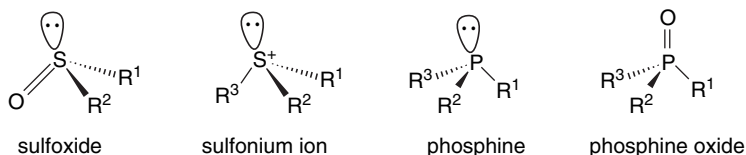
by *Newman projection formulas*. Figure 2.5 shows 2,3,4-trihydroxybutanal (now also with its carbohydrate names, erythrose and threose) as Fischer projection formulas as well as extended and Newman representations.

Because the Fischer projection formulas represent an eclipsed conformation of the carbon chain, the relative orientation of two adjacent substituents is opposite from the extended staggered representation. Adjacent substituents that are *anti* in an extended representation are on the same side of a Fischer projection formula, whereas adjacent substituents that are *syn* in an extended representation are on opposite sides in a Fischer projection. As with extended representations, an enantiomeric pair represented by Fischer projection formulas has the opposite configuration at *all stereogenic centers* (depicted as left or right.)

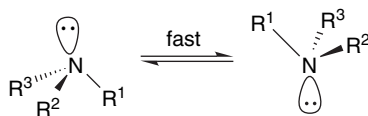
2.1.5. Other Types of Stereogenic Centers

Although asymmetrically substituted carbon atoms are by far the most common type of stereogenic center in organic compounds, several other kinds of stereogenic centers are encountered. Tetravalent nitrogen (ammonium) and phosphorus (phosphonium) ions are obvious extensions. Phosphine oxides are also tetrahedral and are chiral if all three substituents (in addition to the oxygen) are different. Not quite

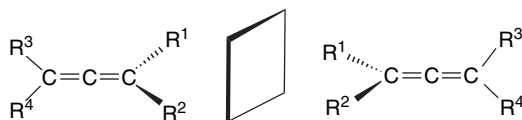
so evident are the cases of *trivalent* sulfur and phosphorus compounds, including sulfonium salts, sulfoxides, and phosphines. The heteroatom in these structures is approximately tetrahedral, with an electron pair occupying one of the tetrahedral positions. Because there is a relatively high energy barrier to inversion of these tetrahedral molecules, they can be obtained as pure enantiomers.



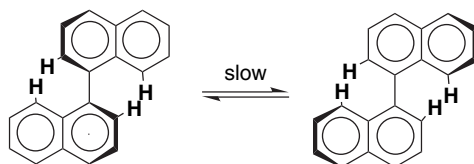
Trivalent nitrogen compounds are also approximately tetrahedral in shape. In this case, however, the barrier to inversion is small and the compounds cannot be separated as pure enantiomers at normal temperatures.



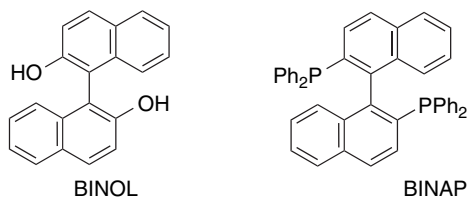
Allenes (see p. 6 for a discussion of bonding in allenes) can be chiral. An allene having nonidentical substituents at both sp^2 carbons gives nonsuperimposable mirror images.



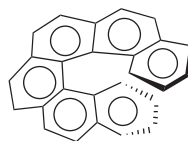
Molecules with shapes analogous to screws are also chiral, since they can be right-handed or left-handed. There are several kinds of molecules in which steric factors impose a screwlike shape. A very important case is 1,1'-binaphthyl compounds. Steric interactions between the 2 and 8' hydrogens prevent these molecules from being planar, and as a result, there are two nonsuperimposable mirror image forms.



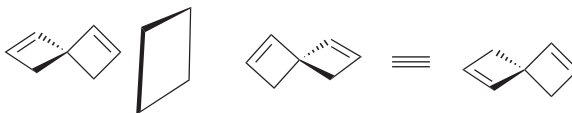
A particularly important example is the 2,2'-diol, which is called BINOL. Another important type includes 1,1'-binaphthyl diphosphines, such as BINAP.⁵ BINOL and BINAP are useful chiral ligands in organometallic compounds that serve as catalysts for hydrogenations and other reactions. In Section 2.5.1.1, we discuss how compounds such as BINOL and BINAP have been used to develop *enantioselective hydrogenation catalysts*.



A spectacular example of screw-shaped chirality is hexahelicene, in which the six fused benzene rings cannot be planar and give rise to right-handed and left-handed enantiomers. The specific rotation $[\alpha]_{589}$ is about 3700.⁶ Hexahelicene can be racemized by heating. The increased molecular vibration allows the two terminal rings to slip past one another. The activation energy required is 36.2 kcal/mol.⁷



Many *spiro* compounds are chiral. In *spiro* structures, two rings share a common atom. If neither ring contains a plane of symmetry, *spiro* compounds are chiral. An example is *S*-(+)-*spiro*[3,3]hepta-1,5-diene.⁸



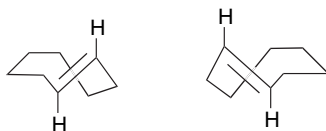
The *E*-cycloalkenes are also chiral. *E*-cyclooctene is a good example. Examination of the structures below using molecular models demonstrates that the two mirror images cannot be superimposed.

⁵. A. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).

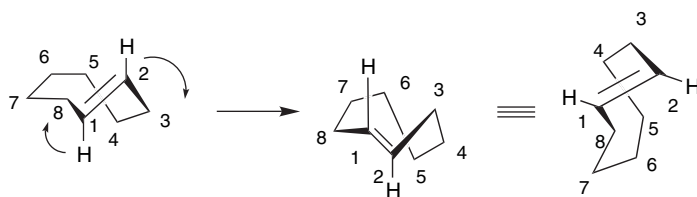
⁶. M. S. Newman and D. Lednicer, *J. Am. Chem. Soc.*, **78**, 4765 (1956).

⁷. R. H. Martin and M. J. Marchant, *Tetrahedron*, **30**, 347 (1974).

⁸. L. A. Hulshof, M. A. McKervey, and H. Wynberg, *J. Am. Chem. Soc.*, **96**, 3906 (1974).

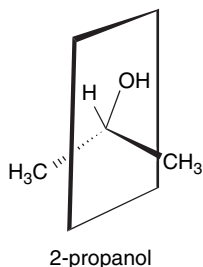


E-cyclooctene is subject to thermal racemization. The molecular motion allows the double bond to slip through the ring, giving the enantiomer. The larger and more flexible the ring, the easier the process. The rates of racemization have been measured for *E*-cyclooctene, *E*-cyclononene, and *E*-cyclodecene. For *E*-cyclooctene the half-life is 1 h at 183.9° C. The activation energy is 35.6 kcal/mol. *E*-cyclononene, racemizes much more rapidly. The half-life is 4 min at 0° C, with an activation energy of about 20 kcal/mol. *E*-cyclodecene racemizes immediately on release from the chiral platinum complex used for its preparation.⁹



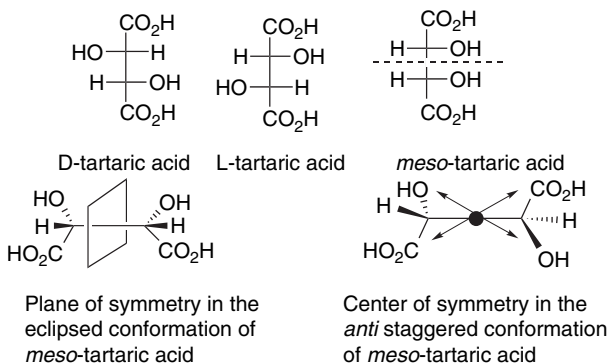
2.1.6. The Relationship between Chirality and Symmetry

Molecules that possess certain elements of symmetry are not chiral, because the element of symmetry ensures that the mirror image forms are superimposable. The most common example is a *plane of symmetry*, which divides a molecule into two halves that have identical placement of substituents on both sides of the plane. A trivial example can be found at any tetrahedral atom with two identical substituents, as, for example, in 2-propanol. The plane subdivides the 2-H and 2-OH groups and the two methyl groups are identical.

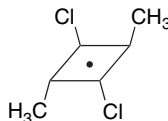


⁹. A. C. Cope and B. A. Pawson, *J. Am. Chem. Soc.*, **87**, 3649 (1965); A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **87**, 3644 (1965).

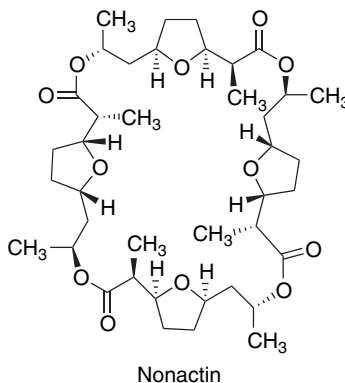
More elaborate molecules can also have a plane of symmetry. For example, there are only three stereoisomers of tartaric acid (2,3-dihydroxybutanedioic acid). Two of these are chiral but the third is achiral. In the achiral stereoisomer, the substituents are located with respect to each other in such a way as to generate a plane of symmetry. Compounds that contain two or more stereogenic centers but have a plane of symmetry are called *meso forms*. Because they are achiral, they do not rotate plane polarized light. Note that the Fischer projection structure of *meso*-tartaric acid reveals the plane of symmetry.



A less common element of symmetry is a *center of symmetry*, which is a point in a molecule through which a line oriented in any direction encounters the same environment (structure) when projected in the opposite direction. For example, *trans, trans*-2,4-dichloro-1,3-dimethylcyclobutane has a center of symmetry, but no plane of symmetry. It is achiral.

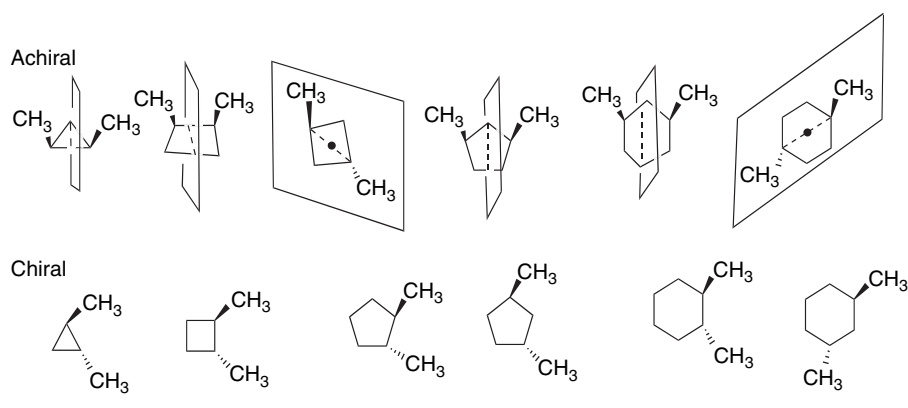


Another very striking example is the antibiotic nonactin. Work out problem 2.15 to establish the nature of the of symmetry in nonactin.



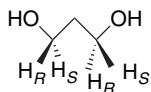
Various di- and polysubstituted cyclic compounds provide other examples of molecules having elements of symmetry. Since chirality depends on *configuration*, not *conformation*, cyclic molecules can be represented as planar structures to facilitate recognition of symmetry elements. These planar structures clearly convey the *cis* and *trans* relationships between substituents. Scheme 2.1 gives some examples of both chiral and achiral dimethylcycloalkanes. Note that in several of the compounds there is both a center and a plane of symmetry. Either element of symmetry ensures that the molecule is achiral.

Scheme 2.1. Chiral and Achiral Disubstituted Cycloalkanes

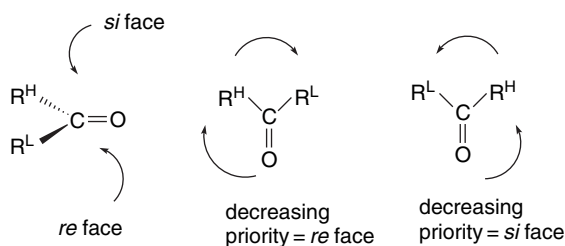


2.1.7. Configuration at Prochiral Centers

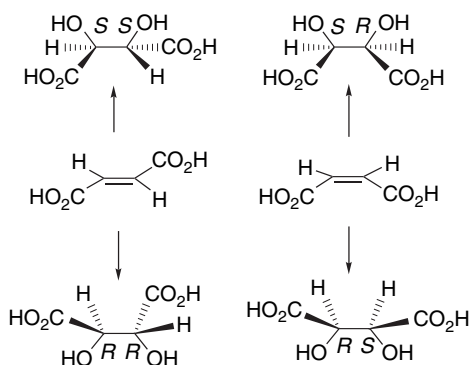
Prochiral centers have two identical ligands, such as two hydrogens, and are achiral. In many situations, however, these identical ligands are *topologically nonequivalent* or *heterotopic*. This occurs when the other two substituents are different. If either of the identical groups is replaced by a different ligand, a stereogenic center is created. The two positions are called *enantiotopic*. The position, which if assigned a higher priority, gives an *R* configuration is called *pro-R*. The position, which if assigned a higher priority, gives an *S* configuration is called *pro-S*. Propane-1,3-diol is an example of a prochiral molecule. The C(1) and C(3) positions are prochiral, but the C(2) is not, because its two hydroxymethyl ligands are identical.



Unsymmetrically substituted carbonyl groups are prochiral centers, since addition of a fourth ligand generates a stereogenic center. These are designated by determining the Cahn-Ingold-Prelog priority order. The carbonyl group is said to have an *re* face and an *si* face.



Achiral reagents do not distinguish between the two faces, but chiral reagents do and give unequal amounts of enantiomeric products. Other trigonal centers, including carbon-carbon double bonds, present two prochiral faces. For example, *E*- and *Z*-butenedioic acid (maleic and fumaric acid) generate different stereoisomers when subjected to *syn*-dihydroxylation. If the reagent that is used is chiral, the *E*-isomer will generate different amounts of the *R,R* and *S,S* products. The *S,R* and *R,S* forms generated from the *Z*-isomer are *meso* forms and will be achiral, even if they are formed using a chiral reagent.



The concept of heterotopic centers and faces can be extended to diastereotopic groups. If one of two equivalent ligands in a molecule is replaced by a test group, the ligands are diastereotopic when the resulting molecules are diastereomers. Similarly, if a transformation at opposite faces of a trigonal center generates two different diastereomers, the faces are diastereotopic. There is an important difference between enantiotopic and diastereotopic centers. Two identical ligands at enantiotopic centers are in *chemically equivalent environments*. They respond identically to probes, including chemical reagents, that are achiral. They respond differently to chiral probes, including chiral reagents. Diastereotopic centers are *topologically nonequivalent*. That is, their environments in the molecule are different and they respond differently to achiral, as well as to chiral probes and reagents. As a consequence of this nonequivalence, diastereotopic protons, as an example, have different chemical shifts and are distinguishable in NMR spectra. Enantiotopic protons do not show separate NMR signals. Two diastereotopic protons give rise to a more complex NMR pattern. Because of their chemical shift difference, they show a geminal coupling. An example of this effect can be seen in the proton NMR spectra of 1-phenyl-2-butanol, as shown in

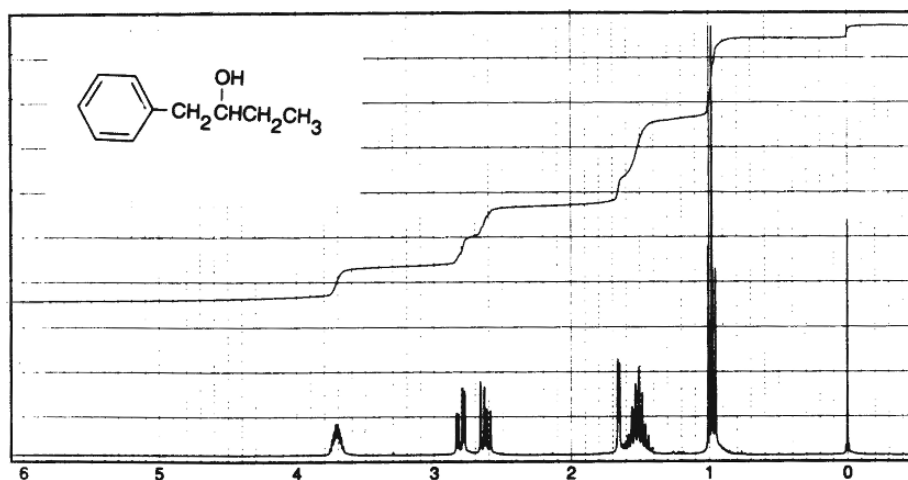
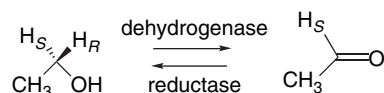


Fig. 2.6. NMR spectrum of 1-phenyl-2-butanol showing the diastereotopic nature of C(1) protons. Reproduced from *Aldrich Library of ^{13}C and ^1H NMR Spectra*, Vol. 2, 1993, p. 386.

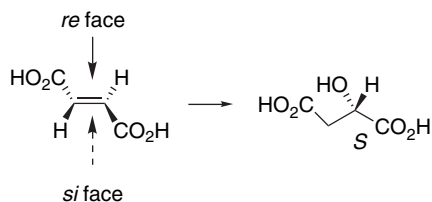
Figure 2.6. The C(1) CH_2 group appears as a quartet near 2.8 ppm with further coupling to the C(2) proton. The C(1) hydrogens are diastereotopic. The C(3) hydrogens are also diastereotopic, but their nonidentity is not obvious in the multiplet at about 1.6 ppm.

Because biological reactions involve chiral enzymes, enantiotopic groups and faces typically show different reactivity. For example, the two methylene hydrogens in ethanol are enantiotopic. Enzymes that oxidize ethanol, called *alcohol dehydrogenases*, selectively remove the pro-*R* hydrogen. This can be demonstrated by using a deuterated analog of ethanol in the reaction.



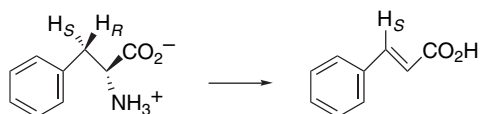
Conversely, *reductases* selectively reduce acetaldehyde from the *re* face.

Fumaric acid is converted to L-malic acid (*S*-2-hydroxybutanedioic acid) by the enzyme *fumarase*. The hydroxy group is added stereospecifically from the *si* face of the double bond.



Enzymes also distinguish between diastereotopic groups and faces. For example, L-phenylalanine is converted to cinnamic acid by the enzyme *phenylalanine ammonia*

lyase. The reaction occurs by an *anti* elimination involving the amino group and the 3-*pro-R* hydrogen.

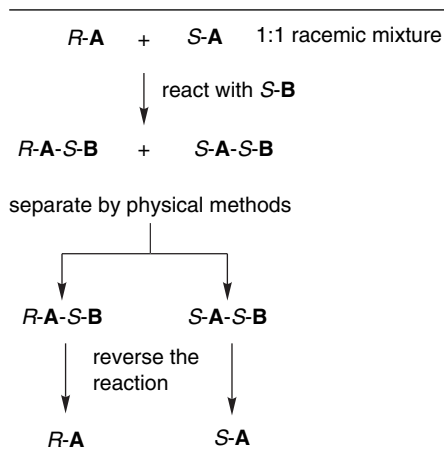


2.1.8. Resolution—The Separation of Enantiomers

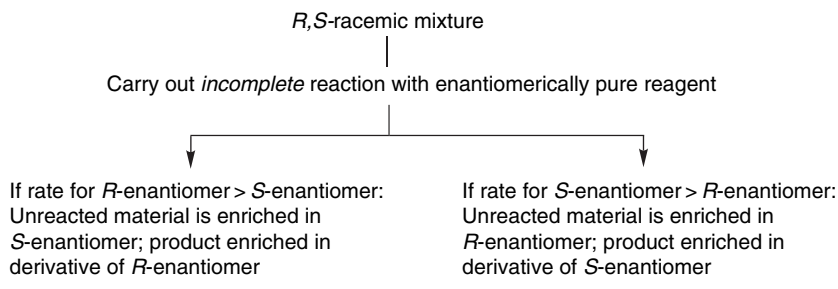
Since all living cells and organisms involve reactions of enantiomerically pure materials such as carbohydrates, proteins, and DNA, most naturally occurring chiral compounds exist in enantiomerically pure form. Chemical reactions, however, often produce racemic mixtures. This is *always* the case if only racemic and/or achiral reactants, reagents, catalysts, and solvents are used. The products of chemical reactions can be enantiomerically enriched or enantiopure only if chiral starting materials, reagents, catalysts or solvents are used. (See Section 2.5 for a discussion of enantioselective reactions.) Racemic mixtures can be separated into the two enantiomeric forms. The process of separating a racemic mixture into its enantiomers is called *resolution*, and it can be accomplished in several different ways.

Historically, the usual method was to use an existing enantiomerically pure compound, often a naturally occurring material, as a *resolving agent*. When a racemic mixture of **A** (*R,S*-**A**) reacts with a pure enantiomer (*S*-**B**), the two products are *diastereomeric*, namely *R,S*-**AB** and *S,S*-**AB**. As diastereomers have differing physical properties, they can be separated by such means as crystallization or chromatography. When the diastereomers have been separated, the original reaction can be reversed to obtain enantiomerically pure (or enriched) samples. The concept is summarized in Scheme 2.2. Scheme 2.3 describes an actual resolution.

Scheme 2.2. Conceptual Representation of Resolution through Separation of Diastereomeric Derivatives



Scheme 2.4. Conceptual Basis of Kinetic Resolution



Another means of resolution depends on the difference in rates of reaction of two enantiomers with a chiral reagent. The rates of reaction of each enantiomer with a single enantiomer of a chiral reagent are different because the transition structures and intermediates (R -substrate... R -reagent) and (S -substrate... R -reagent) are *diastereomeric*. *Kinetic resolution* is the term used to describe the separation of enantiomers on the basis of differential reaction rates with an enantiomerically pure reagent. Scheme 2.4 summarizes the conceptual basis of kinetic resolution.

Because the separation is based on differential rates of reaction, the degree of resolution that can be achieved depends on both the *magnitude of the rate difference and the extent of reaction*. The greater the difference in the two rates, the higher the enantiomeric purity of both the reacted and unreacted enantiomer. The extent of enantiomeric purity can be controlled by controlling the degree of conversion. As the extent of conversion increases, the enantiomeric purity of the *unreacted enantiomer increases*.¹⁰ The relationship between the relative rate of reaction, extent of conversion, and enantiomeric purity of the unreacted enantiomer is shown graphically in Figure 2.8.

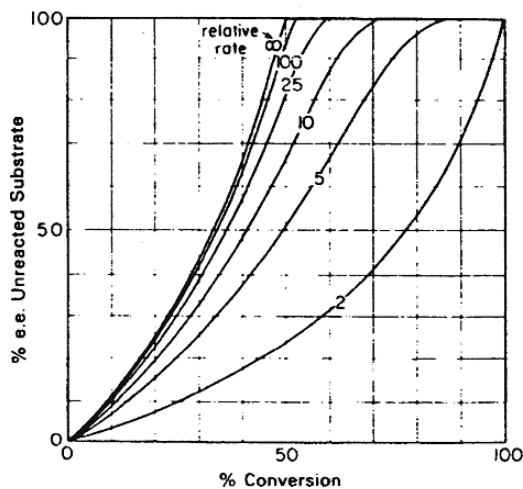


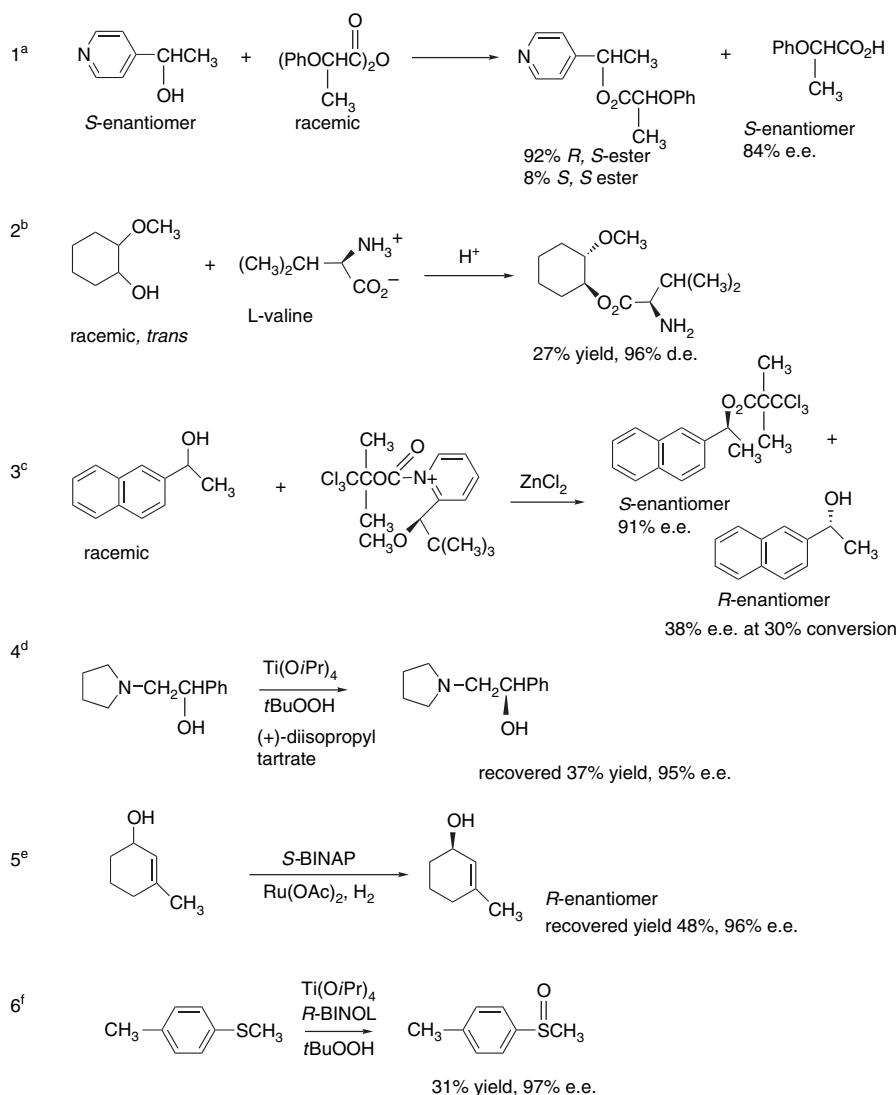
Fig. 2.8. Dependence of enantiomeric excess on relative rate of reaction and extent of conversion with a chiral reagent in kinetic resolution. Reproduced from *J. Am. Chem. Soc.*, **103**, 6237 (1981), by permission of the American Chemical Society.

¹⁰ V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981).

Of course, the high conversion required for high enantiomeric purity when the relative reactivity difference is low has a serious drawback. The *yield of the unreacted substrate is low* if the overall conversion is high. Relative reactivity differences of < 10 can achieve high enantiomeric purity only at the expense of low yield.

Scheme 2.5 gives some specific examples of kinetic resolution procedures. Entries 1 to 3 in Scheme 2.5 are acylation reactions in which esters are formed. Either the

Scheme 2.5. Examples of Kinetic Resolution



a. U. Salz and C. Rüchardt, *Chem. Ber.*, **117**, 3457 (1984).

b. P. Stead, H. Marley, M. Mahmoudian, G. Webb, D. Noble, Y. T. Ip, E. Piga, S. Roberts, and M. J. Dawson, *Tetrahedron: Asymmetry*, **7**, 2247 (1996).

c. E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, **118**, 1809 (1996).

d. S. Miyano, L. D. Lu, S. M. Viti, and K. B. Sharpless, *J. Org. Chem.*, **48**, 3608 (1983).

e. M. Kitmura, I. Kasahara, K. Manabe, R. Noyori, and H. Takaya, *J. Org. Chem.*, **53**, 708 (1988).

f. N. Komatsu, M. Hashizuma, T. Sugita, and S. Uemura, *J. Org. Chem.*, **58**, 7624 (1993).

alcohol or the acylation reagent is enantiopure. The enantioselectivity is a result of differential interactions in the TS (transition structure) and the reactions are carried to partial conversion to achieve kinetic resolution. These reactions presumably proceed via the typical addition-elimination mechanism for acylation (see Section 7.4) and do not have the benefit of any particular organizing center such as a metal ion. The observed enantioselectivities are quite high, and presumably depend primarily on steric differences in the diastereomeric TSs. Entries 4 and 5 involve enantioselective catalysts. Entry 4, is an oxidative cleavage that involves a complex of Ti(IV) with the chiral ligand, diisopropyl tartrate. It is sufficiently selective to achieve 95% e.e. at the point of about 67% completion. The other enantiomer is destroyed by the oxidation. Entry 5 uses a hydrogenation reaction with the chiral BINAP ligand (see p. 130 for structure). The *S*-enantiomer is preferentially hydrogenated and the *R*-enantiomer is obtained in high e.e. In both of these examples, the reactant coordinates to the metal center through the hydroxy group prior to reaction. The relatively high e.e. that is observed in each case reflects the high degree of order and discrimination provided by the chiral ligands at the metal center. Entry 6 is the oxidative formation of a sulfoxide, using BINOL (see p. 130) as a chiral ligand and again involves a metal center in a chiral environment. We discuss enantioselective catalysis further in Section 2.5.

Enzymes constitute a particularly important group of enantioselective catalysts,¹¹ as they are highly efficient and selective and can carry out a variety of transformations. Enzyme-catalyzed reactions can be used to resolve organic compounds. Because the enzymes are derived from L-amino acids, they are chiral and usually one enantiomer of a reactant (substrate) is much more reactive than the other. The interaction with each enantiomer is diastereomeric in comparison with the interaction of the enzyme with the other enantiomer. Since enzymatic catalysis is usually based on a specific fit to an "active site," the degree of selectivity between the two enantiomers is often very high. For enzymatic resolutions, the enantioselectivity can be formulated in terms of two reactants in competition for a single type of catalytic site.¹² Enzymatic reactions can be described by *Michaelis-Menten kinetics*, where the key parameters are the equilibrium constant for binding at the active site, *K*, and the rate constant, *k*, of the enzymatic reaction. The rates for the two enantiomers are given by

$$v_R = k_R[R]/K_R \text{ and } v_S = k_S[S]/K_S \quad (2.6)$$

In a resolution with the initial concentrations being equal, $[S] = [R]$ the enantiomeric selectivity ratio *E* is the relative rate given by

$$E = \frac{k_S/K_S}{k_R/K_R} \quad (2.7)$$

Figure 2.9 shows the relationship between the e.e. of unreacted material and product as a function of the extent of conversion and the value of *E*.

The most generally useful enzymes catalyze hydrolysis of esters and amides (esterases, lipases, peptidases, acylases) or interconvert alcohols with ketones and aldehydes (oxido-reductases). Purified enzymes can be used or the reaction can be done by incubating the reactant with an organism (e.g., a yeast) that produces an

¹¹ J. B. Jones, *Tetrahedron*, **42**, 3351 (1986); J. B. Jones, in *Asymmetric Synthesis*, J. D. Morrison, ed., Vol. 5, Academic Press, Chap. 9; G. M. Whitesides and C.-H. Wong, *Angew. Chem. Int. Ed. Engl.*, **24**, 617 (1985).

¹² C.-S. Chen, Y. Fujimoto, G. Girdaukas, and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).

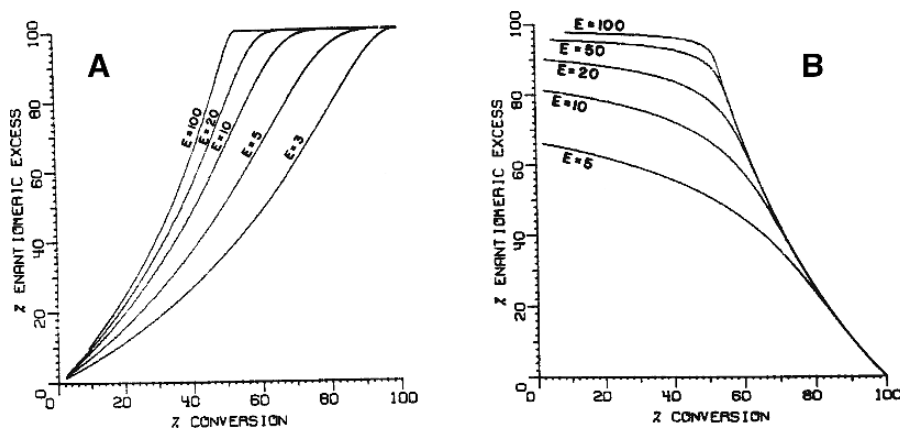
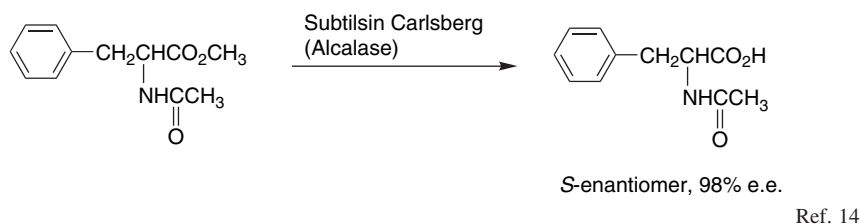
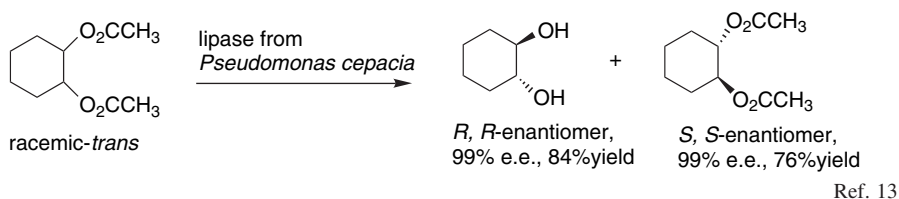


Fig. 2.9. Plots of enantiomeric excess as a function of extent of conversion for various values of E : (A) unreacted starting material; (B) product. Reproduced from *J. Am. Chem. Soc.*, **104**, 7294 (1982), by permission of the American Chemical Society.

appropriate enzyme during fermentation. Two examples are shown below. The main restriction on enzymatic resolution is the relatively limited range of reactions and substrates to which it is applicable. Enzymes usually have high substrate specificity, that is, they show optimal reactivity for compounds that are similar in structure to the natural substrate. Topic 2.2 gives further information about the application of enzymatic resolution.



13. G. Caron and R. J. Kazlauskas, *J. Org. Chem.*, **56**, 7251 (1991).

14. J. M. Roper and D. P. Bauer, *Synthesis*, 1041 (1983).

2.2. Conformation

The structural aspects of stereochemistry discussed in the previous section are the consequences of *configuration*, the geometric arrangement fixed by the chemical bonds within the molecule. Now, we want to look at another level of molecular structure, *conformation*. Conformations are the different shapes that a molecule can attain without breaking any covalent bonds. They differ from one another as the result of rotation at one or more single bond. The energy barrier for rotation of carbon-carbon single bonds is normally small, less than 5 kcal/mol, but processes that involve several coordinated rotations can have higher energy requirements. *Conformational analysis* is the process of relating conformation to the properties and reactivity of molecules.

2.2.1. Conformation of Acyclic Compounds

Ethane is a good molecule with which to begin. The two methyl groups in ethane can rotate with respect to one another. There are two unique conformations, called *staggered* and *eclipsed*. The eclipsed conformation represents the maximum energy and the staggered is the minimum. The difference between the two is 2.88 kcal/mol, as shown in Figure 2.10. As a result, any individual molecule is likely to be in the

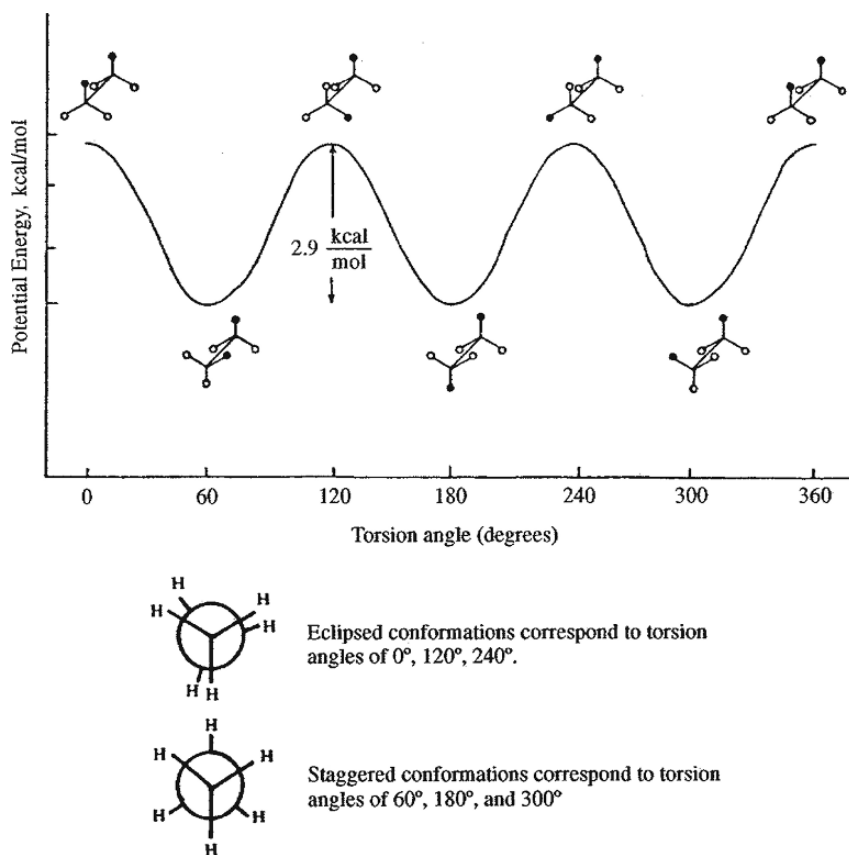
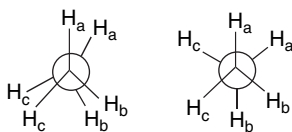
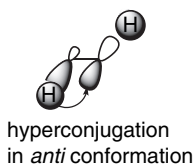


Fig. 2.10. Potential energy as a function of torsion angle for ethane.

staggered conformation at any given instant, but each molecule can rapidly traverse through the eclipsed conformation. The rate of rotation is about $6 \times 10^9 \text{ s}^{-1}$ at 25°C .



Shortly, we will learn that for some hydrocarbon molecules, van der Waals repulsions are a major factor in conformational preferences and energy barriers, but that is not the case for ethane. Careful analysis of the van der Waals radii show that the hydrogens do not come close enough to account for the barrier to rotation.¹⁵ Furthermore, the barrier of just under 3 kcal is applicable to more highly substituted single bonds. The barrier becomes significantly larger only when additional steric components are added, so the barrier must be an intrinsic property of the bond and not directly dependent on substituent size. The barrier to rotation is called the *torsional barrier*. There are analogous (although smaller) barriers to rotation about C–N and C–O bonds. Topic 1.3 probes further into the origin of the torsional barrier in small molecules. The conclusion reached is that the main factor responsible for the torsional barrier is σ – σ^* delocalization (hyperconjugation), which favors the staggered conformation.



The interplay between the torsional barrier and nonbonded (van der Waals) interactions can be illustrated by examining the conformations of *n*-butane. The relationship between energy and the torsion angle for rotation about the C(2)–C(3) bond is presented in Figure 2.11. The potential energy diagram of *n*-butane resembles that of ethane in having three maxima and three minima, but differs in that one of the minima is lower than the other two and one of the maxima is of higher energy than the other two. The minima correspond to staggered conformations. Of these, the *anti* is lower in energy than the two *gauche* conformations. The energy difference between the *anti* and *gauche* conformations in *n*-butane is about 0.6 kcal/mol.¹⁶ The maxima correspond to eclipsed conformations, with the highest-energy conformation being the one with the two methyl groups eclipsed with each other.

The rotational profile of *n*-butane can be understood as a superimposition of van der Waals repulsion on the ethane rotational energy profile. The two *gauche* conformations are raised in energy relative to the *anti* by an energy increment resulting from the van der Waals repulsion between the two methyl groups of 0.6 kcal/mol. The

¹⁵ E. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, p. 599.

¹⁶ G. J. Szasz, N. Sheppard, and D. H. Rank, *J. Chem. Phys.*, **16**, 704 (1948); P. B. Woller and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **94**, 5310 (1972).

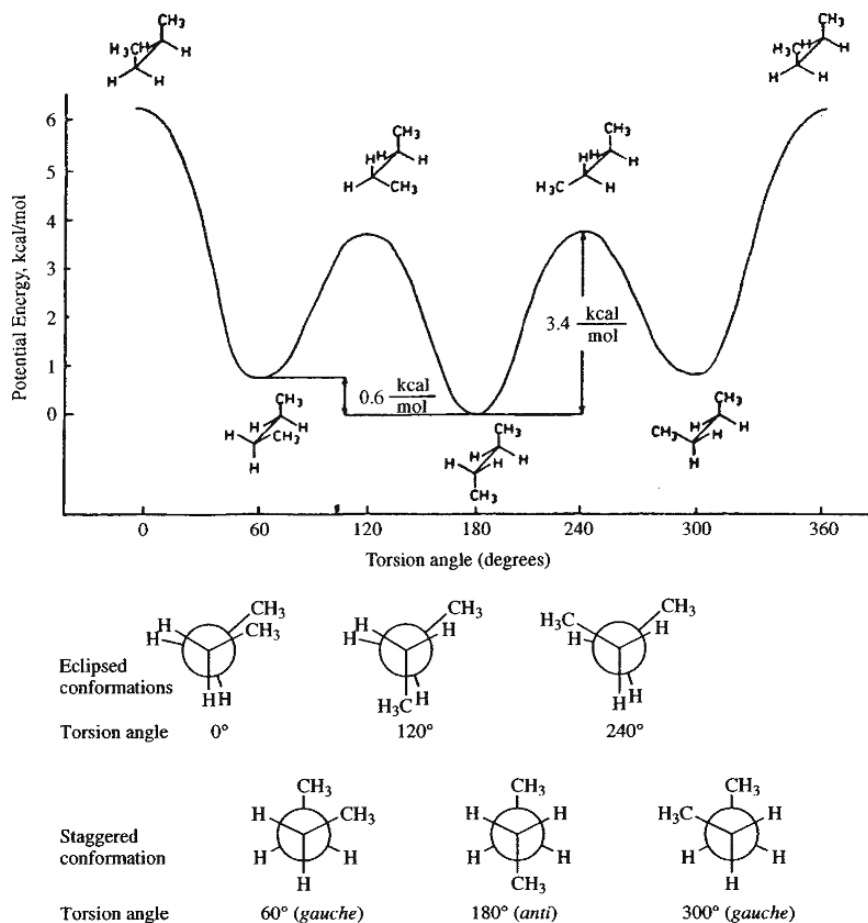


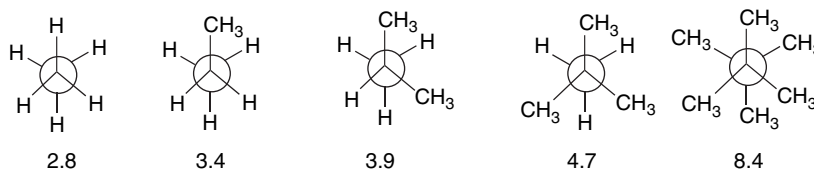
Fig. 2.11. Potential energy diagram for rotation about the C(2)–C(3) bond in *n*-butane.

eclipsed conformations all incorporate 2.8 kcal/mol of torsional strain relative to the staggered conformations, just as in ethane. The methyl-methyl eclipsed conformation is further strained by the van der Waals repulsion between the methyl groups. The van der Waals repulsion between methyl and hydrogen is smaller in the other eclipsed conformations. The methyl/methyl eclipsed barrier is not known precisely, but the range in experimental and theoretical values is between 4.0 and 6.6 kcal/mol, with the most recent values being at the low end of the range.¹⁷

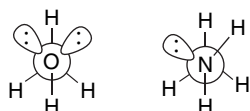
The conformation of other simple hydrocarbons can be interpreted by extensions of the principles illustrated in the analysis of rotational barriers in ethane and *n*-butane. The staggered conformations correspond to torsional minima and the eclipsed conformations to torsional maxima. Of the staggered conformations, *anti* forms are more stable than *gauche*. Substitution of a methyl group for hydrogen on one of the carbon atoms produces an increase of 0.4–0.6 kcal/mol in the height of the rotational energy barrier. The barrier in ethane is 2.88 kcal/mol. In propane, the barrier is 3.4 kcal/mol, corresponding to an increase of 0.5 kcal/mol for methyl-hydrogen eclipsing. When

¹⁷ N. L. Allinger, R. S. Grev, B. F. Yates, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **112**, 114 (1990); W. A. Herrebout, B. J. van der Veken, A. Wang, and J. R. Durig, *J. Phys. Chem.*, **99**, 578 (1995).

two methyl-hydrogen eclipsing interactions occur, as in 2-methylpropane, the barrier is raised to 3.9 kcal/mol. The increase in going to 2,2-dimethylpropane, in which the barrier is 4.7 kcal/mol, is 1.8 kcal/mol for the total of three methyl-hydrogen eclipsing interactions. For 2,2,3,3-tetramethylbutane, in which there are three methyl-methyl interactions, the barrier is 8.4 kcal/mol. Rotational barriers in kcal/mol are shown below.



The magnitudes of the barriers to rotation of many small organic molecules have been measured.¹⁸ The experimental techniques used to study rotational processes include microwave spectroscopy, electron diffraction, ultrasonic absorption, and infrared spectroscopy.¹⁹ Some representative barriers are listed in Table 2.1. As with ethane, the barriers in methylamine and methanol appear to be dominated by *hyperconjugative stabilization* of the *anti* conformation. The barrier decreases ($2.9 \rightarrow 2.0 \rightarrow 1.1$) in proportion to the number of anti H–H arrangements ($3 \rightarrow 2 \rightarrow 1$). (See Topic 1.1 for further discussion.)²⁰



The conformation of simple alkenes can be considered by beginning with propene. There are two families of conformations available to terminal alkenes: *eclipsed* and *bisected* conformations, as shown below for propene. The eclipsed conformation is preferred by about 2 kcal/mol and represents a barrier to rotation of the methyl group.^{21,22} A simple way to relate the propene rotational barrier to that of ethane is to regard the π bond as a “banana bond” (see p. 7). The bisected conformation of propene is then seen to correspond to the eclipsed conformation of ethane, while the more stable eclipsed conformation corresponds to the staggered conformation of ethane.²³

¹⁸. For reviews, see (a) J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968); (b) J. E. Andersen, in *The Chemistry of Alkenes and Cycloalkenes*, S. Patai and Z. Rappoport, eds., Wiley, Chichester, 1992, Chap. 3II. D.

¹⁹. Methods for determination of rotational barriers are discussed in Ref. 18a and by E. Wyn-Jones and R. A. Pethrick, *Top. Stereochem.*, **5**, 205 (1969).

²⁰. J. K. Badenhoop and F. Weinhold, *Int. J. Quantum Chem.*, **72**, 269 (1999); V. Pophristic and L. Goodman, *J. Phys. Chem. A.*, **106**, 1642 (2002).

²¹. J. R. Durig, G. A. Guirgis, and S. Bell, *J. Phys. Chem.*, **93**, 3487 (1989).

²². Detailed analysis of the rotation shows that it is coupled with vibrational processes. L. Goodman, T. Kundu, and J. Leszczynski, *J. Phys. Chem.*, **100**, 2770 (1996).

²³. K.-T. Lu, F. Weinhold, and J. C. Weisshaar, *J. Chem. Phys.*, **102**, 6787 (1995).

Table 2.1. Rotational Barriers of Compounds of Type $\text{CH}_3 - \text{X}^a$

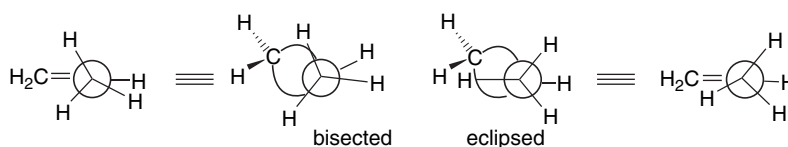
Alkanes ^a	Barrier (kcal/mol)	Heteroatom compounds	Barrier (kcal/mol)
$\text{CH}_3 - \text{CH}_3$	2.9	$\text{CH}_3 - \text{NH}_2^c$	2.0
$\text{CH}_3 - \text{CH}_2\text{CH}_3$	3.4	$\text{CH}_3 - \text{NHCH}_3^c$	3.0
$\text{CH}_3 - \text{CH}(\text{CH}_3)_2$	3.9	$\text{CH}_3 - \text{N}(\text{CH}_3)_2^c$	4.4
$\text{CH}_3 - \text{C}(\text{CH}_3)_3$	4.7	$\text{CH}_3 - \text{OH}^d$	1.1
$(\text{CH}_3)_3\text{C} - \text{C}(\text{CH}_3)_3$	8.4 ^b	$\text{CH}_3 - \text{OCH}_3^d$	4.6

a. Taken from the compilation of J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968).

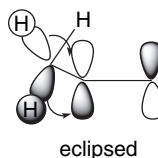
b. Footnote 9, J. E. Andersen, A. de Meijere, S. I. Kozhushkov, L. Lunazzi, and A. Mazzanti, *J. Org. Chem.*, **68**, 8494 (2003).

c. M. L. Senent and Y. G. Meyers, *J. Chem. Phys.*, **105**, 2789 (1996).

d. V. Pophristic, L. Goodman, and N. Guchhait, *J. Phys. Chem. A*, **101**, 4290 (1997).



The conformation of propene is influenced by hyperconjugation. The methyl substituent has an overall stabilizing effect (2.7 kcal) on the double bond, as can be concluded from the less negative heat of hydrogenation compared to ethene (see Section 3.1.1). This stabilization arises from $\sigma - \pi^*$ interactions. The major effect is a transfer of electron density from the methyl $\sigma \text{ C-H}$ bonds to the empty π^* orbital.

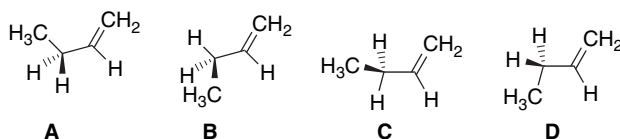


Computational approaches can provide an indication of the magnitude of the interaction. A “block-localized” wave function calculation estimates a stabilization of about 5.4 kcal/mol at the 6-31G** level.²⁴ The computation also shows a shortening of the C(2)–C(3) single bond as the result of the $\sigma - \pi^*$ delocalization. Because the extent of hyperconjugation differs between the two unique conformers, this factor contributes to the energy difference between them. The energy difference between the eclipsed and bisected conformations has been broken into components, as described for ethane in Topic 1.3. The hyperconjugation component is the major factor. At the MP2/6-311(3d,2p) level of computation, the $\text{CH}_3 - \text{C} =$ bond length is 1.4952 Å, versus 1.5042 Å in the staggered conformation. The corresponding difference in energy is the largest component of the energy barrier and results from adjustments in the bond length in response to the rotation.²⁵

²⁴. The block-localized calculations are conceptually similar to NBO analysis (see Section 1.4.2) in that they compare a calculation in which the orbitals are strictly localized with the unrestricted calculation to estimate the effect of delocalization. Y. Mo and S. D. Peyerimhoff, *J. Chem. Phys.*, **109**, 1687 (1998).

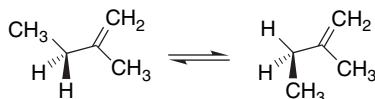
²⁵. T. Kundu, L. Goodman, and J. Leszczynski, *J. Chem. Phys.*, **103**, 1523 (1995).

With more highly substituted terminal alkenes, additional conformations are available, as indicated for 1-butene.

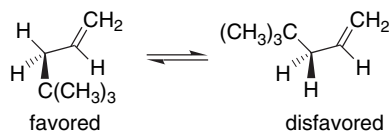


Conformations **A** and **B** are of the eclipsed type, whereas **C** and **D** are bisected. It has been determined by microwave spectroscopy that the eclipsed conformations are more stable than the bisected ones and that **B** is about 0.15 kcal more stable than **A**.²⁶ MO calculations at the HF/6-31G* level found relative energies of 0.00, -0.25, 1.75, and 1.74 kcal/mol, respectively, for **A**, **B**, **C**, and **D**.²⁷ More recently, experimental far-IR spectroscopy and MP2/6-31G++(3df,3pd) computations indicate a difference of about 0.2 kcal (favoring **B**).²⁸

Further substitution can introduce van der Waals repulsions that influence conformational equilibria. For example, methyl substitution at C(2), as in 2-methyl-1-butene, introduces a methyl-methyl *gauche* interaction in the conformation analogous to **B**, with the result that in 2-methyl-1-butene the two eclipsed conformations are of approximately equal energy.²⁹



Increasing the size of the group at C(3) increases the preference for the eclipsed conformation analogous to **B** at the expense of **A**. 4,4-Dimethyl-1-pentene exists mainly in the hydrogen-eclipsed conformation.



This interaction is an example of *1,3-allylic strain*.³⁰ This type of steric strain arises in eclipsed conformations when substituents on the double bond and the C(3) group, which are coplanar, are large enough to create a nonbonded repulsion. The conformation of alkenes is an important facet with regard to the stereoselectivity of addition

²⁶ S. Kondo, E. Hirota, and Y. Morino, *J. Mol. Spectrosc.*, **28**, 471 (1968).

²⁷ W. J. Hehre, J. A. Pople, and A. J. P. Devaquet, *J. Am. Chem. Soc.*, **98**, 664 (1976).

²⁸ S. Bell, B. R. Drew, G. A. Guirgis, and J. R. Daring, *J. Mol. Struct.*, **553**, 199 (2000).

²⁹ T. Shimanouchi, Y. Abe, and K. Kuchitsu, *J. Mol. Struct.*, **2**, 82 (1968).

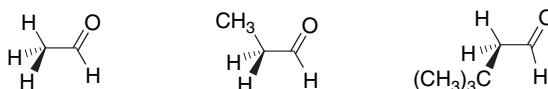
³⁰ R. W. Hoffmann, *Chem. Rev.*, **89**, 1841 (1989).

reactions of alkenes. Allylic strain and other conformational factors contribute to the relative energy of competing TSs, and can lead to a preference for a particular stereoisomeric product.

The preferred conformations of carbonyl compounds, like 1-alkenes, are eclipsed rather than bisected, as shown below for ethanal and propanal. The barrier for methyl group rotation in ethanal is 1.17 kcal/mol.³¹ Detailed analysis has indicated that small adjustments in molecular geometry, including σ -bond lengthening, must be taken into account to quantitatively analyze the barrier.³² The total barrier can be dissected into nuclear-nuclear, electron-electron, nuclear-electron, and kinetic energy (Δt), as described in Topic 1.3 for ethane. MP2/6-311+G (3df,2p) calculations lead to the contributions tabulated below. The total barrier found by this computational approach is very close to the experimental value. Contributions to the ethanal energy barrier in kcal/mol are shown below.

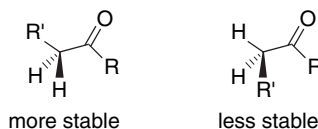
ΔV_{nn}	-10.621
ΔV_{ee}	-5.492
ΔV_{ne}	+18.260
Δt	-0.938
Δ total	+1.209

In propanal, it is the methyl group, rather than the hydrogen, that is eclipsed with the carbonyl group in the most stable conformation. The difference in the two eclipsed conformations has been determined by microwave spectroscopy to be 0.9 kcal/mol.³³ A number of other aldehydes have been studied by NMR and found to have similar rotameric compositions.³⁴ When the alkyl substituent becomes too sterically demanding, the hydrogen-eclipsed conformation becomes more stable. This is the case with 3,3-dimethylbutanal.



preferred conformations for ethanal, propanal, and 3, 3-dimethylbutanal

Ketones also favor eclipsed conformations. The preference is for the rotamer in which the alkyl group, rather than a hydrogen, is eclipsed with the carbonyl group because this conformation allows the two alkyl groups to be *anti* rather than *gauche* with respect to the other carbonyl substituent.



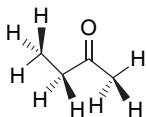
³¹ I. Kleiner, J. T. Hougen, R. D. Suenram, F. J. Lovas, and M. Godefroid *J. Mol. Spectros.*, 153, 578 (1992); S. P. Belov, M. Y. Tretyakov, I. Kleiner, and J. T. Hougen, *J. Mol. Spectros.*, 160, 61 (1993).

³² L. Goodman, T. Kundu, and J. Leszczynski, *J. Am. Chem. Soc.*, 117, 2082 (1995).

³³ S. S. Butcher and E. B. Wilson, Jr., *J. Chem. Phys.*, 40, 1671 (1964).

³⁴ G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.*, 87, 2864 (1965).

The conformational profile for 2-butanone has been developed from analysis of its infrared spectrum.³⁵ The dominant conformation is *anti* with a C(1)H and the C(4) methyl group eclipsed with the carbonyl.



The C(3)–C(4) rotational barrier is 2.48 kcal/mol, similar to the ethane barrier, while the C(1)–C(2) rotational barrier is 0.67 kcal/mol. Figure 2.12 shows the rotational potential energy diagram for 2-butanone as calculated at the HF/6-31G level. The preferred conformation of 3-methyl-2-butanone is similar.³⁶

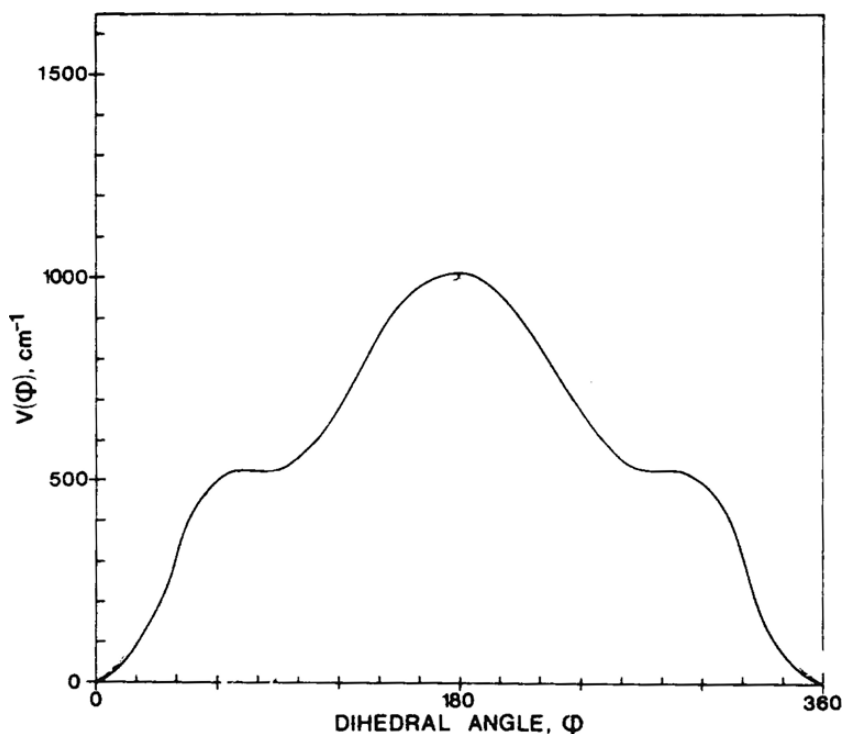
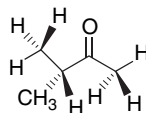


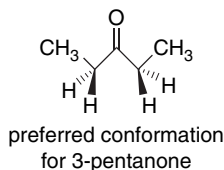
Fig. 2.12. Calculated potential energy diagram (HF/6-31G) for rotation about C(2)–C(3) bond of 2-butanone. Reproduced from *Can. J. Chem.* **69**, 1827 (1991), by permission of the National Research Council Press.

³⁵. J. R. Durig, F. S. Feng, A. Y. Wang, and H. V. Phan, *Can. J. Chem.*, **69**, 1827 (1991).

³⁶. T. Sakurai, M. Ishiyama, H. Takeuchi, K. Takeshita, K. Fukushi, and S. Konaka, *J. Mol. Struct.*, **213**, 245 (1989); J. R. Durig, S. Shen, C. Zeng, and G. A. Guirgis, *Can. J. Anal. Sci. Spectrosc.* **48**, 106 (2003).

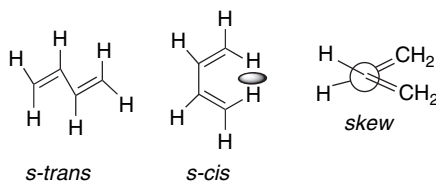


Moreover, electron diffraction studies of 3-pentanone indicate the methyl-eclipsed conformation shown below to be the most stable rotamer.³⁷



The pattern, then, is that methyl and unbranched alkyl groups prefer to be eclipsed with the carbonyl group.

1,3-Dienes adopt conformations in which the double bonds are coplanar, so as to permit optimum π -orbital overlap and electron delocalization. The two alternative planar conformations for 1,3-butadiene are referred to as *s-trans* and *s-cis*. In addition to the two planar conformations, there is a third conformation, referred to as the *skew* conformation, which is cisoid but not planar. Various types of structural studies have shown that the *s-trans* conformation is the most stable one for 1,3-butadiene.³⁸ A small amount of the skew conformation is also present in equilibrium with the major conformer.³⁹ The planar *s-cis* conformation incorporates a van der Waals repulsion between the hydrogens on C(1) and C(4), which is relieved in the skew conformation.



The barrier for conversion of the skew conformation to the *s-trans* is 3.9 kcal/mol. The energy maximum presumably refers to the conformation in which the two π bonds are mutually perpendicular. The height of this barrier gives an approximation of the stabilization provided by conjugation in the planar *s-trans* conformation. Various MO calculations find the *s-trans* conformation to be 2–5 kcal/mol lower in energy than either the planar or skew cisoid conformations.⁴⁰ Most high-level MO calculations

³⁷. C. Romers and J. E. G. Creutzberg, *Rec. Trav. Chim.*, **75**, 331 (1956).

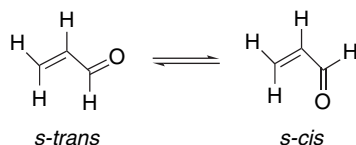
³⁸. A. Almennigen, O. Bastiansen, and M. Traetteburg, *Acta Chem. Scand.*, **12**, 1221 (1958); K. K. Kuchitsu, T. Fukuyama, and Y. Morino, *J. Mol. Struct.*, **1**, 643 (1967); R. L. Lipnick and E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **95**, 6370 (1973).

³⁹. K. B. Wiberg and R. E. Rosenberg, *J. Am. Chem. Soc.*, **112**, 1509 (1990).

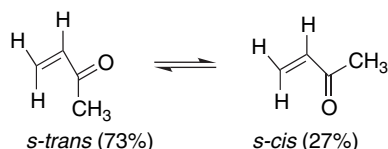
⁴⁰. A. J. P. Devaquet, R. E. Townshend, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4068 (1976); K. B. Wiberg, P. R. Rablen, and M. Marquez, *J. Am. Chem. Soc.*, **114**, 8654 (1992); M. Head-Gordon and J. A. Pople, *J. Phys. Chem.*, **97**, 1147 (1993).

favor the skew conformation over the planar *s-cis*, but the energy differences found are quite small.^{39,41}

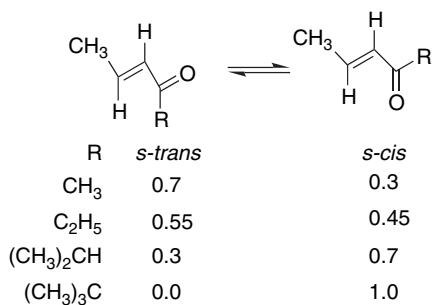
The case of α,β -unsaturated carbonyl compounds is analogous to that of 1,3-dienes, in that conjugation favors coplanarity of the $C=C-C=O$ system. The rotamers that are important are the *s-trans* and *s-cis* conformations. Microwave data indicate that the *s-trans* form is the only conformation present in detectable amounts in 2-propenal (acrolein).⁴²



The equilibrium distribution of *s-trans* and *s-cis* conformations of substituted α,β -unsaturated ketones depends on the extent of van der Waals interaction between the C(1) and the C(4) substituents.⁴³ Methyl vinyl ketone has the minimal unfavorable van der Waals repulsions and exists predominantly as the *s-trans* conformer.



When larger alkyl groups are substituted for methyl, the ratio of the *s-cis* form progressively increases as the size of the alkyl group increases.⁴⁴



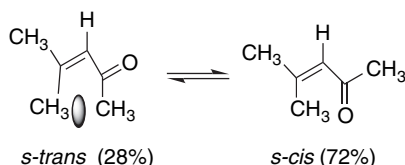
An unfavorable methyl-methyl interaction destabilizes the *s-trans* conformation of 4-methylpent-3-en-2-one (mesityl oxide) relative to the *s-cis* conformation, and the equilibrium favors the *s-cis* form.

⁴¹ J. Breulet, T. J. Lee, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **106**, 6250 (1984); D. Feller and E. R. Davidson, *Theor. Chim. Acta*, **68**, 57 (1985).

⁴² E. A. Cherniak and C. C. Costain, *J. Chem. Phys.*, **45**, 104 (1966).

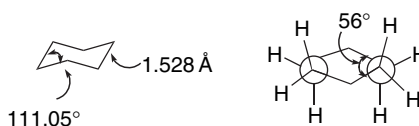
⁴³ G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, *J. Am. Chem. Soc.*, **95**, 6365 (1973).

⁴⁴ A. Bienvenue, *J. Am. Chem. Soc.*, **95**, 7345 (1973).



2.2.2. Conformations of Cyclohexane Derivatives

The conformational analysis of six-membered ring compounds is particularly well developed. Cyclohexane and its derivatives lend themselves to thorough analysis because they are characterized by a small number of energy minima. The most stable conformations are separated by barriers that are somewhat higher and more easily measured than rotational barriers in acyclic compounds or other ring systems. The most stable conformation of cyclohexane is the chair. Electron diffraction studies in the gas phase reveal a slight flattening of the chair, compared with the geometry obtained using tetrahedral molecular models. The torsion angles are 55.9° , compared with 60° for the “ideal” chair conformation, and the axial C–H bonds are not perfectly parallel, but are oriented outward by about 7° . The C–C bonds are $1.528 \text{ \AA}$, the C–H bonds are $1.119 \text{ \AA}$, and the C–C–C angles are 111.05° .⁴⁵

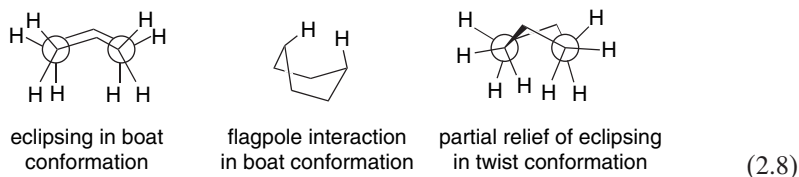


Two nonchair conformations of cyclohexane that have normal bond angles and bond lengths are the *twist* and the *boat*,⁴⁶ both of which are less stable than the chair. A direct measurement of the chair-twist energy difference has been made using low-temperature IR spectroscopy.⁴⁷ The chair was determined to be 5.5 kcal/mol lower in energy than the twist. The twist and the boat conformations are more flexible than the chair, but are destabilized by torsional strain, as the bonds along the “sides” of the boat are eclipsed. In addition, the boat conformation is further destabilized by a van der Waals repulsion between the “flagpole” hydrogens. Both this van der Waals repulsion and the torsional strain are somewhat reduced in the twist conformation.

⁴⁵ H. J. Geise, H. R. Buys, and F. C. Mijlhoff, *J. Mol. Struct.*, **9**, 447 (1971).

⁴⁶ For a review of nonchair conformations of six-membered rings, see G. M. Kellie and F. G. Riddell, *Top. Stereochem.* **8**, 225 (1974).

⁴⁷ M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, **97**, 3244 (1975).



Interconversion of chair forms is known as *conformational inversion*, and occurs by rotation about the carbon-carbon bonds. For cyclohexane, the first-order rate constant for ring inversion is 10^4 – 10^5 sec^{-1} at 27°C . The enthalpy of activation is 10.8 kcal/mol.⁴⁸ Calculation of the geometry of the transition state by *molecular mechanics* (see Section 2.3) suggests a half-twist form lying 12.0 kcal/mol above the chair. According to this analysis, the half-twist form incorporates 0.2 kcal/mol of strain from bond length deformation, 2.0 kcal/mol of bond angle strain, 4.4 kcal/mol of van der Waals strain, and 5.4 kcal/mol of torsional strain.⁴⁹ Figure 2.13 presents a two-dimensional energy diagram illustrating the process of conformational inversion in cyclohexane. The boat form is not shown in the diagram because the chair forms can interconvert without passing through the boat. The boat lies 1–2 kcal/mol above the twist conformation and is a transition state for interconversion of twist forms.⁵⁰

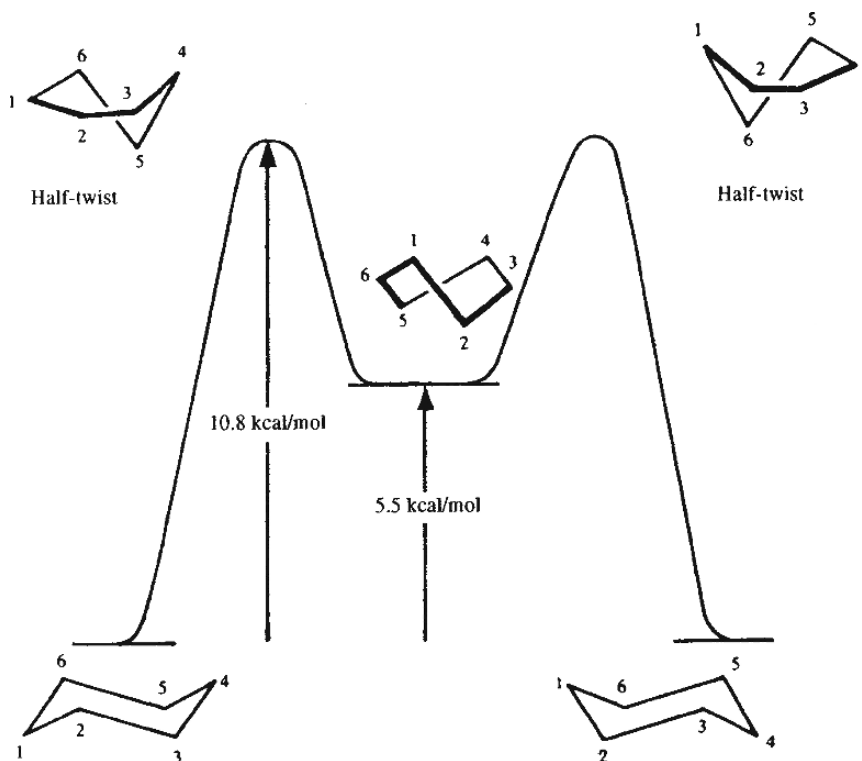


Fig. 2.13. Energy diagram for ring inversion of cyclohexane.

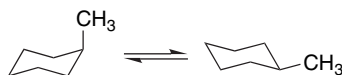
⁴⁸. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **89**, 760 (1967).

⁴⁹. N. L. Allinger, M. A. Miller, F. A. van Catledge, and J. A. Hirsch, *J. Am. Chem. Soc.*, **89**, 4345 (1967); N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1997).

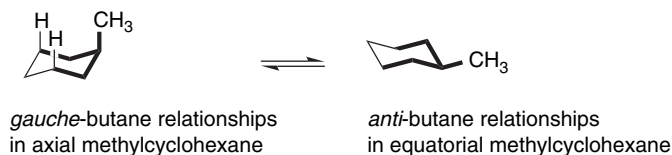
⁵⁰. N. Leventis, S. B. Hanna, and C. Sotiriou-Leventis, *J. Chem. Educ.* **74**, 813 (1997); R. R. Sauers, *J. Chem. Educ.* **77**, 332 (2000).

Visual models, additional information and exercises on Cyclohexane Conformations can be found in the Digital Resource available at: Springer.com/carey-sundberg.

Substitution on a cyclohexane ring does not greatly affect the rate of conformational inversion, but does change the equilibrium distribution between alternative chair forms. All substituents that are axial in one chair conformation become equatorial on ring inversion, and vice versa. For methylcyclohexane, ΔG for the equilibrium is -1.8 kcal/mol, corresponding to a composition with 95% of the equatorial methyl conformation.



Two factors contribute to the preference for the equatorial conformation. The equatorial methyl conformation corresponds to an *anti* arrangement with respect to the C(2)–C(3) and C(6)–C(5) bonds, whereas the axial methyl group is in a *gauche* relationship to these bonds. We saw earlier that the *gauche* conformation of *n*-butane is 0.5–0.6 kcal/mol higher in energy than the *anti* conformation. In addition, there is a van der Waals repulsion between the axial methyl group and the axial hydrogens at C(3) and C(5). Interactions of this type are called *1,3-diaxial interactions*.



Energy differences between conformations of substituted cyclohexanes can be measured by several methods, as can the kinetics of the ring inversion processes. NMR spectroscopy is especially valuable for both thermodynamic and kinetic studies.⁵¹ Depending on the rate of the process, the difference in chemical shift between the two sites and the field strength of the spectrometer, the observed spectrum will be either a weighted average spectrum (rapid site exchange, $k > 10^5 \text{ sec}^{-1}$) or a superposition of the spectra of the two conformers reflecting the equilibrium composition (slow site exchange, $k < 10^3 \text{ sec}^{-1}$). At intermediate rates of exchange, broadened spectra are observed. Analysis of the temperature dependence of the spectra can provide the activation parameters for the conformational process. Figure 2.14 illustrates the change in appearance of a simple spectrum.

For substituted cyclohexanes, the slow-exchange condition is met at temperatures below about -50°C . Data for the half-life for conformational equilibration of

⁵¹ G. Binsch, *Top. Stereochem.* **3**, 97 (1968); F. G. Riddell, *Nucl. Magn. Reson.*, **12**, 246 (1983); J. Sandstrom, *Dynamic NMR Spectroscopy*, Academic Press, New York, 1982; J. L. Marshall, *Nuclear Magnetic Resonance*, Verlag Chemie, Deerfield Beach, FL, 1983; M. Oki, *Applications of Dynamic NMR to Organic Chemistry*, VCH Publishers, Deerfield Beach, FL, 1985; Y. Takeuchi and A. P. Marchand, eds., *Applications of NMR Spectroscopy in Stereochemistry and Conformational Analysis*, VCH Publishers, Deerfield Beach, FL, 1986.

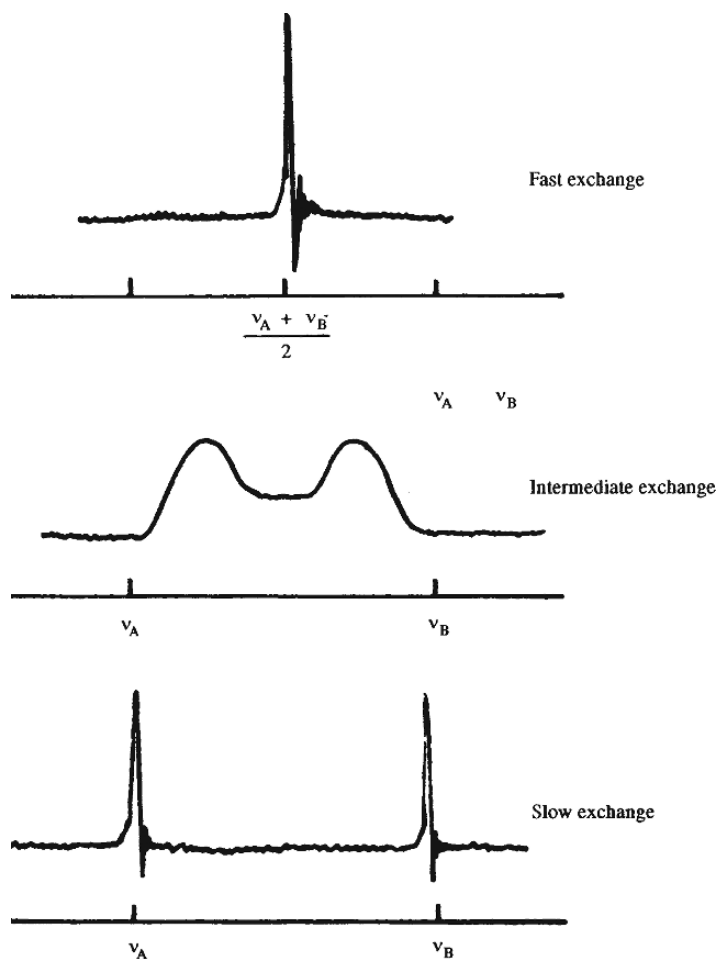


Fig. 2.14. Appearance of NMR spectra for system undergoing site exchange at various rates.

chlorocyclohexane as a function of temperature is shown below. From these data, it can be seen that conformationally pure solutions of equatorial chlorocyclohexane can be maintained at low temperature.⁵²

**Half-Life for Conformation Inversion
for Chlorocyclohexane at Various
Temperatures**

Temperature (°C)	Half-Life
25	1.3×10^{-5} s
-60	2.5×10^{-2} s
-120	23 min
-160	22 yr

⁵². F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.*, **91**, 3223 (1969).

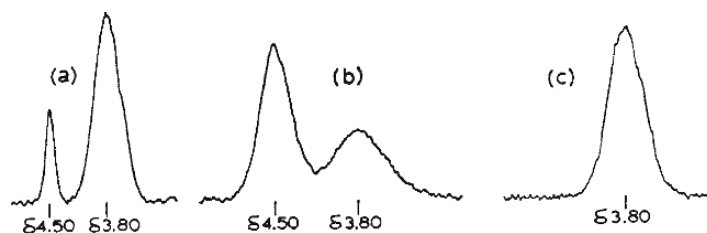
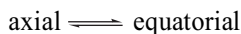


Fig. 2.15. 60-MHz ^1H -NMR spectrum for the C(1)H in chlorocyclohexane: (a) axial-equatorial equilibrium at -115°C ; (b) axial-enriched mixture at -150°C ; (c) pure equatorial conformer at -150°C . Reproduced from *J. Am. Chem. Soc.*, **91**, 3223 (1969), by permission of the American Chemical Society.

Crystallization of chlorocyclohexane at low temperature provided crystals containing only the equatorial isomer. When the solid is dissolved at -150°C , the NMR spectrum of the solution exhibits only the signal characteristic of the equatorial conformer. When the solution is warmed to -115° , the conformational equilibrium is reestablished. The appearance of the 60-MHz spectrum of the $\text{H}-\text{C}-\text{Cl}$ hydrogen is shown in Figure 2.15.

The free-energy difference between conformers is referred to as the *conformational free energy*. For substituted cyclohexanes it is conventional to specify the value of $-\Delta G_c$ for the equilibrium:



As ΔG_c is negative when the equatorial conformation is more stable than the axial, the value of $-\Delta G_c$ is positive for groups that favor the equatorial position. The larger the $-\Delta G_c$, the greater the preference for the equatorial position.

The case of iodocyclohexane provides an example of the use of NMR spectroscopy to determine the conformational equilibrium constant and the value of $-\Delta G_c$. At -80°C , the NMR shows two distinct peaks in the area of the CHI signal as shown in Figure 2.16.⁵³ The multiplet at higher field is a triplet of triplets with coupling constants of 3.5 and 12 Hz. This pattern is characteristic of a hydrogen in an axial position with two axial-axial couplings and two axial-equatorial couplings. The broader peak at lower field is characteristic of a proton at an equatorial position and reflects the four equatorial-equatorial couplings of such a proton. The relative area of the two peaks is 3.4:1 in favor of the conformer with the axial hydrogen. This corresponds to a $-\Delta G_c$ value of 0.47 kcal/mol for the iodo substituent.

Another method for measuring conformational free energies involves establishing an equilibrium between diastereomers differing only in the orientation of the designated substituent group. The equilibrium constant can then be determined and used to calculate the free-energy difference between the isomers. For example, *cis*- and *trans*-*t*-butylcyclohexanol can be equilibrated using a nickel catalyst in refluxing benzene to give a mixture containing 28% *cis*-4-*t*-butylcyclohexanol and 72% *trans*-*t*-butylcyclohexanol.⁵⁴

⁵³ F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.*, **91**, 334 (1969).

⁵⁴ E. L. Eliel and S. H. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965).

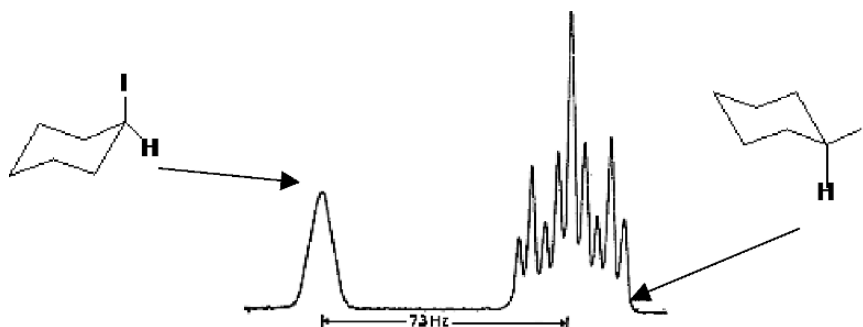
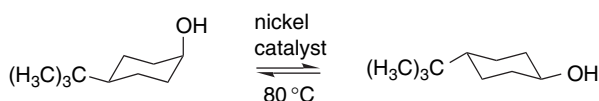


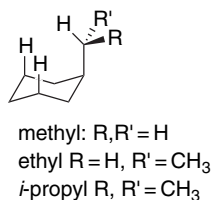
Fig. 2.16. NMR spectrum of iodocyclohexane at -80°C . Only the low field CHI signal is shown (100 MHz). Reproduced from *J. Am. Chem. Soc.*, **91**, 344 (1969), by permission of the American Chemical Society.



Assuming that only conformations that have the *t*-butyl group equatorial are significant, the free-energy change for the equilibration is equal to the free-energy difference between an axial and equatorial hydroxy group. The equilibrium constant leads to a value of $-\Delta G_c = 0.7 \text{ kcal/mol}$ for the hydroxy substituent. This approach also assumes that the *t*-butyl group does not distort the ring or interact directly with the hydroxy group.

There are several other methods available for determining conformational free energies.⁵⁵ Values for many substituents in addition to those listed in Table 2.2 have been compiled.⁵⁶

The methyl, ethyl, and isopropyl groups have similar conformational energies, with isopropyl being only slightly greater than methyl and ethyl. The similar values for the three substituents reflects the fact that rotation about the bond between the substituent and the ring allows each group to adopt a conformation that minimizes the effect of the additional methyl substituent in the ethyl and isopropyl groups.



A *t*-butyl substituent in the axial orientation experiences a strong van der Waals repulsion with the *syn*-axial hydrogens that cannot be relieved by rotation about the bond to the ring. As a result, the $-\Delta G_c$ value for *t*-butyl group is much larger than for the other alkyl groups. A value of about 5 kcal/mol has been calculated by *molecular*

⁵⁵ F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 139 (1971).

⁵⁶ E. L. Eliel, S. H. Wilen, and L. N. Mander *Stereochemistry of Organic Compounds*, Wiley, New York, 1993, pp. 696–697.

Table 2.2. Conformational Free Energies ($-\Delta G_c$) for Some Substituent Groups^a

Substituent	$-\Delta G_c$	Substituent	$-\Delta G_c$
F	0.26 ^b	C ₆ H ₅	2.9 ^c
Cl	0.53 ^b	CN	0.2 ^b
I	0.47 ^b	CH ₃ CO ₂	0.71 ^b
CH ₃	1.8 ^c	HO ₂ C	1.35 ^d
CH ₃ CH ₂	1.8 ^c	C ₂ H ₅ O ₂ C	1.1–1.2 ^d
(CH ₃) ₂ CH	2.1 ^c	HO (aprotic solvent)	0.52 ^d
(CH ₃) ₃ C	> 4.7 ^d	HO (protic solvent)	0.87 ^d
CH ₂ =CH	1.7 ^c	CH ₃ O	0.60 ^d
HC≡C	0.5 ^f	O ₂ N	1.16 ^b

a. For a more extensive compilation see E. L. Eliel, S. H. Wilen, and L. N. Mander

Stereochemistry of Organic Compounds, Wiley, New York, 1993, pp. 696–697.

b. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.*, **3**, 140 (1971).

c. N. L. Allinger and L. A. Freiburg, *J. Org. Chem.*, **31**, 804 (1966).

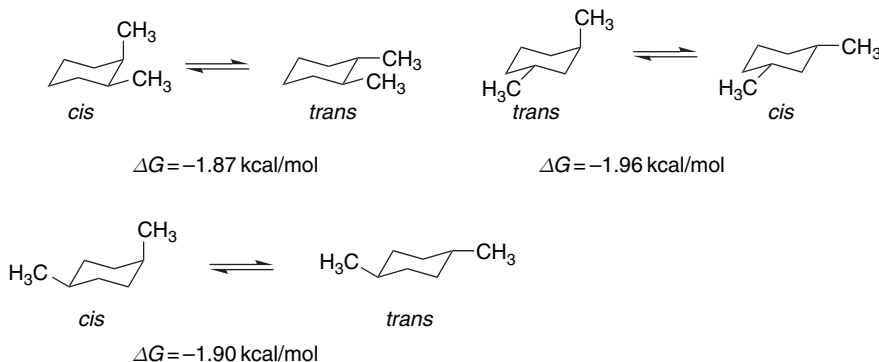
d. J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).

e. E. L. Eliel and M. Manoharan, *J. Org. Chem.*, **46**, 1959 (1981).

mechanics.⁵⁷ Experimental attempts to measure the $-\Delta G_c$ value for *t*-butyl have provided only a lower limit, because very little of the axial conformation is present and the energy difference is similar to that between the chair and twist forms of the cyclohexane ring.

The strong preference for a *t*-butyl group to occupy the equatorial position makes it a useful group for the study of *conformationally biased systems*. A *t*-butyl substituent ensures that the conformational equilibrium lies heavily to the side having the *t*-butyl group equatorial but does not stop the process of conformational inversion. It should be emphasized that “conformationally biased” is not synonymous with “conformationally locked.” Because ring inversion can still occur, it is incorrect to think of the systems being “locked” in a single conformation.

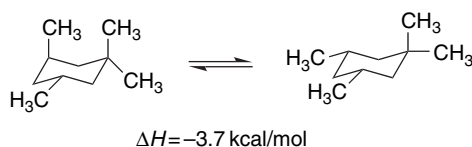
When two or more substituents are present on a cyclohexane ring, the interactions between the substituents must be included in the analysis. The dimethylcyclohexanes provide a case in which a straightforward interpretation is in good agreement with the experimental data. The ΔG of the equilibrium for the *cis* $\rightleftharpoons$ *trans* isomerization is given for 1,2-, 1,3-, and 1,4-dimethylcyclohexane.⁴⁹



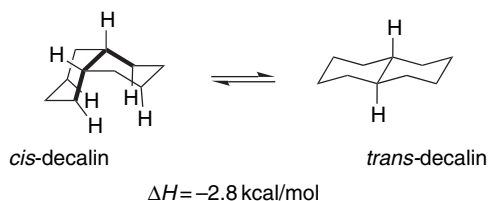
⁵⁷ N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. VanCatledge, *J. Am. Chem. Soc.*, **90**, 1199 (1968); B. van de Graf, J. M. A. Baas, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **97**, 268 (1978); J. M. A. Baas, A. van Veen, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **99**, 228 (1980); S. Antunez and E. Juaristi, *J. Org. Chem.*, **61**, 6465 (1996).

The more stable diastereomer in each case is the one in which both methyl groups are equatorial. The ΔG difference favoring the diequatorial isomer is about the same for each case (about 1.9 kcal/mol) and is very close to the $-\Delta G_c$ value of the methyl group (1.8 kcal/mol). This implies that there are no important interactions present that are not also present in methylcyclohexane. This is reasonable since in each case the axial methyl group interacts only with the 3,5-diaxial hydrogens, just as in methylcyclohexane. Moreover, both of the 1,2-dimethyl isomers have similar *gauche* interactions between the two methyl groups.

Conformations in which there is a 1,3-diaxial interaction between substituent groups *larger than hydrogen* are destabilized by van der Waals repulsion. Equilibration of *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane, for example, results in a mixture favoring the *cis* isomer by 3.7 kcal/mol.⁵⁸ This provides a value for a 1,3-diaxial methyl-methyl interaction that is 1.9 kcal/mol higher than the 1,3-methyl-hydrogen interaction.



The decalin (decahydronaphthalene) ring provides another important system for the study of conformational effects in cyclohexane rings. Equilibration of the *cis* and *trans* isomers favors the *trans* isomer by about 2.8 kcal/mol. Note that this represents a change in configuration, not conformation. The energy difference can be analyzed by noting that the *cis* isomer has an inter-ring *gauche*-butane interaction that is not present in the *trans* isomer. There are also cross-ring interactions between the axial hydrogens on the concave surface of the molecule.

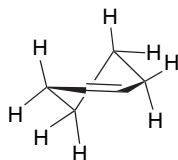


There is an important difference between the *cis*- and *trans*-decalin systems with respect to their conformational flexibility. Owing to the nature of its ring fusion, *trans*-decalin is incapable of chair-chair inversion; *cis*-decalin is conformationally mobile and undergoes ring inversion at a rate only slightly slower than cyclohexane ($\Delta G^\ddagger = 12.3\text{--}12.4 \text{ kcal/mol}$).⁵⁹ The *trans*-decalin system is a “conformationally locked” system and can be used to compare properties and reactivity of groups in axial or equatorial environments.

⁵⁸. N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

⁵⁹. F. R. Jensen and B. H. Beck, *Tetrahedron Lett.*, 4523 (1966); D. K. Dalling, D. M. Grant, and L. F. Johnson, *J. Am. Chem. Soc.*, **93**, 367 (1971); B. E. Mann, *J. Magn. Resonance*, **21**, 17 (1976).

The effect of introducing sp^2 -hybridized atoms into acyclic molecules was discussed in Section 2.2.1, and it was noted that torsional barriers in 1-alkenes and aldehydes are somewhat smaller than in alkanes. Similar effects are seen when sp^2 centers are incorporated into six-membered rings. Whereas the energy barrier for ring inversion in cyclohexane is 10.3 kcal/mol, it is reduced to 7.7 kcal/mol in methylenecyclohexane⁶⁰ and to 4.9 kcal/mol in cyclohexanone.⁶¹ The conformation of cyclohexene is described as a half-chair. Structural parameters determined on the basis of electron diffraction and microwave spectroscopy reveal that the double bond can be accommodated into the ring without serious distortion. The C(1)–C(2) bond length is 1.335 Å, and the C(1)–C(2)–C(3) bond angle is 123°. ⁶² The substituents at C(3) and C(6) are tilted from the usual axial and equatorial directions and are referred to as *pseudoaxial* and *pseudoequatorial*.



half-chair conformation
of cyclohexene

There have been both experimental and theoretical studies of the conformational process. According to NMR studies, the E_a for ring inversion is 5.3 kcal/mol.⁶³ An IR study gave a significantly higher barrier of about 10 kcal/mol.⁶⁴ A more recent theoretical study using both MO and DFT calculations found the barrier to be about 5.5–6.0 kcal/mol.⁶⁵ The preference for equatorial orientation of a methyl group in cyclohexene is less than in cyclohexane, because of the ring distortion and the removal of one 1,3-diaxial interaction. A value of 1 kcal/mol has been suggested for the $-\Delta G_c$ value for a methyl group in 4-methylcyclohexene.⁶⁶

Alkylidenecyclohexanes bearing alkyl groups of moderate size at C(2) tend to adopt the conformation with the alkyl group axial, in order to relieve unfavorable interactions with the alkylidene group. This results from van der Waals repulsion between the alkyl group in the equatorial position and *cis* substituents on the exocyclic

⁶⁰ J. T. Gerig, *J. Am. Chem. Soc.*, **90**, 1065 (1968).

⁶¹ F. R. Jensen and B. H. Beck, *J. Am. Chem. Soc.*, **90**, 1066 (1968).

⁶² J. F. Chiang and S. H. Bauer, *J. Am. Chem. Soc.*, **91**, 1898 (1969); L. H. Scharpen, J. E. Wollrab, and D. P. Ames, *J. Chem. Phys.*, **49**, 2368 (1968).

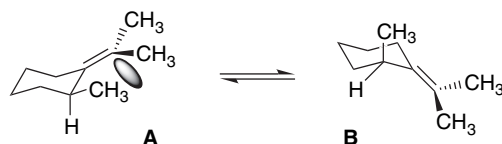
⁶³ F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.*, **87**, 3147 (1965).

⁶⁴ V. E. Rivera-Gaines, S. J. Leibowitz, and J. Laane, *J. Am. Chem. Soc.*, **113**, 9735 (1991).

⁶⁵ S. V. Shishkina, O. V. Shiskin, and J. Leszczynski, *Chem. Phys. Lett.*, **354**, 428 (2002).

⁶⁶ B. Rickborn and S.-Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

double bond, and is an example of 1,3-allylic strain.⁶⁷ The repulsive energy is small for methylenecyclohexanes, but molecular mechanics calculations indicate that the axial conformation **B** is 2.6 kcal/mol more stable than **A** with an exocyclic isopropylidene group.⁶⁸



An alkyl group at C(2) of a cyclohexanone ring is more stable in the equatorial than in the axial orientation. The equatorial orientation is eclipsed with the carbonyl group and corresponds to the more stable conformation of open-chain ketones (see p. 148). This conformation also avoids 3,5-diaxial interactions with *syn*-diaxial hydrogens. Conformational free energies ($-\Delta G_c$) for 2-alkyl substituents in cyclohexanones have been determined by equilibration studies. The value for the methyl group is similar to cyclohexanes, whereas the values for ethyl and isopropyl are somewhat smaller. This is attributed to a compensating repulsive steric interaction with the carbonyl oxygen for the larger substituents.⁶⁹



The $-\Delta G_c$ of an alkyl group at C(3) of cyclohexanone is less than that of a alkyl group in cyclohexane because of reduced 1,3-diaxial interactions. A C(3) methyl group in cyclohexanone has a $-\Delta G_c$ of 1.3–1.4 kcal/mol.⁵⁴

2.2.3. Conformations of Carbocyclic Rings of Other Sizes

The most important structural features that influence the conformation and reactivity of cycloalkanes differ depending on whether small (cyclopropane and cyclobutane), common (cyclopentane, cyclohexane, and cycloheptane), medium (cyclooctane through cycloundecane), or large (cyclododecane and up) rings are

⁶⁷ F. Johnson, *Chem. Rev.* **68**, 375 (1968); R. W. Hoffmann, *Chem. Rev.*, **89**, 1841 (1989).

⁶⁸ N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968); P. W. Rabideau, ed., *The Conformational Analysis of Cyclohexenes, Cyclohexadiene and Related Hydroaromatic Compounds*, VCH Publishers, Weinheim, 1989.

⁶⁹ N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961); B. Rickborn, *J. Am. Chem. Soc.*, **84**, 2414 (1962); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience, New York, 1965, pp. 113–114.