FRANCIS A. CAREY
and RICHARD J. SUNDBERG

ADVANCED ORGANIC CHEMISTRY

SECOND EDITION

Part A: Structure and Mechanisms

Advanced Organic Chemistry

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PART B: Reactions and Synthesis

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Preface to the Second Edition

The purpose of this edition is the same as that of the first edition, that is, to provide a deeper understanding of the *structures* of organic compounds and the *mechanisms* of organic reactions. The level is aimed at advanced undergraduates and beginning graduate students. Our goal is to solidify the student's understanding of basic concepts provided in an introduction to organic chemistry and to fill in much more information and detail, including quantitative information, than can be presented in the first course in organic chemistry.

The first three chapters consider the fundamental topics of bonding theory, stereochemistry, and conformation. Chapter 4 discusses the techniques that are used to study and characterize reaction mechanisms. The remaining chapters consider basic reaction types with a broad coverage of substituent effects and stereochemistry being provided so that each reaction can be described in good, if not entirely complete, detail.

The organization is very similar to the first edition with only a relative shift in emphasis having been made. The major change is the more general application of qualitative molecular orbital theory in presenting the structural basis of substituent and stereoelectronic effects. The primary research literature now uses molecular orbital approaches very widely, while resonance theory serves as the primary tool for explanation of structural and substituent effects at the introductory level. Our intention is to illustrate the use of both types of interpretation, with the goal of facilitating the student's ability to understand and apply the molecular orbital concepts now widely in use.

As in the first edition, the specific reactions discussed have been chosen to illustrate a point and no effort has been made to trace the origin of a particular explanation or observation. Thus references to a particular example do not imply any indication of priority. We have also tried to cite references to reviews which will give readers the opportunity to consider specific reactions from a much more comprehensive and detailed point of view than is possible in this text.

Some of the problems are new. The general level is similar to that in the first edition and it is expected that most of the problems will present a considerable degree of challenge to the typical student, since most represent application of the ideas presented in the text to different systems and circumstances, rather than review or repetition of the material which was explicitly presented in the text. References to the literature material upon which the problems are based are given at the end of the book for nearly all the problems.

The companion volume, Part B, has also been substantially revised to reflect the major developments in synthetic procedures that have taken place since the initial material was prepared. Part B extends the material of Part A with particular emphasis on the synthetic application of organic reactions. We believe that the material in Parts A and B can serve to prepare students to assimilate and apply the extensive primary and review literature of organic chemistry.

We thank colleagues who have provided comments and encouragement regarding the first edition. We hope that we will continue to receive suggestions concerning the organization and presentation of the material and also information concerning errors and omissions.

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Charlottesville, Virginia
January 1983

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Chemical Bonding and Molecular Structure

Introduction

Organic chemistry is a broad field which includes activities that intersect with such diverse areas as biology, medicine and pharmacology, materials science, chemical and petroleum engineering, and fundamental studies of molecular structure. The purpose of this text is to provide coverage of a central core of organic chemistry. This core of knowledge can be applied within organic chemistry or to other fields, such as those named above, which require significant contributions from organic chemistry. One organizational approach to organic chemistry divides it into three main areas. These areas are *structure*, *dynamics*, and *synthesis*. *Structure* includes the description of organic molecules and the methods for determining, analyzing, and predicting molecular geometry and bonding. *Dynamics* refers to the chemical and physical properties and transformations of molecules. *Synthesis* includes those activities which permit chemists to assemble new molecules and to convert existing substances into new compounds. These three areas are all interrelated, but synthesis is built on knowledge of both structure and reactions (chemical dynamics), while understanding dynamic processes ultimately rests on detailed knowledge about molecular structure. A firm grounding in the principles of structure and chemical bonding is therefore an essential starting point for fuller appreciation of dynamics and synthesis. In this first chapter we will discuss the ideas that have proven most useful to organic chemists for describing and correlating facts, concepts, and theories about the structure of organic molecules.

Structural formulas serve as key devices for communication of chemical information, but it is important to recognize at the outset that the relationship of a structural formula to molecular structure is a symbolic one. The current system of structural

formulas arose largely as a result of chemistry done in the last half of the nineteenth century. Elemental analyses, interrelation of various compounds, and systematic investigation of the reactivity of various "functional groups" permitted organic chemists to deduce correctly much information about molecular structure. For many molecules, it became possible to draw conclusions as to which atoms were directly connected. Lines drawn between atoms were used to represent direct connections or bonds. It also came to be recognized that the various elements could accommodate characteristic numbers of bonds. The capacity of an element to form bonds was called valence and the number of bonds a given element could form was called its *valence number.* These structural deductions predated modern concepts of atomic and molecular structure and of the nature of the forces that bind atoms. With the advent of quantum mechanics and new experimental techniques for accurate determination of such basic structural parameters as bond lengths and bond angles, structural formulas have taken on added significance as symbols and have been joined by other devices, including molecular models, stereoscopic drawings, and computer-drawn graphic displays of atomic positions and electron distribution. Regardless of the ingenuity with which a structural formula or other model is designed and constructed, it is still only a representation of a molecule, exaggerating certain features while minimizing others. Quantum theory, especially as applied by molecular orbital methods, has provided mathematical models of molecules which may be expressed numerically or as graphic descriptions of orbitals and electron density. These mathematical models also are only approximate representations of molecules as they truly are, since the quantum mechanical description of all organic molecules requires significant approximations to permit mathematical solution.

Theories of bonding attempt to describe the nature of chemical bonding both qualitatively and quantitatively. These theories, especially as they apply to organic chemistry, are the subject of this chapter.

1.1. Valence Bond Approach to Chemical Bonding

The idea put forth by G. N. Lewis in 1916 that chemical bonding could result from a sharing of electron pairs between two atoms was a fundamental advance.[1] Lewis' suggestion was largely intuitive, but was put on the sound ground of quantum mechanics with Heitler and London's treatment of the hydrogen molecule in 1927. This treatment marked the beginning of what we now know as *valence bond theory.*[2] An important feature of this theory was the conclusion that most of the binding

1. G. N. Lewis, *J. Am. Chem. Soc.* **38**, 762 (1916).
2. W. Heitler and F. London, Z. Phys. **44**, 455 (1927). For a historical review, see M. Simonetta, in *Structural Chemistry and Molecular Biology*, A. Rich and N. Davidson (eds.), W. H. Freeman, San Francisco, 1968, pp. 769–782.

energy between two atoms at their equilibrium internuclear distance results from exchange (resonance) of the electrons between the two nuclei. This conclusion arose in a natural way from the Heitler–London calculations. If electron 1 were constrained to association only with nucleus 1, and electron 2 with nucleus 2, then the calculated binding energy was a small fraction of the experimentally determined bond energy. If this constraint were removed so that the electrons were indistinguishable and permitted to interact equally with both nuclei, the calculated potential energy curve exhibited a deep minimum at the equilibrium internuclear distance. The energy difference associated with this minimum corresponded quite well with the experimental bond energy. The covalent bond represented by a line in the simple notation H–H then took on more precise meaning. It symbolized the presence of two bonding electrons in the region between the two nuclei. The region of space occupied by an electron is called an orbital and in the H_2 molecule the bonding arises from the two electrons in an orbital formed by overlap of the spherically symmetrical $1s$ atomic orbital of each hydrogen atom. Similarly, the bonding orbitals of other molecules must arise from the atomic orbitals of the constituent atoms.

Application of valence bond theory to more complex molecules usually proceeds by writing as many plausible Lewis structures as possible, and assuming that the actual molecule is a hybrid of these "canonical forms." The molecular wave function is then given by the summation of the products of the individual wave functions and weighting factors proportional to the contribution of the canonical forms to the overall structure. As a simple example, the hydrogen chloride molecule would be considered a hybrid of the limiting canonical forms H–Cl, H^+Cl^-, and H^-Cl^+. The mathematical treatment of molecular structure in terms of valence bond theory can be expanded to encompass more complex molecules. However, as the number of atoms and electrons increases the mathematical expression of the structure, the wave function, rapidly becomes complex. For this reason, qualitative concepts which arise from the valence bond treatment of simple molecules have been applied to larger molecules. The key ideas which are used to adapt the concepts of valence bond theory to complex molecules are *hybridization* and *resonance.* In this qualitative form, valence bond theory describes molecules in terms of orbitals which are mainly localized between two atoms. The shapes of these orbitals are assumed to be similar to orbitals described by more quantitative treatment of simpler molecules.

The concepts of *directed valence* and *orbital hybridization* were developed by Linus Pauling soon after the description of the hydrogen molecule by the valence bond theory. These concepts were applied to a question of specific concern to organic chemistry, the tetrahedral orientation of the bonds to carbon.[3] Pauling reasoned that since covalent bonds require mutual overlap of orbitals, stronger bonds result from better overlap. Orbitals that possess directional properties such as p orbitals should therefore be more effective than spherically symmetric s orbitals.

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

Fig. 1.1. Idealized view of σ-bond formation by overlap of (a) an s and a p orbital and (b) two p orbitals.

Covalent bond formation between two atoms involving overlap of a p orbital of one atom with an s or p orbital of another is illustrated in Fig. 1.1. The electron distribution that results is cylindrically symmetric with respect to the internuclear axis and defines a σ bond.

The electronic configuration of carbon in its ground state, established unambiguously by spectroscopic measurements as $1s^2$, $2s^2$, $2p^2$, precluded a simple rationalization of the bonding in organic compounds in terms of the atomic orbitals of the ground state carbon atom. Pauling suggested that the four valence orbitals ($2s$, $2p_x$, $2p_y$, $2p_z$) were replaced by a set of four equivalent hybrid orbitals, designated sp^3. The approximate shapes of these orbitals are shown in Fig. 1.2. Notice particularly that the probability distribution is highly directional for the sp^3 orbital, with the region of greatest probability concentrated on one side of the nucleus.

Orbital hybridization has two important consequences: First, four bonds, rather than two, may be formed to carbon. Second, the highly directional sp^3 orbitals provide for more efficient overlap. Thus, although carbon with one electron in each of four equivalent sp^3-hybridized orbitals would be of higher energy than the spectroscopic ground state, the energy required in a formal sense to promote two electrons from a $2s$ orbital to sp^3 orbitals is more than compensated for by the formation of four bonds rather than two, each of which is stronger due to the directional properties of the hybrid orbitals. Tetrahedral geometry is predicted by the mathematical description of hybridization. Methane, with four identical ligands to carbon, is a perfect tetrahedron, with each H–C–H angle equal to 109.5°.

The descriptive valence bond approach to the bonding in ethylene and acetylene and their congeners is analogous to that of methane. In ethylene (Fig. 1.3), each carbon bears three ligands and sp^2 hybridization, wherein three sp^2 orbitals are

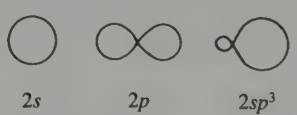


Fig. 1.2. Cross section of angular dependence of orbitals.

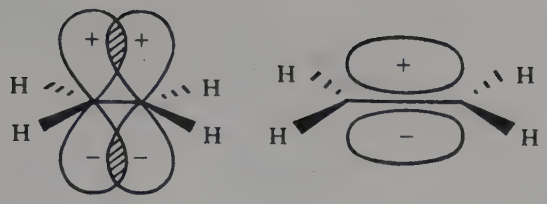


Fig. 1.3. The π bond in ethylene.

generated from the $2s$ and two of the $2p$ orbitals, is invoked. The three sp^2 orbitals are coplanar and orthogonal to the remaining $2p$ orbital. A σ bond is formed between the two carbon atoms by overlap of an sp^2 orbital of each. The four hydrogens are bonded by σ-bonds involving hydrogen $1s$ orbitals and the remaining sets of two sp^2 hybrids. Additional bonding between the two carbon atoms is portrayed as resulting from overlap of the nonhybridized p orbitals on each carbon atom, each of which contains one electron. This overlap is somewhat less efficient than that of the σ bond and defines a π bond. The electron distribution in a π bond is concentrated above and below the plane of the σ framework. The molecule is planar, and the plane defined by the nuclei represents a nodel plane for the π system. The probability of finding an electron associated with a π system in this plane is zero.

The hybridization at each carbon atom of acetylene is sp, and the two carbon atoms are considered as bonded by a σ bond and two π bonds, as shown in Fig. 1.4.

The relation between the number of ligands on carbon (its coordination number), hybridization, and molecular geometry is summarized in Table 1.1.

Unless all the ligands on a particular carbon atom are identical, there will be deviations from perfectly symmetrical structures. In contrast to methane and carbon tetrachloride, where the bond angles are 109.5°, the C–C–C angle in cyclohexane is 111.5°. The H–C–H angle in formaldehyde is 118°, rather than 120°. Benzene, however, is a regular hexagon with 120° bond angles.

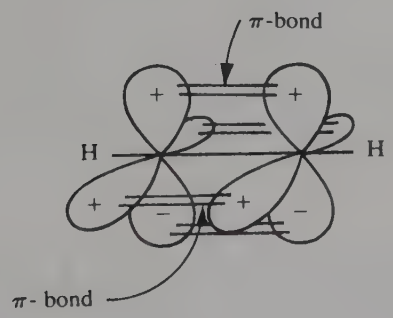


Fig. 1.4. π-Bonding in acetylene.

Table 1.1. Dependence of Structure on Hybridization of Carbon

Number of ligands	Hybridization	Geometry	Examples
4	sp^3	Tetrahedral	Methane, cyclohexane, methanol, carbon tetrachloride
3	sp^2	Trigonal	Ethylene, formaldehyde, benzene methyl cation, carbonate ion
2	sp	Linear	Acetylene, carbon dioxide, hydrogen cyanide, allene

Significant deviations in bond angles are found in cyclopropanes, cyclobutanes, and bicyclic molecules. The additional energy introduced into these molecules relative to corresponding open chain species is referred to as *angle strain*. Since the three carbon atoms of a cyclopropane are required by geometry to be the vertices of an equilateral triangle, the internuclear angles are 60°. This arrangement represents a serious distortion of the normal tetrahedral angle and engenders certain unique chemical and physical properties. In order to develop a model to describe the bonding in cyclopropane, it is assumed that any carbon atom will adopt that hybridization that produces the most stable bonding arrangement.[4] The orbitals used for forming the carbon–carbon bonds in cyclopropane can overlap more effectively if they have more p character than a normal sp^3 bond, since additional p character corresponds to a reduced bond angle. Consequently, the orbitals used for bonding to hydrogen must have increased s-character. Attempts to describe this adjustment in hybridization quantitatively have led to assignment of numerical values to the "percent s character" in the C–H bonds. The values of 33% and 17%, respectively, have been suggested for the C–H and C–C bonds of cyclopropane on the basis of nuclear magnetic resonance (NMR) measurements.[5] The picture that emerges for cyclopropane is one in which the region of maximum orbital overlap does not correspond to the internuclear axis, and the C–C bonds are described as "bent bonds" (Fig. 1.5). The terms *internuclear angle* and *interorbital angle* are in most cases synonymous, but this coincidence breaks down in compounds that possess a high degree of angle strain—for cyclopropane, the internuclear angle is 60°, and the interorbital angle is approximately 104°.[6]

The synthesis of highly strained molecules presents not only a challenge to the chemist's imagination and skill, but also an opportunity to test bonding theories by providing molecules restricted by geometry from assuming unstrained bond angles.

4. For a review of various descriptions of the bonding in cyclopropane, see A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **18**, 809 (1979).
5. F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.* **89**, 5962 (1967).
6. K. Mislow, *Introduction to Stereochemistry*, W. A. Benjamin, New York, 1965, p. 19.

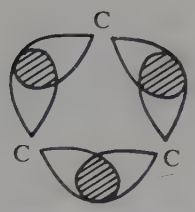
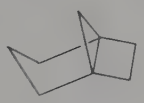


Fig. 1.5. Bent bonds in cyclopropane.

One such molecule is tricyclo[3.2.1.$0^{1,5}$]octane (a 3,2,1-propellane).[7] A novel feature of this compound is that the bridgehead carbon is severely flattened. In order to



attain this geometry, the hybridization must approximate sp^2, which makes the three methylene groups roughly coplanar and requires that the central bond between the two bridgehead carbon atoms be a p–$p\,\sigma$ bond. The strain energy of 3,2,1-propellane is 67 kcal/mol, as compared to 27 kcal/mol for cyclopropane.[8] Because of its increased ground state energy, the molecule is exceptionally reactive and undergoes a variety of reactions involving cleavage of the central bond under mild conditions; e.g., bromination occurs instantaneously at −50 °C. We will return to the subject of strained molecules in Section 3.8, Chapter 3.

A second concept which makes valence bond theory useful for the structural description of complex molecules is *resonance theory.* Resonance theory represents an extension of valence bond theory that applies to molecules for which more than one Lewis structure can be written. Its usefulness to organic chemistry lies in its being a convenient way of depicting electron delocalization, particularly in conjugated systems and in reactive intermediates. We will use resonance arguments in this qualitative way, rather than in their fullest form of development, which is an extensive mathematic treatment intended as an alternative to molecular orbital theory.[9] The elements of resonance theory necessary for qualitative applications are simple and can be summarized as follows:

a) Whenever alternative Lewis structures can be written for a molecule or fragment differing only in assignment of electrons among the nuclei, with the nuclear positions being relatively constant for all the structures, then

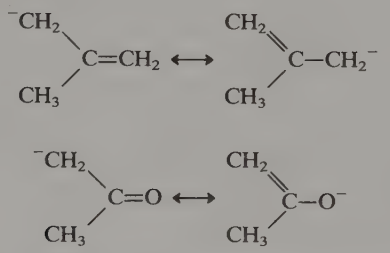
7. K. B. Wiberg and G. J. Burgmaier, *J. Am. Chem. Soc.* **94**, 7396 (1972).
8. K. B. Wiberg, H. A. Connon, and W. E. Pratt, *J. Am. Chem. Soc.* **101**, 6970 (1979).
9. G. W. Wheland, *Resonance in Organic Chemistry*, John Wiley and Sons, New York, 1955; W. A. Goddard, III, and R. C. Ladner, *J. Am. Chem. Soc.* **93**, 6750 (1971); P. J. Hay, W. J. Hunt, and W. A. Goddard, III, *J. Am. Chem. Soc.* **94**, 8293 (1972); G. Levin and W. A. Goddard, III, *J. Am. Chem. Soc.* **97**, 1649 (1975).

the molecule is not adequately represented by a single Lewis structure, but has properties of all of them.

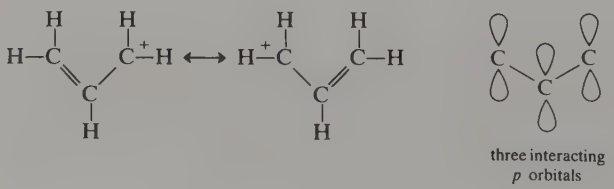
b) Some Lewis structures are more stable than others. The structures that approximate the actual molecule most closely are those that incorporate these features: maximum number of covalent bonds, minimum separation of unlike charges, and placement of any negative charge on the most electronegative atom (or any positive charge on the most electropositive atom). Stated another way, the most favorable (lowest-energy) resonance structure makes the greatest contribution to the true (hybrid) structure. All structures are restricted to the maximum number of valence electrons for each atom, which is two for hydrogen and eight for the first-row elements.

c) In most cases, the delocalization of electrons, as represented by the writing of alternative Lewis structures, is associated with enhanced stability relative to a single localized structure. This association is not always true, however, since molecules and ions are known in which electron delocalization would apparently produce an increase in energy relative to a localized model.

The use of resonance concepts can be illustrated by referring to the relative equilibrium constants for deprotonation of isobutene and acetone. Deprotonation of acetone is more favorable than deprotonation of isobutene by some 15 pK units. A resonance-stabilized anion is generated in each case, but one of the contributing structures for the anion of acetone has its negative charge on oxygen. The anion of isobutene has its negative charge on carbon in both Lewis structures. Since oxygen is more electronegative than carbon, the anion of acetone will be of lower energy than the anion of isobutene, and the equilibrium constant for deprotonation of acetone will be more favorable.

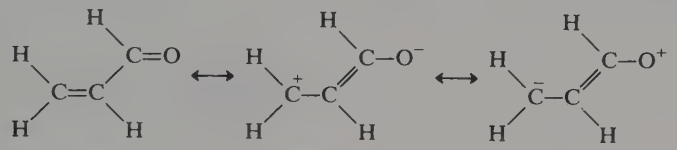


Resonance considerations become particularly important in *conjugated systems*, that is, molecules in which a series of contiguous atoms have orbitals that permit strong electronic interactions over an array of three or more atoms. In the allyl cation, for example, the π system extends over three atoms:



Two equivalent structures can be drawn, and the true structure is intermediate between these. The most direct consequence is that the positive charge is located to an equal extent on the two terminal carbon atoms. The electrons are *delocalized* over the π system. A second structural consequence is that the allyl cation adopts a planar geometry, because a planar structure maximizes the overlap of the three p orbitals. As a result, there is an energy barrier to rotation about the carbon–carbon bonds in the allyl cation. This barrier has not been directly measured but estimates based on appropriate thermodynamic cycles or on extrapolation from methyl derivatives are about 25–28 kcal/mol.[10]

Carbonyl compounds having carbon–carbon double bonds adjacent to the carbonyl group represent another system in which certain structural properties can be attributed to resonance interactions. While only a single uncharged structure can be drawn for a conjugated unsaturated carbonyl compound, a second charged



structure is important. It places a negative charge on oxygen and leaves the β-carbon atom with a positive charge. A third structure would be expected to make a much less important contribution. This structure reverses the charges and is unfavorable because of the positive charge on oxygen. Some of the structural properties that are in accord with this resonance picture are as follows: The C=O bond is not so strong as in a saturated carbonyl compound. This lesser strength is revealed by the infrared (IR) spectrum, which shows that a conjugated carbonyl group is stretched more easily than a saturated analog. Carbon-13 NMR spectroscopy also reveals that the β-carbon atom is more deshielded than in an isolated carbon–carbon double bond, reflecting net shift of electron density from this carbon to the more electronegative oxygen atom.

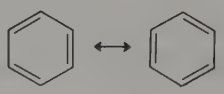
Judgment must be exercised in cases in which two of the resonance criteria are in conflict. For example, the Lewis structure **B** is an important contributor to the resonance hybrid for the rate-determining intermediate formed in the nitration of

A **B**

anisole, even though the structure has a positive charge on oxygen. This unfavorable feature is compensated for by an additional covalent bond in this structure, compared to structure **A**, in which the positive charge is on carbon.

10. H. Mayr, W. Förner, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **101**, 6032 (1979); N. L. Allinger and J. H. Siefert, *J. Am. Chem. Soc.* **97**, 752 (1975).

Benzene is a very familiar example of a molecule that is not adequately represented by any one valence bond structure. Literal interpretation of a single structure erroneously suggests alternating "short" and "long" C–C bond distances around the ring. Actually, benzene is perfectly hexagonal:



A second structure with the alternate disposition of double bonds is necessary to better describe the benzene ring. The hypothetical cyclohexatriene molecule with its π electrons restricted to the area between alternating pairs of carbons is a less

cyclohexatriene benzene

favorable energetic situation than a structure in which these electrons can be distributed uniformly around the ring. A principal contribution to the higher energy of cyclohexatriene is the greater repulsion between electrons when they are restricted to the smaller area in cyclohexatriene. There is in fact no way to restrict these electrons to regions between particular carbon atoms, and cyclohexatriene does not exist. The stabilization resulting from the electron delocalization that occurs in conjugated systems is often referred to as *resonance energy*. Unfortunately, this energy is not a measurable quantity, since the hypothetical reference molecules do not exist. Attempts at calculation of resonance energies depend on assumptions about a localized reference point. They are thus grounded on opinion, rather than on a measurable physical quantity. Values for the resonance energy of benzene, for example, range from 20 to 40 kcal/mol. It is certainly clear that benzene is stabilized as the result of the electron delocalization implied by resonance structures, but by just how much is experimentally indeterminate.

It must be emphasized that resonance structures do not represent separate molecules. A single structure exists. Resonance structures are the alternative descriptions that, taken together, describe the real molecule. To use resonance theory in a qualitative way to predict features of structure and reactivity one must make judgements about the qualitative weighting of all the possible contributing structures. The student's objective should be to develop both a capacity for making such judgements and a recognition of the limitations to the reliability of predictions made on the basis of qualitative resonance theory. Much more will be said about resonance theory and resonance structures, particularly in Chapter 9, where aromaticity and aromatic substitution are discussed.

Table 1.2. Bond Lengths (Å)[a]

sp^3	C–H	1.09	sp^3–sp^3	C–C	1.54	sp^2–sp^2	C–C	1.46	C–O	1.42
sp^2	C–H	1.086	sp^3–sp^2	C–C	1.50	sp^2–sp^2	C=C	1.34	C=O	1.22
sp	C–H	1.06	sp^3–sp	C–C	1.47	sp–sp	C≡C	1.20		

a. From experimental values tabulated for simple molecules by M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.* **99**, 4907 (1977).

1.2. Bond Energies, Lengths, and Dipoles

Of the various geometric parameters associated with molecular shape, the one most nearly constant from molecule to molecule and most nearly independent of remote substituent effects is bond length. Bond lengths to carbon depend strongly on the hybridization of the carbon involved, but are little influenced by other factors. Table 1.2 lists the interatomic distances for several of the most important types of bonds. The near constancy of bond lengths from molecule to molecule reflects the fact that the properties of individual bonds are, to a good approximation, independent of the remainder of the molecule. Other features of molecular structure which are closely related to bond strength, such as force constants for bond stretching are also very similar from molecule to molecule.

Table 1.3. Bond Energies (kcal/mol)

A. Some Common Bond Energies[a]

H–H	103	C–H	98	C=C	145
C–C	81	N–H	92	C≡C	198
O–O	34	O–H	109	N≡N	225
Cl–Cl	57	Cl–H	102	C=O	173
Br–Br	45	Br–H	87	C–O	79
I–I	36	I–H	71	C–N	66

B. Some Specific Bond Dissociation Energies[b]

H_3C–H	104	H_3C–CH_3	88	H_3C–F	108
CH_3CH_2–H	98	H_5C_2–CH_3	85	H_3C–Cl	84
H_2C=CH–H	104	$(CH_3)_2CH$–CH_3	83	H_3C–Br	70
H_2C=$CHCH_2$–H	85	$PhCH_2$–CH_3	70	H_3C–I	56
$PhCH_2$–H	85	H_5C_2–C_2H_5	82	H_3C–OH	91
H_2N–H	103	$(CH_3)_2CH$–$CH(CH_3)_2$	78		
CH_3NH–H	92				
CH_3O–H	102	H_2C=CH_2	163[c]		
		HC≡CH	230[c]		

a. From Table 1, G. J. Janz, *Thermodynamic Properties of Organic Compounds*, Academic Press, New York, 1967.
b. Except where noted, from J. A. Kerr, *Chem. Rev.* **66**, 465 (1966).
c. From S. W. Benson, *J. Chem. Educ.* **42**, 502 (1965).

Table 1.4. Standard Heats of Formation of Some Hydrocarbons (kcal/mol)[a]

A. Saturated Hydrocarbons

C_4		C_8	
n-Butane	−30.15	*n*-Octane	−49.82
i-Butane	−32.15	2-Methylheptane	−51.50
C_5		3-Methylheptane	−50.82
n-Pentane	−35.00	4-Methylheptane	−50.69
i-Pentane	−36.90	2,2-Dimethylhexane	−53.71
Neopentane	−36.97	2,3-Dimethylhexane	−51.13
C_6		2,4-Dimethylhexane	−52.44
n-Hexane	−39.96	3,3-Dimethylhexane	−52.61
2-Methylpentane	−41.66	2,2,3-Trimethylpentane	−52.61
3-Methylpentane	−41.02	2,2,4-Trimethylpentane	−53.57
2,3-Dimethylbutane	−42.49	2,2,3,3-Tetramethylbutane	−53.99
2,2-Dimethylbutane	−44.35		

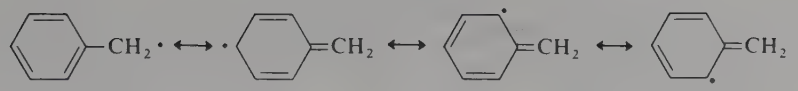
B. Alkenes

C_4		C_6	
1-Butene	−.03	1-Hexene	−9.96
trans-2-Butene	−2.67	*trans*-2-Hexene	−12.56
cis-2-Butene	−1.67	*cis*-2-Hexene	−11.56
2-Methylpropene	−4.04	*trans*-3-Hexene	−12.56
C_5		*cis*-3-Hexene	−11.56
1-Pentene	−5.00	2-Methyl-1-pentene	−13.56
trans-2-Pentene	−7.59	3-Methyl-1-pentene	−11.02
cis-2-Pentene	−6.71	4-Methyl-1-pentene	−11.66
2-Methyl-1-butene	−8.68	2-Methyl-2-pentene	−14.96
3-Methyl-1-butene	−6.92	3-Methyl-2-pentene	−14.32
2-Methyl-2-butene	−10.17	2,3-Dimethyl-1-butene	−14.78
		3,3-Dimethyl-1-butene	−14.25
		2,3-Dimethyl-2-butene	−15.91

a. From F. D. Rossini, K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. C. Pimentel, *Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds*, Carnegie Press, Pittsburgh, 1953.

Table 1.3 gives some bond-energy data. Part A includes some common bond energies, including those for some simple diatomic molecules, and approximate values for some of the types of bonds found most often in organic molecules. The assumption that bond energies are independent of the remainder of the molecule is a rather rough one. Part B of Table 1.3 lists some specific C–H, C–C, and other bond energies. It is apparent that some are rather substantially different from the generalized values. For example, the CH_2–H bond dissociation energies listed for propene and toluene are 85 kcal/mol, which is substantially less than for a C–H bond in methane (104 kcal). The reason for the relative weakness of these bonds is that the allyl and benzyl radicals which are produced by the bond dissociations

$$H_2C{=}CH{-}CH_2{\cdot} \longleftrightarrow {\cdot}H_2C{-}CH{=}CH_2$$



are stabilized by resonance. A similar explanation lies behind the diminished strength of the sp^3–sp^3 carbon–carbon bond in ethylbenzene. The general trend toward weaker C–C bonds with increased substitution that can be recognized in Table 1.3 reflects the increased stability of substituted radicals relative to primary radicals.

Smaller, but nevertheless significant, differences in energies of organic molecules also result from less apparent differences in structure. Table 1.4 gives the heats of formation of some hydrocarbons. These energy values represent the heat evolved on formation of the compound from its constituent elements under standard conditions. The heats of formation therefore permit precise comparison of the stability of *isomeric compounds*. The more negative the heat of formation, the greater the stability. Direct comparison of compounds having different elemental composition is not meaningful, since the total number of bonds formed is then different.

Part A of Table 1.4 shows all the acyclic C_4–C_6 hydrocarbons and a number of the C_8 hydrocarbons. A general trend is discernible in the heats of formation data. Branched-chain hydrocarbons are more stable than straight-chain hydrocarbons. For example, the ΔH_f° for *n*-octane is −49.82 kcal/mol, whereas the most highly branched isomer possible, 2,2,3,3-tetramethylbutane, is the most stable of the octanes, with a ΔH_f° of −53.99 kcal/mol. Similar trends are observed in the other series.

Part B of Table 1.4 gives heats of formation for the C_4, C_5, and some of the C_6 alkenes. A general relationship is also observed for the alkenes: The more highly substituted the double bond, the more stable the compound. There are also other factors that enter into alkene stability. *trans*-Alkenes are usually more stable than *cis*-alkenes, probably largely because of increased nonbonded repulsions in the *cis*

Table 1.5. Heats of Hydrogenation of Some Alkenes (kcal/mol)[a]

$CH_3CH{=}CHCH_3$	*cis*	28.6
	trans	27.6
$CH_3CH{=}CHC(CH_3)_3$	*cis*	30.8
	trans	26.5
$(CH_3)_3CCH{=}CHC(CH_3)_3$	*cis*	36.2
	trans	26.9
$(CH_3)_3CCH_2CH{=}CHCH_2C(CH_3)_3$	*cis*	26.9
	trans	26.0

a. In acetic acid; from R. B. Turner, A. D. Jarrett, P. Goebel, and B. J. Mallon, *J. Am. Chem. Soc.* **95**, 790 (1973).

Table 1.6. Atomic and Group Electronegativities

A. Atomic Electronegativities[a]

H 2.1	C 2.5; **2.35**	N 3.0; **3.16**	O 3.5; **3.52**	F 4.0; **4.00**
	Si 1.8; **1.64**	P 2.1; **2.11**	S 2.5; **2.52**	Cl 3.0; **2.84**
		As 2.0; **1.99**	Se 2.4; **2.40**	Br 2.8; **2.52**
				I 2.5

B. Empirical Electronegativities for Some Organic Functional Groups[b]

CH_3	2.3	H	2.28	F	3.95
CH_2Cl	2.75	NH_2	3.35	Cl	3.03
$CHCl_2$	2.8	$^+NH_3$	3.8	Br	2.80
CCl_3	3.0	NO_2	3.4	I	2.28
CF_3	3.35	OH	3.7		
Ph	3.0				
$CH{=}CH_2$	3.0				
$C{\equiv}CH$	3.3				
$C{\equiv}N$	3.3				

a. From L. Pauling, *The Nature of the Chemical Bond*, third edition, Cornell University Press, Ithaca, New York, 1960. Boldface values from G. Simons, M. E. Zandler, and E. R. Talaty, *J. Am. Chem. Soc.* **98**, 7869 (1976).
b. From P. R. Wells, *Prog. Phys. Org. Chem.* **6**, 111 (1968).

isomer.[11] Table 1.5 gives the heats of hydrogenation for some pairs of *cis*- and *trans*-alkenes. Since hydrogenation leads to the same saturated product, the difference in the two heats of hydrogenation corresponds to the energy difference between the two compounds. This difference is seen to increase from 1.0 kcal/mol to nearly 10 kcal/mol as the groups increase in size from methyl to *t*-butyl.[12]

Another important property of chemical bonds is their *polarity*. In general, it is to be expected that the pair of electrons in a covalent bond will be subject to a probability distribution that favors one of the two atoms. The tendency of an atom to attract electrons is called *electronegativity*. There are a number of different approaches to assigning electronegativities and most are numerically scaled to a definition originally proposed by Pauling.[13] Table 1.6, Part A, gives the original Pauling values and also a more recent set based on theoretical calculation of electron distributions. The concept of electronegativity can also be expanded to include organic functional groups. Part B of Table 1.6 gives some numerical values which are scaled to be numerically consistent with elemental electronegativities. These electronegativity values can serve to convey a qualitative impression of the electron-attracting capacity of these groups.

11. For a theoretical discussion, see N. D. Epiotis, R. L. Yates, and F. Bernardi, *J. Am. Chem. Soc.* **97**, 5961 (1975).
12. A review of the use of heats of hydrogenation for evaluation of the enthalpy of organic molecules is given in J. L. Jensen, *Prog. Phys. Org. Chem.* **12**, 189 (1976).
13. For references to other electronegativity scales, see G. Simons, M. E. Zandler, and E. R. Talaty, *J. Am. Chem. Soc.* **98**, 7869 (1976).

Table 1.7. Bond and Group Dipoles for Some Organic Functional Groups[a]

Bond moments[b]		Bond moments[b]		Group moments[b]	
C—H	0.4	C—N	0.22	MeO	1.3
C—F	1.41	C—O	0.74	NH_2	1.2
C—Cl	1.46	C=O	2.3	CO_2H	1.7
C—Br	1.38	C≡N	3.5	COMe	2.7
C—I	1.19			NO_2	3.1
				CN	4.0

a. From C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill Book Company, New York, 1955, pp. 244, 253.
b. In e.s. units $\times 10^{18}$.

The unequal distribution of electron density in covalent bonds produces a bond dipole having as units the product of charge and distance.[14] Bonds with significant bond dipoles are described as being polar. The bond and group dipole moments of some typical substituents are shown in Table 1.7. It is possible to estimate with a fair degree of precision the dipole moment of a molecule as the vector sum of the component bond dipoles. A qualitative judgment of bond polarity can be made by comparing the difference in electronegativity of the bound atoms or groups. The larger the difference, the greater will be the bond dipole.

The polarity of covalent bonds is considered to be the basis of a number of structure–reactivity relationships in organic chemistry. The pK_a values of some derivatives of acetic acid are presented in Table 1.8. These data illustrate that substitution of a more electronegative atom or group for hydrogen increases the equilibrium constant for ionization. The highly electronegative fluorine atom causes a larger increase in acidity than the less electronegative chlorine atom. A slight acid weakening effect is observed when propionic acid is compared with acetic acid. Care must be taken in interpreting acidity solely in terms of electronegativity effects, since it was shown very early in studies of structure–reactivity relationships that entropy effects are, in fact, more important than enthalpy effects in the ionization of substituted acetic acids.[15] Measurements of acidities in the gas phase have established that propionic acid is actually a stronger acid than acetic acid, and indicate that the reversal observed in aqueous solution is probably a reflection of the larger solvation energy of the acetate ion relative to the propionate ion.[16] Nevertheless, if we restrict ourselves to substituents that are highly electronegative, and for which

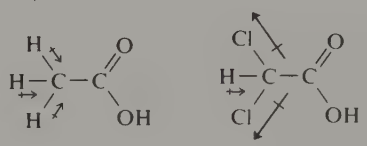
14. For more detailed discussions, see L. E. Sutton, in *Determination of Organic Structures by Physical Methods*, Vol. 1, E. A. Braude and F. C. Nachod (eds.), Academic Press, New York, 1955, Chap. 9; V. I. Minkin, O. A. Osipov, and Y. A. Zhdanov, *Dipole Moments in Organic Chemistry*, Plenum Press, New York, 1970.
15. L. P. Hammett, *J. Chem. Phys.* **4**, 613 (1936).
16. R. Yamdagni and P. Kebarle, *J. Am. Chem. Soc.* **95**, 4050 (1973).

Table 1.8. pK_a Values for Some Substituted Acetic Acids[a]

Cl_3CCO_2H	0.65	$HOCH_2CO_2H$	3.83
Cl_2CHCO_2H	1.29	CH_3CO_2H	4.76
FCH_2CO_2H	2.66	$CH_3CH_2CO_2H$	4.88
$ClCH_2CO_2H$	2.86		

a. From H. C. Brown, D. H. McDaniel, and O. Häfliger, in *Determination of Organic Structures by Physical Methods*, Vol. 1, E. A. Braude and F. C. Nachod (eds.), Academic Press, New York, 1955, p. 567.

enthalpy effects are correspondingly significant, we can describe a simple scheme in which polarization of bonds serves to rationalize substituent effects on acidity. Consider dichloroacetic acid. Two quite polar C–Cl bonds have replaced the slightly polar C–H bonds:



For the equilibrium

$$RCO_2H + H_2O \rightleftharpoons RCO_2^- + H_3O^+$$

dissociation places a negative charge on the carboxylate residue and increases the electron density in the vicinity of the carboxyl carbon. For acetic acid, where R = CH_3 this increase in charge occurs adjacent to a carbon bearing a slight negative charge, resulting from the small polarity of the C–H bonds. In the case of dichloroacetic acid, R = $CHCl_2$, the corresponding carbon is slightly positive,

because of the reversed polarity of the carbon–chlorine bonds. Clearly, the buildup of negative charge is more favorable in the second case than in the first. As a result, the extent of ionization of dichloroacetic acid is greater, i.e., it is a stronger acid because of the electron-withdrawing effect of the chlorine substituents. Structure and reactivity effects which result from polarization of σ-bonds are termed *inductive effects.* They are primarily electrostatic in nature and are short-range forces so that the effect caused by a bond dipole rapidly diminishes as the polar bond becomes more distant from the site of the reaction.

It is always important to keep in mind the *relative* aspect of substituent effects. Thus, the effect of the chlorine atoms in the case of dichloroacetic acid is primarily to lower the energy of the dissociated anion. The acid is more highly dissociated

than in the unsubstituted case because of this preferential stabilization of the anion. It is the energy difference between the dissociated and undissociated species, not their absolute energies, that determines the extent of ionization. Furthermore, substituent groups can interact with the remainder of the molecule by other mechanisms as well. The detailed understanding of substituent effects depends on being able to separate inductive effects from these other factors. This problem will be discussed in more detail in Chapter 4.

The ideas about bond length, bond energies, and polarity which have been discussed in this section are very useful because of the relative constancy of bond properties from molecule to molecule. Thus, data obtained from simple well-studied models can often provide a good guide to the properties of substances which have yet to be studied in detail. Organic chemists have usually discussed this transferability of properties of bonds in terms of valence bond theory and its view of molecules as a collection of atoms connected by individual bonds with specific properties characteristic of that type of bond. This has been a highly fruitful pattern of thought and remains in use in organic chemistry. As we shall see in the next section, there is an alternative description of molecules which is also highly useful and informative.

1.3. Molecular Orbital Methods

The second broad approach to the description of molecular structure which is of importance in organic chemistry is molecular orbital theory. Molecular orbital (MO) theory discards the idea that bonding electron pairs are localized between specific atoms in a molecule and instead pictures electrons as being distributed among a set of molecular orbitals of discrete energies. In contrast to the orbitals described by valence bond theory, which are centered on two specific atoms, these orbitals can extend over the entire molecule. The theory is based on the Schrödinger equation,

$$H\psi = E\psi$$

in which ψ is a wave function describing an orbital, H is the Hamiltonian operator, and E is the energy of an electron in a particular orbital. The wave function describes the interaction of the electron with the other electrons and nuclei of the molecule. The total electronic energy is the sum of the individual electron energies:

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

In order to make the mathematics tractable, a number of approximations are made. The choice of approximations has produced a variety of molecular orbital methods, the judicious application of which can provide a valuable insight into questions of bonding, structure, and dynamics. The discussion that follows will not be

sufficiently detailed for the reader to understand fully how the calculations are performed or the details of the approximations. Instead, the nature of the information obtained will be described, and the ways in which organic chemists have applied the results of MO theory will be illustrated. For more detailed treatments, several excellent sources are available.[17]

All but the crudest molecular orbital calculations are done on computers and there is a necessary trade-off between the accuracy of the calculations and the expense in terms of computer time. In general, the more severe the approximations, the more limited is the range of applicability of the particular calculation. The organic chemist who wishes to make use of the results of molecular orbital calculations must therefore make a judgement about the applicability of the various methods to the particular problem. In general, the programs which are used for the calculations are available and the complexity of use tends to increase with the sophistication of the calculation.[18]

Mathematically, the molecular orbitals are treated as linear combinations of atomic orbitals, so that the wave function, ψ, is expressed as a sum of individual atomic orbitals multiplied by appropriate weighting factors (coefficients):

$$\psi = c_1\phi_1 + c_2\phi_2 + \cdots c_n\phi_n$$

The coefficients indicate the contribution of each atomic orbital to the molecular orbital. This method of representing the molecular orbital wave function in terms of combinations of atomic orbital wave functions is known as the *linear combination of atomic orbitals–molecular orbital (LCAO–MO) approximation.* The combination of atomic orbitals chosen is called the *basis set.* A minimal basis set for molecules containing C, H, O, and N would consist of $1s$, $2s$, $2p_x$, $2p_y$, and $2p_z$ orbitals for C, O, and N, and a $1s$ orbital for hydrogen. Inclusion of additional orbitals in the basis set leads to an extended basis set. The basis sets are mathematical expressions describing the properties of the atomic orbitals.

Two main streams of computational techniques branch out from this point. These are referred to as *ab initio* and *semiempirical* calculations. In both the *ab initio* and semiempirical treatments, mathematical formulation of the wave functions which describe hydrogen-like orbitals are used. Examples of wave functions that are commonly used are Slater-type orbitals (abbreviated STO) and Gaussian-type orbitals (GTO). There are individual variations which are designated by further additions to the abbreviations. Both *ab initio* and semiempirical calculations then treat the combination of orbitals by iterative computations which establish a self-

17. H. H. Jaffe, *Acc. Chem. Res.* **2**, 136 (1969); M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969; W. J. Hehre, *Acc. Chem. Res.* **9**, 399 (1976); W. T. Borden, *Modern Molecular Orbital Theory for Organic Chemists*, Prentice-Hall, Englewood Cliffs, New Jersey, 1975; H. E. Zimmerman, *Quantum Mechanics for Organic Chemists*, Academic Press, New York, 1975; I. G. Csizmadia, *Theory and Practice of MO Calculations on Organic Molecules*, Elsevier, Amsterdam, 1976.

18. Most computation programs have been made available via the Quantum Chemistry Program Exchange, Chemistry Department, Indiana University, Bloomington, Indiana.

consistent electrical field and minimize the energy of the system. The various semiempirical methods differ in the approximations which are made concerning repulsions between electrons in different orbitals. The approximations are then corrected for by "parameterization," wherein parameters are included in the fundamental protocol to make the results match *ab initio* calculations on known systems or experimental data. The reliability and accuracy of these methods has evolved over the past 15–20 years. The earliest semiempirical methods to be applied extensively to organic molecules included the Extended Hückel Theory (EHT)[19] and CNDO (complete neglect of differential overlap)[20] methods. These methods give correct representations of the shapes and trends in charge distribution in the various molecular orbitals, but are only roughly reliable for describing molecular geometry. These methods tend to make very large errors in calculation of the energy of molecules. More recent semiempirical calculations can give excellent representations of charge distributions, molecular geometry, and ground state molecular energies. Among these methods are MINDO-3,[21] MNDO,[22] and INDO.[23] (These acronyms refer to semidescriptive titles of the calculation method, specifically "modified intermediate neglect of differential overlap," "modified neglect of differential overlap," and "intermediate neglect of differential overlap.") There are differences among the methods, however, in the range of types of compounds for which the results are satisfactory. This is particularly true for the methods which are parameterized to agree with experimental data.

Ab initio calculations are iterative procedures which are based on *self-consistent field–molecular orbital* (SCF–MO) methods. Electron–electron repulsion is specifically taken into account. Normally, calculations are approached by the Hartree–Fock closed-shell approximation, which treats a single electron at a time interacting with an aggregate of all the other electrons. Self-consistency is achieved by a procedure in which a set of orbitals is assumed, and the electron–electron repulsion is calculated; this energy is then used to calculate a new set of orbitals, which in turn are used to calculate a new repulsive energy. The process is continued until convergence occurs and self-consistency is achieved.[24]

The individual *ab initio* calculations are further identified by abbreviations for the basis sets which are used to represent the orbitals. These abbreviations include, for example, STO-3G,[25] 4-31G,[26] and 6-31G.[27] A fundamental difference between *ab initio* methods and the semiempirical methods is the absence of parameters to

19. R. Hoffmann, *J. Chem. Phys.* **39**, 1397 (1963).
20. J. A. Pople and G. A. Segal, *J. Chem. Phys.* **44**, 3289 (1966).
21. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.* **97**, 1285, 1294, 1302 (1975).
22. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.* **99**, 4907 (1977).
23. J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.* **47**, 2026 (1967).
24. C. C. J. Roothaan, *Rev. Mod. Phys.* **23**, 69 (1951); R. Pariser and R. G. Parr, *J. Chem. Phys.* **21**, 767 (1953); J. A. Pople, *J. Phys. Chem.* **61**, 6 (1957).
25. W. J. Hehre, R. F. Stewart, and J. A. Pople, *J. Chem. Phys.* **51**, 2657 (1971).
26. R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.* **54**, 724 (1971).
27. W. J. Hehre, R. Ditchfield, and J. A. Pople, *J. Chem. Phys.* **56**, 2257 (1972).

adjust the results toward specified points of agreement with other calculations or experimental data. In general the *ab initio* calculations make fewer assumptions and therefore the computations are considerably more complex than for the semiempirical methods. Present methods can give excellent results on ground state molecular geometry and charge distributions. They also give excellent agreement with experiment in the calculation of relative molecular energy. The *ab initio* methods can also be used to explore reaction pathways and other dynamic processes by calculating energy as a function of structural distortions and thereby describing the energy surface of the system.

The relative merits of the various methods have been discussed somewhat in the literature.[28] In general, it can be stated that the *ab initio* type calculations will be more reliable but the semiempirical calculations are considerably faster in terms of computer time. Roughly speaking, there is an increase of a factor of about 100 in going from CNDO type to *ab initio* STO-3G calculations. A choice of methods is normally made on the basis of prior evidence that the computational method is adequate for the problem at hand and, whenever possible, critical evaluation of the calculated results against the best experimental data which are available.

Typical results of all types of MO calculation include the energy of each MO, the total electronic energy of the molecule relative to the separated atoms, and the coefficients of the AO's in each MO. Such basic information may be applied directly to a number of physical and chemical properties. The total electronic energy obtained by summing the energies of the occupied orbitals is an estimate of the stability of the molecule. It can be compared with known thermochemical data or used to predict the relative stability of isomeric molecules. Structural effects can be probed by calculating the total energy as a function of molecular geometry. The minimum energy found would be expected to correspond to the preferred structure of the molecule.

The coefficients for the AO's that comprise each MO may be related to the electron density at each atom by the equation

$$q_r = \sum_j n_j c_{jr}^2$$

which gives the electron density at atom r as the sum over all the occupied molecular orbitals of the product of the number of electrons in each orbital and the square of the coefficient at atom r in each orbital. To illustrate, consider methyl cation (CH_3^+), using calculations employing the CNDO/2 approximation.

If the carbon 1s orbital is omitted, the wave functions for the seven molecular orbitals that result from combination of the three hydrogen 1s orbitals with carbon

28. J. A. Pople, *J. Am. Chem. Soc.* **97**, 5306 (1975); W. J. Hehre, *J. Am. Chem. Soc.* **97**, 5308 (1975); T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. N. Lipscomb, *J. Am. Chem. Soc.* **100**, 6595 (1978); M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.* **101**, 5558 (1979); W. J. Hehre, *Acc. Chem. Res.* **9**, 399 (1976).

Table 1.9. Coefficients of Wave Functions Calculated for Methyl Cation by the CNDO/2 Approximation[a]

Orbital	C_{2s}	C_{2p_x}	C_{2p_y}	C_{2p_z}	H	H	H
ψ_1	0.7915	0.0000	0.0000	0.0000	0.3528	0.3528	0.3528
ψ_2	0.0000	0.1431	0.7466	0.0000	0.0999	0.4012	−0.5011
ψ_3	0.0000	0.7466	−0.1431	0.0000	0.5210	−0.3470	−0.1740
ψ_4	0.0000	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
ψ_5	−0.6111	0.0000	0.0000	0.0000	0.4570	0.4570	0.4570
ψ_6	0.0000	0.5625	−0.3251	0.0000	−0.5374	0.5377	−0.0003
ψ_7	0.0000	0.3251	0.5625	0.0000	−0.3106	−0.3101	0.6207

a. The orbital energies (eigenvalues) are not given. The lowest-energy orbital is ψ_1; the highest-energy orbital, ψ_7.

$2s$, $2p_x$, $2p_y$, and $2p_z$ are computed to have the coefficients shown in Table 1.9.[29]

The electron densities are calculated from the coefficients of ψ_1, ψ_2, and ψ_3 only because these are the occupied orbitals for the six-valence-electron system. The carbon atom is calculated to have 3.565 electrons (exclusive of those in the $1s$ level), and each of the hydrogen atoms is calculated to have 0.812 electron. Since carbon in its neutral form has four electrons, its net charge in methyl cation is +0.435 (4−3.565). Each hydrogen atom has a charge of +0.188 (1−0.812). A sample calculation of hydrogen electron density is as follows:

$$q_H = 2(0.3528)^2 + 2(0.0999)^2 + 2(0.5210)^2$$

$$q_H = 0.812$$

Further examination of Table 1.9 reveals that the lowest unoccupied molecular orbital is ψ_4. This orbital is unique among all the orbitals in that it is a pure p orbital localized on carbon, as indicated by the coefficients. The coefficients are zero for every AO in ψ_4, except for the coefficient of C_{2p_z}, which is 1.

The use of molecular orbital methods to probe the relationship between structure and energy can be illustrated by a study of CH_3^+, $CH_3^{\cdot}$, and CH_3^-. The study employed *ab initio* Gaussian-70 calculations and the 4-31G basis set and was aimed at exploring the optimum geometry and resistance to deformation in these important reaction intermediates.[30] Figure 1.6 is a plot of the calculated energy as a function of deformation from planarity for the three species. While CH_3^+ and $CH_3^{\cdot}$ are found to have minimum energy at $\beta = 0$, that is when the molecule is planar, CH_3^- is calculated to have a nonplanar equilibrium geometry. This calculated result is in good agreement with a variety of experimental observations which we will discuss in Chapters 5, 7, and 11 when these intermediates are described in more detail.

29. Taken from unpublished output data of calculations reported by H. S. Tremper and D. D. Shillady, *J. Am. Chem. Soc.* **91**, 6341 (1969).
30. E. D. Jemmis, V. Buss, P. v. R. Schleyer, and L. C. Allen, *J. Am. Chem. Soc.* **98**, 6483 (1976).

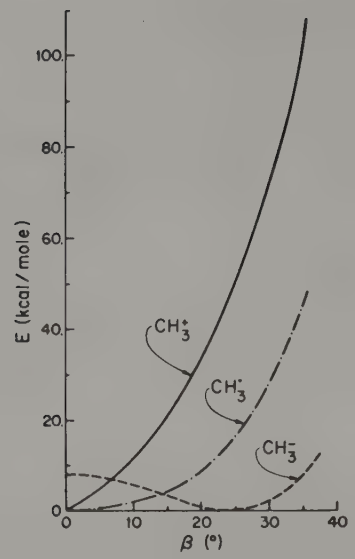
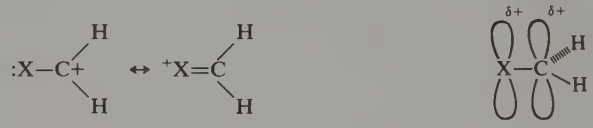


Fig. 1.6. Total energy as a function of distortion from planarity for methyl cation, methyl radical and methyl anion. Reproduced from Ref. 30.

Substituent effects on intermediates such as these can also be analyzed by MO methods. Take for example methyl cations where adjacent substituents with lone pairs of electrons can form strong π bonds which can be expressed in either valence



bond or MO terminology. An *ab initio* study using 4-31G basis set orbitals gave

Table 1.10. Charge Transfer and Stabilization by Substituents on the Methyl Cation

Substituent X	Electron density in C $2p_z$ orbital	Stabilization in kcal/mol[a]
F	0.35	2.1
OH	0.49	48
NH_2	0.58	93
CH_3	0.31	30

a. As calculated using Gaussian 70 programs and 4-31G basis set. Ref. 31.

Table 1.11. Calculated Stabilization of Methyl Anion by Substituent Groups

Substituent	Stabilization[a] in kcal/mol	Substituent	Stabilization[a] in kcal/mol
BH_2	68	$C{\equiv}N$	61
CH_3	2	NO_2	98
NH_2	5	$CH{=}CH_2$	38
OH	15	CF_3	57
F	25	$CH{=}O$	72

a. As calculated by Gaussian 70 program using 4–31G basis set. Ref. 32.

the charge densities shown in Table 1.10.[31] The table also shows the calculated stabilization resulting from electron release by the substituent.

The π-donor effects of the fluoro, oxygen, and nitrogen groups are partially counterbalanced by the electron withdrawal through the polar σ bond. In the case of the oxygen and nitrogen substituents the π-donor effect is dominant and these substituents strongly stabilize a carbonium ion. For the fluorine substituent the balance is much closer and the overall stabilization is calculated to be quite small. We will turn to the case of the methyl group and its stabilization of a carbonium ion a little later.

In the case of the methyl anion stabilization will result from electron-accepting substituents. Table 1.11 gives some stabilization energies calculated for a range of substituents.[32] Those substituents, BH_2, $C{\equiv}N$, NO_2, and $CH{=}O$, which have a low-lying π orbital capable of accepting electrons from the carbon $2p_z$ orbital are strongly stabilizing. Electronegative substituents without π-acceptor capacity reveal a weaker capacity to stabilize the anion. The order is $F > OH > NH_2$ which parallels the ability of these substituents to act as σ-electron acceptors. The strong effect of the trifluoromethyl group is a combination of both σ- and π-bond effects.

1.4. Qualitative Application of Molecular Orbital Theory

As with valence bond theory, the full mathematical treatment of MO theory is too elaborate to apply to all situations and it is important to develop from the fundamental ideas of molecular orbital theory and the detailed calculations on specific systems, ideas which can be applied without the need for detailed calculation.

31. Y. Apeloig, P. v. R. Schleyer, and J. A. Pople, *J. Am. Chem. Soc.* **99**, 1291 (1977).
32. A. Pross, D. J. DeFrees, B. A. Levi, S. K. Pollack, L. Radom, and W. J. Hehre, *J. Org. Chem.* **46**, 1693 (1981).

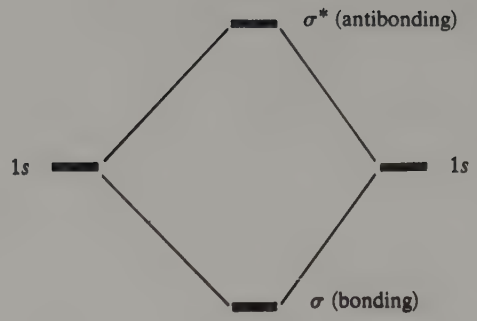


Fig. 1.7. Graphic description of combination of two 1*s* orbitals to give two molecular orbitals.

A key tool for this type of analysis is a qualitative molecular orbital energy diagram. The construction of qualitative energy level diagrams may be accomplished without recourse to detailed calculations by keeping some basic principles in mind. These principles can be illustrated by referring to some simple examples. Consider first diatomic species formed from atoms in which only the 1*s* orbitals are sufficiently low in energy to be important in the bonding scheme. The two 1*s* orbitals can combine in either a bonding or an antibonding manner to give two molecular orbitals, as indicated in Fig. 1.7.

The number of molecular orbitals (bonding + nonbonding + antibonding) is equal to the sum of the atomic orbitals in the basis set from which they are generated. The bonding combination is characterized by a positive overlap in which the coefficients are of like sign, while the antibonding combination is characterized by a negative overlap with coefficients of opposite sign.

Orbitals are then occupied by electrons, the total number of which depends on the species being discussed, beginning with the orbital of lowest energy and placing a maximum of two electrons in each orbital (the Aufbau principle). Since a total of four electrons could be accommodated by the two orbitals depicted in Fig. 1.6, this qualitative energy level diagram could be applied to systems such as H_2^+ (one electron), H_2 (two electrons), He_2^+ (three electrons), or He_2 (four electrons). A reasonable conclusion would be that H_2 would be the most stable of these homonuclear diatomic species because it has the largest net number of electrons in bonding orbitals (two). The He_2 molecule has no net bonding because the antibonding orbital contains two electrons and cancels the bonding contribution of the occupied bonding orbital. Both H_2^+ and He_2^+ have one more electron in bonding orbitals than in antibonding orbitals. They have been determined to have bond energies of 61 and 60 kcal/mol, respectively. The bond energy of H_2, for the purposes of comparison, is 103 kcal/mol.

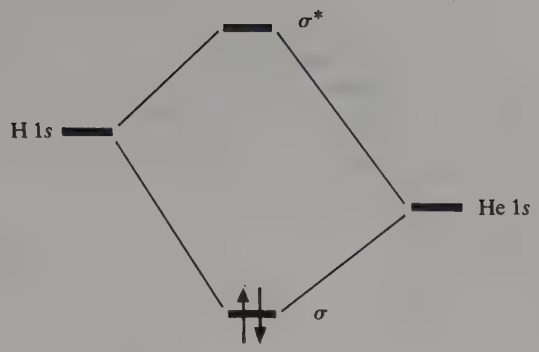


Fig. 1.8. Energy level diagram for HHe^+.

A slight adjustment allows the energy level diagram to be applied to heteronuclear diatomic species such as HHe^+. Rather than being a symmetrical diagram, the He 1*s* level is lower than the H 1*s* level due to the increased nuclear charge on

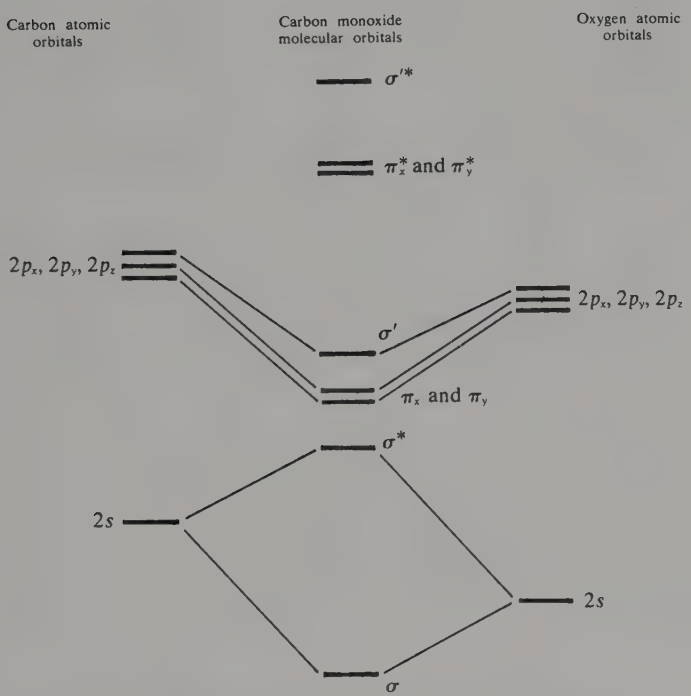


Fig. 1.9. Energy levels in the carbon monoxide molecule. (Adapted from H. B. Gray and G. P. Haight, *Basic Principles of Chemistry*, W. A. Benjamin, New York, 1967, p. 289.)

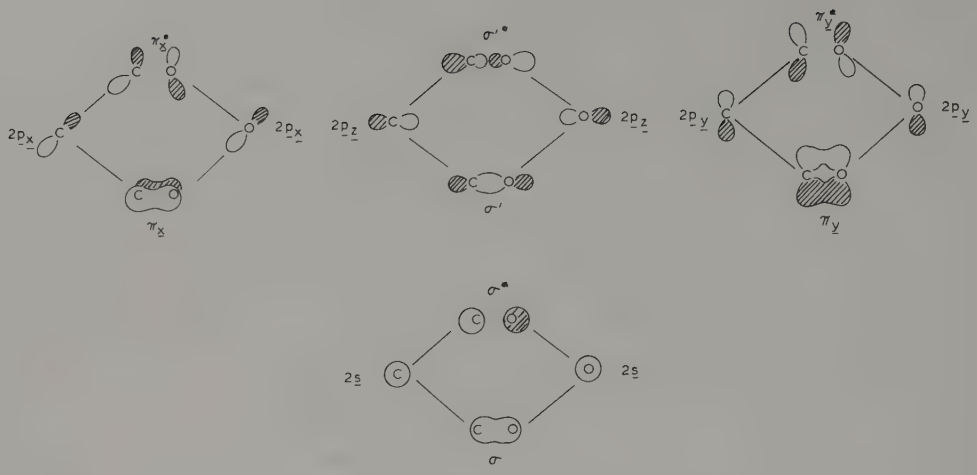


Fig. 1.10. Interaction of atomic orbitals of carbon and oxygen leading to molecular orbitals or carbon monoxide.

helium. The diagram that results from this slight modification is shown in Fig. 1.8. Exact calculations for the HHe^+ ion indicate a bond energy of 43 kcal/mol.[33]

Proceeding next to heteronuclear diatomic molecules containing more than four electrons, these same ideas may be extended. The carbon monoxide molecule has fourteen electrons, and the basis orbitals for each atom are $1s$, $2s$, $2p_x$, $2p_y$, and $2p_z$. The energy levels can be approximated very well if only the valence electrons and orbitals are included and the four electrons corresponding to those in the carbon $1s$ and oxygen $1s$ orbitals are ignored. This approximation is valid because the energy gap between the $1s$ and $2s$ levels is large, and the mixing of energy levels is therefore small. This leaves ten valence electrons to be distributed among eight valence molecular orbitals generated from combining four valence atomic orbitals from carbon with four from oxygen, as illustrated in Fig. 1.9. Figure 1.10 illustrates in a qualitative way the interactions between the atomic orbitals that give rise to the molecular orbitals.

Figure 1.10 shows the various combinations of atomic orbitals which interact with one another. Each pair of atomic orbitals leads to a bonding and antibonding combination. The $2s$ orbitals give the σ and σ^* orbitals. The $2p_x$ and $2p_y$ combinations form molecular orbitals which are π in character. The $2p_z$ combination gives a σ-type orbital labeled σ' as well as the corresponding antibonding orbital. The

33. H. H. Michels, *J. Chem. Phys.* **44**, 3834 (1966).

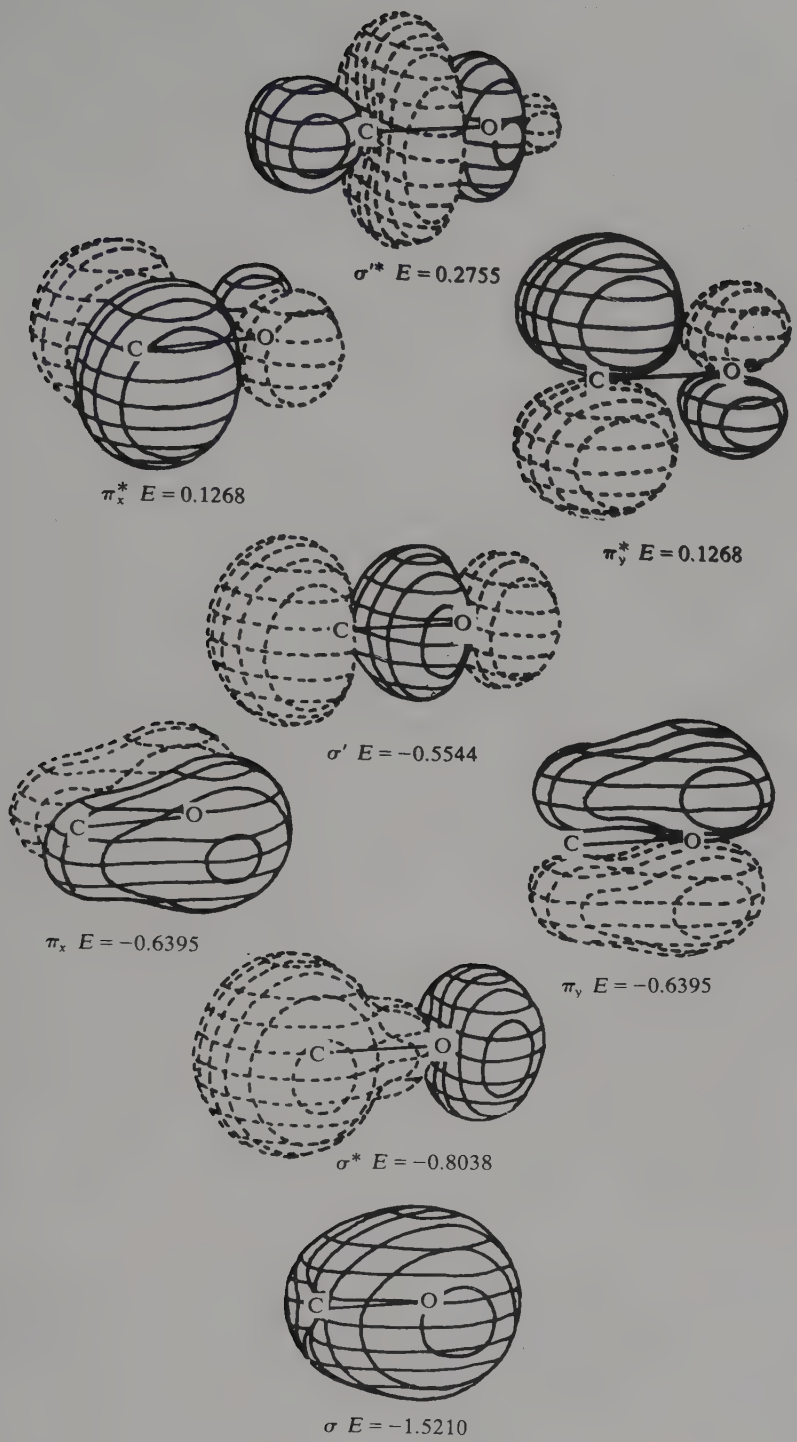


Fig. 1.11. Representation of the molecular orbitals of carbon monoxide. Energies are given in atomic units = 27.21 eV. (From W. L. Jorgensen and L. Salem, *The Organic Chemist's Book of Orbitals*, Academic Press, New York, 1973. Reproduced by permission.)

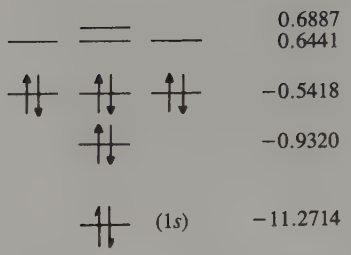


Fig. 1.12. Molecular orbital energy diagram for methane. Energies are in atomic units.

lower five orbitals are doubly occupied, accounting for the ten valence shell electrons in the molecule. Of these five occupied orbitals, one is antibonding, resulting in a net of six bonding electrons, in agreement with the triple bond found in the Lewis structure for carbon monoxide. The shapes of the molecular orbitals can also be depicted as in Fig. 1.11. Here the nodes in the molecular orbitals are represented by a change from full to dashed lines and the size of the lobes are scaled to represent atomic coefficients. One gains from these pictures an impression of the distortion of the bonding π orbital toward oxygen as a result of the greater electronegativity (higher nuclear charge) of the oxygen atom.

Just as we were able to state some guiding rules for qualitative application of resonance theory, it is possible to state some conditions by which to test the correctness of a molecular orbital energy level diagram derived by qualitative considerations.

a) The total number of molecular orbitals must equal the number of atomic orbitals from which they were constructed.
b) The symmetry of the molecular orbitals must conform to the symmetry of the molecule in such a way that the MO's are either symmetric or antisymmetric with respect to all of the symmetry elements of the molecule.
c) Atomic orbitals that are orthogonal do not interact. Thus no two carbon $2p$ orbitals will contribute to the same molecular orbital.
d) The relative energy of the molecular orbitals increases with the number of nodes in the molecular orbital.

By applying these rules and by recognizing the elements of symmetry present in the molecule, it is possible to construct molecular orbital diagrams for more complex molecules. In the succeeding paragraphs the MO diagrams of methane and ethylene are constructed from these kinds of considerations.

Figure 1.12 gives the results of an *ab initio* SCF calculation for the methane molecule.[34]

34. W. E. Palke and W. N. Lipscomb, *J. Am. Chem. Soc.* **88**, 2384 (1966).

This particular calculation used as a basis set the $1s$, $2s$, and three $2p$ orbitals of carbon and the $1s$ orbitals of the four hydrogens. The lowest molecular orbital is principally $1s$ in character. A significant feature of this and other MO calculations of methane is that unlike a picture involving localized bonds derived from sp^3-hybrid carbon orbitals, there are not four equivalent orbitals. We can obtain an understanding of this feature of the MO picture by a qualitative analysis of the origin of the methane molecular orbitals. For simplicity, we will consider the orbitals to be derived from the carbon $2s$, $2p_x$, $2p_y$, and $2p_z$ orbitals and ignore the carbon $1s$ orbital. The most convenient frame of reference for the tetrahedral methane molecule is described by a cube with hydrogen atoms at alternate corners and the carbon atom, centered in the cube, as shown in Fig. 1.13.

This orientation of the molecule reveals that methane possesses three twofold symmetry axes, one each along the x, y, and z axes. Because of this molecular symmetry, the proper molecular orbitals of methane must possess symmetry with respect to these same axes. There are two possibilities: the orbital may be unchanged by 180° rotation about the axis (symmetric), or it may be transformed into an orbital of identical shape but opposite sign by the symmetry operation (antisymmetric). The carbon $2s$ orbital is symmetric with respect to each axis, but the three $2p$ orbitals are each antisymmetric to two of the axes and symmetric with respect to one. The combinations which give rise to molecular orbitals that meet these symmetry requirements are shown in Fig. 1.14.

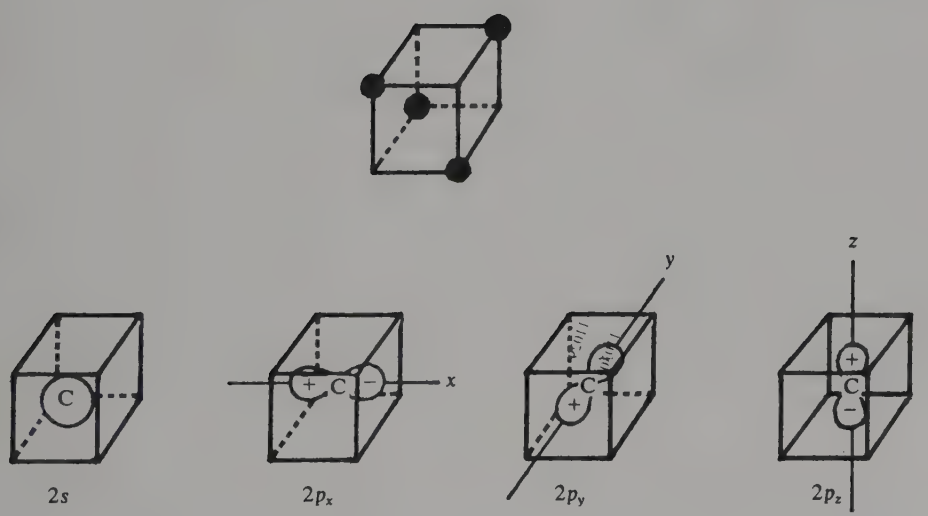


Fig. 1.13. Atomic orbitals of carbon relative to methane in a cubic frame of reference.

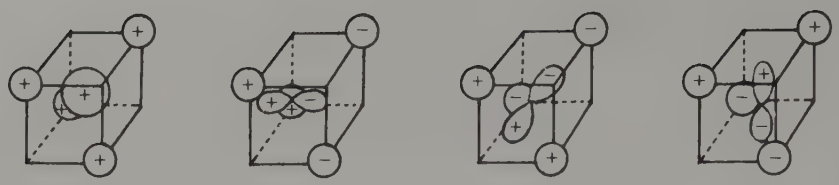


Fig. 1.14. Atomic orbital combinations giving rise to bonding molecular orbitals for methane.

The bonding combination of the carbon 2*s* orbital with the four 1*s* hydrogen orbitals leads to a molecular orbital that encompasses the entire molecule and has no nodes. Each of the MO's derived from carbon 2*p* orbitals has a node at carbon. The three combinations are equivalent, but higher in energy than the MO with no nodes. The four antibonding orbitals arise from similar combinations, but with the carbon and hydrogen orbitals having opposite signs in the regions of overlap.

The most direct and practical way to assess the validity of the conclusions based on MO considerations versus intuition based on qualitative notions of localized valence bonds is to measure the binding energies of the electrons in methane. The *ionization potential* is the energy required to remove an electron from a molecule and is quite high for most organic molecules, being on the order of 200 kcal/mol. The methods of choice for determining ionization potentials are photoelectron spectroscopy[35] and ESCA (electron spectroscopy for chemical analysis).[36] These techniques are complementary, in that ionization potentials up to about 20 eV (1 eV = 23.06 kcal/mol) are determined by photoelectron spectroscopy, corresponding to the binding energy of the valence electrons, while ESCA measures binding energies of core electrons. An ultraviolet source (photoelectron spectroscopy) or X-ray source (ESCA) emits photons, which are absorbed by the sample, resulting in ejection of an electron and formation of a positive ion. The kinetic energy of the emitted electron is determined and related to its binding energy by the equation

$$\text{binding energy} = \text{photon energy} - \text{kinetic energy of emitted electron}$$

This equation is the same as for the photoelectric effect observed for electron emission from metallic surfaces, except that the work function term has been replaced by the energy required to remove an electron, i.e., the ionization potential. These measurements allow the construction of molecular orbital energy diagrams directly from experimental data and provide a way of critically examining bonding theories.

35. For a review, see C. R. Brundle and M. B. Robin, *Photoelectron Spectroscopy*, in *Determination of Organic Structures by Physical Methods*, Vol. 3, F. C. Nachod and J. J. Zuckerman (eds.), Academic Press, New York, 1971, Chap. 1.
36. D. W. Turner, *Ann. Rev. Phys. Chem.* **21**, 107 (1970).

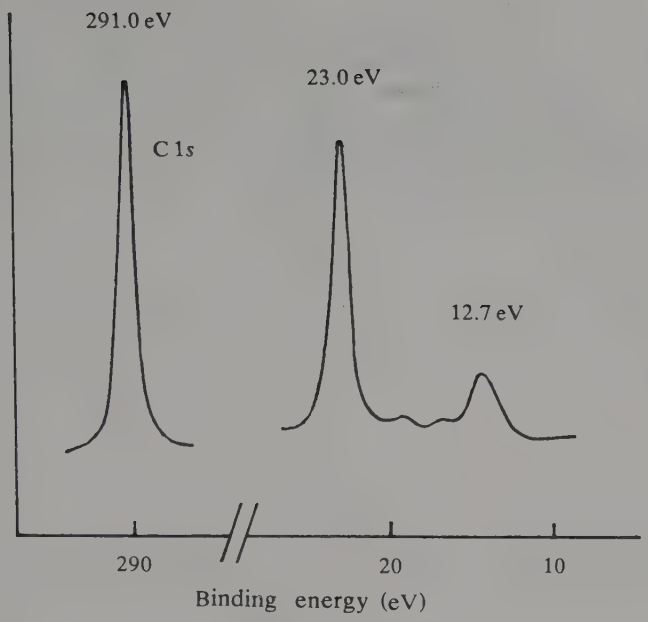
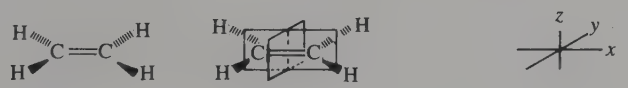


Fig. 1.15. ESCA spectrum of methane.

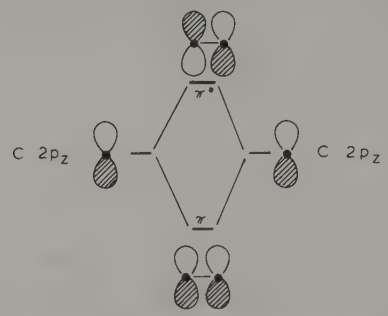
The ESCA spectrum of methane is presented in Fig. 1.15, where it can clearly be seen to be consistent with molecular orbital theory. There are two bands for the valence electrons at 12.7 and 23.0 eV, in addition to the band for the core electrons at 291 eV.[37] It should be emphasized that these values are the binding energies of electrons in the three orbitals of differing energy, and are *not* the energies required for successive ejection of first one, then a second, and then a third electron. The intensities bear no relation to the number of orbitals or number of electrons, and differ from each other because the cross sections for ionization are different.

The construction of the molecular orbitals of ethylene is very similar to the process used for carbon monoxide, but the total number of atomic orbitals is greater, twelve instead of eight because of the additional atomic orbitals from hydrogen. We first must define the geometry of ethylene. Ethylene is known to be a planar molecule.



37. U. Gelius, in *Electron Spectroscopy*, D. A. Shirley (ed.), American Elsevier New York, 1972, pp. 311–344.

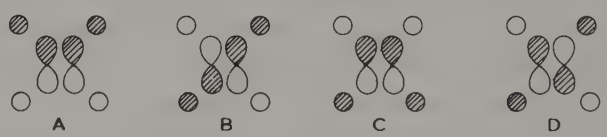
This defines three important elements of symmetry, the molecular plane and two planes which bisect the molecule. All molecular orbitals must be either symmetric or antisymmetric with respect to each of these symmetry planes in order to be an acceptable orbital. The orbitals arising from the carbon $2p_z$ orbitals have nodes in the molecular plane. These orbitals do not interact with any of the other orbitals and thus give rise to the familiar π and π^* orbitals.



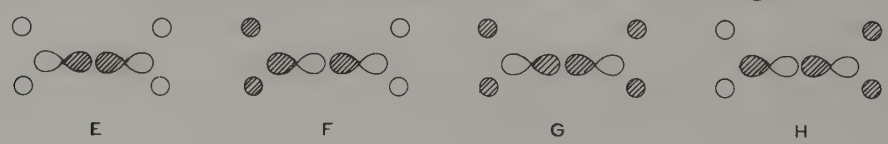
The π orbital is symmetric with respect to both the x–z plane and the y–z plane. It is antisymmetric with respect to the molecular (x–y) plane. On the other hand, π^* is antisymmetric with respect to the y–z plane.

The orbitals which remain are the four H 1s, two C 1s, and four C 2p orbitals. All lie in the molecular plane and can interact with one another. The combinations using the C 2s and H 1s orbitals can take only two forms which meet the molecular symmetry requirements. One, σ, is bonding between all atoms whereas σ^* is antibonding between all nearest-neighbor atoms.

Let us next consider the interaction of $2p_y$ with the four hydrogen 1s orbitals. There are four possibilities which conform to the molecular symmetry:



Orbital **A** is bonding between all nearest-neighbor atoms, whereas **B** is bonding within the CH_2 units but antibonding with respect to the two carbons. The orbital labeled **C** is C–C bonding but antibonding with respect to the hydrogens. Finally, orbital **D** is antibonding with respect to all nearest-neighbor atoms. Similarly, the $2p_x$ orbitals must be considered. Again, four possible combinations arise. Notice that the nature of the overlap of the p orbitals is different from the $2p_y$ case, so that the two sets of MO's would be expected to have different energies:



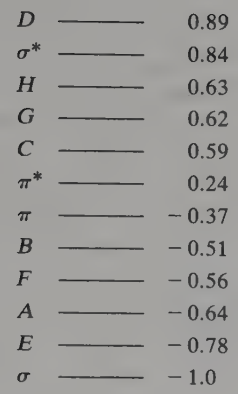


Fig. 1.16. Ethylene molecular orbital energy levels. Energies are given in atomic units.

The final problem in construction of a qualitative MO diagram is the relative placement of the orbitals. There are some guidelines which are useful. First, since π-type interactions are normally weaker than σ type, we expect the separation between σ and σ^* to be greater than between π and π^*. Within the sets **ABCD** and **EFGH** we can order $\mathbf{A} < \mathbf{B} < \mathbf{C} < \mathbf{D}$ and $\mathbf{E} < \mathbf{F} < \mathbf{G} < \mathbf{H}$ on the basis that C–H bonding interactions will outweigh C–C antibonding interactions. Similarly, C–H antibonding interactions will outweigh C–C bonding interactions arising from relatively weak *p–p* overlaps. Relative placement of the set **ABCD** with respect to **EFGH** is not qualitatively obvious. Calculations give the results shown in Fig. 1.16.[38] Pictorial representations of the orbitals are given in Fig. 1.17. The designations used for the orbitals in Fig. 1.17 are derived from a spectroscopic nomenclature system and need not concern us.

The kind of qualitative considerations which have been used to construct the ethylene molecular orbitals do not give an indication of how much each atomic orbital contributes to the individual molecular orbitals. These coefficients are obtained only by solution of one of the types of molecular orbital calculations. Without these coefficients we cannot specify the exact shapes of the molecular orbitals. However, the qualitative ideas do permit conclusions about the *symmetry* of the orbitals. As will be seen in Chapter 10, just knowing the symmetry of the molecular orbitals provides very useful insight into many chemical reactions.

38. W. L. Jorgensen and L. Salem, *The Organic Chemist's Book of Orbitals*, Academic Press, New York, 1973.

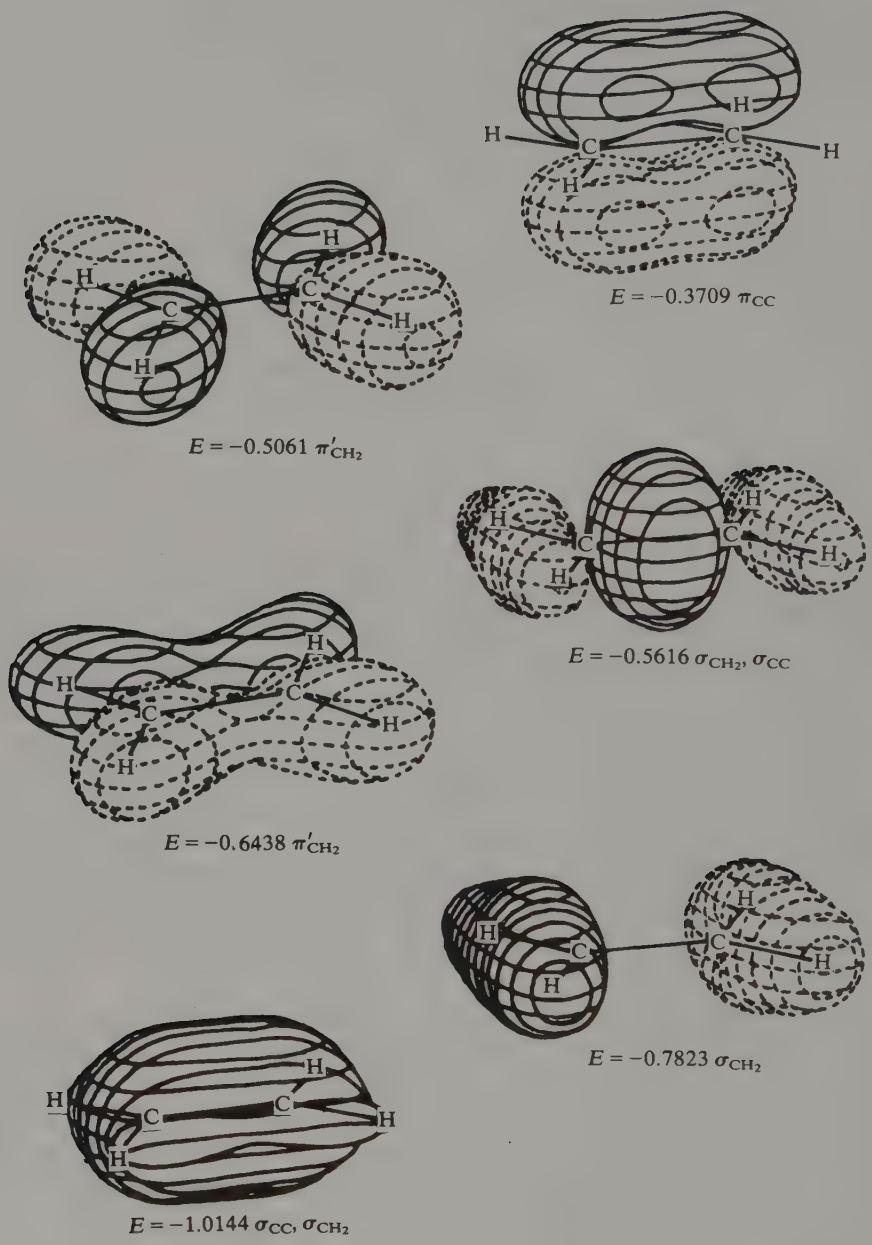
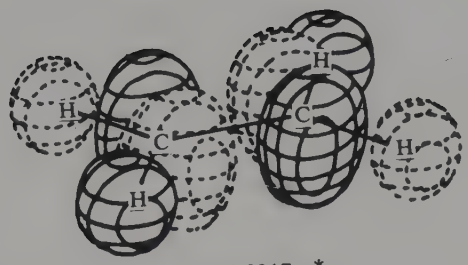
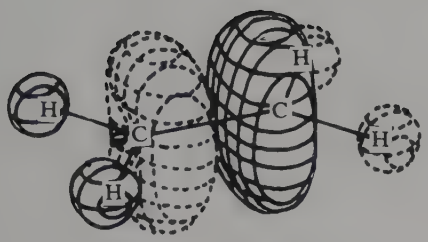


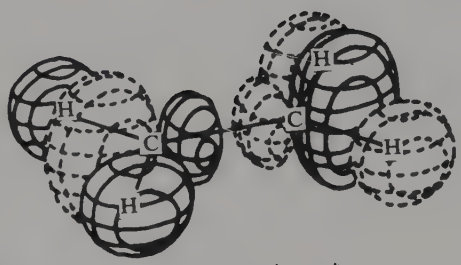
Fig. 1.17. Representations of the molecular orbitals of ethylene. (From W. L. Jorgensen and L. Salem, *The Organic Chemist's Book of Orbitals*, Academic Press, New York, 1973. Reproduced by permission.)



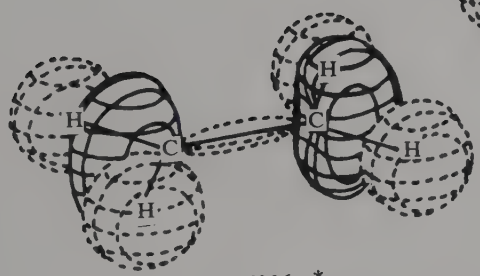
$E = 0.8917\ \pi^*_{CH_2}$



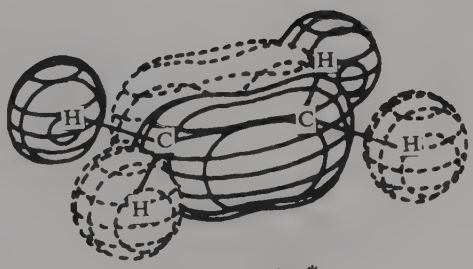
$E = 0.8453\ \sigma^*_{CC}, \sigma^*_{CH_2}$



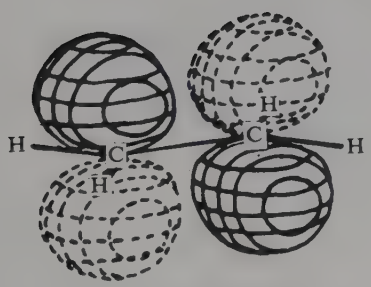
$E = 0.6395\ \sigma^*_{CH_2}, \sigma^*_{CC}$



$E = 0.6206\ \sigma^*_{CH_2}$

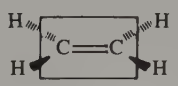


$E = 0.5868\ \pi^*_{CH_2}$



$E = 0.2426\ \pi^*_{CC}$

Figures 1.18–1.20 are another type of representation of the ethylene molecule derived from molecular orbital calculations. Figure 1.18 is a log scale plot of the σ-electron density. It shows the highest density around the nuclear positions as indicated by the pronounced peaks corresponding to the atomic positions but also indicates the continuous nature of the σ-electron distribution. A representation of the π-electron density is given in Fig. 1.19. This represents the density in a plane



bisecting the molecule perpendicular to the plane of the molecule. The diagram shows that the π-electron density drops to zero in the nodal plane of the π system. Figure 1.20 is a representation of the combined σ- and π- electron density in this same plane.

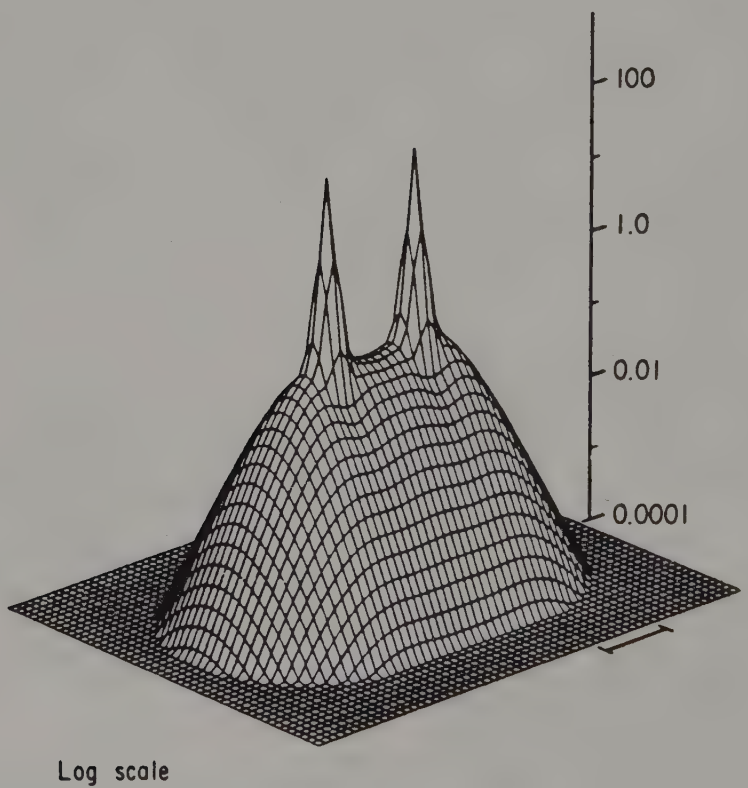


Fig. 1.18. Log scale of σ-electron density in a plane bisecting the carbon atoms and perpendicular to the plane of the molecule. (From A. Streitwieser, Jr., and P. H. Owens, *Orbital and Electron Density Diagrams*, Macmillan, New York, 1973. Reproduced with permission.)

Before the advent of high-speed computers enabled detailed molecular orbital calculations to be performed routinely, it was essential that greatly simplifying approximations be applied to the complex molecular systems of interest to organic chemists, so that worthwhile information of a theoretical nature could be extracted. One of the most useful of these approximations was that espoused in Hückel molecular orbital (HMO) theory as it relates to conjugated systems. HMO theory is based on the approximation that the π system can be treated independently of the σ framework of conjugated double bonds, and that it is the π system that is of paramount importance in determining the physical, chemical, and spectral properties of aromatic and polyolefinic compounds. The rationalization for treating the σ and

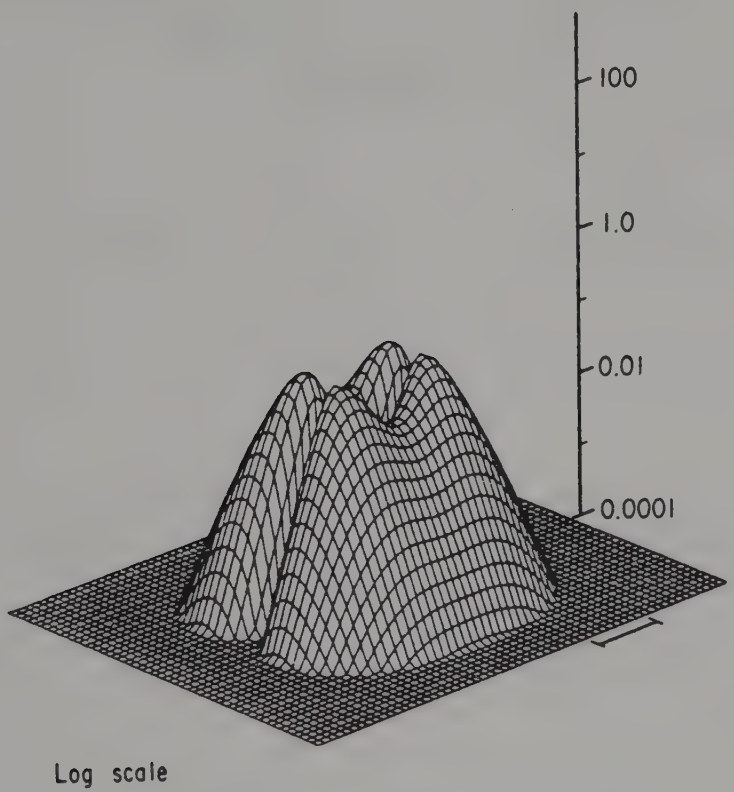


Fig. 1.19. Log scale plot of π-electron density in a plane bisecting the carbon atoms and perpendicular to the plane of the molecule. (From A. Streitwieser, Jr., and P. H. Owens, *Orbital and Electron Density Diagrams*, Macmillan, New York, 1973. Reproduced with permission.)

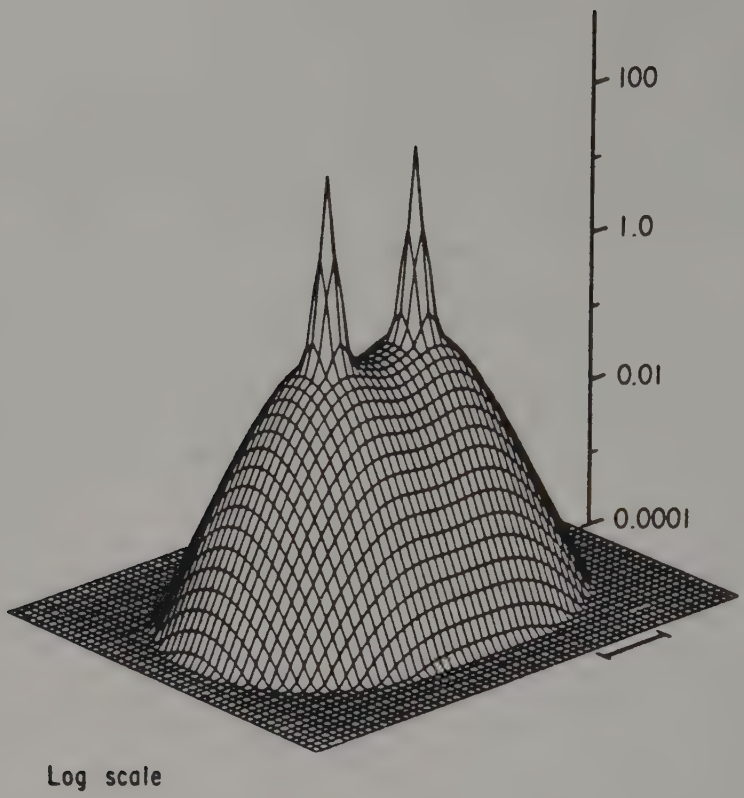


Fig. 1.20. Log scale plot of total electron density in a plane bisecting the carbon atoms and perpendicular to the molecular plane. (From A. Streitwieser, Jr., and P. H. Owens, *Orbital and Electron Density Diagrams*, Macmillan, New York, 1973. Reproduced with permission.)

π systems as independent of each other depends on their orthogonality. The σ skeleton of a planar conjugated system lies in the nodal plane of the π system and does not interact with it. Because of its simplicity, HMO theory has been extremely valuable in the development of an understanding of molecular orbital concepts among organic chemists; in favorable cases, it permits a fairly thorough analysis to be made of real chemical systems.

Using the HMO approximation, the π-electron wave function is expressed as a linear combination of p_x atomic orbitals (for the case in which the plane of the molecule coincides with the y–z plane of the coordinate axis), in much the same way as described previously for the generalized MO method. Minimizing the total π-electron energy of the molecule with respect to the coefficients (the variation method) leads to a series of equations from which the coefficients can be extracted by way of a secular determinant. The mathematical operations involved in solving the

equations are not difficult.[39] We will not describe them in detail, but will instead concentrate on the interpretation of the results of the calculations. For many systems, the Hückel MO energies and atomic coefficients have been tabulated.[40]

The most easily obtainable information from such calculations are the relative orderings of the energy levels and, as mentioned in the previous paragraph, the atomic coefficients. Solutions are readily available for a number of general cases of frequently encountered delocalized systems, which we will illustrate by referring to some typical examples. Consider first *linear polyenes* of formula C_nH_{n+2}, such as 1,3-butadiene, 1,3,5-hexatriene, and so forth. The energy levels for such compounds are given by the expression

$$E = \alpha + m_j\beta$$

where

$$m_j = 2\cos\frac{j\pi}{n+1} \qquad \text{for} \quad j = 1, 2, \ldots, n$$

and n is the number of carbon atoms in the conjugated chain. This calculation generates a series of molecular orbitals with energies expressed in terms of the quantities α and β, which symbolize the *Coulomb integral* and *resonance integral*, respectively. The Coulomb integral, α, is related to the binding of an electron in a $2p$ orbital, and this is taken to be a constant for all carbon atoms but will vary for heteroatoms as a result of the difference in electronegativity. The resonance integral β, is related to the energy of an electron in the field of two or more nuclei. In the Hückel method β is assumed to be zero when nuclei are separated by distances greater than the normal bonding distance. The approximation essentially assumes that the electron is affected only by nearest-neighbor nuclei. Both α and β are negative numbers and represent unspecified units of energy.

The coefficient corresponding to the contribution of the $2p$-AO of atom r to the jth MO is given by

$$c_{rj} = \left(\frac{2}{n+1}\right)^{1/2}\left(\sin\frac{rj\pi}{n+1}\right)$$

Carrying out the numerical operations for 1,3,5-hexatriene gives the results shown in Table 1.12.

Since the molecule is a six-π-electron system, ψ_1, ψ_2, and ψ_3 are all doubly occupied, giving a total π-electron energy of $6\alpha + 6.988\beta$. The general solution for this system is based on the assumption that the electrons are delocalized. If

39. J. D. Roberts, *Notes on Molecular Orbital Calculations*, W. A. Benjamin, New York, 1961; A. Streitwieser, Jr., *Molecular Orbital Theory for Organic Chemists*, John Wiley and Sons, New York, 1961.
40. C. A. Coulson and A. Stretwieser, Jr., *Dictionary of π-Electron Calculations*, W. H. Freeman San Francisco, 1965.

Table 1.12. Energy Levels and Coefficients for HMO's of 1,3,5-Hexatriene

π-Orbital: ψ_j	m_j	c_1	c_2	c_3	c_4	c_5	c_6
ψ_1	1.802	0.2319	0.4179	0.5211	0.5211	0.4179	0.2319
ψ_2	1.247	0.4179	0.5211	0.2319	−0.2319	−0.5211	−0.4179
ψ_3	0.445	0.5211	0.2319	−0.4179	−0.4179	0.2319	0.5211
ψ_4	−0.445	0.5211	−0.2319	−0.4179	0.4179	0.2319	−0.5211
ψ_5	−1.247	0.4179	−0.5211	0.2319	0.2319	−0.5211	0.4179
ψ_6	−1.802	0.2319	−0.4179	0.5211	−0.5211	0.4179	−0.2319

this assumption were not made and the molecule were considered to be composed of alternating single and double bonds, the total π-electron energy would have been $6\alpha + 6\beta$, or identical to that for three ethylene units. The difference between the electron energy calculated for a system of delocalized electrons and that calculated for alternating single and double bonds is referred to as the *delocalization energy*, and is a measure of the extra stability afforded a molecule containing delocalized electrons compared to a molecule containing localized "bonds." The calculated delocalization energy (DE) for 1,3,5-hexatriene is 0.988β. The value of β (as expressed in conventional energy units) is a matter of long-standing dispute. One of the popularly used values is 18 kcal/mol, and is pegged to a figure of 36 kcal/mol for the "resonance energy" (RE) of benzene, for which the calculated π-DE is 2β. Since agreement is not universal as to the significance or value of the RE of benzene, its use as a standard for the calibration of β is open to question.

Inspection of the coefficients and a feeling for the way they translate into symmetry properties of orbitals can be used in an extremely powerful way to aid in understanding a number of aspects of organic reactions. Such considerations apply particularly well to concerted reactions and will be described in detail in Chapter 10. It can be seen in Table 1.12. that the coefficients are all of like sign in the lowest-energy orbital, ψ_1, and that the number of times that a sign change appears in the wave function increases with the energy of the orbital. A change in sign of the coefficients of the AO's on adjacent atoms corresponds to an antibonding interaction between the two, and a node exists at some point between them. Thus, ψ_1 has no nodes, ψ_2 has one, ψ_3 has two, and so on up to ψ_6, which has five nodes and no bonding interactions in its combination of AO's. A diagrammatic view of the bonding and antibonding interactions among the AO's of 1,3,5-hexatriene is presented in Fig. 1.21. Notice that for the bonding orbitals ψ_1, ψ_2, and ψ_3, there are more bonding interactions (positive overlap) than antibonding interactions (negative overlap), while the opposite is true of the antibonding orbitals.

The success of simple HMO theory in dealing with the relative stabilities of cyclic conjugated polyenes is impressive. Simple resonance arguments lead to con-

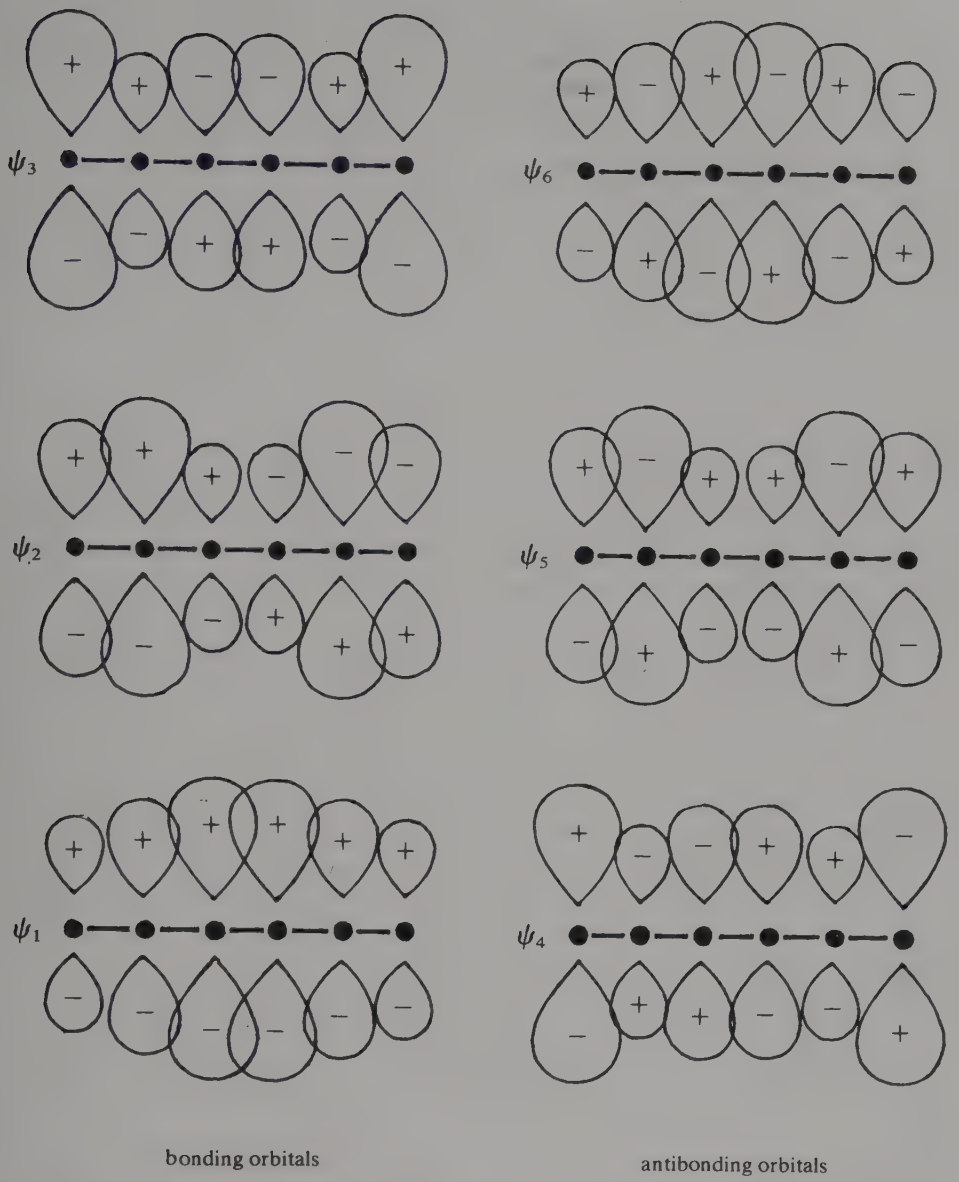


Fig. 1.21. Graphic representation of π-molecular orbitals of 1,3,5-hexatriene as combinations of $2p$ AO's. The sizes of the orbitals are roughly proportional to the coefficients of the Hückel wave functions.

fusion when one tries to compare the unique stability of benzene with the elusive quality of cyclobutadiene. This contrast is readily explained by *Hückel's rule*, which states that a species will be aromatic if it is composed of a planar monocyclic array of atoms, each of which contributes a p orbital to the π system and the total number

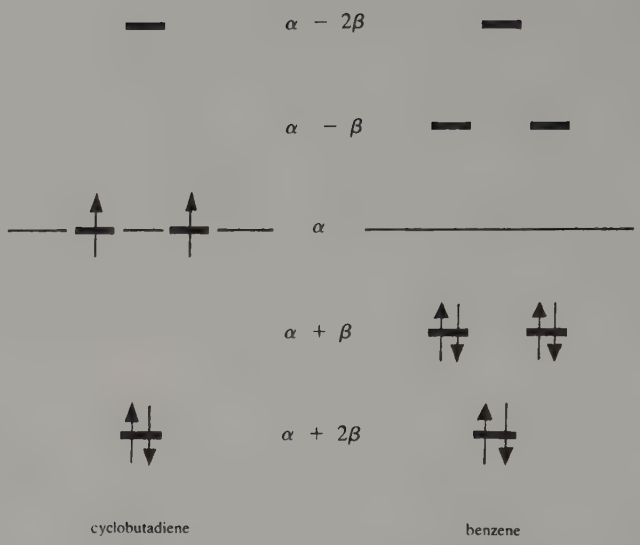


Fig. 1.22. Energy level diagrams for cyclobutadiene and benzene.

of electrons in that π system is equal to $4n + 2$, where n is an integer. By this criterion, benzene, with six π electrons, is aromatic, while cyclobutadiene, with four, is not. A clearer understanding of the theoretical basis for Hückel's rule can be gained by examining the results of HMO calculations. For cyclic polyenes, the general solution for the energy levels is

$$E = \alpha + m_j\beta$$

where

$$m_j = 2\cos\frac{2j\pi}{n} \quad \text{for} \quad j = 0, \pm1, \pm2, \ldots, \begin{cases} \pm(n-1)/2 \text{ for } n \text{ odd} \\ \pm n/2 \text{ for } n \text{ even} \end{cases}$$

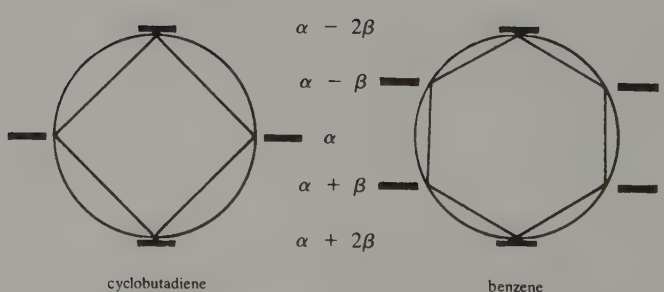


Fig. 1.23. Energy level diagrams for cyclobutadiene and benzene, illustrating the application of Frost's circle.

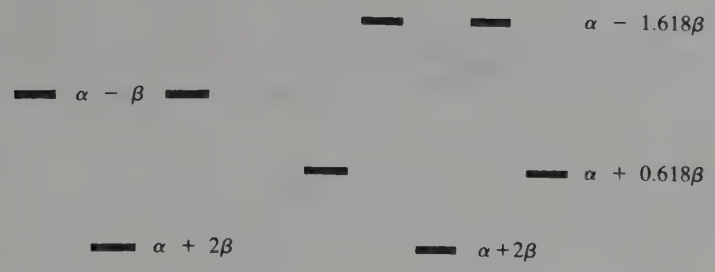


Fig. 1.24. Energy-level diagrams for C_3H_3 and C_5H_5 systems.

and n is the number of carbon atoms in the ring. This solution gives the energy level diagrams for cyclobutadiene and benzene shown in Fig. 1.22.

The total π-electron energy of benzene is $6\alpha + 8\beta$, corresponding to a DE of 2β. Cyclobutadiene is calculated to have a triplet ground state (for a square geometry) and zero DE, since the π-electron energy is $4\alpha + 4\beta$, the same as that for two independent double bonds. Thus, at this level of approximation, HMO theory predicts no stabilization for cyclobutadiene from resonance and furthermore predicts that the molecule will have unpaired electrons which would lead to very high reactivity. The extreme instability of cyclobutadiene is then understandable. More detailed MO calculations modify this picture somewhat. They predict that cyclobutadiene will be a rectangular molecule, as will be discussed in Chapter 9. These calculations, nevertheless, agree with HMO theory in concluding that there will be no stabilization of butadiene resulting from the conjugated double bonds.

A useful mnemonic device for quickly setting down the HMO's for cyclic systems is *Frost's circle.*[41] If a regular polygon of n sides is inscribed in a circle of diameter 4β with one corner at the lowest point, the points at which the corners of the polygon touch the circle define the energy levels. Thus, for benzene and cyclobutadiene, the energy levels obtained with Frost's circle are as shown in Fig. 1.23.

The energy level diagrams for charged C_3H_3 and C_5H_5 systems are readily constructed, and are presented in Fig. 1.24. Cyclopropenyl cation has a total of two π-electrons, which occupy the bonding HMO, and a total π-electron energy of $2\alpha + 4\beta$. This gives a π-DE of 2β and is indicative of a stabilized species. Addition of two more π electrons to the system to give cyclopropenide anion requires population of higher-energy antibonding orbitals and a net destabilization of the molecule. The opposite is true for the C_5H_5 case, where the anionic species is stabilized and the cationic species is not. Monocyclic conjugated systems are referred to as *annulenes*,

41. A. A. Frost and B. Musulin, *J. Chem. Phys.* **21**, 572 (1953).

and there exists ample experimental evidence to support the conclusions based on application of HMO theory to neutral and charged annulenes. The relationship between stability and structure in cyclic conjugated systems will be explored more fully in Chapter 9.

While Hückel's $4n+2$ rule applies only to monocyclic systems, HMO theory is not so limited in this respect. HMO calculations of fused-ring systems are carried out in much the same way as for monocyclic species, and yield secular determinants for which the solutions afford energy levels and coefficients. The secular determinants encountered here are usually more complex than for more simple molecules and typically require computer solution, although use of group theory to factor large matrices into smaller ones does permit hand calculation in some instances.

While the Hückel method has now been supplanted by more complete treatments for theoretical analysis of organic reactions, the pictures of the π orbitals of both linear and cyclic conjugated polyene systems are correct as to the symmetry and relative energy of the orbitals. In many reactions where the π system is the primary site of reactivity these orbitals correctly describe the behavior of the systems. For that reason the student should develop a familiarity with the qualitative description of the π orbitals of typical linear polyenes and conjugated cyclic hydrocarbons. These orbitals will be the basis for further discussion in Chapters 9 and 10.

1.6. PMO Theory

The construction of molecular orbital diagrams under the guidance of the general principles which have been outlined and symmetry restrictions can lead to useful insights into molecular structure. Now we need to consider how these structural concepts can be related to reactivity. In valence bond terminology, structure is related to reactivity in terms of substituent effects. The impact of inductive effects and resonance effects on the stability of reactants, transition states, and intermediates is assessed. In molecular orbital theory, we will want to consider how the various molecular orbitals of the reactants interact with one another. The general framework for such considerations is called *perturbation molecular orbital theory*, or PMO for short.[42] The physical basis for this interpretation of reactivity is the fact that molecular orbitals do interact with one another as a reaction proceeds. The reaction process, indeed, is the transformation of the molecular orbitals of the reactants into those of the product(s), with the accompanying changes in bond type. PMO theory suggests that the course of a chemical reaction can be predicted by analyzing how the approaching reactant molecules mutually perturb the molecular

42. C. A. Coulson and H. C. Longuet-Higgins, *Proc. R. Soc. London Ser. A* **192**, 16 (1947); L. Salem, *J. Am. Chem. Soc.* **90**, 543 (1968); M. J. S. Dewar and R. C. Dougherty, *The PMO Theory of Organic Chemistry*, Plenum Press, New York, 1975; G. Klopman, *Chemical Reactivity and Reaction Paths*, Wiley–Interscience, New York 1974, Chap. 4.

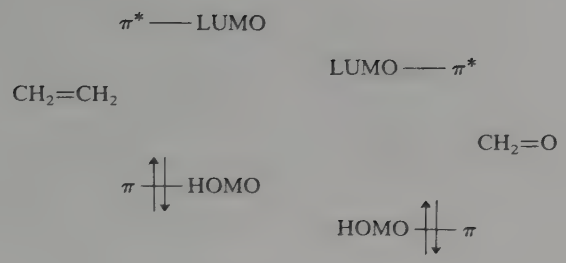


Fig. 1.25. Relative energy of the π and π^* orbitals in ethylene and formaldehyde.

orbitals of the reaction partner. PMO theory also makes use of the idea of frontier orbital control, which proposes that the most important interactions will be between a particular pair of orbitals.[43] These orbitals are the highest filled orbital of one reactant (the HOMO, highest occupied molecular orbital) and the lowest unfilled (LUMO, lowest unoccupied molecular orbital) orbital of the other reactant. The basis for concentrating attention on these two orbitals is that they will usually be the closest in energy of the interacting orbitals. A basic postulate of PMO theory is that interactions are strongest between orbitals that are close in energy. Frontier orbital control proposes that these strong initial interactions can then guide the course of the reaction as it proceeds to completion. A further general feature of PMO theory is that only MO's of matching symmetry can interact to lead to bond formation. Thus, analysis of a prospective reaction path by PMO theory will direct attention to the relative energy and the symmetry of the interacting orbitals.

These ideas can be illustrated here by considering some very simple cases. We will return to frontier orbital theory in more detail in Chapter 10. Let us consider the fact that the double bonds of ethylene and formaldehyde have very different chemical reactivities. Formaldehyde readily reacts with nucleophiles whereas ethylene is more reactive than formaldehyde to electrophiles. We have already described the ethylene MO's in Figure 1.16 and 1.17. How will those of formaldehyde differ? In the first place, the higher atomic number of oxygen provides two additional electrons so that in place of the CH_2 group of ethylene the oxygen of formaldehyde has two pairs of essentially nonbonding electrons. The key change, however, has to do with the frontier orbitals, the π (HOMO) and π^* (LUMO) orbitals. These are illustrated in Fig. 1.25. One significant difference between the two molecules is the lower energy of the π and π^* orbitals of formaldehyde. These are lower in energy than

43. K. Fukui, *Acc. Chem. Res.* **4**, 57 (1971); I. Fleming, *Frontier Orbital and Organic Chemical Reactions*, Wiley, New York, 1976; L. Salem, *Electrons in Chemical Reactions*, Wiley, New York, 1982, Chap. 6.

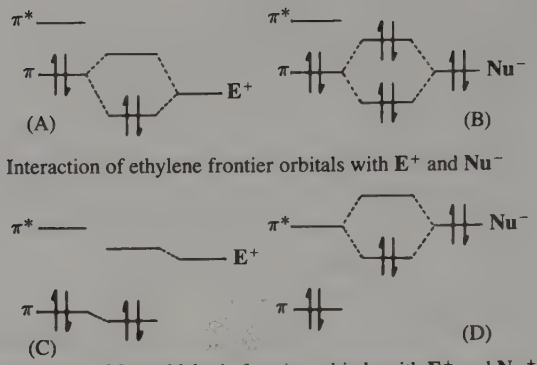


Fig. 1.26. PMO description of interaction of ethylene and formaldehyde with an electrophile ($\mathbf{E}^+$) and nucleophile ($\mathbf{Nu}^-$).

the corresponding ethylene orbitals because they are derived from the lower lying (more electronegative) $2p_z$ orbital of oxygen. Because of its lower energy the π^* orbital is a better acceptor of electrons from the HOMO of any attacking nucleophile. On the other hand, we also can see why ethylene is more reactive to electrophiles than formaldehyde. In electrophilic attack it is the HOMO orbital that is involved as an electron donor to the attacking electrophile. In this case that fact that the HOMO of ethylene lies higher in energy than the HOMO of formaldehyde will mean that electrons can more easily be attracted by the approaching electrophile.

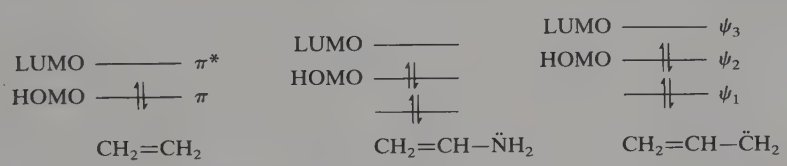
Perturbation theory can be expressed in a quantitative way. We will not consider the quantitative theory here but do want to point out two features of the quantitative theory which underlie the qualitative application of PMO theory. One principle is that the degree of perturbation is a function of the degree of overlap of the orbitals. Thus in the qualitative application of PMO theory, it is important to consider the shape of the orbitals (as indicated quantitatively by their coefficients) and the proximity which can be achieved within the limits of the geometry of the reacting molecules. Secondly, the strength of a perturbation depends on the relative energy of the interacting orbitals. The closer in energy, the greater will be the mutual splitting of the orbitals. This principle, if used in conjunction with reliable estimates of relative orbital energies, can be of value in predicting the relative importance of various possible interactions.

Let us illustrate these ideas by returning to the comparisons of the reactivity of ethylene and formaldehyde toward a nucleophilic species and an electrophilic species. The interactions (perturbations) which arise as both a nucleophile and electrophile approach are sketched in Fig. 1.26.

The electrophilic species $\mathbf{E}^+$ must have a low-lying empty orbital. The strongest interaction will be with the ethylene π orbital and this leads to a strong perturbation which has a stabilizing effect. The same species would lie closer to π^* of formaldehyde since the formaldehyde orbitals are shifted to lower energy. The strongest interaction would then be with π^* but since both π^* and $\mathbf{E}^+$ are empty orbitals it does not

lead to any stabilizing interaction. The conclusion is that such an electrophile will undergo a strong stabilizing attraction on approaching within bonding distance of ethylene but will not for formaldehyde. In the case of **Nu**$^-$, a strong bonding interaction with π^* of formaldehyde is possible (D). In the case of ethylene the strongest interaction will be with π, but this is not a net stabilizing interaction since both orbitals are filled and the lowering of one orbital is canceled by the raising of the other. Thus we conclude that a nucleophile can interact in a bonding way with the formaldehyde LUMO.

The ideas of PMO theory can be used in a slightly different way to describe substituent effects. Let us consider, for example, the effect of a π-donor substituent or a π-acceptor substituent on the MO levels of ethylene and upon the reactivity of the substituted ethylenes. We can take the amino group as an example of a π-donor substituent. The overall shape of the π orbitals from aminoethylene will be similar to those of an allyl anion but with some distortion since the system is no longer symmetrical. If the amino substituent is properly aligned, it provides two π electrons which give a total of four π electrons, the same as for the allyl anion. The highest charge density should be on the terminal atoms, that is the nitrogen atom and the β carbon. Furthermore the HOMO should be considerably higher in energy than the HOMO in ethylene. The HOMO in aminoethylene will resemble ψ_2 of the allyl anion. It will not be quite so high in energy as the allyl ψ_2 because of the higher electronegativity of the nitrogen atom, but it will be substantially higher than the HOMO of ethylene. Thus we expect aminoethylene, with its high-lying HOMO, to be more reactive toward electrophiles than ethylene. On the other hand, the LUMO will now correspond to the higher energy ψ_3 of the allyl anion so we expect aminoethylene to be even less reactive toward nucleophiles than is ethylene.

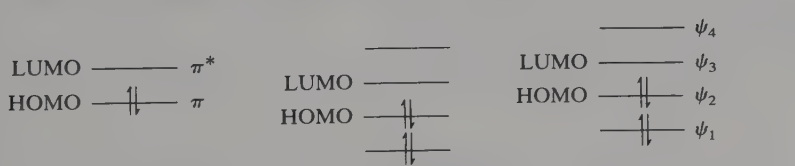


π MO energy levels for ethylene with a π-donor substituent.

An example of a π-acceptor group would be the formyl group as in acrolein.

$$CH_2{=}CHCH{=}O$$

In this case, the π-molecular orbitals should resemble those of butadiene. Relative to butadiene, however, the acrolein orbitals will lie somewhat lower in energy because of the effect of the more electronegative oxygen atom. This factor will also increase the electron density at oxygen relative to carbon.



π MO energy levels for ethylene with a π-acceptor substituent.

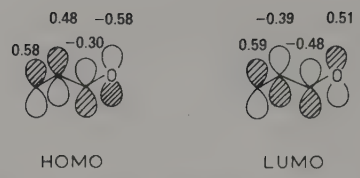


Fig. 1.27. Orbital coefficients for the HOMO and LUMO of acrolein. From K. N. Houk and P. Strozier, *J. Am. Chem. Soc.* **95**, 4094 (1973).

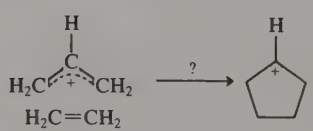
The LUMO, which will be the frontier orbital in reactions with nucleophiles, has a large coefficient on the β-carbon atom, whereas the two occupied orbitals are distorted in such a way as to have larger coefficients on oxygen. The overall effect is that the LUMO is relatively low-lying and has a high coefficient at the β carbon. The frontier orbital theory therefore predicts nucleophiles will react preferentially at the β-carbon atom. We cannot assign a numerical value to the coefficient without a calculation. Figure 1.27 gives the orbital coefficients as derived from CNDO calculations.

Notice that the MO picture gives the same qualitative picture of the substituent effect as described by resonance structures. The amino group is pictured by resonance as an electron donor which causes a buildup of charge at the β carbon, whereas the formyl group is an electron acceptor which diminishes electron density at the β carbon.

$$CH_2{=}CH{-}\ddot{N}H_2 \leftrightarrow {}^{-}CH_2{-}CH{=}\overset{+}{N}H_2 \qquad CH_2{=}CH{-}CH{=}O \leftrightarrow {}^{+}CH_2{-}CH{=}CH{-}O^{-}$$

The chemical reactivity of these two substituted ethylenes is in agreement with the ideas encompassed by both the MO and resonance descriptions. Enamines, as amino-substituted alkenes are called, are very reactive toward electrophilic species and it is the β carbon which is the principal site of reactivity. For example, enamines are protonated on the β carbon. Acrolein is an electrophilic alkene, as predicted, and the nucleophile attacks the β carbon.

Frontier orbital theory also provides the basic framework for analysis of the effect that the symmetry of orbitals has upon reactivity. One of the basic tenets of PMO theory is that the symmetries of two orbitals must match to permit a strong interaction between them. This symmetry requirement used in the context of frontier orbital theory can be a very powerful tool for predicting reactivity. As an example, let us examine the approach of an allyl cation and an ethylene molecule and ask whether the following reaction is likely to occur.



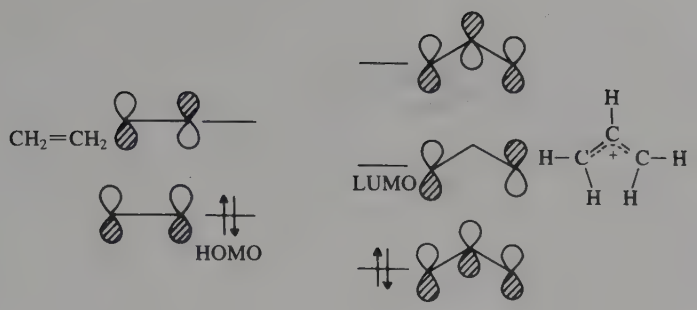
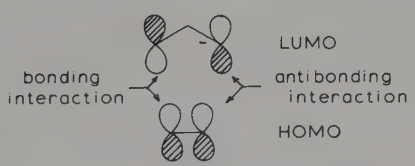


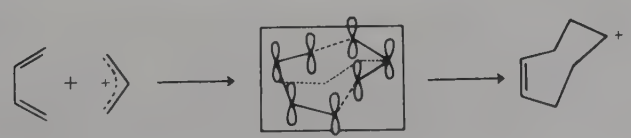
Fig. 1.28. MO's for ethylene and the allyl cation.

The positively charged allyl cation would be expected to be the electron acceptor in any initial interaction with ethylene. Therefore to consider this reaction in terms of PMO theory, the question we need to answer is "do the ethylene HOMO and allyl cation LUMO interact favorably as the reactants approach one another?" The orbitals which are involved are shown in Fig. 1.28. If we analyze a symmetrical approach which would be necessary to simultaneously form the two new bonds, we see that the symmetries of the two orbitals do not match. Any bonding interaction developing at one end would be canceled by an antibonding interaction at the other end. The conclusion that is drawn from this analysis in terms of PMO theory is that



this particular reaction process is not feasible. We would need to consider other modes of approach to analyze the problem more thoroughly, but this analysis indicates that simultaneous (concerted) bond formation between ethylene and the allyl cation is not possible.

Let us now consider another hypothetical reaction, this time between the allyl cation and butadiene. Again the assumption will be made that it is the π electrons which will govern the course of the reaction. We will also be slightly more formal about the issue of symmetry. This can be done by recognizing the elements of symmetry which would be maintained as the reaction proceeded. If the reaction is to proceed in a single step, the geometry must permit simultaneous overlap of the orbital on the carbons where new bonds are being formed. The geometry of approach which is shown permits such a simultaneous overlap.



This arrangement would maintain a plane of symmetry during the course of the reaction. The plane bisects butadiene between C-2 and C-3 and the allyl cation at C-2. The orbitals can be classified as symmetric (*S*) or antisymmetric (*A*) with respect to this plane. This gives rise to the MO diagram shown in Fig. 1.29. Since strong interactions will occur only between orbitals of the same symmetry, the mutual perturbations of the approaching reactants will affect the orbital energy levels as shown in the diagram. As in all such perturbations one orbital of the interacting pair will be stabilized and the other moved to higher energy. The perturbed orbitals at some point on the way to the transition state are shown in the diagram. Eventually, when the reaction has proceeded to completion, a new set of orbitals belonging to the product will have been formed. These are shown in the center of the diagram but we will be considering only the initial perturbed set. The lowest-lying π orbitals of both butadiene and the allyl cation are filled. These will interact with one moving down in energy and the other up. These two changes in energy are partially compensating with the total energy change being a net increase in energy of the system. Both the HOMO and LUMO are antisymmetric and will interact strongly, but in this case, since only two electrons are involved, only the effect of the decreasing energy will have an effect on the total energy. The energy of the other orbital makes no contribution since it is empty. This HOMO–LUMO interaction then contributes a net bonding contribution as the transition state is approached. From this analysis we conclude that there is the possibility of a favorable bonding interaction between the two reactant species. Notice that the reaction is only *permitted* and nothing can be said about its actual efficiency or energy require-

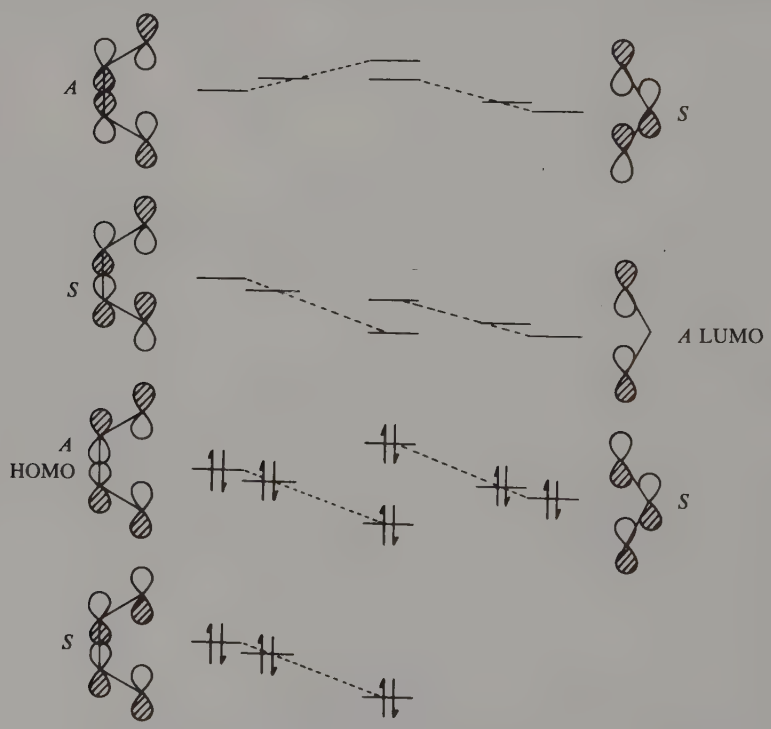
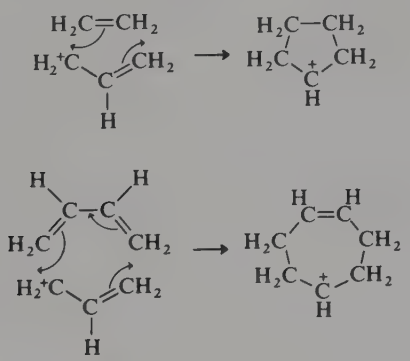


Fig. 1.29. MO diagram showing mutual perturbation of MO's of butadiene and the allyl cation.

ment on the basis of the analysis given. Such matters as steric hindrance to approach of the reactants and the geometric requirements for satisfactory overlap of the orbitals could still cause the reaction to proceed with difficulty. The analysis does establish, however, that there is a pathway by which the orbitals of the reactants can interact in a way that is favorable for reaction.

A more complete analysis of interacting molecules would examine all the involved molecular orbitals in a similar way. A *correlation diagram* would be constructed to determine which reactant orbital is transformed into which product orbital. Reactions which permit smooth transformation of the reactant orbitals to product orbitals without the intervention of high-energy transition states or intermediate can be identified in this way. If no such transformation is possible, a much higher activation energy is likely since the absence of a smooth transformation implies that bonds must be broken before they can be reformed. This treatment is more complete than the frontier orbital treatment since it focuses attention not only on the reactant but also on the product. We will describe such analysis in detail in Chapter 10. The PMO approach which has been described here is a useful and simple way to apply MO theory to reactivity problems in a qualitative way and we will employ it in subsequent chapters to problems in reactivity which are best described in MO terms.

It is worth noting that in the case of the reaction of ethylene and butadiene with the allyl cation the MO description has provided a prediction which would not have been recognized by a pictorial application of valence bond terminology. Thus



we can write an apparently satisfactory description of both reactions. It is only on considering the symmetry of the interacting orbitals that we find reason to suspect that only the second reaction is possible.

1.7. Interaction between π and σ Systems—Hyperconjugation

One of the key assumptions of the Hückel approximation is the noninteraction of the π-orbital system with the σ-molecular framework. This, as was mentioned, is a good approximation for completely planar molecules where the σ framework is in the nodal plane of the π system. For other molecules, as for example when an sp^3 carbon is added as a substituent group, this approximation is no longer entirely valid. Qualitative application of molecular orbital theory can be enlightening in describing interactions between the π system and substituent groups. In valence

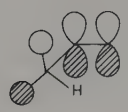
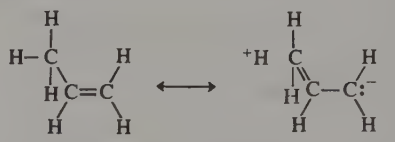
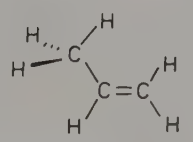


Fig. 1.30. Interactions between two hydrogen 1*s* orbitals and carbon $2p_z$ orbitals stabilizes the eclipsed conformation of propene.

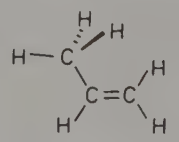
bond theory a special type of resonance called hyperconjugation is used to describe such interactions. For example, much chemical and structural evidence indicates that alkyl groups substituted on a carbon–carbon double bond act as electron donors to the π system. In valence bond language "no-bond" resonance structures are introduced to indicate such electronic interaction.



The molecular orbital picture of such interactions flows from the idea that individual orbitals encompass the entire molecule. Thus, while the MO description of ethylene involved no interaction between the C-$2p_z$ orbitals with the H-1*s* orbitals (see page 32 to recall this discussion), this strict separation would not exist in propene since the hydrogens of the methyl group are not in the nodal plane of the π bond. The origin of interaction of these hydrogens with the π orbital can be indicated as in Fig. 1.30 which shows propene in a geometry in which two of the hydrogen 1*s* atomic orbitals are in a position to interact with the $2p_z$ orbital of carbon 2. An *ab initio* calculation using a STO-3G basis set was carried out on propene in two distinct geometries, eclipsed, and staggered. The calculation of the optimum molecular geometry shows a slight lengthening of the C–H bonds because of the electron



eclipsed



staggered

release to the π system. These calculations also reveal a barrier to rotation of the methyl group of about 1.5–1.8 kcal/mol. Interaction between the hydrogens and the π system favor the eclipsed conformation to this extent.[44] Let us examine the reason for the preference for the eclipsed conformation. This issue can be approached

44. W. J. Hehre, J. A. Pople, and A. J. P. Devaquet, *J. Am. Chem. Soc.* **98**, 664 (1976); A Pross, L. Radom, and N. V. Riggs, *J. Am. Chem. Soc.* **102**, 2253 (1980).

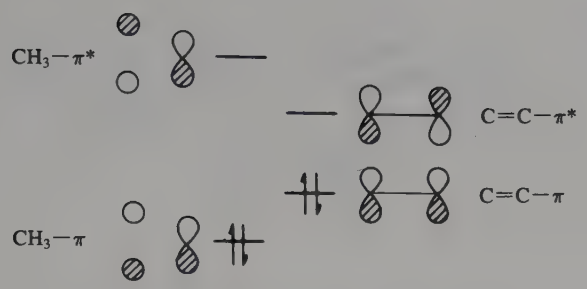


Fig. 1.31. Interactions between CH_3-π and CH_3-π^* orbitals and carbon $2p_z$ orbitals.

by analyzing the interactions between the carbon $2p_z$ orbitals and the CH_3 fragment in a little more detail. The bonding and antibonding combinations which arise from interaction of the appropriate CH_3-π and CH_3-π^* orbitals with the $2p_z$ orbital are shown in Fig. 1.31. The strongest interaction is a repulsive one between the filled CH_3-π and C=C-π orbitals. It is this interaction which is primarily responsible for the favored eclipsed conformation. The eclipsed structure minimizes the repulsion by maximizing the separation between the hydrogens and the π bond. The second interaction is the stabilizing hyperconjugative one between CH_3-π and C=C-π^*. This is a bonding interaction since π^* is an empty orbital and can accept electron density from CH_3-π. It is this bonding interaction which transfers additional electron density to the terminal carbon of the double bond. There is the possibility of a corresponding interaction between C=C-π and CH_3-π^* which can become important in systems where the π orbital of the double bond is of higher energy. Notice that there is a correspondence between the MO picture and the valence bond resonance structure in that both specify a net transfer of electron density from C–H bonds to the π bond with a net strengthening of the bond between C-2 and C-3 but with a weakening of the C-1–C-2 π bond.

One of the fundamental structural facets of organic chemistry, which has been explained most satisfactorily in MO terms, is the existence of a small barrier to rotation about single bonds. In ethane, for example, it is known that the staggered conformation is about 3 kcal/mol more stable than the eclipsed conformation so that the eclipsed conformation represents a barrier for transformation of one staggered conformation into another by rotation. Valence bond theory offers no

staggered eclipsed

immediate qualitative explanation since the σ bond which is involved is cylindrically symmetrical. A steric argument based on repulsions between hydrogens also fails

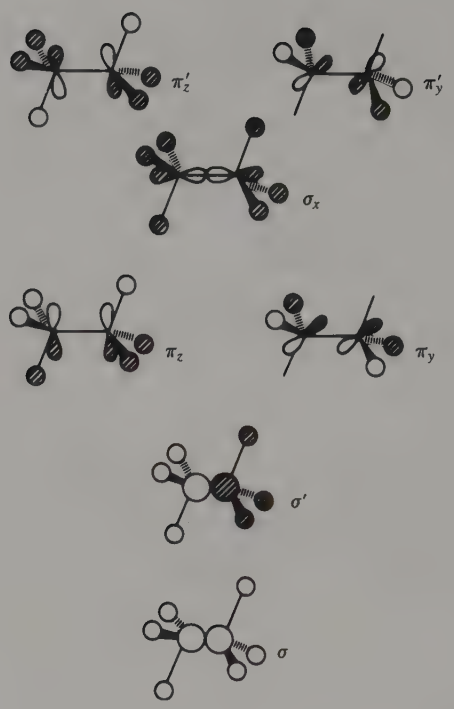


Fig. 1.32. Molecular orbitals of ethane revealing π character of π_z, π_y, π'_z and π'_y orbitals. Only the filled orbitals are shown.

since on detailed examination of this hypothesis it is found that the hydrogens are too small and too distant from one another to account for the observed energy. Molecular orbital ideas and calculations, however, succeed in correctly predicting and calculating the magnitude of the ethane rotational barrier.[45]

Since ethane contains two carbon atoms and six hydrogens the molecular orbitals will be constructed from six H 1*s*, two C 2*s* and six C 2*p* orbitals. Figure 1.32 depicts the seven bonding MO's, assuming the staggered geometry. The σ, σ', and σ_x orbitals are not affected much by the rotation of the two CH_3 groups with respect to one another because the H 1*s* orbitals all have the same sign within each CH_3 group. The other MO's, however, are of a π type, having a nodal plane derived from the nodal plane of the C 2*p* orbitals involved. The extent of the overlap in these orbitals clearly changes as the two CH_3 groups are rotated with respect to one another. Analysis of the relative magnitude of the bonding and antibonding interactions that take place as rotation occurs indicates that the change in energy of these two pairs of MO is the source of the ethane rotational barrier.

45. R. Hoffmann, *J. Chem. Phys.* **39**, 1397 (1963); R. M. Pitzer and W. N. Lipscomb, *J. Chem. Phys.* **39**, 1995 (1963); J. A. Pople and G. A. Segal *J. Chem. Phys.* **43**, 5136 (1956); J. P. Lowe, *J. Am. Chem. Soc.* **92**, 3799 (1970).

Throughout the course of this text we will encounter examples of reactivity and structural differences which are best understood in light of the molecular orbital picture. The basic concepts that will be used in such interpretations have been introduced in this chapter.

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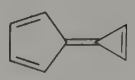
Problems

(References for these problems will be found on page 699.)

1. Use thermochemical relationships to obtain the required information.
   (a) The heats of formation of cyclohexane, cyclohexene, and benzene are, respectively, −29.5, −1.1, and +19.8 kcal/mol. Estimate the resonance energy of benzene using these data.
   (b) Calculate ΔH for the air oxidation of benzaldehyde to benzoic acid given that the heats of formation of benzaldehyde and benzoic acid are −8.8 and −70.1 kcal/mol, respectively.
   (c) Using the appropriate heats of formation in Table 1.4, calculate the heat of hydrogenation of 2-methyl-1-pentene.

2. Suggest an explanation for the following observations:

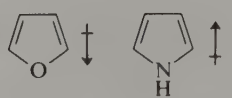
(a) The dipole moment of the hydrocarbon calicene has been estimated to be as large as 5.6 D.



calicene

(b) The measured dipole moment of *p*-nitroaniline (6.2 D) is larger than the value calculated using empirical group moments (5.2 D).

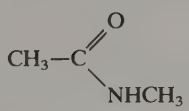
(c) The dipole moment of furan is smaller than and in the opposite direction from that of pyrrole.

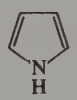


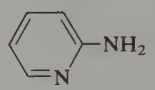
0.71 D 1.80 D

3. Predict the preferred site of protonation for each of the following molecules:

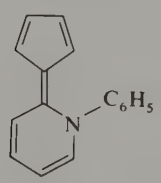
(a) $C_6H_5CH{=}N{-}C_6H_5$

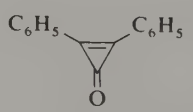
(b) 

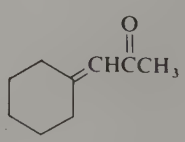
(c) 

(d) 

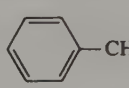
4. What physical properties such as absorption spectra, bond length, dipole moment, etc., could be examined to obtain evidence of resonance interactions in the following molecules? What deviations from "normal" physical properties would you expect to find?

(a) 

(b) 

(c) 

5. Certain C–H bonds have significantly lower bond dissociation energies than do the "normal" C–H bonds in saturated hydrocarbons. Offer a structural rationalization of the lowered bond energy in each of the following compounds, relative to the saturated hydrocarbon C–H bond taken as a reference. (The bond dissociation energies are given in kcal/mol.)

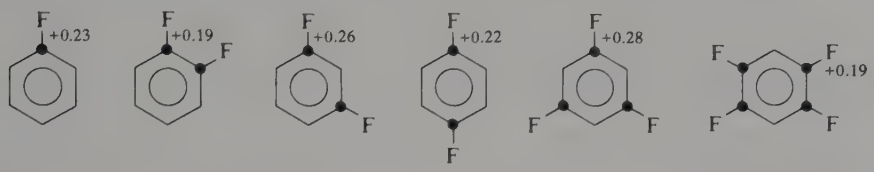
(a) 

(85) versus $CH_3{-}H$ (103)

(b) $HOCH_2-H-H$ (92) versus CH_3-H (103)

(c) $CH_3\overset{\overset{O}{\|}}{C}-H$ (88) versus CH_3CH_2-H (98)

6. Charge densities for a series of fluorobenzenes calculated by the CNDO/2 MO method are as shown:



Can the relative magnitudes of the charges at the fluorine-substituted carbon atoms be rationalized on the basis of inductive effects? Resonance effects? What relationship do you believe would be observed between the X-ray photoelectron spectra (ESCA) of the compounds and the charges as calculated by CNDO?

7. Construct a qualitative MO diagram showing how the π-molecular orbitals in the following molecules are modified by the addition of the substituent:

   (a) vinyl fluoride, compared to ethylene

   (b) acrolein, compared to ethylene

   (c) acrylonitrile, compared to ethylene

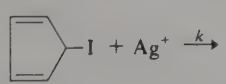
   (d) benzyl cation, compared to benzene

   (e) propene, compared to ethylene

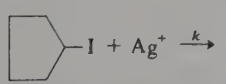
   (f) fluorobenzene, compared to benzene

8. Predict which compound would give the faster (k) or more complete (K) reaction. Explain the basis for your prediction.

   (a)

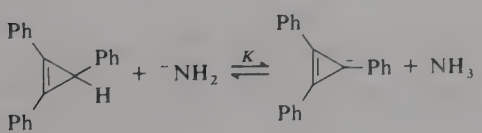


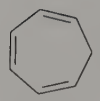
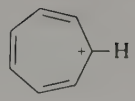
   or



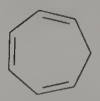
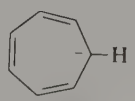
   (b) $Ph_3CH + {}^-NH_2 \overset{K}{\rightleftharpoons} Ph_3C^- + NH_3$

   or



(c) Ph_3C^+ +  $\overset{K}{\rightleftharpoons}$ Ph_3CH + 

or

Ph_3C^- +  $\overset{K}{\rightleftharpoons}$ Ph_3CH + 

9. Construct a qualitative MO diagram for the H-bridged ethyl cation by analyzing the interaction of the ethylene MO's given in Figure 1.17 with a proton approaching the center of the ethylene molecule from a direction perpendicular to the molecular plane. Indicate which ethylene orbitals will be lowered by this interaction and which will be raised or left relatively unchanged. Assume that the hydrogens of ethylene are slightly displaced away from the direction of approach of the proton.

10. The reaction of 2,4-cyclopentadienyl iodide with silver ion is extremely slow. When the carbocation corresponding to ionization of a 2,4-cyclopentadienyl halide is generated at low temperature it gives an EPR spectrum that indicated that the molecule is a ground state triplet, that is, it has two unpaired electrons. A quantitative measure of carbonium ion stability is called pK_{R+} and is equal to log K for the reaction:

$$ROH + H^+ \rightleftharpoons R^+ + H_2O$$

The pK_{R+} of the cyclopentadienyl cation has been estimated to be ~ -40, which indicates that the ion is much less easy to form than, for example, the allyl cation which has $pK_{R+} = \sim -20$. Discuss how these observations can be related to the Hückel MO theory for cyclic conjugated systems.

11. Two of the π-MO's of pentadienyl are given below. Specify which one is of lower energy, and classify each as to whether it is bonding, nonbonding, or antibonding. Explain your reasoning.

$$\psi_x = 0.50\phi_1 + 0.50\phi_2 - 0.50\phi_4 - 0.50\phi_5$$

$$\psi_y = 0.58\phi_1 - 0.58\phi_3 + 0.58\phi_5$$

12. Sketch the nodal properties of the highest occupied molecular orbital of pentadienyl cation ($CH_2{=}CHCH{=}CHCH_2^+$).

13. Calculate the energy levels and coefficients for 1,3-butadiene using Hückel MO theory.

14. (a) Estimate from HMO theory the delocalization energy, expressed in units of β, of cyclobutenyl dication ($C_4H_4^{2+}$).

(b) Estimate, in units of β, the energy associated with the long-wavelength UV-VIS absorption of 1,3,5,7-octatetraene. Does it appear at longer or shorter wavelengths than the corresponding absorption for 1,3,5-hexatriene?

15. Addition of methylmagnesium bromide to 2-methylcyclohexanone followed by iodine-catalyzed dehydration of the resulting alcohol gave three alkenes in the ratio A:B:C = 3:31:66. Each isomer gave a mixture of *cis*- and *trans*-1,2-dimethylcyclohexane on catalytic hydrogenation. When the alkene mixture is heated with a small amount of sulfuric acid, the ratio A:B:C is changed to 0.0:15:85. Assign structures to A, B, and C.

16. The propellanes are highly reactive substances which readily undergo reactions involving rupture of the central bond. It has been suggested that the polymerization of propellanes occurs by a dissociation of the central bond:

Somewhat surprisingly perhaps, it has been found that [1.1.1] propellane is considerably *less reactive* than [2.2.1]propellane. Use the theoretically calculated enthalpy data below to estimate the bond dissociation energy of the central bond in each of the three propellanes shown. How might this explain the relative reactivity of the [1.1.1] and [2.2.1]propellanes?

Enthalpy for addition of hydrogen to give the corresponding bicycloalkane

[2.2.1]propellane + H_2 → bicyclo[2.2.1]heptane, $\Delta H = -99$ kcal/mol
[2.1.1]propellane + H_2 → bicyclo[2.1.1]hexane, $\Delta H = -73$ kcal/mol
[1.1.1]propellane + H_2 → bicyclo[1.1.1]pentane, $\Delta H = -39$ kcal/mol

Assume that the bond dissociation energy of the bridgehead hydrogens in each bicycloalkane is 104 kcal/mol. Indicate and discuss any other assumptions you have made.

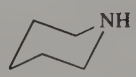
17. Examine the following thermochemical data pertaining to hydrogenation of unsaturated eight-membered ring hydrocarbons to give cyclooctane:

Unsaturated ring hydrocarbon	$-\Delta H$ (kcal/mol)
cis,cis,cis,cis-1,3,5,7-Cyclooctatetraene	97.96
cis,cis,cis-1,3,5-Cyclooctatriene	76.39
cis,cis,cis-1,3,6-Cyclooctatriene	79.91
cis,cis-1,5-Cyclooctadiene	53.68
cis,cis-1,4-Cyclooctadiene	52.09
cis,cis-1,3-Cyclooctadiene	48.96
trans-Cyclooctene	32.24
cis-Cyclooctene	22.98

(a) Discuss the differences observed in each isomeric series of compounds, and offer an explanation for these differences.

(b) Comment on whether the conjugation present in cyclooctatetraene has a stabilizing or destabilizing effect on the C=C bonds.

18. Cyclic amines such as piperidine and its derivatives show substantial differences in the properties of the axial C–2 and C–6 versus the equatorial C–2 and C–6 C–H bonds.



The axial C–H bonds are *weaker* than the equatorial C–H bonds as can be demonstrated by a strongly shifted C–H stretching frequency in the IR. Axial C–2 and C–6 methyl groups *lower* the ionization potential of the lone pair electrons on nitrogen substantially more than do equatorial C–2 or C–6 methyl groups. Discuss the relationship between these observations and provide a rationalization in terms of qualitative MO theory.

19. (a) The strain energy of spiropentane (62.5 kcal/mol) is considerably greater than twice that of cyclopropane (27.5 kcal/mol). Suggest an explanation.

(b) The fractional *s*-character in bonds to carbon in organic molecules may be estimated by its relation to ^{13}C–^{13}C coupling constants, as determined by NMR. Estimate the fractional *s*-character of C(1) in its bond to C(3) of spiropentane, given the following information:

$$s_{1(3)} = \frac{J_{^{13}C-^{13}C}}{K s_{3(1)}}$$

where K is a constant equal to 550 Hz, the ^{13}C–^{13}C coupling constant J between C(1) and C(3) is observed to be 20.2 Hz, and $s_{3(1)}$ is the *s*-character at C(3) in its bond to C(1).

(c) One source cites the central carbon–carbon bond distance in bicyclo[1.1.0]butane as 1.64 Å; another source reports it to be 1.50 Å. Which do you believe is more likely to be the correct bond distance? Why?

bicyclo[1.1.0]butane

20. The ionization potential of ethylene is 10.52 eV. How will the ionization potential change as a result of the introduction of the substituents in acrylonitrile and vinyl acetate? Explain your reasoning.

2

Stereochemical Principles

Introduction

Given a combination of atoms expressed only by a molecular formula, many quite different molecular structures that differ from each other in the nature or sequence of bonding of the atoms in space are possible. Each individual molecular assembly is called an *isomer*, and the *constitution* of a compound is a particular combination of bonds and sequences of atoms of given molecular formula. For example, propanal, acetone, cyclopropanol, and 2-methyloxirane each correspond to the molecular formula C_3H_6O, but differ in constitution.

When structures of the same constitution differ in respect to the spatial arrangement of certain atoms or groups, they are *stereoisomers*, and the considerations that are significant in analyzing their interrelationships are topological. If the relationship between two stereoisomers is that of an object and its nonsuperimposable mirror image, the two structures are *enantiomeric*, and each structure is said to be *chiral*. Stereoisomers that are not enantiomers are *diastereomers*, a classification that also includes geometric isomerism in alkenes. Stereoisomers are distinguished from each other by specifying their *configuration*.[1,2]

In addition to constitution and configuration, there is a third significant level of structure, that of *conformation*. Conformational isomerism is generally taken to refer to discrete molecular arrangements generated by rotation about formal single bonds. This aspect of stereochemistry will be dealt with more fully in Chapter 3.

The material in this chapter is stereochemical, emphasizing and formalizing configurational relationships. These relationships will be considered from two points of view: static and dynamic. We will be concerned with the fundamental principles of

1. The IUPAC rules and definitions for fundamental stereochemistry are given with examples in *J. Org. Chem.* **35**, 2849 (1970).
2. K. Mislow and M. Raban, *Top. Stereochem.* **1**, 1 (1967); J. K. O'Loane, *Chem. Rev.* **80**, 41 (1980).

stereochemistry and the conventions adopted to describe the spatial arrangement of three-dimensional objects. We will also examine stereochemical effects on chemical reactivity, both in this chapter and in Chapter 3, to provide a basis for further discussions to be encountered throughout this text.

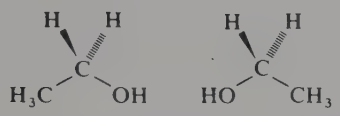
2.1. Enantiomeric Relationships

Since *chirality* is a term used to describe a condition in which an object and its mirror image are not superimposable, it is capable of being described without recourse to any measurable physical or chemical properties. The relationship between chirality and *optical activity* is historically such a close one, however, that chemists are prone to use the descriptions *optically active* and *chiral* interchangeably. Optical activity refers to one *property* of chiral molecules, namely, the ability to rotate the plane of polarized light. Measurements of optical activity have proven to be highly useful, especially in the study of reaction mechanisms, where the stereochemical relationship between starting material and product, as indicated by the sign and magnitude of the optical rotation, provides valuable information about the topology of the transition states and intermediates involved. The mechanics of measuring optical rotation will not be discussed here, since they are well described in most introductory organic chemistry texts.[3] It should be pointed out that both the sign and magnitude of optical rotation are dependent on conditions of measurement, including temperature, solvent, and, most important, the wavelength of light incident on the sample. Measurement of rotation as a function of wavelength is quite useful in structural studies, and provides more information than measurement of the optical rotation at a single wavelength. This technique is called *optical rotatory dispersion.*[4,5] The resulting plot of rotation against wavelength is called an ORD curve. The shape of the ORD curve is determined by the configuration of the molecule and can in many cases be used to establish the configuration of the molecule. Enantiomeric compounds give mirror image ORD curves and these can therefore be used to distinguish between enantiomers. By convention, single wavelength measurements are usually made at the 589-nm emission wavelength of sodium arc lamps. This wavelength is known as the sodium D line and optical rotations measured at this wavelength are designated α_D.[5]

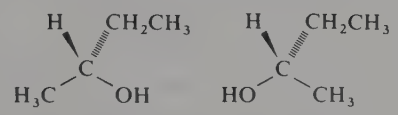
Enantiomers in which the chiral center is tetracoordinate represent the largest class of chiral molecules. Molecules that are not chiral are *achiral.* The tetrahedral

3. For a more detailed description, see G. C. Barrett, in *Elucidation of Organic Structures by Physical and Chemical Methods*, Second Edition, Vol. IV, Part 1, K. W. Bentley and G. W. Kirby (eds.), Wiley–Interscience, New York, 1972, Chap. VIII.
4. P. Crabbé, *Top. Stereochem.* **1**, 93 (1967); C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill, New York, 1960.
5. Unless otherwise stated, all optical rotations given in this book will correspond to that of the sodium D line.

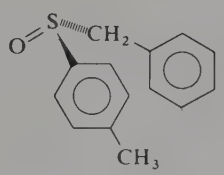
orientation of ligands to sp^3 carbon requires that when any two of the ligands are identical, the molecule is achiral; conversely, when four nonidentical ligands are present, the molecule must be chiral. It is seen that with two identical substituents, the molecule has a plane of symmetry. *A molecule with a plane of symmetry will be superimposable on its mirror image and is achiral.* With four different substituents on sp^3 carbon, no symmetry elements (with the trivial exception of a C_1 axis) are present, and the molecules are commonly described as possessing an asymmetric carbon atom. Ethanol is an example of an achiral molecule. The plane defined by



the three atoms C(2)–C(1)–(O) is a plane of symmetry. 2–Butanol is an example of nonsuperimposable mirror images in a chiral molecule:



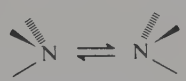
The necessary criterion that an object not be superimposable on its mirror image can be met by compounds in which the chiral center is other than tetracoordinate carbon. Many such examples are known, including sulfoxides in which the substituents on sulfur are different. These molecules are nonplanar, with significant barriers to pyramidal inversion.



$[\alpha]_D$ +252°(*c* 1, acetone)

Ref. 6

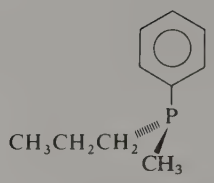
In principle, amines substituted with three different groups are capable of optical activity, since they are chiral, but the activation energies for pyramidal



inversion are too low to allow isolation of enantiomers. The activation energies for pyramidal inversion of phosphines are much higher, and many optically active

6. C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963); C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.* **87**, 5404 (1965); A. Kjaer, *Tetrahedron* **30**, 1551 (1974).

phosphines have been prepared.

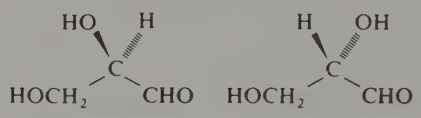


Ref. 7

$[\alpha]+35°$ (c 2, methanol)

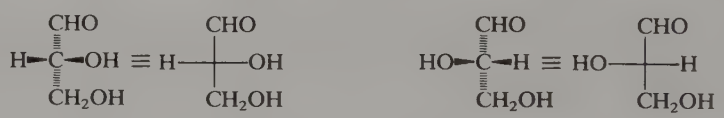
The chirality, or handedness, of a molecule is described by specifying its configuration. The conventions that have achieved the widest use are the *Fischer convention*, employing the descriptors D and L, and the *Cahn–Ingold–Prelog convention*, employing the descriptors *R* and *S*.

The Fischer convention relates the configuration at an asymmetric center to that of (+)-glyceraldehyde, which was chosen as a standard. This enantiomer was arbitrarily assigned the configuration shown which was then defined as D. The levorotatory isomer of glyceraldehyde was assigned the mirror image configuration defined as L. Subsequent determination of the configurations of sodium rubidium tartrate by X-ray crystallographic methods established that the configurations arbitrarily assigned to (+)- and (−)-glyceraldehyde were correct.



D-(+)-glyceraldehyde L-(−)-glyceraldehyde

It is convenient in employing the Fischer convention to use projection formulas. These Fischer projections are obtained by orienting the molecule so that the most highly oxidized carbon atom of the main chain is at the top, with the vertical bonds from the asymmetric carbon atom directed "back" and the horizontal bonds directed "forward." The D and L forms of glyceraldehyde then become as shown in the following three-dimensional representations and Fischer projection formulas:

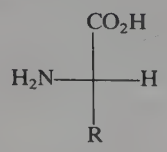


D L

The configuration of a chiral molecule is specified as D or L, depending on whether its configuration is analogous to that of D- or L-glyceraldehyde. This convention has been widely adopted in sugar chemistry and in designating the configuration of optically active α-amino acids. All the amino acids (except for

7. L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and P. Beck, *Tetrahedron Lett.*, 161 (1961).

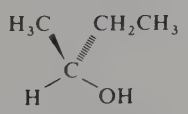
glycine, which is achiral) obtained from the hydrolysis of proteins have the L configuration at the α-carbon atom. This configuration corresponds to the Fischer projection:



It should be emphasized at this point that there is no simple relationship between the sign of rotation and the configuration of different molecules. The amino acid L-alanine, for example, is dextrorotatory.

The analogies between substituents in the glyceraldehyde enantiomers and those in amino acids and carbohydrates are sufficiently straightforward so as to cause little difficulty in application of the Fischer convention. When the compound in question deviates significantly from glyceraldehyde in terms of its substituents, then the analogies are not always obvious. The alternative method of specifying configuration is the Cahn–Ingold–Prelog convention or, as it was termed by its originators, the *sequence rule.*[8] This convention has displaced the Fischer convention as the preferred means of specifying configurations. It is unambiguous in its application since it is based on a completely objective criterion, the atomic numbers of the atoms bonded to a chiral center.

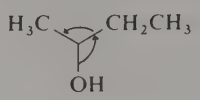
Assignment of configuration to a chiral molecule proceeds by first ordering the substituents at the asymmetric center according to decreasing atomic number. The atom with the highest atomic number is of highest priority; the atom of lowest atomic number is of lowest priority. If the molecule is oriented so that the group of lowest priority is directed away from the viewer, then the order of appearance of the remaining substituents determines the configuration. Configurations are specified as either *R* (Latin *rectus*, "right") or *S* (Latin *sinister*, "left") depending on whether the order of decreasing priorities appears clockwise or counterclockwise, respectively. If two atoms directly bonded to the asymmetric center are identical, then priority is determined by comparing the substituents on each of these atoms with regard to their atomic numbers. An atom that is multiply bonded is counted as one substituent for each formal bond. Examples of the assignment of configuration for some typical molecules are shown below:



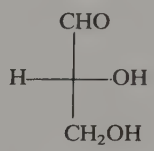
(*S*)-2-butanol

8. R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.* **5**, 385 (1966). See also the Appendix in Ref. 1 (p. 61).

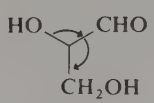
The configuration of the 2-butanol enantiomer is established as *S* as follows: The highest-priority atom bonded to the asymmetric center is O; the lowest is H. The remaining two atoms are each C, and the choice as to which of these, the methyl group or the ethyl group, is of higher priority is made by comparing their ligands. The methyl group has (H, H, H), while the ethyl group has (C, H, H); therefore, the ethyl group is of higher priority than the methyl group. The complete priority list is: OH, CH_3CH_2, CH_3, H. When viewed from the side opposite the lowest-priority ligand, then the remaining groups appear in order of decreasing priority in counterclockwise fashion, and the configuration is *S*:



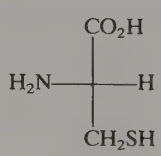
D-Glyceraldehyde is of the *R*-configuration:



The order of decreasing priority of the ligands directly attached to the asymmetric center is: OH, CHO, CH_2OH, H. The aldehyde group is of higher priority than the hydroxymethyl group because, in working outward, the carbon of the aldehyde group has as its substituents (O, O, H) and the hydroxymethyl group has (O, H, H). Notice that the doubly bonded oxygen of the aldehyde group is counted twice. When the molecule is oriented so that the hydrogen is away from the viewer, the substituents appear clockwise in order of decreasing priority:



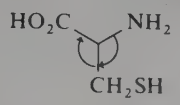
Since the Cahn–Ingold–Prelog and the Fischer conventions are based on different principles, there is no direct correlation between them. That D-glyceraldehyde (Fischer convention) corresponds to *R*-glyceraldehyde (sequence rule) is only coincidence. One need only examine the case of cysteine to be convinced that there is no direct correspondence. The Fischer projection of L-cysteine is shown:



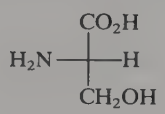
L-cysteine

Application of the sequence rules gives as the priorities: NH_2, CH_2SH, CO_2H, H. The mercaptomethyl substituent is of higher priority than the carboxyl group

because the substituents on the two carbon atoms are, respectively, (S, H, H) and (O, O, H), with sulfur having priority over oxygen because of its higher atomic number. The order of appearance of substituents is clockwise according to decreasing priority, and L-cysteine has the *R* configuration:



It should also be noted that assignment of symbols that are descriptive of a configuration according to an established convention need not bear any relationship to chemical processes. L-Cysteine and L-serine may be interconverted by chemical reactions that do not involve the asymmetric center and that therefore leave the orientation of the ligands at that carbon unperturbed. Because of the atomic number criterion employed for assigning substituent priorities in the Cahn–Ingold–Prelog convention, however, L-cysteine has the *R* configuration and L-serine has the



L-serine

S configuration. (Hydroxymethyl is lower priority than carboxyl in serine, mercaptomethyl is higher priority than carboxyl in cysteine.)

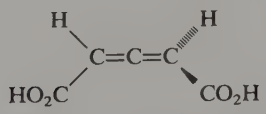
When the chiral center is tricoordinate, as in the case of optically active sulfoxides, sulfonium salts, and phosphines, then a "phantom atom" of atomic number zero is assumed to occupy the fourth site of the presumed tetrahedron. Application of the sequence rules in the usual manner yields *R* as the configuration of (+)-benzyl *p*-tolyl sulfoxide, and *S* as the configuration of (+)-phenylethylmethylphosphine, the structures of which have been presented previously (see pp. 63–64).

Chirality may exist in many molecules that do not possess a chiral center. Such compounds may possess a chiral plane or a chiral axis, and are said to be dissymetric with respect to either that plane or that axis.[9] Certain optically active allenes, biaryls, alkylidenecyclohexanes, and spiranes provide examples of axially dissymmetric molecules (chiral axis). *trans*-Cycloalkenes exemplify planar dissymmetry in molecules. The configurations of these classes may be specified by the Cahn–Ingold–Prelog convention using the usual *R* and *S* descriptors. Special subrules, which we will not describe here, are applied to this purpose. The interested reader is referred to Refs. 8 (see p. 65) and 9 for details. Scheme 2.1 presents some molecules that are optically active because of planar or axial dissymmetry, and for which the absolute configurations have been determined.

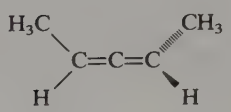
9. G. Krow, *Top. Stereochem.* **5**, 31 (1969).

Scheme 2.1. Planar and Axially Dissymmetric Molecules of Established Configuration

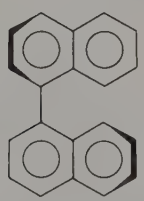
1[a] *R*-(−)-Glutinic acid



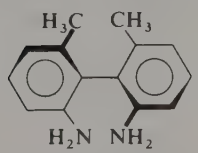
2[b] *R*-(−)-1,3-Dimethylallene



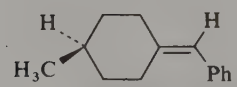
3[c] *S*-(+)-1,1′-Binaphthyl



4[d] *R*-(+)-2,2′-Diamino-6,6′-dimethylbiphenyl

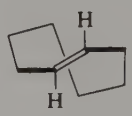


5[e] *S*-(+)-1-Benzylidene-4-methylcyclohexane



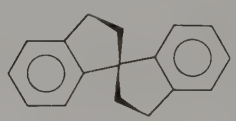
6[f] *R*-(+)-Twistane

7[g] *R*-(−)-*trans*-Cyclooctene



8[h] *S*-(+)-Spiro[3.3]-hepta-1,5-diene

9[i] *R*-(+)-1,1′-Spirobiindan



a. W. C. Agosta, *J. Am. Chem. Soc.* **86**, 2638 (1964).
b. W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.* **90**, 6741 (1968).
c. P. A. Browne, M. M. Harris, R. Z. Mazengo, and S. Singh, *J. Chem. Soc. C*, 3990 (1971).
d. L. H. Pignolet, R. P. Taylor, and W. DeW. Horrocks, Jr., *Chem. Commun.*, 1443 (1968).
e. J. H. Brewster and J. E. Privett, *J. Am. Chem. Soc.* **88**, 1419 (1966).
f. M. Tichý, *Tetrahedron Lett.*, 2001 (1972).
g. A. C. Cope and A. S. Mehta, *J. Am. Chem. Soc.* **86**, 1268 (1964).
h. L. A. Hulshof, M. A. McKervey, and H. Wynberg, *J. Am. Chem. Soc.* **96**, 3906 (1974).
i. J. H. Brewster and R. T. Prudence, *J. Am. Chem. Soc.* **95**, 1217 (1973); R. K. Hill and D. A. Cullison, *J. Am. Chem. Soc.* **95**, 1229 (1973).

Diastereomers are defined as stereoisomers that are not related as an object and its mirror image. Consider the four structures in Fig. 2.1. These structures exemplify the four possible combinations of two nonequivalent chiral centers in the stereoisomers of 2,3,4-trihydroxybutanal. The configurations at C-2 and C-3 are indicated according to the Cahn–Ingold–Prelog convention. Each structure is stereoisomeric with respect to any of the others. The 2*R*,3*R* and 2*S*,3*S* isomers are enantiomeric, as is the 2*S*,3*R* and 2*R*,3*S* pair. The 2*R*,3*R* isomer is diastereomeric with respect to the 2*R*,3*S* isomer, since they are stereoisomers but not enantiomers. The mirror image of 2*R*,3*R* is 2*S*,3*S*, and any object can have only one mirror image.

Unlike enantiomers, diastereomers can differ in chemical and physical properties. They can have different melting points, boiling points, refractive indices, solubility characteristics, dipole moments, and so on, and can afford different products on reaction with a given reagent. Their optical rotations can differ both in magnitude and in sign.

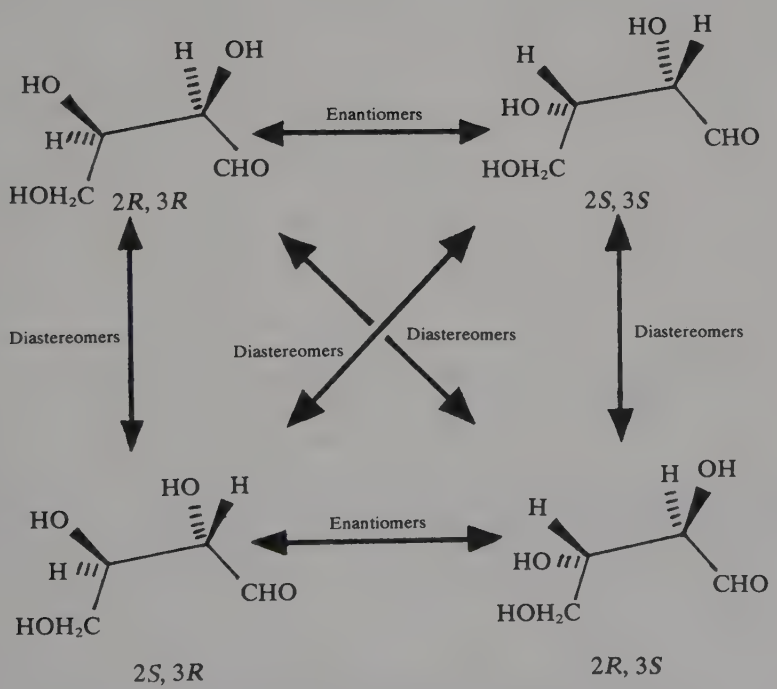
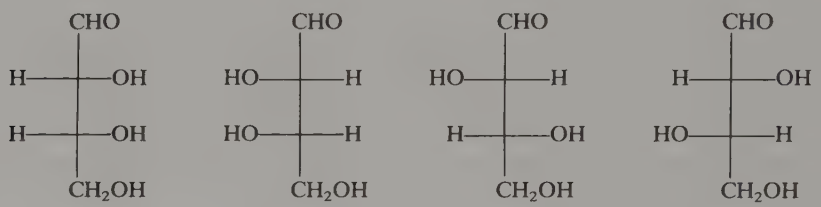
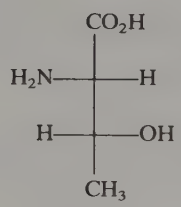


Fig. 2.1. Stereoisomeric relationships in 2,3,4-trihydroxybutanal.

The specification of configurations in diastereomeric species is quite simple, with each chiral center being designated *R* or *S* according to the sequence rules when the Cahn–Ingold–Prelog convention is used. An extension of the Fischer convention to systems with more than one asymmetric center that is based on carbohydrate structures and terminology is still used in relatively simple cases. This convention can be illustrated with the same stereoisomeric 2,3,4-trihydroxybutanals just discussed. The 2*R*,3*R* and 2*S*,3*S* isomers are D- and L-erythrose, respectively. The 2*S*,3*R* and 2*R*,3*S* isomers are D- and L-threose, respectively. The Fischer projection formulas are shown below:

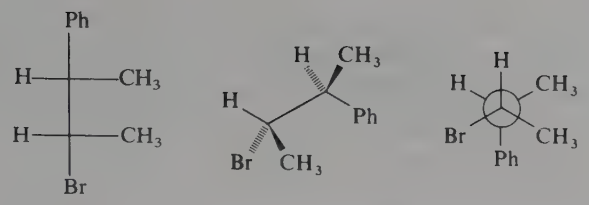


In the Fischer convention, a particular stereochemical series is D or L according to whether the configuration at the *highest numbered asymmetric center* is analogous to D- or L-glyceraldehyde. The configuration at C-3 in erythrose and threose therefore determines the enantiomeric series to which each belongs. An exception to this rule is in the case of α-amino acids, in which the enantiomeric series is determined by the configuration at the α-carbon atom. Thus, L-threonine has the configuration

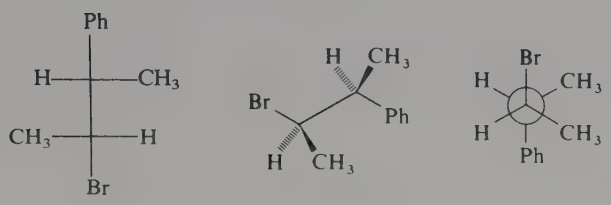


Notice how the configurational relationship between the two adjacent asymmetric centers in threose has been carried over into the name of an amino acid.

Extension of the Fischer convention to compounds with two asymmetric centers uses *erythro* and *threo* to describe relative configurations at the two centers when analogies between substituents are apparent. Fischer projection formulas, sawhorse diagrams, and Newman projection formulas are given for the *erythro*- and *threo*-isomers of 2-bromo-3-phenylbutane. Since two of the substituents are the same on each carbon atom (hydrogen and methyl), the phenyl and bromine, as uncommon substituents, are taken as analogous. In sighting down the C–C axis of a Newman projection, analogous substituents appear in the same sense (clockwise or counterclockwise) in an *erythro* form, and in opposite senses in a *threo* form.



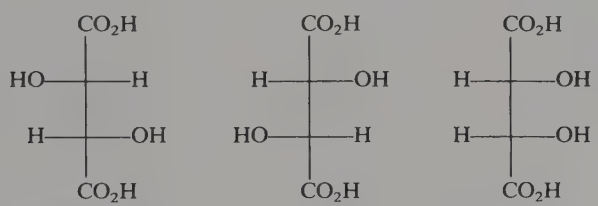
erythro-2-bromo-3-phenylbutane



threo-2-bromo-3-phenylbutane

Unfortunately, as with the Fischer system itself, the designations *erythro* and *threo* depend upon subjective judgements as to which substituents should be considered "*similar.*" In current practice assignments have become almost arbitrary, so that they must be defined for the specific system in question. Protocols which would define terms analogous to *erythro* and *threo* on the basis of the Cahn–Ingold–Prelog sequence rules have recently been proposed but it is not certain at this point what system will eventually be adopted.[10]

When a molecule has two chiral centers that are identically substituted, the number of stereoisomers is reduced from four to three, as in the case of tartaric acid. The three stereoisomers are the D and L forms (enantiomers) and the diastereomeric *meso* form. The *meso* form has a plane of symmetry. It is thus superimposable on its mirror image and is optically inactive. The three possible stereoisomers of tartaric acid are shown below:

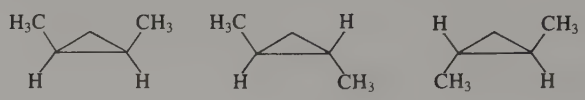


D-tartaric acid L-tartaric acid *meso*-tartaric acid

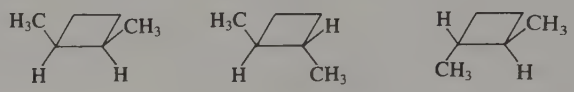
Incorporation of chiral centers into cyclic structures produces some interesting consequences. If we consider dimethylcycloalkanes, the *cis*-dimethyl structures will be achiral, since they possess a plane of symmetry. A *trans*-dimethylcycloalkane

10. F. A. Carey and M. E. Kuehne, *J. Org. Chem.* **47**, 3811 (1982); D. Seebach and V. Prelog, *Angew. Chem. Int. Ed. Engl.* **21**, 654 (1982).

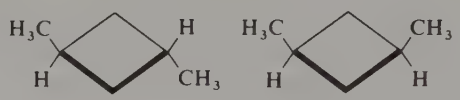
will be chiral when the ring is odd. When the ring is even, whether it will be chiral or achiral depends on the substitution pattern. Inspection of the dimethylcyclopropanes and dimethylcyclobutanes serves to illustrate these stereochemical features. The three possible stereoisomers of 1,2-dimethylcyclopropane are



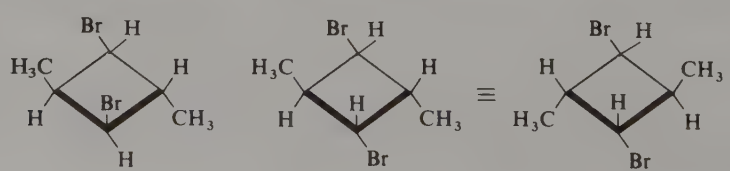
The three possible stereoisomers of 1,2-dimethylcyclobutane are



The two possible stereoisomers of 1,3-dimethylcyclobutane are



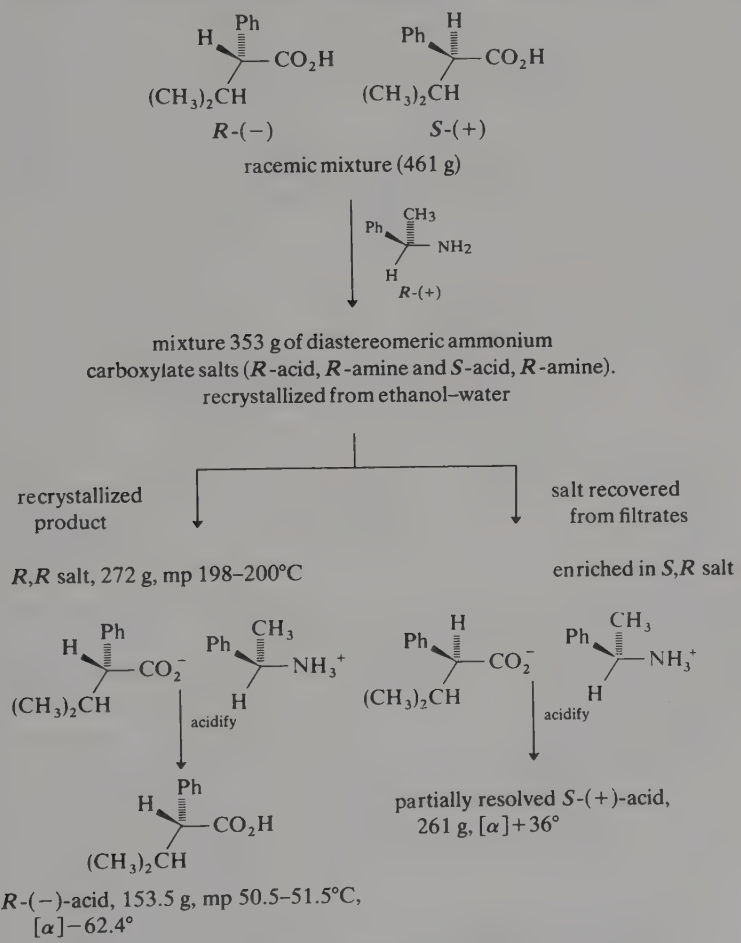
Three stereoisomers are possible from 1,2-dimethylcyclopropane and 1,2-dimethylcyclobutane, each giving rise to a *meso* form (*cis*) and a pair of enantiomers (*trans*). Only two stereoisomers of 1,3-dimethylcyclobutane are possible, and each is achiral. The *cis*-1,3 orientation has two symmetry planes, one passing through C-1 and C-3, the other through C-2 and C-4. The *trans*-1,3 orientation has a plane of symmetry passing through C-1 and C-3. Continuing to examine the stereochemical properties of the *trans*-1,3-dimethylcyclobutane system raises some other interesting points. Let us consider what happens if we introduce substituents at C-2 and C-4. If these substituents are *cis* to each other, the symmetry plane remains and the molecule is achiral. If the substituents are *trans* to each other, the symmetry plane vanishes. Is *trans*-1,3-dimethyl-*trans*-2,4-dibromocyclobutane chiral? Inspection of the molecule and its mirror image reveals that the two are superimposable. This molecule is an example of one that has a center of symmetry—in this case corresponding to the center of the cyclobutane ring—and is representative of another important relationship between symmetry and chirality: *A molecule with a center of symmetry will be superimposable on its mirror image and is achiral.*



As is evident from these examples of molecules that have more than one chiral center, there are no absolute generalizations that relate the number of chiral centers to the number of stereoisomers, since some of the forms may be superimposable on their mirror images. The maximum number of stereoisomers possible for a system with n distinct asymmetric centers is 2^n.

Diastereomeric relationships provide the basis on which a number of important processes depend. *Resolution* is the separation of a mixture containing equal quantities of enantiomers (termed a *racemate* or *racemic mixture*) into its components. Separation is ordinarily effected by converting the mixture of enantiomers into a mixture of diastereomers by treatment with an optically active reagent (the

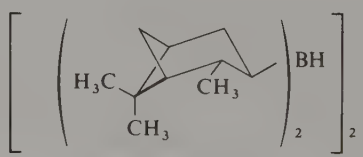
Scheme 2.2. Resolution of 2-Phenyl-3-methylbutanoic Acid[a]



a. C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.* **32**, 2797 (1967).

resolving agent).[11] Since the diastereomers will have different physical and chemical properties, they can be separated by conventional methods and the enantiomers regenerated in a subsequent step. An example of this method is shown in Scheme 2.2 for the resolution of a racemic carboxylic acid by way of diastereomeric salt formation using an optically active amine. The *R*-acid-*R*-amine and *S*-acid-*R*-amine salts are separated by fractional recrystallization, and the resolved carboxylic acid is freed from its amine salt by acidification.

An alternative means of resolution depends on the differences in rates of reactions of enantiomers with a chiral reagent. The transition state energies for reaction of one chiral molecule with another can be different for each enantiomer. If a racemic mixture (*R* molecule + *S* molecule) reacts with an optically active reagent (*R* reagent), the two transition states (*R* molecule $\cdots$ *R* reagent) and (*S* molecule $\cdots$ *R* reagent) bear a diastereomeric relationship to each other. *Kinetic resolution* is the term used to describe the separation of enantiomers by selective reaction with an optically active reagent. A very useful application of this technique is the resolution of allenes by preferential reaction of one enantiomer with an optically active borane. Hydroboration of the allenes occurs at different rates, and the reaction mixture becomes enriched in the less reactive enantiomer. An allene that has been partially resolved by this technique was presented as an example of an axially dissymmetric molecule in Scheme 2.1 (p. 68 ; entry 2, 1,3-dimethylallene).[12] By allowing 1 mol of 1,3-dimethylallene to react with 0.33 mol of the optically active hydroborating agent tetra-3-pinanyldiborane, obtained by reaction of α-pinene with diborane, only 67% of the racemic allene mixture is hydroborated, and distillation of the reaction mixture allows the unreacted allene to be recovered. The recovered 1,3-dimethylallene had $[\alpha]_{578}$ $-22°$.

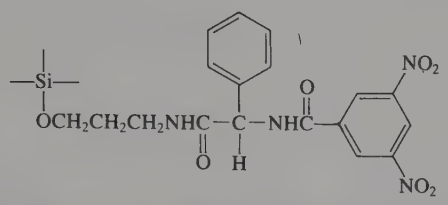


tetra-3-pinanyldiborane

Other methods of resolution depend upon the difference in *noncovalent* binding between two enantiomers to a chiral substance. This is the basis for resolution by chromatography on optically active absorbants. The noncovalent binding between enantiomers and the chromatographic adsorbant establishes disastereomeric complexes and these have differing binding affinities. The positions of the equilibrium between the bound and the unbound states are different for the two enantiomers. This means that the two enantiomers will move through the column at different rates and can be separated. Although this principle has long been recognized, it is

11. For reviews of resolving agents and resolution methods, see S. H. Wilen, *Top. Stereochem.* **6**, 107 (1971); S. H. Wilen, A Collet, and J. Jacques, *Tetrahedron* **33**, 2725 (1977).
12. W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.* **90**, 6741 (1968); W. R. Moore, H. W. Anderson, and S. D. Clark, *J. Am. Chem. Soc.* **95**, 835 (1973).

only fairly recently, with the development of techniques for preparing optically active adsorbants and improvement in chromatographic methods, that this method of resolution has become very practical. A study which demonstrates the present capability of the technique reports the resolution of a number of aromatic compounds on a 1–8-g scale. The adsorbant is a silica which has been derivatized with a chiral reagent. Specifically, hydroxyl groups on the silica surface are covalently bound to a derivative of *R*-phenylglycine. Using medium-pressure chromatography



apparatus, the racemic mixture is passed through the column and, when resolution is successful, the separated enantiomers are isolated as completely resolved fractions.[13]

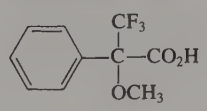
Preparation of optically active materials by use of chiral catalysts is based on the same principle. While the reactant is part of a complex or intermediate containing a chiral catalyst, its environment is asymmetric. The shape of the reactive complex can then control the stereochemistry of subsequent reactions. If the reaction creates a new chiral center in the reactant molecule, there can be a preference for formation of one enantiomer over the other. We will discuss specific examples of such processes in Section 11.3 of Part B.

Enzymes constitute a particularly important group of chiral catalysts. Enzymes are highly efficient and selective catalysts for a variety of biological transformations. Most of these transformations involve chiral substrates, and it is usual to observe that one enantiomer is significantly more reactive than the other. The reason is that the enzymes themselves are chiral, and the interaction of an enzyme with one enantiomer bears a diastereomeric relationship to the interaction of the enzyme with the other enantiomer; thus, one enzyme–substrate interaction is favored over the other. Enzyme-catalyzed reactions have been used to resolve organic molecules when one enantiomer is a preferred substrate for the enzyme.

The differing physical properties of diastereomers is also the basis for a particularly sensitive method of assessing the optical purity of compounds. Although, in principle, this can be done by measuring the optical rotation, this value is reliable only if the rotation of the pure enantiomer is accurately known. This will never be the case for a newly prepared material and is also often in question for previously prepared compounds. If a derivative is prepared in which a new chiral center is introduced, the two enantiomers will give different diastereomers. Since these will have different physical properties in general, they have different NMR spectra. These spectra are distinguished by somewhat different chemical shifts. A pure

13. W. H. Pirkle and J. M. Finn, *J. Org. Chem.* **47**, 4037 (1982).

enantiomer will give a single spectrum but a racemic mixture will lead to a superposition of the spectra of the two diastereomers. A sample which is only partially optically pure will give the superimposed spectra in a ratio which is the same as the ratio of the enantiomers that were originally present. The most widely used derivatizing agent for this purpose is a compound known as *Mosher's reagent.*[14] One reason that this compound has been particularly useful is that the aromatic ring usually induces markedly different chemical shifts in the two diastereomers that are formed.



Mosher's reagent

As stated earlier, geometric isomers of alkenes are broadly classified as diastereomeric, since they are stereoisomers that are not enantiomers. The usual specification of geometry as *cis* or *trans* is deeply entrenched, but suffers from the same problems of ambiguity as does the Fischer convention, in that it is based on analogies that are not always obvious. The *sequence rule* has been applied to this problem.[15] Here again, the most important criterion is that of atomic number. The four substituents on a carbon–carbon double bond are taken in pairs and compared as to whether the higher-atomic-number substituent of each pair is on the same side or on opposite sides of the double bond. If they are on the same side, the descriptor used is *Z* (German *zusammen*, "together"); if they are on opposite sides, the descriptor used is *E* (German *entgegen*, "opposite"). As in applying the sequence rule to chiral centers, if the atoms directly attached to the double bond have the same atomic number, then priorities are assigned by comparing the atoms attached to these. The system may be also applied to multiply bonded systems other than C=C, such as, for example, C=N. It is much preferred over the *syn* and *anti* nomenclature used for configurations of oximes. As in the case of chiral centers, if the atom of the double bond does not have two substituents (as in the case of oximes), then a "phantom ligand" is assumed having atomic number zero. Scheme 2.3 presents some stereoisomeric compounds named according to the sequence rule applied to multiple bonds.

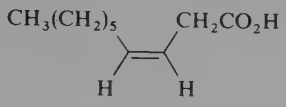
2.3. Dynamic Stereochemistry

Until now, we have emphasized the stereochemical properties of molecules as objects, without concern for processes. When the topological features of a rate

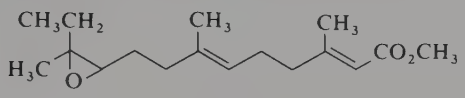
14. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).
15. J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Am. Chem. Soc.* **90**, 509 (1968).

Scheme 2.3. Stereoisomeric Alkenes and Related Molecules with the Double-Bond Geometry Named According to the Sequence Rule

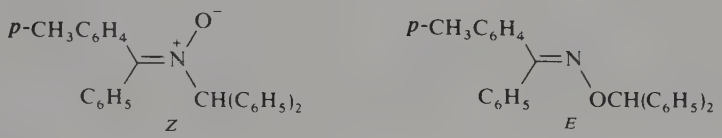
1[a] (*Z*)-3-Decenoic acid (the sex pheromone of the furniture carpet beetle)



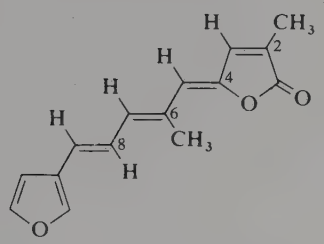
2[b] Methyl (2*E*,6*E*,10*Z*)-10,11-epoxy-3,7,11-trimethyltridecadienoate (the juvenile hormone of the tobacco hornworm)



3[c] Nitrones and oxime ethers



4[d] (2*Z*,4*Z*,6*E*,8*E*)-9-(3′-Furyl)-2,6-dimethylnona-2,4,6,8-tetraen-4-olide (dihydrofreelingyne)



a. H. Fukui, F. Matsumara, M. C. Ma, and W. E. Burkholder, *Tetrahedron Lett.* 3536 (1974).
b. R. C. Jennings, K. J. Judy, and D. A. Schooley, *J. Chem. Soc. Chem. Commun.*, 21 (1975).
c. T. S. Dobashi and E. J. Grubbs, *J. Am. Chem. Soc.* **95**, 5070 (1973).
d. C. F. Ingham and R. A. Massy-Westropp, *Aust. J. Chem.* **27**, 1491 (1974).

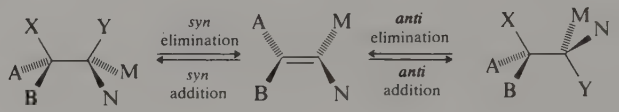
process are considered, the term *dynamic stereochemistry* applies. The rate processes of organic chemistry are many, ranging from chemical reactions associated with bond breaking and bond making, to lower-energy processes such as separation of ion pairs by diffusion through a solvent. In order to understand any rate process thoroughly, it is essential not only that the stereochemical relationship between starting and product states be established, but also that the spatial relationships in proposed intermediates and transition states be consistent with the experimental observations.

In describing the stereochemical properties of rate processes, we can distinguish between two types: stereospecific reactions and stereoselective reactions.[16]

A *stereospecific reaction* is one in which stereoisomeric starting materials afford stereoisomerically different products under the same reaction conditions.

A *stereoselective reaction* is one in which a single reactant has the capacity of forming two or more stereoisomeric products in a particular reaction, but where it is observed that one is formed preferentially.

The stereochemistry of the most familiar reaction types such as addition, substitution, and elimination are described by terms which specify the stereochemistry of the process. Addition and elimination reactions are classified as *syn* or *anti*, depending on whether the covalent bonds made or broken are on the same or opposite faces of the plane of the double bond. The terms *syn* and *anti* used in this context have replaced *cis* and *trans* when referring to processes, so as to avoid confusion with descriptions of alkene stereoisomerism.



Reactions are also classified as proceeding with retention or inversion of configuration, or with racemization. While it is most convenient to use chiral substrates to probe the stereochemistry of a reaction in order to determine whether the path followed is one of retention, inversion, or racemization, it should be emphasized that the stereochemistry of a reaction is a property of the mechanism, not of the means of determining it. Thus, it is altogether proper to speak of the hydrolysis of methyl iodide as proceeding with inversion, even though the stereochemistry is not evident from considering the achiral structures of the starting material and the product. We will use the term *retention of configuration* to apply to processes in which the spatial arrangement of the stereochemically significant atoms is the same in the reactant and product. *Inversion of configuration* will be applied to processes in which the spatial arrangement of the stereochemically significant atoms bears an enantiomeric relationship in reactant and product. A process which results in formation of both possible enantiomers of a product from a single enantiomer of the reactant is said to involve *racemization.* If the product contains equal amounts of the enantiomers, there has been *complete racemization* but *partial racemization* is also common. The special case of racemization at one chiral center of a diastereomer is called *epimerization* since stereochemical integrity can be maintained at the other chiral centers in the molecule.

Some stereospecific reactions are listed in Scheme 2.4. Examples of stereoselective reactions are presented in Scheme 2.5. As can be seen in Scheme 2.4, the starting materials in these stereospecific processes are stereoisomeric pairs and the products

16. E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, p. 436.

are stereoisomeric with respect to each other. Each reaction proceeds cleanly to give a single stereoisomer without contamination by the alternative stereoisomer. Detailed discussion of the mechanisms of these reactions will be deferred until later sections of this text, but some comments may be made about several of the reactions to illustrate the concept of stereospecificity in organic reactions.

Entries 1 and 2 are typical of concerted *syn* addition to alkene double bonds. On treatment with peroxyacetic acid, the *cis*-alkene affords only the *cis*-oxirane, while the *trans*-alkene affords only the *trans*-oxirane. Similarly, addition of dibromocarbene to *cis*-2-butene yields exclusively *cis*-2,3-dimethyl-1,1-dibromocyclopropane, and only *trans*-2,3-dimethyl-1,1-dibromocyclopropane is formed from *trans*-2-butene. It should be noted that there are numerous examples of stereospecific *anti* addition to alkenes as well, as will be seen in Chapter 6.

Nucleophilic substitution reactions of the direct displacement type proceed with inversion of configuration at the carbon atom bearing the leaving group. Thus, *cis*-4-*t*-butylcyclohexyl *p*-toluenesulfonate is attacked by thiophenoxide ion to give *trans*-4-*t*-butylcyclohexyl phenyl thioether. The stereoisomeric *trans*-*p*-toluenesulfonate gives the *cis*-phenyl thioether. In the optically active 2-octyl system, enantiomeric 2-octyl *p*-toluenesulfonates also react with inversion of configuration when attacked by acetate ion and afford enantiomeric acetates (entry 4).

Entry 5 is an example of a stereospecific *anti* elimination reaction of an alkyl halide in which the transition state requires the proton being removed and the bromide lost to be in an *anti* orientation with respect to each other. The diastereomeric *threo*- and *erythro*-1,2-diphenyl-1-bromopropanes undergo base-catalyzed β-elimination to produce stereoisomeric products. Entry 6 is an example of pyrolytic elimination requiring a *syn* orientation of the proton being removed and the amine oxide nitrogen atom. This elimination reaction is a concerted one in which the proton is abstracted by the oxygen of the amine oxide group.

The stereoselective reactions in Scheme 2.5 include examples that are completely stereoselective (entries 2 and 3), one that is highly stereoselective (entry 6), and others in which the stereoselectivity is modest to only slight (entries 1, 4, 5, and 7). In the highly stereoselective acid-catalyzed ring opening of methylcyclopropyl carbinol (entry 2) and the addition of formic acid to norbornene (entry 3), only a single stereoisomer is produced in each reaction. Reduction of 4-*t*-butylcyclohexanone by lithium aluminum hydride is typical of the reduction of unhindered cyclohexanones in that the major diastereomer produced is the more stable alcohol. Such reactions have been extensively studied, mainly by varying the structure of the hydride donor, and a number of reducing agents are now available that provide for some control of the stereoselectivity of reduction.

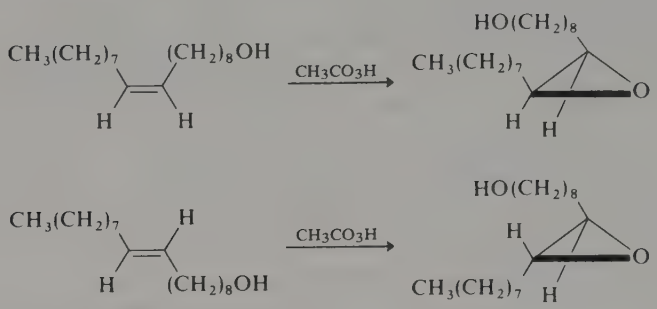
At the other extreme, the alkylation of 4-*t*-butylpiperidine with benzyl chloride (entry 7) provides only slightly more of one diastereomer than of the other. It is also observed that the ratio can be reversed by changing solvents.

We have previously seen (Scheme 2.4, entry 5) that the dehydrohalogenation of alkyl halides is a stereospecific reaction requiring an *anti* orientation of the proton and halide leaving group in the transition state. The elimination reaction is also

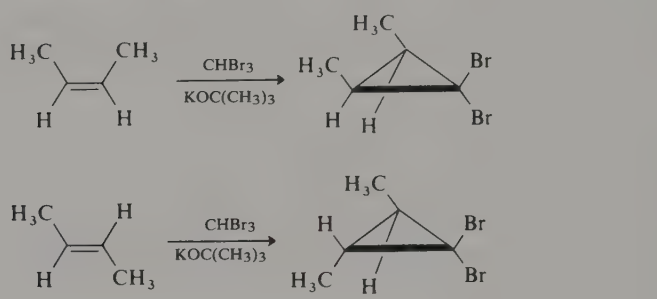
Scheme 2.4.

A. Stereospecific addition to alkenes

1[a] Epoxidation

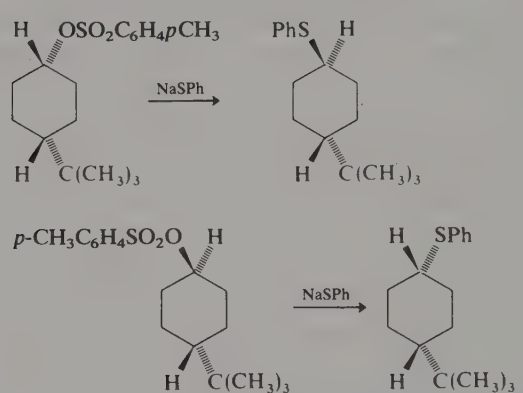


2[b] Addition of dibromocarbene



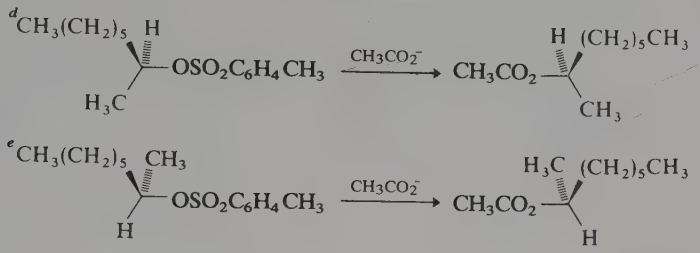
B. Nucleophilic substitution

3[c] *cis*- and *trans*-4-*t*-Butylcyclohexyl *p*-toluenesulfonate



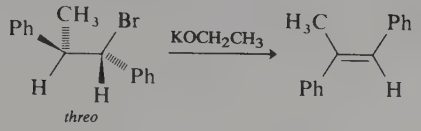
moderately stereoselective (Scheme 2.5, entry 1), in the sense that the more stable olefin is formed preferentially. Base-catalyzed elimination of 2-iodobutane affords three times as much *trans*-2-butene as *cis*-2-butene.

4[d,e] *S*-(+)- and *R*(−)-2-Octyl *p*-toluenesulfonate

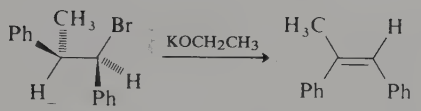


C. Elimination

5[f] Dehydrohalogenation

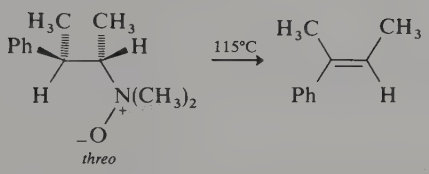


threo

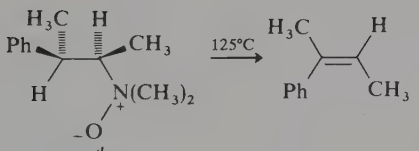


erythro

6[g] Pyrolysis of amine oxides



threo



erythro

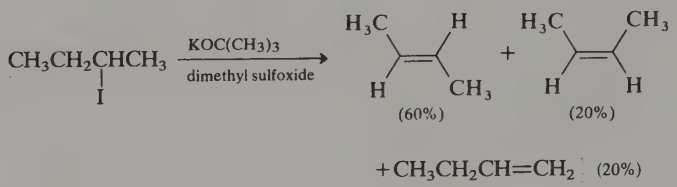
a. L. P. Witnauer and D. Swern, *J. Am. Chem. Soc.* **72**, 3364 (1950).
b. P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.* **78**, 3409 (1956).
c. E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.* **79**, 5995 (1957).
d. A. Streitwieser, Jr., and A. C. Waiss, Jr., *J. Org. Chem.* **27**, 290 (1962).
e. H. Phillips, *J. Chem. Soc.*, 2552 (1925).
f. D. J. Cram, F. D. Greene, and C. H. DePuy, *J. Am. Chem. Soc.* **78**, 790 (1956).
g. D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.* **76**, 5740 (1954).

Moderate stereoselectivity is also seen in the addition of phenoxycarbene to cyclohexene, in which the product ratio is apparently influenced by steric considerations that favor introduction of the larger group (PhO– versus H–) in the less crowded of two possible orientations.

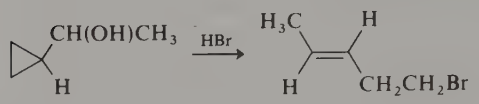
Scheme 2.5.

A. Formation of alkenes

1[a] Dehydrohalogenation

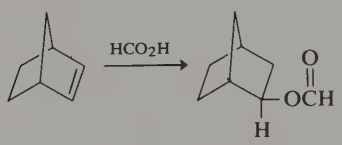


2[b] Acid-catalyzed ring-opening of cyclopropylcarbinols

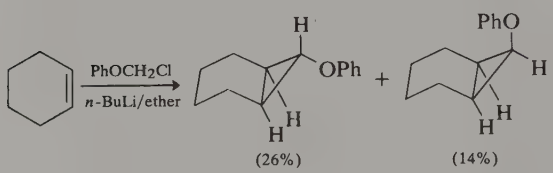


B. Addition to alkenes

3[c] Addition of formic acid to norbornene



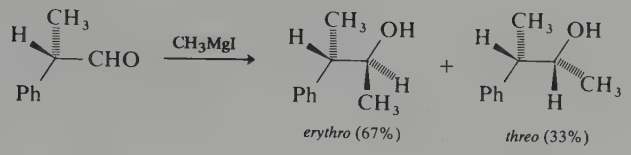
4[d] Addition of phenoxycarbene to cyclohexene



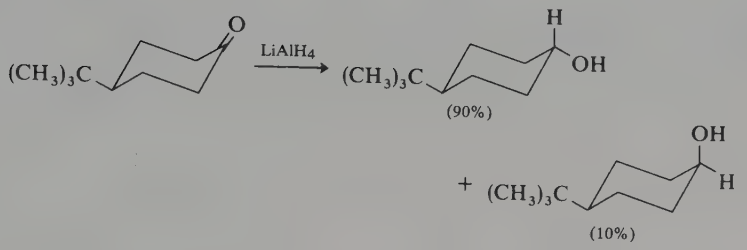
The addition of methylmagnesium iodide to 2-phenylpropanal is stereoselective in producing twice as much *erythro*-3-phenyl-2-butanol as *threo*. The selective formation of a particular configuration at a new chiral center generated in a reaction involving a chiral molecule is one example of *asymmetric induction*. The transition states for formation of the *erythro* and *threo* products are diastereomeric and of different energy; hence, the product corresponding to the lower-energy transition state will predominate. Mention should also be made here that while the reaction as written is for addition of methylmagnesium iodide to *S*-2-phenylpropanal, identical proportions of diastereomers would be produced for the case of *R*-2-

C. Addition to carbonyl groups

5[e]

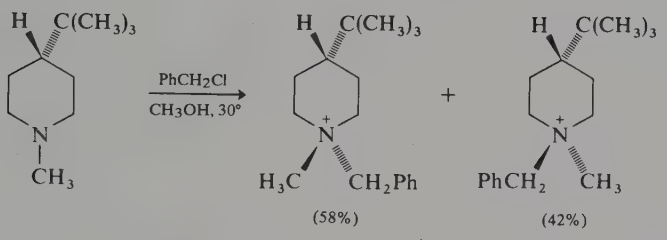


6[f]



D. Formation of quaternary ammonium salts

7[g]



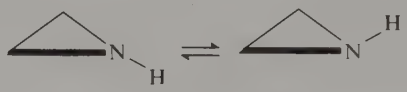
a. R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.* **95**, 3405 (1973).
b. M. Julia, S. Julia, and S.-Y. Tchen, *Bull. Soc. Chim. Fr.*, 1849 (1961).
c. D. C. Kleinfelter and P. von R. Schleyer, *Org. Synth.* **V**, 852 (1973).
d. U. Schöllkopf, A. Lerch, and W. Pitteroff, *Tetrahedron Lett.*, 241 (1962).
e. D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.* **74**, 5828 (1952).
f. E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.* **82**, 1367 (1960).
g. A. T. Bottini and M. K. O'Rell, *Tetrahedron Lett.*, 423 (1967).

phenylpropanal. The *erythro*-isomer would again dominate, with the only difference being that it, as well as the minor *threo*-isomer, would be enantiomeric to the structures given in Scheme 2.5.

Standing in contrast to stereospecific and stereoselective processes are the racemization processes which cause formation of both configurations at centers of chirality. The most common mechanistic course by which organic molecules are racemized is by cleavage of one of the ligands from an asymmetric carbon atom to give a planar or rapidly inverting tricoordinate intermediate. In the absence of any special solvation effects, such an intermediate is capable of being captured equally

well from either side, and will then produce equal quantities of the two possible enantiomeric products. A familiar example of such a process is nucleophilic substitution proceeding through a carbocation and this case will be discussed in detail in Section 5.8.

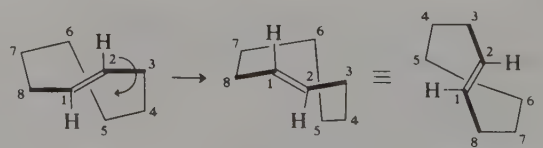
Racemization can also occur by processes that do not involve bond cleavage. An example of this is pyramidal inversion at trivalent nitrogen, sulfur or phosphorus. The rate of racemization of such compounds depends upon the barrier to pyramidal inversion. For ammonia and primary, secondary and tertiary amines, the barrier is very low and therefore inversion (and racemization in the case of chiral substances) is very rapid at room temperature. Acyclic amines do not exhibit optical activity based on chirality at nitrogen. Incorporation of the nitrogen into a small ring serves to raise the barrier to pyramidal inversion, due, presumably, to an increase in the energy of the planar transition state, in which bond angles on the order of 120° are required. For aziridine, the energy barrier to pyramidal inversion is 12 kcal/mol.



Ref.17

While the barriers for inversion of pyramidal compounds of first-row elements are normally low so that inversion is fast, the heavier elements have much higher barriers to inversion. The preferred bonding angle at sulfur, phosphorus, and other heavier elements is about 100° for most trivalent derivatives. This means that a much greater distortion of molecular geometry is required to reach the planar transition state. Typical barriers for trisubstituted phosphines are 30–35 kcal/mol, while for sulfoxides the barriers are about 35–45 kcal/mol. Phosphines and sulfoxides can therefore be isolated in optically active form and undergo inversion only at high temperatures.[18]

As was illustrated in Scheme 2.1, there are many molecules which are chiral but which do not contain chiral carbon atoms. The optical activity of such substances frequently depends upon the barrier to conformation changes which effect racemization. For example, the lowest energy path for racemization of *trans*-cycloalkenes is a rotation of the plane of the double bond through an angle of 180°. This rotation is most easily seen by working with molecular models. It is represented below for the case of *trans*-cyclooctene, in which the rotation of the plane is about the C(8)–C(1) and the C(2)–C(3) bonds.

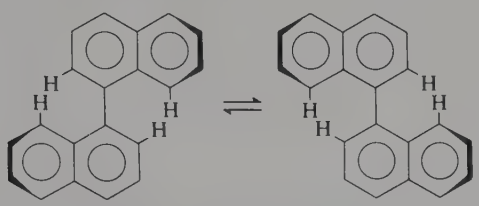


R-(−) *S*-(+)

17. W. M. Tolles and W. D. Gwinn, *J. Chem. Phys.* **42**, 2253 (1965).
18. For a review of pyramidal inversion, see J. B. Lambert, *Top. Stereochem.* **6**, 19 (1971).

The ease of rotation will depend on the ring size. It is observed that *trans*-cyclooctene is quite stable to thermal racemization, and can be recovered with no loss in rotation after seven days at 61°C.[19] When the ring size is larger, it becomes easier for rotation of the plane of the double bond through the belt of the ring atoms to occur, and racemization takes place more readily. The half-life for racemization of *trans*-cyclononene is 5 min at 0°C.[20] The resolution of *trans*-cyclodecene has been accomplished using the techniques developed for *trans*-cyclooctene and *trans*-cyclononene, but it racemizes immediately on its release from the chiral platinum complex employed for its resolution.[20]

The dynamic stereochemistry of biaryls is similar. The energy barrier for racemization of optically active 1,1-binaphthyl (see Scheme 2.1, entry 3, p. 68) is 21–23 kcal/mol.[21] The two rings are not coplanar in the ground state, and the process by which racemization takes place is rotation about the 1,1′ bond.



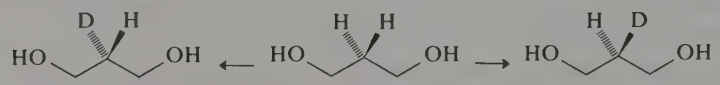
Rotation about the 1,1′ bond is resisted by van der Waals interactions between the hydrogens shown in the structures. These hydrogens crowd each other significantly when the two naphthyl groups are coplanar, and interconversion of enantiomers requires the hydrogens to move past each other. The effect of *ortho* substitution on the rate of racemization of optically active biphenyls has been thoroughly investigated and shown to be dependent on the size of substituents.[22] The consequences of finite, sometimes large, barriers to rotation about carbon–carbon single bonds are many and will be discussed in detail in the next chapter of this text, which is concerned with conformational analysis.

2.4. Prochiral Relationships

It is frequently necessary, particularly in enzymic processes, to distinguish between like ligands that, even though they are bonded to the same atom, may be

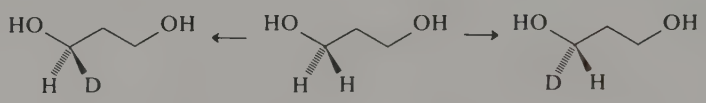
19. A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. VanAuken, and H. J. S. Winkler, *J. Am. Chem. Soc.* **85**, 3276 (1963); the activation energy is 35.6 kcal/mol: A. C. Cope and B. A. Pawson, *J. Am. Chem. Soc.* **87**, 3649 (1965).
20. A. C. Cope, K. Banholzer, H. Keller, B. A. Pawson, J. J. Whang, and H. J. S. Winkler, *J. Am. Chem. Soc.* **87**, 3644 (1965).
21. A. K. Colter and L. M. Clemens, *J. Phys. Chem.* **68**, 651 (1964).
22. F. H. Westheimer, in *Steric Effects in Organic Chemistry*, M. S. Newman (ed.), Wiley, New York, 1956, Chap. 12.

topologically nonequivalent. Let us consider 1,3-propanediol as an example. If a process occurs in which a proton at C(2) is substituted by another ligand, say, deuterium, the two possible substitution modes generate identical products. The two protons at C(2) are therefore topologically, as well as chemically, equivalent, and are termed *homotopic* ligands.



Substitution products are superimposable. There is a plane of symmetry defined by the atoms H–C(2)–D.

If a similar process occurred involving the two protons at C(1), a stereochemically different situation would result. Substitution of a proton at C(1) with deuterium produces a chiral product, 1-*deuterio*-1,3-propanediol:

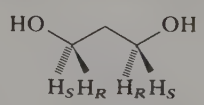


(*R*)-1-*deuterio*-1,3-propanediol

(*S*)-1-*deuterio*-1,3-propanediol

The two protons at C(1) are topologically nonequivalent, since substitution of one produces a product that is stereoisomerically distinct from that produced by substitution of the other. Ligands of this type are termed *heterotopic*, and, because the products of substitution are enantiomers, the definition can be made more precise.[23] Ligands that on substitution produce enantiomers are *enantiotopic.* If a chiral assembly is generated when a point ligand is replaced by a new point ligand, the original assembly is *prochiral.* Both C(1) and C(3) of 1,3-propanediol are *prochiral centers.*

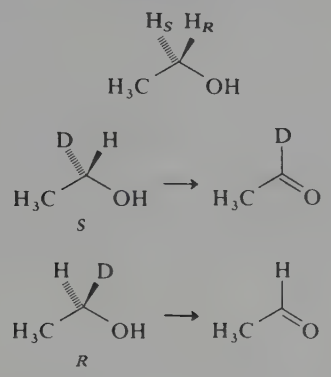
The sequence rule may be applied directly to the specification of heterotopic ligands in prochiral molecules using the descriptors *pro-R* and *pro-S.* This application is accomplished by selecting one of the heterotopic ligands at the prochiral center and arbitrarily assigning it a higher priority than the other, without disturbing the priorities of the remaining ligands. If application of the sequence rule results in an assignment of *R* as the configuration of the prochiral center, then the selected ligand is *pro-R.* If the prochiral center is *S*, then the selected ligand is *pro-S.* It is customary to designate prochirality in structures by a subscript *R* or *S* at the appropriate atoms. For 1,3-propanediol, the prochiral hydrogens are indicated:



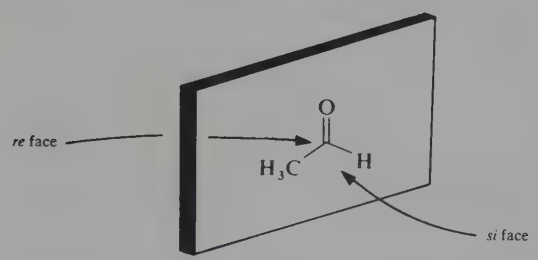
Enantiotopic atoms or groups are equivalent in all chemical respects except toward a chiral reagent. An important enzymic reaction that discriminates between enantiotopic ligands is the oxidation of ethanol catalyzed by *liver alcohol*

23. E. L. Eliel, *J. Chem. Ed.* **57**, 52 (1980); K. R. Hanson, *J. Am. Chem. Soc.* **88**, 2731 (1966).

dehydrogenase and *yeast alcohol dehydrogenase*. Both enzymes require nicotinamide adenine dinucleotide (NAD^+) as a coenzyme. Ethanol is a prochiral molecule, and it has been clearly shown that oxidation to acetaldehyde involves the loss of the *pro-R* hydrogen to the coenzyme.[24] Incubation of (*S*)-1-*deuterio*-ethanol with the enzyme–coenzyme system produces exclusively acetaldehyde-1-*d*, while the same treatment of (*R*)-1-*deuterio*-ethanol affords acetaldehyde containing no deuterium.



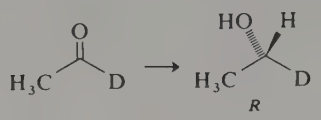
The enzyme-catalyzed interconversion of acetaldehyde and ethanol serves to illustrate a second important feature of prochiral relationships, that of *prochiral faces*. Addition of a fourth ligand, different from the three already present, to the carbonyl carbon of acetaldehyde will produce a chiral molecule. The original molecule is thus exhibiting to the attacking reagent two faces that bear a mirror-image relationship to each other and are enantiotopic. These two faces may be classified as *re* (from *rectus*) or *si* (from *sinister*), according to the sequence rule. If the substituents viewed from a particular face appear clockwise in order of decreasing priority, then that face is *re*; if counterclockwise, then *si*. The *re* and *si* faces for acetaldehyde are shown:



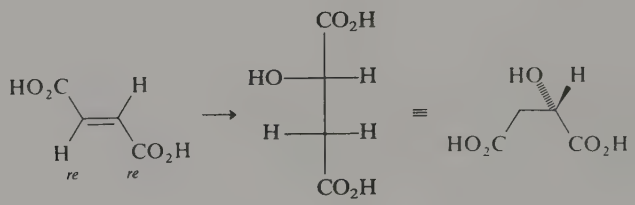
Reaction of an achiral reagent with a molecule exhibiting enantiotopic faces will produce equal quantities of enantiomers, and an optically inactive product will result. Sodium borohydride, for example, will reduce acetaldehyde-1-*d* to racemic 1-*deuterio*-ethanol. Discrimination between the prochiral faces by a chiral reagent is possible, however, and an optically active product can result. Enzymatic reduction of

24. For summaries of the evidence leading to this determination, see D. Arigoni and E. L. Eliel, *Top. Stereochem.* **4**, 127 (1969); A. R. Battersby and J. Staunton, *Tetrahedron* **30**, 1707 (1974).

acetaldehyde-1-*d* produces *R*-1-*deuterio*-ethanol, $[\alpha]_D - 0.28°C$ free of its enantiomer.[25] The reaction is completely stereoselective, with hydrogen being transferred to the *si* face of the substrate.



Fumaric acid is converted to L-malic acid by hydration in the presence of the enzyme *fumarase*. From the structure of the substrate and the configuration of the product, it is apparent that the hydroxyl group has been added to the *si* face of one of the carbon atoms of the double bond. Each of the trigonal carbon atoms of an alkene has its face specified separately. The molecule of fumaric acid is viewed from the *re–re* face as written.

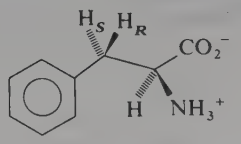


The concept of heterotopic atoms, groups, and faces can be extended from enantiotopic to diastereotopic types in a manner analogous to the distinction between enantiomers and diastereomers. If two nominally equivalent ligands in a molecule are replaced by a test group and the molecules generated are diastereomeric, then the ligands are diastereotopic. Similarly, if attack at one face of a trigonal atom generates a molecule diastereomeric with that produced on attack at the alternate face, the faces are diastereotopic.

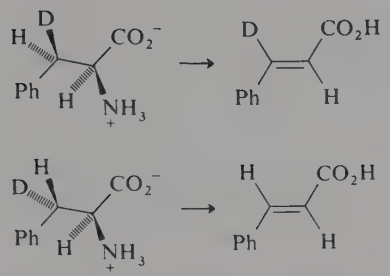
As an example of a molecule with diastereotopic ligands, consider the amino acid L-phenylalanine. The two protons at C(3) are diastereotopic, since substitution of either of them would generate a molecule with two chiral centers. Because the chiral center already present is *S*, the two molecules would be diastereomeric, with one being 2*S*,3*R* and the other 2*S*,3*S*. As in the case of enantiotopic protons, diastereotopic protons are designated *pro-R* or *pro-S*. Again, bioorganic reaction mechanisms are often probed using isotopically labeled substrates to differentiate between diastereotopic ligands. The enzyme *phenylalanine ammonia lyase* catalyzes the conversion of phenylalanine to *trans*-cinnamic acid by a process involving *anti* elimination of the amino group and the 3-*pro-S* proton. This stereochemical course

25. H. R. Levy, F. A. Loewus, and B. Vennesland, *J. Am. Chem. Soc.* **79**, 2949 (1957).

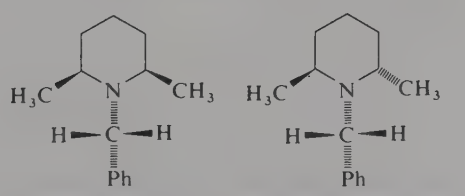
has been demonstrated using deuterium-labeled L-phenylalanine, as shown[26]:



diastereotopic protons
in L-phenylalanine



An important property of diastereotopic ligands is that they are chemically nonequivalent toward achiral as well as chiral reagents, and that they can be distinguished by physical probes, most particularly by NMR spectroscopy. The environments of diastereotopic groups are topologically nonequivalent. A consequence of this nonequivalence is that they experience different shielding effects and have different chemical shifts in the NMR. (Enantiotopic groups have the same chemical shift.) A clear example of this shift can be seen in the proton NMR spectra of the *N*-benzyl derivatives of *cis*- and *trans*-2,6-dimethylpiperidine.[27] The methylene protons of the benzyl group of the *cis*-isomer are enantiotopic, and appear as a sharp singlet. The methylene protons of the *trans*-isomer are diastereotopic, and appear as a four-line AB system.



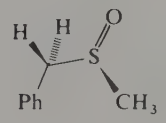
cis-isomer-methylene protons of benzyl group enantiotopic

trans-isomer-methylene protons of benzyl group diastereotopic

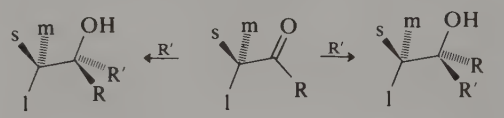
Chemical differences between diastereotopic ligands are readily observable. The protons adjacent to sulfoxide groups undergo base-catalyzed hydrogen deuterium exchange in deuterated solvents easily. In benzyl methyl sulfoxide, the

26. R. H. Wightman, J. Staunton, A. R. Battersby, and K. R. Hanson, *J. Chem. Soc. Perkin Trans. I*, 2355 (1972).
27. R. K. Hill and T.-H. Chan, *Tetrahedron* **21**, 2015 (1965); for an analysis of this effect, see G. R. Franzen and G. Binsch, *J. Am. Chem. Soc.* **95**, 175 (1973); for a review of chemical shift nonequivalence in prochiral groups, see W. B. Jennings, *Chem. Rev.* **75**, 307 (1975).

benzylic methylene protons are diastereotopic, hence chemically nonequivalent, and are exchanged at different rates.[28]



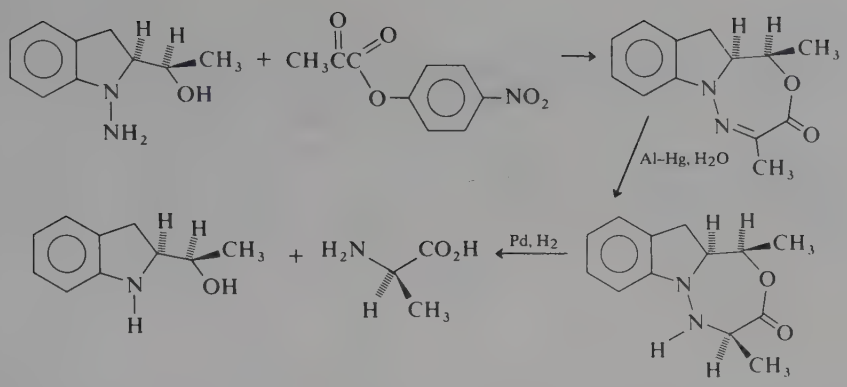
Addition to carbonyl groups in chiral molecules is perhaps the best-known example of a reaction involving preferential attack at one of two diastereotopic faces of a trigonal atom, and has been referred to earlier (see Scheme 2.5, entry 5, p. 83). The major diastereomer formed in these processes may be predicted on the basis of an empirical rule proposed by Donald J. Cram.[29] Like all empirical rules, Cram's rule is experimentally rather than mechanistically based, and should not be considered as an attempt to explain the observed facts, but to correlate them. If the substrate is oriented so that the two smallest groups of the chiral center flank the carbonyl group, then the major diastereomer produced will correspond to addition of the new ligand from the side of the smallest substituent.



minor diastereomer major diastereomer

Reaction sequences which produce new chiral centers in such a way that there is a preference for one configuration over the other are called asymmetric syntheses.[30] There are many ways of accomplishing this goal and we will discuss the topic in more depth in Section 11.3 of Part B. One example can serve here to illustrate how an asymmetric synthesis can be achieved. An efficient asymmetric synthesis of α amino acids has been developed.[31] The key step is the stereoselective reduction of a carbon–nitrogen double bond in which the hydrogen atom addition is highly preferred from one diastereotopic face over the other. The sequence is shown for the synthesis of D-alanine. The optical purity observed is 96% in this instance, with optical yields of 92%–97% reported for other amino acids prepared by this method. The chirality which is present in the reactant molecule directs the course of the hydrogen addition step which creates the new chiral center. This occurs as the result of a steric effect. It is easier for the hydrogen to approach from the

28. T. Durst, *Intra-Sci. Chem. Rep.* **7**, 63 (1973).
29. D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.* **85**, 1245 (1963), and previous papers in this series.
30. J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions*, 2nd Printing, American Chemical Society, Washington, D.C., 1976; H. B. Kagan and J. C. Fiaud, *Top. Stereochem.* **10**, 175 (1978).
31. E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *J. Am. Chem. Soc.* **92**, 2488 (1970).



less bulky side of the molecule. After the reduction stage the newly created chiral product is obtained by a reaction which also releases the original chiral center in a form in which it can be reconverted to the chiral reagent.

General References

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K. Mislow, *Introduction to Stereochemistry*, W. A. Benjamin, New York, 1966.
G. Natta and M. Farina, *Stereochemistry*, Harper and Row, New York, 1972.
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B. Testa, *Principles of Organic Stereochemistry*, Marcel Dekker, New York, 1979.

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R. Bentley, *Molecular Asymmetry in Biology*, Vols. I and II, Academic Press, New York, 1969, 1970.
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Stereoselective and Stereospecific Reactions

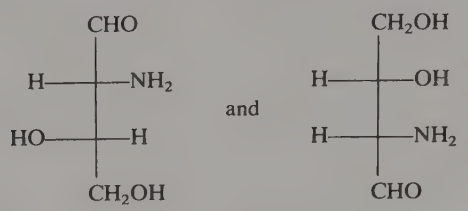
J. D. Morrison and H. S. Mosher, *Asymmetric Organic Reactions*, 2nd Printing, American Chemical Society, Washington, D.C., 1976.
Y. Izumi and A. Tai, *Stereodifferentiating Reactions*, Academic Press, New York, 1977.

Problems

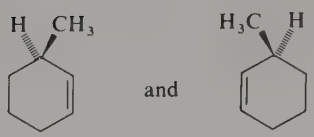
(*References for these problems will be found on page 700.*)

1. Indicate whether the relationship in each of the following pairs of compounds is identical, enantiomeric, or diastereomeric:

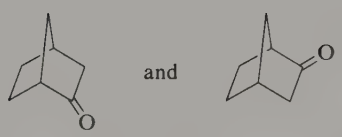
(a)



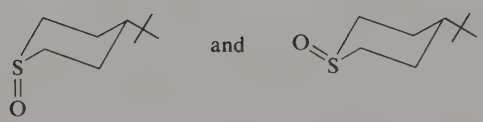
(b)



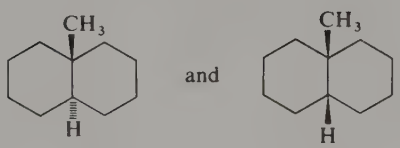
(c)



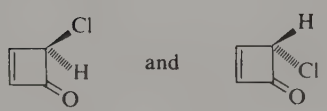
(d)



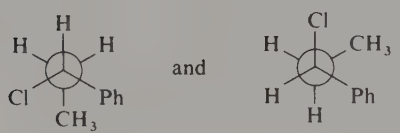
(e)



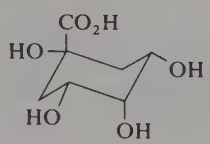
(f)



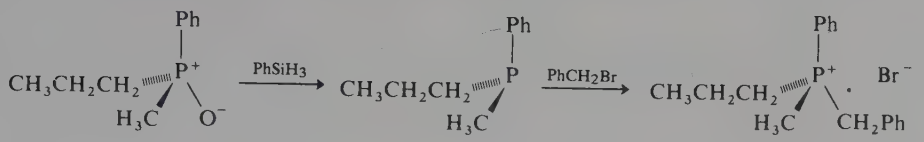
(g)



2. The structure originally proposed for cordycepic acid, $[\alpha]_D = +40.3°$, has been shown to be incorrect. Suggest a reason to be skeptical about the original structure, which is given below:

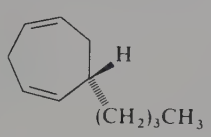


3. Each reaction in the sequence shown is reported to proceed with retention of configuration; yet the starting material has the *R* configuration, and the product has the *S* configuration. Reconcile this apparent contradiction.

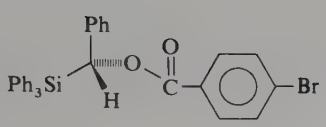


4. Using the sequence rule, specify the configuration at each chiral center in the following molecules:

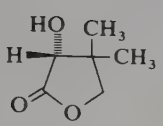
(a)



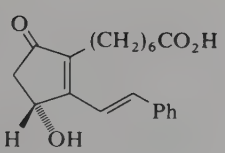
(b)



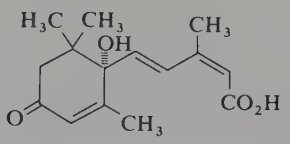
(c)



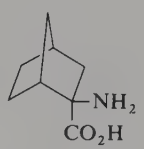
(d)



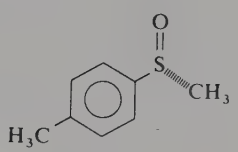
(e)



(f)

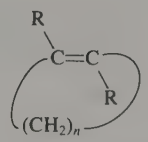


(g)



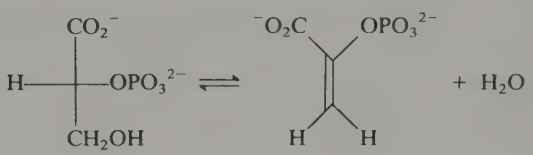
5. Draw structural formulas for each of the following compounds, clearly showing stereochemistry:
   (a) (*E*)-3,7-dimethyl-2,6-octadien-1-ol (geraniol)
   (b) (*R*)-4-methyl-4-phenyl-2-cyclohexenone
   (c) L-*erythro*-2-(methylamino)-1-phenylpropan-1-ol [(−)-ephedrine]
   (d) (7*R*,8*S*)-7,8-epoxy-2-methyloctadecane (the sex attractant of the female gypsy moth)
   (e) methyl (1*S*)-cyano-(2*R*)-phenylcyclopropanecarboxylate
   (f) (*Z*)-2-methyl-2-butenol
   (g) (*E*)-(3-methyl-2-pentenylidene)triphenylphosphorane

6. The racemization of medium-ring *trans*-cycloalkenes depends upon ring size and substitution, as indicated by the data below. Discuss these relative reactivities in terms of the structures of the cycloalkenes and the mechanism of racemization.



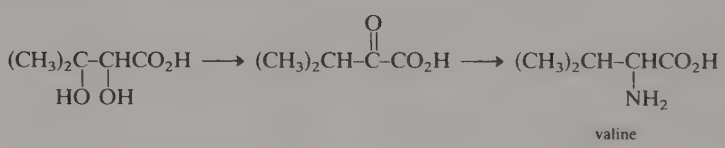
Ring size	n	R	$t_{1/2}$ for racemization
8	6	H	10^5 years at 25°
9	7	H	10 sec at 25°
10	8	CH_3	3 days at 100°
12	10	CH_3	1 day at 25°

7. The enzyme enolase catalyzes the following reaction:



When (2*R*,3*R*)-2-phosphoglycerate-3-*d* was used as the substrate, the *E* isomer of phosphoenolpyruvate-3-*d* was produced. Is the stereochemistry of elimination *syn* or *anti*?

8. An important sequence in valine biosynthesis in bacteria is



The stereochemical aspects of this sequence have been examined, using a diol substrate in which one of the methyl groups has been replaced by CD_3. Given the information that labeled starting diol of configuration 2*R*,3*R* produces labeled valine of configuration 2*S*,3*S*, deduce whether the C(3)-hydroxyl group is replaced with overall retention or inversion of configuration.

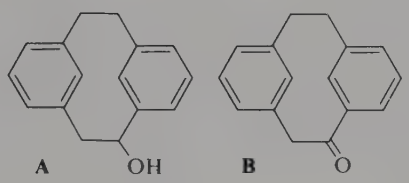
9. Draw structural formulas for the possible stereoisomers of 1-carboethoxy-4-methylspiropentane.

10. Give the product(s) described for each reaction. Specify all aspects of stereochemistry.
    (a) stereospecific *anti* addition of bromine to *cis*- and *trans*-cinnamic acid
    (b) solvolysis of (*S*)-3-bromooctane in methanol with 6% racemization

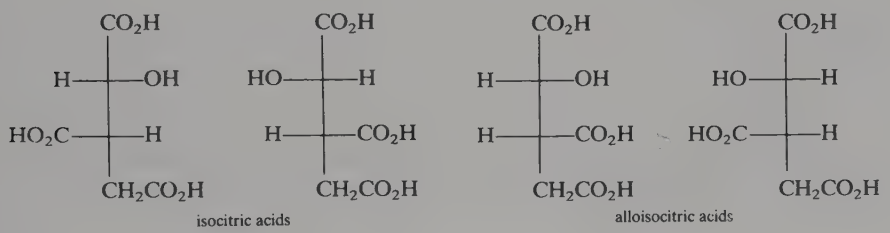
(c) stereospecific *syn* elimination of acetic acid from (*R*,*S*)-1,2-diphenylpropyl acetate

(d) stereoselective epoxidation of bicyclo[2.2.1]hept-2-ene proceeding 94% from the *exo* direction

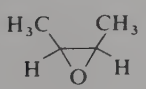
11. Compound **A** can be resolved to give an optically pure substance, $[\alpha]_D^{25} = -124°$. Oxidation gives the pure ketone **B**, which is optically active, $[\alpha]_D^{25} \simeq -439°$. Heating the alcohol **A** gives partial conversion (an equilibrium is established) to an isomer with $[\alpha]_D^{25} = +22°$. Oxidation of this isomer gives the enantiomer of the ketone **B**. Heating either ketone leads to the racemic mixture. Explain the stereochemical relationships between these compounds.

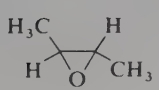


12. Assign configurations, using the sequence rule, to each chiral center of the stereoisomeric isocitric acids and allocitric acids:



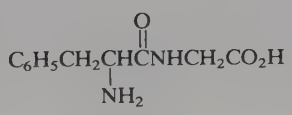
13. Some of the compounds shown contain diastereotopic atoms or groups. Which possess this characteristic? For those that do, indicate the atoms or groups that are diastereotopic and indicate which atom or group is pro-*R* and which is pro-*S*.

(a) 

(b) 

(c) $C_6H_5CHCO_2CH(CH_3)_2$
OCH_3

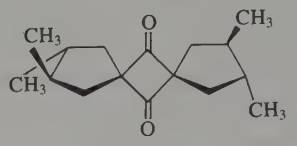
(d) $(CH_3)_2CHCHCO_2H$
NH_2

(e) 

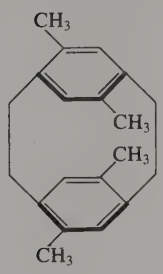
14. Indicate which of the following molecules are chiral and which are achiral. For each molecule that is achiral indicate the element of symmetry which is present in the molecule.

(a)

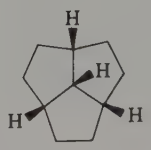
(b)



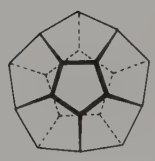
(c)



(d)

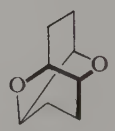


(e)

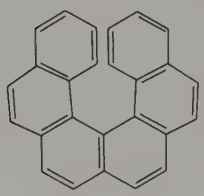


$C_{20}H_{20}$ (dodecahedrane)

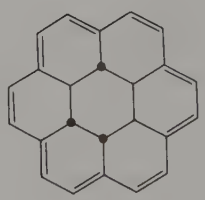
(f)



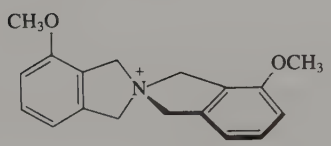
(g)

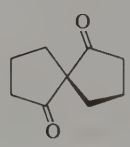


(h)

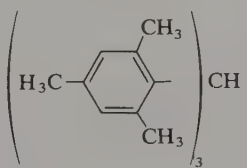


(i)

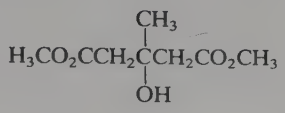




15. The NMR spectrum of the highly hindered molecule trimesitylmethane indicates that there are two enantiomeric species present in solution, the interconversion of which is separated by a barrier of 22 kcal/mol. Discuss the source of the observed chirality of this molecule.



16. A synthesis of the important biosynthetic intermediate mevalonic acid starts with the enzymatic hydrolysis of the diester **A** by pig liver esterase. The *pro-R* group is selectively hydrolyzed. Draw a three-dimensional structure of the product.

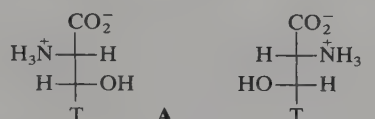


A

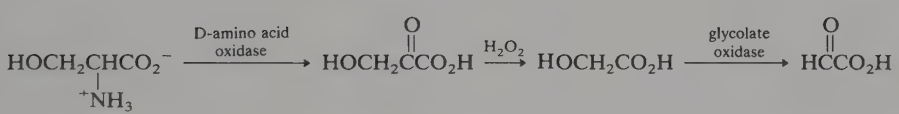
17. One of the diastereomers of 2,6-dimethylcyclohexyl benzyl ether exhibits two doublets for the benzylic protons in its NMR spectrum. Deduce the stereochemistry of this isomer.

18. 1,2-Diphenyl-1-propanol may be prepared in either of two ways:
    a) lithium aluminum hydride redution of 1,2-diphenyl-1-propanone
    b) reaction of 2-phenylpropanal with phenylmagnesium bromide.
    Which method would you choose to prepare the *threo* isomer. Explain.

19. A mixture of tritium (^3H = T) labeled **A** and **B** was carried through the reaction sequence shown:

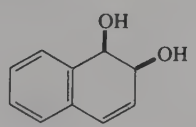


A **B**

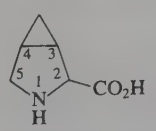


D-Amino acid oxidase will oxidize only serine having the *R* configuration at C-2. Glycolate oxidase will remove only the pro-*R* hydrogen of glycolic acid. Does the product ($O{=}CHCO_2H$) contain tritium? Explain your reasoning.

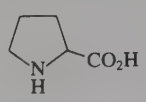
20. Enzymatic oxidation of naphthalene by bacteria proceeds by way of the intermediate *cis*-diol shown. Which prochiral faces of C-1 and C-2 of naphthalene are hydroxylated in this process?



21. An amino acid having the constitution shown has been isolated from horse chestnuts. It is configurationally related to L-proline and has the *R* configuration at C-3. Write a stereochemically correct representation for this compound.



(horse-chestnut amino acid)



(proline—no stereochemistry implied)

3

Conformational, Steric, and Stereoelectronic Effects

The total energy of a molecule is directly related to its geometry. Several aspects of molecular geometry can be recognized, and, to some extent, the energetic consequences can be dissected and attributed to specific structural features. Among the factors which contribute to total energy and have a recognizable connection with molecular geometry are nonbonded repulsions, ring strain in cyclic systems, and destabilization resulting from distortion of bond lengths or bond angles from optimal values. Conversely, there are stabilizing interactions which have geometric constraints. Most of these can be classed as stereoelectronic effects; that is, a particular geometric relationship is required to maximize the stabilizing interaction. In addition there are other molecular interactions, such as hydrogen bonds and dipole–dipole interactions, where the strength of the interaction will be strongly dependent on geometric factors. A molecule will adopt the minimum energy geometry that is available by rotations about single bonds. The various shapes that a given molecule can attain by these rotations are called *conformations*. The principles on which analysis of conformational equilibria and rotational processes are based have been developed using a classical mechanical framework, for the most part. More recently, the problem of detailed interpretation of molecular geometry has also been attacked from the molecular orbital viewpoint.

Many molecules exhibit *strain* caused by nonideal geometry. The molecule will minimize the energetic consequences by whatever changes of bond angle or length are available to it. These structural adjustments, however, cannot compensate entirely for the unfavorable consequences of nonideal bonding arrangements, and such molecules will be less stable than one would calculate by simply summing the energies of all the bonds in the molecule. This decreased stability is called *strain energy*. This chapter will focus on these interrelated topics: the sources of strain in molecules and the response of molecular geometry to various types of strain.

From a molecular orbital viewpoint, the energy of a molecule is the sum of the energy of the occupied molecular orbitals. Calculations of molecules in different spatial arrangements reveals that the energy can vary greatly as a function of geometry. The physical picture of this is given in terms of the effectiveness of orbital overlap. Maximum overlap between orbitals which have a bonding interaction lowers the total molecular energy while overlap of antibonding orbitals raises the energy of the molecule. The term *stereoelectronic effect* can be used to encompass these relationships between molecular structure and energy which can be traced to the contributions of specific orbital interactions.

3.1. Steric Strain and Molecular Mechanics

A system of analyzing the energy differences among molecules and among various geometries of a particular molecule has been developed, based on some fundamental concepts formalized by Westheimer.[1] The method is now known by the term *molecular mechanics*, although the expressions *empirical force field calculations* or the *Westheimer method* are sometimes applied.[2]

A molecule will adopt the geometry that minimizes its total energy. The minimum-energy geometry will be strained to a degree dependent on the extent to which its structural parameters deviate from their ideal values. The energy for a particular kind of distortion is given by the product of the amount of distortion and the restoring force acting on it. The total *steric energy* (E_{steric}) can be formulated as the sum of several contributors:

$$E_{\text{steric}} = E(r) + E(\theta) + E(\phi) + E(d)$$

where $E(r)$ is the energy increment associated with stretching or compression of single bonds, $E(\theta)$ is the strain energy of bond-angle distortion, $E(\phi)$ is the torsional strain, and $E(d)$ are the energy increments that result from nonbonded interactions between atoms or groups.

The mathematical expressions for the force fields are derived from classical mechanical potential energy functions. The energy required to stretch bonds or to bend bond angles increases as the square of the distortion.

Bond stretching:

$$E(r) = 0.5k_r(r - r_0)^2$$

1. F. H. Westheimer, in *Steric Effects in Organic Chemistry*, M. S. Newman (ed.), Wiley, New York, 1956, Chap. 12.
2. For reviews, see J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.* **19**, 531 (1968); D. B. Boyd and K. B. Lipkowitz, *J. Chem. Educ.* **59**, 269 (1982); P. J. Cox, *J. Chem. Educ.* **59**, 275 (1982); N. L. Allinger, *Adv. Phys. Org. Chem.* **13**, 1 (1976); E. Osawa and H. Musso, *Top. Stereochem.* **13**, 117 (1982); U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington D.C., 1982.

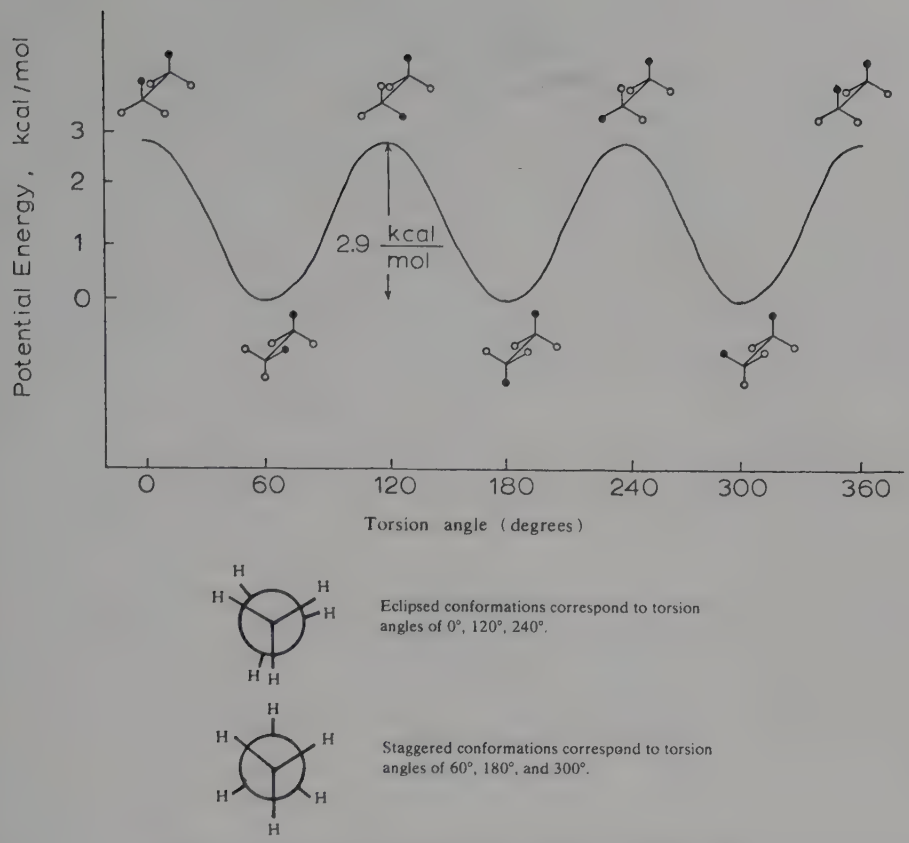


Fig. 3.1. Potential energy as a function of torsion angle for ethane.

where k_r is the stretching force constant, r the bond length, and r_0 the normal bond length.

Bond-angle bending:

$$E(\theta) = 0.5k_\theta(\Delta\theta)^2$$

where k_θ is the bending force constant and $\Delta\theta$ is the deviation of the bond angle from its normal value.

The torsional strain is a sinusoidal function of the *torsion angle*. (In the context of its use in structural organic chemistry, torsion angle is synonymous with the more familiar, but less precise, *dihedral angle*.[3]) For molecules with a threefold barrier such as ethane, the form of the torsional barrier is

$$E(\phi) = 0.5V_0(1 + \cos 3\phi)$$

where V_0 is the rotational energy barrier and ϕ is the torsion angle. For hydrocarbons

3. For applications of the concept of torsion angle to conformational descriptions, see R. Bucourt, *Top. Stereochem.* **8**, 159 (1974).

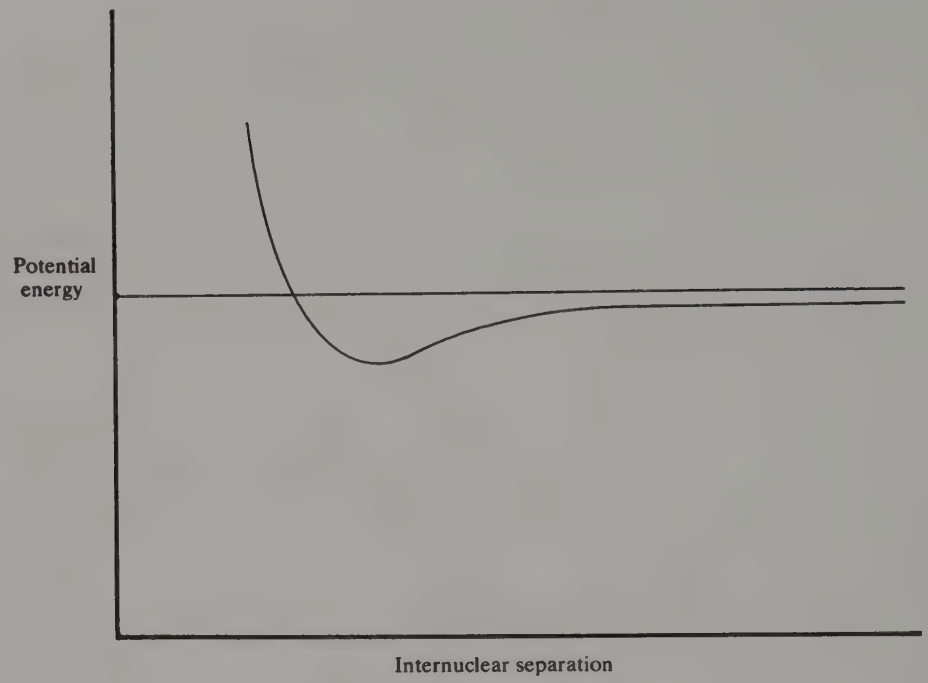


Fig. 3.2. Energy as a function of internuclear distance for nonbonded atoms.

V_0 can be taken as being equal to the ethane barrier (2.8–2.9 kcal/mol). The potential energy diagram for rotation about the C–C bond of ethane is given in Fig. 3.1. The ethane barrier may be taken as a standard rotational barrier for acyclic hydrocarbons when analyzing the contribution of torsional strain to the total steric strain. The stereoelectronic origin of the ethane barrier was discussed in Chapter 1. Any steric interactions which are present in more highly substituted systems will make an additional contribution to the barrier.[4]

Nonbonded interaction energies are the most difficult contribution to evaluate, and may be attractive or repulsive. When two uncharged spherical atoms approach each other, the interaction between them is very small at large distances, becomes increasingly attractive as the separation approaches the sum of their van der Waals radii, then becomes strongly repulsive as the atoms approach each other with a separation less than the sum of their van der Waals radii. This behavior is represented graphically by the familiar Morse potential diagram in Fig. 3.2. The attractive interaction results from a mutual polarization of the electrons of each atom by the other. Such attractive forces are called *London forces* or *dispersion forces*, and are normally weak interactions. London forces vary inversely with the sixth power of internuclear distance, and therefore become unimportant at large distances. At

4. L. S. Bartell, *J. Am. Chem. Soc.* **99**, 3279 (1977); N. L. Allinger, D. Hindman, and H. Hönig, *J. Am. Chem. Soc.* **99**, 3282 (1977).

Table 3.1. Van der Waals Radii of Several Atoms and Groups (Å)[a]

H	1.20			CH_3	2.0		
N	1.55	P	1.80				
O	1.52	S	1.80				
F	1.47	Cl	1.75	Br	1.85	I	1.98

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

distances smaller than the sum of the van der Waals radii, the attractive forces are overwhelmed by repulsion between the atoms. Table 3.1 lists van der Waals radii of atoms commonly encountered in organic molecules.

The interplay between torsional strain and nonbonded interactions can be illustrated by examining conformational isomerism in *n*-butane. The diagram relating potential energy to torsion angle for rotation about the C(2)–C(3) bond is presented in Fig. 3.3.

The potential energy diagram of *n*-butane resembles that of ethane in having three energy maxima and three minima, but differs from it in that one of the minima is of lower energy than the other two, and one of the maxima is of higher energy than the other two. The minima correspond to staggered conformations, of which 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 0.8 kcal/mol.[5] The maxima correspond to eclipsed conformations, with the highest-energy conformation being the one with the two methyl groups eclipsed with each other. The methyl–methyl eclipsed conformation is about 2.6 kcal/mol higher in energy than the methyl–hydrogen eclipsed conformations and 6 kcal/mol higher in energy than the staggered *anti* conformation.

The rotational profile of *n*-butane can be understood as a superimposition of van der Waals forces on the ethane potential energy diagram. The two *gauche* conformations are raised in energy relative to the *anti* by an energy increment resulting from a van der Waals repulsion between the two methyl groups of 0.8 kcal/mol. The eclipsed conformations all incorporate 2.8 kcal/mol of torsional strain relative to the staggered conformations. The methyl–methyl eclipsed conformation is further strained by van der Waals repulsion between methyl groups. The van der Waals repulsions between methyl and hydrogen are smaller in the other eclipsed conformations. If we subtract the torsional-strain contribution of 2.8 kcal/mol we conclude that the methyl–methyl eclipsing interaction destabilizes the 0° conformation by an additional 3.2 kcal/mol of van der Waals strain. The 120° and 240° eclipsed conformations are strained by 0.6 kcal/mol over and above

5. This is the value most usually quoted (actually 0.77 kcal/mol) which was obtained by Raman spectroscopy: G. J. Szasz, N. Sheppard, and D. H. Rank, *J. Chem. Phys.* **16**, 704 (1948); a value of 0.68 kcal/mol has been obtained by NMR: P. B. Woller and E. W. Garbisch, Jr., *J. Am. Chem. Soc.* **94**, 5310 (1972).

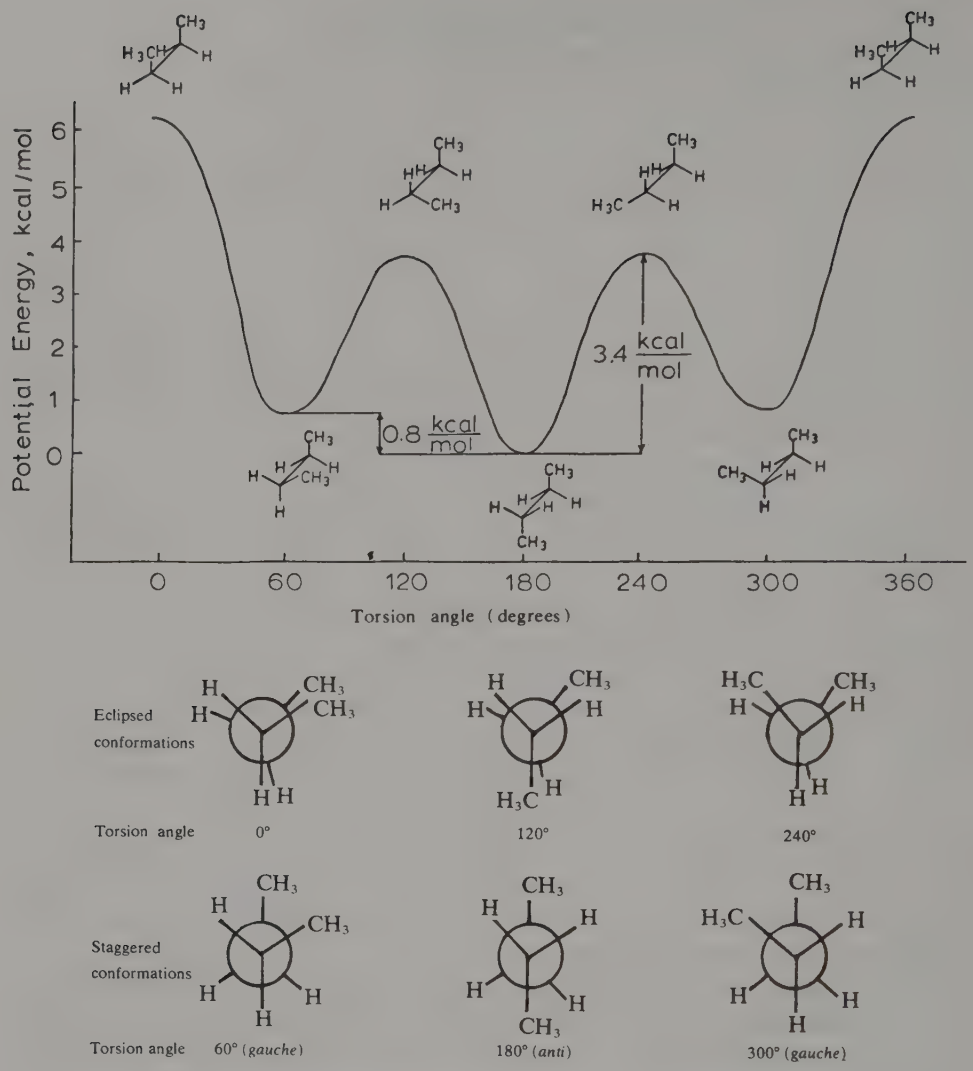


Fig. 3.3. Potential energy diagram for rotation about C(2)–C(3) bond of *n*-butane.

the torsional strain incorporated into each, or by 0.3 kcal/mol for each of two methyl–hydrogen van der Waals repulsions.

The populations of the various conformers are related to the energy differences between them by the equation

$$\Delta G^\circ = -RT \ln K$$

where the symbols have their customary meanings. For the case of *n*-butane, the equilibrium

$$gauche \rightleftharpoons anti$$

has $\Delta H^\circ = -0.8$ kcal/mol. Since there are two enantiomeric *gauche* conformers, the

Table 3.2. Composition–Equilibrium–Free-Energy Relationships[a]

More stable isomer (%)	Equilibrium constant (K)	Free energy ΔG°_{25} (kcal/mol)
50	1	0.0
55	1.22	−0.119
60	1.50	−0.240
65	1.86	−0.367
70	2.33	−0.502
75	3.00	−0.651
80	4.00	−0.821
85	5.67	−1.028
90	9.00	−1.302
95	19.00	−1.744
98	49.00	−2.306
99	99.00	−2.722
99.9	999.00	−4.092

a. From E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962.

free-energy change is related to the enthalpy change by an entropy of mixing:

$$\Delta S^\circ = -R \ln 2$$

and

$$\Delta G^\circ = \Delta H^\circ - T\,\Delta S^\circ$$

$$\Delta G^\circ = -0.8 \text{ kcal/mol} - (-RT \ln 2)$$

At 298°K

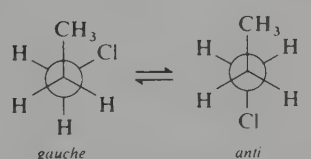
$$\Delta G^\circ = -0.8 \text{ kcal/mol} + 0.41 \text{ kcal/mol} = -0.39 \text{ kcal/mol}$$

and

$$K = (anti)/(gauche) = 1.9$$

corresponding to a distribution of 66% *anti* and 34% *gauche*. The relationships among free energy, equilibrium constant, and percent composition are summarized in Table 3.2.

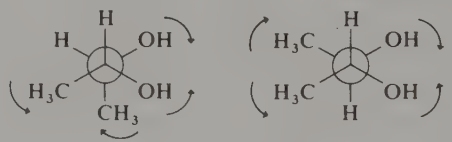
An example of attractive nonbonded interactions can be found in some halogenated hydrocarbons. This is illustrated for the case of *n*-propyl chloride, where the *gauche* conformation is slightly preferred over the *anti* conformation at equilibrium. The *gauche* is favored not only on entropy grounds, but on enthalpy grounds as well. For the equilibrium



$\Delta H = 0.3 \pm 0.3$ kcal/mol. The lower energy of the *gauche* form is thought to

result from stabilizing London forces betwen the methyl group and the chlorine, which are separated by a distance approximating the sum of their van der Waals radii in the *gauche* conformation.

Another type of interaction that can significantly stabilize *gauche* conformations relative to *anti* conformations is intramolecular hydrogen bonding, such as exists in *vic*-diols. The IR spectra of *vic*-diols are characterized by separate absorptions for free and hydrogen-bonded O—H stretching.[6] The separation between the absorptions is related to the proximity of the two hydroxyl groups involved. The separation $\Delta\nu$ is 32 cm^{-1} for ethylene glycol, indicating qualitatively the presence of the *gauche* conformation in dilute solution. The hydroxyl groups in the *anti* conformation are too far removed from each other to form an intramolecular hydrogen bond. This technique is fairly sensitive to structural changes. The diastereomeric 2,3-butanediols, for example, exhibit different values of $\Delta\nu$. The *meso*-isomer has a shift of 42 cm^{-1}, while that for the *d,l* form is 49 cm^{-1}. This difference is reasonable, since hydrogen bonding between the two *gauche* hydroxyl groups tends to bring them together by decreasing the O–C–C–O torsion angle. This decrease has the effect of increasing the CH_3–C–C–CH_3 torsion angle in the chiral isomer and reducing it in the *meso* form.



meso *chiral*

The separation of the total steric strain into component elements of bond length strain, bond angle strain, torsional strain, and nonbonded interactions is qualitatively useful in the manner just described, and will be employed extensively to rationalize structural effects of a steric nature on equilibria and reactivity. It is especially noteworthy that quantitative application of the principles of molecular mechanics to the calculation of ground state geometries, heats of formation, and strain energies of organic molecules has been developed to a high level and is extraordinarily successful. Minimization of the total strain energy of a molecular assembly, expressed by a multiparameter equation, can be accomplished by an iterative computation.[7] Techniques for such calculations have been described and refined to the point that geometries of hydrocarbons of moderate size may be calculated to an accuracy of 0.01 Å in bond length and 1–2° in bond angle.[8] Satisfactory results have also been obtained in more diverse systems, including alkenes; molecules containing oxygen nitrogen, and halogen heteroatoms; organosilicon compounds; carbonium ions; and dynamic processes.[9]

6. L. P. Kuhn, *J. Am. Chem. Soc.* **80**, 5950 (1958).
7. J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 4537 (1961); **84**, 3355 (1962); K. B. Wiberg, *J. Am. Chem. Soc.* **87**, 1070 (1965).
8. N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *J. Am. Chem. Soc.* **89**, 4345 (1967), N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).
9. For a summary, see N. L. Allinger, *Adv. Phys. Org. Chem.* **13**, 1 (1976).

Table 3.3. Rotational Energy Barriers of Compounds of the Type CH_3–X[a]

Compound	Barrier height (kcal/mol)
Alkanes	
1. CH_3–CH_3	2.88
2. CH_3–CH_2CH_3	3.4
3. CH_3–$CH(CH_3)_2$	3.9
4. CH_3–$C(CH_3)_3$	4.7
5. CH_3–SiH_3	1.7
Haloethanes	
6. CH_3–CH_2F	3.3
7. CH_3–CH_2Cl	3.7
8. CH_3–CH_2Br	3.7
9. CH_3–CH_2I	3.2
Heteroatom substitution	
10. CH_3–NH_2	1.98
11. CH_3–$NHCH_3$	3.62
12. CH_3–OH	1.07
13. CH_3–OCH_3	2.7

a. Taken from the compilation of J. P. Lowe, *Prog. Phys. Org. Chem.* **6**, 1 (1968); Barriers are those for rotation about the bond indicated in the formula.

3.2. Conformations of Acyclic Molecules

Simple hydrocarbons represent rather well-behaved extensions of the conformational principles illustrated previously in the analysis of rotational equilibria in ethane and *n*-butane. The staggered conformations correspond to potential energy minima, the eclipsed conformations to potential energy maxima. Of the staggered conformations, *anti* forms are more stable than *gauche*. The magnitudes of the barriers to rotation of many small organic molecules have been measured.[10] Some representative examples are listed in Table 3.3. The experimental techniques used to study rotational isomerism include microwave spectroscopy, electron diffraction, ultrasonic absorption, and infrared spectroscopy.[11]

Substitution of methyl groups for hydrogen atoms on one of the carbon atoms produces a regular increase of about 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 two methyl–hydrogen eclipsing interactions occur, as in 2-methylpropane, the barrier is raised to 3.9 kcal/mol. The increase in going to

10. For a review, see J. P. Lowe, *Prog. Phys. Org. Chem.* **6**, 1 (1968).
11. Methods for determination of rotational barriers are described in Ref. 10 and by E. Wyn-Jones and R. A. Pethrick, *Top. Stereochem.* **5**, 205 (1969).

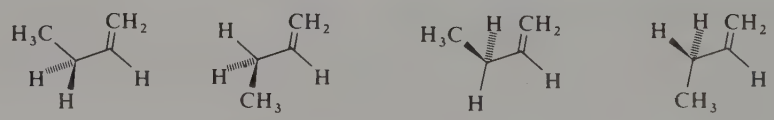
2,2-dimethylpropane, in which the barrier is 4.7 kcal/mol, is 1.8 kcal/mol for the total of three methyl–hydrogen eclipsing interactions.

The rotational barrier in methylsilane (Table 3.3, entry 5) is significantly smaller than that of ethane (1.7 versus 2.88 kcal/mol), probably because of decreased electron–electron repulsions resulting from the longer silicon–carbon bond length of 1.87 Å, compared to 1.54 Å for ethane.

The haloethanes all have similar rotational barriers of 3.2–3.7 kcal/mol. The increase in the barrier height relative to ethane is thought to be a van der Waals repulsion effect. The heavier halogens have larger van der Waals radii, but also longer bond lengths, so that the net effect is relatively constant for all the halogens.

Changing the nature of the atom bonded to a methyl group from carbon to nitrogen to oxygen, in going from ethane to methylamine to methanol, produces a regular decrease in the rotational barrier from 2.88 to 1.98 to 1.07 kcal/mol. One explanation for these observations is based on analysis of CNDO calculations.[12] The calculations indicate π-bond character between the central atoms, and an antibonding interaction between eclipsed hydrogens. The 3:2:1 ratio observed for the ethane, methylamine, and methanol barriers follows naturally from the number of H–H antibonding interactions in the eclipsed conformations. Entries 11 and 13 in Table 3.3 present data relating the effect of methyl substitution on methanol and methylamine, and indicate a greater sensitivity toward substitution than that exhibited by ethane. Where the propane barrier is 3.4 kcal/mol, the barrier in dimethylamine is 3.6 kcal/mol, and that in dimethyl ether is 2.7 kcal/mol. Thus, methyl–hydrogen eclipsing raised the rotational energy barrier 0.5 kcal/mol in ethane, but by 1.6 kcal/mol in methylamine and methanol. This greater sensitivity to substitution can be ascribed to increased van der Waals repulsions in dimethylamine and dimethyl ether, brought about by the shorter C–N and C–O bond lengths relative to the C–N bond length.

Rotational isomerism about the C(2)–C(3) single bond of terminal alkenes offers an interesting contrast to the examples we have discussed to this point.[13] The case of 1-butene is illustrative. The conformations to be considered are as follows:



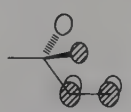
Conformations **A** and **B** can be termed eclipsed, and **C** and **D** *bisected.* These designations refer to the torsional angle between the double bond and the adjacent sp^3 carbon atom, which is 0° in **A** or **B** and 60° in **C** and **D**. The stable rotamers, as determined by microwave spectroscopy, are the eclipsed conformations **A** and

12. J. A. Pople and G. A. Segal, *J. Chem. Phys.* **43**, S136 (1965).
13. For a review, see G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.* **5**, 167 (1969).

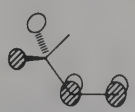
B. Conformation **B** (hydrogen eclipsed) is slightly more stable than **A** (methyl-eclipsed).[14] The enthalpy difference is only about 0.15 kcal/mol.

The preference for eclipsed conformations around the sp^2–sp^3 bond of alkenes rotational barriers are relatively low, that for propene being about 2 kcal/mol. Simple substituent effects appear straightforward. 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.[15] Increasing the steric requirements of the group at C-3 increases the preference for eclipsed conformations analogous to **B** at the expense of **A**. For example, 4,4-dimethyl-1-pentene exists mainly in the hydrogen-eclipsed conformation.

The origin of the preference for conformer **B** can be explained in terms of molecular orbital theory by focusing attention on the interaction between the double bond and the π component of the local orbitals associated with the methyl group. The dominant interaction is a repulsive one between the filled methyl group orbitals and the filled π orbital of the double bond. This repulsive interaction is greatest in the staggered conformation which brings these orbitals closer together than in the eclipsed conformation.[16]

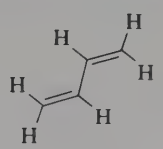


major repulsive interaction

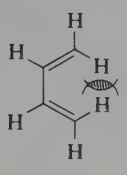


reduced repulsive interaction

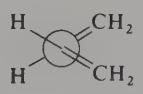
1,3-Dienes would be expected to adopt conformations in which the double bonds are coplanar, so as to permit effective orbital overlap and electron delocalization. The two alternative planar conformations for 1,3-butadiene are referred to as *s-trans* and *s-cis*. Various types of studies have shown that the *s-trans* conformation is the most stable one for 1,3-butadiene.[17,18] The energy difference between the stable conformation and a second less favorable conformation is 2.8 ± 0.3 kcal/mol. Two conformations have been considered as possibilities for the less stable conformation. The planar *s-cis* incorporates a van der Waals repulsion between the hydrogens on C-1 and C-4. This is relieved in the skew conformation,



s-trans



s-cis

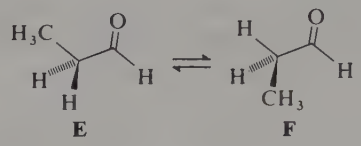


skew

14. S. Kondo, E. Hirota, and Y. Morino, *J. Mol. Spectrosc.* **28**, 471 (1968).
15. T. Shimanouchi, Y. Abe, and K. Kuchitsu, *J. Mol. Struct.* **2**, 82 (1968).
16. W. J. Hehre, J. A. Pople, and A. J. P. Devaquet, *J. Am. Chem. Soc.* **98**, 664 (1976).
17. M. E. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.* **101**, 3657 (1979) and references therein.
18. R. L. Lipnick and E. W. Garbisch, Jr., *J. Am. Chem. Soc.* **95**, 6370 (1973).

but at the expense of reduced overlap of the π system across C-2 and C-3. The IR and UV spectra of samples of 1,3-butadiene which have an increased content of the higher-energy conformer have been recorded under matrix isolation conditions. These data favor the planar *s-cis* geometry for the second conformer.[17] The energy barrier for the conformational change to the more stable *s-trans* conformation is found to be about 3.9 kcal/mol, which agrees with a value determined from Raman spectral data.[19] This energy maximum presumably refers to the conformation (transition state) where the two π bonds are mutually perpendicular. Various MO calculations find the *s-trans* conformer to be 2–5 kcal/mol lower in energy than either the planar or skew form of the *s-cis* conformation.[20]

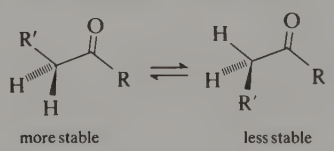
The preferred conformations of carbonyl compounds, like 1-alkenes, are eclipsed rather than bisected. Interestingly, it is the alkyl group, rather than the hydrogen, that is eclipsed with the carbonyl group. For propionaldehyde, conformation **E** has been determined by microwave spectroscopy to be 0.9 kcal/mol more stable than **F**[21]:



E **F**

A number of aldehydes have been studied by NMR and found to have analogous rotameric compositions.[22] Only when the substituent is exceptionally sterically demanding, as in $(CH_3)_3CCH_2CHO$, does the hydrogen-eclipsed conformation become more stable. The barrier heights are somewhat smaller than for the analogous 1-alkenes. For acetaldehyde, the rotational barrier is 1.1 kcal/mol, versus 2.0 kcal/mol for propene.[23]

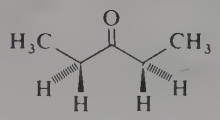
Ketones appear to resemble aldehydes in also favoring eclipsed conformations. The preference for the rotamer in which the substituent, rather than a hydrogen, is eclipsed with the carbonyl group should be more pronounced for a ketone than for an aldehyde. Such a conformation then allows the substituents to be *anti*, where the alternative rotamer would have the substituents *gauche*.



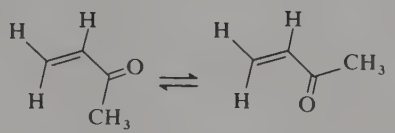
more stable less stable

17. See p. 109.
19. J. R. Durig, W. E. Buey, and A. R. H. Cole, *Can. J. Phys.* **53**, 1832 (1976); L. A. Carreira, *J. Chem. Phys.* **62**, 3851 (1975).
20. A. J. P. Devaquet, R. E. Townshend, and W. J. Hehre, *J. Am. Chem. Soc.* **98**, 4068 (1976) and references therein.
21. S. S. Butcher and E. B. Wilson, Jr., *J. Chem. Phys.* **40**, 1671 (1964).
22. G. J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.* **87**, 2864 (1965).
23. R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.* **26**, 1695 (1957).

Electron diffraction studies of 3-pentanone indicate the conformation shown to be the most stable rotamer, in accord with this generalization.[24]

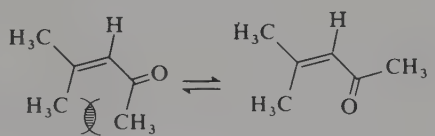


The case of α,β-unsaturated carbonyl compounds is analogous to that of 1,3-dienes, in that electronic considerations favor coplanarity of the atoms of the C=C—C=O system. The rotamers that appear important are the *s-trans* and *s-cis* conformations. Microwave data indicate that the *s-trans* form is the only conformation present in acrolein in detectable amounts.[25] The equilibrium distribution of *s-trans* and *s-cis* conformations of α,β-unsaturated ketones depends on van der Waals interactions between substituents.[26] Methyl vinyl ketone has no unfavorable van der Waals repulsions between substituents, and exists predominantly as the *s-trans* conformer:



s-trans (73%) *s-cis* (27%)

An unfavorable methyl–methyl interaction destabilizes the *s-trans* conformation of mesityl oxide relative to the *s-cis* conformation, and the equilibrium favors



s-trans (28%) *s-cis* (72%)

the *s-cis* form. Both NMR and IR correlations have been developed which can provide an indication of the conformation of α,β-unsaturated carbonyl compounds.[27]

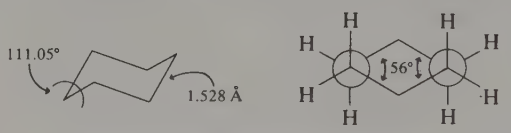
3.3. Conformations of Cyclohexane Derivatives

A particularly well-understood aspect of conformational analysis is concerned with compounds containing six-membered rings. Aside from the importance of such

24. C. Romers and J. E. G. Creutzberg, *Rec. Trav. Chim.* **75**, 331 (1956)
25. E. A. Cherniak and C. C. Costain, *J. Chem. Phys.* **45**, 104 (1966).
26. For an extensive compilation of equilibrium data for conformations of α,β-unsaturated carbonyl compounds, see G. Montaudo, V. Librando, S. Caccamese, and P. Maravigna, *J. Am. Chem. Soc.* **95**, 6365 (1973).
27. D. D. Faulk and A. Fry, *J. Org. Chem.* **35**, 364 (1970); J. K. Groves and N. Jones, *Tetrahedron* **25**, 223 (1969); F. H. Cottee, B. P. Straughan, C. J. Timmons, W. F. Forbes, and R. Shilton, *J. Chem. Soc. B*, 1146 (1967).

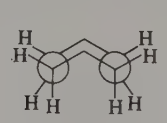
compounds in many classes of natural products, a major reason for the depth of study and resulting detailed knowledge has to do with the nature of the system itself. Cyclohexane and its derivatives lend themselves well to thorough analysis, since they are characterized by a small number of energy minima. The most stable conformations are separated by rotational energy barriers that are somewhat higher, and more easily measured, than rotational barriers in noncyclic compounds or in 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 that obtained when 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 Å, the C–H bonds are 1.119 Å, and the C–C–C angles are 111.05°.[28]

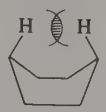


structural features of cyclohexane chair conformation

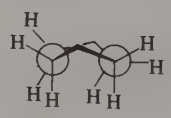
Two other nonchair conformations of cyclohexane that have normal bond angles and bond lengths may be considered, the *twist* and the *boat*.[29] Both the twist and the boat conformation are less stable than the chair. Strain energy calculations indicate that the twist conformation is about 5 kcal/mol, and the boat about 6.4 kcal/mol, higher in energy than the chair.[8] A direct measurement of the chair-twist energy difference has been made using[30] low-temperature IR spectroscopy. The chair was determined to be 5.5 kcal/mol lower in enthalpy than the twist. The twist and boat conformations are more flexible than the chair, but are destabilized by increments of torsional strain due to eclipsing interactions. In addition, the boat conformation is further destabilized by a van der Waals repulsion between the "flagpole" hydrogens, which are separated from each other by about 1.83 Å, a distance considerably less than the sum of their van der Waals radii of 2.4 Å.



eclipsing in boat conformation



flagpole interaction in boat conformation



partial relief of eclipsing in twist conformation

28. H. J. Geise, H. R. Buys, and F. C. Mijlhoff, *J. Mol. Struct.* **9**, 447 (1971).
29. For a review of nonchair conformations of six-membered rings, see G. M. Kellie and F. G. Riddell, *Top. Stereochem.* **8**, 225 (1974).
8. See p. 106.
30. M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.* **97**, 3244 (1975).

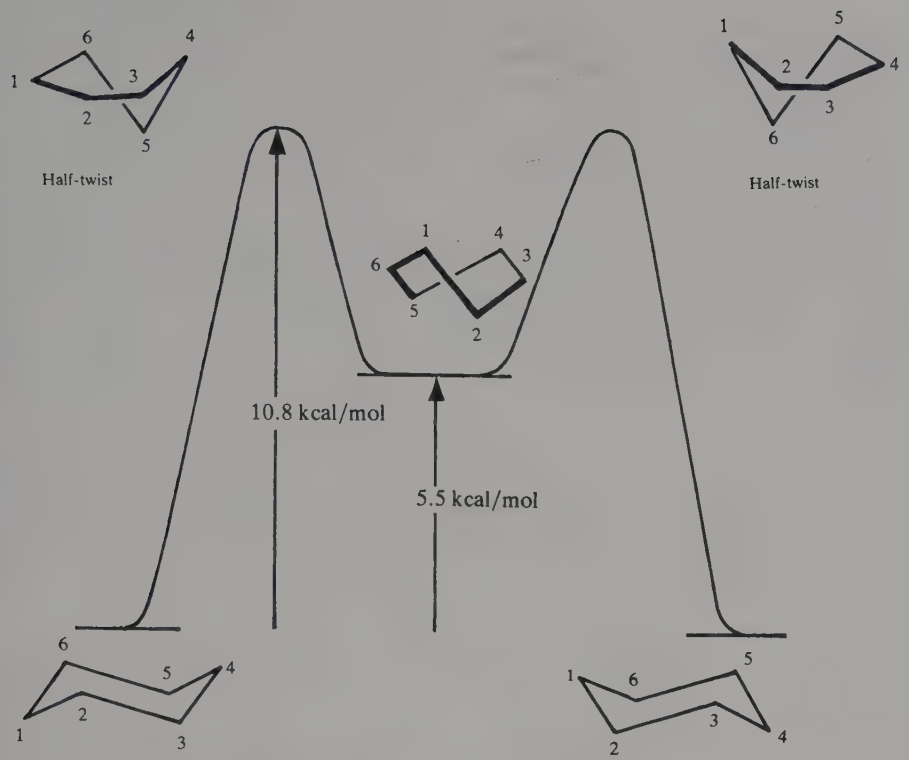


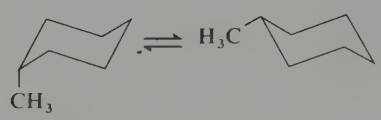
Fig. 3.4. Energy diagram for ring inversion of cyclohexane. [For a rigorous analysis of ring inversion in cyclohexane, see H. M. Pickett and H. L. Strauss, *J. Am. Chem. Soc.* **92**, 7281 (1970).]

Interconversion of chair forms is known as conformational inversion, and occurs by rotation about carbon–carbon bonds. For cyclohexane, the first-order rate constant for ring inversion is 10^4–10^5 sec^{-1} at 300 °K. The enthalpy of activation is 10.8 kcal/mol.[31] Calculation of the geometry of the transition state by molecular mechanics suggests a half-twist form lying 12.0 kcal/mol above the chair. The transition state has incorporated 0.2 kcal/mol of compression energy from bond 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.[8] Figure 3.4 presents a diagram illustrating the process of conformational inversion in cyclohexane and relating the energies of the conformations just described. The boat form is not shown in the diagram, because two chair forms may interconvert without passing through the boat. The boat lies only 1–2 kcal/mol above the twist conformation, and is a low-energy transition state for interconversion of alternative twist forms.

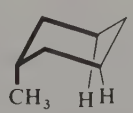
Substitution on a cyclohexane ring does not significantly affect the rate of conformational inversion, but does affect the equilibrium distribution between alternative chair forms. All substituents that were axial in one chair conformation

31. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.* **89**, 760 (1967).
8. See p. 106.

become equatorial on ring inversion, and vice versa. For methylcyclohexane, ΔG° for the equilibrium



is -1.8 kcal/mol, corresponding to a composition of 95% equatorial methylcyclohexane. The preference of a methyl substituent for the equatorial orientation may be related conceptually to the greater stability of the *anti* conformation of *n*-butane compared to the *gauche* conformation. The axial methyl group of methylcyclohexane forms part of two *gauche*-butane fragments, while an equatorial methyl group is stereochemically similar to an *anti*-butane conformation. We have seen earlier that the *gauche* conformation of *n*-butane is 0.8 kcal/mol higher in energy than the *anti*, and the observation that an axial methylcyclohexane, possessing two such *gauche*-butane arrangements, is 1.8 kcal/mol less stable than the equatorial is quantitatively consistent with this analysis.



gauche-butane arrangements in axial methylcyclohexane

anti-butane arrangements in equatorial methylcyclohexane

As is evident from the figure, the dominant van der Waals repulsion in the axial methyl conformer is between the methyl group and the axial hydrogens at C(3) and C(5). Interactions of this type are called *1,3-diaxial interactions.* Substituents that are in a 1,3-diaxial orientation with respect to each other are said to be *syn*-axial. The repulsion between the axial methyl group and the *syn*-axial hydrogens will cause a slight flattening of the ring. This is borne out by molecular mechanics calculations, which indicate smaller torsion angles for the axial methylcyclohexane conformation than for the equatorial.[32]

Energy differences between conformations of substituted cyclohexanes can be measured by several physical methods, as can the kinetics of ring inversion processes. Nuclear magnetic resonance spectroscopy has been especially valuable in both thermodynamic and kinetic studies.[33] Ring inversion in cyclohexanes, as mentioned previously, causes equatorial substituents and axial substituents to switch places. In NMR terminology, this switching is considered a *site exchange process.* Under conditions of rapid site exchange (first-order rate constant $>10^5$ sec^{-1}), the observed spectrum appears as the time-averaged spectrum of each conformation. Under conditions of slow exchange (first-order rate constant $<10^2$ sec^{-1}), the spectrum

32. C. Altona and M. Sundaralingam, *Tetrahedron* **26**, 925 (1970).
33. G. Binsch, *Top. Stereochem.* **3**, 97 (1968); T. M. Ivanova and G. P. Kugatova-Shemyakina, *Russ. Chem. Rev.* **39**, 510 (1970).

appears as a superposition of the spectra of individual conformations. Intermediate exchange rates give broadened signals. Thus, at low temperatures, where the slow-exchange condition is met, the equilibrium constant can be determined by measuring the areas under the signals corresponding to distinct conformers. Line-shape analysis allows the rate constants for exchange to be determined at intermediate temperatures, from which may be extracted the activation parameters for ring inversion. The NMR spectra for the two-site exchange process under conditions of fast, intermediate, and slow exchange rates are depicted in Fig. 3.5.

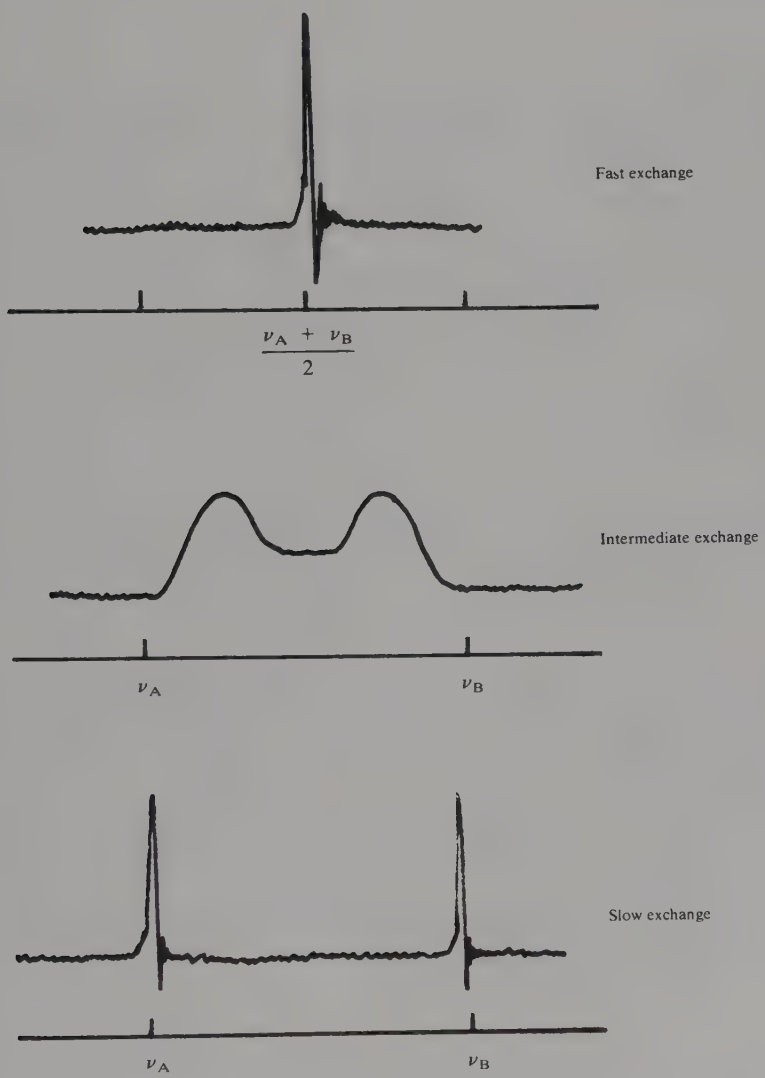


Fig. 3.5. Appearance of NMR spectra for system undergoing two-site exchange (A⇌B).

Table 3.4. Half-Life for Conformational Inversion of Cyclohexyl Chloride at Various Temperatures[a]

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

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

For typical substituted cyclohexanes, the slow-exchange condition is met at temperatures below about −50°C. Table 3.4 presents data for the half-life for conversion of the equatorial conformation of cyclohexyl chloride to the axial conformation as a function of temperature.

From these data, it can be seen that conformationally pure solutions of equatorial cyclohexyl chloride could be maintained at low temperatures. This has been experimentally accomplished.[34] Low-temperature crystallization of cyclohexyl chloride affords only the equatorial conformation in the crystal. Redissolving the crystals in fresh solvent at −150°C gives a solution the NMR spectrum of which exhibits signals characteristic of the equatorial chloride, with no trace of the axial conformer. When the solution is warmed, the conformational equilibrium is reestablished.

The free-energy difference between conformers is referred to as the *conformational free energy*, or sometimes as the *A value*. For substituted cyclohexanes, we will follow the convention of specifying the value of $-\Delta G°$ for the equilibrium written as

$$\text{axial} \rightleftharpoons \text{equatorial}$$

Since $\Delta G°$ will be negative when the equatorial conformation is more stable than the axial, the value of $-\Delta G°$ is positive for the case of substituent groups which favor the equatorial position. The larger the $-\Delta G°$, the greater is the preference for the equatorial position.

An example of the use of NMR spectroscopy in determining the equilibrium constant between conformers, and therefore the value of $-\Delta G°$, can be found in the case of cyclohexyl iodide. At −80°C, the NMR spectrum of cyclohexyl iodide is well resolved, and clearly indicates the presence of two conformations (Fig. 3.6).[35] The region of the spectrum shown is for the proton on the carbon atom that bears the

34. F. R. Jensen and C. H. Bushweller, *J. Am. Chem. Soc.* **91**, 3223 (1969).
35. F. R. Jensen, C. H. Bushweller, and B. H. Beck, *J. Am. Chem. Soc.* **91**, 334 (1969).

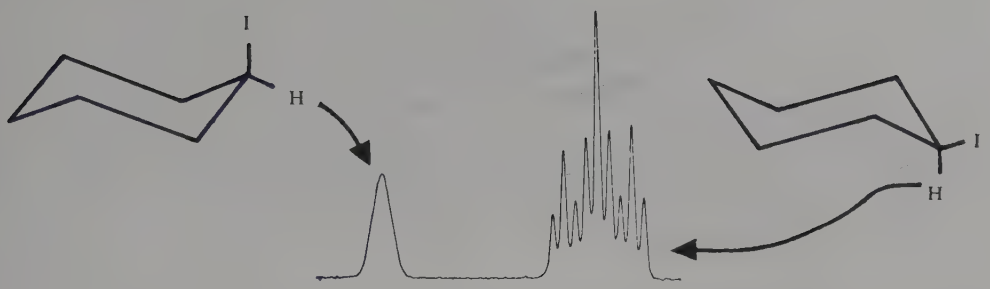
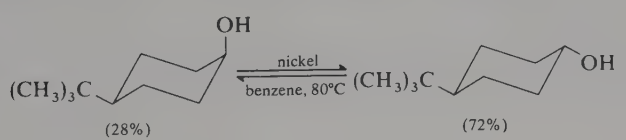


Fig. 3.6. NMR spectrum of cyclohexyl iodide at −80°C. Only the lowest field signals are shown (100-MHz spectrum). [Reproduced from *J. Am. Chem. Soc.* **91**, 344 (1969), by permission of the American Chemical Society.]

iodine. The multiplet at higher field is a triplet of triplets with vicinal coupling constants of 3.5 and 12 Hz. This multiplet may be assigned to the axial methine proton in equatorial cyclohexyl iodide, since it will be coupled to the adjacent equatorial protons by a small *gauche* coupling constant and to the adjacent axial protons by a larger *anti* coupling constant. The multiplet at lower field appears as a broad peak and is assigned to the equatorial methine proton of axial cyclohexyl iodide. It appears as a broad peak because the equatorial methine proton is coupled approximately equally to the vicinal equatorial protons and axial protons by small *gauche* coupling constants. If the coupling constants were equal, the signal would appear as a quintet. The relative area of the axial methine proton to the equatorial methine proton is 3.4 and corresponds to a $-\Delta G°$ value of 0.47 kcal/mol.

Conformational free-energy values for many substituent groups on cyclohexane rings have been determined by NMR methods; some are recorded in Table 3.5. Conformational free energies measured at low temperatures are not believed to vary much from their values at room temperature.

A second important method for measuring conformational free energies involves establishing an equilibrium between *diastereomers* differing only in the orientation of a 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*-4-*tert*-butylcyclohexanol can be equilibrated using a nickel catalyst in refluxing benzene to give a mixture containing 28% *cis*-4-*tert*-butylcyclohexanol and 72% *trans*-4-*tert*-butylcyclohexanol.[36]



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

Table 3.5. Conformational Free Energies ($-\Delta G°$) for Substituent Groups

Substituent	$-\Delta G°$ (kcal/mol)	Ref.
-F	0.24–0.28	a
-Cl	0.53	a
-Br	0.48	a
-I	0.47	a
$-CH_3$	1.8	b
$-CH_2CH_3$	1.8	b
$-CH(CH_3)_2$	2.1	b
$-C(CH_3)_3$	>4.5	c
$-CH=CH_2$	1.7	d
$-C_6H_5$	2.9	d
-CN	0.15–0.25	a
$-O_2CCH_3$	0.71	a
$-CO_2H$	1.35	c
$-CO_2C_2H_5$	1.1–1.2	c
-OH (aprotic solvents)	0.52	c
-OH (protic solvents)	0.87	c
$-OCH_3$	0.60	c
$-NO_2$	1.16	a
-HgBr	0	a

a. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 140 (1971).
b. N. L. Allinger and L. A. Freiberg, *J. Org. Chem.* **31**, 804 (1966).
c. J. A. Hirsch, *Top. Stereochem.* **1**, 199 (1967).
d. E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).

If one assumes that only conformations that have the *tert*-butyl group equatorial are significant, and that the *tert*-butyl group does not distort the geometry of the cyclohexane ring, then the free-energy change for the equilibration is equal to the free-energy change for the conformational interconversion of axial cyclohexyl to equatorial cyclohexanol. The equilibrium constant for the reaction leads to a value of $-\Delta G°$ of 0.7 kcal/mol for the hydroxyl substituent.

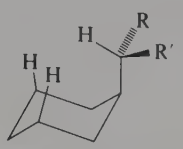
The various methods available for determining conformational free energies have been reviewed and compared.[37] Several compilations of conformational free energies are available.[38] Values for some of the most frequently encountered groups are given in Table 3.5.

Among the halogen substituents, fluorine is the least conformationally demanding, and the preference for the equatorial orientation is nearly the same for chlorine, bromine, and iodine. The larger van der Waals radii of iodine and bromine relative to chlorine are compensated for by the greater C–I and C–Br bond lengths, which decrease the repulsion between the halogen and the *syn*-axial hydrogens. The

37. F. R. Jensen and C. H. Bushweller, *Adv. Alicyclic Chem.* **3**, 139 (1971).
38. J. A. Hirsch, *Top. Stereochem.* **1**, 199 (1967); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience, New York, 1965, pp. 436–443; M. Charton and B. I. Charton, *J. Chem. Soc. B*, 43 (1967).

electrons in the C–I and C–Br bonds are also more polarizable, and lead to increased attractive interactions between the halogen and other atoms.

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



methyl substituent: $R = R' = H$
ethyl substituent: $R = H, R' = CH_3$
isopropyl substituent: $R = R' = CH_3$

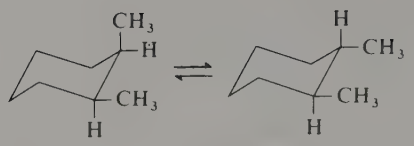
A *tert*-butyl substituent experiences a strongly repulsive van der Waals interaction with *syn*-axial hydrogens in the axial orientation, and cannot relieve the attendant strain by rotation about the bond to the ring. The conformational free energy of a *tert*-butyl group has been calculated by molecular mechanics to be 5.4 kcal/mol.[39] Experimental attempts to measure directly the energy difference between an axial and an equatorial *tert*-butyl group provide only a lower limit. The energy difference between an axial and an equatorial *tert*-butyl group is very similar to the energy difference between the chair and the twist conformations of cyclohexane, and therefore any equilibration measurement is complicated by the presence of nonchair conformations.

The strong preference for a *tert*-butyl group to occupy the equatorial orientation has made it a highly useful group for the study of conformationally biased systems. It should be emphasized that "conformationally biased" is not synonymous with "conformationally locked." A *tert*-butyl group will ensure that the *equilibrium* lies heavily to the side having the *tert*-butyl group equatorial, but it does not stop the process of conformational inversion. Since ring flipping still occurs, it is inappropriate to speak of such systems as being locked in a single conformation.

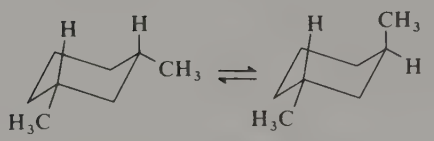
When two or more substituents are present on a cyclohexane ring, the stereochemical considerations are similar, except that interactions between the substituents must also be included in the analysis. The dimethylcyclohexanes provide a straightforward example of disubstitution in six-membered rings in which qualitative considerations are supported by thermodynamic data.

For 1,2-, 1,3-, and 1,4-dimethylcyclohexane, the experimentally determined free-energy changes for the equilibria *cis* $\rightleftharpoons$ *trans* are given below.[40]

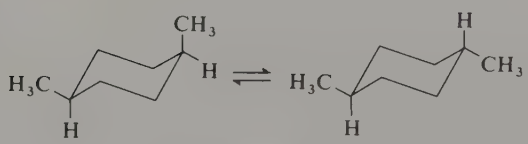
39. N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Am. Chem. Soc.* **90**, 1199 (1968).
40. The experimentally determined values are taken from the tabulation in Ref. 8.



cis $\Delta G^\circ = -1.87$ kcal/mol *trans*



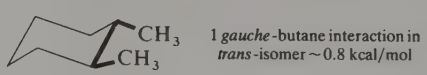
cis $\Delta G^\circ = +1.96$ kcal/mol *trans*



cis $\Delta G^\circ = -1.90$ kcal/mol *trans*

The more stable diastereomer in each case is the one having both methyl groups equatorial. The free-energy difference favoring the diequatorial isomer is about the same for each equilibrium (about 1.9 kcal/mol), and is close to that for the conformational equilibrium between equatorial and axial methylcyclohexane (1.8 kcal/mol). This near agreement is reasonable, since the equilibria are, in all cases, established between an isomer having no axial substituents and an isomer with one axial methyl substituent.

The energy differences between diastereomers may also be approximated by considering the number of *gauche*-butane interactions in each.

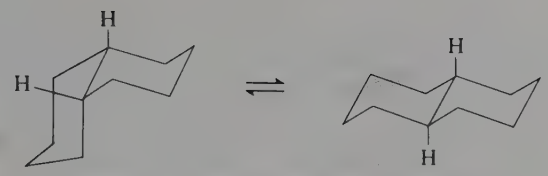


1 *gauche*-butane interaction in *trans*-isomer ~0.8 kcal/mol

3 *gauche*-butane interactions in *cis*-isomer ~2.4 kcal/mol

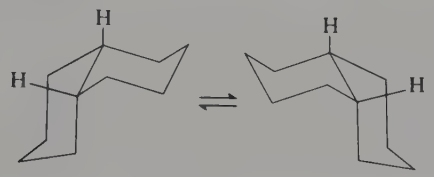
Counting only those *gauche*-butane interactions that involve the substituent groups, the predicted energy difference between the two configurational isomers is ~1.6 kcal/mol.

The equilibration of *cis*- and *trans*-decalin can be analyzed in an analogous way. *cis*-Decalin contains three more *gauche*-butane interactions than does *trans*-decalin, and would be expected to be ~2.4 kcal/mol higher in enthalpy. The experimentally determined enthalpy difference is 2.7–3.0 kcal/mol.

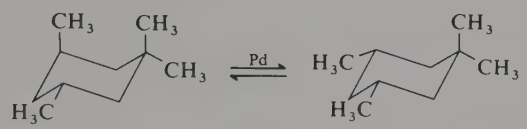


cis-decalin $\Delta H^\circ = -2.7$–3.0 kcal/mol *trans*-decalin

There is an important difference between the *cis*- and *trans*-decalin systems with respect to their conformational properties. *trans*-Decalin, because of the nature of the ring fusion, is incapable of ring inversion. *cis*-Decalin is conformationally mobile and undergoes ring inversion at rates only slightly slower than cyclohexane ($\Delta G^\ddagger$ = 12.3–12.4 kcal/mol in methylene chloride or toluene solution).[41]



Conformations in which there is a 1,3-diaxial interaction between substituent groups more sterically demanding than hydrogen are appreciably destabilized. Equilibration of *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane provides a direct measure of the 1,3-diaxial methyl–methyl interaction, determined to be 3.7 kcal/mol.[42] This is about 1.9 kcal/mol larger than for the 1,3-methyl-hydrogen interaction.



$\Delta H^\circ = -3.7$ kcal/mol

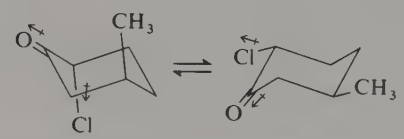
The effect of introducing sp^2-hybridized atoms into open-chain molecules has been discussed previously, and it has been noted that the torsional barriers in 1-alkenes and in aldehydes and ketones are smaller than those in alkanes. Similar properties carry over to incorporation of sp^2 centers in six-membered rings. Whereas the free energy of activation for ring inversion in cyclohexane is 10.3 kcal/mol, the barrier is reduced to 7.7 kcal/mol in methylenecyclohexane,[43] and to 4.9 kcal/mol in cyclohexanone.[44] The decrease in activation energy is related to the lower torsional barriers for rotation about sp^2–sp^3 bonds, and to the decreased steric requirements of a carbonyl or methylene group.

41. 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**, 3678 (1971); B. E. Mann, *J. Magn. Resonance* **21**, 17 (1976).
42. N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.* **83**, 2145 (1961).
43. J. T. Gerig, *J. Am. Chem. Soc.* **90**, 1065 (1968).
44. F. R. Jensen and B. H. Beck, *J. Am. Chem. Soc.* **90**, 1066 (1968).

By analogy with acyclic aldehydes and ketones, an alkyl group at C(2) of a cyclohexanone would be expected to be 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 aldehydes and ketones. By analogy to derivatives of cyclohexane, an alkyl group at C(2) would also be expected to be more stable in the equatorial orientation, owing to decreased 1,3-diaxial interactions relative to the axial orientation. Equilibration studies of 2,6-dialkylcyclohexanones indicate that this is, indeed, the case. The conformational free energy of a methyl group at C(2) of a cyclohexanone is similar to the cyclohexane value, with somewhat smaller values observed for ethyl and isopropyl groups.[45]

The conformational energy of an alkyl substituent at C(3) of a cyclohexanone is substantially less than that of an alkyl group in cyclohexane because of reduced 1,3-diaxial interactions. A C(3) methyl group in cyclohexanone has a $-\Delta G°$ of about 1.3–1.4 kcal/mol between the axial and the equatorial orientations, with the equatorial being the more stable.[36]

The preferred conformation of 2-bromo- and 2-chlorocyclohexanones depends on the polarity of the medium. In solvents of low dielectric constant, the bromine or chlorine substituent is more stable in the axial orientation. In carbon tetrachloride, the axial conformation of 2-bromocyclohexanone is favored by 3:1 over the equatorial conformation.[46] Optical rotatory dispersion measurements on optically active *trans*-2-chloro-5-methylcyclohexanone demonstrate that the preferred conformation in octane of this compound is the one in which both the chlorine and the methyl group are axial.[47] The conformational equilibrium is reversed in the more polar solvent methanol, in which the diequatorial conformer becomes the more stable.

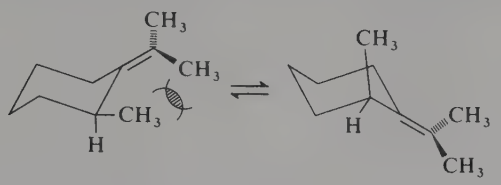


more stable conformer in octane — more stable conformer in methanol

The *α-haloketone effect*, as this phenomenon is known, is believed to be a result of dipolar interactions between the carbonyl group and the carbon–halogen bond The bond dipoles largely cancel in conformation with an axial chlorine but are additive for the equatorial chlorine. The conformation with the smaller dipole moment is the one with the axial chlorine, and this conformation is favored in solvents of low dielectric constants.

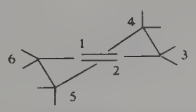
45. N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.* **83**, 994 (1961); B. Rickborn, *J. Am. Chem. Soc.* **84**, 2414 (1962).
36. See p. 117.
46. J. Allinger and N. L. Allinger, *Tetrahedron* **2**, 64 (1958).
47. C. Djerassi, *Optical Rotary Dispersion*, McGraw-Hill, New York, 1960, pp. 125, 126.

It has been suggested that alkylidenecyclohexanes bearing alkyl groups of moderate size at C(2) will tend to adopt the conformation with the alkyl group axial in order to relieve unfavorable van der Waals interactions with the alkylidene group.[48] The effect (termed *allylic strain*) is expected to be minimal in methylenecyclohexane, while strain-energy calculations indicate that the axial conformation **H** is 2.6 kcal/mol more stable than **G** when the isopropylidene group is introduced.[49]



G **H**

The half-chair is indicated to be the preferred conformation for cyclohexene on the basis of electron diffraction and microwave spectroscopy.[50] The structural parameters reveal the double bond to be accommodated in the ring without appreciable distortion. The C(1)–C(2) bond length is 1.335 Å, and the C(1)–C(2)–C(3) bond angle is 123°. The substituents at C(3) and C(6) are tilted from the usual



half-chair conformation of cyclohexene

axial and equatorial directions, and are usually referred to as *pseudoaxial* and *pseudoequatorial*. The activation energy for ring inversion is 5.3 kcal/mol.[51] Substitution of a methyl group at C(3) or C(4) of cyclohexene is opposed by one less 1,3-diaxial interaction than in cyclohexane. Accordingly, the preference for the equatorial orientation of a methyl group in cyclohexene is somewhat less than in cyclohexane. A value of 1 kcal/mol has been suggested for the conformational energy of the methyl group in 4-methylcyclohexene based on epoxidation rates.[52]

3.4. Carbocyclic Rings Other Than Six Membered

The most important structural features that influence the conformation and reactivity of cycloalkanes differ depending on whether small (cyclopropane and

48. F. Johnson, *Chem. Rev.* **68**, 375 (1968).
49. N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.* **90**, 5773 (1968).
50. 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).
51. F. A. L. Anet and M. Z. Haq, *J. Am. Chem. Soc.* **87**, 3147 (1965).
52. B. Rickborn and S.-Y. Lwo, *J. Org. Chem.* **30**, 2212 (1965).

Table 3.6. Strain Energies of Cycloalkanes

Cycloalkane	Strain energy (kcal/mol)[a]
Cyclopropane	28.1[b]
Cyclobutane	26.3
Cyclopentane	7.3
Cyclohexane	1.4
Cycloheptane	7.6
Cyclooctane	11.9
Cyclononane	15.5
Cyclodecane	16.4
Cyclododecane	11.8

a. Estimated values taken from E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **95**, 8005 (1973).
b. Estimated value taken from P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.* **92**, 2377 (1970).

cyclobutane), common (cyclopentane, cyclohexane, and cycloheptane), medium (cyclooctane through cycloundecane), or large (cyclododecane and up) rings are considered. The small rings are dominated by angle strain and torsional strain. The common rings are relatively low in strain, their conformational preferences being most influenced by torsional factors. Medium rings exhibit conformational preferences and chemical properties indicating that cross-ring van der Waals interactions between substituents play an important role. Large rings, because of the larger number of atoms involved, become increasingly more flexible and conformationally complicated with respect to the number of minimum energy conformations that can be adopted. Table 3.6 presents data on the strain energies of various cycloalkanes.

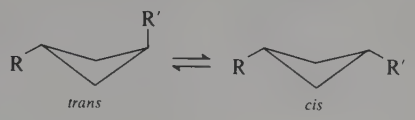
Small rings are very highly strained. Strain energy decreases to a minimum at the chair conformation of cyclohexane, increases progressively to a peak at cyclodecane, then gradually decreases as the ring becomes larger and more closely resembles a linear alkane in its properties.

The cyclopropane ring is necessarily planar, and questions of conformation do not apply. The most important structural information obtained by electron diffraction measurements relate to the C–C bond lengths, which are slightly shorter than normal at 1.510 Å, and to the H–C–H angle of 115°, which is opened up somewhat relative to the angle in cyclohexane.[53]

Two conformations are possible for cyclobutanes, a flat planar structure or a puckered one. Cyclobutane itself has been determined to possess a puckered geometry in the gas phase by electron diffraction.[54] A puckered conformation is also consistent with equilibration studies of 1,3-disubstituted cyclobutanes, which indi-

53. O. Bastiansen, F. N. Fritsch, and K. Hedberg, *Acta Crystallogr.* **17**, 538 (1964).
54. A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta Chem. Scand.* **15**, 711 (1961).

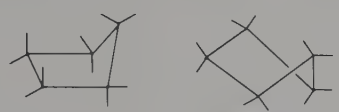
cate that the *cis*-isomer is more stable than the *trans*. Such observations are consistent with the equatorial-like orientation of *cis* substituents in a nonplanar geometry, but are contrary to expectation for a planar geometry, where the van der Waals repulsions would be greater for the *cis* than for the *trans*.



R = R′ = Br $\quad \Delta G° = -0.4$ kcal/mol (Ref. 55a)
R = CH_3; R′ = CO_2CH_3 $\quad \Delta G° = -0.3$ kcal/mol (Ref. 55b)

The energy difference between puckered and planar conformations in cyclobutanes appears to be small. The geometries of some substituted cyclobutanes in the crystal have been determined to be planar by X-ray diffraction. Examples of both planar and puckered structures have been found. For example, cyclobutanedicarboxylic acid, when crystallized by itself, has a planar four-membered ring, but, when cocrystallized with its disodium salt, has a puckered four-membered ring.[56,57]

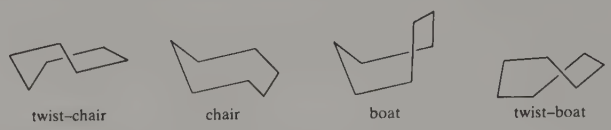
Cyclopentane is nonplanar, with the two most easily described geometries being the envelope (C_s symmetry) and the half-chair (C_2 symmetry).[57]



In the envelope conformation, one carbon atom is displaced from the plane of the other four. In the half-chair conformation, three carbon atoms are coplanar, while one atom is displaced above and another below the plane. The energy differences between conformers are small, and cyclopentane exists in a shallow potential well in which rapid interconversion of conformers occurs.[58] All the carbon atoms in effect take turns in being the out-of-plane carbon in the envelope form. This low-energy motion by which five envelope conformations interconvert is called a *pseudorotation*. The same kind of motion interconverts the various equivalent half-chair conformations. Substituted cyclopentanes also adopt puckered geometries, which may be either envelope or half-chair, depending on the nature of the substitution.

55. a. K. B. Wiberg and G. M. Lampman, *J. Am. Chem. Soc.* **88**, 4429 (1966); b. N. L. Allinger and L. A. Tushaus, *J. Org. Chem.* **30**, 1945, (1965).
56. T. N. Margulis and M. S. Fischer, *J. Am. Chem. Soc.* **89**, 223 (1967); E. Adman and T. N. Margulis, *J. Am. Chem. Soc.* **90**, 4517 (1968).
57. For reviews of the conformation of four- and five-membered rings, see A. C. Legon, *Chem. Rev.*, **80**, 231 (1980); B. Fuchs, *Top. Stereochem.* **10**, 1 (1978).
58. W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Am. Chem. Soc.* **92**, 5013 (1970); J. B. Lambert, J. J. Papay, S. A. Khan, K. A. Kappauf, and E. S. Magyar, *J. Am. Chem. Soc.* **96**, 6112 (1974).

As ring size increases, there are progressively more conformations that need to be considered. For cycloheptane, four conformations have been calculated to be particularly stable.[59] Of these four, the twist–chair is indicated to be the most stable by NMR investigation of dimethyl derivatives, in accordance with the calculations.[60]



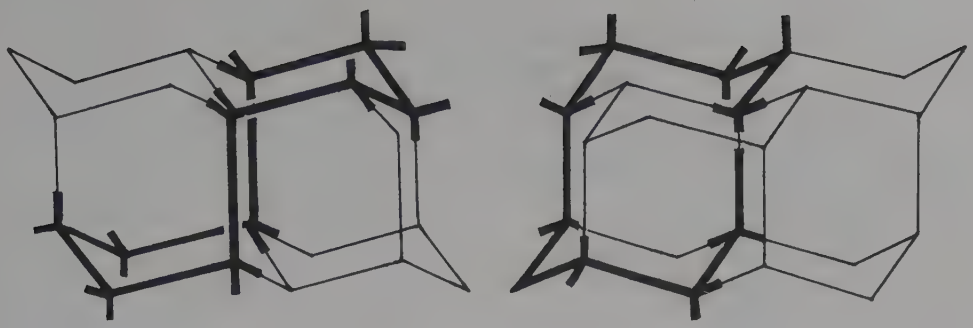
The total energy spread between conformations is small. The least stable of the four is the boat, and it is calculated to be only 2.7 kcal/mol higher in energy than the twist–chair. Pseudorotation among the various twist–chair conformations occurs rapidly.[61]

In the case of cyclooctane, a total of 11 conformations have been suggested for consideration and their relative energies calculated. The boat–chair conformation was calculated to be the most stable conformation.[59] This prediction was confirmed by analysis of temperature-dependent ^{19}F NMR spectra of 1,1-difluorocyclooctane and 1,1,4,4-tetrafluorocyclooctane.[62] A few of the most stable cyclooctane conformations are shown below:

Interconversion of conformers occurs readily, with activation energies in the 5–8 kcal/mol range.

The conformational problems existing with cycloalkanes of ten carbon atoms or more are, in principle, quite complicated. As far as the single most stable conformation for even-membered rings is concerned, however, an interesting fact has emerged that is quite simple. Based on the well-established stability of the diamond-lattice structure, in which all carbons are tetrahedral and part of a continuous system of perfect cyclohexane chair-type rings, it might be anticipated that for systems of sufficient flexibility, the lowest-energy conformation(s) would correspond to the one(s) that could be traced in the diamond lattice, since this would correspond to an all-chair type of conformation. Computer-assisted analysis of diamond-lattice sections has provided the best conformations for all rings up to 24 carbon atoms.[63]

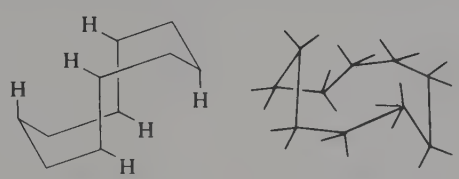
59. J. B. Hendrickson, *J. Am. Chem. Soc.* **89**, 7036 (1967).
60. J. B. Hendrickson, R. K. Boeckman, Jr., J. D. Glickson, and E. Grunwald, *J. Am. Chem. Soc.* **95**, 494 (1973).
61. D. F. Bocian, H. M. Pickett, T. C. Rounds, and H. L. Strauss, *J. Am. Chem. Soc.* **97**, 687 (1975).
62. J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Knorr, and J. D. Roberts, *J. Am. Chem. Soc.* **91**, 1386 (1969); see also F. A. L. Anet and M. St. Jacques, *J. Am. Chem. Soc.* **88**, 2585, 2586 (1966).
63. M. Saunders, *Tetrahedron* **23**, 2105 (1967).



Side view Front view

Fig. 3.7. Equivalent diamond-lattice conformations of cyclodecane (boat–chair–boat).

Studies of cyclodecane derivatives by X-ray crystallographic methods have demonstrated that the boat–chair–boat conformation is adopted in the solid state.[64] The relationship of this boat–chair–boat conformation of cyclodecane to the diamond lattice is shown in Fig. 3.7. (Notice that "boat" as used here is not the same as boat used in describing cyclohexane itself.) In the gas phase, the boat–chair–boat conformation is the dominant conformation for cyclodecane, according to electron diffraction measurements.[65] At 130°C in the gas phase, the boat–chair–boat conformation is adopted by 49 ± 3% of the cyclodecane molecules, and the twist–boat–chair conformation by 35 ± 3%. The remaining molecules are divided evenly between boat–chair–chair and twist–boat–chair–chair conformations.



boat–chair–boat twist–boat–chair

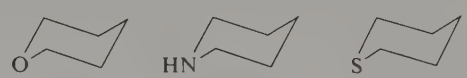
As was indicated in Table 3.6 (p. 124), cyclodecane is significantly more strained than cyclohexane. Examination of the boat–chair–boat conformation reveals that the source of most of this strain is the close van der Waals contacts between two sets of three hydrogens on either side of the molecule. The hydrogens involved are shown in the drawing. Distortion of the molecule to twist forms to relieve this interaction introduces torsional strain.

64. J. D. Dunitz, in *Perspectives in Structural Chemistry*, Vol. II, J. D. Dunitz and J. A. Ibers (eds.), John Wiley and Sons, New York, 1968, pp. 1–70.
65. R. L. Hilderbrandt, J. D. Wieser, and L. K. Montgomery, *J. Am. Chem. Soc.* **95**, 8598 (1973).

3.5. Conformational Analysis of Heterocyclic Molecules

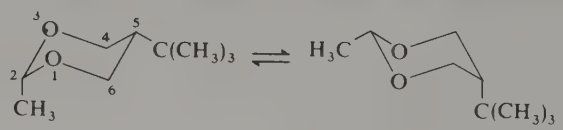
The incorporation of atoms other than carbon into cyclic molecules produces changes in many of the structural parameters, and consequently affects the conformational characteristics of the molecule. In this section, we will describe some stereochemical features of heterocycles in which the heteroatom is oxygen, nitrogen, or sulfur. These are the most common and important of the heterocycles, the most thoroughly studied, and the best understood.[66] For the purpose of elaborating conformational principles, the discussion will be limited to six-membered rings, so that the properties may be considered in the context of a ring system possessing a limited number of low-energy conformations. Five-membered heterocyclic molecules will not be discussed, other than to point out that they include a large number of biologically very important compounds and are the subject of intense current study. As with cyclopentane itself, however, pseudorotation equilibria dominate the conformational analysis of five-membered heterocycles and tend to mask the effect of the heteroatom.

The most obvious changes that occur on introduction of a heteroatom into a six-membered ring have to do with bond lengths and bond angles. Both the carbon–oxygen and carbon–nitrogen bond lengths (1.43 and 1.47 Å, respectively) are shorter than the carbon–carbon bond length of 1.54 Å, while the carbon–sulfur bond length (1.82 Å) is longer. The normal valence angles are somewhat smaller than tetrahedral at oxygen and nitrogen, and significantly so for sulfur, for which the normal C–S–C angle is about 100°. The six-membered heterocycles of oxygen (tetrahydropyran), nitrogen (piperidine), and sulfur (thiane) all closely resemble the chair conformation of cyclohexane, modified so as to accommodate the bond lengths and bond angles characteristic of the heteroatom. The heterocyclic rings are all somewhat more puckered than cyclohexane itself.



tetrahydropyran piperidine thiane

Another important feature associated with heterocyclic rings is the reduced steric repulsions for axial substituents which results from replacement of a methylene group in cyclohexane by oxygen, nitrogen, or sulfur. This effect is readily apparent in *cis*-2-methyl-5-*tert*-butyl-1,3-dioxane, in which the preferred conformation has



preferred conformation

66. For reviews, see J. B. Lambert and S. I. Featherman, *Chem. Rev.* **75**, 611 (1975); F. G. Riddell, *The Conformational Analysis of Heterocyclic Compounds*, Academic Press, New York, 1980; E. L. Eliel, *Acc. Chem. Res.* **3**, 1 (1970); F. G. Riddell, *Q. Rev. Chem. Soc.* **21**, 364 (1967).

Table 3.7. Conformational Free Energies for Substituents in 1,3-Dioxanes and 1,3-Dithianes[a]

	$-\Delta G°$ (kcal/mol)[b]						
		1,3-Dioxane			1,3-Dithiane		
Substituent	Cyclohexane	2–	4–	5–	2–	4–	5–
CH_3–	1.7	>3.5	2.9	0.8	1.8	1.7	1.0
CH_3CH_2–	1.75			0.7	1.5		0.8
$(CH_3)_2CH$–	2.15			1.0	1.9		0.8
$(CH_3)_3C$–	>4.4			1.4	2.7		

a. Taken from: E. L. Eliel and R. O. Hutchins, *J. Am. Chem. Soc.* **91**, 2703 (1969) and E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.* **90**, 3444 (1968).
b. For the equilibrium written as axial⇌equatorial.

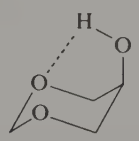
the *tert*-butyl group axial and the methyl group equatorial.[67] The divalent oxygen has no substituents so that the 1,3-diaxial interaction, which is the main unfavorable interaction for axial substituents in cyclohexanes, is not present.

It is consistently seen that 5-alkyl substituents in 1,3-dioxane exhibit a smaller equatorial preference than they do in cyclohexane. This decreased preference has been attributed to decreased van der Waals repulsions in the axial orientation, since there are now no hydrogens that are *syn*-axial to the 5-alkyl substituent. A 2-alkyl substituent, on the other hand, has a greater preference for the equatorial orientation in 1,3-dioxane than in cyclohexane, presumably because the decreased C–O bond length (relative to C–C) brings an axial 2-alkyl group into closer contact with the *syn*-axial hydrogens at C(4) and C(6), resulting in an increased van der Waals repulsion. Similarly, an axial 4-alkyl substituent in a 1,3-dioxane suffers a greater van der Waals repulsion with the axial hydrogen at C(2) than it does in cyclohexane. Table 3.7 presents $-\Delta G°$ values for several alkyl groups in 1,3-dioxanes and 1,3-dithianes, along with their comparative $-\Delta G°$ values in cyclohexane. The general point to be recognized is that the conformational free energy is a function not only of the size of the group but also of the molecular environment which it encounters.[68]

The decreased preference for the equatorial orientation of a 5-alkyl group in 1,3-dioxanes and 1,3-dithianes is evident from these data. It is also interesting that the increased preference for the equatorial orientation of a 2- or 4-methyl group in 1,3-dioxane disappears in going to 1,3-dithiane. The conformational free energies of 2-alkyl substituents in 1,3-dithianes are very similar to those of cyclohexane (actually slightly smaller) because of the longer C–S bond length compared to C–O.

67. E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.* **90**, 3444 (1968).
68. For a review of conformational analysis of dioxanes, see M. J. O. Anteunis, D. Tavernier, and F. Borremans, *Heterocycles* **4**, 293 (1976).

When a polar substituent is present, interactions between the substituent and the ring heteroatom can become important. In some cases, the interactions are straightforward and readily assessed. For example, the preferred conformation of 5-hydroxy-1,3-dioxane has the hydroxyl group in the axial position.[69] This conformation is favored because hydrogen bonding of the hydroxyl group with the ring oxygen is possible only when the hydroxyl group is axial, and would serve as a stabilizing force for this conformation.



The effect of other polar substituents is not always so readily explainable. It is known from considerable experience in carbohydrate chemistry that pyranose sugars substituted with an electron-withdrawing group such as halogen or alkoxy at C(1) are often more stable when the substituent occupies an axial orientation, rather than an equatorial one. This tendency is not limited to carbohydrates, but carries over to simple ring systems as well, such as 2-substituted tetrahydropyrans. The phenomenon is known as the *anomeric effect*, since it involves a substituent at the anomeric position in carbohydrate pyranose rings.[70] Scheme 3.1 lists several compounds that exhibit the anomeric effect, along with some measured equilibrium distributions. In entries 1–3, the equilibria are between diastereoisomers, while entries 4–6 illustrate the anomeric effect in conformationally mobile systems. In all cases, the more stable isomer is written on the right.

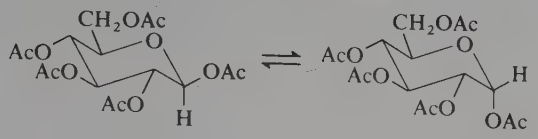
The magnitude of the anomeric effect depends on the nature of the substituent and decreases with increasing dielectric constant of the medium. The effect of the substituent can be seen by comparing the related 2-chloro- and 2-methoxy-substituted tetrahydropyrans in entries 2 and 3. The 2-chloro compound exhibits a significantly greater preference for the axial orientation than the 2-methoxy. Entry 3 also provides data relative to the effect of solvent polarity, where it is observed that the equilibrium constant is larger in carbon tetrachloride (ε 2.2) than in acetonitrile (ε 37.5).

Compounds in which conformational, rather than configurational, equilibria are influenced by the anomeric effect are depicted in entries 4–6. Single crystal X-ray diffraction studies have unambiguously established that all the chlorine atoms of *trans, syn, trans*-2,3,5,6-tetrachloro-1,4-dioxane occupy axial sites in the crystal. Each chlorine in the molecule is bonded to an anomeric carbon, and is subject to the

69. J. L. Alonso and E. B. Wilson, *J. Am. Chem. Soc.* **102**, 1248 (1980); N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Webber, *J. Chem. Soc.*, 4157 (1963).
70. For reviews, see P. L. Durette and D. Horton, *Adv. Carbohydr. Chem. Biochem.* **26**, 49 (1971); R. U. Lemieux, *Pure Appl. Chem.* **25**, 527 (1971); Ref. 38b, pp. 375–377; E. L. Eliel, *Angew. Chem. Int. Ed. Engl.* **11**, 739 (1972); W. A. Szarek and D. Horton (eds.), *Anomeric Effect*, ACS Symposium Series #87, American Chemical Society, Washington D.C., 1979; A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.

Scheme 3.1. Equilibria in Compounds That Exhibit the Anomeric Effect

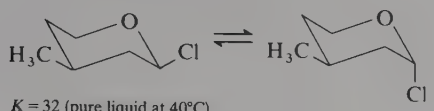
1[a] Glucose pentaacetate



ß *α*

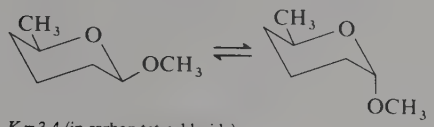
$K = 5$ (in 50% acetic acid : acetic anhydride, 0.1 M H_2SO_4 at 25°C)
$\Delta H° = -1.4$ kcal/mol

2[b] 2-Chloro-4-methyltetrahydropyran



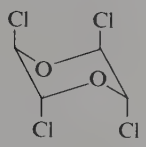
$K = 32$ (pure liquid at 40°C)

3[c] 2-Methoxy-6-methyltetrahydropyran



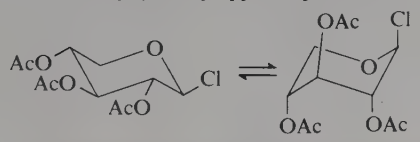
$K = 3.4$ (in carbon tetrachloride)
$K = 1.8$ (in acetonitrile)

4[d] *trans, syn, trans*-2,3,5,6-Tetrachloro-1,4-dioxane



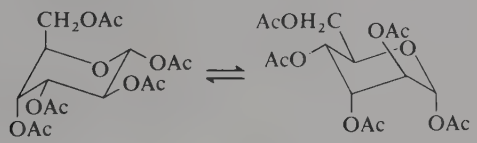
Equilibrium constant not known in solution; crystalline form has all chlorines axial.

5[e] Tri-*O*-acetyl-β-D-xylopyranosyl chloride



The NMR spectrum in $CDCl_3$ indicates that the all-axial form is strongly favored. The equilibrium constant is not known.

6[f] α-D-Altropyranose pentaacetate



only form present at equilibrium by NMR analysis

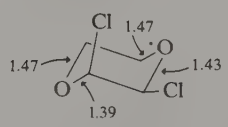
a. W. A. Bonner, *J. Am. Chem. Soc.* **73**, 2659 (1951).
b. C. B. Anderson and D. T. Sepp, *J. Org. Chem.* **32**, 607 (1967).
c. E. L. Eliel and C. A. Giza, *J. Org. Chem.* **33**, 3754 (1968).
d. E. W. M. Rutten, N. Nibbering, C. H. MacGillavry, and C. Romers, *Rec. Trav. Chim.* **87**, 888 (1968).
e. C. V. Holland, D. Horton, and J. S. Jewell, *J. Org. Chem.* **32**, 1818 (1967).
f. B. Coxon, *Carbohydr. Res.* **1**, 357 (1966).

anomeric effect. Equally striking is the observation that all the substituents of the tri-*O*-acetyl-β-D-xylopyranosyl chloride shown in entry 5 are in the axial orientation *in solution*. Here, no special crystal packing forces can be invoked to rationalize the preferred conformation. The anomeric effect of a single chlorine is sufficient to drive the equilibrium in favor of the conformation that puts three acetoxy groups in axial positions.

Several structural factors have been considered as possible causes of the anomeric effect. In classical localized bond terminology, it can be recognized that there will be a dipole–dipole interaction between the polar bonds at the anomeric carbon. This dipole–dipole interaction is reduced in the axial conformation and this factor might contribute to the anomeric effect, but does not appear to be likely to be large enough to account for the total effect. More recently, molecular orbital theory has been applied to the question. From this viewpoint, the anomeric effect can be expressed as resulting from an interaction between the lone-pair electrons on the pyran oxygen and the σ bond to the C(2) substituent.[71] When the C–X bond is axial, an interaction between an occupied *p*-type orbital on oxygen (lone-pair electrons) with the antibonding σ^* orbital of the C–X combination is possible. This permits delocalization of the lone-pair electrons and would be expected to shorten the C–O bond while lengthening the C–X bond. There is some direct structural

MO representation resonance representation

evidence which supports this interpretation, since the C–O bond lengths are shortened and the C–X bonds are lengthened. An example of such data can be found from the X-ray crystal structure determination of *cis*-2,3-dichloro-1,4-dioxane.[72]



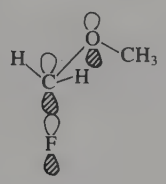
Bond lengths are given in Å. The axial C–Cl bond length is 1.82 Å; the equatorial C–Cl bond length is 1.78 Å.

The normal carbon–chlorine bond distance is 1.79 Å, and, as can be seen, the equatorial C–Cl distance is observed to be almost exactly that. The axial C–Cl distance, however, is significantly longer (1.82 Å), consistent with electron release

71. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971); S. David, O Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Am. Chem. Soc.* **95**, 3806 (1973): F. A Van-Catledge, *J. Am. Chem. Soc.* **96**, 5693 (1974).
72. C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.* **4**, 39 (1969).

into a carbon–chlorine antibonding orbital, weakening the C–Cl bond. The carbon–oxygen bond lengths, moreover, depend on the orientation of the chlorine on carbon in a way that is completely consistent with the explanation proposed. Electron delocalization is more important when the chlorine is axial; the carbon–oxygen bond has more double-bond character and is shorter (1.39 versus 1.43) than when the chlorine is equatorial.

The anomeric effect is not restricted to cyclic systems. The same interaction occurs in the *gauche* conformation of other compounds where an oxygen atom and another electronegative atom are bound to the same carbon by σ bonds. An example is methoxymethyl fluoride, where the *gauche* conformation is dominant, according to MO calculations.[73] The basis for this preference is the delocalization of the oxygen lone pair electrons through interaction with the σ^* orbital of the C–F combination. The *gauche* conformation is required for the proper alignment of these orbitals. Molecular orbital calculations predict and experimental structural



data confirm that the *gauche* conformation is preferred in molecules such as methoxymethanol[74] and methanediol.[75] In fact, the same ideas can be applied quite generally to molecules which contain adjacent nonbonded electrons and polar bonds. Not all systems prefer the *gauche* conformation, but the mutual interactions between lone-pair electrons and polar bonds is a major factor in determining the preferred conformations of such molecules.[76]

The importance and generality of the anomeric effect emphasize the fact that molecular conformation is not solely governed by nonbonded steric interactions. Both attractive and repulsive electronic interactions which have specific geometric (stereoelectronic) requirements are also a significant factor in determining molecular conformation.

3.6. Molecular Orbital Methods Applied to Conformational Analysis

The molecular mechanics approach to conformational analysis has the virtue of describing molecular properties in terms that are physically easily understood.

73. G. A. Jeffrey and J. H. Yates, *J. Am. Chem. Soc.* **101**, 820 (1979).
74. G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.*, **38**, 81 (1974).
75. G. A. Jeffrey, J. A. Pople, and L. Radom, *Carbohydr. Res.* **25**, 117 (1972).
76. S. Wolfe, *Acc. Chem. Res.* **5**, 102 (1972); S. Wolfe, M.-H. Whangbo, and D. J. Mitchell, *Carbohydr. Res.* **69**, 1 (1979).

Moreover, the use of carefully chosen potential functions can give highly precise information as to the relative energies of various molecular arrangements. Certainly the quality of the strain-energy calculations performed on hydrocarbons testifies to the capabilities of classical mechanics in simple systems. Concurrent with the improvement in the methodology of molecular mechanical calculations has been the development of approaches to conformational analysis based on molecular orbital (MO) methods.[77] Both molecular mechanics and MO methods view conformational processes similarly. Preferred conformations are determined by assuming (or, better, by systematic computer-searching) certain geometries and determining their relative energies. The rotational barrier is determined by calculating energies as a function of torsion angle. The maximum energy along the minimum-energy path then corresponds to the transition state geometry, and its energy relative to the ground state geometry is the rotational energy barrier. The terminology used in molecular mechanics is that of valence bond theory, where we speak of bond-length compression, bond-angle strain, dipolar interactions of individual bond dipoles, and so on, and it should be evident that the rationalizations resulting from consideration of the results of MO calculations will be quite different. We shall also see in this section that MO methods accurately predict conformational equilibria in molecules in which there are interactions between nonbonded pairs of electrons, a type of system in which molecular mechanics methods may fail.

Several of the more common MO methods were mentioned in Chapter 1, and it was noted that most of the methods were very good at predicting minimum-energy geometries. There have been several calculations of the rotational energy barrier in ethane and related molecules that have matched the experimentally determined barriers quite well. Rather than elaborating on all the conformational equilibria that have been treated by MO methods, the emphasis in this section will be on the unique information available through MO calculations that is not directly provided by molecular mechanics calculations.

As it is useful in molecular mechanics to dissect the total strain into its component elements, so it has proven useful to analyze the total energy of a molecule as given by MO calculations as the sum of four terms:

$$E_T = V_{ne} + V_{nn} + V_{ee} + T$$

where E_T is the total energy, V_{ne} is the nuclear–electron attraction, V_{nn} is the nuclear–nuclear repulsion, V_{ee} is the electron–electron repulsion, and T is the electron kinetic energy.[78] Only the nuclear–electron interaction term is attractive, the last three terms being repulsive. By observing the calculated changes in the attractive and repulsive terms as rotation occurs between nuclei, internal rotation barriers may be described as *attractive dominant* or *repulsive dominant.* A barrier is

77. J.-M. Lehn, in *Conformational Analysis, Scope and Present Limitations,* G. Chiurdoglu (ed.), Academic Press, New York, 1971, p. 129.
78. L. C. Allen, *Chem. Phys. Lett.* **2**, 597 (1968); L. C. Allen and H. Basch, *J. Am. Chem. Soc.* **93**, 6373, (1971).

Table 3.8. Energy-Component Changes for Ethane and Ethyl Fluoride: Conversion of Staggered Conformation to Eclipsed[a]

Energy-component change		Ethane (kcal/mol)[b]	Ethyl fluoride (kcal/mol)[b]
Attractive	ΔV_{ne}	−20.07	−60.31
Repulsive	ΔV_{nn}	4.69	21.40
	ΔV_{ee}	9.53	28.36
	ΔT	8.43	13.14
Sum of repulsive terms		22.65	62.90
Net energy change		2.58	2.59

a. Taken from L. C. Allen and H. Basch, *J. Am. Chem. Soc.* **93**, 6373 (1971).
b. The energies have been converted from atomic units to kcal/mol by multiplying by 627.5.

characterized as attractive dominant or repulsive dominant according to which component realizes the greatest absolute change during rotation. Analysis of the changes in the individual terms on rotation provides some insight into the physical nature of the process, and allows substituent effects to be examined in more detail than simply their effect on the overall barrier height.

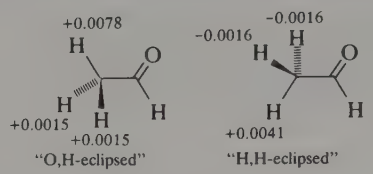
A case in point concerns the barriers in ethane and in ethyl fluoride. The calculated internal rotation barriers are almost identical (2.58 kcal/mol for ethane and 2.59 kcal/mol for ethyl fluoride by *ab initio* SCF methods), and the experimentally determined barriers are similar (2.87 ± 0.12 kcal/mol for ethane and 3.33 ± 0.05 kcal/mol for ethyl fluoride). Table 3.8 lists the differences in energy components for the staggered and eclipsed forms of ethane and ethyl fluoride obtained by analysis of the results of the *ab initio* calculations.

It is apparent that the similarity in the rotational barriers of ethane and ethyl fluoride results from a cancellation of increases in the attractive and repulsive terms on substitution of a fluorine for hydrogen. The barriers in both molecules are repulsive dominant. All of the energy-component changes in ethyl fluoride are larger than the analogous values in ethane. The nearly identical rotational barriers are therefore not indicative of a general lack of sensitivity of rotational barriers to substituents, but rather in this case to the substituent exerting similar large effects on the attractive and repulsive components of the barrier.

Most barriers to internal rotation turn out to be repulsive dominant. Such is the case for methanol, methylamine, propane, propene, hydrazine, and, as has been seen, ethane and ethyl fluoride. Attractive dominant barriers are indicated for acetaldehyde, hydroxylamine, and hydrogen peroxide.

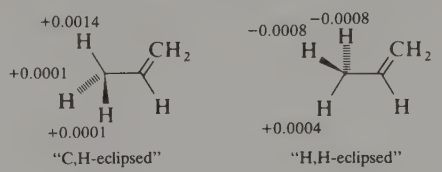
The cases of propene and acetaldehyde are interesting and illustrate a way in which overlap populations can provide insight into the rotational process. A positive overlap in MO theory corresponds to a bonding interaction; a negative overlap, to a nonbonded repulsion. As was discussed previously, the most stable conformations of acetaldehyde and propene have the methyl C–H bond eclipsed with the carbon–oxygen or carbon–carbon double bond.

The overlap populations for the methyl hydrogens of acetaldehyde with the carbonyl oxygen in the two conformations are shown below[79]:



There is a net positive overlap of +0.0108 in the O,H-eclipsed conformation between the methyl hydrogens and the carbonyl oxygen, which is reduced significantly to +0.0009 in the less stable H,H-eclipsed conformation. These "bonding interactions" indicated by overlap populations translate into attractive energy components of sufficient magnitude to cause the rotational energy barrier of acetaldehyde to be attractive dominant.

The corresponding overlap populations for propene, which has a repulsive dominant barrier, are in the same direction, but are much smaller[80]:

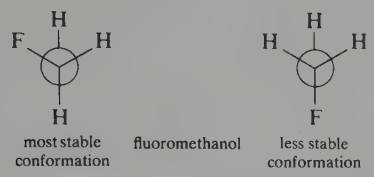


The C,H-eclipsed conformation is again the most stable, but because the overlap populations are much less, the translation into attractive terms is small and the barrier is dominated by the repulsive terms. In qualitative terms, the acetaldehyde barrier can be considered to be dominated by an attractive interaction between the π-methyl group orbital and the C=O antibonding orbital. The propene conformation is dominated by the repulsive interaction between the π methyl group orbital and the filled π orbital of the double bond.

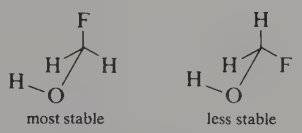
The capability of describing dynamic processes by the changes in several parameters, and of doing it in at least a semiquantitative way through extraction of the energy-component terms of an *ab initio* calculation, can provide explanations to some effects not otherwise easily explained. For example, the attractive term V_{ne} can be large in compounds possessing lone pairs or polar bonds or both. Such compounds can also experience large contributions to their total energy from the V_{ee} term, which is repulsive. The molecular geometry adopted in the ground state will reflect contributions from both V_{ne} and V_{ee}, and it may be difficult to assess their relative importance on simple inspection. As often occurs in organic chemistry, understanding often comes after the fact as a rationalization of observed behavior. A small molecule that has been the subject of detailed *ab initio* analysis of its rotational

79. R. B. Davidson and L. C. Allen, *J. Chem. Phys.* **54**, 2828 (1971).
80. M. L. Unland, J. R. Van Wazer, and J. H. Letcher, *J. Am. Chem. Soc.* **91**, 1045 (1969).

energy profile is fluoromethanol (FCH_2OH). The presence of a polar C–F bond on carbon and lone pairs on oxygen leads to large nuclear–electron attraction and electron–electron repulsion terms, which are dependent on the F–C–O–H torsion angle. The most stable conformation of FCH_2OH is calculated to be staggered with the fluorine and hydroxyl hydrogen *gauche*. The *anti* orientation of these substituents represents a maximum energy conformation, and lies 12.6 kcal/mol higher.[76]

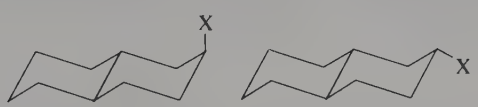


If these two conformations are shown from a different perspective it becomes clear that fluoromethanol is another example of the anomeric (or *gauche*) effect discussed in Section 3.5. The *gauche* arrangement permits a lone pair on oxygen to be in an *anti*-periplanar relationship to the C–F bond.



3.7. Conformational Effects on Reactivity

Conformational effects on reactivity have been particularly thoroughly studied in cyclohexane systems. The difference between an axial and an equatorial environment of a functional group can lead to significant differences in the reaction rate. One of the most common ways of studying the effect of orientation on reactivity is to use an appropriately placed *t*-butyl or other large substituent to ensure that the reacting group is overwhelmingly in the equatorial or axial position. The *trans*-decalin system is conformationally rigid, so stereoisomeric decalin derivatives also offer axial–equatorial pairs of functional groups for comparison.

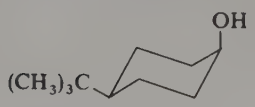


Scheme 3.2 gives some data that illustrate the difference in reactivity between groups in axial and equatorial positions. It should be noted that a group can be either more or less reactive in an axial position than when in an equatorial position.

76. See p. 133.

Scheme 3.2. Effects of Functional-Group Orientation on Rates and Equilibria

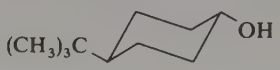
cis-4-*t*-Butylcyclohexanol



Relative rate of oxidation (CrO_3) = 3.23[a]
Relative rate of acetylation = 1.00[b]

versus

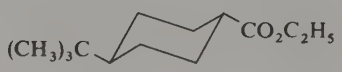
trans-4-*t*-Butylcyclohexanol



Relative rate of oxidation (CrO_3) = 1.00[a]
Relative rate of acetylation = 3.70[b]

Relative rate of saponification = 1.00[c]

versus



Relative rate of saponification = 19.8[c]

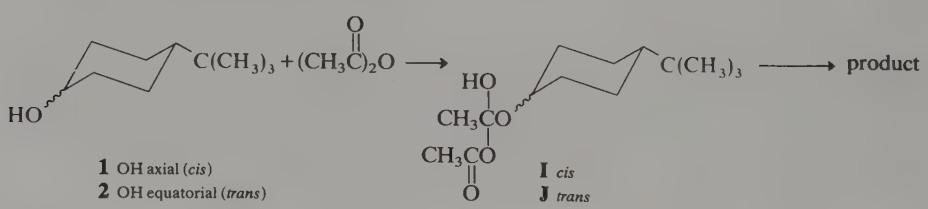
$pK_a = 8.23$[d]

versus

$pK_a = 7.79$[d]

a. E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J.-C. Richer, *J. Am. Chem. Soc.* **88**, 3327 (1966).
b. E. L. Eliel and F. J. Biros, *J. Am. Chem. Soc.* **88**, 3334 (1966).
c. E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.* **83**, 2351 (1961).
d. R. D. Stolow, *J. Am. Chem. Soc.* **81**, 5806 (1959).

The effect of conformation on reactivity is intimately associated with the details of the mechanism of a reaction. The examples in Scheme 3.2 can illustrate some of the ways in which substituent orientation can affect reactivity. It has been shown that oxidation of *cis*-4-*t*-butylcyclohexanol is faster than oxidation of the *trans* isomer, but the rates of acetylation are in the opposite direction. Let us consider acetylation first. The rate of the reaction will depend on the free energy of activation for the rate-determining step. For acetylation, this step presumably involves nucleophilic attack by the hydroxyl group on the acetic anhydride, with the rate-determining step being formation of the tetrahedral intermediates **I** and **J**. An approximate energy diagram is given in Fig. 3.8.



Because its hydroxyl group occupies an equatorial position, the *trans* isomer **2** is more stable than the *cis* isomer **1** by an amount equal to $-\Delta G^\circ$ for the hydroxyl

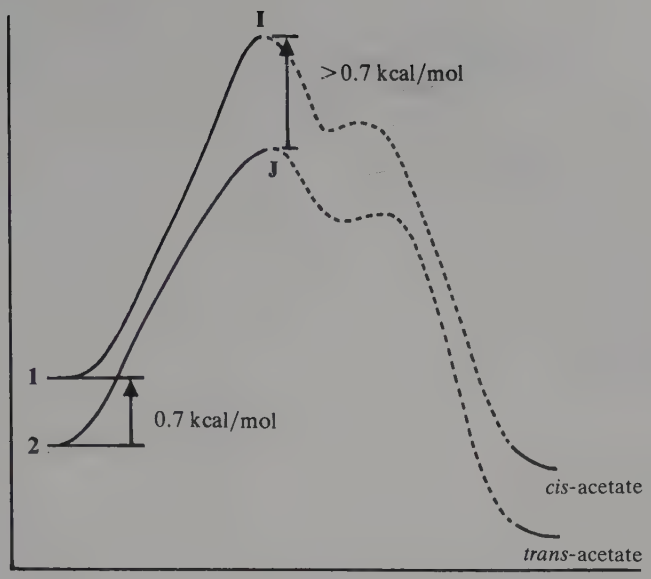
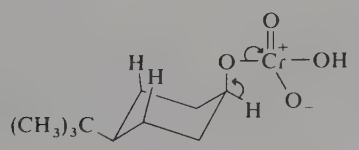


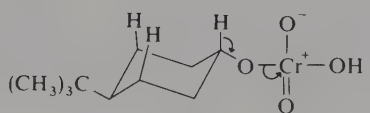
Fig. 3.8. Approximate energy diagram for acetylation of *cis*- and *trans*-4-*t*-butylcyclohexanol.

group. It can be assumed that the transition state for the reaction will be a species resembling the tetrahedral intermediates **I** and **J**. Since the substituent group has become effectively larger as the acetylating reagent becomes bonded to the hydroxyl group, the value of $-\Delta G°$ for the substituent at the transition state should be *greater than* 0.7 kcal/mol. Intermediate **I**, then, must be higher in energy than **J** by more than 0.7 kcal/mol. One can then predict that **1** will acetylate more slowly than **2**, because a larger free energy of activation is involved. That **1** does react more slowly than **2** is in accord with this analysis.

Extensive studies have established that axial cyclohexanols are more reactive than equatorial alcohols toward chromic acid oxidation.[81] The basis for this effect must again be sought in the free energies of activation for the reaction. The available evidence is consistent with rate-determining elimination in a chromate ester intermediate. The transition state for oxidation involves cleavage of the C–H bond and loss of chromium. An approximate energy diagram is given in Fig. 3.9.



K



L

81. E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J.-C. Richer, *J. Am. Chem. Soc.* **88**, 3327 (1966); P. Müller and J.-C. Perlberger, *J. Am. Chem. Soc.* **98**, 8407 (1976).

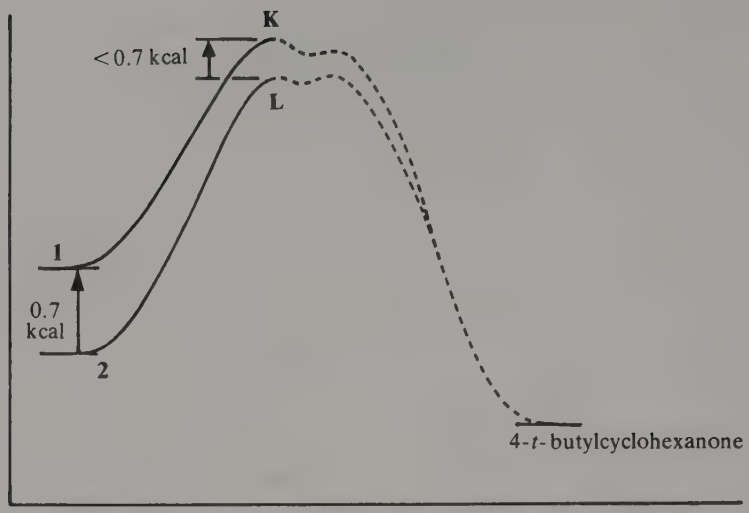
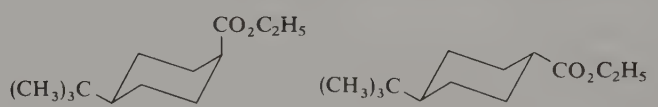


Fig. 3.9. Approximate energy diagram for oxidation of *cis*- and *trans*-4-*t*-butylcyclohexanol.

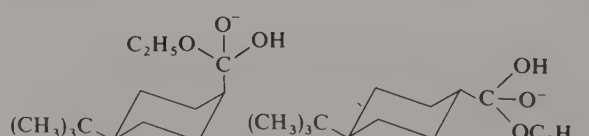
The diaxial interactions that are responsible for a large portion of the conformational free energy of the hydroxyl group are relieved in the transition state as the reaction proceeds toward sp^2 hybridization at the carbon atom undergoing oxidation. The energy difference between the stereoisomeric transition states is less then the energy difference between the stereoisomeric alcohols. Under these circumstances, the more strained starting material, in this case the *cis* isomer having the axial hydroxyl group, is the more reactive.

A similar analysis of the hydrolysis of the esters **3** and **4** is possible. From Table 3.5 (p. 118), we see that the conformational free energy of the carbethoxy substituent is 1.2 kcal/mol. The *cis* isomer should be placed above **4**, then, by about



3 **4**

1.2 kcal/mol. The saponification transition states resemble intermediates **M** and **N**. The substituent group increases in size as the transition state is reached, and, as a result, the difference in energy between **M** and **N** is greater than 1.2 kcal/mol. As a



M **N**

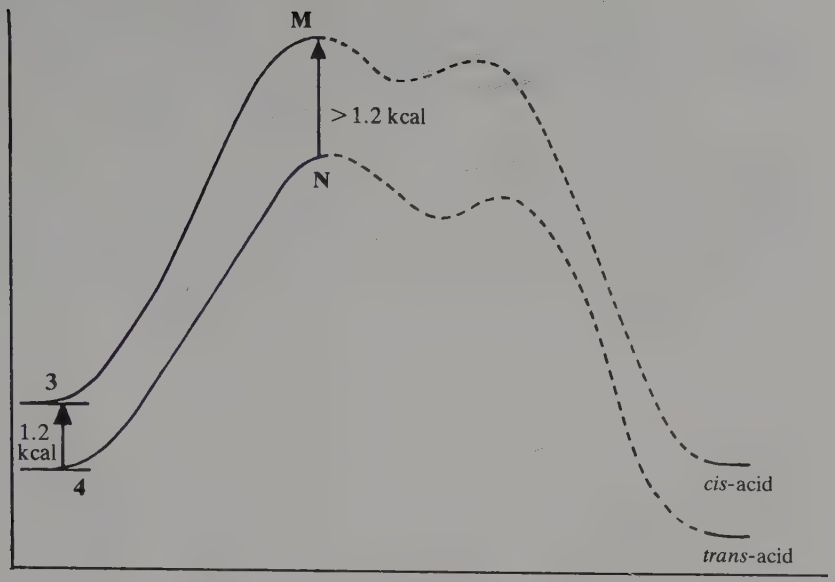


Fig. 3.10. Approximate energy diagram for saponification of ethyl esters of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid.

result, the *trans* ester **4** hydrolyzes significantly faster than the *cis* compound. An approximate energy diagram is given in Fig. 3.10.

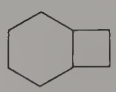
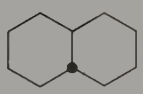
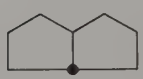
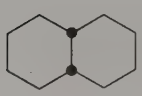
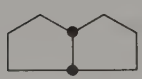
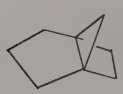
These examples serve to illustrate some of the ways in which conformation can affect reactivity. In later chapters and in Part B, other examples will be given as specific reactions are discussed. One other important point relating conformation to reactivity will be raised in Chapter 4. This is the Curtin–Hammett principle, which states an important limitation on the validity of arguments that attribute reactivity differences to conformational effects.

3.8. Angle Strain and Its Effect on Reactivity

Many of the conformational effects on reactivity can be described and analyzed in terms of the difference between van der Waals interactions in the ground state and the transition state. Some cyclic molecules contain another type of strain, known as angle strain, resulting from distortion of bond angles from optimal values. We would now like to consider how such distortions might effect reactivity.

Table 3.9 gives some data on the total strain present in some cyclic, bicyclic, and tricyclic compounds. Six-membered rings are nearly strain free, while the strain

Table 3.9. Strain Energies in Some Alicyclic Compounds (kcal/mol)[a]

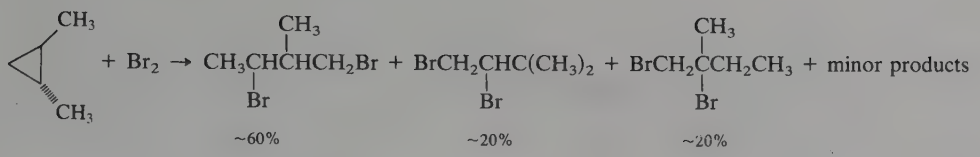
	29[b]		63[c]
	56[b]		65.9
	26[c]		56.1
	7.0		33.5
	1.0		29.6
	1.0		18.4
	4.1		12.0
	67[e]		96[f]

a. Data from S. Chang, D. McNally, S. Shary-Tehrany, M. J. Hickey, and R. H. Boyd, *J. Am. Chem. Soc.* **92**, 3109 (1970), except where noted otherwise.
b. G. L. Closs, in *Advances in Alicyclic Chemistry*, Vol. 1, H. Hart and G. J. Karabatsos (eds.), Academic Press, New York, 1966, p. 67.
c. P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.* **92**, 2377 (1970).
d. J. D. Cox, *Tetrahedron* **19**, 1175 (1963).
e. K. B. Wiberg, H. A. Connon, and W. E. Pratt, *J. Am. Chem. Soc.* **101**, 6970 (1979).
f. D. S. Kabakoff, J.-C. G. Bünzli, J. F. M. Oth, W. B. Hammond, and J. A. Berson, *J. Am. Chem. Soc.* **97**, 1510 (1975).

in smaller rings increases from 6–7 kcal in cyclopentane rings to about 30 kcal/mol in cyclopropane. In more complicated structures total strain increases as molecular geometry requires greater distortion from optimal bond angles.

Because of the increased ground state energy resulting from angle strain, reactions which lead to ring opening often proceed much more readily than do similar reactions in unstrained systems. For example, while normal saturated hydrocarbons are inert to bromine, in the dark, cyclopropanes rapidly give ring-opened products.[82] These products arise from ring opening to yield a carbonium ion, followed

82. J. B. Lambert and B. A. Iwanetz, *J. Org. Chem.* **37**, 4082 (1972); J. B. Lambert and K. Kobayashi, *J. Org. Chem.* **41**, 671 (1976); P. S. Skell, J. C. Day, and K. H. Shea, *J. Am. Chem. Soc.* **98**, 1195 (1976).

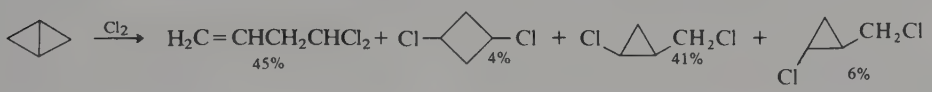


by capture by bromide ion. The two minor products arise from rearrangement of the carbonium ion intermediate.

Bicyclo[1.1.0]butane is an example of a molecule in which very severe strain results in decreased stability and greatly enhanced reactivity. The central bond in

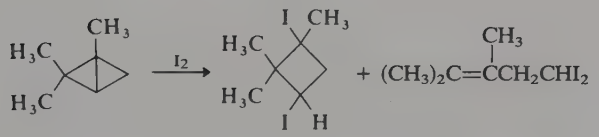
bicyclo[1.1.0]butane

bicyclo[1.1.0]butane is formed from nearly pure *p* orbitals of the two bridgehead carbons.[83] Bicyclo[1.1.0]butane and its derivatives undergo ring opening very readily with the halogens, weak acids, and a variety of other reagents. The products are derived from cleavage of both the central and the peripheral bonds:



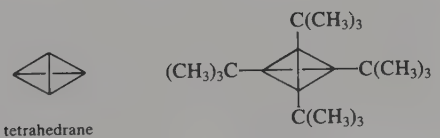
Ref. 83

Ref. 84



Ref. 85

The molecule tetrahedrane represents still one more increment of angle strain.



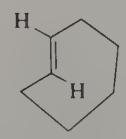
tetrahedrane

83. J. M. Schulman and G. J. Fisanick, *J. Am. Chem. Soc.* **92**, 6653 (1970); R. D. Bertrand, D. M. Grant, E. L. Allred, J. C. Hinshaw, and A. B. Strong, *J. Am. Chem. Soc.* **94**, 997 (1972); D. R. Whitman and J. F. Chiang, *J. Am. Chem. Soc.* **94**, 1126 (1972).
84. K. B. Wiberg and G. Szeimies, *J. Am. Chem. Soc.* **92**, 571 (1970).
85. W. R. Moore, K. G. Taylor, P. Muller, S. S. Hall, and Z. L. F. Gaibel, *Tetrahedron Lett.*, 2365 (1970).

The parent compound has not yet been synthesized although the tetra-*t*-butyl derivative is known. Molecular orbital calculations estimate that the breaking of a C–C bond in tetrahedrane would require only about 10 kcal/mol, indicating the molecule would have only short existence even at moderately low temperatures.[86] The tetra-*t*-butyl derivative can be generated at low temperature and is stable up to about 100°.[87] The *t*-butyl groups are believed to exert a steric effect which stabilizes the ring. Besides the simple hindrance preventing approach of an external reagent, the bond stretching which would initiate rupture of a single bond is opposed since it increases steric repulsion between the *t*-butyl groups.

The effect of angle strain on reactivity has at least two important components. The first is primarily a manifestation of energetics. Because of the higher ground state energy of angle-strained molecules, they will tend to react particularly rapidly in reactions which relieve the angle strain. But there is also a stereoelectronic component to the reactivity of these strained compounds. The angle distortion has an effect on the shapes of orbitals. This can be described in terms of "bent bonds" or hybridization change. The orbitals, in either case, are modified in comparison with the orbitals of unstrained molecules, not only in being higher in energy but also varying with respect to spatial distribution.

Alkenes exhibit large strain energies when factors of molecular geometry do not permit all the bonds to the two sp^2-hybridized carbons to be coplanar. An example that illustrates the twisting of an olefinic π system can be found in *trans*-cycloheptene:



With only five methylene units available to bridge the *trans* positions, the molecule is highly strained and very reactive. Isolation of *trans*-cycloheptene has not been possible, but evidence for its formation has been obtained by trapping experiments.[88] The olefin is generated in the presence of a reagent expected to react rapidly with it—in this case, the very reactive Diels–Alder diene 2,5-diphenyl-3,4-isobenzofuran. The adduct isolated has the structure anticipated for that derived from *trans*-cycloheptene. *trans*-Cyclooctene is significantly strained, but less so than *trans*-cycloheptene. As the ring size is increased, the amount of strain decreases. The *trans* isomers of both cyclononene and cyclodecene are less stable than the corresponding *cis* isomers, but for cycloundecene and cyclododecene, the *trans* isomers are more stable than the *cis*.[89] Table 3.10 gives data concerning the relative stability of C_7 through C_{12} cycloalkenes.

86. H. Kollmar, *J. Am. Chem. Soc.* **102**, 2617 (1980).
87. G. Maier, S. Pfriem, U. Schafer, and R. Matusch, *Angew. Chem. Int. Ed. Engl.* **17**, 520 (1978).
88. E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.* **87**, 934 (1965).
89. A. C. Cope, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.* **82**, 1744 (1960).

Table 3.10. Relative Stabilities of *cis*- and *trans*-Cycloalkenes

Cycloalkene	$\Delta H°$(*trans* ⇌ *cis*) (kcal/mol)	Ref.
Cycloheptene	−20.3	a
Cyclooctene	−9.7	b
Cyclononene	−2.8	b
Cyclodecene	−3.5	b
Cycloundecene	+0.1	b
Cyclododecene	+0.4	b

a. Calculated value, from N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.* **94**, 5734 (1972).
b. From R. B. Turner and W. R. Meador, *J. Am. Chem. Soc.* **79**, 4133 (1957); A. C. Cope, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.* **82**, 1744 (1960).

The geometry of bicyclic rings can also cause distortion of the coplanarity of olefinic systems. One example of this is bicyclo[2.2.1]hept-1-ene:

Attempts to construct a model of this molecule will show that the geometry of the bicyclic system does not permit coplanarity of the substituents bonded to the sp^2 carbons. As a result of the excessive strain, the molecule has at most transitory existence.[90] The absence of such "bridgehead double bonds" in organic compounds was noted long ago and formulated as *Bredt's rule*. As the structural basis for Bredt's rule became clear, it became evident that the prohibition against bridgehead double bonds could not be absolute.[91] When the bridges of the bicyclic system are large enough to permit planarity of the π system, bridgehead olefins will be capable of existence. It has been proposed that the limit for unstable but isolable bridgehead olefins is reached when the largest ring containing the olefinic linkage contains eight atoms. Bridgehead olefins in which the largest ring is of seven atoms are expected to be capable of only short existence.[92] These proposals have subsequently been tested and verified by the development of successful syntheses of the bridgehead alkenes that are shown as examples in Scheme 3.3.[93] The strained double bonds in these molecules are exceptionally reactive, and undergo a variety of addition reactions. The total strain in the bridgehead alkenes can be computed effectively by molecular

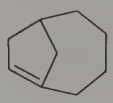
90. R. Keese and E.-P. Krebs, *Angew. Chem. Int. Ed. Engl.* **11**, 518 (1972).
91. G. Köbrich, *Angew. Chem. Int. Ed. Engl.* **12**, 464 (1973).
92. J. R. Wiseman, *J. Am. Chem. Soc.* **89**, 5966 (1967); J. R. Wiseman and W. A. Pletcher, *J. Am. Chem. Soc.* **92**, 956 (1970).
93. For reviews of the synthesis and properties of bridgehead alkenes, see G. L. Buchanan, *Chem. Soc. Rev.* **3**, 41 (1974); K. J. Shea, *Tetrahedron* **36**, 1683 (1980); R. Keese, *Angew. Chem. Int. Ed. Engl.* **14**, 528 (1975).

Scheme 3.3. Bridgehead Olefins[a]

Bicyclo[3.3.1]non-1-ene[b,c]

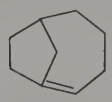
(24)

Bicyclo[4.2.1]non-1(8)-ene[c,d]



(25)

Bicyclo[4.2.1]non-1(2)-ene[c,d]

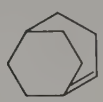


(30)

Bicyclo(3.3.1)oct-1-ene[e]

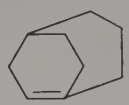
(37)

Bicyclo[3.2.2]non-1-ene[d]



(34)

Bicyclo[3.2.2]non-1(7)-ene[d]

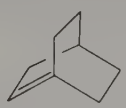


(36)

Adamantene[g]

(37)

Bicyclo[2.2.2]oct-1-ene[h]



(38)

a. Strain energies calculated by molecular mechanics (Ref. 94) are given in parentheses in kcal/mol.
b. J. R. Wiseman and W. A. Pletcher, *J. Am. Chem. Soc.* **92**, 956 (1970); J. A. Marshall and H. Faubl, *J. Am. Chem. Soc.* **89**, 5965 (1967); M. Kim and J. D. White, *J. Am. Chem. Soc.* **99**, 1172 (1977).
c. K. B. Becker, *Helv. Chem. Acta* **60**, 81 (1977).
d. J. R. Wiseman, H.-F. Chan, and C. J. Ahola, *J. Am. Chem. Soc.* **91**, 2812 (1969).
e. W. G. Dauben and J. D. Robbins, *Tetrahedron Lett.*, 151 (1975).
f. Transitory existence only; J. R. Wiseman and J. A. Chong, *J. Am. Chem. Soc.* **91**, 7775 (1969).
g. Transitory existence only; A. H. Alberts, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 3047 (1973); J. E. Gano and L. Eizenberg, *J. Am. Chem. Soc.* **95**, 972 (1973); D. J. Martella, M. Jones, Jr., and P. v. R. Schleyer, *J. Am. Chem. Soc.* **100**, 2896 (1978); R. T. Conlin, R. D. Miller and J. Michl, *J. Am. Chem. Soc.* **101**, 7637 (1979).
h. A. D. Wolf and M. Jones, Jr., *J. Am. Chem. Soc.* **95**, 8209 (1973); H. H. Grootveld, C. Blomberg, and F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.*, 542 (1973).

mechanics methods. The strain energies calculated in this way are included in Scheme 3.3. This total strain energy can also be dissected in such a way as to indicate the fraction of the total strain which is due to the twist at the carbon–carbon double bond. This strain proves to be a fairly reliable predictor of the stability of compounds which incorporate bridgehead double bonds.[94]

94. W. F. Maier and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **103**, 1891 (1981).

Scheme 3.4. Relative Rates of Ring Closure as a Function of Ring Size

	Reaction	Ring size =	Relative rate 3	4	5	6	7	8
1.[a]	$Br(CH_2)_xCO_2^-$	→ lactone	8.3×10^{-4}	0.31	90	1	0.0052	6×10^{-5}
2.[b]	$Br(CH_2)_xNH_2$	→ cyclic amine	0.07	0.001	100	1	0.002	—
3.[c]	$PhC(=O)(CH_2)_xCl$	→ nucleophilic participation in solvolysis	—	0.37	36	1	0.13	—
4.[d]		→ cyclic ether formation	—	—	—	1	0.01	4×10^{-4}
5.[e]	$ArSO_2\bar{N}(CH_2)_xCl$	→ cyclization	17	33	—	1	—	—

a. C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.* **99**, 2591 (1977); L. Mandolini, *J. Am. Chem. Soc.* **100**, 550 (1978).
b. D. F. DeTar and W. Brooks, Jr., *J. Org. Chem.* **43**, 2245 (1978); D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.* **102**, 4505 (1980).
c. D. J. Pasto and M. P. Serve, *J. Am. Chem. Soc.* **87**, 1515 (1965).
d. G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.* **96**, 1422 (1974).
e. R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc. Perkin Trans. II*, 1215 (1973).

3.9. Relationships between Ring Size and Facility of Ring Closure

Many examples of intramolecular reactions have served to establish a rough correlation between the rate of a reaction and the size of a ring being formed. Although different reaction types exhibit large quantitative differences, so that there are exceptions, the order $5 > 6 > 3 > 7 > 4 > 8$–10 is a rough guide of relative reactivity for many systems. Some quantitative data on typical reactions involving nucleophilic substitution or participation are shown in Scheme 3.4.

The dissection of the energy of activation of typical ring closure reactions usually shows some consistent features. The $\Delta H^{\ddagger}$ for three- and four-membered rings is normally higher than $\Delta H^{\ddagger}$ for the five- and six-membered rings, while $\Delta S^{\ddagger}$ is least negative for the three-membered rings, of comparable magnitude for four-, five- and six-membered rings and then becomes more negative as the ring size increases above seven. The $\Delta H^{\ddagger}$ reflects the strain which develops in the closure of three-membered rings, while the large negative entropy associated with eight-membered and larger rings, reflects the relative improbability of achieving the desired molecular orientation. Because the combination of the two factors is most favorable for five- and six-membered rings, the maximum rate of ring closure is achieved.

Superimposed on this broad relationship between enthalpy and entropy are more variable and individualized structural features, including changes in solvation and the effect of branching on the intervening chain. Most important, however, are

Table 3.11. Classification of Ring-Closure Types[a]

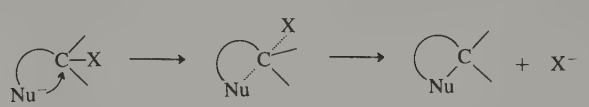
Ring size	Exocyclic bonds			Endocyclic bonds[b]	
	sp (*dig*)	sp^2 (*trig*)	sp^3 (*tet*)	*sp* (*dig*)	sp^2 (*trig*)
3	unfav	fav	fav	fav	fav
4	unfav	fav	fav	fav	unfav
5	fav	fav	fav	fav	unfav
6	fav	fav	fav	fav	fav
7	fav	fav	fav	fav	fav

a. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
b. The category *endo–tet* also exists but is somewhat rare and is not discussed here.

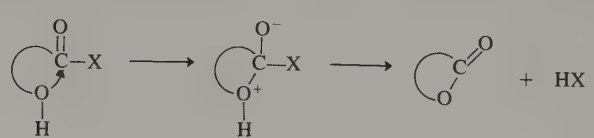
geometric (stereoelectronic) constraints on the transition state for ring closure. There will be a preferred direction of approach in the transition state which will vary depending upon the type of reaction which is involved. While the reactions shown in Scheme 3.3, which are all intramolecular nucleophilic substitutions, reveal a rough general trend $5 > 6 > 3 \sim 7 > 8$, reactions with other mechanisms may exhibit a different kind of relationship. It has been pointed out for example that the formation of cyclopropanes from β-halo carbanions is often *faster* than cyclization of the corresponding γ-halo systems.[95]

A systematic effort to correlate ease of ring closure with the stereoelectronic requirements of the transition state has been discussed by Baldwin and coworkers. They classify ring closures with respect to three factors: (a) ring size, (b) the hybridization at the carbon undergoing reaction, and (c) the relationship of the reacting bond to the forming ring (endocyclic or exocyclic). Consideration of experimental data on ring closure rates reveals certain types are more favorable than others. These relationships are summarized in Table 3.11.

The classifications can be made clear with a few examples. All of the nucleophilic substitutions shown in Scheme 3.3 are of the *exo–tet* classification. The reacting atom is of sp^3 hybridization (tetrahedral) and the reacting bond, that is the bond to the leaving group, is exocyclic to the forming ring. An example of an *exo–trig*

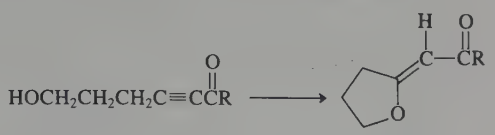


process would be a lactonization of a ω-hydroxycarboxylic acid derivative. An

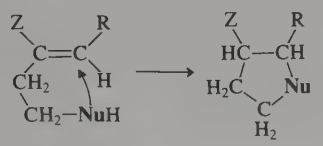


95. C. J. M. Stirling, *J. Chem. Educ.* **50**, 844 (1973).

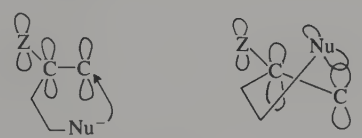
example of an *exo–dig* process would be the base-catalyzed cyclization of ε-hydroxy-α,β-ynone. Let us focus attention on the unfavorable ring closures. Why, for



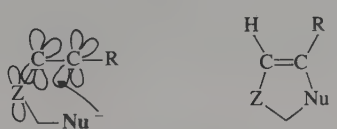
example, should formation of a five-membered ring by an *endo–trig* process be difficult? The answer is provided by consideration of the trajectory of approach of



the nucleophile.[96] If Z, for example, is an electron-attracting conjugating group of the type which would be necessary to activate the double bond to nucleophilic attack, the reaction would involve the LUMO of the conjugated system, a π orbital. The nucleophile cannot approach from the plane of this π system, it must

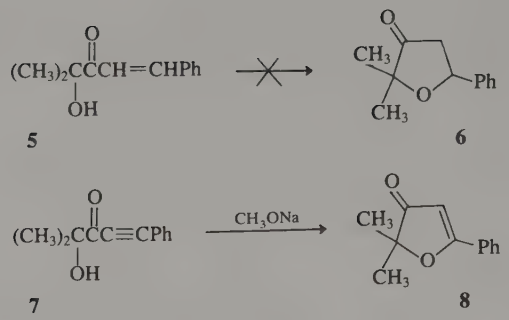


attack from above or below. This would lead to a large distortion from the approximate planarity which characterizes five-membered rings. It is this distortion imposed by stereoelectronic factors which disfavors 5-*endo–trig* cyclization. In contrast, 5-*endo–dig* cyclization is feasible since the acetylenic system provides an orbital which is available with an alternate geometry of approach. As an example of these



relationships, it was found that compound **5** was unreactive toward base-catalyzed cyclization to **6**, even though this compound is a suitable substrate for intermolecular conjugate addition. On the other hand, **7** is readily cyclized to **8** by heating in the presence of sodium methoxide[97]:

96. J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 738 (1976).
97. J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.* **42**, 3846 (1977).

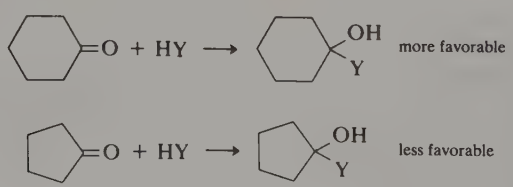


The terms favored and disfavored imply just that. Other factors will determine the absolute ease of a given ring closure, but these relationships point out the need to recognize the specific stereoelectronic requirements which may be imposed on the transition state in ring closure reactions.

3.10. Torsional Strain and Related Stereoelectronic Effects

Torsional strain refers to the component of total molecular energy which results from nonoptimal arrangement of vicinal bonds. Ethane in the eclipsed conformation is strained by 2.8 kcal/mol relative to the staggered conformation and this is an example of torsional strain. This energy barrier is not primarily the result of van der Waals interactions but arises instead from stereoelectronic effects. The basis for the preference for the staggered conformation was considered in Sections 1.7 and 3.2.

The preference for staggered arrangements around single bonds is general for all alkanes and when geometric constraints enforce an eclipsed arrangement the molecule suffers torsional strain. A case in which torsional effects appear to play a major role is in reactions that involve hybridization changes at ring atoms. A general relationship concerning the relative ease of conversion of carbon atoms in a ring from sp^3 to sp^2 or vice versa has been developed. It has been useful in comparing the reactivity of cyclohexanones with that of cyclopentanones. It has been observed in a number of systems that reactions that convert an sp^2 carbon to an sp^3 carbon in a six-membered ring are more favorable than the corresponding reaction in a five-membered ring.



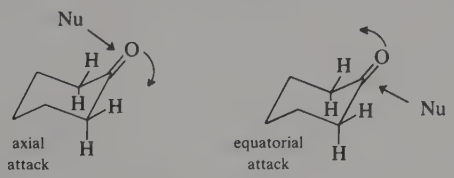
For example, cyclohexanone is reduced by sodium borohydride 23 times faster than cyclopentanone.[98] The explanation for this difference is believed to lie in the

98. H. C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957).

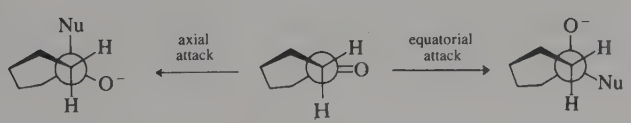
relative torsional strain in the two systems. Converting an sp^2 atom in a five-membered ring to sp^3 increases the number of eclipsing interactions. A similar change in a six-membered ring leads to a completely staggered arrangement of bonds.

Conversely, processes which convert sp^3 carbons to sp^2 carbons are favored for five-membered rings, relative to six-membered rings. This can be illustrated by the data for acetolysis of cyclopentyl versus cyclohexyl tosylate. The former proceeds with an enthalpy of activation of about 3 kcal/mol less than for the cyclohexyl compound. Molecular mechanics calculations were used to separate the components of this energy difference and it was largely accounted for by the torsional strain which is relieved in the cyclopentyl case.[99] Notice that there is an angle strain effect which is operating in the opposite direction, since there will be some resistance to the expansion of the bond angles at the reacting carbon to 120° in the cyclopentyl ring.

Torsional effects can also influence the stereochemistry of reactions. One system which has been examined particularly closely with regard to torsional effects are additions to cyclohexanones. There are two possible directions for nucleophilic attack on cyclohexanones, from the axial and equatorial directions. From many



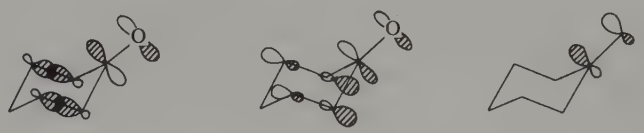
studies of addition of nucleophiles, particularly hydride-reducing agents and organometallic reagents, a rather broad pattern has emerged.[100] Bulky reagents tend to approach from the equatorial direction. This is known as steric approach control and is generally considered to represent primarily a van der Waals type of interaction.[101] Bulky reagents encounter the 3,5-diaxial hydrogens on the trajectory for axial attack. In contrast, smaller nucleophiles usually approach from the axial direction.[102] Torsional strain is believed to be a significant factor in this. In the starting cyclohexanone, the carbonyl group is almost eclipsed with the equatorial C-2 and C-6 hydrogen. This torsional interaction is increased by equatorial attack



99. H.-J. Schneider and F. Thomas, *J. Am. Chem. Soc.* **102**, 1424 (1980); H. C. Brown and G. Ham, *J. Am. Chem. Soc.* **78**, 2735 (1956).
100. E. C. Ashby and J. T. Laemmle, *Chem. Rev.* **75**, 521 (1975).
101. W. G. Dauben, G. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.* **92**, 709 (1970).
102. H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.* **92**, 709 (1970); D. C. Wigfield, *Tetrahedron* **35**, 449 (1979); W. T. Wipke and P. Gund, *J. Am. Chem. Soc.* **98**, 8107 (1976).

since the oxygen must move through a fully eclipsed arrangement, while it is decreased if the nucleophile approaches from the axial direction.[103]

There is another stereoelectronic explanation for the preferred axial approach by small unencumbered nucleophiles.[104] The π orbitals of the carbonyl group are aligned to interact with the bond between C-2 and C-3 and C-6 and C-5. The most stabilizing interactions are between the σ orbitals and the π^* orbital and between the π orbital and σ^*, since these interactions each involve one filled and one unfilled level. An important feature of these interactions is that they will distort the π and π^* orbitals. In particular the π^* orbital will be distorted such that it will have its largest density on the side of the carbon which maximizes overlap with the filled σ orbitals. This orbital is the LUMO for the carbonyl group and it would therefore be expected that nucleophiles would attack preferentially from the axial direction. In contrast, the occupied π orbital, the HOMO, will have increased concentration on the equatorial side to maximize interaction with the σ^* orbitals.



interaction between the σ and C=O π^* orbitals

interaction between the σ^* and C=O π orbitals

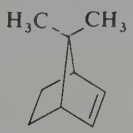
distortion of π^* with larger coefficients on the axial side

The concept that π-orbitals are distorted by adjacent σ orbitals and that these distortions can control stereochemistry can be usefully extended to other systems. The precise origin of stereoelectronic effects which are dominant in causing differential approach to π systems remains a matter of discussion and computation. One school of thought regards σ–π as most important,[105] whereas another view emphasizes the antibonding interaction of the reagent with adjacent bonds.[106] In addition perturbations by substituents and nearby counter ions may alter the importance of the effects.[107] While it is difficult to accurately judge the relative importance of the potential orbital interactions, a key point does emerge. That is, that in addition to the steric factors which have long been recognized to control direction of approach to a carbonyl group, there are also stereoelectronic factors. The carbonyl group is not electronically isolated and the interaction with nearby orbitals appears to have a significant effect on both stereochemistry and reactivity.

Another system in which the factors controlling the direction of reagent approach have been studied systematically is the bicyclo[2.2.1]heptene ring system.

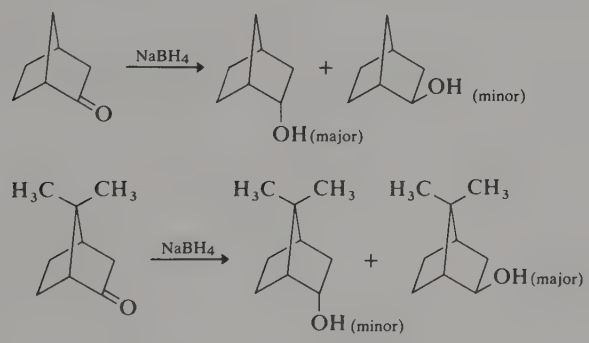
103. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.* 2199 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.* 2205 (1968); J. Klein and D. Lichtenberg, *J. Org. Chem.*, **35**, 2654 (1970).
104. J. Klein, *Tetrahedron Lett.*, 4307 (1973); see also N. T. Anh, *Top. Current Chem.* **88**, 145 (1980).
105. E. M. Burgess and C. L. Liotta, *J. Org. Chem.* **46**, 1703 (1981); O. Eisenstein, J. Klein, and J. M. Lefour, *Tetrahedron* **35**, 225 (1979).
106. P. Caramella, N. G. Rondan, M. N. Paddon-Row, and K. N. Houk, *J. Am. Chem. Soc.* **103**, 2438 (1981); N. G. Rondan, M. N. Paddon-Row, P. Caramella, and K. N. Houk, *J. Am. Chem. Soc.* **103**, 2436 (1982).
107. A. S. Cieplak, *J. Am. Chem. Soc.* **103**, 4540 (1981).

Table 3.12. Comparison of the Stereochemistry of Reactions with Bicyclo[2.2.1]heptene and 7,7-Dimethylbicyclo[2.2.1]heptene[a]

				
Reagent	*exo*	*endo*	*exo*	*endo*
B_2H_6 (hydroboration)	99.5	0.5	22	78
RCO_3H (epoxidation)	99.5	0.5	12	88
H_2, Pd (hydrogenation)	90	10	10	90

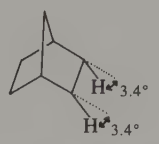
a. H. C. Brown, J. H. Kawakami, and K. T. Liu, *J. Am. Chem. Soc.* **95**, 2209 (1973).

The stereochemistry of a number of reactions has been studied with the parent hydrocarbon and with the 7,7-dimethyl derivative.[108] Some of the results are given in Table 3.12. These reactions reveal a reversal of preferred direction of attack on introduction of the methyl substituents. In the parent system, the *exo* direction of attack is preferred. This is presumably because the single CH_2 group at C(7) offers less steric resistance than the $-CH_2CH_2-$ unit on the *endo* side of the molecule. The *endo* hydrogens are in a relationship to the reacting site that is similar to the 1,3-diaxial interaction in a chair cyclohexane ring. When a *syn*-7-methyl group is present, the relative steric bulk of the two bridges is reversed. The methyl groups have a similar effect in controlling the stereochemistry of reduction of the related ketones.[109]



108. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.* **95**, 2209 (1973).
109. H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.* **88**, 2811 (1966).

The preference for *endo* attack in 7,7-dimethylnorbornene is certainly steric in origin, with the 7-methyl substituent shielding the *exo* direction of approach. The origin of the preferred *exo*-attack in norbornene is more subject to discussion. A purely steric explanation views the *endo* hydrogens at C-5 and C-6 as sterically shielding the *endo* approach. There may be a stereoelectronic factor also. MO calculations reveal a significant distortion from planarity at the alkene with the hydrogens moving 3.4° toward the *endo* direction. This would have the effect of increasing the extension of the π orbital on the *exo* face and decreasing it on the



endo face.[106] This unequal orbital distribution could be a major factor in the favored *exo* approach.

General References

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E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962.
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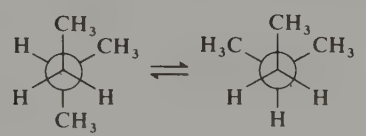
A. Greenberg and J. F. Liebman, *Strained Organic Molecules*, Academic Press, New York, 1978.

Problems

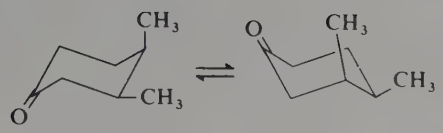
(*References for these problems will be found on page 701.*)

1. Estimate $\Delta H°$ for each of the following conformational equilibria:

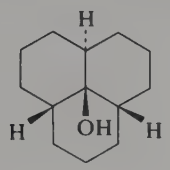
(a) 

106. See p. 152.

(b)



2. Draw a clear three-dimensional representation showing the preferred conformation of *cis,cis,trans*-perhydro-9b-phenalenol (**A**):



A

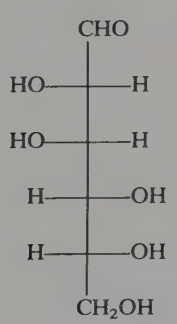
3. The *trans* : *cis* ratio at equilibrium for 4-*t*-butylcyclohexanol has been established for several solvents near 80°C:

Solvent	*trans* (%)	*cis* (%)
Cyclohexane	70.0	30.0
Benzene	72.5	27.5
1,2-Dimethoxyethane	71.0	29.0
Tetrahydrofuran	72.5	27.5
t-Butyl alcohol	77.5	22.5
Isopropanol	79.0	21.0

From these data, calculate the conformational energy of the hydroxyl group in each solvent. Do you notice any correlation between the observed conformational preference and the properties of the solvent? Explain.

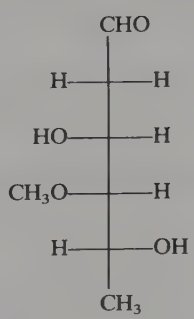
4. Draw clear conformational representations of the β-pyranose forms of each of the following carbohydrates:

(a)



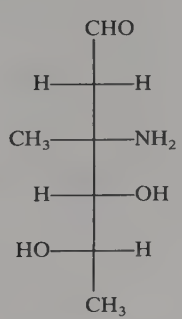
D-mannose

(b)



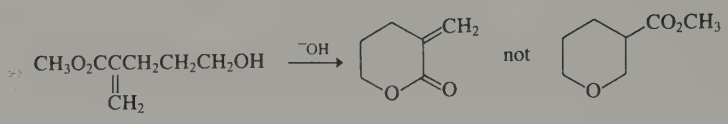
D-chromose A

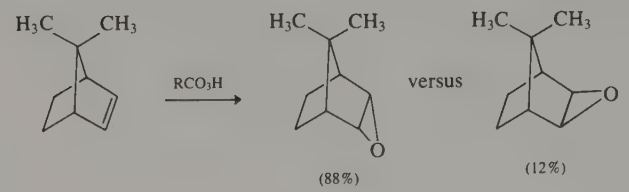
(c)

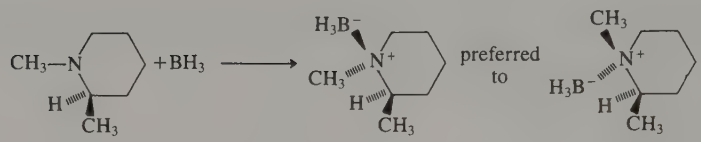


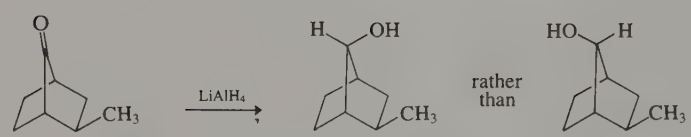
L-vancosamine

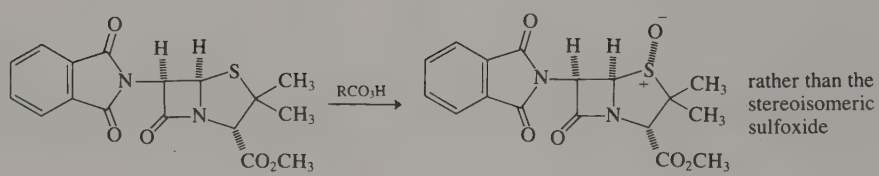
5. Explain the basis for the selective formation of the product shown over the alternative product.

(a) 

(b) 

(c) 

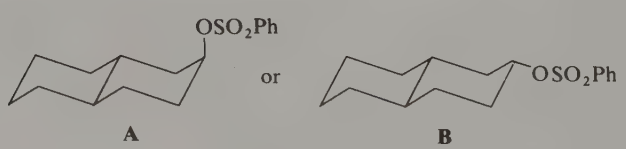
(d) 

(e) 

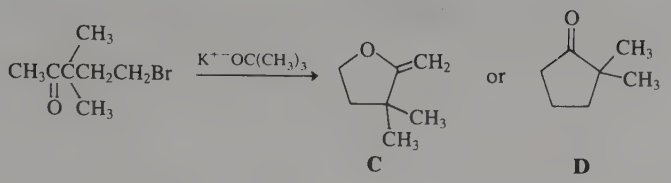
6. The chemical shift of the C(1) methine proton of bromocyclohexane is 3.98 ppm from internal tetramethylsilane at 26°C. On cooling to −75°C, this signal splits into two distinct multiplets centered at 4.60 and 3.82 ppm. Explain these observations and calculate the value of $-\Delta G^\circ$ for a bromine substituent.

7. For the following pairs of reactions, indicate which you would expect to be more favorable and explain the basis of your prediction.

   (a) Which isomer will solvolyze more rapidly in acetic acid?

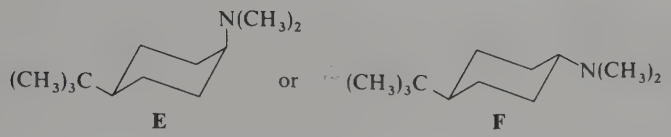


(b) Which will be the major reaction product?



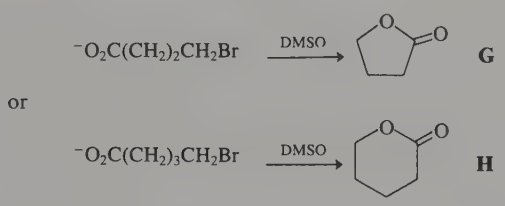
C D

(c) Which isomer will be converted to a quarternary salt more rapidly?

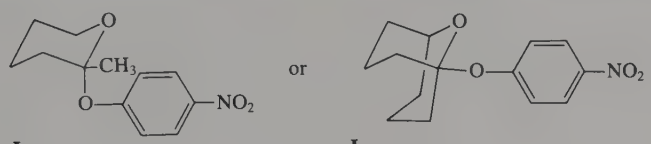


E F

(d) Which lactone will be formed more rapidly?

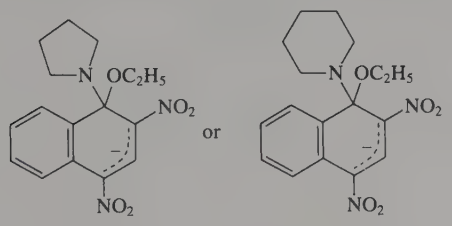


(e) Which compound will undergo hydrolysis more rapidly?



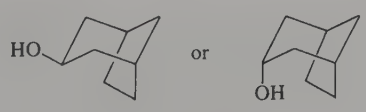
I J

(f) Which compound will aromatize more rapidly by loss of ethoxide ion?



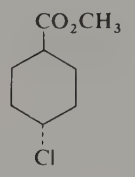
K L

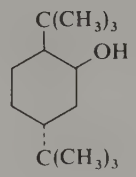
(g) Which compound will be more rapidly oxidized by chromic acid?

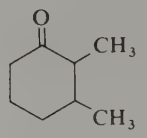


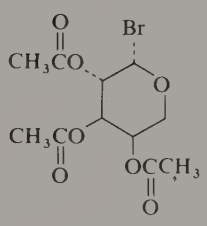
M N

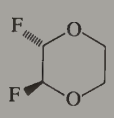
8. Predict the most stable conformation for each of the following molecules and explain the basis of your prediction.

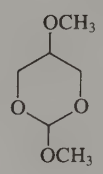
(a) 

(b) 

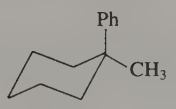
(c) 

(d) 

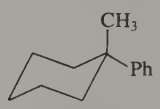
(e) 

(f) 

9. Conformational free energies are usually additive, so long as the two substituents themselves do not have a perturbing influence on one another. When some kind of mutual interaction is present the additivity concept will not be valid. NMR studies have shown that 1-methyl-1-phenylcyclohexane prefers the conformation **A** over **B**, even though the conformational free energy of Ph (2.9 kcal) is greater than that of CH_3 (1.8 kcal). Offer an explanation.



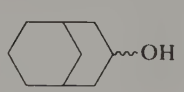
A

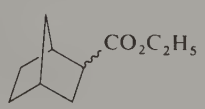


B

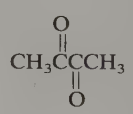
10. Using the data incorporated in Fig. 3.3 and assuming the additivity of *gauche* and eclipsing interactions of similar type, sketch the rotational energy profile you would expect for 2,3-dimethylbutane.

11. The following molecules present possibilities for stereoisomerism and/or the existence of different conformations. For each molecule predict which stereoisomer will be most stable and predict its preferred conformation.

(a) 

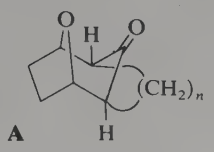
(b) 

(c) 

(d) 

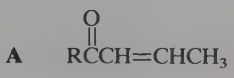
12. Consider the conformations possible for 3-substituted methylenecyclohexanes. Do you expect typical substituents to exhibit larger or smaller preferences for the equatorial orientation, as compared to the same substituent on a cyclohexane ring?

13. Discuss the aspects of stereochemistry that would have to be considered for complete description of the structure of molecules having the general structure **A**. How would the size of the $(CH_2)_n$ bridge affect conformational issues in these molecules?



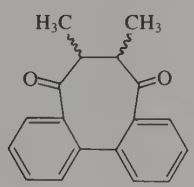
A

14. Predict the preferred conformation of the isomeric (*cis*- and *trans*-) pent-3-en-2-ones, **A**, R = CH_3. How would you expect the conformational picture to change as R becomes successively larger?

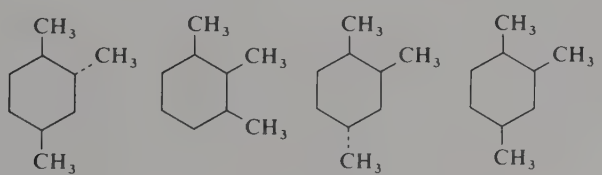


A

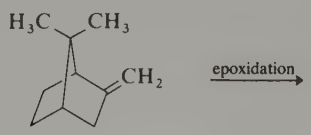
15. Two stereoisomers (**A** and **B**) of the structure shown below have been obtained and separated. One isomer (**A**) shows two methyl peaks (doublets at 1.03 and 1.22 ppm) and two quartets (2.68 and 3.47 ppm) for the CH groups. The other isomer (**B**) shows single signals for the methyl (doublet at 1.25 ppm) and methine protons (broad quartet at 2.94 ppm). The spectra of both compounds show a change with temperature. For isomer **A**, at 95°C, the pairs of methyl doublets and the methine quartet both become single signals (still a doublet and a quartet, respectively). The low-temperature spectrum (−40°C) is unchanged from the room temperature spectrum. For isomer **B** at −40°C, the methyl signals split into two doublets of *unequal intensity* (1.38 and 1.22 ppm in the ratio 9:5). The methine signal also splits into two broad signals at 3.07 and 2.89 ppm, also in the ratio 9:5. From this information, assign the stereochemistry of isomers **A** and **B** and explain the cause of the temperature dependence of the NMR spectra of each isomer.

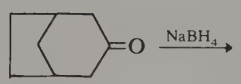


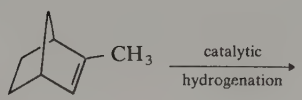
16. Estimate the energy difference between the stable and unstable chair conformations of each of the following trimethylcyclohexanes:



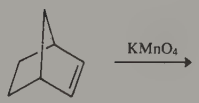
17. Predict the stereochemistry of each of the following reactions:

(a) 

(b) 

(c) 

(d) 

(e) 

4

Study and Description of Organic Reaction Mechanisms

Introduction

The chapters that follow this one will be devoted largely to the description of specific organic reactions. The development of a working understanding of organic chemistry requires the mastery of certain fundamental reaction types that occur in a wide variety of individual reactions. Most organic reactions occur in several steps; these steps constitute the *reaction mechanism*. Knowledge of the detailed mechanism of a reaction often reveals close relationships between reactions that otherwise might appear to be unrelated. Consideration of reaction mechanism is also usually the basis for development of new reaction processes and improvement of existing procedures. In this chapter, the ways in which organic reactions can be studied in order to determine reaction mechanism will be discussed. The chapter considers the types of experimental studies that provide data and the methods by which it is possible to develop information about reaction mechanisms from such data.[1]

4.1. Thermodynamic Data

Any organic reaction will have associated with it a change in enthalpy (ΔH), entropy (ΔS), and free energy (ΔG). The principles of thermodynamics assure us that

1. An extensive discussion of techniques for studying reaction mechanisms is presented in E. S. Lewis (ed.), *Investigation of Rates and Mechanisms of Reactions, Techniques of Organic Chemistry*, Third Edition, Vol. VI, Part I, Interscience, New York, 1974.

ΔH, ΔS, and ΔG are independent of the reaction path. They are interrelated by the fundamental equation

$$\Delta G = \Delta H - T\,\Delta S \tag{4.1}$$

Furthermore, the value of ΔG is related to the equilibrium constant K for the reaction

$$\Delta G = -RT \ln K \tag{4.2}$$

Since these various quantities are characteristic of the reactants and products and are independent of the reaction path, they cannot provide insight into mechanisms. Information about ΔG, ΔH, and ΔS does, however, indicate the feasibility of any specific reaction. The enthalpy of many organic reactions can be estimated from tabulated thermochemical data, or from bond energy data such as those in Table 1.3 (p. 11). The example below indicates the use of bond energy data for estimating the enthalpy of a reaction.

Example 4.1. Calculate the enthalpy change associated with hydrogenation of butene.

$$CH_3CH{=}CHCH_3 + H_2 \longrightarrow CH_3CH_2CH_2CH_3$$

$$-\Delta H = \Sigma \text{ bond energies}_{(\text{formed})} - \Sigma \text{ bond energies}_{(\text{broken})}$$

Bonds formed:			Bonds broken:	
2	C—H	196.4	H—H	103.2
	C—C	80.5	C=C	145
		276.9		248.2

$$\Delta H = -276.9 - (-248.2) = -28.7 \text{ kcal/mol}$$

The hydrogenation is therefore calculated to be exothermic by about 29 kcal/mol.

Calculations of this type can provide only an approximate indication of the enthalpy change to be associated with a given reaction. The generalized bond energies given in Table 1.3 assume that a bond energy is independent of the structure of the rest of the molecule. This is only an approximation, as can be judged by observing the variation in C–H and C–C bond energies as a function of structure in Part B of Table 1.3.

There are extensive compilations of ΔH_f° and ΔG_f° for many compounds. The subscript f designates these as, respectively, the enthalpies and free energies of formation of the compound from its constituent elements. The superscript ° is used to designate data that refer to the substance in its standard state, i.e., the pure substance at 25°C and 1 atm. These compilations can be used to calculate the enthalpy or free energy of a given reaction if the data are available for each reactant and product:

$$\Delta H^\circ = \Sigma \Delta H_{f_{\text{products}}}^\circ - \Sigma \Delta H_{f_{\text{reactants}}}^\circ$$

or

$$\Delta G^\circ = \Sigma \Delta G^\circ_{f_{\text{products}}} - \Sigma \Delta G^\circ_{f_{\text{reactants}}}$$

In the case of hydrogenation of 2-butene, ΔH_f° for butane (gas) is −30.15 kcal/mol, ΔH_f° for *trans*-2-butene (gas) is −2.67 kcal/mol and ΔH_f° for H_2 is 0. Thus, the exact ΔH° of the hydrogenation reaction is −27.5 kcal/mol.

If the data for a compound of interest have not been determined and tabulated, it may be possible to estimate ΔH_f° or ΔG_f° from tabulated data pertaining to individual structural units. Fairly precise procedures have been developed for estimation of thermodynamic characteristics of hydrocarbons and some derivatives by summing the contributions expected for the constituent groups.[2]

Estimation of the free-energy change associated with a reaction permits the calculation of the equilibrium position for a reaction and indicates the feasibility of a given chemical process. A positive ΔG° imposes a limit on the extent to which a reaction can occur. For example, as can be calculated using Eq. (4.2), a ΔG° of 1.0 kcal/mol limits conversion to product at equilibrium to 15%. An appreciably negative ΔG° indicates that the reaction is thermodynamically favorable.

Molecular orbital calculations provide another approach to obtaining estimates of thermodynamic data. The accuracy with which the various computational methods reproduce molecular energies differs substantially. The total stabilization energies calculated even for small hydrocarbons, relative to the separate nuclei and electrons, are very large numbers (typically 50,000–100,000 kcal/mol for C_2 and C_4 species, respectively). This is the energy which comes directly out of an MO calculation. The energy differences which are of principal chemical interest, such as ΔH for a reaction, are likely to be in the range of 0–20 kcal/mol. A very small error, relative to the total energy, in a MO calculation becomes a very large error in a calculated value for a ΔH. Fortunately, the absolute errors for compounds of similar type are likely to be comparable to one another so that *energy differences* between two molecules can be estimated on the basis of MO calculations. Table 4.1 gives some reported calculated ΔH values for some simple reactions and the experimental values. It is clear from the variation in results among the calculations and the deviation from experimental data that the ability to produce reliable estimates of energy depends upon the method which is chosen.

Calculations are frequently done on the basis of *isodesmic reactions* in order to provide for maximum cancellation of errors inherent in the total energies. An isodesmic reaction is defined as a process in which the number of formal bonds of each type is kept constant; that is, the number of C—H, C=C, C=O, etc, bonds on each side of the equation are identical.[3] Although the reaction may not correspond to any real chemical process, the calculation can provide a test of the reliability of

2. G. J. Janz, *Thermodynamic Properties of Organic Compounds*, Academic Press, New York, 1967.
3. W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.* **92**, 4796 (1970).

Table 4.1. ΔH for Some Reactions Calculated by MO Methods[a]

Reaction	Calculation method					
	CNDO/2	MNDO	STO-3G	4-31G	6-31G	Expt.
$CH_3{-}CH_3 + H_2 \rightarrow 2CH_4$					−22.0	−15.6
$CH_3CH{=}CH_2 \rightarrow$ 					+7.8	+7.8
$C_2H_2 + H_2 \rightarrow CH_2{=}CH_2$	−157	−42.7	−64.4	−57.3		−41.8
$C_2H_2 + C_2H_4 \rightarrow CH_2{=}CHCH{=}CH_2$	−203	−3.7	−57.9	−41.3		−41

a. Enthalpy given in kcal/mol. Data for CNDO/2, STO-3G, and 4-31G from T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. N. Lipscomb, *J. Am. Chem. Soc.* **100**, 6595 (1978); data for MNDO from M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.* **101**, 5558 (1979); data for 6-31G from J. A. Pople, *J. Am. Chem. Soc.* **97**, 5306 (1975).

the computational method because of the additivity of enthalpies. The "experimental" ΔH of the process can be obtained by summation of the tabulated ΔH_f° of the participating molecules. Table 4.2 illustrates some isodesmic reactions and shows ΔH values calculated at the 4-31G level.

Of the semiempirical methods only MINDO[4] and MNDO[5] are claimed to be able to reliably estimate energies and the range of this reliability is open to some question.[6] The advanced basis sets such as 4-31G and 6-31G achieve chemically useful accuracy in *ab initio* calculations.[7] Undoubtedly, MO calculations will play an expanding role in estimates of ΔH for reaction but at present users of such data will have to critically assess the reliability of the particular method before applying it for predictive purposes.

Whether ΔH for a projected reaction is based on bond energy data, tabulated thermochemical data, or on molecular orbital computations, there remain some fundamental problems which prevent a final conclusion about a reaction's feasibility. In the first place, most reactions of interest occur in solution, and the enthalpy, entropy, and free energy associated with any such reaction depend on the solvent medium. There are only a limited amount of tabulated data that are directly suitable for treatment of reactions in organic solvents. Estimates of solvation effects must be made in order to apply thermodynamic data which refer to the gas phase or to the pure liquid substance.

There is still an even more basic limitation to the usefulness of thermodynamic data for making predictions about reactions: Thermodynamic data can provide no information about the energy requirements of the pathways that the potential

4. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, *J. Am. Chem. Soc.* **97**, 1294 (1975).
5. M. J. S. Dewar and G. P. Ford, *J. Am. Chem. Soc.* **101**, 5558 (1979).
6. J. A. Pople, *J. Am. Chem. Soc.* **97**, 5307 (1975).
7. T. A. Halgren, D. A. Kleier, J. H. Hall, Jr., L. D. Brown, and W. N. Lipscomb, *J. Am. Chem. Soc.* **100**, 6595 (1978).

Table 4.2. Calculated and Experimental ΔH Values for Some Isodesmic Reactions[a]

Reaction	Calculated ΔH (4-31G) (kcal/mol)	Experimental[b] ΔH (kcal/mol)
$CH_3CH_2CH_3 + CH_4 \rightarrow 2CH_3CH_3$	1.0	1.5
 $+ 3CH_4 \rightarrow 2CH_3CH_3 + CH_2{=}CH_2$	−58	−45.2
$H_2C{=}C{=}O + CH_4 \rightarrow CH_2{=}CH_2 + H_2C{=}O$	12.8	16.5
$CH_3CN + CH_4 \rightarrow CH_3CH_3 + HCN$	12.0	8.9

a. Data from W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.* **92**, 4796 (1970).
b. From thermodynamic data corrected to 0° K.

reaction can follow; that is, thermodynamics provides no information about *rates of chemical reactions.* In the absence of a relatively low-energy pathway, two molecules that can potentially undergo a highly favorable reaction coexist without reaction for indefinite periods of time. It is therefore extremely important to develop an understanding of reaction mechanisms and the energy requirements and rates of the various steps by which organic reactions proceed.

4.2. Kinetic Data

Kinetic data are capable of providing much detailed insight into reaction mechanisms. The rate of a given reaction can be determined by following the disappearance of a reactant or the appearance of product. The extent of reaction is often measured spectroscopically, since spectroscopic techniques provide a rapid, continuous means of monitoring changes in concentration. Numerous other methods are available, however, and may be preferable in certain cases. For example, continuous pH measurement or acid–base titration can be used to follow the course of reactions that consume or generate acids or bases. Conductance measurements provide a means for determining the rates of reactions that generate ionic species; polarimetry is a convenient way of following reactions involving optically active materials. In general, any property that can be measured and related to the concentration of a rectant or product can be used to determine a reaction rate.

The goal of a kinetic study is to establish the quantitative relationship between the concentration of reactants and catalysts and the rate of reaction. Typically, such a study involves rate measurement at enough different concentrations of each reactant so that the *kinetic order* with respect to each reactant can be assessed. A complete investigation allows the reaction to be described by a rate law, which is an algebraic expression containing one or more *rate constants* as well as the concentrations of all reactant species that are involved in the rate-determining step and steps prior to

the rate-determining step. Each concentration term has an exponent that is equal to the order of the reaction with respect to that component. The overall kinetic order of the reaction is equal to the sum of all the exponents in the rate expression. Several examples of rate laws that illustrate the variety observed are presented in Scheme 4.1. Some are simple; others are more complex.

The relationship between a kinetic expression and a reaction mechanism can be appreciated if one considers the several individual steps that constitute the overall reaction mechanism. The expression for the rate of any *single step* in a reaction mechanism will contain a term for the concentration for each reacting species. Thus, for the reaction

$$A+B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} D \xrightarrow{k_3} E+F$$

the rates for the successive steps are

$$\text{step 1:} \quad \frac{d[C]}{dt} = k_1[A][B] - k_{-1}[C]$$

$$\text{step 2:} \quad \frac{d[D]}{dt} = k_2[C]$$

$$\text{step 3:} \quad \frac{d[E]}{dt} = \frac{d[F]}{dt} = k_3[D]$$

Let us further specify that the first step is a very rapid but unfavorable equilibrium, and that $k_2 \ll k_3$, i.e., that the second step is slow relative to the third step. Under these circumstances, the overall rate of the reaction will depend on the rate of the second step and it is called the *rate-determining step.*

Kinetic data provide information only about the rate-determining step and steps preceding it. In the hypothetical reaction under consideration, the final step follows the rate-determining step, and since its rate will not affect the rate of the overall reaction, k_3 will not appear in the rate expression. The rate of the overall reaction will be governed by the second step, which is the bottleneck in the process. The rate of this step is equal to k_2 multiplied by the molar concentration of intermediate C, which may not be measureable. It is therefore necessary to express the rate in terms of the concentration of reactants. In the case under consideration, this can be done by recognizing that [C] is related to [A] and [B] by an equilibrium constant

$$K = \frac{[C]}{[A][B]}$$

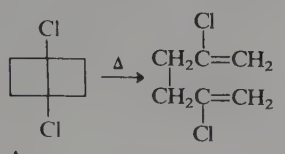
Furthermore, K is related to k_1 and k_{-1} by the requirement that no net change in composition occur at equilibrium:

$$k_{-1}[C] = k_1[A][B]$$

$$[C] = \frac{k_1}{k_{-1}}[A][B]$$

Scheme 4.1. Some Representative Rate Laws

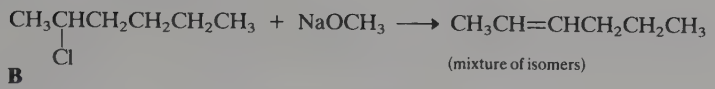
1[a]



A

$$\text{rate} = k[\mathbf{A}]$$

2[b]



B

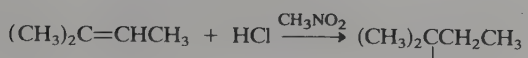
(mixture of isomers)

$$\text{rate} = k[\mathbf{B}][NaOCH_3]$$

3[c]

$$\text{rate} = k[CH_3Cl][GaCl_3^*]^2$$

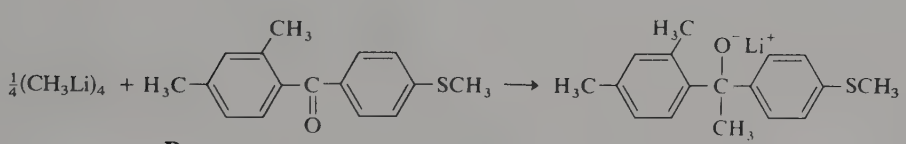
4[d]



C

$$\text{rate} = k[\mathbf{C}][HCl]^2$$

5[e]



D

$$\text{rate} = k[(CH_3Li)_4]^{1/4}[\mathbf{D}]$$

6[f]

E **F**

$$\text{rate} = k_1[\mathbf{E}][\mathbf{F}] + k_2[\mathbf{E}][\mathbf{F}]^2$$

a. E. N. Cain and R. K. Solly, *J. Am. Chem. Soc.* **95**, 7884 (1973).
b. R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.* **90**, 408 (1968).
c. F. P. DeHaan, H. C. Brown, D. C. Conway, and M. G. Gibby, *J. Am. Chem. Soc.* **91**, 4854 (1969).
d. Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Am. Chem. Soc.* **91**, 4199 (1969).
e. S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.* **94**, 7059 (1972).
f. A. S. A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.* **89**, 3020 (1967).

The rate of step 2 can therefore be written in terms of [A] and [B]:

$$\frac{d[D]}{dt} = k_2[C] = k_2\frac{k_1}{k_{-1}}[A][B] = k_{obs}[A][B]$$

Experimentally, it would be observed that the reaction rate would be proportional to both [A] and [B]. Kinetic data are normally handled using the integrated forms of the differential equations. The integrated rate equations for very common rate laws such

as simple first-order and second-order reactions are

$$\text{first-order reaction:} \qquad k = \frac{1}{t} \ln \left(\frac{c_0}{c} \right)$$

$$\text{second-order reaction:} \quad k = \frac{1}{t(a_0 - b_0)} \ln \frac{b_0(a)}{a_0(b)}$$

where a, b, and c refer to concentrations of reactants at time t, and a_0, b_0, and c_0 to initial concentrations. As rate laws become more complicated, the mathematical expressions and their solutions become increasingly complex.

For the simple rate expressions, graphical or numerical analysis of the data directly provides a value for the appropriate rate constant. More complex rate expressions may be analyzed by a variety of graphical or analytical techniques, in conjunction with sufficient changes in the reactant concentrations and other variables to determine the kinetic expression and rate constants unambiguously.

Most organic reactions involve more than one step. It is therefore necessary to consider the kinetic expressions that arise from some of the more important cases of multistep reactions. There may be a rapid equilibrium preceding the rate-determining step. Such a mechanism may operate, for example, in the reaction of an alcohol with hydrobromic acid to give an alkyl bromide:

$$\text{ROH} + \text{H}^+ \underset{k_{-1}}{\overset{\text{fast } k_1}{\rightleftharpoons}} \overset{+}{\text{R}}\text{OH}_2$$

$$\overset{+}{\text{R}}\text{OH}_2 + \text{Br}^- \xrightarrow[k_2]{\text{slow}} \text{RBr} + \text{H}_2\text{O}$$

The overall rate being measured is that of step 2, but there may be no means of directly measuring $[ROH_2^+]$. The concentration of the protonated intermediate ROH_2^+ can be expressed in terms of the concentration of the starting material by taking into consideration the equilibrium constant, which relates [ROH], $[Br^-]$, and $[H^+]$:

$$K = \frac{[\text{ROH}_2^+]}{[\text{ROH}][\text{H}^+]}$$

$$[\text{ROH}_2^+] = K[\text{ROH}][\text{H}^+]$$

$$\text{rate} = k_2 K[\text{ROH}][\text{H}^+][\text{Br}^-] = k_{\text{obs}}[\text{ROH}][\text{H}^+][\text{Br}^+]$$

A useful idea that is often employed in analysis and simplification of kinetic expressions is the *steady state approximation.* It can be illustrated with a hypothetical reaction scheme:

$$\begin{array}{l} \text{A} + \text{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{C} \\ \text{C} + \text{D} \xrightarrow{k_2} \text{E} + \text{F} \\ \hline \text{A} + \text{B} + \text{D} \longrightarrow \text{E} + \text{F} \end{array}$$

If C is a reactive, unstable species, its concentration will never be very large. It must then be consumed at a rate that closely approximates the rate at which it is formed. Under these conditions, it is a valid approximation to set the rate of formation of C equal to its rate of destruction:

$$k_1[A][B] = k_2[C][D] + k_{-1}[C]$$

This approximation permits an expression for [C]:

$$\frac{k_1[A][B]}{k_2[D] + k_{-1}} = [C]$$

The rate of the second step is given by substituting for [C]

$$\text{rate} = k_2[C][D] = k_2 \frac{k_1[A][B]}{k_2[D] + k_{-1}}[D]$$

If $k_2[D]$ is much greater than k_{-1} the rate expression simplifies to

$$\text{rate} = \frac{k_2 k_1[A][B][D]}{k_2[D]} = k_1[A][B]$$

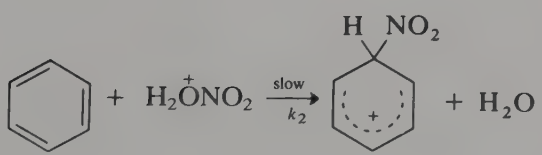
On the other hand, if $k_2[D]$ is much less than k_{-1}, the observed rate expression becomes

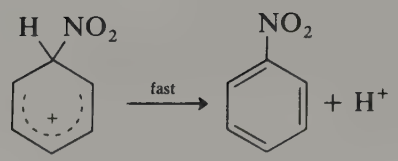
$$\text{rate} = \frac{k_1 k_2[A][B][D]}{k_{-1}}$$

The first situation corresponds to the first step being rate determining. In the second case, it is the second step which is rate determining with the first step being a preequilibrium.

The normal course of a kinetic investigation involves the postulation of likely mechanisms and comparison of the experimental rate law with that expected for the various possibilities. Mechanisms that are incompatible with the observed kinetics can be eliminated as possibilities. Let us consider aromatic nitration by nitric acid in an inert solvent as a typical example, and restrict the mechanisms to be considered to the three shown below. In a normal case, such an arbitrary restriction would not be imposed, but instead all mechanisms compatible with existing information would be considered.

(A) $$2\,HONO_2 \underset{k_{-1}}{\overset{k_1}{\underset{\text{fast}}{\rightleftharpoons}}} H_2\overset{+}{O}NO_2 + NO_3^-$$



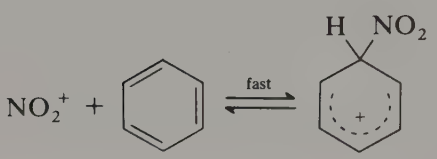


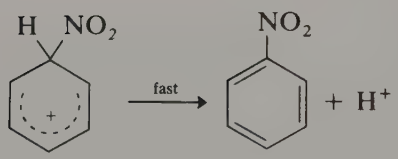
$$\text{rate} = k_2[\overset{+}{\text{H}_2\text{O}}\text{NO}_2][\text{benzene}] = \frac{k_2k_1}{k_{-1}}\frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]}[\text{benzene}]$$

$$= k_{\text{obs}}\frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]}[\text{benzene}]$$

(B) $$2\,\text{HONO}_2 \underset{k_{-1}}{\overset{\text{fast } k_1}{\rightleftharpoons}} \overset{+}{\text{H}_2\text{O}}\text{NO}_2 + \text{NO}_3^-$$

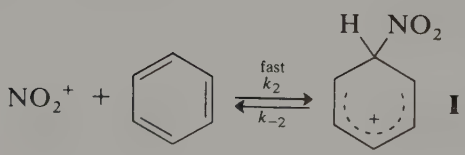
$$\overset{+}{\text{H}_2\text{O}}\text{NO}_2 \xrightarrow[k_2]{\text{slow}} \text{H}_2\text{O} + \text{NO}_2^+$$

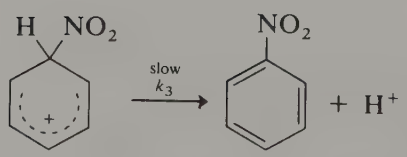




$$\text{rate} = \frac{k_1k_2}{k_{-1}}\frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]} = k_{\text{obs}}\frac{[\text{HONO}_2]^2}{[\text{NO}_3^-]}$$

(C) $$2\,\text{HONO}_2 \underset{k_{-1}}{\overset{\text{fast } k_1}{\rightleftharpoons}} \text{NO}_2^+ + \text{NO}_3^- + \text{H}_2\text{O}$$





The third step is rate controlling, so

$$\text{rate} = k_3[\mathbf{I}]$$

[**I**] can be expressed in terms of the rapid equilibria involved in its formation:

$$k_{-2}[\mathbf{I}] = k_2[NO_2^+][\text{benzene}]$$

$$[NO_2^+] = \frac{k_1[HNO_3]^2}{k_{-1}[NO_3^-][H_2O]}$$

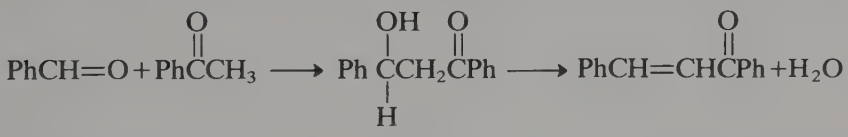
$$\text{rate} = k_3 \frac{k_2[\text{benzene}]k_1[HNO_3]^2}{k_{-2}k_{-1}[NO_3^-][H_2O]}$$

$$\text{rate} = \frac{k_{obs}[HNO_3]^2[\text{benzene}]}{[NO_3^-][H_2O]}$$

Mechanism B has the distinctive feature that it is zero order in the substrate benzene, since the rate-determining step occurs prior to the involvement of benzene. Mechanism B has in fact been established for nitration of benzene in several organic solvents, and the absence of a benzene concentration term in the rate law is an important part of the evidence for this mechanism.[8]

Mechanisms A and C on the other hand provide kinetic expressions which are rather similar in form, differing only in the inclusion of water in the expression for mechanism C. This might or might not be a detectable difference. If the concentration of water is several times higher than that of benzene, its overall concentration will change little during the course of the reaction. Under these conditions the term for the concentration of water would disappear (by being a component of the observed k) so that the form of the kinetic expression alone would not distinguish between mechanism A and C.

As an example of the development of a kinetic expression from a postulated reaction mechanism, we can consider the base-catalyzed reaction of benzaldehyde and acetophenone. Based on general knowledge of base-catalyzed reactions of



carbonyl compounds, a reasonable sequence of steps can be written, but the question of the relative rates of the steps is open. Furthermore, it is known that reactions of this type are generally reversible so that the potential reversibility of each step must be taken into account. A completely reversible mechanism is as follows:

8. J. H. Ridd, *Acc. Chem. Res.* **4**, 248 (1971); J. H. Ridd, in *Studies on Chemical Structure and Reactivity*, J. H. Ridd (ed.), John Wiley and Sons, New York, 1966, Chap. 7.

(1) $$PhCOCH_3 + {}^-OEt \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhCOCH_2^- + EtOH$$

(2) $$PhCOCH_2^- + PhCHO \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} PhCH(O^-)CH_2COPh$$

(3) $$EtOH + PhCH(O^-)CH_2COPh \underset{k_{-3}}{\overset{\text{fast } k_3}{\rightleftharpoons}} PhCH(OH)CH_2COPh + EtO^-$$

(4) $$PhCH(OH)CH_2COPh + EtO^- \xrightarrow{k_4} PhCH{=}CHCOPh + {}^-OH + EtOH$$

Since proton transfer reactions between oxygen atoms are usually very fast, step 3 is assumed to be a rapid equilibrium. With the above mechanisms assumed, let us examine the rate expression which would result, depending upon which of the steps is rate determining.

If step 1 is rate controlling the rate expression would be

$$\text{rate} = k_1[PhCOCH_3][{}^-OEt]$$

Under these conditions the concentration of the second reactant, benzaldehyde would not enter into the rate expression.

If step 1 is an equilibrium and step 2 is rate controlling we have the following rate expression:

$$\text{rate} = k_2[PhCOCH_2{}^-][PhCHO]$$

which on substituting in terms of the rapid prior equilibrium gives

$$\text{rate} = k_2K_1[PhCOCH_3][{}^-OEt][PhCHO]$$

since

$$[PhCOCH_2{}^-] = K_1[PhCOCH_3][{}^-OEt]$$

where K_1 is the equilibrium constant for the deprotonation. If the final step is rate controlling the rate is

$$\text{rate} = k_4[{}^-OEt][PhCH(OH)CH_2COPh]$$

The concentration of the intermediate $PhCH(OH)CH_2COPh$ can be expressed in terms of the three prior equilibria. Using **I** for the intermediate and $\mathbf{I}^-$ for the

conjugate base and neglecting [EtOH] since it is the solvent,

$$K_3 = \frac{[\mathbf{I}][^-OEt]}{[\mathbf{I}^-]} \qquad \text{and} \qquad [\mathbf{I}] = K_3 \frac{[\mathbf{I}^-]}{[^-OEt]}$$

and since $[\mathbf{I}^-] = K_2[PhCOCH_2^-][PhCHO]$ substituting for $[\mathbf{I}^-]$ gives

$$[\mathbf{I}] = K_3 \frac{K_2[PhCOCH_2^-][PhCHO]}{[^-OEt]}$$

substituting for $[PhCOCH_2^-]$ from the equilibrium expression for step 1

$$[\mathbf{I}] = \frac{K_3K_2[PhCHO]}{[^-OEt]} K_1[PhCOCH_3][^-OEt] = K'[PhCHO][PhCOCH_3]$$

and this provides the final rate expression

$$\text{rate} = k_{obs}[^-OEt][PhCHO][PhCOCH_3]$$

The form of this third-order kinetic expression would be identical to that in the case where the second step was rate determining.

Experimental studies of this base-catalyzed condensation have revealed that it is third order indicating that either the second or fourth step is rate determining. Studies on the intermediate isolated from an alternative synthesis have shown that k_4 is about four times as large as k_{-3} so that about 80% of the intermediate goes on to product. These reactions are faster than the second step, so that at the concentrations used, the second step is rate controlling.[9]

These specific examples illustrate the relationship of kinetic studies to determination of a reaction mechanism. Kinetic results can exclude from consideration all mechanisms that require a different rate law. It is often true, however, that related mechanisms give rise to identical predictions about the form of the rate law. In this case, the mechanisms are "kinetically equivalent," and a choice is not possible on the basis of kinetic data alone. A further limitation on the information that kinetic studies provide should also be recognized. Although the data can give the *composition* of the activated complex for the rate-determining step and preceding steps, it provides no information about the *structure.* Sometimes this structure can be inferred from chemical experience, but it is never established by kinetic data alone.

The nature of the rate constant k_r can be discussed in terms of *transition state theory.* A reaction is assumed to involve the attainment of an activated complex that goes on to product at an extremely rapid rate. The rate of decomposition of the activated complex has been calculated from the assumptions of the theory to be 6×10^{12} sec^{-1} at room temperature, and is given by the expression[10]

9. E. Coombs and D. P. Evans, *J. Chem. Soc.* 1295 (1940); D. S. Noyce, W. A. Pryor, and A. H. Bottini, *J. Am. Chem. Soc.* **77**, 1402 (1955).
10. For complete development of these relationships, see M. Boudart, *Kinetics of Chemical Processes,* Prentice-Hall, Englewood Cliffs, New Jersey, 1968, pp. 35–46; or I. Amdur and G. G. Hammes, *Chemical Kinetics, Principles and Selected Topics,* McGraw-Hill, New York, 1966, pp. 43–58.

$$\text{rate of activated complex decomposition} = \frac{\kappa kT}{h} \tag{4.3}$$

in which κ is the transmission coefficient, usually taken to be 1, k is Boltzmann's constant, h is Planck's constant, and T is absolute temperature.

$$\text{rate of reaction} = \frac{\kappa kT}{h}[\text{activated complex}]$$

If the activated complex is considered to be in equilibrium with its component molecules, the attainment of the transition state (T.S.) can be treated as being analogous to a bimolecular reaction:

$$\text{A} + \text{B} \longrightarrow \text{C}$$

$$\text{A} + \text{B} \rightleftharpoons \text{T.S.} \longrightarrow \text{C}$$

$$K^{\ddagger} = \frac{[\text{T.S.}]}{[\text{A}][\text{B}]}$$

The position of the equilibrium is related to the free energy required for attainment of the transition state. The superscript sign (‡) is used to specify that it is a process involving a transition state or "activated complex" that is under discussion:

$$\Delta G^{\ddagger} = -RT \ln K^{\ddagger}$$

This free energy is referred to as the *free energy of activation*. The rate of the reaction is then given by

$$\text{rate} = \frac{\kappa kT}{h}[\text{T.S.}]$$

$$[\text{T.S.}] = K^{\ddagger}[\text{A}][\text{B}]$$

since

$$K^{\ddagger} = e^{-\Delta G^{\ddagger}/RT}$$

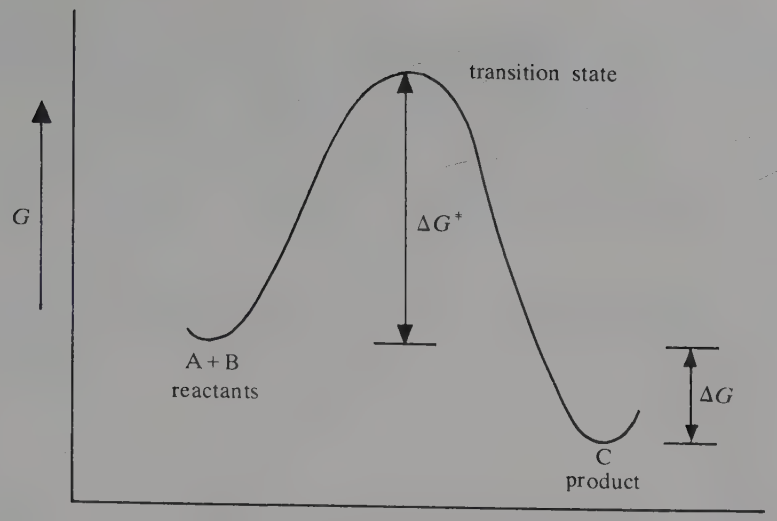
$$\text{rate} = \frac{\kappa kT}{h} e^{-\Delta G^{\ddagger}/RT}[\text{A}][\text{B}] \tag{4.4}$$

Comparison with the form of the expression for the rate of any single reaction step:

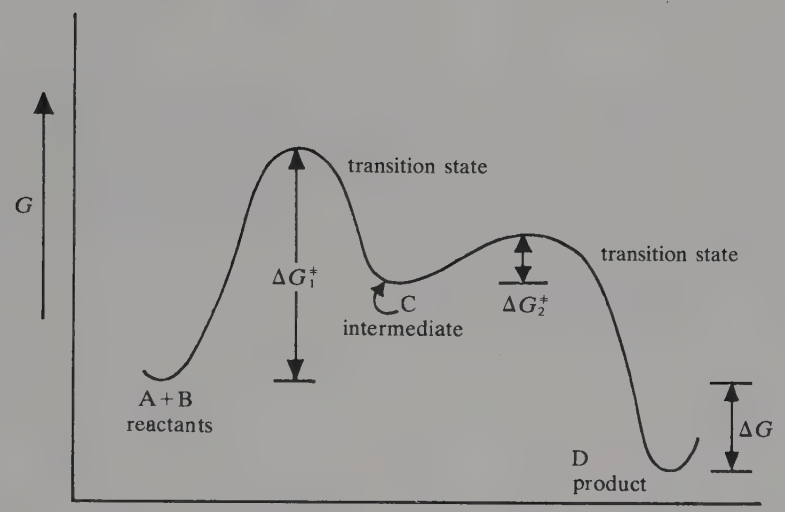
$$\text{rate} = k_r[\text{A}][\text{B}]$$

reveals that the magnitude of $\Delta G^{\ddagger}$ will be the factor determining the magnitude of k_r at any given temperature.

Qualitative features of reaction mechanisms are often described in the context of transition state theory and illustrated with potential energy diagrams. The potential energy diagram for a hypothetical one-step bimolecular reaction and for a two-step reaction are shown in Fig. 4.1. The bottom diagram depicts a two-step



Reaction coordinate for a single-step reaction



Reaction coordinate for a two-step reaction

Fig. 4.1. Potential energy diagrams for single-step and two-step reactions.

reaction in which an intermediate having a finite lifetime is involved. Two transition states are then involved. The higher activation energy of the first transition state in the bottom diagram implies that the first step would be the most energetically demanding, and therefore would be the rate-determining step. These two-dimensional diagrams are useful devices for qualitative discussion of reaction mechanisms. The line is essentially a plot of the free energy of the reacting complex as it progresses along the reaction coordinate from reactants to products.

Such diagrams make clear the difference between an intermediate and a transition state. An intermediate lies in a depression on the potential energy curve. Thus, it will have a finite lifetime and the actual lifetime will depend on the depth of the depression. A shallow depression implies a low activation energy for the subsequent step, and therefore a short lifetime. The deeper the depression, the longer the lifetime of the intermediate. The situation at a transition state is quite different. It has only a fleeting existence and represents an energy maximum on the reaction path.

There is one path between reactants and products that has a lower energy maximum than any other; this is the pathway that the reaction will follow. It is this pathway that is plotted in potential energy diagrams. The line in a potential energy plot represents this lowest-energy pathway across a surface that could be constructed by considering energy as a function of the varying spatial arrangement of the atoms involved in the reaction. The *principle of microscopic reversibility* arises naturally from the transition state theory: *The same pathway that is traveled in the forward direction of a reaction will be traveled in the reverse direction, since it affords the lowest energy barrier for either process.* Thus, information about the nature of a transition state or intermediate deduced by a study of a forward reaction is applicable to the discussion of the reverse process occurring under the same conditions.

Since transition states cannot be directly observed, there is no experimental method for establishing their structure, although their free energy can be measured by determination of the activation energy of the reaction. In recent years, theoretical descriptions of molecules have been applied to successive structures that might be encountered in a transformation from reactant to product. This theoretical description can be done, for instance, by applying one of the MO methods to the reactants, products, and various intermediate geometries. The energy calculated for any given geometry establishes one point on the energy surface. To the extent that the calculations accurately reflect molecular reality, the structure at the transition state can be established by searching out the pathway from reactant to product that requires minimum energy. The maximum energy on this path then corresponds to the transition state.

The temperature dependence of reaction rates can be evaluated by separating the enthalpy and entropy components of Eq. (4.4) which gives

$$k_r = \frac{\kappa k T}{h}(e^{-\Delta H^{\ddagger}/RT})(e^{\Delta S^{\ddagger}/R}) \tag{4.5}$$

The term $(\kappa kT/h)\, e^{\Delta S^{\ddagger}/R}$ varies only slightly with T compared to $e^{-\Delta H^{\ddagger}/RT}$ because of the exponential nature of the latter. To a good approximation, then

$$\frac{k_r}{T} = C e^{-\Delta H^{\ddagger}/RT} \tag{4.6}$$

$$\ln \frac{k_r}{T} = \frac{-\Delta H^{\ddagger}}{RT} + C' \tag{4.7}$$

A plot of $\ln (k_r/T)$ versus $(1/T)$ is then a straight line, and its slope is $-\Delta H^{\ddagger}/R$. Once

$\Delta H^{\ddagger}$ is determined in this manner, $\Delta S^{\ddagger}$ is available from the relationship

$$\Delta S^{\ddagger} = \frac{\Delta H^{\ddagger}}{T} + R \ln \frac{hk_r}{\kappa kT} \tag{4.8}$$

$$= \frac{\Delta H^{\ddagger}}{T} + 4.58 \log \frac{k_r}{T} - 47.4$$

which can be obtained by rearranging Eq.(4.5).

The temperature dependence of reactions can also be expressed in terms of the Arrhenius equation

$$k_r = A\, e^{-E_a/RT} \tag{4.9}$$

$$\ln k_r = -E_a/RT + \ln A \tag{4.10}$$

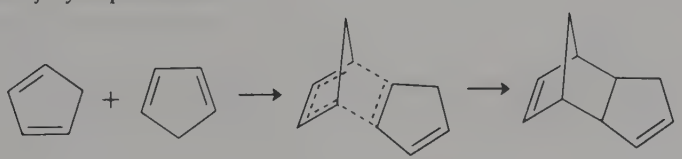
Comparison of the form of Eq. (4.9) with Eq. (4.5) indicates that A in the Arrhenius equation corresponds to $(\kappa kT/h)e^{\Delta S^{\ddagger}/R}$. The Arrhenius equation shows that a plot of $\ln k_r$ versus $1/T$ will have the slope $-E_a/R$.[11] For reactions in solution at constant pressure, $\Delta H^{\ddagger}$ and E_a are related by

$$E_a = \Delta H^{\ddagger} + RT \tag{4.11}$$

The magnitude of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ reflect transition state structure. Atomic positions in the transition state do not correspond to their equilibrium positions in the ground state. The result is a higher internal energy of the activated complex than of the reactants, and this higher energy is reflected in the enthalpy of activation. The entropy of activation is a measure of the degree of order or disorder produced in formation of the activated complex. If translational, vibrational, or rotational degrees of freedom are lost in going to the transition state, there will be a decrease in the total entropy of the system. Conversely, the gaining of translational, vibrational, or rotational degrees of freedom is associated with a positive entropy of activation.

The wide variations possible in enthalpy and entropy of activation are illustrated by the following two reactions.

Dimerization of cyclopentadiene[12]:



gas phase $\Delta H^{\ddagger} = 15.5$ kcal/mol

$\Delta S^{\ddagger} = -34$ cal/mol per degree

11. For full consideration of the relationship between Eqs. (4.5) and (4.9), see I. Amdur and G. G. Hammes, *Chemical Kinetics, Principles and Selected Topics*, McGraw-Hill, New York, 1966, pp. 53–58.
12. A. Wassermann, *Monatsch. Chem.* **83**, 543 (1952).

Decomposition of 1,1′-azobutane[13]:

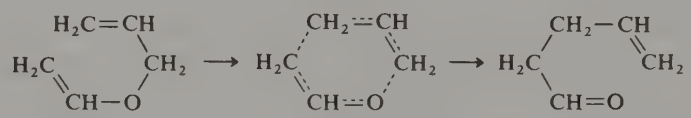
$$\text{Bu—N=N–Bu} \longrightarrow 2\text{Bu}\cdot + \text{N}_2$$

$$\text{gas phase } \Delta H^{\ddagger} = 52 \text{ kcal/mol}$$

$$\Delta S^{\ddagger} = +19 \text{ cal/mol per degree}$$

The relatively low $\Delta H^{\ddagger}$ term for the dimerization of cyclopentadiene is characteristic of concerted reactions (see Chapter 10), in which bond-making accompanies bond-breaking. It differs markedly from $\Delta H^{\ddagger}$ for the thermal decomposition of 1,1′-azobutane, in which the rate-determining step is a homolytic cleavage of a C–N bond, with little new bond-making to compensate for the energy cost of bond-breaking. The entropy of activation, on the other hand, is more favorable in 1,1′-azobutane decomposition, since a translational degree of freedom is being gained in the transition state, leading to two particles from one, while dimerization of cyclopentadiene is accompanied by loss of translational and rotational degrees of freedom.

Unimolecular reactions that take place by way of cyclic transition states typically have negative entropies of activation because of the loss of rotational degrees of freedom with the introduction of a high degree of order in the activated complex. Thus, thermal isomerization of vinyl allyl ether to 4-pentenal has $\Delta S^{\ddagger} = -8$ cal/mol per degree[14]:



It is important to remember that the enthalpy and entropy of activation reflect the response of the reacting system as a whole toward formation of the activated complex, and that the situation is considerably more complicated for reactions occurring in solution than for those occurring in the gas phase. This complexity is particularly true of processes involving the formation or destruction of ionic species in polar solvents, for which intuitive suppositions regarding the degree of solvent reordering in the transition state are risky. The solvolysis of *tert*-butyl chloride in 80% aqueous ethanol, for example, has as its rate-determining step unimolecular ionization of the carbon–chlorine bond to form chloride ion and *tert*-butyl cation. One might guess that this ionization should be reflected in a positive entropy of activation, because two particles are being generated from one in the transition state. Experiment reveals, however, that the entropy of activation is negative by 6.6 cal/mol per degree, forcing the conclusion that the transition state requires, because of its polar character, a greater degree of ordering of solvent molecules than the covalent ground state.[15] This requirement turns out to be generally true.

13. A. U. Blackham and N. L. Eatough, *J. Am. Chem. Soc.* **84**, 2922 (1962).
14. F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.* **72**, 3155 (1950).
15. E. Grunwald and S. Winstein, *J. Am. Chem. Soc.* **70**, 846 (1948).

Reactions that generate electrical charge exhibit negative entropies of activation; those that destroy charge exhibit positive entropies of activation in polar media.

4.3. Substituent Effects and Linear Free-Energy Relationships

In Chapter 1, Section 1.2 (p. 15), the effect of substituent groups on the acid strength of acetic acid and derivatives was discussed qualitatively. It was noted in particular that the presence of groups more electronegative than hydrogen increased the acid strength relative to acetic acid. A number of important relationships between substituent groups and chemical properties have been developed. Some are very useful both for interpretation of reaction mechanisms and for prediction of reaction rates and equilibria.

The most widely applied of these relationships is the *Hammett equation*, which relates rates and equilibria for many reactions of compounds containing phenyl and substituted phenyl groups. It was noted in the 1930's that there is a relationship between the acid strengths of substituted benzoic acids and the rates of other chemical reactions, for instance, the rates of hydrolysis of substituted ethyl benzoates. The correlation is illustrated graphically in Fig. 4.2, which shows log k/k_0, where

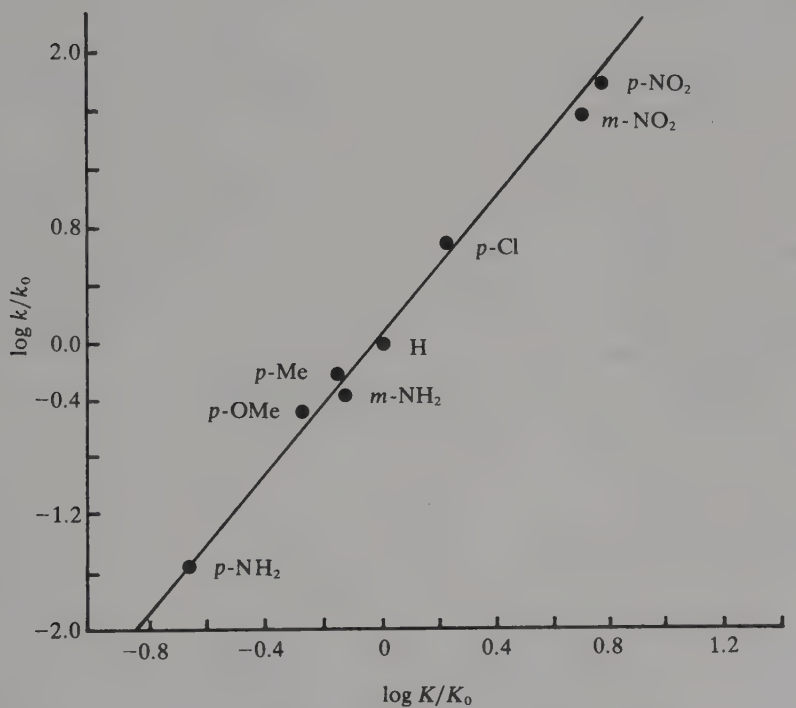


Fig. 4.2. Correlation of acid dissociation constants of benzoic acids with rates of alkaline hydrolysis of ethyl benzoates. [From L. P. Hammett, *J. Am. Chem. Soc.* **59**, 96 (1937).]

$k_0 = k$ for hydrolysis of ethyl benzoate and k is the rate constant for hydrolysis of a substituted ethyl benzoate, plotted against $\log K/K_0$, where K and K_0 are the corresponding acid dissociation constants. Analogous plots for many other reactions of aromatic compounds show a similar linear correlation with the acid dissociation constants of the substituted benzoic acids. Neither the principles of thermodynamics nor theories of reaction rates require that there should be such linear relationships. There are, in fact, numerous reactions that fail to show such correlations. Some insight into the origin of the correlation can be gained by considering the relationship between the linear correlation and the free-energy changes involved in the two processes. The line in Fig. 4.2 defines an equation in which m is the slope of the line:

$$m \log \frac{K}{K_0} = \log \frac{k}{k_0} \tag{4.12}$$

Substituting for K and k with the appropriate free energy or free energy of activation:

$$m(\log K - \log K_0) = \log k - \log k_0$$

$$m(-\Delta G/2.3RT + \Delta G_0/2.3RT) = -\Delta G^{\ddagger}/2.3RT + \Delta G^{\ddagger}/2.3RT$$

$$m(-\Delta G + \Delta G_0) = -\Delta G^{\ddagger} + \Delta G_0^{\ddagger}$$

$$m\Delta\Delta G = \Delta\Delta G^{\ddagger} \tag{4.13}$$

The linear correlation therefore indicates that the change in free energy of activation on introduction of a series of substituent groups is *directly proportional* to the change in free energy of ionization that is brought about by the introduction of the same series of substituents on benzoic acid. The various correlations arising from such directly proportional changes in free energies are called *linear free-energy relationships.*

A linear free-energy relationship between two reaction series can result from one of three circumstances: (1) ΔH is constant, (2) ΔS is constant, or (3) ΔH and ΔS are linearly related. Dissection of the free-energy changes into enthalpy and entropy components has often shown the third case to be operative.[16] This linear relationship is true for the ionization of benzoic acids, the standard reaction, as well as for a number of other systems.

The Hammett free-energy relationship is expressed as in the following equations for equilibria and for rate data, respectively:

$$\log \frac{K}{K_0} = \sigma\rho \tag{4.14}$$

$$\log \frac{k}{k_0} = \sigma\rho \tag{4.15}$$

16. P. D. Bolton, K. A. Fleming, and F. M. Hall, *J. Am. Chem. Soc.* **94**, 1033 (1972); J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955).

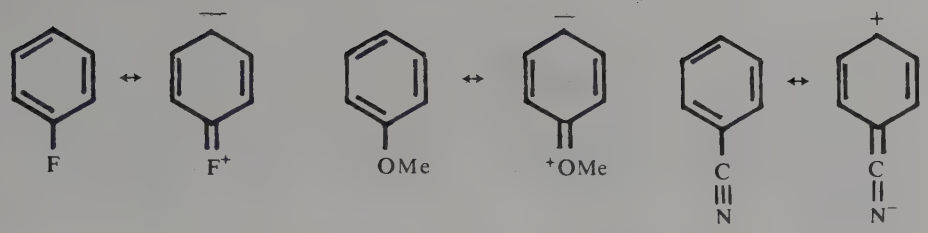


Fig. 4.3. Resonance effects of benzene substituents.

These equations correlate many data pertaining to the reactions of aromatic compounds. The numerical values of the terms σ and ρ are defined by selection of the reference reaction, the ionization of benzoic acids. This reaction is arbitrarily assigned the *reaction constant* $\rho = 1$. The *substituent constant*, σ, can then be determined for a series of substituent groups by measurement of the acid dissociation constant of the substituted benzoic acids. The σ values so defined are used in the correlation of other reaction series, and the ρ values of the reactions are thus determined. The relationship between Eqs. (4.12) and (4.14) is evident when the Hammett equation is expressed in terms of free energy.

For the standard reaction, $\log [K/K_0] = \sigma\rho$:

$$-\Delta G/2.3RT + \Delta G_0/2.3RT = \sigma\rho = \sigma$$

since $\rho = 1$ for the standard reaction. Substituting into Eq.(4.12):

$$m\sigma = -\Delta G^{\ddagger}/2.3RT + \Delta G_0{}^{\ddagger}/2.3RT$$

$$m\sigma = \log k - \log k_0 \qquad (4.16)$$

$$m\sigma = \log \frac{k}{k_0}$$

$$m = \rho$$

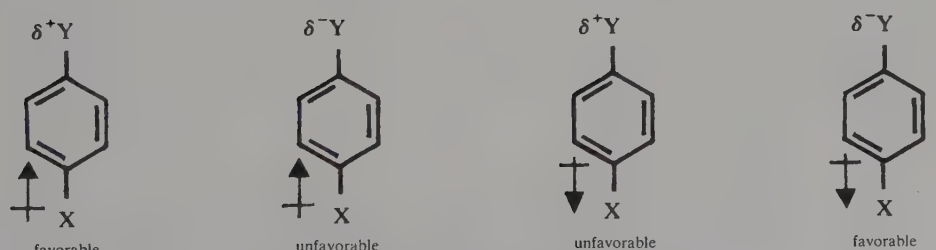


Fig. 4.4. Field effects of benzene substituents.

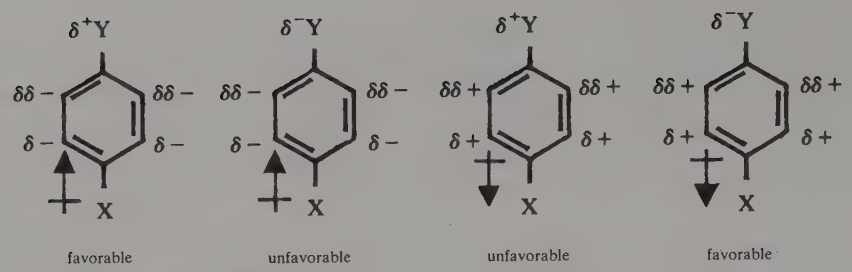


Fig. 4.5. Inductive effects of benzene substituents.

The value of σ reflects the effect the substituent group has on the free energy of ionization of the substituted benzoic acid. The effect of the substituent is believed to represent a combination of factors. In general, a substituent group can cause a polarization of charge density around the ring through the π system in both the reactant and the product or transition state. Figure 4.3 shows these *resonance effects* for several substituents.

There is also an effect that originates with the bond dipole present between groups of differing electronegativity. Substituents with electronegativity higher than an aromatic carbon will place a net positive charge on the substituted carbon atom, while substituents which are less electronegative will have the opposite effect. These dipoles can perturb the electronic situation in the ring in two ways. The presence of the charge separation in the molecule will influence the energy associated with the development of a second center of charge elsewhere in the molecule. This is simply a through space electrostatic interaction and is called a *field effect.* Depending on the particular charge developing at the reacting site, a substituent can either favor or disfavor the reaction. The field effect is illustrated in Fig. 4.4. A second mode of interaction between the bond dipole and the reaction site is by transmittal through the bonds by a successive polarization, as illustrated in Fig. 4.5. This is called the *inductive effect.* The experimental and theoretical results which are presently available indicate that field effects, the through space mechanism, outweigh inductive effects and are the primary means of transmission of the electrostatic effect of polar substituents.[17]

The Hammett equation in the form Eq. (4.14) or Eq. (4.15) is free of complications due to steric effects, since it is applied only to *meta* and *para* substituents. The geometry of the benzene ring ensures that groups in these positions cannot interact sterically with the site of reaction. Tables of σ values for many substituents have been collected; some are shown in Table 4.3. It is clear from the discussion that the σ for any substituent reflects the interaction of the substituent with the reacting site by a

17. M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.* **84**, 3548 (1962); M. J. S. Dewar and A. P. Marchand, *J. Am. Chem. Soc.* **88**, 354 (1966); H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.* **86**, 5188 (1964); C. L. Liotta, W. F. Fisher, G. H. Greene, Jr., and B. L. Joyner, *J. Am. Chem. Soc.* **94**, 4891 (1972); C. F. Wilcox and C. Leung, *J. Am. Chem. Soc.* **90**, 336 (1968).

Table 4.3. Substituent Constants[a]

Substituent Group		σ_m	σ_p	σ^+	σ^-	$\mathscr{F}$	$\mathscr{R}$	σ_I	σ_R^0
Acetamido	CH_3CONH	**0.14**	**0.0**	−0.6	0.47	−0.27			
Acetoxy	CH_3CO_2	0.39	0.31	0.18		0.68	−0.07		
Acetyl	CH_3CO	**0.36**	**0.47**		0.82	0.53	0.20	0.20	0.16
Amino	NH_2	**−0.09**	**−0.30**	−1.3		0.04	−0.68	0.12	−0.50
Bromo	Br	0.37	**0.26**	0.15		0.72	−0.18	0.44	−0.16
t-Butyl	$(CH_3)_3C$	**−0.09**	**−0.15**	−0.26		−0.10	−0.14		
Carbomethoxy	CH_3O_2C	**0.35**	**0.44**		0.74			0.20	0.16
Carboxy	HO_2C	**0.35**	**0.44**		0.73	0.55	0.14		
Chloro	Cl	**0.37**	**0.24**	0.11		0.69	−0.16	0.46	−0.18
Cyano	CN	**0.62**	**0.70**		0.99	0.85	0.18	0.56	0.08
Ethoxy	C_2H_5O	0.1	−0.14	−0.82		0.36	−0.44		
Ethyl	C_2H_5	**−0.08**	**−0.13**	−0.30		−0.07	−0.11		
Fluoro	F	**0.34**	**0.15**	−0.07		0.71	−0.34	0.50	−0.31
Hydrogen	H	**0**	**0**	0	0	0	0	0	0
Hydroxy	OH	0.13	−0.38	−0.92		0.49	−0.64		
Methanesulfonyl	CH_3SO_2	**0.64**	**0.73**		1.05	0.90	0.21	0.60	0.12
Methoxy	CH_3O	**0.10**	−0.12	−0.78		0.41	−0.50	0.27	−0.42
Methyl	CH_3	**−0.06**	**−0.14**	−0.31		−0.05	−0.14	−0.04	−0.13
Nitro	NO_2	**0.71**	**0.81**		1.23	1.11	0.16	0.65	0.15
Phenyl	C_6H_5	**0.05**	**0.05**	−0.18	0.08	0.14	0.09		
Trifluoromethyl	CF_3	**0.46**	**0.53**		0.74	0.63	0.19	0.42	0.08
Trimethylammonio	$(CH_3)_3N^+$	0.99	0.96			1.46	0.0		
Trimethylsilyl	$(CH_3)_3Si$	−0.04	−0.07			−0.05	−0.04		

a. Values of σ_m, σ_p, σ^+, and σ^- from O. Exner in *Correlation Analysis in Chemistry*, N. B. Chapman and J. Shorter (ed.), Plenum Press, New York, 1978, Chap. 10. $\mathscr{F}$ and $\mathscr{R}$ from C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.* **90**, 4328 (1968). Values of σ_I and σ_R^0 from J. Bromilow, R. T. C. Brownlee, V. O. Lopez, and R. W. Taft, *J. Org. Chem.* **44**, 4766 (1979). Values of σ_m and σ_p shown in boldface type are regarded as particularly reliable.

Table 4.4. Reaction Constants[a]

Reaction	ρ
$ArCO_2H \rightleftharpoons ArCO_2^- + H^+$, water	1.00
$ArCO_2H \rightleftharpoons ArCO_2^- + H^+$, EtOH	1.57
$ArCH_2CO_2H \rightleftharpoons ArCH_2CO_2^- + H^+$, water	0.56
$ArCH_2CH_2CO_2H \rightleftharpoons ArCH_2CH_2CO_2^- + H^+$, water	0.24
$ArOH \rightleftharpoons ArO^- + H^+$, water	2.26
$ArNH_3^+ \rightleftharpoons ArNH_2 + H^+$, water	3.19
$ArCH_2NH_3^+ \rightleftharpoons ArCH_2NH_2 + H^+$, water	1.05
$ArCO_2Et + {}^-OH \longrightarrow ArCO_2^- + EtOH$	2.61
$ArCH_2CO_2Et + {}^-OH \longrightarrow ArCH_2CO_2^- + EtOH$	1.00
$ArCH_2Cl + H_2O \longrightarrow ArCH_2OH + HCl$	−1.31
$ArC(Me)_2Cl + H_2O \longrightarrow ArC(Me)_2OH + HCl$	−4.48
$ArNH_2 + PhCOCl \longrightarrow ArNHCOPh + HCl$	−3.21

a. From P. R. Wells, *Linear Free Energy Relationships*, Academic Press, New York, 1968, pp. 12, 13.

combination of resonance and field interactions. Table 4.4 shows a number of ρ values. The ρ value reflects the sensitivity of the reaction to substituent effects. The examples which follow illustrate some of the ways in which the Hammett equation can be used.

Example 4.2. The pK_a of *p*-chlorobenzoic acid is 3.98; that of benzoic acid is 4.19. Calculate σ for *p*-Cl.

$$\sigma = \log \frac{K_{p\text{-Cl}}}{K_H} = \log K_{p\text{-Cl}} - \log K_H$$

$$= -\log K_H - (-\log K_{p\text{-Cl}})$$

$$= pK_{a_H} - pK_{a_{p\text{-Cl}}}$$

$$= 4.19 - 3.98 = 0.21$$

Example 4.3. If the ρ value for alkaline saponification of methyl esters of substituted benzoic acids is 2.38, and the rate constant for saponification of methyl benzoate under the conditions of interest is $2 \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$, calculate the rate constant for hydrolysis of methyl *m*-nitrobenzoate.

$$\log \frac{k_{m\text{-NO}_2}}{k_H} = \sigma_{m\text{-NO}_2}(\rho) = (0.70)(2.38) = 1.69$$

$$\frac{k_{m\text{-NO}_2}}{k_H} = 49$$

$$k_{m\text{-NO}_2} = 98 \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$$

Example 4.4. Using the data in Tables 4.3 and 4.4, calculate how much faster *p*-bromobenzyl chloride will solvolyze in water than *p*-nitrobenzyl chloride.

$$\log \frac{k_{p\text{-Br}}}{k_H} = (-1.31)(0.23), \qquad \log \frac{k_{p\text{-NO}_2}}{k_H} = (-1.31)(0.78)$$

$$\log k_{Br} - \log k_H = -0.30, \qquad \log k_{NO_2} - \log k_H = -1.02$$

$$\log k_{Br} + 0.30 = \log k_H, \qquad \log k_{NO_2} + 1.02 = \log k_H$$

$$\log k_{Br} + 0.30 = \log k_{NO_2} + 1.02$$

$$\log k_{Br} - \log k_{NO_2} = 0.72$$

$$\log \frac{k_{Br}}{k_{NO_2}} = 0.72$$

$$\frac{k_{Br}}{k_{NO_2}} = 5.25$$

Given in Table 4.3 in addition to the σ_m and σ_p values used with the classical Hammett equation are σ^+ and σ^-. These are substituent constant sets which reflect a recognition of the variable extent of resonance participation in different reactions. The σ^+ values reflect direct resonance interaction between an electron donor substituent and a cationic reaction center, whereas the σ^- set pertains to reactions in which there is a direct resonance interaction with an electron-rich reaction site.

Direct resonance interaction with a cationic center

Direct resonance interaction with an anionic center

The underlying physical basis for the failure of Hammet σ_m and σ_p values to correlate certain reactions is that all substituent interactions are some mixture of resonance and field effects. When direct resonance interaction is possible, the extent of resonance effects increases and the substituent constants appropriate to a more "normal" mixture of resonance and field effects then fail. There have been many attempts to develop sets of σ values which take into account extra resonance interactions.

One approach is to correct for added resonance interaction. The approach taken is a modification of the Hammett equation known as the Yukawa–Tsuno equation.[18]

$$\log \frac{K}{K_0} = \rho\sigma + \rho(r)(\sigma^+ - \sigma) \tag{4.17}$$

18. Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Japan* **32**, 971 (1959); J. Hine, *J. Am. Chem. Soc.* **82**, 4877 (1960); B. M. Wepster, *J. Am. Chem. Soc.* **95**, 102 (1973).

The additional parameter r is adjusted from reaction to reaction; it reflects the extent of the additional resonance contribution. A large r corresponds to a reaction with a large resonance contribution, whereas when r goes to zero, the equation is identical with the original Hammett equation. This treatment does not attempt to separate resonance and field effects completely, since some resonance effects are included in the normal σ, but instead corrects for increased resonance interaction. When there is direct conjugation with an electron-rich center, an equation analogous to Eq. (4.17) can be employed, but σ^-, a substituent constant appropriate for such situations, is used instead of σ^+.

Another approach to treatment of the variability of resonance and field effects was devised by Swain and Lupton.[19] Their approach is to decompose substituent effects into field and resonance contributions. The substituent constant could then be expressed as a variable sum of the field and resonance contributions.

$$\sigma = f\mathcal{F} + r\mathcal{R}$$

This treatment requires that *meta*- and *para*-substituted compounds be treated as separate reaction series, since they will have different relative resonance and field contributions, with resonance contributions being stronger in the *para* series. Since the Swain–Lupton treatment uses four parameters, f, r, $\mathcal{F}$, and $\mathcal{R}$ in place of the single σ of the Hammett equation, the mathematical manipulations are somewhat more complex but they can be easily handled by appropriate calculator programs. The result of such a calculation is a "best-fit" correlation in terms of the parameters f, r, $\mathcal{F}$, and $\mathcal{R}$. The computation also gives a "per cent resonance" by comparing the magnitudes of f and r. The numerical reliability of both the substituent constants $\mathcal{F}$ and $\mathcal{R}$ and the question of whether complete separation of resonance and field effects is achieved is a matter of some dispute.[19] The results are nevertheless qualitatively useful in comparing the properties of individual substituent groups and in gaining at least a rough comparison of the interplay of resonance and field effects in different reactions.

The most elaborate and accurate treatment of the problem has been the development of a series of substituent constants σ_R, chosen to reflect the resonance contribution of the substituent under various structural circumstances. This substituent constant is then used in conjunction with a second one σ_I, which reflects the inductive (or field) component of the overall substituent effect. The modified equation, called a *dual-substituent-parameter equation*, takes the form

$$\log \frac{K}{K_0} \quad \text{or} \quad \log \frac{k}{k_0} = \sigma_I \rho_I + \sigma_R \rho_R$$

19. C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.* **90**, 4328 (1968); C. G. Swain, S. H. Unger, N. R. Rosenquist, and M. S. Swain, *J. Am. Chem. Soc.* **105**, 492 (1983); see also S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.* **10**, 1 (1973); J. Shorter, in *Correlation Analysis in Chemistry*, Plenum Press, New York, 1978; M. Charton, *Prog. Phys. Org. Chem.* **13**, 119 (1981); C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.* **16**, 1207 (1973).

where ρ_I and ρ_R are the reaction constants which reflect the sensitivity of the system to inductive (and field) effects and to resonance effects.[20] The ρ_I values have been defined from studies in aliphatic systems where no resonance component should be present. By properly scaling the σ_I values with σ values from aromatic systems it is possible to assign values such that

$$\sigma = \sigma_I + \sigma_R$$

Careful statistical analysis of much data has shown that no single σ_R is applicable to the entire range of reaction types that are encountered. This again reflects the fact that the resonance component is variable and responds to the nature of the particular reaction or structural property. Therefore a series of σ_R values has been established, each of which applies to various reaction types ranging from cases involving direct conjugation with electron-deficient reaction centers to direct conjugation with strong π donors. We will discuss only one of these, σ_R^0, which applies in situations of minimal perturbation of the aromatic ring by any charge development. The σ_R^0 values given in Table 4.3 are based on the use of C-13 chemical shifts as a measure of the sum of resonance and inductive effects. The chemical shift data of substituted benzenes were analyzed to provide the best correlation with the dual-substituent-parameter equation. In nonpolar solvents, which presumably best reflect the inherent molecular properties, $\rho_I = 3.35$ for cyclohexane and 3.37 for carbon tetrachloride. The values of ρ_R are 20.55 for cyclohexane and 20.72 in carbon tetrachloride. The relative magnitudes of ρ_I and ρ_R indicate that the C-13 chemical shift is more responsive to the resonance character of the substituent than to the inductive character.

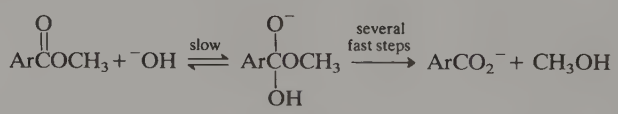
The various dual-substituent-parameter equations can usually improve the correlation of data which give poor correlation with the single-parameter Hammett equation. It must be recognized that in part this is a direct consequence of the introduction of additional parameters. To derive solid mechanistic insight on the basis of such improved correlation requires a critical appraisal of the results and statistical analysis may be required. The details of critical statistical evaluation of free energy correlations have been extensively discussed but this topic is beyond the scope of our coverage.

It should be recognized that all of these approaches to linear free-energy relationships have been developed on an empirical basis. The reaction constants, substituent constants, and whatever other parameters are involved are specified by the definitions employed in the treatment of the correlation. We might ask if insight into substituent effects can be obtained from an alternative perspective, that is, by analyzing the structural perturbations of substituents by molecular orbital calculations. This is a fundamentally challenging task because of the uncertainty of the structure at the transition state and also a large task because of the large number

20. S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.* **10**, 1 (1973).

of calculations which would be involved. One recent approach to the problem calculated the stabilizing (or destabilizing) effect of substituents as a positive charge (electrophile) or negative charge (nucleophile) approaches a benzene ring.[21] The effect of the substituents, as reflected in the calculated stabilization or destabilization, was parallel to that which is indicated by linear free-energy correlations. The amino, hydroxy, and fluoro groups were found to provide extra stabilization to the approach of electrophile in comparison with other substituents where a strong resonance interaction would not be expected. For the approach of a negative charge these substituents were destabilizing and extra stabilization was seen for groups such as nitro, cyano, and sulfonyl. While such calculations have been applied to only a limited number of substituents, it appears that MO calculations lead to the same patterns as are seen with empirical correlations and are in agreement with the idea that substituent effects in aromatic compounds are a combination of field effects and resonance effects.

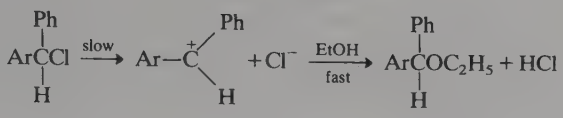
Let us now consider how linear free-energy relationships can provide insight into reaction mechanisms. The choice of benzoic acid ionizations as the reference reaction for the Hammett equation leads to $\sigma > 0$ for electron-withdrawing groups and $\sigma < 0$ for electron-releasing groups, since electron-withdrawing groups favor the ionization of the acid, whereas electron-releasing groups have the opposite effect. Further inspection of the Hammett equation shows that ρ will be positive for reactions that are favored by electron-withdrawing groups and negative for reactions favored by electron-releasing groups. If the rate of a reaction shows a satisfactory correlation with the Hammett equation and a positive ρ value is obtained, the attainment of the transition state in the rate-determining step must be favored in some way by electron-withdrawing substituents. In Example 4.3 (p. 184), the ρ value for saponification of methyl benzoates was given as +2.38, indicating that electron-withdrawing groups facilitate the reaction. This conclusion is in agreement with the saponification mechanism outlined below. The tetrahedral intermediate is negatively charged, and its formation will therefore be favored by substituents that can aid in dispersing negative charge.



The solvolysis of diarylmethyl chlorides in ethanol shows a ρ value of -5.0, indicating that electron-releasing groups strongly facilitate the reaction. This ρ value provides support for a mechanism involving ionization of the halides in the rate-determining step of the reaction. Electron-releasing groups can facilitate the ioniz-

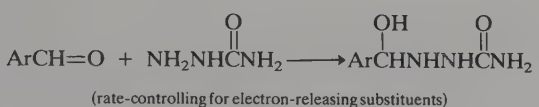
21. E. R. Vorpagel, E. Streitwieser, Jr., and S. D. Alexandratos, *J. Am. Chem. Soc.* **103**, 3777 (1981); for a general review of theoretical treatment of substituent effects, see A. Pross and L. Radom, *Prog. Phys. Org. Chem.* **13**, 1 (1980).

ation by favorable interaction with the electron-deficient carbon that develops in the ionization step.

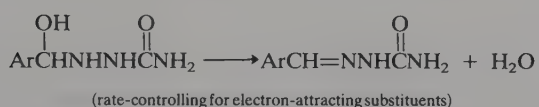


The magnitude of ρ, whether positive or negative, also provides information about the rate-determining step of a reaction. A large ρ indicates high sensitivity to substituent groups and implies that there is a large redistribution of charge involved in forming the transition state.

Not all reactions can be suitably fitted by the Hammett equation or one of its variants. There can be several reasons for this. There may be a change in the mechanism as substituents vary. In a multistep reaction, for example, one step may be rate determining in the region of electron-withdrawing substituents, but a different step may become rate limiting as the substituents become electron releasing. The rate of semicarbazone formation of benzaldehydes shows a nonlinear Hammett plot with ρ of about 3.5 for electron-releasing groups, but ρ near -0.25 for electron-withdrawing groups.[22] The change in ρ is believed to be the result of a change in the rate-controlling step.



(rate-controlling for electron-releasing substituents)



(rate-controlling for electron-attracting substituents)

Any change that modifies the steric situation at the transition state will also result in failure of a linear correlation. It is for this reason that *ortho* substituents have not been included in the usual treatments of the Hammett equation. A change of substitution at the *ortho* position not only causes an electronic perturbation at the reaction center, but also exerts a steric effect.

The substituent constants recorded in Table 4.3 (p. 183), provide valuable insight into the electronic nature of the various functional groups. By comparing σ with σ^+, one gains a qualitative impression of the ability of a given substituent to act as an electron-donating group by resonance. The $\mathcal{F}$ values are indicators of the field and inductive characteristics of the various substituent groups. It should be noted that some groups such as OMe and NH_2 that have strong electron-releasing capabilities by resonance are electron-withdrawing when only field and inductive effects are considered. If $\mathcal{F}$ and $\mathcal{R}$ are taken as the best indicators of field versus resonance interactions, the substituent groups can be classified as in Table 4.5. By comparing σ_m values with σ_p values (Table 4.3), one can see that field effects usually

22. D. S. Noyce, A. T. Bottini, and S. G. Smith, *J. Org. Chem.* **23**, 752 (1958).

Table 4.5. Classification of Substituent Groups

Resonance: Electron-releasing ($-M$)	Electron-releasing ($-M$)		Electron-withdrawing ($+M$)
Field: Electron-releasing ($-I$)	Electron-withdrawing ($+I$)		Electron-withdrawing ($+I$)
Me	AcNH	Br	OH	Ac
Et	AcO	Cl	MeO	CN
$(Me)_3C$	NH_2	F	EtO	NO_2
			Ph	CF_3
				$(Me)_3N^+$

dominate with *meta* substituents, while resonance effects are more important for the *para* substituents. This relationship is reasonable in terms of structure, since the *p* substituents are more favorably situated for resonance interaction.

There is a system for designating the electron-releasing or -attracting properties of substituents. This system is illustrated in Table 4.5. The symbols $+M$ and $-M$ have been used to designate resonance interactions (the M comes from "mesomerism," a synonym of resonance) and the symbols $+I$ and $-I$ for combined field and inductive effects (I for inductive because the importance of field effects was recognized only belatedly).

The development of linear free-energy relationships in purely aliphatic molecules is complicated because steric and conformational effects require more consideration than in the case of *meta* and *para* aromatic substituents. A number of successful treatments of aliphatic systems have been accomplished by separating polar effects from steric effects. We will not discuss these methods here but there are several general reviews which can be consulted for information about this area.[23]

4.4. Isotope Effects

A special type of substituent effect that has proved very valuable in the study of reaction mechanisms is the replacement of an atom by one of its isotopes. Isotopic substitution has most often involved replacing protium by deuterium (or, less often, tritium), but the principle is applicable to nuclei other than hydrogen. The quantita-

23. J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York, 1962, pp. 95–98; P. R. Wells, *Linear Free Energy Relationships*, Academic Press, New York, 1968, pp. 35–44; M. Charton, *Prog. Phys. Org. Chem.* **10**, 81 (1973).

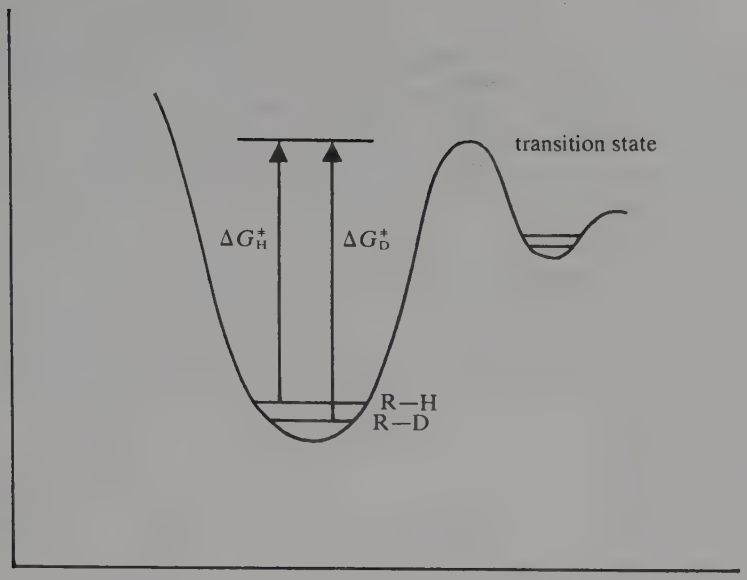


Fig. 4.6. Differing zero-point energies of protium- and deuterium-substituted molecules as the cause of primary kinetic isotope effects.

tive differences are largest, however, for hydrogen. Isotopic substitution has no effect on the qualitative chemical reactivity of the substrate, but it often has an easily measured effect on the rate at which reaction occurs. Let us consider how this modification of the rate arises. Initially, the discussion will concern primary kinetic isotope effects, i.e., reactions in which a bond to the isotopically substituted atom is broken in the rate-determining step. We will use C–H bonds as the specific topic of discussion but the same concepts apply for bonds between other elements.

Any C–H bond is undergoing characteristic vibrations and these vibrations impart some energy to the molecule which is known as the *zero-point* energy. The energy associated with these vibrations is related to the mass of the vibrating atoms. Because of the greater mass of deuterium, the vibrations associated with a C–D bond contribute less to the zero-point energy of a molecule than does the corresponding C–H bond. For this reason, substitution of protium by deuterium lowers the zero-point energy of a molecule. For a reaction involving cleavage of a bond to hydrogen (or deuterium), a vibrational degree of freedom in the normal molecule is converted to a translational degree of freedom on passing through the transition state. Since the energy difference due to the zero-point energy of this vibration disappears at the transition state, its energy is the same for the protonated and deuterated reactants. The lower zero-point energy of the bond to deuterium is therefore reflected in a higher activation energy for bond cleavage and a lower rate of reaction. This is illustrated in Fig. 4.6.

Just how large the rate difference is depends on the nature of the transition state. The maximum effect occurs when the hydrogen being transferred is bound

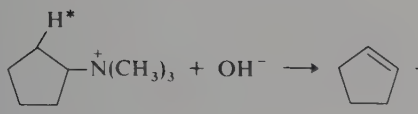
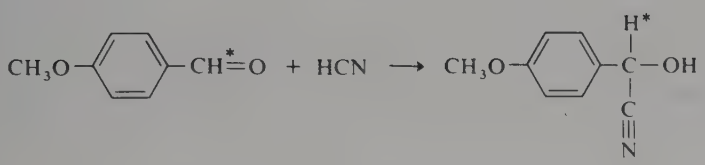
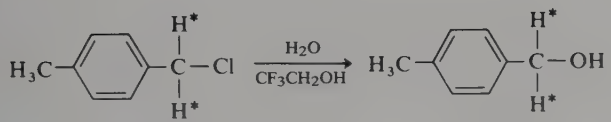
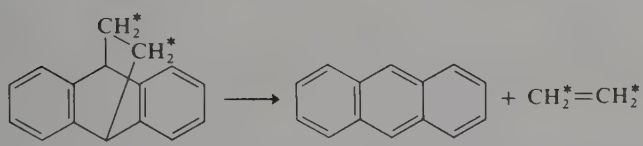
about equally to two other atoms in the transition state. The calculated maximum for the isotope effect k_H/k_D involving C–H bonds is about 7 at room temperature, and becomes lower at higher temperatures.[24] When bond breaking is more or less than half complete at the transition state, the value is less and can be close to 1 if the transition state is very reactant-like or very product-like. Primary isotope effects can provide two very useful pieces of information about a reaction mechanism: First, the existence of a substantial isotope effect—i.e., if k_H/k_D is 2 or more—is strong evidence that the bond to the substituted hydrogen atom is being broken in the transition state of the rate-determining step. Second, the magnitude of the isotope effect provides a qualitative indication of where the transition state lies with regard to product and reactant. A relatively low primary isotope effect implies that the bond to hydrogen is either little or nearly completely broken at the transition state, i.e., the transition state must occur quite close to reactant or product. An isotope effect near the theoretical maximum is good evidence that the transition state involves strong bonding of the hydrogen to both its old and its new bonding partner.

Isotope effects may be observed even when the substituted hydrogen atom is not directly involved in the reaction. Such effects are smaller than primary kinetic isotope effects, usually in the range $k_H/k_D = 0.7–1.5$, and are called secondary kinetic isotope effects. Such isotope effects may be normal ($k_H/k_D > 1$) or inverse ($k_H/k_D < 1$), and are specified as α, β, etc., depending on whether isotopic substitution of deuterium for protium is on the carbon atom undergoing covalency change or farther down the chain. Secondary isotope effects result from either a tightening or loosening of C–H bonds as the transition state is attained. The strength of bonds change because of hybridization changes or other modifications of the structure which may occur. α-Secondary isotope effects, for example, arise from changes in the degree of coordination at carbon in going from the ground state to the transition state. If sp^3-hybridized carbon in the ground state is converted to sp^2-hybridized carbon in the transition state, a hydrogen bonded to that carbon will experience a decreased resistance to C–H bending. The freeing of the bending mode will be greater for a C–H bond than for a C–D bond because its amplitude of vibration is larger (a C–H bond is 0.009 A longer than a C–D bond), and the result will be a normal secondary isotope effect.[25] Reactions that typify such behavior include solvolysis reactions of alkyl halides proceeding through unimolecular rate-determining ionization to a carbonium ion. Entry 5 in Scheme 4.2 gives $k_H/k_D = 1.30$ for the S_N1 hydrolysis of *p*-methylbenzyl chloride.

The reverse will be true when coordination increases in going to the transition state. The bending mode will experience increased restriction, and an inverse isotope effect will be observed. Entry 4 exemplifies such a reaction. Cyanohydrin formation leads to tetracoordinate (sp^3) from tricoordinate carbon (sp^2), and the ratio $k_H/k_D = 0.73$.

24. K. B. Wiberg, *Chem. Rev.* **55**, 713 (1955); F. H. Westheimer, *Chem. Rev.* **61**, 265 (1961).
25. A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Am. Chem. Soc.* **80**, 2326 (1958).

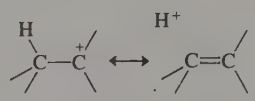
Scheme 4.2. Some Representative Kinetic Isotope Effects

	Reaction	k_H/k_D (°C)[a]
1[b]	$PhCH_2{-}H^* + Br\cdot \longrightarrow Ph{-}CH_2\cdot + H^*{-}Br$	4.6 (77)
2[c]	$(CH_3)_2C(H^*){-}C(=O){-}C(H^*)(CH_3)_2 + OH^- \longrightarrow (CH_3)_2C(H^*){-}C(O^-)=C(CH_3)_2$	6.1 (25)
3[d]		4.0 (191)
4[e]		0.73 (25)
5[f]		1.30 (25)
6[g]		1.37 (50)

a. Temperature of measurement is indicated in parenthesis.
b. K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.* **80**, 3033 (1958).
c. R. A. Lynch, S. P. Vincenti, Y. T. Lin, L. D. Smucker, and S. C. Subba Rao, *J. Am. Chem. Soc.* **94**, 8351 (1972).
d. W. H. Saunders, Jr., and T. A. Ashe, *J. Am. Chem. Soc.* **91**, 4473 (1969).
e. L. do Amaral, H. G. Bull, and E. H. Cordes, *J. Am. Chem. Soc.* **94**, 7579 (1972).
f. V. J. Shiner, Jr., M. W. Rapp, and H. R. Pinnick, Jr., *J. Am. Chem. Soc.* **92**, 232 (1970).
g. M. Taagepera and E. R. Thornton, *J. Am. Chem. Soc.* **94**, 1168 (1972).

Secondary isotope effects are also observed with isotopic substitution at carbon atoms relatively remote from the reaction site. These effects have been studied especially thoroughly in the case of nucleophilic substitution reactions. When deuterium is introduced at the carbon two atoms down the chain (the β carbon), significant secondary isotope effects are observed when carbonium ions are formed as intermediates. It is generally believed that hyperconjugative interactions with the carbonium ion site are responsible for the changes in vibrational force constants

that result in the isotope effect.[26] A reduction in C–H bond strength results from interaction of the electrons from C–H bonds with the developing p orbital of the carbonium ion (hyperconjugation). The fact that normal isotope effects are observed for β substitution of deuterium is consistent with weakening of the C–H bond in the carbonium ion.



Detailed analysis of isotope effects reveals that there are many other factors which contribute to the overall effect in addition to the dominant ones which have been mentioned here. For that reason, it is not possible to quantitatively predict isotope effects. Furthermore, there is not a sharp numerical division between primary and secondary effects, especially in the range between 1 and 2, and either primary or secondary isotope effects may be responsible for low numbers. For that reason, isotope effects are usually used in conjunction with other criteria in the description of reaction mechanisms.[27]

4.5. Characterization of Reaction Intermediates

Identification of the intermediates in a multistep reaction is a major objective of studies of reaction mechanisms. When the nature of each intermediate is fairly well understood, a great deal is known about the reaction mechanism. The amount of an intermediate present in a reacting system at any instant of time will depend on the rates of the steps by which it is formed and the rate of its subsequent reaction. A qualitative indication of the relationship between intermediate concentration and kinetics can be gained by considering a simple two-step mechanism:

$$\text{reactants} \xrightarrow{k_1} \text{intermediate} \xrightarrow{k_2} \text{products}$$

In some reactions, the situation $k_1 > k_2$ exists. Under these conditions the concentration of the intermediate builds up and it then goes more slowly on to product. The possibility of isolating, or at least observing, the intermediate then exists. Any true intermediate isolated from an interrupted reaction, when resubjected to the reaction conditions, will give the expected reaction products. If both k_1 and k_2 are large,

26. For example, V. J. Shiner, W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Am. Chem. Soc.* **90**, 418 (1968); J. G. Jewett and R. P. Dunlap, *J. Am. Chem. Soc.* **90**, 809 (1968); A. J. Kresge and R. J. Preto, *J. Am. Chem. Soc.* **89**, 5510 (1967); G. J. Karabatsos, G. C. Sonnichsen, C. G. Papaioannou, S. E. Scheppele, and R. L. Shone, *J. Am. Chem. Soc.* **89**, 463 (1967).
27. For more complete discussion of isotope effects, see W. H. Saunders, in *Investigation of Rates and Mechanisms of Reactions*, E. S. Lewis (ed), *Techniques of Chemistry Series*, Vol. VI, Part 1, John Wiley and Sons, New York, 1974, pp. 211–255.

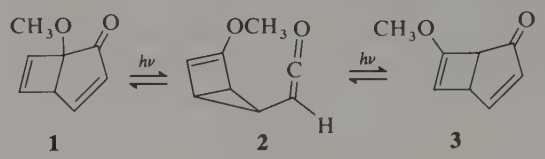
the reaction may proceed too rapidly to permit isolation of the intermediate. Kinetic and spectral studies in such cases should reveal, however, the existence of two distinct phases for the overall reaction: first, formation of intermediate, with a rate constant k_1; second, its subsequent disappearance, characterized by rate constant k_2.

If the rate of formation of an intermediate only slightly exceeds its rate of disappearance, only a small concentration of the intermediate exists at any instant. It is sometimes possible to interrupt a reaction—for example, by rapidly lowering the temperature or by removing a catalyst. If the intermediate is sufficiently stable it may then be isolated, even though the amount would be small. In other cases the intermediates can be "trapped": A compound that is expected to react specifically with the intermediate is added to the reaction system. If trapping is efficient, the intermediate is then diverted from its normal course, and evidence for the existence of the intermediate can be obtained by establishing the identity of the trapped product.

Often, it is more practical to study intermediates present in low concentration by instrumental methods. The theory and practice of instrumental methods of detection of intermediates will be discussed here only very briefly. Instrumental techniques have become very important in the study of reaction mechanisms, however, and examples of the use of instrumental techniques in the detection of intermediates will be found throughout the remainder of the book. Ultraviolet-visible (UV-VIS) spectroscopy has the longest history in this regard, especially if visual detection of colored intermediates is included in this heading. Modern instruments can rapidly scan the UV-VIS region of the spectrum, and the resulting spectra may provide definitive evidence of formation and subsequent disappearance of an intermediate species. The limitation imposed on the use of UV-VIS spectral data is that the intermediate being sought must have appreciable absorption in the range 220–700 nm. The transitions that occur in this region involve promotion of an electron from an orbital that is filled in the ground state to a state in which the electron occupies a normally empty orbital. In organic molecules, electrons associated with σ-bonds undergo these transitions only at higher energies and require light of shorter wavelength than the range of standard UV-VIS spectrometers. Unsaturated molecules, especially molecules with two or more multiple bonds in a conjugated arrangement, normally absorb strongly. The amount of an intermediate that can be detected depends on how strongly it absorbs relative to interfering absorption by other components of the reaction system. In favorable cases, concentrations as low as 10^{-5} M may be detected.

Infrared (IR) spectrometers measure absorption of energy by the excitation of molecular vibrations, including stretching, bending, and twisting of various parts of the molecule. Most organic molecules show a large number of bands in the IR spectrum, and it is usually not possible to assign all the bands to a specific molecular vibration. Nearly all organic functional groups, however, have one or more regions of characteristic absorption. If it is suspected that a particular functional group is present in an intermediate species, examination of the changes of the spectrum in the characteristic regions of absorption of this functional group may permit detection.

An example of IR detection of intermediates can be drawn from a study of the photochemical conversion of **1** to **3**. It was suspected that the ketene **2** might be an



1 **2** **3**

intermediate.[28] Ketenes characteristically absorb near 2100–2130 cm^{-1}. When the photolysis was carried out and the IR spectrum of the solution monitored, it was found that a band appeared at 2118 cm^{-1}, grew, and then decreased as photolysis proceeded. The observation of this characteristic absorption constitutes good evidence for a ketene intermediate. As with UV-VIS spectroscopy, the amount of intermediate that can be detected depends on both the intensity of the absorption band and the presence of interfering bands. Infrared spectroscopy has been usefully combined with the technique of *matrix isolation* to study the identity and detailed structure of highly reactive and unstable intermediates. In this technique the intermediate is trapped in a solid inert gas matrix at very low temperature. Since each molecule is surrounded by inert gas atoms, there is no possibility for intermolecular reactions and the rates of intramolecular reactions are slowed by the low temperature. This method is convenient for reactions which can be conducted in the gas phase in such a way that the intermediates can immediately be condensed with inert gas. Matrix isolation is also a useful way of looking at intermediates generated in photochemical reactions.

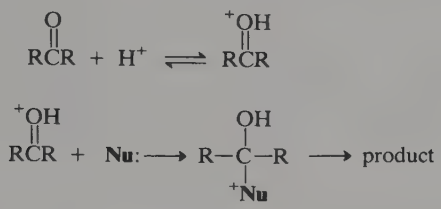
All other spectroscopic methods are equally applicable in principle to the detection of reaction intermediates. Proton magnetic resonance spectroscopy has been very widely used. Here, the excitation involves reorienting the nuclear spin of protons with respect to a magnetic field. The method's principal limitation has been sensitivity. Up until about 1970, a 1–2 mol % concentration was required for detection, but instrumentation advances in nuclear magnetic resonance spectroscopy have increased the potential sensitivity of NMR instruments by several orders of magnitude. With the appropriate instruments, other nuclei that give NMR signals, especially ^{13}C, ^{19}F, and ^{31}P, can also be studied.

Free radicals and other intermediates with unpaired electrons can be detected in extremely low concentration by electron paramagnetic resonance (EPR). This technique involves measurement of the energy absorbed to reorient an electron's spin in a magnetic field. EPR is not only extremely sensitive, but also very specific. Diamagnetic molecules present in the solution give no signals, and the possibility for interference is therefore greatly decreased. The method is, however, strictly limited to reactions involving paramagnetic (unpaired electron) intermediates. In some cases, concentration of radical species in the 10^{-6}–10^{-8} M range can be detected.

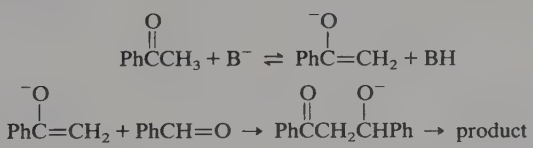
28. O. L. Chapman and J. D. Lassila, *J. Am. Chem. Soc.* **90**, 2449 (1968).

4.6. Catalysis

A detailed understanding of reaction mechanisms requires knowledge of the role catalysts play in the reaction. Catalysts cannot affect the position of equilibrium of a reaction. They function by increasing the rate of one or more steps in a reaction mechanism by opening a reaction path having a lower activation energy. The most general family of catalytic processes are those that involve transfer of a proton. Many reactions involving neutral substrates are strongly catalyzed by proton donors (acids) or proton acceptors (bases). Catalysis occurs when the conjugate base or conjugate acid of the substrate is a more reactive molecule than the neutral species. For example, reactions involving nucleophilic attack at carbonyl groups are often accelerated by acids. This type of catalysis occurs because the conjugate acid of the carbonyl compound is much more electrophilic than the neutral molecule.



Many important organic reactions involve nucleophilic carbon species (carbanions). The properties of carbanions will be discussed in detail in Chapter 7 and in Part B, Chapters 1 and 2. Most C–H bonds are very weakly acidic and have no tendency to form carbanions spontaneously. Reactions that involve carbanion species are therefore often carried out by reaction of a neutral organic molecule with an electrophile in the presence of a base. Under these conditions, a nucleophilic carbon species is formed when the base abstracts a proton from the neutral organic molecule. Base-catalyzed condensation of carbonyl compounds is an example. The reaction of acetophenone and benzaldehyde which was considered in Section 4.2, for example, requires base catalysis to proceed and the kinetics show that the rate is proportional to the catalyst concentration. This is because the neutral acetophenone molecule is not nucleophilic and does not react with benzaldehyde. The enolate formed by deprotonation is much more nucleophilic and the reaction proceeds through this intermediate.



The role that acid and base catalysts play in reactions can be quantitatively studied by kinetic techniques. It is possible to recognize several distinct types of catalysis by acids and bases. The term *specific acid catalysis* is used when the reaction rate is dependent on the *equilibrium* for protonation of the reactant. This type of catalysis is independent of the concentration of the various proton donors present

in solution, and is governed instead by the *hydrogen ion concentration.* For example, in an aqueous buffer system, the rate of the reaction would be a function of the pH, but not of the concentration or identity of the acidic and basic species that constitute the buffer system. The kinetic expression for any such reaction will indicate specific acid catalysis by a term in the concentration of hydrogen ion and the absence of a term for any other acidic contribution to the catalysis. When other species in addition to protonated solvent contribute to the total reaction catalysis, the reaction is said to be subject to *general acid catalysis.* The kinetic expression for such a reaction will reveal contributions to the total rate involving all effective proton donors which are present in the system. The term *specific base catalysis* refers analogously to systems in which only the conjugate base of the solvent appears as a basic catalysts in the rate expression and the term *general base catalysis* to systems in which species in addition to the conjugate base of the solvent function as the proton acceptor.

Specific acid catalysis:

$$\text{rate} = k[H^+][X][Y], \qquad \text{where } [X][Y] = \text{concentration of the reactants}$$

General acid catalysis:

$$\text{rate} = k_1[H^+][X][Y] + k_2[HA^1][X][Y] + k_3[HA^2][X][Y],$$

where HA^1, HA^2 . . . are all kinetically significant proton donors

The experimental detection of general acid catalysis is done by rate measurements at constant pH but changing buffer concentration. Since under these circumstances $[H^+]$ is constant but the concentration of the weak acid component(s) of the buffer (HA^1, HA^2, etc.) change, the observation of a change in rate is evidence of general acid catalysis. If the rate remains constant, the reaction exhibits specific acid catalysis. Similarly, general base catalyzed reactions will show a dependence of the rate on the concentration and identity of the basic constituents of the buffer system.

Specific acid catalysis is observed when reaction proceeds only through a protonated intermediate which is in equilibrium with its corresponding conjugate base. Since the position of this equilibrium is a function of the concentration of protons, only a single-acid catalysis term appears in the kinetic expression. For example, in a two-step reaction scheme involving rate-determining reaction of one reagent with the conjugate acid of a second reagent, the kinetic expression will be as follows:

$$B + H^+ \overset{\text{fast}}{\rightleftharpoons} BH^+$$

$$BH^+ + C \xrightarrow{\text{slow}} B\text{–}C + H^+$$

$$\begin{aligned} \text{rate} &= k_2[BH^+][C] = k_2[C]K[B][H^+] \\ &= k_{obs}[H^+][B][C] \end{aligned}$$

Several situations can lead to the operation of general acid catalysis. General acid catalysis can occur as a result of hydrogen bonding between the reactant R and a proton donor D–H:

$$\text{D—H} + \text{R} \rightleftharpoons \text{D—H} \cdots \text{R}$$

$$\text{D—H} \cdots \text{R} + \text{B} \xrightarrow{\text{slow}} \text{D-H} + \text{R-B}$$

Under these circumstances, a distinct contribution to the rate from each potential hydrogen-bonding species can be anticipated. General acid catalysis is also observed when a rate-determining proton transfer can occur from acids other than protonated solvent:

$$\text{R} + \text{HA} \xrightarrow{\text{slow}} {}^{+}\text{RH} + \text{A}^{-}$$

$${}^{+}\text{RH} \rightarrow \text{product}$$

Each acid HA will then make a contribution to the overall rate of reaction.

A kinetic expression equivalent to general acid catalysis also occurs if a prior equilibrium between reactants and the acid is followed by a rate-controlling deprotonation. Each distinct conjugate base will appear in the overall rate expression:

$$\text{R} + \text{HA} \rightleftharpoons {}^{+}\text{RH} + \text{A}^{-}$$

$${}^{+}\text{RH} + \text{A}^{-} \xrightarrow{\text{slow}} \text{product} + \text{HA}$$

Notice that specific acid catalysis describes a situation where the reactant is in equilibrium with regard to proton transfer and proton transfer is not rate determining. On the other hand each case that leads to general acid catalysis involves proton transfer in the rate-determining step. Because of these differences, the study of rates as a function of pH and buffer concentration can frequently permit conclusions about the nature of the proton transfer step in acid-catalyzed processes.

As might have been expected intuitively, there is a relationship between the effectiveness of a general acid catalyst and its ability to act as a proton donor, as measured by its acid dissociation constant. This relationship can be expressed as in the following equation and is known as the *Brønsted catalysis law*:

$$\log k_{\text{cat}} = \alpha \log K_a + b \tag{4.19}$$

An analogous equation holds for catalysis by bases. This equation requires that the free energies of activation for the catalytic step for a series of acids be directly proportional to the free energy of dissociation for the same series of acids. The proportionality constant α is an indication of the sensitivity of the catalytic step to structural changes, relative to the effect of the same structural changes on acid dissociation. It is often found that a single proportionality constant α is restricted to only closely related structural types of acids, and that α values of different magnitude are revealed by general acids of other structural types.

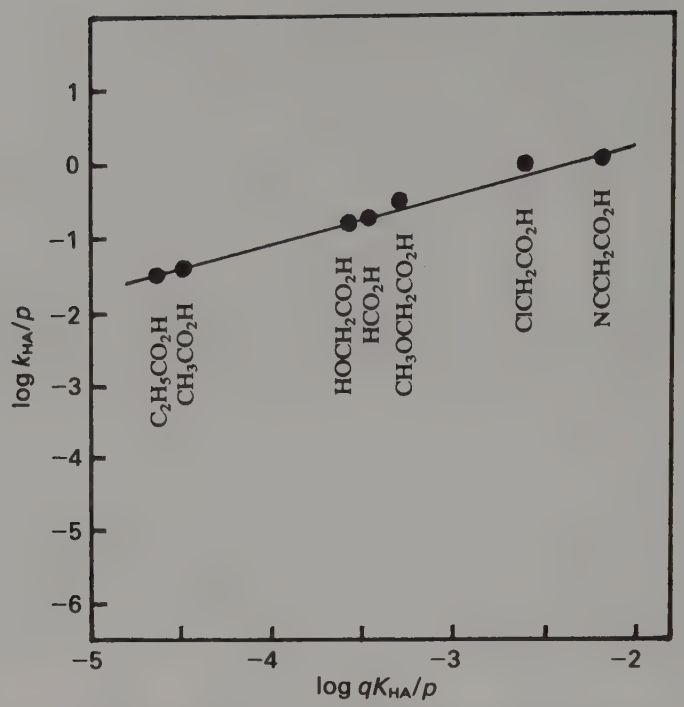
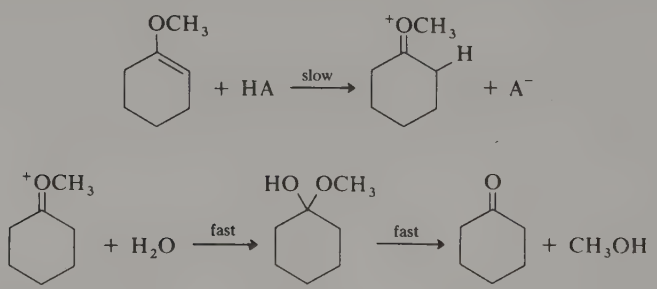


Fig. 4.7. Brønsted relation for the hydrolysis of methyl cyclohexenyl ether. (Adapted from Ref. 29 by permission of the American Chemical Society.)

Figure 4.7 is a plot of a Brønsted relationship for hydrolysis of an enol ether. The plot shows that the effectiveness of the various carboxylic acids as catalysts is related to their dissociation constants. In this particular case, the constant α is 0.70[29]:



It has been suggested that the value of α might convey some information about transition state structure, with the value of α approaching unity as the degree of

29. A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Am. Chem. Soc.* **93**, 413 (1971).

proton transfer becomes more complete. This relationship must be used with caution, however, for there are clearly exceptions.[30]

The details of proton-transfer processes can also be probed by examining *solvent isotope effects*, e.g., by comparing the rates of a reaction in H_2O versus D_2O. The solvent isotope effect can be either normal or inverse, depending on the nature of the proton-transfer process in the reaction mechanism. D_3O^+ is a stronger acid than H_3O^+. As a result, substrates in D_2O solution are somewhat more extensively protonated than in H_2O at identical acid concentration. A reaction that involves a rapid equilibrium protonation will normally proceed faster in D_2O than in H_2O, because of the higher concentration of the protonated reactant. On the other hand, if proton transfer is part of the rate-determining step, the reaction will be faster in H_2O than in D_2O. This is a result of a normal primary isotope effect of the type considered in Section 4.4.

The interpretation of solvent isotope effects can be complicated by the large number of secondary isotope effects that can conceivably operate when it is the solvent molecule that is the site of isotopic substitution. The quantitative evaluation of solvent isotope effects is a very difficult problem. The relationship between the magnitude of the solvent isotope effect and the occurrence of equilibrium protonation as opposed to rate-limiting proton transfer is sufficiently general to be of significant value in mechanistic studies. As with nearly all mechanistic criteria, however, there are circumstances that permit exceptions, so corroborating evidence obtained from other types of studies is always desirable.

Many organic reactions require acid concentrations considerably higher than can be accurately measured on the pH scale, which applies only to relatively dilute aqueous solutions. It is not difficult to prepare solutions in which the formal proton concentration is 10 *M* or more, but these formal concentrations are not a suitable measure of the *activity* of protons in such solutions. For this reason, it has been necessary to develop *acidity functions* that measure the acidity of concentrated acidic solutions. The activity of the hydrogen ion (proton) can be related to the extent of protonation of a series of bases by the equilibrium expression for the protonation reaction,

$$B + H^+ \rightleftharpoons {}^+BH$$

$$K = \frac{(a_{BH}^+)}{(a_{H^+})(a_B)} = \frac{[{}^+BH]\gamma_{BH}^+}{a_{H^+} + [B]\gamma_B}$$

where γ = the activity coefficient for the base and its conjugate acid. A common measure of acidity is referred to as h_0 and it is defined by measuring the extent of protonation of a series of bases for which K has been measured. The relative

30. A. J. Kresge, *J. Am. Chem. Soc.* **92**, 3210 (1970); R. A. Marcus, *J. Am. Chem. Soc.* **91**, 7224 (1969); F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.* **94**, 3907 (1972).

concentration of the base and its conjugate acid then defines h_0 for any particular acidic solution.

$$h_0 = \frac{[^+\text{BH}]\gamma^+_{\text{BH}}}{K[\text{B}]\gamma_{\text{B}}}$$

The quantity H_0 defined as $-\log h_0$ is commonly tabulated and it corresponds to the "pH" of very concentrated acidic solutions.

The problem of determining K independent of measurement of H_0 is the principal problem faced in establishing the H_0 scale for a series of acidic solutions. What is done is to measure K for some base in aqueous solution where $H_0 \approx$ pH. This base can then be used to find the H_0 of a somewhat more acidic solution. The K of a second, somewhat weaker base is then determined in the more acidic solution. This second base can then be used to measure H_0 of a still more acidic solution. By this process of using an overlapping series of bases, the H_0 of successively more acidic solutions can be referenced to the original aqueous measurement.[31] The assumption involved in this procedure is that the ratio of the activity coefficients for the series of bases and the series of cation does not change from solvent to solvent, that is,

$$\frac{\gamma^+_{\text{B}_1\text{H}}}{\gamma_{B_1}} = \frac{\gamma^+_{\text{B}_2\text{H}}}{\gamma_{\text{B}_2}} = \frac{\gamma^+_{\text{B}_3\text{H}}}{\gamma_{\text{B}_3}} \ldots \text{etc.}$$

Not unexpectedly, this procedure reveals some dependence on the particular type of base used, so no absolute H_0 scale can be established. Nevertheless, this technique provides a very useful measure of the relative hydrogen ion activity of concentrated acid solutions that can be used in the study of reactions which proceed only under such high acid concentrations. Table 4.6 gives H_0 values for some water–sulfuric acid mixtures.

4.7. Solvent Effects

Most organic reactions are done in solution, and it is therefore important to recognize some of the general ways in which solvent can affect the course and rates of reaction. Some of the more common organic solvents can be roughly classified as in Table 4.7 on the basis of their structure and dielectric constants. There are important differences between *protic* solvents—solvents that contain relatively mobile protons such as those bonded to oxygen, nitrogen, or sulfur—and *aprotic* solvents. Similarly, *polar* solvents, those that have high dielectric constants, have effects on reaction rates different from those of *nonpolar* solvent media.

31. For reviews of acidity functions, see E. M. Arnett, *Prog. Phys. Org. Chem.* **1**, 223 (1963) and C. H. Rochester, *Acidity Functions*, Academic Press, New York, 1970.

Table 4.6. H_0 as a Function of Composition of Aqueous Sulfuric Acid[a]

$\%H_2SO_4$	H_0	$\%H_2SO_4$	H_0
5	0.24	55	−3.91
10	−0.31	60	−4.46
15	−0.66	65	−5.04
20	−1.01	70	−5.80
25	−1.37	75	−6.56
30	−1.72	80	−7.34
35	−2.06	85	−8.14
40	−2.41	90	−8.92
45	−2.85	95	−9.85
50	−3.38	98	−10.41

a. From M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.* **85**, 878 (1963).

When discussing solvent effects, it is important to distinguish between the macroscopic and the microscopic properties of the solvent. Macroscopic properties refer to properties of the bulk solvent. An important macroscopic property is the dielectric constant which is a measure of the ability of the bulk material to increase the capacitance of a condenser, relative to a vacuum. In terms of structure, the dielectric constant is a function of both the permanent dipole moment of the molecule and its *polarizability*. Polarizability refers to the ease of distortion of the molecule's electrons. Dielectric constants increase with dipole moment and with polarizability. An important property of solvent molecules with regard to reactions is the way in which the solvent molecules interact with the changes in charge

Table 4.7. Dielectric Constants of Some Common Solvents [a]

Aprotic solvents				Protic solvents	
Nonpolar		Polar			
Hexane	1.9	Pyridine	12	Acetic acid	6.1
Carbon tetrachloride	2.2	Acetone	21	Trifluoroacetic acid	8.6
Dioxane	2.2	Hexamethyl phosphoramide	30	*tert*-Butyl alcohol	12.5
Benzene	2.3	Nitromethane	36	Ammonia	(22)
Diethyl ether	4.3	Dimethylformamide	37	Ethanol	24.5
Chloroform	4.8	Acetonitrile	38	Methanol	32.7
Tetrahydrofuran	7.6	Dimethyl sulfoxide	47	Water	78

a. Dielectric constant data are abstracted from the compilation of solvent properties in J. A. Riddick and W. B. Bunger (eds.), *Organic Solvents*, Vol. II of *Techniques of Organic Chemistry*, Third Edition, Wiley–Interscience, New York, 1970.

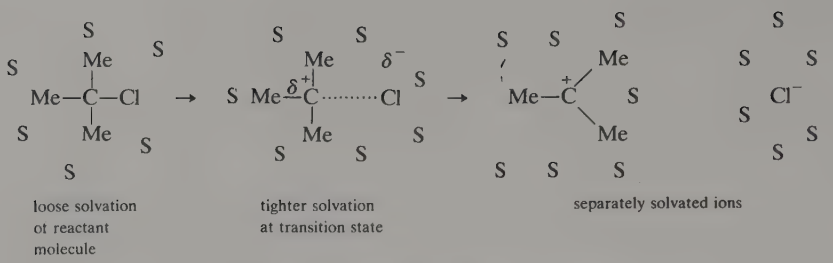


Fig. 4.8. Solvation changes during ionization of *t*-butyl chloride.

distribution that accompany many reactions. The dielectric constant of a solvent has an important effect on its ability to accommodate separation of charge. It is not the only factor, however, since, being a macroscopic property, it conveys little information about the ability of the solvent molecules to interact with solute molecules at close range. These close-range, or microscopic, properties will have a pronounced effect on the energy of the reactants and transition states, and thus on the energy of activation of reactions.

Let us consider how solvent might affect the solvolysis of *t*-butyl chloride. Much evidence, which will be discussed in detail in Chapter 5, indicates that the rate-determining step is ionization of the carbon–chlorine bond. The transition state must reflect some of the charge separation that occurs in the ionization. Figure 4.8 gives a schematic interpretation of the solvation changes which would take place during the ionization of *t*-butyl chloride in a polar solvent S.

The bulk dielectric constant may be a poor indicator of the ability of solvent molecules to facilitate the charge separation in the transition state. The fact that the carbon and chlorine atoms remain partially bonded at the transition state prevents the solvent molecules from actually intervening between the developing charged centers. Instead, the solvent molecules must stabilize the charge by acting on the periphery of the activated complex. This interaction will depend on the detailed structure of the activated complex and the solvent molecule. The ability of a number of solvents to stabilize the transition state of *t*-butyl chloride solvolysis has been measured by comparing the rate of ionization relative to a reference solvent. An 80:20 ethanol–water mixture has been chosen as the reference solvent. The Y value of other solvents is defined by the equation

$$\log \frac{k_{\text{solvent}}}{k_{80\%\text{ ethanol}}} = Y$$

The Y values determined in this way are empirical measures of the solvent's ability to accommodate formation of the dipolar solvolysis transition state. Table 4.8 lists the Y values for some alcohol–water mixtures and for some other solvent systems.[32]

32. For a discussion of other quantitative measures of solvent ionizing power, see C. Reichardt, *Angew. Chem., Int. Ed. Engl.* **18**, 98 (1979).

Table 4.8. *Y* Values for Some Solvent Systems[a]

Ethanol–Water		Methanol–Water			
(% ethanol)	*Y*	(% methanol)	*Y*	Other solvents	*Y*
100	−2.03	100	−1.09	Acetic acid	−1.64
80	0.0	80	0.38	Formic acid	2.05
50	1.65	50	1.97	*t*-Butyl alcohol	−3.2
20	3.05	10	3.28	90% Acetone–Water	−1.85
0	3.49			90% Dioxane–Water	−2.03

a. From A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.* **78**, 2770 (1956).

Notice that among the solvents listed there is a spread of more than 10^6 in the measured rate of solvolysis between *tert*-butyl alcohol and water. This large range of reaction rates demonstrates how important solvent effects can be.

Solvents that fall in the nonpolar aprotic class are not effective at stabilizing the development of charge separation. These molecules have small dipole moments and do not have hydrogen atoms capable of forming hydrogen bonds. Reactions that involve charge separation in the transition state therefore usually proceed much more slowly in solvents of this class than in protic or highly polar aprotic solvents. The reverse is true of reactions in which charge separation is neutralized in the transition state. In such reactions, an increase in solvent polarity stabilizes the reactants with respect to the transition state and slows the reaction rate. Arguing along these lines, the broad relationships outlined in Scheme 4.3 are deduced.

The electrostatic solvent effects discussed in the preceding paragraphs are not the only possible modes of interaction of solvent with reactants and transition states. Specific structural effects may cause either the reactants or transition states to be particularly strongly solvated. Figure 4.9 shows how such solvation effects can affect the relative energies of the ground state and the transition state and cause rate variations from solvent to solvent. Unfortunately, no general theory for correlating or predicting such specific solvation effects has been developed to date.

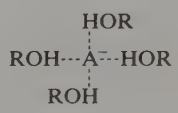
Since a solvent may affect the rates of two competing reactions in different ways, a change in solvent may strongly modify the composition of a product mixture formed from competing reaction paths. Many such instances have been encountered by trial-and-error procedures in synthetic chemistry. An important example of a microscopic solvent effect is the enhanced nucleophilicity of many anions in polar aprotic solvents, relative to their nucleophilicity in hydroxylic solvents of comparable polarity.[33] In hydroxylic solvents, anions are usually strongly solvated by hydrogen

33. A. J. Parker, *Q. Rev. Chem. Soc.* **16**, 163 (1962); C. D. Ritchie, in *Solute-Solvent Interactions*, J. F. Coetzee and C. D. Ritchie (eds.), Marcel Dekker, New York, 1969, Chap. 4.

Scheme 4.3. Effect of Solvent Polarity on Reactions of Various Charge Types

$A^- + B^+ \longrightarrow \overset{\delta-}{A}\cdots\overset{\delta+}{B} \longrightarrow A\text{–}B$	Favored by nonpolar solvent
$A\text{–}B \longrightarrow \overset{\delta-}{A}\cdots\overset{\delta+}{B} \longrightarrow A^- + B^+$	Favored by polar solvent
$A + B \longrightarrow A\cdots B \longrightarrow A\text{–}B$	Relatively insensitive to solvent polarity
$A\text{–}B^+ \longrightarrow \overset{\delta+}{A}\cdots\overset{\delta+}{B} \longrightarrow A + B^+$	Slightly favored by polar solvent
$A^+ + B \longrightarrow \overset{\delta+}{A}\cdots\overset{\delta+}{B} \longrightarrow A\text{–}B^+$	Slightly favored by nonpolar solvent

bonding. This is particularly true for anions that have a high concentration of charge on oxygen or nitrogen:



In aprotic solvents no hydrogen atoms capable of hydrogen bonding are present, and this type of solvation cannot occur. As a result, the electrons of the anion are more easily available for reaction. The polarity of the aprotic solvent involved is important, because if the solvent has a low dielectric constant, solubility is likely to be very low and dissolved ionic compounds are likely to be present as ion pairs and larger aggregates. Reactivity is then greatly reduced because of the strong attractive force

exerted by the cation. Energy must be expended against this attractive force if the

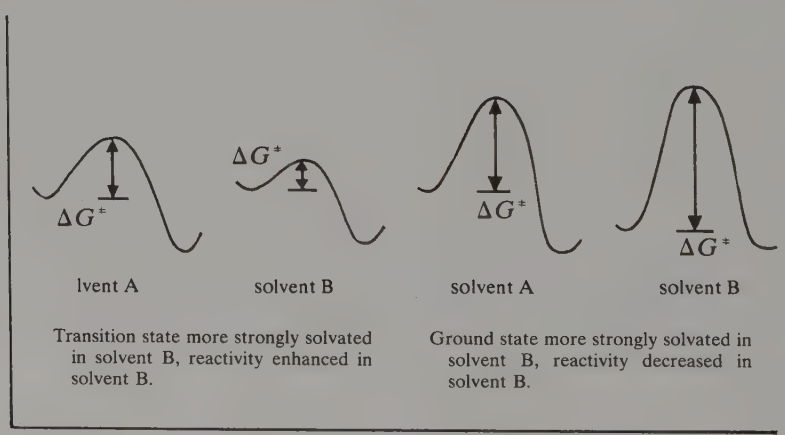
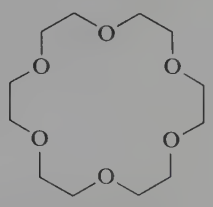


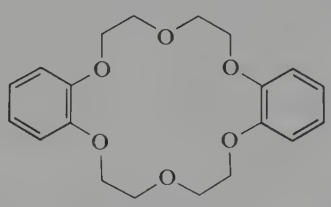
Fig. 4.9. Potential energy diagrams showing effect of preferential solvation of (a) transition state and (b) ground state on the activation energy.

anion is to act as a nucleophile, and reactivity is therefore reduced. Furthermore, most ionic compounds have limited solubility in nonpolar aprotic solvents. The realization that nucleophilicity of anions can be strongly enhanced in polar aprotic solvents has led to important improvements of several types of synthetic processes that involve nucleophilic substitutions or additions.

Particularly striking examples of the effect of specific solvation can be cited from the study of the "crown ethers." These are macrocyclic polyethers that have the property of specifically solvating cations such as Na^+ and K^+.



18-crown-6



dibenzo-18-crown-6

For example, in the presence of 18-crown-6, potassium fluoride is soluble in benzene or acetonitrile and acts as a reactive nucleophile:

$$CH_3(CH_2)_7Br + KF \xrightarrow[\text{benzene}]{\text{18-crown-6}} CH_3(CH_2)_7F \qquad \text{Ref. 34}$$

In the absence of the polyether, potassium fluoride is insoluble in such solvents and unreactive toward alkyl halides. Similar enhancement of the reactivity and solubility of other salts are also observed in the presence of crown ethers. The solubility and reactivity enhancement result because the ionic compound is dissociated to a tightly complexed cation and a "naked" anion. Figure 4.10 shows the tight coordination which can be achieved with a typical crown ether molecule. The complexed cation, since it is surrounded by the organic polyether, has high solubility in the organic solvent. The cation is shielded from solvation in the ion–crown ether complex, which is lipophilic in character. To maintain electroneutrality the anion is also transported into the organic solvent. Since nonpolar solvents do not strongly solvate the anion, the anion can act as a nucleophile without expenditure of energy for desolvation and is therefore much more reactive than the same anion would be in a solvated environment.

A closely related solvent effect can be achieved by use of *phase transfer catalysis.* These catalysts are salts in which one of the ions has large nonpolar substituent groups which confer good solubility in nonpolar solvents. The most familiar examples are quaternary ammonium and quaternary phosphonium salts with several long-chain alkyl substituents. In a two-phase solvent system consisting of water and a nonpolar organic solvent containing a salt, there will be virtually no ions present

34. C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.* **96**, 2250 (1974).

in the organic solvent since ions are much more strongly solvated by water. Addition of a phase transfer catalyst to such a system changes this. Because of the substantial solubility of the highly alkylated cations in the organic layer, anions are extracted from the aqueous phase into the organic phase to maintain electrical neutrality. These anions are only weakly solvated in the organic solvent and so are highly nucleophilic. Section 3.2 of Chapter 3, Part B illustrates some of the useful preparative applications of phase transfer catalysis.

It should always be borne in mind that solvent effects can modify the energy of *both* the reactants and the transition states. It is the *difference* in the two solvation effects that governs the relative reaction rates. Thus, although it is common to see solvent effects discussed solely in terms of reactant solvation or transition state solvation, such discussion is usually an over-simplification. One case that illustrates this is the hydrolysis of esters by hydroxide ion. The reaction is found to be much more rapid in dimethyl sulfoxide–water than in ethanol–water. Reactant solvation can be separated from transition-state solvation by calorimetric measurement of the heat of solution of the reactants in each solvent system. The data in Fig. 4.11 compare the energies of the reactants and transition states for ethyl acetate and

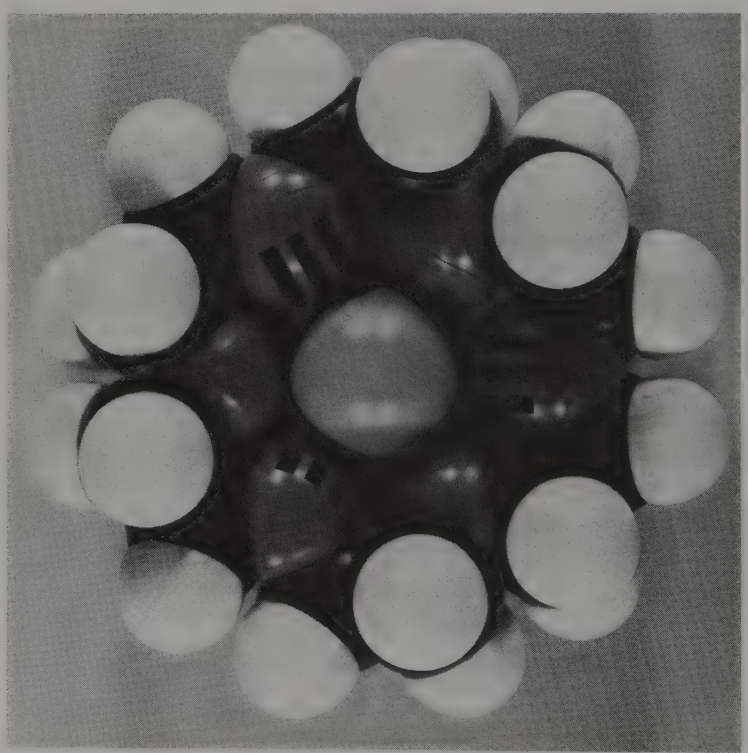


Fig. 4.10. Space-filling molecular model depicting a metal cation complexed by 18-crown-6.

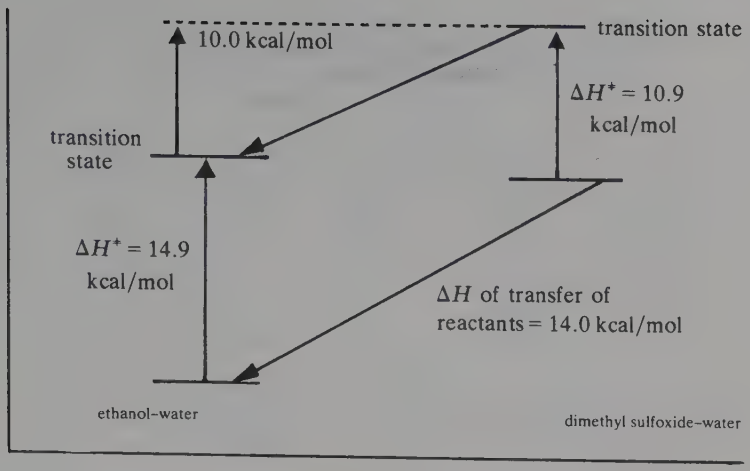


Fig. 4.11. Reactant and transition state solvation in the reaction of ethyl acetate with hydroxide ion. [From P. Haberfield, J. Friedman, and M. F. Pinkston, *J. Am. Chem. Soc.* **94**, 71 (1972).]

hydroxide ion in aqueous ethanol versus aqueous dimethyl sulfoxide. It can be seen that both the reactants and the transition state are more strongly solvated in the ethanol–water medium. The difference in reaction rate, however, comes from the fact that this difference in solvation energies is greater for the small hydroxide ion than for the larger anionic species present at the transition state.

$$^{-}OH + CH_3\overset{\overset{O}{\|}}{C}OC_2H_5 \rightleftharpoons H_3C-\overset{\overset{O^{\delta-}}{\vdots\|}}{\underset{\underset{HO^{\delta-}}{\vdots}}{C}}-OC_2H_5 \longrightarrow \text{product}$$

4.8. Structural Effects in the Gas Phase

Having considered how solvents can strongly affect the properties of molecules in solution, let us consider some of the special features that arise in the gas phase where solvation effects are totally eliminated. Although the majority of organic preparative reactions and mechanistic studies have been conducted in solution, some important reactions are carried out in the gas phase. Also, since current theoretical calculations do not usually treat solvent effects, experimental data from the gas phase are important for comparison with theoretical results. Frequently quite different trends, particularly in substituent effects, are seen when systems in the gas phase are compared to similar systems in solution.

Table 4.9. Comparison of Substituent Contribution to Phenol Ionization in the Gas Phase and Solution[a]

X	Substituent increment in kcal/mol[b]			
	ΔG_{gas}	ΔH_{gas}	ΔG_{H_2O}	ΔH_{H_2O}
m-CH_3	+0.4	+0.4	+0.18	+0.02
p-CH_3	+1.3	+1.3	+0.42	+0.02
m-Cl	−7.9	−7.9	−1.2	−0.3
p-Cl	−6.6	−6.6	−0.7	−0.2
p-NO_2	−25.8	−25.8	−3.8	−0.8

a. Data are from T. B. McMahon and P. Kebarle, *J. Am. Chem. Soc.* **99**, 2222 (1977).
b. The tabulated increments give the change in ΔG and ΔH resulting from replacement of hydrogen by the substituent specified.

It is possible to measure equilibrium constants and heats of reaction in the gas phase by using mass spectrometers of special configuration.[35] With proton transfer reactions, for example, the equilibrium constant can be determined by measuring the ratio of two reactant species competing for a proton. Table 4.9 compares ΔH_{gas} with ΔH_{aq} for a series of phenol ionizations.

A key point to recognize is that the relative magnitude of the substituent effects is much larger in the gas phase. In general terms, this can be explained on the basis that all solvent effects have now been removed. Whereas a phenolate anion in the aqueous phase receives considerable stabilization, particularly by hydrogen bonding, there is no such stabilization in the gas phase. This solvent stabilization would be rather similar in absolute terms for all phenolates in solution and when this stabilization disappears the relative importance of the internal substituent stabilization is magnified. Viewed another way, the strong solvation has a "leveling effect" on the substituent stabilization. The importance of the solvation can also be judged by noting that entropy factors make the largest contribution to ΔG for the reaction in solution. This reflects the extensive solvent organization which accompanies solvation.[36]

35. Discussion of the techniques for gas phase equilibrium measurements can be found in *Ion Cyclotron Resonance Spectrometry*, T. A. Lehman and M. M. Bursey, Wiley–Interscience, New York, 1976 and in *Gas Phase Ion Chemistry*, Vols. 1 and 2, M. T. Bowers (ed.), Academic Press, New York, 1979.
36. L. P. Fernandez and L. G. Hepler, *J. Am. Chem. Soc.* **81**, 1783 (1959); C. L. Liotta, H. P. Hopkins, Jr., and P. T. Kasudia, *J. Am. Chem. Soc.* **96**, 7153 (1974).

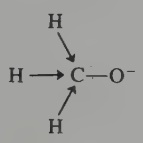
Table 4.10. Acidities of Simple Alcohols in Solution[a]

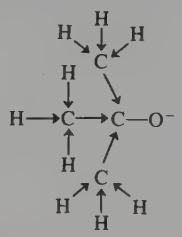
	pK_a	
	H_2O	DMSO
H_2O	15.7	31.4
CH_3OH	15.5	29.0
C_2H_5OH	15.9	29.8
$(CH_3)_2CHOH$		30.2
$(CH_3)_3COH$		32.2

a. Data are from W. N. Olmstead, Z. Margolin, and F. G. Bordwell, *J. Org. Chem.* **45**, 3295 (1980).

Another area of gas phase substituent effects which has attracted considerable interest is the acidity of the simple alcohols methanol, ethanol, isopropyl alcohol, and *t*-butyl alcohol relative to one another and to water. In the gas phase the order is *t*-BuOH > EtOH > MeOH ≫ H_2O.[37] This is different from results in solution. Table 4.10 gives pK_a values for water and DMSO.

These changes in relative acidity can be traced to the great importance of solvation effects in solution. In the gas phase, any substituent effect on the position of equilibrium can be analyzed in terms of its stabilizing or destabilizing effect on the anion. Two factors have been considered to be of primary importance. Inductive effects arising from the H–C bond dipoles should be destabilizing since they tend to increase electron density at the carbon bonded to the oxide substituent. This is the





electron-donating effect of methyl substituents seen in many contexts. However, this effect is evidently not the dominant one since it would lead to a gas phase acidity order opposite from that which is observed. The dominant effect is believed to be induced polarization. That is, the methyl substituents are better able to undergo local electronic distortions to accommodate the negative charge than are the smaller hydrogen atoms.[38] An additional factor is the fact that water has a considerably stronger O–H bond than the alcohols and this accounts for its lowered gas phase

37. J. I. Brauman and L. K. Blair, *J. Am. Chem. Soc.* **92**, 5986 (1970); J. E. Bartmess and R. T. McIver, Jr., *Gas Phase Ion Chemistry*, Vol. 2, M. T. Bowers (ed.), Academic Press, New York, 1979.
38. R. W. Taft, M. Taagepera, J. L. M. Abboud, J. F. Wolf, D. J. DeFrees, W. J. Hehre, J. E. Bartmess, and R. T. McIver, *J. Am. Chem. Soc.* **100**, 7765 (1978).

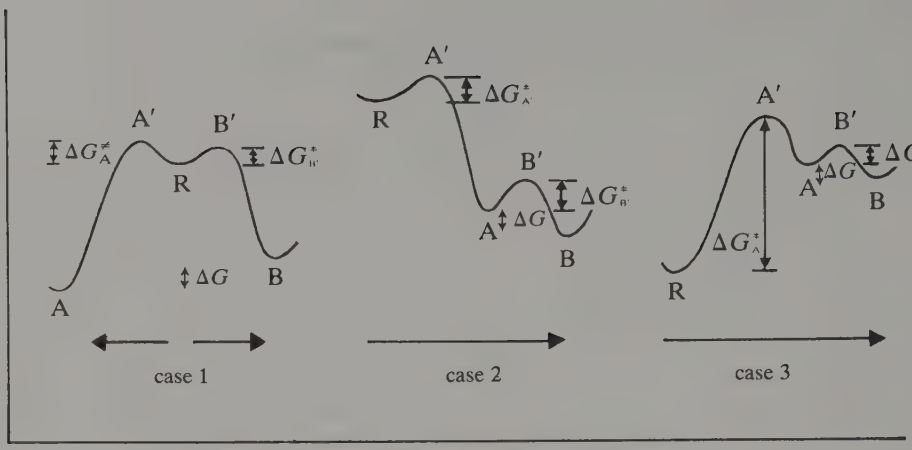


Fig. 4.12. Kinetic versus thermodynamic control.

acidity. In solution these factors are swamped by solvation effects and the order MeOH > EtOH > *i*-PrOH > *t*-BuOH is attributed primarily to increasing steric resistance to solvation of the alkoxide ion with increasing substitution.[39] The acidity of water with respect to alcohols is found to be quite solvent dependent and this apparently reflects a very high sensitivity to solvation of the small hydroxide ion.

4.9. Basic Mechanistic Concepts: Kinetic Versus Thermodynamic Control, Hammond's Postulate, the Curtin–Hammett Principle

Use of two-dimensional potential energy diagrams can provide insight into the important general ideas listed in the heading of this section. There are many organic reactions in which the energy requirements for more than one reaction pathway are rather similar. If a reactant system can simultaneously follow two or more competing paths, it is important to be able to analyze the factors that may permit one reaction path to dominate.

Product composition may be governed by the equilibrium thermodynamics of the system. When this is true, the product composition is said to be governed by *thermodynamic control.* Alternatively, product composition may be governed by competing rates of formation of the possible products. This is called *kinetic control.*

Let us consider cases 1–3 in Fig. 4.12. In case 1, $\Delta G^{\ddagger}$'s for formation of transition states A′ and B′ from the reactant R are much less than $\Delta G^{\ddagger}$'s for

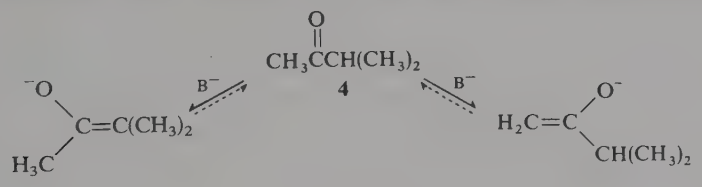
39. W. N. Olmstead, Z. Margolin, and F. G. Bordwell, *J. Org. Chem.* **45**, 3295 (1980).

formation of A′ and B′ from A and B, respectively. If the latter free energies are sufficiently large that the competitively formed products B and A do not return to R, it follows that the ratio of A to B at the end of the reaction will depend not on their relative stabilities, but on their relative rates of formation. The energy diagram in case 1, then, describes a system in which the product composition is governed by *kinetic control.*

In case 2, the lowest $\Delta G^{\ddagger}$ is that for formation of A′ from R. But, the $\Delta G^{\ddagger}$ for formation of B′ from A is not much larger. System 2 might be governed by either kinetic or thermodynamic factors. Conversion of R to A will be only slightly faster than conversion of A to B. If the reaction conditions are carefully adjusted it will be possible for A to accumulate and not proceed to B. Under such conditions A will be the dominant product and the reaction can be said to be under *kinetic control.* Under slightly more energetic conditions A will be transformed to B. When this occurs B will be the dominant product since it is more stable. Since under this second set of conditions A and B are separated by an attainable energy barrier, they will equilibrate. The composition of the product mixture will then be governed by the relative thermodynamic stability of A and B. The product composition will reflect *thermodynamic control.*

In case 3, the barrier separating A and B is very small relative to that for formation of A′ from R. A and B will equilibrate rapidly relative to formation of A. The product mixture will reflect thermodynamic control, with the ratio of A and B being determined by the relative stabilities of the products rather than their rates of formation.

The idea of kinetic versus thermodynamic control can be illustrated by discussing briefly the formation of enolate anions from unsymmetrical ketones. A more complete discussion of this topic is given in Chapter 7 and in Part B, Chapter 1. Any ketone with more than one type of α proton can give rise to at least two enolates when a proton is abstracted. Many studies, particularly those of House,[40] have shown that the ratio of the two possible enolates depends on the reaction conditions. If the base is strong and sterically bulky and there are no hydroxylic solvents present, enolate **6** is the major product. When equilibrium is established between **5** and **6** by making enolate formation reversible by using a hydroxylic solvent, however, the dominant enolate is **5**. Thus, **6** is the product of *kinetic control.* The structural reason



5 6

40. H. O. House, *Rec. Chem. Prog.* **28**, 99 (1967).

is the unhindered nature of the methyl protons, which allows removal of this hydrogen to occur more rapidly than at the competing position. Enolate **5** is the product of *thermodynamic control.* It is more stable than **6**, and when equilibrium is established, it is the dominant species. The greater stability of **5** is associated with its being more highly substituted at the sp^2-carbon atoms and therefore more stable, just as internal olefins are more stable than terminal olefins (Chapter 1).

Because of the crucial role played by the energy of the transition state in determining the rates of chemical reactions, information about the structure of transition states would greatly facilitate the understanding of reaction mechanisms. Since transition states have only transitory existence, however, it has not been possible to make experimental measurements that would directly provide information about the structure of activated complexes. Hammond[41] has discussed the circumstances under which it is valid to relate transition state structure to intermediates, reactants, and products. His statement concerning transition state structure has become known among organic chemists as *Hammond's postulate.* Discussing individual steps in a reaction mechanism, Hammond's postulate states "if two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve only a small reorganization of molecular structure."

This statement can best be discussed with reference to potential energy diagrams. Case 1 in Fig. 4.13 represents a highly exothermic step with a low activation energy. It follows from Hammond's postulate that in this step, the transition state will structurally resemble the reactant since they are relatively close in energy and therefore interconverted by a relatively small structural change. Case 2 describes a step in which the energy of the transition state is a good deal higher than the energy of either the reactant or the product. Neither the reactant nor the product is therefore likely to be a very good model for the transition state. Case 3 illustrates a highly endothermic step. The product of this step is the best model for the transition state in this instance.

The significance of the concept incorporated in Hammond's postulate is that it permits one, in certain instances, to discuss transition-state structure in terms of the intermediates, reactants, or products in a multistep reaction sequence. It is important to remember, however, that the postulate also clearly indicates that in many steps, such comparison is inappropriate, since the transition state may resemble neither reactant nor product very closely. In order to meaningfully discuss transition states as resembling other states in the reaction sequence, it is necessary to have evidence that the energy contents of the two species are similar.

The case of electrophilic aromatic substitution can illustrate a situation in which it is useful to discuss transition state structure in terms of the structure of an intermediate. The *ortho–para*- and *meta*-directing effects of aromatic substituents

41. G. S. Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955).

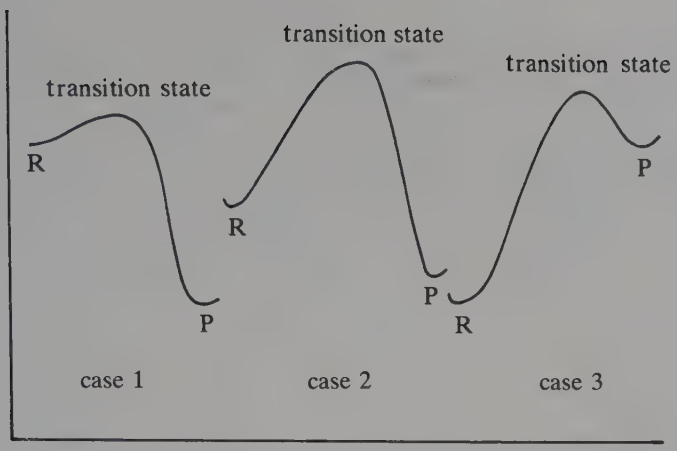
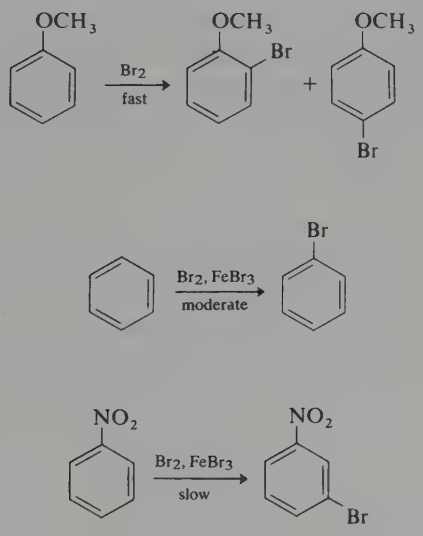


Fig. 4.13. Some typical potential energy diagrams that illustrate the application of Hammond's postulate.

were among the first structure–reactivity relationships to be developed by organic chemists. Certain functional groups were found to activate the aromatic ring and to direct the entering electrophile to the *ortho* and *para* positions, while others were deactivating and led to substitution at the *meta* position. The bromination of anisole, benzene, and nitrobenzene can serve as cases for discussion.



Since the discussion involves rate phenomena, it is inadequate to direct attention only to the reactants. It is the $\Delta G^{\ddagger}$ values for the bromination reactions at the various positions that hold the key to the explanation of the rate and directing effects. But to

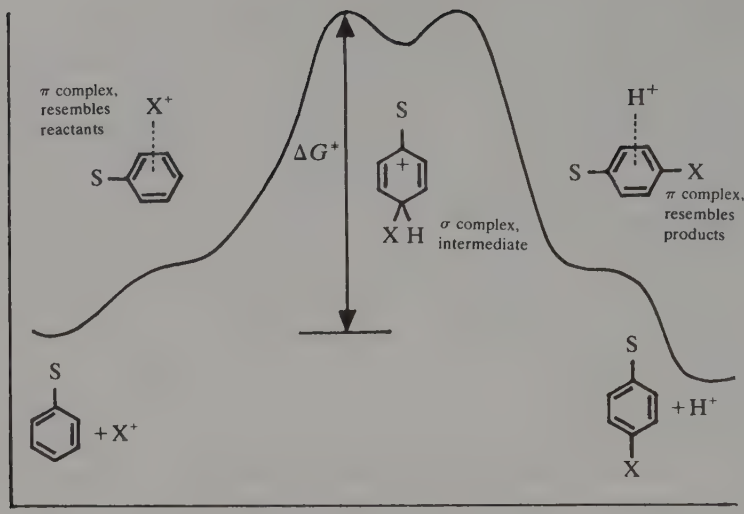


Fig. 4.14. Potential energy diagram for electrophilic aromatic substitution.

discuss $\Delta G^{\ddagger}$ satisfactorily, one must know something about the reaction mechanism. Electrophilic aromatic substitution will be discussed in detail in Chapter 9. Evidence presented there will indicate that electrophilic aromatic substitutions usually involve a distinct intermediate and two less well-defined species. The potential energy diagram in Fig. 4.14 is believed to be a good representation of the energy changes that occur during the process of bromination.[42] By application of the Hammond postulate, it can be concluded that the rate-determining step in the reaction involves formation of a transition state closely resembling the intermediate σ complex. It is then legitimate to discuss the structure of the transition state as closely resembling the intermediate.

Under the conditions of the aromatic brominations being considered, the product composition is governed by kinetic rather than thermodynamic factors. Equilibrium between the *ortho*, *meta*, and *para* bromination products is not established. The isomer ratio is then governed by the relative magnitude of the free energies of activation—$\Delta G_o^{\ddagger}$, $\Delta G_m^{\ddagger}$, and $\Delta G_p^{\ddagger}$ for the *ortho*, *meta*, and *para* transition states, respectively. In Fig. 4.15, a qualitative comparison of these $\Delta G^{\ddagger}$ values is made.

42. R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, Amsterdam, 1965, Chap. 11; P. B. D. DeLaMare and J. H. Ridd, *Aromatic Substitution*, Academic Press, New York, 1959, Chaps. 8–10.

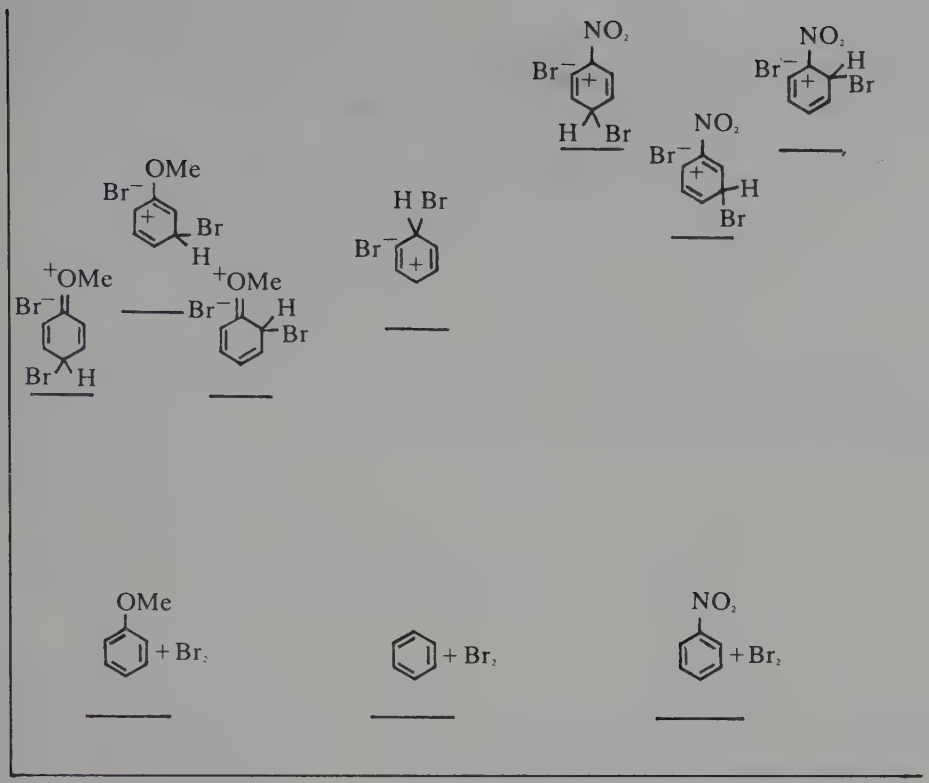
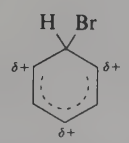
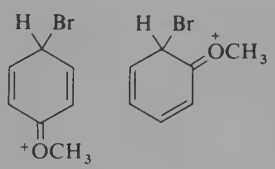


Fig. 4.15. Transition state energies in bromination.

At the transition state a considerable positive charge is distributed on the benzene ring, largely at carbon atoms 2, 4, and 6 relative to the entering bromine atom.

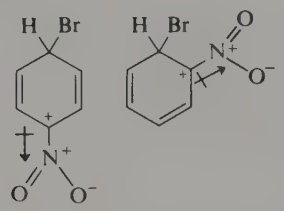


The electron-releasing methoxy group can interact directly with this positive charge in the intermediates which lead to *o*- and *p*-bromoanisole.

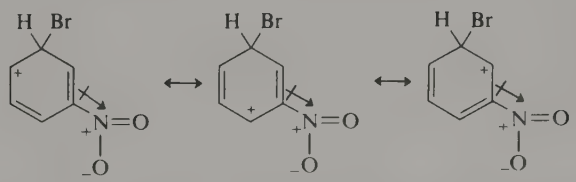


The corresponding species are therefore more stable than those of the *meta* isomer or of benzene, where such resonance interaction with the methoxy group is absent.

The transition states leading to *o*- and *p*-bromonitrobenzene are highly unfavorable, since the developing positive charge is adjacent to the strongly electron-withdrawing nitro group.



The *meta* transition state is less unfavorable, but is still destabilized relative to that of benzene because of the electron-withdrawing nitro group.



The prediction that methoxy is an *ortho–para*-directing and activating group follows directly from this placement of the isomeric transition states. The *meta*-directing and deactivating effect of the nitro group is also explained. This treatment requires some insight into the nature of the transition state for the rate-determining step and emphasizes the need for deducing the properties of transition states in order to understand reaction mechanisms correctly. Aromatic substitution lends itself well to interpretation in terms of the resonance concept. Other systems may require the application of stereolectronic and molecular orbital symmetry ideas to evaluate the relevant transition state energies, but the Hammond postulate applies in any case.

In Chapter 3, equilibria among conformers of organic molecules were discussed. At this point, let us consider in a general way the effect that conformational equilibria can have on a chemical reaction. Under what circumstances can the position of the conformational equilibrium for a reactant determine which of two competing reaction paths will be followed? A potential energy diagram is shown in Fig. 4.16. In most cases, the energy of activation for a conformational interconversion is lower than that for a chemical reaction. If this is the case, then $\Delta G_a^{\ddagger}$ and $\Delta G_b^{\ddagger} \gg \Delta G_c^{\ddagger}$, as shown in Fig. 4.16. The conformers of the reactant are in equilibrium.

$$\mathrm{B} \rightleftharpoons \mathrm{A} \qquad K_c = \frac{[\mathrm{A}]}{[\mathrm{B}]}$$

$$\text{rate of formation of product } P_{\mathrm{A}} = \frac{dP_{\mathrm{A}}}{dt} = k_a[\mathrm{A}] = k_a K_c[\mathrm{B}]$$

$$\text{rate of formation of product } P_{\mathrm{B}} = \frac{dP_{\mathrm{B}}}{dt} = k_b[\mathrm{B}]$$

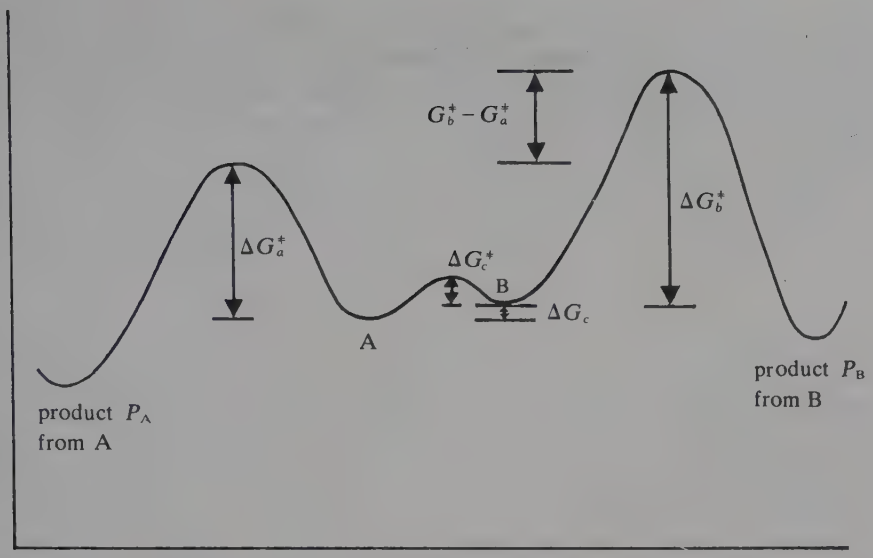


Fig. 4.16. Effect of conformation on product distribution.

$$\text{product ratio} = \frac{dP_A/dt}{dP_B/dt} = \frac{k_a K_c[B]}{k_b[B]} = \frac{k_a K_c}{k_b}$$

According to transition state theory,

$$k_r = \frac{\kappa kT}{h} e^{-\Delta G^{\ddagger}/RT} \quad \text{and} \quad K_c = e^{-(-\Delta G_c)/RT}$$

$$\text{product ratio} = \frac{(\kappa kT/h)\, e^{-\Delta G_a^*/RT} e^{+\Delta G_c/RT}}{(\kappa kT/h)\, e^{-\Delta G_b^*/RT}}$$

$$= e^{(-\Delta G_a^* + \Delta G_b^* + \Delta G_c)RT}$$

But from Fig. 4.16,

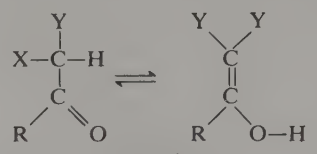
$$\Delta G_b^{\ddagger} - \Delta G_a^{\ddagger} + \Delta G_c = G_b^{\ddagger} - G_a^{\ddagger}$$

The product ratio is therefore not determined by ΔG_c but instead depends primarily on the *relative* energy of the two transition states.

The conclusion[43] that the ratio of products formed from conformational isomers is not determined by the conformer population ratio is known as the *Curtin–Hammett*

43. D. Y. Curtin, *Rec. Chem. Prog.* **15**, 111 (1954); E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962, pp. 151, 152, 237, 238.

principle. The same arguments can be applied to other energetically facile interconversions of two reactants that can lead to different products. For example, many organic molecules may undergo proton shifts (*tautomerism*) rapidly and easily, and the chemical reactivity of the two isomers may be quite different. It is not valid



tautomerism

however, to attempt to deduce the ratio of the two tautomers from the course of subsequent chemical reactions that have activation energies *greater* than that of the tautomerism. Just as in the case of conformational isomerism, the ratio of product formed in subsequent reactions will not be controlled by the position of a facile preequilibrium. While the rate of formation of the products is dependent upon the relative concentration of the two conformers, since $\Delta G_b^{\ddagger}$ is decreased relative to $\Delta G_a^{\ddagger}$ to the extent of the difference in the two conformational energies, the preequilibrium is established rapidly, relative to the two competing reactions.[44]

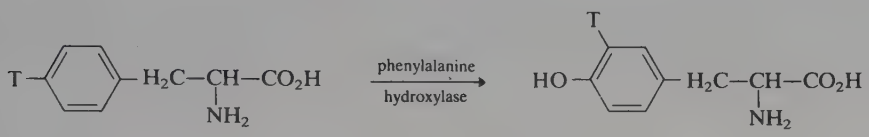
4.10. Isotopes in Labeling Experiments

The relationship between kinetic isotope effects and reaction mechanisms was discussed in Section 4.4. A quite different use of isotopes in mechanistic studies involves their use as labels in ascertaining the fate of a given atom. Again, as in kinetic experiments, the substitution of an isotope will not qualitatively affect the course of the reaction. The nuclei most commonly used for tracer experiments have been deuterium and carbon-14. There are several means of locating the position of deuterium atoms in organic molecules. In contrast to protium, deuterium does not show an NMR signal under standard operating conditions, and the disappearance of a particular signal in the NMR spectrum can provide the information needed to recognize the location of a deuterium. Direct detection of deuterium can be done on appropriately equipped NMR spectrometers. Mass spectrometric and infrared measurements also have the capability of determining the location of deuterium in a labeled molecule. Carbon-14 is detected on the basis of its radioactivity.

Tritium can also be used effectively as a label. It is introduced into only a small fraction of the reactant molecules to be studied. Because it is radioactive, very low

44. For a more complete discussion of the relationship between conformational equilibria and reactivity, see J. I. Seeman, *Chem. Rev.* **83**, 83 (1983).

concentrations of tritium can be detected by counting techniques. Many excellent examples of its use can be found in the study of the details of biological reactions. For example, when 4-*tritio*-phenylalanine was introduced into animals, it was expected that the tritium would be lost to the medium in the course of the substitution reaction, which leads to the formation of 4-hydroxyphenylalanine. When the 4-hydroxyphenylalanine produced was examined, however, it was found to have a level of radioactivity indicating that most of the tritium remained in the molecule. The



hydrogen shift detected by this experiment has since been found to occur in many biological oxidations of aromatic molecules, and has been given the name *NIH shift*.[45] The discovery of this facet of the process has since resulted in much new insight into the mechanism of biological oxidations.

The location of carbon is often studied in the course of determining organic reaction mechanisms, particularly in cases where migration of a group or rearrangement of the molecular skeleton is a good possibility. Most such studies in the literature have been carried out with radioactive ^{14}C. The product can be subjected to a degradation that permits the various carbons under study to be separated in smaller molecular fragments. Counting the level of radioactivity of the various degradation fragments permits the fate of the original labeled carbon to be determined. Since NMR spectrometers capable of detecting ^{13}C have now become widely available, this isotope is being used more frequently in tracer studies. Since the location of a ^{13}C can be done spectroscopically, the frequently difficult chemical degradation required in ^{14}C work is unnecessary.[46]

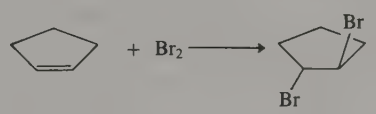
4.11. Stereochemistry

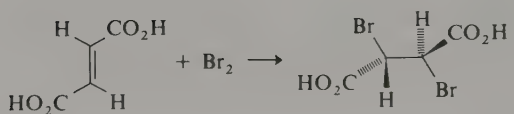
The study of the stereochemistry of organic reactions often leads to detailed insight into reaction mechanisms. Instrumental techniques including IR spectro-

45. From its discovery by scientists at the National Institutes of Health; for an account of this discovery, see G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science* **157**, 1524 (1967).
46. For other examples of use of isotopic labels in mechanistic studies, see V. F. Raaen, in *Investigation of Rates and Mechanisms of Reactions*, E. S. Lewis (ed.), *Techniques of Chemistry*, Vol. VI, Part 1, Wiley, New York, 1974, pp 257–284, and *Isotopes in Organic Chemistry*, Vols. 1–4, E. Buncel and C. C. Lee (ed.), Elsevier, New York, 1975–1978.

scopy, NMR spectroscopy, optical rotatory dispersion, and circular dichroism measurements have made it possible to determine the stereochemistry of many organic molecules without the need for chemical interrelation with reference compounds of known stereochemistry. Mechanistic postulates frequently make unambiguous predictions about the stereochemical outcome of the reaction. The study of the stereochemistry is therefore a widely used method for gaining insight into reaction mechanisms. Throughout the chapters dealing with specific types of reactions, consideration is given to the stereochemistry of the reactions and to the relationship between stereochemistry and reaction mechanism. As an example, the bromination of alkenes can be cited. A very simple mechanism for bromination is given below:

A molecule of bromine becomes complexed to the double bond of the alkene, and reorganization of the electrons then gives the product. This mechanism can be shown to be incorrect for most alkenes on the basis of the stereochemistry of the products. Most alkenes give the product that results from addition of the two bromine atoms from opposite sides of the carbon–carbon double bond.





These results serve to rule out the simple one-step mechanism suggested above. The correct mechanism and the evidence in its favor will be discussed in Chapter 6.

To conclude this chapter, it is important to emphasize a logical point about the determination of reaction mechanisms: A proposed mechanism can never really be proven; rather, it is a case of alternatives being eliminated. Having in mind a mechanism that explains all the facts at hand does not constitute proof that the mechanism is correct. That conclusion is possible only when *all* alternatives have been excluded. A key stage in a mechanistic investigation, therefore, is the enumeration of the various possibilities. Thus a chemist approaching a mechanistic study must cast as broad as possible a vision on the problem. The principal basis for enumerating mechanistic possibilities is accumulated chemical experience in related systems and the inherent structural features of the system. The range of mechanistic possibilities, particularly in rearrangements and multistep processes rapidly becomes large.

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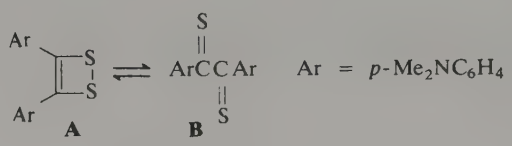
Problems

(References for these problems will be found on page 702.)

1. Measurement of the equilibrium constant for the interconversion of the dithiete **A** and the dithione **B** yielded the data given below. Calculate $\Delta G°$, $\Delta H°$, and $\Delta S°$.

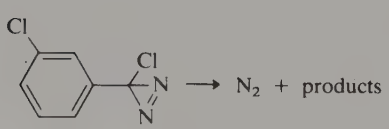


Temp. (°C)	K
−2.9	16.9
11.8	11.0
18.1	8.4
21.9	7.9
29.3	6.5
32.0	6.1
34.9	5.7
37.8	5.3
42.5	4.6

2. Calculate the enthalpy and entropy of activation ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) at 40°C for the acetolysis of *m*-chlorobenzyl *p*-toluenesulfonate from the data given:

Temp. (°C)	$k \times 10^5$, sec^{-1}
25.0	0.0136
40.0	0.085
50.1	0.272
58.8	0.726

3. Calculate the activation parameters, ΔE_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ at 100°C from the data given for the reaction shown below:

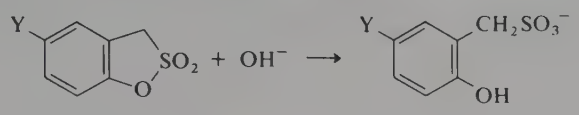


Temp. (°C)	$k \times 10^4$, sec^{-1}
60.0	0.30
70.0	0.97
75.0	1.79
80.0	3.09
90.0	8.92
95.0	15.90

4. Of all the substituents listed in Table 4.3 only one is assigned both a σ^+ and a σ^- value. This is the phenyl substituent. Furthermore, the signs of σ^+ and σ^-

are different. Discuss the reasons that the phenyl group has both a σ^+ and a σ^- value and explain why they are of a different sign.

5. Determine the value of ρ for the reaction shown from the data given:

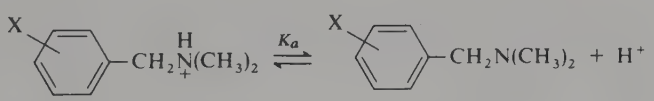


Y	k (M^{-1} sec^{-1})
H	37.4
CH_3O	21.3
CH_3	24.0
Br	95.1
NO_2	1430

6. The pseudo-first-order rate constants for the acid-catalyzed hydration of substituted styrenes are given. Plot the data against σ and σ^+ and determine ρ and ρ^+. Interpret the significance of the results.

Substituent	$k \times 10^8$
p-CH_3O	488,000
p-CH_3	16,400
H	811
p-Cl	318
p-NO_2	1.44

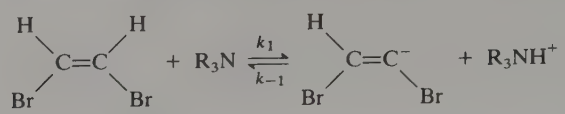
7. The basicity of a series of substituted benzyldimethylamines has been measured. Determine whether these basicity data are correlated by the Hammett equation. What is the value of ρ? What interpretation do you put on its sign?

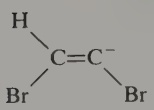


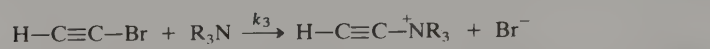
X	pK_a
p-CH_3O	9.32
p-CH_3	9.22
p-F	8.94
H	9.03
m-NO_2	8.19
p-NO_2	8.14
p-Cl	8.83
m-Cl	8.67

8. Write the rate law that would describe the rate of product formation for each of the following systems:

(a)

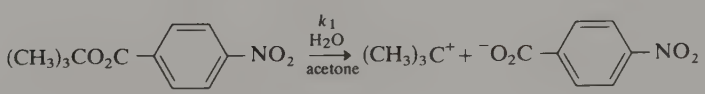


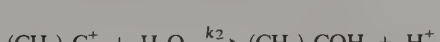




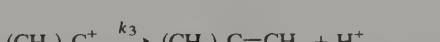
if the second step is rate controlling and the first step is a preequilibrium.

(b)



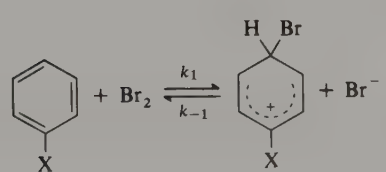


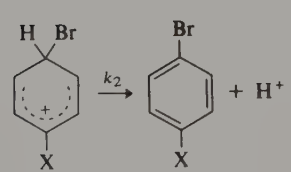
and

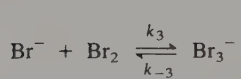


if the competing product-forming steps are faster than the first step.

(c)







assuming that the σ complex is a steady state intermediate. The final step is a rapid equilibrium that converts some of the initial Br_2 to unreactive Br_3^-. What is the rate expression if the intermediate goes to product much faster than it reverts to starting material and if the equilibrium constant for tribromide ion formation is large?

(d) $PhC(=O)CH(CH_3)_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhC(OH)=C(CH_3)_2$

$PhC(OH)=C(CH_3)_2 + Cr(VI) \xrightarrow{k_2}$ products

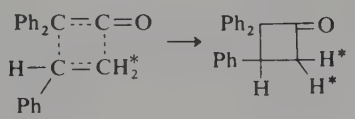
where no assumption is made as to the relative magnitude of k_1, k_{-1}, and k_2

9. Predict whether normal or inverse isotope effects will be observed for each reaction below. Explain. Indicate any reactions in which you would expect $k_H/k_D > 2$. The isotopically substituted hydrogens are marked with asterisks.

(a) $CH_3CH_2^*CH(OSO_2Ar)CH_2^*CH_3 \xrightarrow[H_2O]{EtOH} CH_3CH_2^*\overset{+}{C}HCH_2^*CH_3$

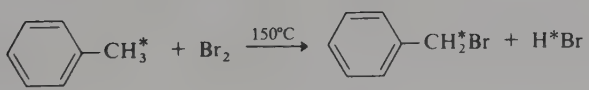
$\longrightarrow CH_3CH_2^*CH(OH)CH_2^*CH_3 + CH_3CH_2^*CH(OCH_2CH_3)CH_2^*CH_3$

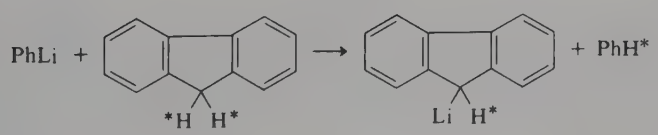
(b) $CH_3^*CHCH_3^* + {}^-OH \longrightarrow CH_3^*C(=NO_2^-)CH_3^* + H_2O$

(c) $Ph_2C{=}C{=}O + PhCH{=}CH_2^* \longrightarrow$  $\longrightarrow$

(d) $CH_3CH_2CH^*(OC_2H_5)_2 \underset{fast}{\overset{H^+}{\rightleftharpoons}} CH_3CH_2C(H^*)(+OC_2H_5)-OC_2H_5 \xrightarrow{slow} CH_3CH_2C(H^*)=\overset{+}{O}C_2H_5$

$CH_3CH_2C(H^*)=\overset{+}{O}C_2H_5 + H_2O \xrightarrow{fast} CH_3CH_2CH^*{=}O + C_2H_5OH$

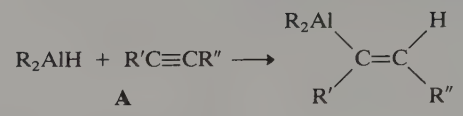
(e) 

(f) 

(g) $H_2^*C{=}CHCH_2OC(=S)Ph \xrightarrow{100°C} PhC(=O)SCH_2^*CH{=}CH_2$

(h) $H_2^*C{=}CH_2^* + Ag^+ \rightleftharpoons \left[H_2^*C(Ag){=}CH_2^* \right]^+$

10. Reactions of dialkylaluminum hydrides with acetylenes give addition products:



The rate expression for the reaction is

$$-\frac{d[\mathbf{A}]}{dt} = k[\mathbf{A}][(R_2AlH)_3]^{1/3}$$

Propose a mechanism that could account for the overall four-thirds order kinetics and the appearance of the dialkylaluminum hydride concentration to the one-third power.

11. The Cannizzaro reaction is a disproportionation which takes place in strongly basic solution and converts benzaldehyde to benzyl alcohol and sodium benzoate.

$$2\,PhCH{=}O + NaOH \xrightarrow{H_2O} PhCO_2^-Na^+ + PhCH_2OH$$

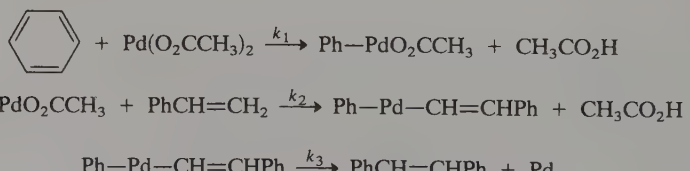
Several mechanisms have been postulated, all of which propose a *hydride ion* transfer as a key step. On the basis of the following results, postulate one or more mechanisms which are consistent with all the data provided. Indicate the significance of each observation with respect to the mechanism(s) you postulate.

(1) When the reaction is carried out in D_2O, the benzyl alcohol contains no deuterium in the methylene group.
(2) When the reaction is carried out in $H_2{}^{18}O$ both the benzyl alcohol and sodium benzoate contain ^{18}O.
(3) The reaction rate is given by the expression

$$\text{rate} = k_{obs}[PhCH{=}O]^2[^-OH]$$

(4) The rates of substituted benzaldehydes are correlated by the Hammett equation with $\rho = +3.76$.
(5) The solvent isotope effect k_{D_2O}/k_{H_2O} is 1.90.

12. A mechanism for olefin arylation by palladium(II) is given below. The isotope effect k_H/k_D was found to be 5 when benzene-d_6 was used. When styrene-β,β-d_2 was used, no isotope effect was observed. Which step is rate-determining?



13. A scale for solvent ionizing power, Y^+, applicable in solvolysis reactions of cationic substrates, has been developed. For example,

$$S + (C_2H_5)_3O^+PF_6^- \rightarrow (C_2H_5)_2O + C_2H_5S^+ + PF_6^-$$

S = solvent

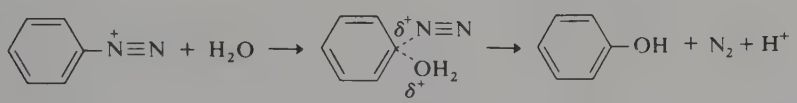
The numerical values of Y^+ are found to be related to Y, the measure of solvent ionizing power for neutral substrates, by the equation

$$Y^+ = -0.09\,Y$$

Explain, in qualitative terms (a) why Y^+ is negative with respect to Y and (b) why Y^+ is smaller in magnitude than Y (as is indicated by the coefficient of 0.09).

14. Two mechanisms are among those that have been postulated for decomposition of aryl diazonium salts in aqueous solution containing nucleophilic anions, A^-:

Mechanism A



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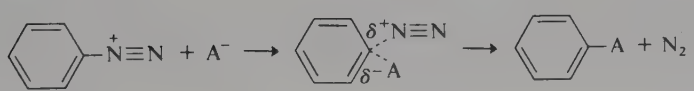
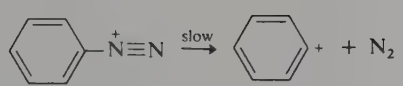
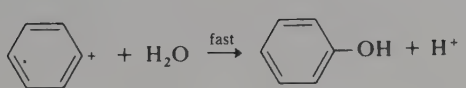
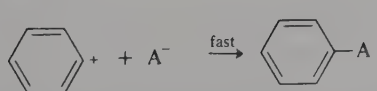


Mechanism B





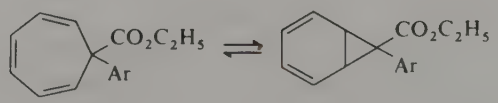
and



Indicate how each of the following techniques might be applied to distinguishing between these mechanisms:

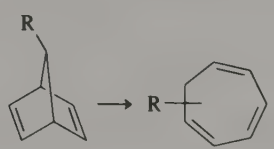
(a) kinetic studies
(b) rate and product composition as a function of $[A^-]$
(c) solvent isotope effect studies
(d) isotope effect resulting from substitution of D for H at *ortho* positions
(e) substituent effect studies

15. Cycloheptatrienes are in many cases in rapid equilibrium with an isomeric bicyclo[4.1.0]heptadiene. The thermodynamics of the valence isomerism has been studied in a number of instances and some of the data are given below. Calculate the equilibrium constant for each case at 25°C. Calculate the temperature at which $K = 1$ for each system. Are the signs of the enthalpy and entropy as you would expect them to be? Can you discern any pattern of substituent effects from the data?



Ar	$\Delta H°$ (kcal/mol)	$\Delta S°$ (eu)
Phenyl	−5.4	−16.8
p-Nitrophenyl	−3.5	−11.0
p-Methoxyphenyl	−2.3	−7.4

16. Bicyclo[2.2.1] heptadiene rearranges at elevated temperatures to cycloheptatriene and toluene. The reaction is facilitated by substituents at C-7 such as phenyl and alkoxy, in which case cycloheptatrienes are the dominant products.

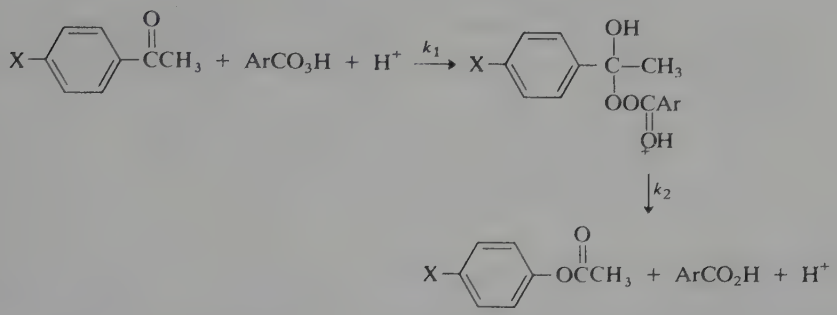


For R = *t*-butoxy, the rate data are given for several temperatures in decane. The reaction is about 50% faster in ethoxyethanol than in decane. Calculate the

Temp. (°C)	k (sec^{-1})
139.8	7.28×10^{-6}
154.8	3.37×10^{-5}
170.3	1.43×10^{-4}

activation parameters at 150°C. Although precisely comparable data are not available, E_a for the gas phase isomerization of norbornadiene is ~50 kcal/mol. Draw a sketch showing the degree of transition state stabilization or destabilization caused by the alkoxy substituent. Is there any basis for regarding the bond cleavage in the rate-determining step to be heterolytic or homolytic? How do you propose that the effect of the substituent group R operates? Can you propose an experiment that might support your proposal?

17. Oxidation of substituted acetophenones with *m*-chloroperoxybenzoic acid correlates with σ^+ with $\rho = -1.36$. Which step in the mechanism given is rate determining?



18. Match the ρ values with the appropriate reactions. Explain your reasoning.
Reaction constants: +2.45, +0.75, −2.39, −7.29
Reactions:
(a) nitration of substituted benzenes
(b) ionization of substituted benzenethiols
(c) ionization of substituted benzenephosphonic acids
(d) reaction of substituted *N,N*-dimethylanilines with methyl iodide.

19. Comparison of the gas phase acidity of benzoic acids with pK_a values of the same compounds in aqueous solution provides some interesting relationships.

(1) The trend in acidity as a function of substituent is the same but the magnitude of the substituent effects is much larger in the gas phase. (The $\Delta\Delta G°$ for any given substituent is about ten times larger in the gas phase.)
(2) Whereas acetic acid and benzoic acid are of comparable acidity in water, benzoic acid is much more acidic in the gas phase.
(3) While the substituent effect in the gas phase is assumed to be nearly entirely an enthalpy effect, it can be shown that in solution the substituent effect is largely the result of changes in ΔS.

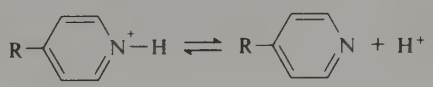
Discuss how the change from gas phase to water solution can cause each of these effects.

20. It has been suggested that the chemical shift of aromatic ring carbons might provide a good indication of the intrinsic electron-releasing or electron-attracting capacity of substituents in circumstances where there is no perturbation by an approaching reagent. Such a perturbation is always present in substituent effects determined on the basis of reactivity. The measured chemical shifts from benzene for the carbon *para* to the substituent are given below. Plot these against σ, σ^+, and what conclusions do you draw from these plots? If you have access to an appropriate program and computer, determine the "per cent resonance" associated with the chemical shift, as determined by the Swain–Lupton equation.

R	$\Delta\delta^a$	R	$\Delta\delta^a$
NH_2	−9.86	CN	3.80
OCH_3	−7.75	CCH_3	4.18
F	−4.49	CO_2CH_3	4.12
Cl	−2.05	SO_2CH_3	4.64
Br	−1.62	NO_2	5.53
CH_3	−2.89	CH=O	5.51
CF_3	3.19		

a. $\Delta\delta$ is the change in chemical shift in CCl_4 from benzene in ppm; a negative sign indicates increased shielding.

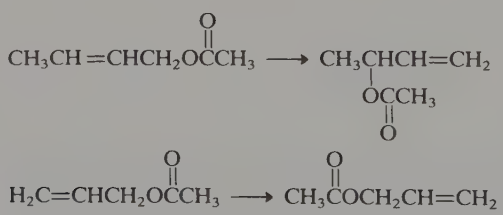
21. The ionization of a series of 4-substituted pyridines has been studied, and both equilibrium acidities (pK_a) and enthalpies of ionization have been recorded at 25°C:



R	pK_a	$\Delta H°$ (kcal/mol)
H	5.21	4.8
NH_2	9.12	11.3
OCH_3	6.58	6.8
CH_3	6.03	6.1
Cl	3.83	3.6
Br	3.75	3.5
CN	1.86	1.3

Calculate $\Delta S°$ for ionization of each compound. Comment on the contribution of $\Delta H°$ and $\Delta S°$ terms to the free energy of ionization. Test the data for linear free-energy correlations. Are the linear free-energy correlations dominated by entropy or enthalpy terms?

22. Allyl esters undergo rearrangement reactions at 300°C and above. Two examples are shown, one of which is "degenerate," since the product and reactant are identical:



At least three distinct mechanisms can be written for these reactions. Write down some possible mechanisms, and suggest isotopic labeling studies that could distinguish among the possibilities you have proposed.

23. Estimates of the heat of solvation of various ionic species in DMSO as compared to water have been made, and can be expressed as enthalpies of transfer. Some data are given below. Discuss their significance.

$$X^{\pm}_{H_2O} \longrightarrow X^{\pm}_{DMSO}$$

X	$\Delta H_{transfer}$ (kcal/mol)
K^+	−8.8
Na^+	−7.1
Cl^-	+4.9

24. A study of the aromatic nitration reaction in aqueous nitric acid revealed that when no aromatic substrate was present, an incorporation of ^{18}O from labeled water into nitric acid occurred. The rate of this exchange process was identical with the rate of nitration of several reactive aromatic hydrocarbons. Discuss how this result is consistent with mechanism B on page 170, but not with mechanisms A or C.

$$HNO_3 + H_2{}^{18}O \longrightarrow HN^{18}O_3 + H_2O$$

5

Nucleophilic Substitution

Introduction

It is fair to say that the single reaction that has received the greatest attention of organic chemists is nucleophilic substitution at saturated carbon atoms. The reaction is of great synthetic utility and many individual observations had accumulated before systematic efforts at characterizing the reaction by mechanistic studies began. The task of creating a coherent mechanistic interpretation was undertaken by C. K. Ingold and E. D. Hughes in England in the 1930's. Their studies laid the basis for current understanding.[1] Since those initial investigations, organic chemists have continued to study substitution reactions, and the level of detailed information about this area is greater than for any of the other broad classes of reactions we will consider. The field provides an excellent opportunity to illustrate the application of techniques which provide mechanistic information and also is one where structure of reaction intermediates and transition states has received very careful scrutiny. From these accumulated data a very satisfactory conceptual interpretation has developed. We can provide only a small selection of these details to illustrate the general concepts. The area of nucleophilic substitution will also illustrate clearly the fact that while large conceptual treatments can outline the broad features to be expected for a given system, the precise details will reveal aspects which are characteristic of specific systems. As the chapter unfolds the reader should come to appreciate both the depth and breadth of the general conceptual understanding and the characteristics of some of the individual systems.

Nucleophilic substitution reactions may involve several different combinations of charged and uncharged species as reactants. The equations presented in Scheme

1. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Second Edition, Cornell University Press, Ithaca, New York, 1969.

Scheme 5.1. Representative

A. Neutral substrate + neutral nucleophile

$$RX + Y: \longrightarrow RY^+ + X:^-$$

1[a] $CH_3CH_2I + (CH_3CH_2CH_2CH_2)_3P: \xrightarrow[\text{acetone}]{} (CH_3CH_2CH_2CH_2)_3\overset{+}{P}CH_2CH_3\ I^-$ (quantitative)

2[b] $PhC(CH_3)_2Cl + CH_3CH_2OH \longrightarrow PhC(CH_3)_2\overset{+}{O}(H)CH_2CH_3 \xrightarrow{-H^+} PhC(CH_3)_2OCH_2CH_3$ (87%)

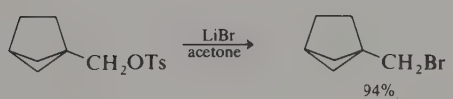
3[c] $CH_3CH(OSO_2C_6H_4CH_3)CH_2CH_3 + H_2O \xrightarrow[\text{acetone}]{} CH_3CH(\overset{+}{O}H_2)CH_2CH_3 \xrightarrow{-H^+} CH_3CH(OH)CH_2CH_3$ (77%)

(The *p*-toluenesulfonate group is commonly referred to as *tosylate* and abbreviated −OTs.)

B. Neutral substrate + anionic nucleophile

$$RX + Y:^- \longrightarrow RY + X:^-$$

4[d] $CH_3CH(Br)CH_2C{\equiv}N \xrightarrow[\text{acetone}]{NaI} CH_3CH(I)CH_2C{\equiv}N$ (96%)

5[e] 

(94%)

6[f] $CH_3CH(OTs)(CH_2)_5CH_3 + PhS^- \xrightarrow[\text{ethanol}]{} CH_3CH(SPh)(CH_2)_5CH_3$

5.1 illustrate the cases of:

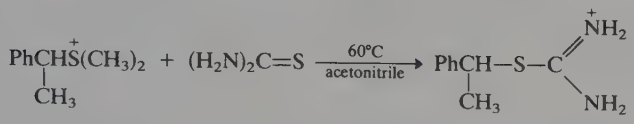
(A) neutral substrate + neutral nucleophile
(B) neutral substrate + anionic nucleophile
(C) cationic substrate + neutral nucleophile
(D) cationic substrate + anionic nucleophile

These four types of reactions are by far the most common, although others such as anionic substrate + anionic nucleophile can occur if sufficiently reactive reactants are

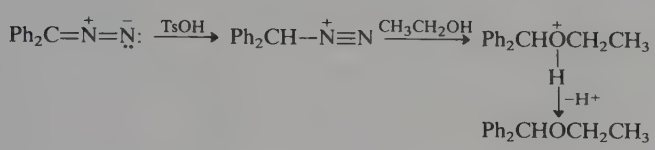
C. Cationic substrate + neutral nucleophile

$$RX^+ + Y: \longrightarrow RY^+ + X:$$

7[g]



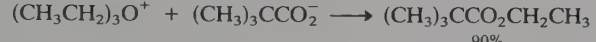
8[h]



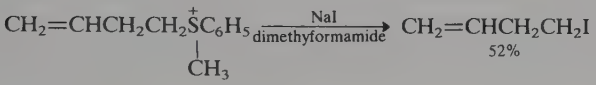
D. Cationic substrate + anionic nucleophile

$$RX^+ + Y:^- \longrightarrow RY + X:$$

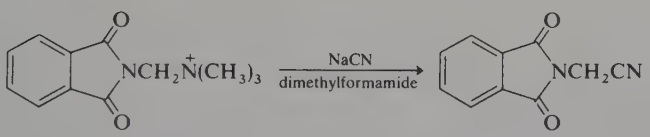
9[i]



10[j]



11[k]



a. S. A. Buckler and W. A. Henderson, *J. Am. Chem. Soc.* **82**, 5795 (1960).
b. R. L. Buckson and S. G. Smith, *J. Org. Chem.* **32**, 634 (1967).
c. J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, Jr., *J. Am. Chem. Soc.* **74**, 4283 (1952).
d. M. S. Newman and R. D. Closson, *J. Am. Chem. Soc.* **66**, 1553 (1944).
e. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.* **85**, 3188 (1963).
f. H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.* **27**, 736 (1962).
g. H. M. R. Hoffmann and E. D. Hughes, *J. Chem. Soc.*, 1259 (1964).
h. J. D. Roberts and W. Watanabe, *J. Am. Chem. Soc.* **72**, 4869 (1950).
i. D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
j. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).
k. H. Hellman, I. Loschmann, and F. Lingens, *Chem. Ber.* **87**, 1690 (1954).

chosen. The factors that influence the reactivity of nucleophiles and substrates will be among the topics considered in this chapter.

The equations in Scheme 5.1 illustrate the relationship of product and substrate in nucleophilic substitution reactions, but say nothing of mechanism. In order to approach an understanding of the mechanism of such reactions, let us begin with a review of the limiting cases as defined by Hughes and Ingold. These limiting cases are the *ionization mechanism* (S_N1, substitution–nucleophilic–unimolecular) and the *direct displacement mechanism* (S_N2, substitution–nucleophilic–bimolecular).

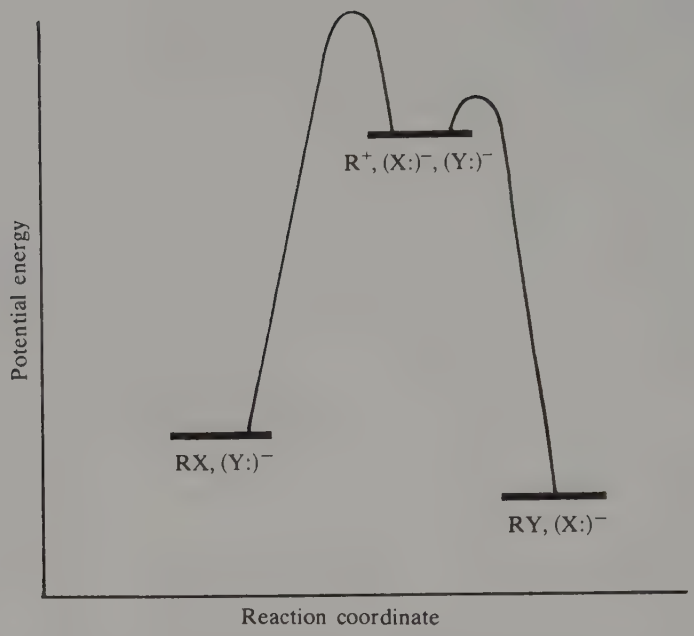


Fig. 5.1. Potential energy diagram for nucleophilic substitution by the ionization (S_N1) mechanism.

5.1. The Limiting Cases—Substitution by the Ionization (S_N1) Mechanism

The ionization mechanism for nucleophilic substitution proceeds by rate-determining heterolytic dissociation of the substrate to a tricoordinate carbocation (also referred to as a *carbonium ion* or *carbenium ion*)[2] and the leaving group. This dissociation is followed by rapid combination of the highly electrophilic carbocation with Lewis bases present in the medium. A two-dimensional potential energy diagram representing this process for a neutral substrate and an anionic nucleophile is shown in Fig. 5.1.

The consequences of this mechanism are evident. The reaction will exhibit first-order kinetics overall, with the rate of decomposition of the substrate being

2. Tricoordinate carbocations are customarily called *carbonium ions*; for a clear discussion of terminology and a suggestion favoring the view that the term *carbonium ion* be reserved for pentacoordinate carbocations, with tricoordinate carbocations being referred to as *carbenium ions*, see G. A. Olah, *J. Am. Chem. Soc.* **94**, 808 (1972). Current practice uses both terms and also terms such as *methyl cation* and *butyl cation* to describe carbonium ions. *Chemical Abstracts* uses as specific names methylium, ethylium, etc. We will use carbonium ion as a generic term for trivalent carbocations. We will use methyl cation, ethyl cation, etc., when referring to specific ions.

independent of the concentration or nature of the nucleophile, i.e., for

$$RX \xrightarrow{\text{slow } k_1} R^+ + X:^-$$

$$R^+ + Y:^- \xrightarrow{\text{fast } k_2} RY$$

$$\text{rate} = -\frac{d[RX]}{dt} = -\frac{d[Y:^-]}{dt} = k_1[RX]$$

Employing the common assumption that stabilization of the carbocation intermediate will stabilize the transition state leading to its formation, it follows that ionization will be facilitated by factors that either lower the energy of the carbonium ion–anion pair or raise the energy of the ground state. The rate of ionization will therefore depend on structural and medium effects in a predictable way.

Structural effects include both electronic and steric effects. The more obvious electronic effects are stabilization of the carbonium ion by electron release and stabilization of the leaving group by increasing its ability to accept an electron pair from the initial covalent bond. Steric effects are pronounced because of the change in coordination between the covalent substrate and the tricoordinate carbocation. Most commonly, bulky groups that are compressed in the tetracoordinate ground state spread apart in going to the transition state, and ionization is facilitated. If geometrical constraints preclude planarity in the carbonium ion, this constraint will be reflected in an increased energy of activation.

The response of the ionization mechanism to medium effects will depend on the charge type of the substrates. These relationships follow the general pattern discussed in Section 4.7. Ionization of a neutral substrate produces charge separation in the transition state, and the effect of solvent polarity will be more pronounced in the transition state than in the ground state. Solvents with higher dielectric constants will lower the energy of the transition state more than solvents of lower dielectric constant. Ionization of cationic substrates (alkyldiazonium ions, trialkylsulfonium salts) leads to dispersal of charge in the transition state and, ignoring solvation entropy effects, should be enhanced by less polar solvents. Added salts in the reaction medium can, in principle, act in two ways. A common ion (for example, chloride ion in hydrolysis of triphenylmethyl chloride) will suppress ionization by a mass law effect, while other salts which do not participate directly in the reaction will have a modest rate-enhancing effect by increasing the effective dielectric constant of the medium.

The stereochemical course of nucleophilic substitution on an optically active substrate where the chiral center is the carbon atom bearing the leaving group is less readily predictable. The ionization mechanism proposes rate-determining formation of a carbonium ion intermediate that is achiral, because it contains a plane of symmetry. If the carbonium ion is sufficiently long-lived under the reaction conditions to diffuse away from the leaving group, it will become symmetrically solvated and can produce only racemic product. If this condition is not met, the solvation is dissymetric, and optically active product of retained or inverted configuration may be obtained. The extent of inversion or retention will depend upon the details of

the system. Examples of these effects will be encountered in later portions of this chapter.

A further consequence of the ionization mechanism is that if the same carbonium ion can be generated from more than one precursor, the subsequent reactions it undergoes should be independent of its origin. But, as in the case of stereochemistry, our faith in this prediction must be tempered by the fact that the ionization produces an ion pair initially, rather than dissociated ions, and the leaving group is sufficiently close to the carbonium ion to influence further reactions until the two species have diffused apart.

5.2. The Limiting Cases—Substitution by the Direct Displacement (S_N2) Mechanism

The direct displacement mechanism is concerted, without an intermediate and with a single rate-determining transition state. According to this mechanism, the substrate is attacked by the nucleophile from the side opposite the leaving group, with bond making to the nucleophile increasing along the reaction coordinate simultaneously with bond breaking between the carbon atom and the leaving group. The ideal transition state involves trigonal bipyramid geometry at pentacoordinate carbon. The nucleophile and the leaving group are both coordinated to the central carbon at the transition state. A potential energy diagram depicting the direct displacement mechanism is presented in Fig. 5.2.

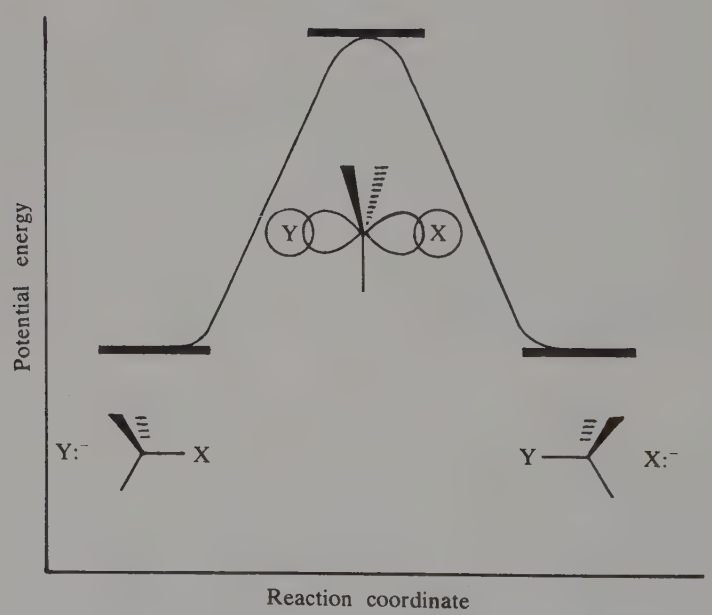


Fig. 5.2. Potential energy diagram for nucleophilic substitution by the direct displacement (S_N2) mechanism.

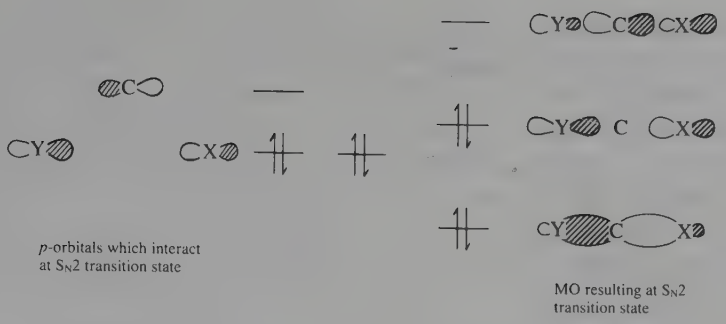
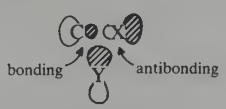


Fig. 5.3. MO description of the transition state for an S_N2 displacement at carbon.

The frontier orbital approach provides a description of the bonding interactions which occur in the S_N2 process. The frontier orbitals are a filled lone-pair orbital on the approaching nucleophile and the σ^* anti-bonding orbital involving the carbon undergoing substitution and the leaving group. This antibonding orbital has a large lobe on carbon directed away from the C–X bond.[3] This favors back-side approach

by the nucleophile since the strongest initial interaction will be between the filled orbital on the nucleophile and this empty antibonding orbital. Front-side approach is disfavored both because the density of the σ^* orbital is less in the region between carbon and the leaving group and because a front-side approach would involve both a bonding and an antibonding interaction with the orbital, since it has a nodal surface between the two atoms. The molecular orbital picture also predicts that



inversion would take place since the development of the transition state would be accompanied by rehybridization of the carbon to the trigonal geometry characteristic of sp^2 hybridization. The rehybridization to sp^3 would complete inversion as the new bond between the central carbon and the nucleophile became fully developed.

A molecular orbital description of the transition state for an S_N2 process can be obtained by considering the case of a trigonal bipyramidal carbon interacting with two equivalent occupied orbitals, one from the leaving group and one from the nucleophile. Such a transition state is represented in Figure 5.3 using p orbitals for the nucleophile and leaving group. The orbital on carbon which is involved in

3. L. Salem, *Chem. Brit.* **5**, 449 (1969).

the reaction will also be p in character because of the bipyramidal geometry. The energy of this transition state will be lowered by an interaction with adjacent substituents which can stabilize these orbitals. It should be noted that both are π in character, so that substituents with low-lying empty orbitals with the π symmetry appropriate for overlap will stabilize this transition state and facilitate the reaction. The vinyl, phenyl, and carbonyl groups can provide such stabilization and, as we shall see later, these groups do enhance S_N2 reactivity.

The consequences of the concerted displacement mechanism include both kinetic and stereochemical implications. The kinetics of the bimolecular process must be consistent with a second-order rate expression, first order in substrate and first order in nucleophile. For

$$RX + Y:^- \xrightarrow{k} RY + X:^-$$

$$\text{rate} = -\frac{d[RX]}{dt} = -\frac{d[Y:^-]}{dt} = k[RX][Y:^-]$$

Since the attacking species is involved intimately in the rate-determining step, not only will the rate depend on its concentration, but also the chemical nature of the nucleophile will be very important in determining the rate of the reaction.

Structural effects will therefore be important with respect to both the substrate and the nucleophile. Since the degree of coordination increases at the reacting carbon atom in going to the transition state, the rate of direct displacement will be sensitive to the size of the attached groups and to the steric bulk of the nucleophile. The optimum substrate from a steric viewpoint would be CH_3X, with the ease of attack at carbon becoming increasingly more difficult as alkyl groups are substituted for hydrogens. As in the case of the ionization mechanism, the better the leaving group can accommodate an electron pair, the more facile will be its cleavage. Since nucleophilic participation assists the departure of the leaving group in the S_N2 transition state, however, we would anticipate that leaving-group effects on rate would be less pronounced in the direct displacement mechanism than in the ionization mechanism.

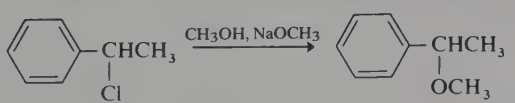
Again, it should be possible to make general predictions about the effect of solvent on the reaction rate. In the case of an anionic nucleophile reacting with a neutral substrate, charge is dispersed in the transition state for direct displacement, relative to the ground state. An increase in the dielectric constant of the medium will stabilize the ground state more than the transition state, leading to an increase in the activation energy and a decreased rate. This effect will be discussed more completely in Section 5.5.

The points we have emphasized in this brief overview of the S_N1 and S_N2 mechanism are kinetics and stereochemistry. These have traditionally been the most important pieces of evidence in ascertaining whether a particular nucleophilic substitution reaction follows an ionization or direct displacement pathway. There are limitations to the generalization that reactions exhibiting first-order kinetics react by the S_N1 mechanism, and those exhibiting second-order kinetics react by the S_N2 mechanism. Many nucleophilic substitution reactions are carried out under

conditions in which the nucleophile is present in overwhelming excess. Its concentration therefore does not vary within experimental error during the course of a reaction, and the kinetics become pseudo-first-order. The most common instance of this occurring is in solvolysis reactions in which the nucleophilic species is the solvent. Kinetic order cannot distinguish between a solvolysis taking place by concerted displacement and one proceeding by an ionization process. It is also often observed that the stereochemical test does not provide clear-cut answers, corresponding neither to complete inversion of configuration nor to complete racemization. Thus, it is not unusual to find examples in which the data do not allow assignment of a limiting-case mechanism to a nucleophilic substitution reaction. Such behavior has been described as "borderline,"[4] and the problem that must be addressed is whether borderline behavior results from competition between S_N1 and S_N2 pathways or is indicative of a mechanism or mechanisms different from S_N1 and S_N2. The types of compounds that exhibit borderline behavior include most secondary alkyl substrates, primary benzylic, and some secondary benzylic systems. These are among the most commonly encountered structural types in nucleophilic substitution reactions, so it is important that attempts at understanding the mechanistic details of borderline behavior be made.

5.3. Detailed Mechanistic Descriptions and Borderline Mechanisms

In their early work Hughes and Ingold considered that S_N1 and S_N2 pathways could be competitive reactions of a single substrate, and that borderline behavior resulted from a blend of the two processes. For example, they found that methanolysis of 1-phenylethyl chloride at 70°C is accelerated by sodium methoxide:



The kinetic order with respect to sodium methoxide is nonintegral. The reaction is neither first- nor second-order overall. The kinetic data could be fitted to the equation

$$\text{rate} = k_1\left[\begin{array}{c}C_6H_5CHCH_3\\ \\ Cl\end{array}\right] + k_2\left[\begin{array}{c}C_6H_5CHCH_3\\ \\ Cl\end{array}\right]\left[NaOCH_3\right]$$

where k_1 is the first-order rate constant for the S_N1 process and k_2 is the second-order rate constant for the S_N2 process. Analysis of the rate data led to the suggestion that at sodium methoxide concentrations of 3.5 *M*, 61% of the total reaction was occurring by an S_N2 mechanism and 39% by an S_N1 mechanism.[5]

4. S. Winstein, E. Grunwald, and H. W. Jones, *J. Am. Chem. Soc.* **73**, 2700 (1951).
5. E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1201 (1937).

This view of nucleophilic substitution reactions as concurrent S_N1 and S_N2 processes has persisted and is still occasionally offered as an explanation in some mechanistic studies. Most organic chemists, including Hughes and Ingold,[6] moved toward the idea that S_N1 and S_N2 define the extremes of a mechanistic continuum. At the S_N1 extreme, there is no covalent interaction of substrate and nucleophile in the transition state for cleavage of the bond between carbon and the leaving group. At the S_N2 extreme, bond making to the external nucleophile is highly advanced. In between these two extremes lies a large borderline area characterized by varying degrees of covalent interaction between substrate and nucleophile.

Detailed kinetic investigations, primarily concerned with salt effects on solvolysis reactions, led to the recognition of the importance of ion pairs in nucleophilic substitution. This work is most closely associated with Saul Winstein, who proposed the involvement of two distinct ion pair intermediates in solvolysis reactions.[7] This concept has since been refined and elaborated on by others, and is the most generally accepted interpretation of nucleophilic substitution reactions.[8]

Winstein suggested that in addition to the dissociated carbonium ion and counterion of the leaving group, two ion pair intermediates were required to reconcile the available data on kinetics, salt effects, and stereochemistry of solvolysis reactions. The process of ionization generates a carbonium ion and counterion in proximity to each other. This species is called an *intimate ion pair.* One process available to the intimate ion pair is conversion to a *solvent-separated ion pair,* in which one or more solvent molecules have inserted between the carbonium ion and the leaving group. Conversion of the solvent-separated ion pair to "free ions" occurs by diffusion of the solvated carbonium ion and counterion away from each other, and is referred to as *dissociation.*

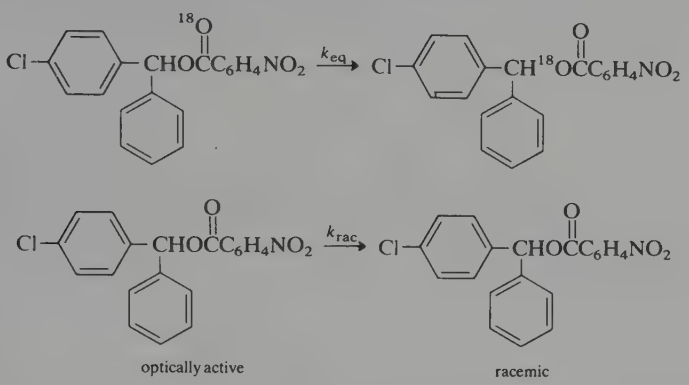
$$\underset{}{R{-}X} \overset{\text{ionization}}{\rightleftharpoons} \underset{\substack{\text{intimate}\\ \text{ion pair}}}{R^+X^-} \rightleftharpoons \underset{\substack{\text{solvent-}\\ \text{separated}\\ \text{ion pair}}}{R^+\|X^-} \overset{\text{dissociation}}{\rightleftharpoons} \underset{\substack{\text{dissociated}\\ \text{ions}}}{R^+ + X^-}$$

Not shown in the description above, but assumed to be important, is solvation at the rear side of R^+ in the ion pairs. According to this scheme, attack by a nucleophile or solvent can occur on the covalent substrate, the intimate ion pair, the solvent-separated ion pair, or on the dissociated carbonium ion. Nucleophilic attack on the covalent substrate or on the intimate ion pair will be akin to a displacement process and will take place with inversion of configuration. At the solvent-separated ion pair stage, collapse of the solvent shell can occur from the front to produce retention

6. M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 634 (1954).
7. S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck, and G. C. Robinson, *J. Am. Chem. Soc.* **78**, 328 (1956); S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc. Spec. Publ.* **No. 19**, 109, (1965).
8. J. M. Harris, *Prog. Phys. Org. Chem.* **11**, 89 (1974); D. J. Raber, J. M. Harris, and P. v. R. Schleyer, in *Ion Pairs*, M. Szwarc (ed.), John Wiley and Sons, New York, 1974, Chapter 3; T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.* **14**, 1 (1977).

of configuration or from the back to produce inversion, or the carbonium ion can become symmetrically solvated to produce racemic product. The macroscopic properties of the nucleophilic substitution reaction result from competition among these various processes.

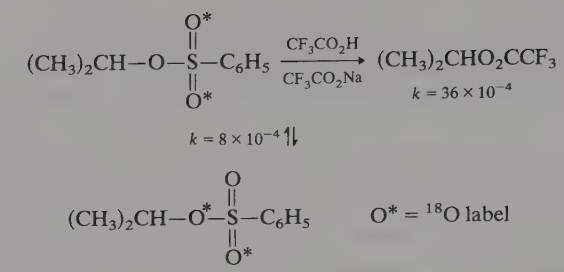
Several lines of evidence support the essential correctness of this scheme, especially the involvement of more than one ion pair intermediate. In 80% aqueous acetone, the rate constant for equilibration of the ^{18}O label in *p*-chlorobenzhydryl *p*-nitrobenzoate and the rate constant for racemization of optically active *p*-chlorobenzhydryl *p*-nitrobenzoate can each be measured[9].



At 100°C, $k_{eq}/k_{rac} = 2.3$. If it is assumed that ionization to *p*-nitrobenzoate ion completely randomizes the ^{18}O label, then k_{eq} is a measure of the total ion pair return, and k_{rac} is a measure of the extent of racemization associated with this return. The greater rate of equilibration compared to racemization is indicative of ion-pair return with predominant retention of configuration. In the presence of added sodium azide (0.14 *M*), k_{eq} is about the same, but k_{rac} goes to zero. This means that the highly nucleophilic azide ion intercepts the intermediate that would return with racemization, but is not intercepting the intermediate that returns with retention of configuration. The intermediate that is more easily intercepted is the solvent-separated ion pair, and the intermediate that is difficult to intercept is the intimate ion pair.

Various other cases have been studied in which isotopic labeling studies reveal that the bond between the leaving group and carbon is able to break without net substitution having occurred. A particularly significant case, since it applies to secondary tosylates which frequently exhibit borderline behavior, is isopropyl benzenesulfonate. During solvolysis of this compound in trifluoroacetic acid it is found that exchange among the sulfonate oxygens occurs at about one-third the rate of solvolysis[10]:

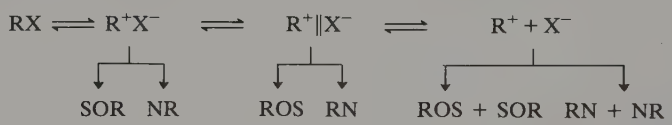
9. H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.* **86**, 120 (1964).
10. C. Paradisi and J. F. Bunnett, *J. Am. Chem. Soc.* **103**, 946 (1981).



This implies that ion pair formation and recombination is occurring competitively with ion pair diffusion and/or ion pair formation–substitution.

The "special salt effect" is another factor that requires at least two ion pair intermediates to be adequately explained.[11] Addition of salts typically causes an increase in the rate of solvolysis of secondary alkyl arenesulfonates that is linear with salt concentration. The effect of added lithium perchlorate is anomalous toward certain substrates in producing an initial sharp increase in the solvolysis rate, followed by the expected linear increase at higher lithium perchlorate concentrations. Winstein ascribed this to exchange between lithium perchlorate and the solvent-separated ion pair to form a solvent-separated carbonium ion perchlorate ion pair that does not undergo return to the intimate ion pair or covalent substrate. This new ion pair can go on only to product, and its formation leads to an increase in solvolysis rate more pronounced than for a simple medium effect.

Since ion pairs are undoubtedly important species, the question has arisen as to whether they might be universal intermediates. R. A. Sneen suggested that ion pairs are involved not only in S_N1 and borderline processes but also in displacements exhibiting the stereochemical and kinetic characteristics of the S_N2 process.[12] He suggested the following scheme which proposes that the S_N2 process results from stereospecific reaction of a nucleophile with the intimate ion pair:



where the solvent is SOH, and N^- is a nucleophilic anion.

Attack by solvent can occur with inversion of configuration at the intimate ion pair stage, with retention of configuration at the solvent-separated ion pair stage (simply a collapse of front-side solvation), or with racemization at the dissociated-ion stage. Attack by an external nucleophile can occur with inversion at the intimate ion-pair stage, or with racemization at the dissociated-ion stage. In most secondary systems, including those described as borderline, attack by nucleophile would occur at the intimate ion pair stage, leading to inversion of configuration. The reservation

11. S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.* **80**, 169 (1958).
12. R. A. Sneen and H. M. Robbins, *J. Am. Chem. Soc.* **94**, 7868 (1972); R. A. Sneen, *Acc. Chem. Res.* **6**, 46 (1973).

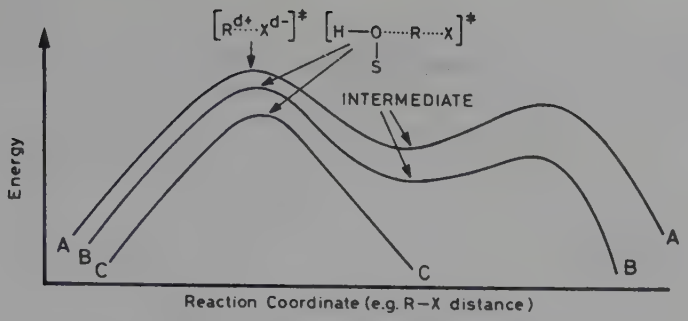


Fig. 5.4. Potential energy diagrams for substitution mechanisms. A is the S_N1 mechanism. B is the S_N2 mechanism with intermediate ion pair or pentacoordinate species. C is the classical S_N2 mechanism. Reproduced from T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.* **14**, 1 (1977).

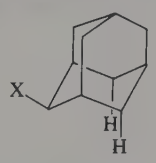
most commonly expressed concerning the universality of the ion pair mechanism has to do with the intervention of ion pairs in reactions of methyl and other primary substrates. Since primary carbonium ions are highly unstable, it seems unlikely that the required ionization would occur at rate sufficient to accommodate the range of successful substitution reactions on primary halides and sulfonates. The most generally held view remains that the S_N2 mechanism represents a distinct process characterized by the onset of bonding to the nucleophile *before* ionization has occurred.[13]

Current mechanistic thinking envisages the limiting S_N1 ionization and concerted S_N2 processes as being bridged by a range of transition state and intermediate structures differing in the extent of nucleophilic participation by the solvent and in the extent of charge separation at the transition state.[14] Also recognized is the importance of ion pair intermediates which may be in equilibrium with substrate and can react with nucleophile with second-order kinetics. These possibilities are illustrated in Fig. 5.4 which shows the potential energy diagrams characteristic of the S_N1, concerted S_N2 and S_N2 (intermediate) versions of the substitution mechanism. These mechanisms are seen to differ in the depth of the depression corresponding to the charge-separated intermediate. For the concerted S_N2 mechanism, charge separation is never achieved because the nucleophile smoothly bonds to the reaction center as the leaving group departs. In the S_N2 (intermediate) process the minimum is shallow, corresponding to an intermediate with a short lifetime. This could be a charge-dispersed species with partial bonding to a nucleophile or an ion pair intermediate. Solvent participation would be important at this intermediate. The S_N1 process is characterized by a more pronounced minimum in energy at the intermediate, corresponding to greater carbonium ion stability. Since the rate of ionization in

13. D. J. McLennan, *Acc. Chem. Res.* **9**, 281 (1976).
14. A general discussion of the relationship between structure, solvent nucleophilicity, and substitution mechanisms is given by T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.* **14**, 1 (1977).

an S_N1 process is independent of the nucleophile, it follows that the transition state for ionization is reached without nucleophilic participation. The specific behavior of a particular system will depend upon all the variables which characterize a substitution process. These include especially the nucleophilicity and ionizing power of the solvent, the nature and concentration of other nucleophilic species, and reactant structure, particularly the ease of back-side approach.

The important role of nucleophilic solvent participation in solvolysis reactions should be noted. Since in solvolysis no nucleophile other than the solvent participates, it is clear that a change toward an S_N1-type mechanism should occur as solvent nucleophilicity decreases. The types of solvents which minimize nucleophilic participation are those in which high electronegativity of the constituent atoms reduces the basicity and polarizability of the solvent molecules. Trifluoroacetic acid and fluorinated alcohols are regarded as being the least nucleophilic of solvents commonly used in solvolysis studies.[15] These solvents are used to define the characteristics of reactions proceeding without nucleophilic solvent participation. Solvent nucleophilicity increases with electron-releasing capacity of the molecule. The order trifluoroacetic acid < trifluoroethanol < acetic acid < water < ethanol gives a qualitative indication of the trend in solvent nucleophilicity. Substrate structure also will influence the degree of nucleophilic participation of solvent. Solvation is minimized by steric hindrance and the 2-adamantyl system is regarded as being a secondary substrate which cannot accommodate significant back-side nucleophilic participation.



The 2-adamantyl system has been studied as a model reactant for defining the characteristics of ionization without nucleophilic participation. The degree of nucleophilic participation in other reactions can then be estimated by comparison with the 2-adamantyl system.

5.4. Carbonium Ions

It is clear that since carbonium ions are key intermediates in many nucleophilic substitution reactions, we will need to develop a grasp of the structural properties of carbonium ions and, in particular, the nature of substituent effects. The critical step of any ionization mechanism for nucleophilic substitution is the generation of a tricoordinate carbocation in the rate-determining step. It is essential, then, that

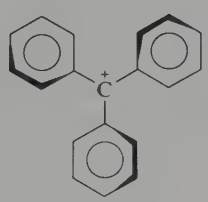
15. T. W. Bentley, C. T. Bowen, D. H. Morten, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **103**, 5466 (1981).

such a species not be prohibitively high in energy. The production of carbonium ions in the gas phase is a particularly unfavorable process. The heat of formation of $(CH_3)_3C^+$ (*tert*-butyl cation) is +162 kcal/mol, compared with −32 kcal/mol for $(CH_3)_3CH$.[16] The reaction

$$(CH_3)_3CCl \rightarrow (CH_3)_3C^+ + Cl^-$$

again in the gas phase, is very endothermic, with ΔH estimated to be +157 kcal/mol.[17] Activation energies of this magnitude would lead to unobservably slow reactions at normal temperatures. Carbonium ion formation in solution, on the other hand, is facilitated by solvation of the ions produced, and there is an abundance of evidence lending credence to the belief that the intermediacy of carbonium ions in nucleophilic substitution reactions is energetically attainable. The earliest studies were concerned with a very stable class of carbonium ions, those of the triarylmethyl type, and were spurred by the observations that triphenylmethyl chloride (trityl chloride) gave conducting solutions when dissolved in liquid sulfur dioxide, and produced colored, salt-like materials when treated with Lewis acids such as aluminum chloride.[18]

In contrast to triphenylmethyl chloride, which is covalent, triphenylmethyl perchlorate is ionic. The carbocation nature of triphenylmethyl perchlorate is definitively supported by an X-ray crystal structure determination.[19] The salt-like structure is confirmed. The three bonds to the central carbon atom are coplanar, but the three phenyl rings are at an angle of 54° to the plane of the central carbon, giving the cation the overall appearance of a propeller-shaped species. The propeller shape is also indicated for triarylmethyl cations in solution, from analysis of their temperature-dependent NMR spectra.[20] The twisting of the aromatic rings with respect to each other is presumed to result from van der Waals repulsions between the *ortho* hydrogens.



Because of their stability and ease of generation, triarylmethyl cations have been the subject of numerous quantitative studies aimed at determining the effects of structure on carbonium ion stability. Most of these studies have utilized ultraviolet

16. R. G. McLoughlin and J. C. Traeger, *J. Am. Chem. Soc.* **101**, 5791 (1979).
17. A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1962, p. 181.
18. Reviews of the arylmethyl cations include C. D. Nenitzescu, Chap. 1, Vol. I and H. H. Freedman, Chap. 28, Vol. IV in *Carbonium Ions*, G. A. Olah and P. v. R. Schleyer (eds.), Wiley–Interscience, New York, 1968, 1973.
19. A. H. Gomes de Mesquita, C. H. MacGillavry, and K. Eriks, *Acta Crystallogr.* **18**, 437 (1965).
20. I. I. Schuster, A. K. Colter, and R. J. Kurland, *J. Am. Chem. Soc.* **90**, 4679 (1968).

Table 5.1. Values of H_R for Sulfuric Acid–Water Mixtures[a]

Sulfuric acid (%)	H_R
1	0.92
3	0.37
5	−0.07
10	−0.72
25	−2.55
50	−6.60
70	−11.52
80	−14.12
90	−16.72
92	−17.24
94	−17.78
96	−18.45
98	−19.64

a. At 25°C; the values are taken from N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.* **77**, 3044 (1955).

spectroscopy as the probe and have taken advantage of the difference in electronic spectra between the carbonium ion and a covalent precursor, usually the corresponding triarylcarbinol. This permits determination of the equilibrium constant for the reaction

$$R^+ + H_2O \rightleftharpoons ROH + H^+$$

The stability of a carbonium ion can then be represented by its pK_{R^+}, which is given by

$$pK_{R^+} = \log \frac{[R^+]}{[ROH]} + H_R$$

where H_R is an acidity function defined for the medium.[21] (See Section 4.6 to review the general principles of acidity functions.) In dilute aqueous solution, H_R is equivalent to pH, and pK_{R^+} becomes the pH at which the carbonium ion and the alcohol are present in equal concentrations at equilibrium. In strongly acidic media, for example, >0.1 *M* perchloric acid, pH is no longer an accurate indicator of the proton-donating power of the medium. Comparison with the H_0 acidity function discussed in Section 4.6 shows that H_R increases considerably more steeply than the H_0 function. Notice also that the effect of increasing the concentration of sulfuric acid is not linear. (See Table 5.1.) In the range 1%–50% sulfuric acid, H_R becomes more negative by 7.5 units, but in the range 50%–98% sulfuric acid, it becomes more negative by 13 units.

Carbonium ion stabilities may then be compared by reference to pK_{R^+}. The more positive the pK_{R^+} value, the more stable the carbonium ion. Stability in this

21. N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.* **77**, 3044 (1955).

Table 5.2. Values of pK_{R^+} for Some Carbonium Ions[a]

Carbonium ion	pK_{R^+}
Triarylmethyl Cations	
Triphenylmethyl	−6.63
4,4′,4″-Trimethyltriphenylmethyl	−3.56
4-Methoxytriphenylmethyl	−3.40
4,4′-Dimethoxytriphenylmethyl	−1.24
4,4′,4″-Trimethoxytriphenylmethyl	+0.82
4,4′,4″-Trichlorotriphenylmethyl	−7.74
4-Nitrotriphenylmethyl	−9.15
4,4′,4″-Trinitrotriphenylmethyl	−16.27
4,4′,4″-Tri(dimethylamino)triphenylmethyl	+9.36
Sesquixanthydryl[b]	+9.05
Diarylmethyl Cations	
Diphenylmethyl	−13.3
4,4′-Dimethyldiphenylmethyl	−10.4
4,4′-Dimethoxydiphenylmethyl	−5.71
2,2′,4,4′,6,6′-Hexamethyldiphenylmethyl	−6.6
4,4′-Dichlorodiphenylmethyl	−13.96
Miscellaneous Carbonium Ions	
Tricyclopropylmethyl cation[c]	−2.3
Tropylium cation (cycloheptatrienyl cation)[d]	+4.7
Triphenylcyclopropenyl cation[e]	+3.1
Trimethylcyclopropenyl cation[f]	+7.8
Tricyclopropylcyclopropenyl cation[g]	+9.7

a. Unless otherwise indicated, the pK_{R^+} values are taken from: N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Am. Chem. Soc.* **77**, 3044 (1955); for an extensive compilation of similar data, see H. H. Freedman, in *Carbonium Ions*, Vol. IV, G. A. Olah and P. v. R. Schleyer (eds.), Wiley–Interscience, New York, 1973, Chap. 28.

b. J. C. Martin and R. G. Smith, *J. Am. Chem. Soc.* **86**, 2252 (1964).

c. N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *J. Am. Chem. Soc.* **87**, 4533 (1965).

d. W. E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **76**, 3203 (1954).

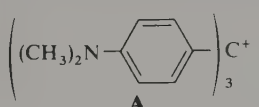
e. R. Breslow, H. Höver, and H. W. Chang, *J. Am. Chem. Soc.* **83**, 2375 (1961).

f. J. Ciabattoni and E. C. Nathan, III, *Tetrahedron Lett.*, 4997 (1969).

g. K. Komatsu, I. Tomioka, and K. Okamoto, *Tetrahedron Lett.*, 947 (1980), R. A. Moss and R. C. Munjal, *Tetrahedron Lett.*, 1221 (1980).

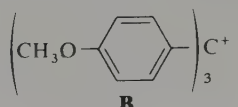
sense refers to the carbonium ion in equilibrium with the parent alcohol, and does not imply kinetic stability. Some carbonium ions are easily generated, but undergo rapid, irreversible conversion to other materials such as polymers or rearranged products. Table 5.2 presents the pK_{R^+} values of a number of relatively stable carbonium ions. The data clearly indicate the sensitivity of carbonium ions to stabilization by electron-releasing substituents. Substitution by *para*-methoxy groups increases the value of pK_{R^+}; substitution by *para*-nitro groups makes pK_{R^+} more negative. By referring the pK_{R^+} values to H_R for water–sulfuric acid mixtures given in Table 5.1, one can appreciate the sensitivity of carbonium ion stability to the electron-releasing or -withdrawing properties of the substituent. Triphenylmethyl cation and triphenylcarbinol exist in equal concentrations at equilibrium in 50% sulfuric acid. The

corresponding figures for 4,4′,4″-trimethoxytriphenylmethyl cation and 4,4′,4″-trinitrotriphenylmethyl cation in equilibrium with equal concentrations of their corresponding alcohols are 1.2% and 88% sulfuric acid, respectively. The greater electron-releasing properties of a dimethylamino substituent compared to a methoxy substituent can be seen in the relative stabilities of the two cations **A** and **B**.



A

4,4′,4″-tri(dimethylamino) triphenylmethyl cation, pK_{R^+} +9.36



B

4,4′,4″-trimethoxy triphenylmethyl cation, pK_{R^+} +0.82

The diarylmethyl cations listed in Table 5.2 are 6–7 pK_{R^+} units less stable with respect to the corresponding carbinols than the triarylmethyl cations, illustrating the cumulative, although not necessarily linear, effect of increasing stabilization by aryl groups.

Primary benzylic cations (monoarylmethyl cations) are not sufficiently stable with respect to equilibration with the parent alcohol to have their pK_{R^+} values determined. The 2,4,6-trimethylbenzyl cation is a rather stable example of this type of carbonium ion, and has a pK_{R^+} of −17.4, corresponding to equal concentrations of carbonium ion and alcohol in 93% sulfuric acid.

One of the most important and general trends in organic chemistry is the increase in carbonium ion stability with additional alkyl substitution at the carbonium ion site. This stability relationship is fundamental to understanding many aspects of reactivity, including nucleophilic substitution. In recent years it has been possible to put the stabilization effect on a quantitative basis. One approach has been gas phase measurements which determine the proton affinity of alkenes resulting in carbocation formation. From these data the hydride affinity of the carbonium ion can be obtained. These data provide a thermodynamic basis for comparison of the

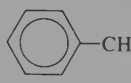
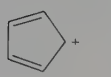
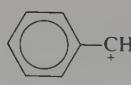
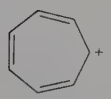
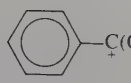
$$R^+ + H^- \rightarrow R{-}H, \qquad -\Delta H^\circ = \text{hydride affinity}$$

relative stability of nonisomeric carbocations. As shown in Table 5.3, the stability order found tertiary > secondary > primary > methyl is the same as the kinetic order which is observed in solvolysis studies.

Since the data upon which these stability measurements rest pertain to the gas phase it is important to consider the possible changes that solvent effects might have on structure–stability relationships. It has been possible to obtain thermodynamic data for the ionization of alkyl chlorides by reaction with SbF_5 in non-nucleophilic solvents such as SO_2ClF.[22] As long as subsequent reactions of the carbonium ions can be avoided, the thermodynamic data provide a measure of the

22. E. M. Arnett and N. J. Pienta, *J. Am. Chem. Soc.* **102**, 3329 (1980).

Table 5.3. Hydride Affinity of Some Carbocations

	Hydride affinity (kcal/mol)[a]		
CH_3^+	314[b]	$CH_2{=}CHCH_2^+$	256
$CH_3CH_2^+$	274[b]	$CH_2{=}CH\overset{+}{C}HCH_3$	237
$(CH_3)_2CH^+$	247[b]	$CH_2{=}CH\overset{+}{C}(CH_3)_2$	225
$(CH_3)_3C^+$	230[b]	$CH_3CH{=}CH\overset{+}{C}HCH_3$	225
	223		233
	258		226
	200		220

a. Except where noted data is from D. H. Aue and M. T. Bowers, in *Gas Phase Ion Chemistry*, M. T. Bowers (ed.), Academic Press, New York, 1979.
b. F. A. Houle and J. L. Beauchamp, *J. Am. Chem. Soc.* **101**, 4067 (1979).

relative ease of carbonium ion formation in solution. It has been found that the

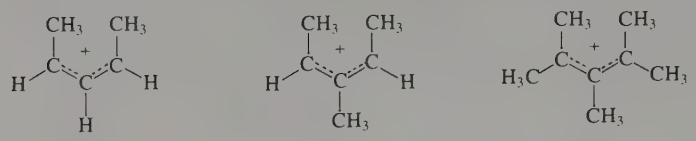
$$RCl + SbF_5 \xrightarrow{SO_2ClF} R^+ + [SbF_5Cl]^-$$

solvation energy for carbonium ions in this solvent is quite small and the individual values for the various carbonium ions are quite similar. As a result, there is an excellent correlation between the solution results and gas phase data in terms of both the stability order and the energy difference between various carbonium ions. A plot of the enthalpy of ionization versus hydride affinity for a series of carbonium ions gives a good correlation with a correlation coefficient of 0.973. The slope of the line is 1.63, revealing a greater dependence of stability on structure in the gas phase. This presumably reflects stabilization by association with the counterion in solution. The difference in hydride affinity indicates a gap of 17 kcal/mol between tertiary and secondary carbonium ions, and a somewhat larger one is found between secondary and primary carbonium ions (see Table 5.3). The ionization energy difference between *t*-butyl chloride ($\Delta H = -24.8$ kcal/mol) and 2-propyl chloride ($\Delta H = -15.3$ kcal/mol) suggests that this gap is narrowed to 9.5 kcal/mol in SO_2ClF solution.

An independent measurement of the energy difference between secondary and tertiary cations in solution comes from a calorimetric measurement of the enthalpy of isomerization of the 2-butyl cation to the *t*-butyl cation.[23] This value was measured

23. E. W. Bittner, E. M. Arnett, and M. Saunders, *J. Am. Chem. Soc.* **98**, 3734 (1976).

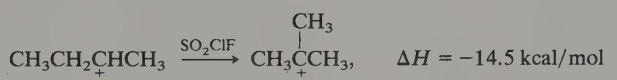
Scheme 5.2. Rotational Energy Barriers for Allyl Cations (kcal/mol)[a]



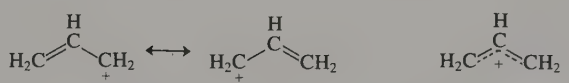
18.7 18.1 13.8

a. From J. M. Bollinger, J. M. Brinich, and G. A. Olah, *J. Am. Chem. Soc.* **92**, 4025 (1970).

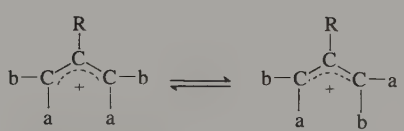
by reaction of 2-butyl chloride with SbF_5 in SO_2ClF. The 2-butyl cation is initially formed and the evolution of heat associated with the subsequent rearrangement can then be determined.



Any other structural effect which reduces the electron deficiency at a carbonium ion center will have the effect of stabilizing the carbocation. Allyl cations are stabilized by delocalization involving the adjacent double bond. The π-electron



delocalization requires appropriate geometry for orbital alignment. In the case of the allyl cation a structural consequence is a significant barrier to rotation about the bonds between carbons. The exact height of the barrier depends upon the substituent groups a, b, and R. Some values which have been measured are shown in Scheme 5.2.



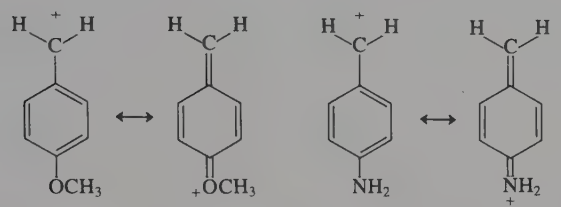
Benzyl cation stability is strongly affected by the substituents on the benzene ring. A molecular orbital approach to estimating the stabilizing influence of substituents using STO-3G level calculations indicates that such strong π donors as *p*-amino and *p*-methoxy stabilize the benzyl cation by 26 and 14 kcal/mol, respectively. On the other hand, electron-attracting groups such as *p*-cyano and *p*-nitro are destabilizing by 12 and 20 kcal/mol, respectively.[24]

24. W. J. Hehre, M. Taagepera, R. W. Taft, and R. D. Topsom, *J. Am. Chem. Soc.* **103**, 1344 (1981).

Table 5.4. Destabilization of 2-Propyl Cation by Electron-Withdrawing Substituents

Z	Solvolysis rate relative to Z = H	Destabilization (kcal/mol) energy relative to Z = H
CN	$\sim 10^{-3}$ [a]	9.9[b]
CF_3	$\sim 10^{-6}$ [c]	37.3[b]
CH=O	—	6.1[b]

a. P. G. Gassman and J. J. Talley, *J. Am. Chem. Soc.* **102**, 1214 (1980).
b. M. N. Paddon-Row, C. Santiago, and K. N. Houk, *J. Am. Chem. Soc.* **102**, 6561 (1980).
c. K. M. Koshy and T. T. Tidwell, *J. Am. Chem. Soc.* **102**, 1216 (1980).

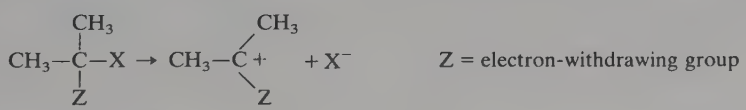


Adjacent atoms with one or more lone pairs of electrons strongly stabilize a carbonium ion. Alkoxy and dialkylamino groups are familiar examples of this effect.

$$CH_3\ddot{O}-\overset{+}{C}H_2 \leftrightarrow CH_3\overset{+}{\ddot{O}}=CH_2, \qquad (CH_3)_2\ddot{N}-\overset{+}{C}H_2 \leftrightarrow (CH_3)_2\overset{+}{N}=CH_2$$

Although these structures have a positive charge on a more electronegative atom, they benefit from an additional bond which satisfies the octet rule at each atom. These "carbonium ions" are well represented by the doubly bonded structures. This stabilization persists even with fluorine, although the π-donor effect of the fluorine atom is counterbalanced by its inductive effect. The gas phase stability order $F_2\overset{+}{C}H > F\overset{+}{C}H_2 > F_3\overset{+}{C} > H_3\overset{+}{C}$ reflects these two opposing trends.[25]

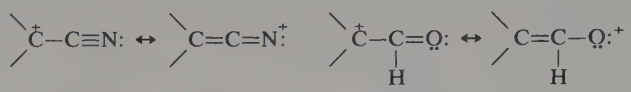
Electron-withdrawing groups which are substituted directly on the cationic site are destabilizing. Table 5.4 gives an indication of the relative retardation of ionization processes and the destabilization calculated by molecular orbital (4-31G) calculations. The trifluoromethyl group, which exerts a powerful inductive effect, is strongly



destabilizing on the basis of both kinetic data and the MO calculations. The cyano and formyl groups are less so. In fact, the destabilization is considerably less than

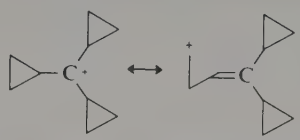
25. R. J. Blint, T. B. McMahon, and J. L. Beauchamp, *J. Am. Chem. Soc.* **96**, 1269 (1974).

would be predicted on the basis of inductive substituent constants. Both the cyano and formyl groups can act as π donors, even though the effect is to place partial positive charge on nitrogen and oxygen atoms, respectively. The relevant resonance structures are depicted below:

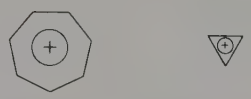


Such interactions are reflected in MO energies, bond lengths, and charge distributions.[26] The resonance structures are essentially nitrogen and oxygen analogs of the familiar allyl cation. The effect of this π delocalization is to attenuate the unfavorable inductive electron withdrawal by these substituents.

Several very stable carbonium ions are included in the "Miscellaneous" part of Table 5.2. These ions are remarkably stable, considering that they do not bear electron-releasing heteroatom substituents such as oxygen or nitrogen. The tricyclopropylmethyl cation is half-formed from tricyclopropylcarbinol in 23% sulfuric acid, conditions less acidic than those for formation of triphenylmethyl cation from triphenylcarbinol.[27] A cyclopropyl substituent therefore must have a substantial electron-releasing effect. The stabilization of carbonium ions by cyclopropyl substituents is believed to result from interaction of the electrons in the ring C–C bonds with the positive center. The strain in the three-membered ring is reflected in higher *p*-character in these bonds; the electrons are of higher energy than electrons in normal C–C bonds, and more able to be delocalized into the vacant *p*-orbital of the carbonium ion carbon. In valence bond terminology, the effect is one of carbon–carbon hyperconjugation enhanced by the strain in the ring bonds. For tricyclopropylmethyl cation, alternative resonance structures such as those shown below may be written to describe the electron delocalization:



Tropylium cation and the substituted cyclopropenyl cations cited in Table 5.2 are of interest in that their ease of formation provides experimental support for the Hückel $4n + 2$ rule of aromatic stability. Both types contain planar monocyclic systems of sp^2-hybridized atoms with two π electrons ($n = 0$) in the cyclopropenyl cations and six π electrons ($n = 1$) in tropylium cation.



tropylium cation cyclopropenyl cation

26. D. A. Dixon, P. A. Charlier, and P. G. Gassman, *J. Am. Chem. Soc.* **102**, 3957 (1980); M. N. Paddon-Row, C. Santiago, and K. N. Houk, *J. Am. Chem. Soc.* **102**, 6561 (1980).
27. For a review of cyclopropylmethyl cations, see H. G. Richey, Jr., in *Carbonium Ions*, Vol. III, G. A. Olah and P. v. R. Schleyer (eds.), Wiley–Interscience, New York, 1972, Chap. 25.

Carbonium ion stabilities may be linked to the S_N1 mechanism by comparing pK_{R^+} values with solvolysis rates. A linear relationship has been found to exist between the relative rates of solvolysis of diarylchloromethanes in methanol, ethanol, and 2-propanol and the pK_{R^+} of the corresponding diarylcarbinol.[28] The most reasonable explanation for this correlation is that the free energy of activation for solvolysis of the diarylmethyl chlorides corresponds to that required for ionization of the carbon–chlorine bond to a carbonium ion-chloride ion pair.

A major advance in techniques for direct study of carbonium ions was made during the decade of the 1960's with the application of NMR spectroscopy in so-called "superacid" media to the direct spectroscopic study of carbonium ions. This technique made it possible to observe alkyl cations and other less stable ions, the pK's of which are not readily measured. In fact, the method is so versatile and the information gained so much more valuable than simple stability measurements that it is now the method of first choice in probing carbonium ion structure.

The term *superacid* refers to media of high proton-donating power, that is, more acidic than 96%–100% sulfuric acid. Furthermore, the nucleophilicity of the medium is quite low, and stable solutions containing carbonium ions in concentrations suitable for NMR study can be prepared.[29] Fluorosulfonic acid, FSO_3H, is a very useful superacid. It is a better proton donor than sulfuric acid, as measured by H_0 ($FSO_3H = -13.9$, $H_2SO_4 = -12.1$), is not very viscous and has a low freezing point of $-89°$.[30] The low viscosity and low freezing point are desirable properties in any solvent employed in NMR investigations. Fluorosulfonic acid combined with antimony pentafluoride is an even more potent protonating agent, and dilution with liquid sulfur dioxide gives a fluid medium of low freezing point. The ability of this medium to protonate very weakly basic substrates, including hydrocarbons, has led to its being dubbed "magic acid."[31] Antimony pentafluoride, either neat or diluted with sulfur dioxide, has been employed to generate carbonium ions from alkyl halides. Anhydrous hydrogen fluoride has H_0 of -10, which makes it a very effective protonating agent by itself; in combination with SbF_5, its acidity is considerably enhanced.

Scheme 5.3 illustrates the use of superacid media in the study of carbonium ion generation, structure, and reactions by NMR spectroscopy. The behavior of primary, secondary, and tertiary aliphatic alcohols on being dissolved in FSO_3H–SbF_5–SO_2 at $-60°C$ provides direct support for the dictum that tertiary carbonium ions are more stable than secondary, which are more stable than primary. Primary and secondary alcohols are protonated under these conditions, and the protonated alcohols are the species observed (entry 1), while *tert*-butyl alcohol yields *tert*-butyl cation at rates too

28. N. C. Deno and A. Schriesheim, *J. Am. Chem. Soc.* **77**, 3051 (1955).
29. G. A. Olah, M. B. Comisarow, C. A. Cupas, and C. U. Pittman, Jr., *J. Am. Chem. Soc.* **87**, 2997 (1965).
30. R. J. Gillespie, *Acc. Chem. Res.* **1**, 202 (1968).
31. G. A. Olah and J. Lukas, *J. Am. Chem. Soc.* **89**, 4739 (1967); G. A. Olah and R. H. Schlosberg, *J. Am. Chem. Soc.* **90**, 2726 (1968).

Scheme 5.3. Protonation and Ionization

Aliphatic alcohols in FSO_3H–SbF_5–SO_2

1[a] $ROH \xrightarrow{-60^\circ C} \overset{+}{R}OH_2$

R = methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *n*-amyl, isoamyl, neopentyl, *n*-hexyl, neohexyl

2[a] $(CH_3)_2CHCH_2OH \xrightarrow{-60^\circ C} (CH_3)_2CHCH_2\overset{+}{O}H_2 \xrightarrow{-30^\circ C} (CH_3)_3C^+$

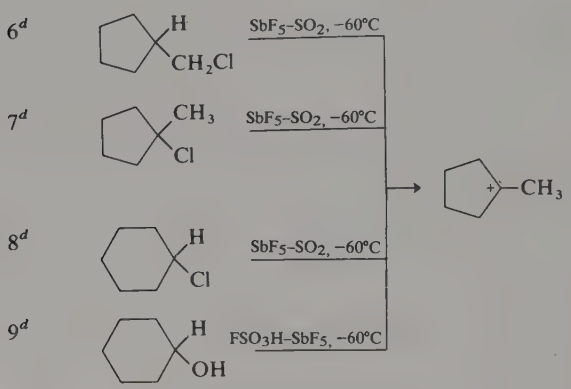
3[a] $(CH_3)_3COH \xrightarrow{-60^\circ C} (CH_3)_3C^+$

Alkyl halides in antimony pentafluoride

4[b] $CH_3\underset{\displaystyle F}{\underset{|}{C}}HCH_2CH_3 \xrightarrow{-110^\circ C} CH_3\overset{+}{C}HCH_2CH_3 \xrightarrow{-40^\circ C} (CH_3)_3C^+$

5[c] $CH_3OCH_2Cl \xrightarrow{-60^\circ C} CH_3O\overset{+}{C}H_2$

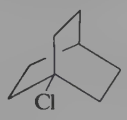
Cyclopentylmethyl and cyclohexyl systems



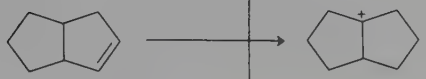
fast to measure. The rates of cleavage of protonated primary and secondary alcohols depend on their structure. Protonated *sec*-butyl alcohol cleaves with rearrangement to $(CH_3)_3C^+$ and water slowly at −60°C, protonated isobutyl alcohol cleaves with rearrangement at −30°C, and protonated *n*-butyl alcohol at 0°C. It is typical of reactions in superacid media that the most stable ion of an isomeric family is observed because, under conditions in which the ions are long-lived, intramolecular hydride shifts and rearrangement processes occur that lead ultimately to the most thermodynamically stable carbonium ion. Thus, $(CH_3)_3C^+$ is formed as the only detectable carbonium ion from all the butanol isomers, and *tert*-amyl and *tert*-hexyl cations from the C_5 and C_6 alcohols. If the ionization is carried out at −110°C, it is possible to detect secondary alkyl cations, as in the case of *sec*-butyl cation (entry 4), and to

Bicyclooctyl systems in SbF_5–SO_2ClF, −78°C

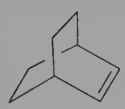
10[e]



11[e]

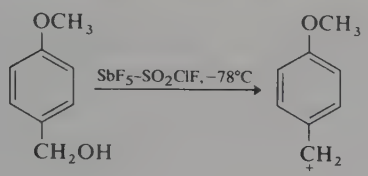


12[e]

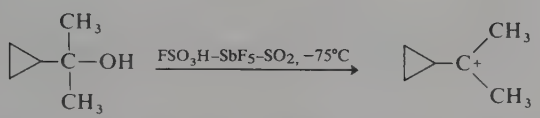


Benzylic and cyclopropylcarbinyl systems

13[f]



14[g]



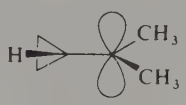
a. G. A. Olah, J. Sommer, and E. Namanworth, *J. Am. Chem. Soc.* **89**, 3576 (1967).
b. M. Saunders, E. L. Hagen, and J. Rosenfeld, *J. Am. Chem. Soc.* **90**, 6882 (1968).
c. G. A. Olah and J. M. Bollinger, *J. Am. Chem. Soc.* **89**, 2993 (1967).
d. G. A. Olah, J. M. Bollinger, C. A. Cupas, and J. Lukas, *J. Am. Chem. Soc.* **89**, 2692 (1967).
e. G. A. Olah and G. Liang, *J. Am. Chem. Soc.* **93**, 6873 (1971).
f. G. A. Olah, R. D. Porter, C. L. Juell, and A. M. White, *J. Am. Chem. Soc.* **94**, 2044 (1972).
g. C. U. Pittman, Jr., and G. A. Olah, *J. Am. Chem. Soc.*, **87**, 2998 (1965).

monitor kinetically its rearrangement to *tert*-butyl cation. Primary carbonium ions cannot be detected under these conditions. Protonated methanol is stable up to +50°C and protonated ethanol to +30°C, whereupon extensive decomposition occurs, leading to unidentified materials. Protonated *n*-propyl alcohol undergoes slow conversion at 0°C to *tert*-butyl cation.

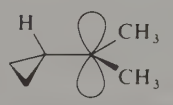
Entries 6–9 and 10–12 illustrate the tendency for rearrangements to occur leading to the most stable cation in each particular system. The tertiary 1-methylcyclopentyl cation is the only ion observed from a variety of precursors containing five- and six-membered rings. The tertiary bicyclo[3.3.0]octyl cation is formed from all bicyclooctyl precursors. As previously mentioned, the tendency to rearrange to thermodynamically stable ions by multiple migrations is a consequence

of the much-reduced nucleophilicity of the medium employed. It is more pronounced than the tendency toward rearrangement in nucleophilic substitution reactions. Rearrangements under solvolytic conditions will be discussed in Section 5.11.

An early success of NMR studies in superacid media dealt with the determination of the preferred conformation of cyclopropylcarbinyl cations. The NMR spectrum of dimethylcyclopropylcarbinyl cation (entry 14) exhibits signals for two nonequivalent methyl groups, clearly supporting the "bisected" conformation. An alternative conformation, the "perpendicular" conformation, would exhibit a single peak for two equivalent methyl groups. Subsequent work established the rotational

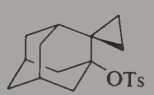


bisected conformation

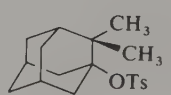


perpendicular conformation

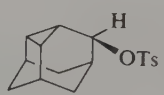
barrier as 13.7 kcal/mol.[32] Solvolysis rate studies are in accord with NMR measurements in indicating a greater stabilization of the bisected conformation of a cyclopropylcarbinyl cation than the perpendicular conformation. Tosylate **2**, in which the cyclopropane ring is locked into an orientation so as to afford a perpendicular cyclopropylcarbinyl cation on ionization, undergoes acetolysis 300 times more slowly than the model compound **3**.[33] Tosylate **4**, locked into the bisected geometry on ionization, undergoes acetolysis at least 10^5 times faster than 2-adamantyl tosylate **5**.[34]



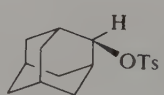
2



3



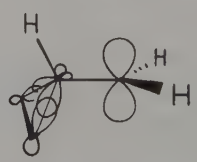
4



5

Molecular orbital concepts provide an explanation for the preference for the bisected conformation. In the bisected conformation of the cyclopropylcarbinyl cation, the bent σ bonds of the cyclopropane ring are arranged in such a way as to

bisected conformation

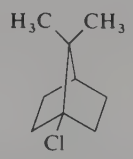


perpendicular conformation

32. C. U. Pittman, Jr., and G. A. Olah, *J. Am. Chem. Soc.* **87**, 5123 (1965); D. S. Kabakoff and E. Namanworth, *J. Am. Chem. Soc.* **92**, 3234 (1970).
33. B. R. Ree and J. C. Martin, *J. Am. Chem. Soc.* **92**, 1660 (1970).
34. J. E. Baldwin and W. D. Foglesong, *J. Am. Chem. Soc.* **90**, 4303 (1968).

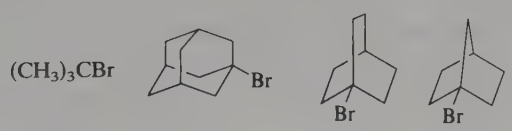
permit overlap with the *p* orbital, allowing the electrons in these bonds to stabilize the carbonium ion. In the perpendicular conformation, the alignment is much less satisfactory. The C–H bond is aligned to permit hyperconjugation but the C–C bonds are not well aligned for interaction.

Up to this point in our discussion, we have considered only carbonium ions in which the cationic carbon is sp^2-hybridized or nearly so, and in which the geometry at the cationic center is planar. When either of these conditions is not met, the carbonium ion is of higher energy. Discussing first the geometric requirement, one of the classic experiments of organic chemistry was that carried out by Bartlett and Knox, who showed the inertness of 1-chloroapocamphane toward nucleophilic substitution reactions.[35]



Starting material could be recovered unchanged after refluxing 48 h in ethanolic silver nitrate. The low reactivity was ascribed to the strain that develops on formation of a carbonium ion at the bridgehead position. The structure of the bicyclic system precludes adoption of a planar geometry around the cationic carbon, and requires a greater activation energy for the ionization step. Direct displacement of chloride with inversion of configuration is impossible, so the S_N2 mechanism is also precluded.

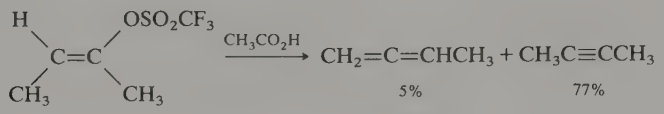
The apocamphyl case is an extreme one, and bridgehead carbonium ions in other systems are more accessible.[36] Inclusion of more atoms in the bridge gives a more flexible molecule and allows carbonium ion formation to proceed with a somewhat lower activation energy. Thus, the relative solvolysis rates of the bridgehead bromides 1-bromoadamantane, 1-bromobicyclo[2.2.2]octane, and 1-bromobicyclo[2.2.1]heptane in 80% ethanol at 25°C are 1, 10^{-3}, and $^{-10}$. Under the same conditions, the rate of solvolysis of *tert*-butyl bromide is 1000 times that of 1-bromoadamantane. The 1-adamantyl cation is sufficiently stable to be generated in antimony pentafluoride in concentrations sufficient for observation by NMR.[37]

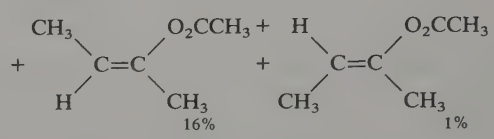


Carbonium ions in which the cationic carbon is *sp* hybridized are of higher energy because of the greater electronegativity associated with increasing *s* character.

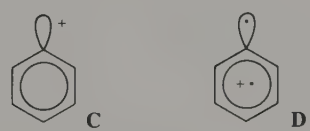
35. P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.* **61**, 3184 (1939).
36. A review of bridgehead carbonium ions is given by R. C. Fort, Jr., in *Carbonium Ions*, Vol. IV, G. A. Olah and P. v. R. Schleyer (ed.), Wiley–Interscience, New York, 1973, Chap. 32.
37. P. v. R. Schleyer, R. C. Fort, Jr., W. E. Watts, M. B. Comisarow, and G. A. Olah, *J. Am. Chem. Soc.* **86**, 4195 (1964).

It has been estimated that vinyl cation, $CH_2{=}CH^+$, lies between ethyl cation and methyl cation in its stability. The intermediacy of substituted vinyl cations in solvolysis reactions has been demonstrated, but no evidence has yet been presented for their direct observation by NMR.[38] Even the addition of stabilizing substituents such as methoxyphenyl has failed to yield observable vinyl cations.[39] Vinyl cations are, however, intermediates in solvolysis reactions involving very good leaving groups, specifically trifluoromethanesulfonates (triflates). The products of such reactions are allenes, acetylenes, and vinyl esters. For both trifluoroacetic acid and acetic acid solvolysis the vinyl esters are mixtures of *Z* and *E* isomers, ruling out a stereospecific substitution.[40]





The phenyl cation represents another extremely unstable cation. Here, the ring geometry opposes rehybridization so that the vacant orbital retains sp^2 character.



There exists the possibility of an electron transfer from the π system, leading to structure **D**, which would have two unpaired electrons. A molecular orbital calculation at the 4-31G level has indicated that the singlet structure **C** is more stable than the triplet structure by about 20 kcal/mol, but it is highly distorted with the C–C–C bond angle at the divalent carbon calculated to be 145°.[41,42] Phenyl cations are formed by the thermal decomposition of aryldiazonium ions.[43] The relatively high stability of arylidiazonium ions, even in comparison with primary aliphatic diazonium ions, reflects the instability of the phenyl cation. The cation is also extremely reactive,

38. P. J. Stang, *Prog. Phys. Org. Chem.* **10**, 205 (1973); G. Modena and U. Tonellato, *Adv. Phys. Org. Chem.* **9**, 185 (1971).
39. H.–U. Siehl and M. Hanack, *J. Am. Chem. Soc.* **102**, 2686 (1980).
40. R. H. Summerville, C. A. Senkler, P. v. R. Schleyer, T. E. Dueber, and P. J. Stang, *J. Am. Chem. Soc.* **96**, 1100 (1974).
41. J. D. Dill, P. v. R. Schleyer, J. S. Binkley, R. Seeger, J. A. Pople, and E. Haselbach, *J. Am. Chem. Soc.* **98**, 5428 (1976).
42. J. D. Dill, P. v. R. Schleyer, and J. A. Pople, *J. Am. Chem. Soc.* **99**, 1 (1977).
43. C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.* **97**, 783 (1975).

being able to *recapture nitrogen* under certain reaction conditions.[44] Attempts to observe formation of phenyl cations by ionization of aryl triflates and related compounds with very reactive leaving groups have so far failed to provide any case where phenyl cations are formed by S_N1 ionization of a neutral molecule.[45]

5.5. Nucleophilicity and Solvent Effects

The term *nucleophilicity* is generally accepted to refer to the effect of a Lewis base on the *rate* of a nucleophilic substitution reaction and may be contrasted with *basicity*, which is usually defined in terms of an equilibrium process. Quite clearly, the relative nucleophilicities of various species may differ from reaction to reaction, and it will not be possible to set down an absolute scale of nucleophilicities. This situation is exactly analogous to that of basicity, in which the relative strengths of Lewis bases depend on the reference acid. We will wish to gain some impression of the factors which govern nucleophilicity and also to understand the relationship between nucleophilicity and basicity.[46]

Factors that influence nucleophilicity have been assessed by numerous investigations, usually in the context of the limiting S_N2 case, since it is here that any special properties of the nucleophile will be most apparent. The observed rate of an S_N2 reaction will be directly related to the effectiveness of the entering group in displacing the leaving group. The effect of nucleophilicity in limiting S_N1 reactions will not be evident in the rate of destruction of substrate, but will affect the product distribution resulting from partitioning of the carbocation intermediate among the various pathways that are possible.

Many properties may have an influence on nucleophilicity[47] but among those which are most significant are (1) the solvation energy of the nucleophile, (2) the strength of its bond to carbon, (3) its effective size, (4) the electronegativity of the attacking atom, and (5) the polarizability of the attacking atom.[48]

A high solvation energy will lower the ground state energy relative to the transition state in which the charge is more diffuse, and result in a decreased rate of reaction. A stronger bond to carbon will be reflected in a more stable, lower-energy transition state and an increase in reactivity. A bulkier nucleophile will be less reactive than a smaller one because the trigonal bipyramidal geometry of the S_N2

44. R. G. Bergstrom, R. G. M. Landells, G. W. Wahl, Jr., and H. Zollinger, *J. Am. Chem. Soc.* **98**, 3301 (1976).
45. L. R. Subramanian, M. Hanack, L. W. K. Chang, M. A. Imhoff, P. v. R. Schleyer, F. Effenberger, W. Kurtz, P. J. Stang, and T. E. Dueber, *J. Org. Chem.* **41**, 4099 (1976).
46. For a general review of nucleophilicity, see R. F. Hudson, in *Chemical Reactivity and Reaction Paths*, G. Klopman (ed.), John Wiley and Sons, New York, 1974, Chap. 5.
47. J. F. Bunnett, *Ann. Rev. Phys. Chem.* **14**, 271 (1963).
48. A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1962.

transition state is more sterically demanding than the ground state. A more electronegative atom will bind its electrons more tightly than a less electronegative one, and require a greater energy expenditure to achieve a transition state that involves donation of an electron pair to an electrophilic site. The polarizability of an atom is related to the ease with which its electron distribution is distorted by the presence of an external electric field. Generally, polarizability increases in going down the periodic table, reflecting the increasing ease of distortion of electron shells of higher energy, and represents a stabilizing interaction in the transition state for the direct displacement mechanism.

Empirical measures of nucleophilicity may be obtained quite readily by comparing relative rates of reaction of a standard substrate with various nucleophiles. Rather than tabulate rate constant data, it has become customary to express this property in terms of a *nucleophilic constant* (n). Swain and Scott proposed to correlate solvolysis rates by the equation

$$\log (k/k_0) = sn + s'e$$

based on the push–pull concept of nucleophilic substitution.[49] According to this equation, the relative rate is considered to depend on the nucleophilic push of the medium (n), the electrophilic pull on the leaving group (e), and the sensitivity of the substrate (s and s') to each of these. A scale of nucleophilicities (n_{CH_3Br}) was determined by comparing the rate of nucleophilic substitution on methyl bromide in water at 25°C with the rate of hydrolysis of methyl bromide in pure water. This choice of standard conditions was not entirely satisfactory, and has been discarded in favor of methyl iodide as the standard substrate and methanol at 25°C as the standard solvent and nucleophile. Thus

$$n_{CH_3I} = \log (k_{\text{nucleophile}}/k_{CH_3OH}) \qquad \text{in } CH_3OH, 25°C$$

Table 5.5 lists nucleophilic constants for a number of species according to this definition.

It is apparent from Table 5.5 that nucleophilicity toward methyl iodide does not correspond to basicity toward proton donors in any direct way. Azide ion, phenoxide ion, and bromide ion are equally nucleophilic toward methyl iodide ($n_{CH_3I} = 5.8$), yet differ enormously in basicity. The pK_a's of their conjugate acids are, respectively, 4.74, 9.89, and −7.7. Conversely, azide ion and acetate ion are nearly identical in basicity, yet azide ion is 1.5 log units more nucleophilic. We also find that triethylamine is *more basic* than triethylphosphine (pK_a of conjugate acid 10.70 versus 8.69), but *less nucleophilic* ($n_{CH_3I} = 6.7$ versus 8.7). The correlation with basicity is better if the attacking atom is the same. Thus, the order of nucleophilicity, $CH_3O^- > C_6H_5O^- > CH_3CO_2^- > NO_3^-$ parallels the order of Brønsted basicity.

49. C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.* **75**, 141 (1953).

Table 5.5. Nucleophilic Constants of Various Nucleophiles[a]

Nucleophile	n_{CH_3I}	pK_a of conjugate acid
CH_3OH	0.0	−1.7
NO_3^-	1.5	−1.3
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	−5.7
$(CH_3)_2S$	5.3	
NH_3	5.5	9.25
N_3^-	5.8	4.74
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	−7.7
CH_3O^-	6.3	15.7
HO^-	6.5	15.7
NH_2OH	6.6	5.8
NH_2NH_2	6.6	7.9
$(CH_3CH_2)_3N$	6.7	10.70
CN^-	6.7	9.3
$(CH_3CH_2)_3As$	7.1	
I^-	7.4	−10.7
HO_2^-	7.8	
$(CH_3CH_2)_3P$	8.7	8.69
$C_6H_5S^-$	9.9	6.5
$C_6H_5Se^-$	10.7	
$(C_6H_5)_3Sn^-$	11.5	

a. Data from R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.* **89**, 1827 (1967); R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.* **90**, 319 (1968); P. L. Bock and G. M. Whitesides, *J. Am. Chem. Soc.* **96**, 2826 (1974).

Nucleophilicity usually decreases in going across a row in the periodic table in what is most simply ascribable to an electronegativity effect. Thus $HO^- > F^-$, $(CH_3CH_2)_3P > (CH_3)_2S$, and $C_6H_5S^- > Cl^-$. Nucleophilicity usually increases in going down a column, as evidenced by $I^- > Br^- > Cl^- > F^-$ and $C_6H_5Se^- > C_6H_5S^- > C_6H_5O^-$. There are exceptions, however, of which the order $(CH_3CH_2)_3P > (CH_3CH_2)_3As > (CH_3CH_2)_3N$ is an example. While decreasing electronegativity acts to increase the nucleophilicity of heavier atoms in a particular group, it is generally accepted that the greater polarizability and decreased solvation of the heavier atoms are the most important factors.

Clearly there is a conceptual relationship between the properties called nucleophilicity and basicity. Both involve formation of a new bond by donation of an electron pair to an electrophilic species. If we speak of basicity in the Brønsted sense, the process of acting as base will always involve formation of a bond to hydrogen. There are many organic reactions where a given chemical species might act either as a nucleophile or as a Brønsted base. Scheme 5.4 lists some examples.

Scheme 5.4. Competition between Nucleophilicity and Basicity

S_N1 Substitution	$Y\!:$ acts as a nucleophile	$Y\!: + R_2\overset{+}{C}CHR'_2 \rightarrow R_2\underset{\displaystyle Y}{\underset{\vert}{C}}CHR'_2$
versus		
E_1 Elimination	$Y\!:$ acts as a base	$Y\!: + R_2\overset{+}{C}CHR'_2 \rightarrow R_2C{=}CR'_2 + HY$
S_N2 Substitution	$Y\!:$ acts as a nucleophile	$Y\!: + R_2CHCH_2Br \rightarrow R_2CHCH_2Y + Br^-$
versus		
E_2 Elimination	$Y\!:$ acts as a base	$Y\!: + R_2CHCH_2Br \rightarrow RCH{=}CH_2 + HY + Br^-$
Nucleophilic addition at a carbonyl carbon	$Y\!:$ acts as a nucleophile	$Y\!: + R_2CH\overset{\displaystyle O}{\overset{\Vert}{C}}R' \rightarrow R_2CH\underset{\displaystyle Y}{\underset{\vert}{\overset{\displaystyle O^-}{\overset{\vert}{C}}}}R'$
versus		
Enolate formation	$Y\!:$ acts as a base	$Y\!: + R_2CH\overset{\displaystyle O}{\overset{\Vert}{C}}R' \rightarrow R_2C{=}\overset{\displaystyle O^-}{\overset{\vert}{C}}R' + HY$

It is therefore a great deal of interest to be able to predict which chemical species $Y^-\!:$ will act as nucleophiles and which will act as bases. Later in this text, we will discuss quantitative measures of basicity. These basicity scales are based on the ability of a substance to remove protons and refer to equilibria or are related to equilibrium measurements. The definition of basicity in aqueous solution is given in thermodynamic terms by the *equilibrium constant*, which indicates the ability of a substance to remove protons from water:

$$B\!: + H_2O \rightleftharpoons \overset{+}{B}H + {}^-OH, \qquad K_b = \frac{[\overset{+}{B}H][{}^-OH]}{[B\!:]}$$

Scales for bases which are too weak to study in aqueous solution employ other solvents but are related to the equilibrium in aqueous solution. These equilibrium constants give a measure of *thermodynamic basicity* but we also need to have some concept of *kinetic basicity*. For the reactions in Scheme 5.4, for example, it is of great practical importance to know how a given substance will react with an alkyl halide. Will nucleophilicity, leading to substitution, or basicity, leading to elimination, be the dominant property?

The most useful qualitative approach for making predictions in this regard is the hard-soft–acid-base concept.[50] This concept suggests that reactions will occur most readily between species that are matched with respect to hardness and softness.

50. R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.* **89**, 1827 (1967); R. G. Pearson, *J. Chem. Educ.* **45**, 581, 643 (1968); R. G. Pearson (ed.), *Hard and Soft Acids and Bases*, Dowden, Hutchinson and Ross, Stroudsburg, Pennsylvania, 1973; T. L. Ho, *Chem. Rev.* **75**, 1 (1975).

Table 5.6. Hardness and Softness of Some Common Ions and Molecules

	Bases (Nucleophiles)	Acids (Electrophiles)
Soft:	RSH, RS^-, I^-, R_3P $^-C{\equiv}N$, $:\bar{C}{\equiv}O^+$, RCH=CHR benzene	I_2, Br_2, RS—X, RSe—X, RCH_2—X Cu(I), Ag(I), Pd(II), Pt(II), Hg(II) zerovalent metal complexes
Borderline:	Br^-, N_3^-, $ArNH_2$ pyridine	Cu(II), Zn(II), Sn(II) R_3C^+, R_3B
Hard:	H_2O, HO^-, ROH, RO^-, RCO_2^- F^-, Cl^-, NO_3^-, NH_3, RNH_2	H—X, H^+, Li^+, Na^+, K^+ Mg^{2+}, Ca^{2+}, Al(III), Sn(IV), Ti(IV) R_3Si—X,

Hard nucleophiles prefer hard electrophiles, while soft nucleophiles prefer soft electrophiles. This concept can be related to the particular problem of nucleophilic substitution versus deprotonation since the proton is a hard electrophile, whereas an sp^3 carbon is a soft electrophile. As a result soft nucleophiles will be more likely to effect substitution, whereas hard anions are more likely to attack the proton and act as a base. The property of "softness" primarily reflects polarizability. Soft nucleophiles are those having easily distorted electronic clouds. Softness also tends to imply a late transition state with strong mutual interaction between the nucleophile and electrophile. The property of hardness primarily reflects charge concentration. A species with a high and localized charge distribution will be hard. This pertains to both electrophiles and nucleophiles. The hardest nucleophiles (bases) are the most electronegative elements in their anionic states. Thus, fluoride, hydroxide, and alkoxide ions are good examples of hard nucleophiles. The proton and electropositive metal cations are the hardest electrophiles. Hard–hard combinations tend to be dominated by charge distribution. This also correlates with an early transition state; that is, the reaction pathway is chosen early on the reaction coordinate and primarily on the basis of charge distribution, with the incipient bond being only slightly formed. Table 5.6 gives a classification of some common acids and bases encountered in organic chemistry in terms of hardness and softness.

Another significant structural correlation regarding nucleophilicity is the observation that nucleophiles in which the attacking atom is directly bonded to an atom possessing a lone-pair exhibit anomalously high nucleophilicities. We see in Table 5.5 that HO_2^- is more nucleophilic than HO^- ($n_{CH_3I} = 7.8$ versus 6.5). The enhanced nucleophilicity of such species is called the *alpha effect*, and is apparent in neutral nucleophiles as well. Both hydrazine and hydroxylamine are more nucleophilic than ammonia, although each is a weaker Brønsted base.

Various explanations have been put forth for the alpha effect.[51] One view is that the ground state of the nucleophile is destabilized by lone-pair–lone-pair

51. For discussion and leading references, see G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron* **26**, 4549 (1970); W. B. England, P. Kovacic, S. M. Hanrahan, and M. B. Jones, *J. Org. Chem.* **45**, 2057 (1980).

repulsions, which decrease in going to the transition state. Another view is that the transition state is stabilized by electron release from the hetero atom. According to this reasoning, the process of bond formation is akin to that of a two-electron transfer,

$$Y^- \longrightarrow Y^+ + 2e^-$$

for which a lone pair on an adjacent hetero atom should provide stabilization:

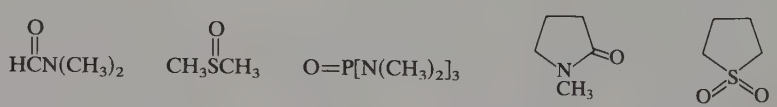
$$:X\text{–}Y^- \longrightarrow :X\text{–}Y^+ + 2e^-$$

$$:X\text{–}Y^+ \longleftrightarrow {}^+X{=}Y$$

MO calculations have suggested that the adjacent heteroatom increases the polarizability of the attacking atom and raises the energy of the HOMO; in some of these "supernucleophiles" the HOMO is antibonding.[52] The alpha effect may have a differing extent of contribution from these factors for different nucleophile–electrophile pairs.

The nucleophilicity of an anion depends very much on its degree of solvation. Most of our qualitative generalizations, as well as quantitative rate data, have come from studies made in protic media. In hydrogen-bonding solvents, an anion is subject to strong solvation forces that lower its ground state energy. Nucleophilic substitution reactions carried out in aprotic solvents often occur more readily than comparable reactions in protic solvents, and anions that are customarily considered to be poorly nucleophilic exhibit enhanced displacing powers. The major deterrent to studies in aprotic solvents, compared to protic ones, is one of solubility—salts of alkali metal cations are sometimes insufficiently soluble to produce high concentrations of anionic species.

Nucleophilic reactivity is strongly enhanced in highly polar aprotic solvents such as *N*,*N*-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, *N*-methylpyrrolidone, and sulfolane. Each of these molecules possesses at least one highly polar bond with high electron density at oxygen. These oxygen atoms strongly solvate hard cations such as Li^+, Na^+, or K^+, but do not strongly solvate anions. Thus salts which are dissolved in solvents of this type give rise to relatively unsolvated anions and such anions are strongly nucleophilic.



Because of the importance of solvation on nucleophilicity, the order of reactivity of nucleophiles can be quite solvent dependent. In general, hard nucleophiles will be strongly solvated in protic solvents and therefore relatively less reactive, whereas soft nucleophiles will be more weakly solvated. The reactivity of all anionic

52. M. M. Heaton, *J. Am. Chem. Soc.* **100**, 2004 (1978).

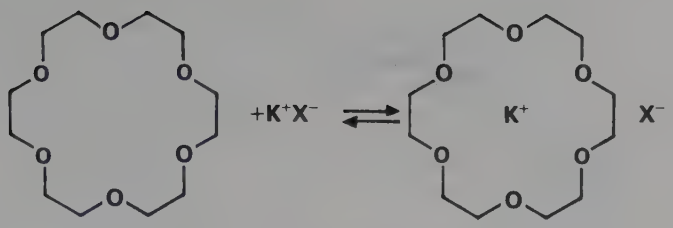


Fig. 5.5. Structure of macrocyclic polyether 18-crown-6.

nucleophiles is enhanced in aprotic solvents since the nucleophiles are then less strongly solvated. In methanol, for example, the relative reactivity order $N_3^- > I^- > CN^- > Br^- > Cl^-$ is observed, with the range of reactivity toward saturated sulfonates being 5–20, depending upon the sulfonate. In DMSO, the order becomes $CN^- > N_3^- > Cl^- > Br^- > I^-$ and the reactivity range is enhanced to 30–60.[53]

The solubility of ionic substances in relatively nonpolar aprotic solvents can be greatly enhanced by using catalytic quantities of macrocyclic polyethers, such as 18-crown-6, the structure of which is shown in Fig. 5.5. These macrocyclic ethers selectively solvate the cation, both enhancing solubility and also leaving the anion in a very weakly solvated state. The anions behave under these conditions as highly reactive species, sometimes termed *naked anions.* A study of the relative rates of nucleophilic substitution on benzyl tosylate by potassium salts in acetonitrile in the presence of 18-crown-6 revealed a pronounced leveling effect.[54] All the potassium halides (fluoride, chloride, bromide, and iodide) were approximately equal in their reactivity. Potassium acetate was observed to be almost ten times more reactive than potassium iodide under these conditions—a reversal of the normal reactivity of acetate ion versus iodide ion in nucleophilic substitution reactions. As measured by n_{CH_3I} values in Table 5.5, iodide is 3 log units, i.e., 10^3 times, more reactive than acetate ion in the protic solvent methanol.

In interpreting many displacement reactions, particularly solvolysis, it is also important to be able to characterize the nucleophilicity of the solvent. Assessments of solvent nucleophilicity are made by comparing the rates of substitution of standard substrates in various media. A useful measure of solvent nucleophilicity is one based on the Winstein–Grunwald relationship

$$\log (k/k_0) = lN + mY$$

where N and Y are measures of, respectively, solvent nucleophilicity and solvent

53. R. Fuchs and L. L. Cole, *J. Am. Chem. Soc.* **95**, 3194 (1973); D. Landini, A. Maia and F. Montanari, *J. Am. Chem. Soc.* **100**, 2796 (1978); R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Am. Chem. Soc.* **90**, 5049 (1968);
54. C. L. Liotta, E. E. Grisdale, and H. P. Hopkins, Jr., *Tetrahedron Lett.* 4205 (1975).

Table 5.7. Solvent Nucleophilicity Values (N)[a]

Solvent	N
Ethanol	+0.09
Methanol	+0.01
50% Aqueous ethanol	−0.20
Water	−0.26
Acetic acid	−2.05
Formic acid	−2.05
Trifluoroethanol	−2.78
97% $(CF_3)_2CHOH$–H_2O	−3.93
Trifluoroacetic acid	−4.74

a. From F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **98**, 7667 (1976).

ionizing power, and l and m reflect the sensitivity of the substrate to each of these properties.[4,55] Values of N can be determined for various solvents by specifying a standard substrate for which l is assigned the value 1.00, and a standard solvent for which N is assigned the value 0.00. The standard substrate is taken as methyl p-toluenesulfonate (tosylate), and the standard solvent is 80% (vol/vol) aqueous ethanol. Then

$$N = \log(k/k_0) - mY$$

where k/k_0 is the ratio of the pseudo-first-order rate constants for solvolysis of methyl tosylate in the solvent to the rate constant in 80% aqueous ethanol. The measurement of Y was discussed in Section 4.7. Methyl tosylate is very insensitive to solvent ionizing power ($m = 0.30$), hence its choice as the standard substrate. Values of Y have been tabulated for a number of solvents. Application of this equation gives the values of N listed in Table 5.7.

Solvolysis reactions in media of low nucleophilicity are characterized by increased tendencies toward carbonium ion rearrangements and increased racemization when optically active substrates are employed. We have seen examples of extensive rearrangements in our discussion of carbonium ions generated in superacid media, in which the observed ion was quite often the most stable possible ion of a particular system. A later section of this chapter deals with the stereochemistry of nucleophilic substitution reactions, and examples of solvent nucleophilicity effects on stereochemistry will be encountered there.

4. See p. 243.
55. F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **98**, 7667 (1976).

Table 5.8. Relative Solvolysis Rates of 1-Phenylethyl Esters and Halides[a,b]

Leaving group	k_{rel}
$CF_3SO_3^-$ (triflate)	1.4×10^{8}
p-Nitrobenzenesulfonate	4.4×10^{5}
p-Toluenesulfonate	3.7×10^{4}
$CH_3SO_3^-$ (mesylate)	3.0×10^{4}
I^-	91
Br^-	14
$CF_3CO_2^-$	2.1
Cl^-	1.0
F^-	9×10^{-6}
p-Nitrobenzoate	5.5×10^{-6}
$CH_3CO_2^-$	1.4×10^{-6}

a. Data from D. S. Noyce and J. A. Virgilio, *J. Org. Chem.* **37**, 2643 (1972).
b. In 80% aqueous ethanol at 75°C.

5.6. Leaving-Group Effects

The nature of the leaving group will influence the rate of nucleophilic substitution reactions proceeding by either the direct displacement or the ionization mechanism. Since the leaving group departs with the pair of electrons of its covalent bond to the substrate, a correspondence with electronegativity is expected. Provided the atom that is directly attached to the substrate is the same, such a relationship is usually observed. A linear relationship has been demonstrated between the ionization of substituted benzoic acids and the rates of reaction of substituted ethyl arenesulfonates with ethoxide ion in ethanol.[56] In contrast to nucleophilicity, no approach toward specifying leaving-group effectiveness in terms of a single parameter has achieved general acceptance, and it is usual to see such correlations presented as summaries of relative rates.

Table 5.8 lists relative rates of solvolysis of 1-phenylethyl esters and halides in 80% aqueous ethanol at 75°C.[57] Most of the values in this table have been estimated, and the relative reactivities have more qualitative than quantitative significance. The relative reactivities parallel electron withdrawal by substituents in an anticipated fashion. Trifluoroacetate is about 10^6 times more reactive than acetate, and *p*-nitrobenzenesulfonate is about 10^1 times more reactive than *p*-toluenesulfonate. The order of reactivity of the halide leaving groups, $I > Br > Cl \gg F$, is interesting in

56. M. S. Morgan and L. H. Cretcher, *J. Am. Chem. Soc.* **70**, 375 (1948).
57. D. S. Noyce and J. A. Virgilio, *J. Org. Chem.* **37**, 2643 (1972).

Table 5.9. Relative Solvolysis Rates of Ethyl Sulfonates and Halides[a]

Derivatives compared	k_{rel}	Solvent, 25°C
Triflate/tosylate	3×10^4	Acetic acid
Triflate/brosylate	5×10^3	Acetic acid
Triflate/iodide	4.5×10^5	Ethanol
Triflate/bromide	1.5×10^5	80% Ethanol

a. From A. Streitwieser, Jr., C. L. Wilkins, and E. Kiehlmann, *J. Am. Chem. Soc.* **90**, 1598 (1968).

that it is opposite to the order of electronegativity of the atoms. This is believed to be related to the carbon–halogen bond strengths and to a polarizability effect, just as in the case of the nucleophilicity of the halide ions, where an identical reactivity order is observed. The C–I bond (~50 kcal/mol) is much weaker than the C–F bond (~100 kcal/mol). A more polarizable leaving group will stabilize the transition state for cleavage of its bond to carbon in much the same way that a polarizable nucleophile will stabilize the transition state for displacement of another ligand from carbon.

Sulfonate esters are exceedingly useful substrates in nucleophilic substitution reactions because of their high level of reactivity and because, unlike alkyl halides, they may be prepared from alcohols by reactions that do not directly involve the carbon atom at which subsequent substitution is to be effected. These properties are particularly important in cases where the stereochemical and structural integrity of the substrate must be maintained in converting an alcohol to a derivative capable of undergoing nucleophilic substitution. Sulfonate esters are commonly prepared by reaction of an alcohol with a sulfonyl halide in the presence of pyridine:

$$ROH + R'SO_2Cl \xrightarrow{pyr} ROSO_2R'$$

Tertiary alcohols are converted to sulfonate esters with difficulty, and, because of their high reactivity, it is often impossible to isolate the sulfonate ester. Special procedures are sometimes effective,[58] but more commonly, tertiary alcohols are converted to *p*-nitrobenzoates for solvolytic studies.

Trifluoromethanesulfonate (triflate) is an exceptionally good leaving group, enabling nucleophilic substitution reactions to be carried out on normally unreactive substrates. Acetolysis of cyclopropyl triflate, for example, occurs 10^5 times faster than acetolysis of cyclopropyl tosylate.[59] Similar rate enhancements are seen in systems in which the direct displacement mechanism is operative, as summarized in Table 5.9.

58. H. M. R. Hoffmann, *J. Chem. Soc.*, 6748 (1965).
59. T. M. Su, W. F. Sliwinski, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **91**, 5386 (1969).

Table 5.10. Tosylate/Bromide Rate Ratios for Solvolysis of RX in 80% Ethanol[a]

R	k_{OTs}/k_{Br}
Methyl	11
Ethyl	10
Isopropyl	40
tert-Butyl	4000
1-Adamantyl	9750

a. From J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **92**, 2539 (1970).

It would be anticipated that the limiting S_N1 and S_N2 mechanisms would differ in their sensitivity to the effectiveness of the leaving group. The ionization mechanism should exhibit a much more pronounced dependence on leaving-group ability because it requires cleavage of the bond to the leaving group without assistance by the nucleophile. Table 5.10 presents data on the variation of the relative leaving-group abilities of tosylate and bromide as a function of substrate structure. The dependence is as expected, with smaller differences in reactivity between tosylate and bromide observed for unhindered primary and secondary systems than for tertiary systems.

A poor leaving group can be made more reactive by coordination to an electrophilic species. Hydroxide ion is such a poor leaving group that under normal circumstances it is not displaced from sp^3 carbon by another Lewis base. It has been estimated that the reaction

$$CH_3OH + Br^- \longrightarrow CH_3Br + HO^-$$

is endothermic by 16 kcal/mol.[60] Since the activation energy for the reverse process is about 21 kcal/mol, the reaction as written would have an activation energy of about 37 kcal/mol and be too slow to measure. Protonation of an alcohol improves the leaving-group ability to the extent that water is about as good a leaving group as bromide. A practical result is that primary alcohols may be converted to alkyl bromides by heating with sodium bromide and sulfuric acid, whereas no reaction occurs in neutral solution. The leaving-group ability of halide atoms is enhanced by coordination to metal ions, and it is common practice to use silver salts as catalysts in substitution reactions of alkyl halides.

One of the best leaving groups is molecular nitrogen departing from diazonium ions. Diazonium ions are generated by nitrosation of primary amines. Diazonium ions derived from aliphatic amines are very unstable and immediately decompose

60. R. A. Ogg, Jr., *Trans. Faraday Soc.* **31**, 1385 (1935).

with the loss of nitrogen. Because a neutral molecule is eliminated, rather than an

$$RNH_2 + HONO \rightarrow R{-}\underset{H}{N}{-}N{=}O + H_2O$$

$$R{-}\underset{H}{N}{-}N{=}O \rightarrow RN{=}NOH \xrightarrow{H^+} R{-}\overset{+}{N}{\equiv}N + H_2O$$

$$R{-}\overset{+}{N}{\equiv}N + \mathbf{Nu}^-\!: \rightarrow R{-}\mathbf{Nu} + N_2$$

anion, there is no electrostatic attraction (ion pairing) between the products of the dissociation step. As a result, the carbonium ions generated by diazonium ion decomposition frequently exhibit markedly different behavior from those generated from neutral reactants under solvolysis conditions.[61]

5.7. Steric and Other Substituent Effects on Substitution and Ionization Rates

Examples of effects of substrate structure on the rates of nucleophilic substitution reactions have appeared in the preceding sections of this chapter. Additionally, some special effects will be covered in detail in succeeding sections. This section will emphasize the role steric effects can play in nucleophilic substitution reactions.

Reactions with good nucleophiles in solvents of low ionizing power are sensitive to the degree of substitution at the carbon atom undergoing substitution. Reactions of this type most closely approach the direct-displacement limit, and are retarded by steric crowding in the transition state. The relative rates of reaction of alkyl chlorides with iodide ion in acetone are methyl, 93; ethyl, 1.0; and isopropyl, 0.0076.[62] This rate relationship is an example of a case where this crowding effect is dominant. More generally, a statistical analysis of rate data for 18 sets of nucleophilic substitution reactions of substrates of the type XCH_2Y, where Y is a leaving group and X is H or alkyl, indicated that the steric effect of X was a very important factor.[63] Table 5.11 records some of the data bearing on this point. Notice that the fourth entry, involving solvolysis with acetic acid as solvent shows a diminished sensitivity to the steric effects. This reflects a looser transition state with less nucleophilic participation than the other examples. In weakly nucleophilic media of high dielectric constant, ionization efficiency, which reflects the stability of the carbonium ion intermediate, becomes the dominant factor in determining reactivity. The relative rates of formolysis of alkyl bromides at 100°C are methyl, 0.58; ethyl, 1.00; isopropyl, 26.1; and *tert*-butyl, about 10^8.[64] The effect of substituting a methyl group for a hydrogen substituent is sensitive to the extent of nucleophilic participation in the transition state. A large CH_3/H rate ratio is expected if solvent participa-

61. C. J. Collins, *Acc. Chem. Res.* **4**, 315 (1971); A. Streitwieser, Jr., *J. Org. Chem.* **22**, 861 (1957).
62. J. B. Conant and R. E. Hussey, *J. Am. Chem. Soc.* **47**, 476 (1925).
63. M. Charton, *J. Am. Chem. Soc.* **97**, 3694 (1975).
64. L. C. Bateman and E. D. Hughes, *J. Chem. Soc.*, 1187 (1937); 945 (1940).

Table 5.11. Rate Constants for Nucleophilic Substitution in Primary Alkyl Substrates[a]

Reaction	$10^5 k$ for XCH_2–				
	X = H–	CH_3–	CH_3CH_2–	$(CH_3)_2CH$–	$(CH_3)_3C$–
$XCH_2Br + LiCl$, acetone	600	9.9	6.4	1.5	0.00026
$XCH_2Br + Bu_3P$, acetone	26,000	154	64	4.9	
$XCH_2Br + NaOCH_3$, methanol	8140	906	335	67	
XCH_2OTs, acetic acid	0.052	0.044		0.018	0.0042

a. From M. Charton, *J. Am. Chem. Soc.* **97**, 3694 (1975).

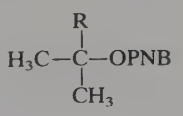
tion is small since this corresponds to development of a substantial positive charge on carbon at the transition state. If substantial nucleophilic participation is involved, this ratio will decrease, because the favorable electronic effect of the methyl group will be reduced by a steric factor opposing nucleophilic participation. The relative rate of acetolysis of *tert*-butyl bromide to isopropyl bromide at 25°C is $10^{3.7}$, while that of 2-methyl-2-adamantyl bromide to 2-adamantyl bromide is $10^{8.1}$:

k_{rel} $\frac{R = CH_3}{R = H}$, $10^{3.7}$ $\quad$ k_{rel} $\frac{R = CH_3}{R = H}$, $10^{8.1}$

Ref. 65

The reason for the differing response to methyl substitution is that acetolysis of isopropyl bromide is solvent assisted. Comparable solvent participation in the ionization of 2-adamantyl bromide is hindered by the hydrogens indicated in the structural drawing, as was discussed earlier.

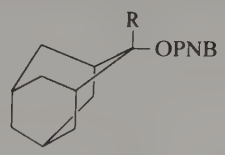
Steric effects of another kind become important in highly branched substrates, in which ionization is facilitated by relief of steric crowding in going from the tetrahedral ground state to the transition state for ionization.[66] The relative hydrolysis rates in 80% aqueous acetone of *tert*-butyl *p*-nitrobenzoate and 2,3,3-trimethyl-2-butyl *p*-nitrobenzoate are 1 : 4.4:



k_{rel} $\frac{R = \textit{tert}\text{-butyl}}{R = CH_3}$, 4.4

65. J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **92**, 2540 (1970).
66. H. C. Brown, *Science* **103**, 385 (1946); H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1972, Chap. VIII; E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.* **97**, 2892 (1975).

Table 5.12. Relative Hydrolysis Rates of 2-Alkyl-2-adamantyl *p*-Nitrobenzoates[a]

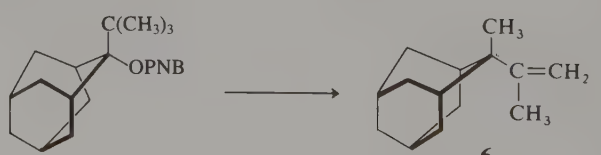


R	k_{rel}, 25°C[b]
CH_3–	2.0
CH_3CH_2–	15.4
$(CH_3)_3CCH_2$–	20.0
$(CH_3)_2CH$–	67.0
$(CH_3)_3C$–	4.5×10^5

a. From J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 4628 (1972).
b. Relative to *tert*-butyl *p*-nitrobenzoate = 1.

This effect has been called *B-strain* (back-strain), and in this example provides a modest rate enhancement resulting from relief of ground state strain. As the size of the groups is increased, the acceleration caused by steric effects increases substantially. When all the three carbinyl substituents are *tert*-butyl, for example, solvolysis occurs at a rate 13,500 times faster than the *tert*-butyl systems.[67] Large B-strain effects are observed in rigid systems such as the 2-alkyl-2-adamantyl *p*-nitrobenzoates. Table 5.12 records pertinent relative rate data. The repulsive van der Waals interaction between the substituent and the *syn*-axial hydrogens is relieved as the hybridization of C(2) goes from sp^3 to sp^2. As the alkyl group becomes more sterically demanding, the ground state energy increases more than the transition state energy.

One feature of the reactions of these strained substrates is their reluctance to form strained products. The cationic intermediates usually escape to elimination products in preference to substitution products. Rearrangement reactions are common. 2-Methyl-2-adamantyl *p*-nitrobenzoate gives 82% methyleneadamantane by elimination and 18% 2-methyl-2-adamantanol by substitution on hydrolysis in 80% acetone. Elimination accounts for 95% of the product from 2-neopentyl-2-adamantyl *p*-nitrobenzoate. The major product (83%) from 2-*tert*-butyl-2-adamantyl *p*-nitrobenzoate is the rearranged alkene **6**:



6

67. P. D. Bartlett and T. T. Tidwell, *J. Am. Chem. Soc.* **90**, 4421 (1968).

Table 5.13. α-Substituent Effects[a]

$X\text{–}CH_2Cl + I^- \rightarrow X\text{–}CH_2I + Cl^-$

X	Relative rate	X	Relative rate
$CH_3CH_2CH_2$–	1	PhC(=O)–	3.2×10^4
$PhSO_2$–	0.25	N≡C–	3×10^3
$CH_3C(=O)$–	3.5×10^4	$C_2H_5OC(=O)$–	1.7×10^3

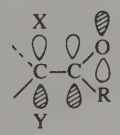
a. Data from F. G. Bordwell and W. T. Branner, Jr., *J. Am. Chem. Soc.* **86**, 4545 (1964).

Although steric effects and substituent effects leading to carbonium ion stabilization are of greatest importance in governing the mechanism and relative rate of nucleophilic substitution processes, there are other substituent effects that are recognized to be of importance. We have mentioned earlier in this chapter that arylmethyl and allylic cations are stabilized by electron delocalization. It is therefore easy to understand why substitution reactions of the ionization type proceed more rapidly in such systems than in simple alkyl systems. It has also been observed that nucleophilic substitutions of the direct displacement type also take place more readily. Allyl chloride is 33 times more reactive than ethyl chloride toward iodide ion in acetone, and benzyl chloride is 93 times more reactive.[62] It has been suggested that these enhanced rates reflect stabilization of the S_N2 transition state through overlap of the *p*-type orbital—which develops at the carbon atom undergoing attack—with the neighboring π-system.[68] In molecular orbital terminology, this stabilization of the transition state can be understood in terms of the MO diagram given in Fig. 5.3. The key structural effect will be the fact that the π system of the vinyl or phenyl substituent can be properly aligned with the π-type orbital which is formed in the S_N2 transition state. Interaction of this orbital with the *lowest unfilled* orbital of the conjugated system can lower the energy of the transition state.

Substitution reactions proceeding by rate-determining ionization occur very slowly on α-haloketones, aldehydes, acids, esters, nitriles, and related compounds. The electron-withdrawing properties of such substituents strongly destabilize a carbonium ion intermediate. Substitution by the direct-displacement mechanism, however, occurs quite readily. As is evident from Table 5.13, these reactions occur

62. See p. 274.
68. A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1962, p. 13.

many times faster than direct displacement on an analogous alkyl halide. Steric effects may be responsible in part for the observed acceleration, since it is reasonable that a carbonyl substituent provides less steric resistance to an incoming nucleophile than does a methylene group. It is also believed that a significant stabilizing electronic interaction may be involved, much like that just described for direct displacements in allyl and benzyl halides. The adjacent carbonyl group can lower the energy of the π-type orbital in the S_N2 transition state by interaction with the empty π^* orbital of the carbonyl group. It should be noted that not all electron-



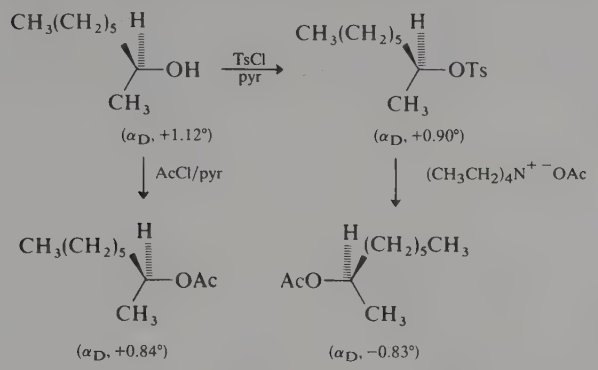
attracting groups exhibit this type of rate enhancement. The sulfonyl and trifluoromethyl substituents, which are non-conjugating, retard the rate of S_N2 substitution at an adjacent carbon.[69]

5.8. Stereochemistry of Nucleophilic Substitution

Studies of the stereochemical course of nucleophilic substitution reactions have proven to be a powerful tool for consideration of mechanism. The stereochemistry of bimolecular nucleophilic substitution reactions corresponds to 100% inversion of configuration in primary and secondary systems, in accord with the prediction of the limiting S_N2 mechanism.[70] For many solvolyses and other reactions in secondary and tertiary systems where S_N1 or borderline mechanisms operate, the stereochemical outcome is more variable. In discussing the stereochemical course of nucleophilic substitution, we must distinguish between the gross observed stereospecificity and the stereospecificity of the actual substitution step. In many reactions, the product, the substrate, or both are not optically stable under the reaction conditions, and the observed stereospecificity is less than that of the actual substitution process. An example of this is found in the acetolysis of optically active 2-octyl tosylate at 75°C, in which the observed stereochemistry corresponds to 93% inversion of configuration after 5 h (1.4 half-lives), but decreases to 40% inversion of configuration after 260 h (75 half-lives). Control experiments demonstrated that both starting tosylate and product acetate were racemized slowly under the reaction conditions and, further, that optically inactive acetate was formed by addition of acetic acid to octene formed by concurrent elimination. When the stereochemical course of the actual substitution process was corrected for the loss of optical activity due to these reactions, it was found to be stereospecific inversion of configuration.[71]

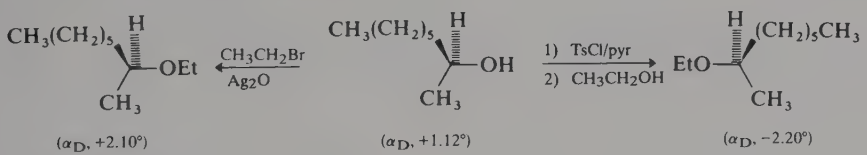
69. F. G. Bordwell and W. T. Brannen, *J. Am. Chem. Soc.* **86**, 4645 (1964).
70. Stereochemical courses of reactions will be expressed as percent inversion or retention of configuration with the difference from 100% understood to be racemization.
71. A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, Jr., *J. Am. Chem. Soc.* **87**, 3682 (1965).

The method by which the stereochemical course of a nucleophilic substitution reaction is determined can be illustrated for the case of 2-octyl tosylate:



(+)-2-Octyl acetate has the same configuration as (+)-2-octanol, since it can be prepared from the alcohol by a reaction that does not involve the chiral center. The overall process alcohol ⟶ tosylate ⟶ acetate must therefore proceed with overall inversion of configuration, because (−)-2-octyl acetate is formed. The formation of the tosylate from the alcohol does not involve the chiral center, so it must be the nucleophilic substitution step which proceeds with inversion of configuration. Comparison of the rotations of (+)-acetate and (−)-acetate quantitatively fixes the stereochemistry as 100% inversion of configuration in the displacement of tosylate by acetate ion. Notice that relation of the configurations and magnitudes of rotations in this sequence does not require that the absolute configurations be known nor does the chiral substrate need to be optically pure, i.e., exclusively one enantiomer. The stereochemical course of the reaction may be determined by comparing signs and magnitudes of rotation in a relative, rather than an absolute, way. In fact, the 2-octanol used in the example was only about 11% optically pure.

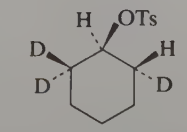
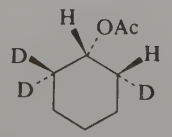
Similarly, the stereochemistry of ethanolysis of 2-octyl tosylate was determined to be clean inversion of configuration[72]:

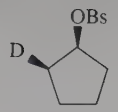
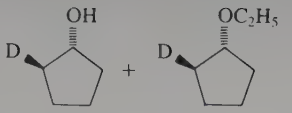
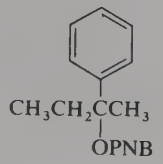
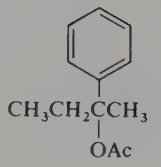
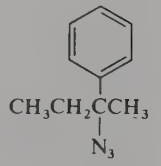
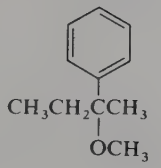


The stereochemistry of nucleophilic substitution reactions has been examined for substrates ranging in complexity from primary alkyl to triarylmethyl. A summary of representative examples is presented in Table 5.14. Chiral 1-butanol-1-*d* and its derivatives have small, but measurable, optical rotations and provide useful substrates for the important case of substitution in primary systems. Entry 1 in Table 5.14 illustrates the stereospecific inversion observed in 1-butyl-1-*d* *p*-bromobenzenesulfonate, even toward nucleophiles as weak as formic acid. This inversion is indicative of a high degree of solvent participation in the displacement

72. A. Streitwieser, Jr., and A. C. Waiss, Jr., *J. Org. Chem.* **27**, 290 (1962).

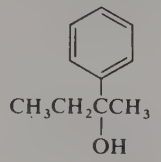
Table 5.14. Stereochemical Course of Nucleophilic Substitution Reactions

	Substrate[a]	Reaction conditions	Product[a]	Stereochemistry	Ref.
Primary					
1	$CH_3CH_2CH_2CHDOBs$	Acetic acid, 99°C	$CH_3CH_2CH_2CHDOAc$	96 ± 8% inversion	b
		Formic acid, 99°C	$CH_3CH_2CH_2CHDOCHO$	99 ± 6% inversion	b
2	$(CH_3)_3CCHDOTs$	Sodium azide in hexamethylphosphoramide, 90°C	$(CH_3)_3CCHDN_3$	98 ± 2% inversion	c
3	$C_6H_5CHDOTs$	Acetic acid, 25°C	$C_6H_5CHDOAc$	82 ± 1% inversion	d
Secondary					
4	$CH_3\underset{\displaystyle OTs}{\underset{\vert}{C}}H(CH_2)_5CH_3$	Tetraethylammonium acetate in acetone, reflux	$CH_3\underset{\displaystyle OAc}{\underset{\vert}{C}}H(CH_2)_5CH_3$	100% inversion	d
5	$CH_3\underset{\displaystyle OBs}{\underset{\vert}{C}}H(CH_2)_5CH_3$	75% aqueous dioxane, 65°C	$CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}H(CH_2)_5CH_3$	77% inversion	e
		75% aqueous dioxane containing 0.06 *M* sodium azide, 65°C	$CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}H(CH_2)_5CH_3$	100% inversion	e
			$CH_3\underset{\displaystyle N_3}{\underset{\vert}{C}}H(CH_2)_5CH_3$	100% inversion	e
6		Acetic acid		100% inversion	f

7		80% ethanol–water		>97% inverson	g
8	$C_6H_5CHCH_3$ Cl	Potassium acetate in acetic acid, 50°C	$C_6H_5CHCH_3$ OAc	15% inversion	h
		Tetraethylammonium acetate in acetone, 50°C	$C_6H_5CHCH_3$ OAc	65% inversion	h
		60% aqueous ethanol	$C_6H_5CHCH_3$ OH	33% inversion	i
Tertiary					
9		Potassium acetate in acetic acid, 23°C		5±2% inversion	j
		Sodium azide in methanol, 65°C		56±1% inversion	j
				14% inversion	j

continued

Table 5.14. continued.

Substrate[a]	Reaction conditions	Product[a]	Stereochemistry	Ref.
	90% aqueous acetone		38% retention	k

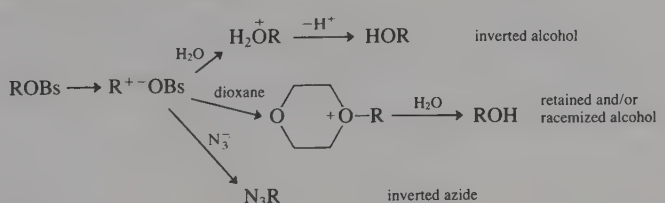
a. Abbreviations used: OBs = *p*-bromobenzenesulfonate; OTs = *p*-toluenesulfonate; OAc = acetate; OPNB = *p*-nitrobenzoate.
b. A. Streitwieser, Jr., *J. Am. Chem. Soc.* **77**, 1117 (1955).
c. B. Stephenson, G. Solladie, and H. S. Mosher, *J. Am. Chem. Soc.* **94**, 4184 (1972).
d. A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, Jr., *J. Am. Chem. Soc.*, **87**, 3682 (1965).
e. H. Wiener and R. A. Sneen, *J. Am. Chem. Soc.* **87**, 287 (1965).
f. J. B. Lambert, G. J. Putz, and C. E. Mixan, *J. Am. Chem. Soc.* **94**, 5132 (1972); see also J. E. Nordlander, and T. J. McCrary, *J. Am. Chem. Soc.* **94**, 5133 (1972).
g. K. Humski, V. Sendijarevic, and V. J. Shiner, *J. Am. Chem. Soc.* **98**, 2865 (1976); K. Humski, V. Sendijarevic, and V. J. Shiner, *J. Am. Chem. Soc.* **95**, 7722 (1973).
h. J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.* **59**, 2536 (1937).
i. V. J. Shiner, Jr., S. R. Hartshorn, and P. C. Vogel, *J. Org. Chem.* **38**, 3604 (1973).
j. L. H. Sommer and F. A. Carey, *J. Org. Chem.* **32**, 800 (1967).
k. H. L. Goering and S. Chang, *Tetrahedron Lett.*, 3607 (1965).

step, and is fully in accord with a direct displacement mechanism involving a pentacoordinate transition state or intermediate.

Neopentyl systems are typically resistant to nucleophilic substitution reactions. They are primary, so do not form stable carbonium ions, but the *tert*-butyl substituent effectively hinders back-side attack. The rate of displacement, for example, of bromide from neopentyl bromide by potassium iodide in acetone is 470 times slower than the corresponding reaction of *n*-butyl bromide.[73] Under conditions that favor ionization, rearrangement usually occurs, and the products are derived from *tert*-amyl cation. Substitution reactions of neopentyl tosylate without skeletal rearrangement can be effected, however, by using good nucleophiles in hexamethylphosphoric triamide as solvent. The use of optically active neopentyl-1-*d* tosylate allows the stereochemistry to be established. Complete inversion of configuration was observed, again consistent with a direct displacement of the leaving group (entry 2).

High, but not 100%, inversion of configuration was observed in the acetolysis of chiral benzyl-1-*d* tosylate (entry 3). The decreased stereospecificity was attributed to racemization of the substrate under the reaction conditions. Substitution on benzyl tosylate may reasonably be expressed as proceeding via displacement on the substrate or intimate ion pair. Entry 4 shows that displacement on 2-octyl tosylate occurs stereospecifically with inversion.

The results cited in entry 5 serve to illustrate the importance of solvation of the ion pair intermediates in nucleophilic substitution reactions of secondary substrates. The results show that partial racemization occurs in aqueous dioxane but that an added nucleophile (azide ion) results in complete inversion, both in the product resulting from reaction with azide ion and from the reaction with water. In aqueous dioxane, the ion-pair intermediate may be solvated by water molecules or by dioxane. Inverted product results from solvation by water, but solvation by dioxane cannot collapse to a stable product. Subsequent solvent reorganization can lead to symmetrical solvation with water displacing dioxane. Alternatively, attack of water on the dioxane-solvated ion could lead to *retained* configuration, since two inversions would have occurred. In the presence of .06 *M* sodium azide, both 2-octanol and 2-octyl azide are formed with complete inversion of configuration. In the presence of the very nucleophilic azide ion, the weakly nucleophilic dioxane does not compete effectively and the route to retained alcohol is precluded. Only inverted alcohol formed by way of the initial ion-pair intermediate by back-side solvation with water is observed. These results are consistent with the intimate ion pair being the rate-determining intermediate.[74]



73. P. D. Bartlett and L. J. Rosen, *J. Am. Chem. Soc.* **64**, 543 (1942).
74. H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.* **87**, 292 (1965).

Nucleophilic substitution in cyclohexyl systems is quite slow and is often accompanied by extensive elimination. The stereochemisty has been determined to be comparable to that of other secondary systems by using a deuterium-labeled substrate (entry 6). The substitution process occurs with complete inversion of configuration. Analysis of the NMR spectrum of the product revealed a small amount (15%) of rearrangement attending solvolysis in acetic acid, which increased to 35% in formic acid and 75% in trifluoroacetic acid. The rearrangement process presumably involves a 1,2 shift of deuterium *anti* to the leaving group. The extent of rearrangement increases with decreasing solvent nucleophilicity, as would be expected.

Stabilization of a carbonium ion intermediate by conjugation with an aromatic ring, as in the 1-phenylethyl system shown in entry 8, leads to nucleophilic substitution with diminished stereospecificity. A thorough analysis of stereochemical, kinetic, and isotope effect data on solvolysis reactions of 1-phenylethyl chloride has been carried out.[75] For the ion pair equilibria

$$\begin{array}{ccccccc} RX & \underset{80}{\rightleftharpoons} & R^+X^- & \overset{13}{\rightleftharpoons} & R^+ \| X^- & \overset{0}{\rightleftharpoons} & R^+ + X^- \\ & & \uparrow\downarrow & & & & \\ XR & \overset{6}{\rightleftharpoons} & X^-R^+ & \overset{1}{\rightleftharpoons} & X^- \| R^+ & & \end{array}$$

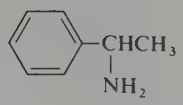
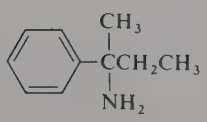
it appears that the rate-determining step is formation of the solvent-separated ion pair, and that most of the product is formed by attack on this intermediate. It has been estimated that for every 100 molecules of 1-phenylethyl chloride that undergo ionization to an intimate ion pair (in trifluoroethanol as solvent), 80 return to starting material of retained configuration, 7 invert their configuration at the intimate ion pair stage, and 13 go on to products via the solvent-separated ion pair.

As is evident from the results shown for the tertiary benzylic substrate 2-phenyl-2-butyl *p*-nitrobenzoate in entry 9, the simple expectation of practically complete racemization in nucleophilic substitution in tertiary systems is not rigorously adhered to. In weakly nucleophilic media such as potassium acetate in acetic acid, this ideal is almost achieved, and the product is only slightly inverted. Use of a good nucleophile like azide ion, however, leads to product with a significant (56%) degree of inversion of configuration. This can be attributed to nucleophilic attack on the ion pair intermediate prior to symmetrical solvation. More surprising is the observation of net retention of configuration in the hydrolysis of optically active 2-phenyl-2-butyl *p*-nitrobenzoate in aqueous acetone. Control experiments established alkyl–oxygen cleavage, not acyl–oxygen cleavage, in the hydrolysis. It is possible that this is an example of solvent collapse from the front at the solvent-separated ion pair stage. The bulky tertiary system hinders solvation at the rear; hydrogen bonding to the departing *p*-nitrobenzoate ion by water in the solvent-separated ion pair would facilitate capture of the carbonium ion at its front face.

75. V. J. Shiner, Jr., S. R. Hartshorn, and P. C. Vogel, *J. Org. Chem.* **38**, 3604 (1973).

Table 5.15. Stereochemical Course of Deamination Reactions in Acetic Acid

$$RNH_2 \xrightarrow{NaNO_2,\ CH_3CO_2H} ROAc$$

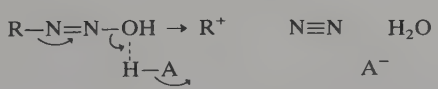
	Amine	Stereochemistry of acetate ester formation
1[a]	$CH_3CH_2CH_2CHDNH_2$	69% inversion
2[b]	$CH_3CHCH_2CH_3$ (NH$_2$ on CH)	28% inversion
3[c]		10% retention
4[d]		24% retention

a. A. Streitwieser, Jr., and W. D. Schaeffer, *J. Am. Chem. Soc.* **79**, 2888 (1957).
b. K. B. Wiberg, Dissertation, Columbia University, 1950.
c. R. Huisgen and C. Ruchardt, *Justus Liebigs Ann. Chem.* **601**, 21 (1956).
d. E. H. White and J. E. Stuber, *J. Am. Chem. Soc.* **85**, 2168 (1963).

Nucleophilic substitution reactions that occur under conditions of amine diazotization often differ significantly in stereochemistry, as compared with that seen in halide or arenesulfonate solvolysis. Diazotization occurs via an *N*-nitroso amine which decomposes to a carbonium ion, molecular nitrogen, and water:

$$R{-}NH_2 \rightarrow R{-}\underset{H}{N}{-}N{=}O \rightarrow R{-}N{=}N{-}OH \xrightarrow{H^+} R{-}\overset{+}{N}{\equiv}N + H_2O \rightarrow R^+ + N_2$$

The alkyldiazonium ion is expected to have an exceedingly short lifetime and a single-step process may more accurately describe the elimination step[76]:

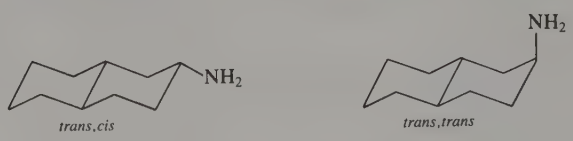


Thus, in contrast to an ionization process from a neutral substrate, which initially generates an intimate ion pair, the deamination reaction generates an ion pair in which the cation and anion are somewhat separated at the instant of formation. The results of four significant deamination reactions are summarized in Table 5.15. It can be seen (entry 1) that displacement of nitrogen on the 1-butyldiazonium ion is much less stereospecific than the 100% inversion observed on acetolysis of the

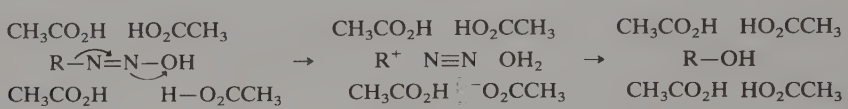
76. H. Maskill and M. C. Whiting, *J. Chem. Soc., Perkin Trans. II.*, 1462 (1976).

corresponding brosylate. Similarly, the secondary system (entry 2) affords 2-butyl acetate with only 28% inversion of configuration. Furthermore, a crossover to net retention of configuration is observed as the alkyl group becomes better able to stabilize a carbonium ion. The small net retention (10%) observed in deamination of 1-phenylethylamine increases to 28% retention in the tertiary benzylic system 2-phenyl-2-butylamine.

A thorough study of stereochemical effects has been made using the conformationally rigid 2-decalylamines:



In solvent systems containing low concentrations of water in acetic acid, dioxane, or sulfolane, the alcohol product (capture by water) occurs with retention, whereas the ester product (capture by acetic acid solvent) is a mixture of retained and inverted product. These results can be rationalized in terms of a hydrated ion pair formed by decomposition of the diazotized intermediate[77]:



The water molecule formed in the elimination step is evidently captured primarily from the front side, leading to retained configuration for the alcohol. The ester product can be formed by solvent collapse from the front or back side or by capture of the acetate ion. It is clear that the two stereoisomeric amines *do not form the same intermediate*, even though a simple mechanistic picture would show the 2-decalyl ion as a common intermediate. The product composition is very significantly different for the two starting materials. Similar results have been found for the *cis*- and *trans*-4-*t*-butylcyclohexylamines.[76] Some of the data are summarized in Table 5.16. The general picture which arises from these and other diazotization studies then is one of a very rapid collapse of the cationic intermediate with the product ratio and stereochemistry determined by the immediate solvation environment.

A few nucleophilic substitution reactions have been observed to proceed with a high degree of retention of configuration. The most familiar example is the reaction of alcohols with thionyl chloride which under some conditions gives predominantly product of retained configuration. The mechanistic designation S_Ni (substitution nucleophilic, internal) was initially applied to this category of reaction. Although the S_Ni mechanism at one time was postulated to involve front-side displacement involving a four-center transition state,[78] no such process has been documented in

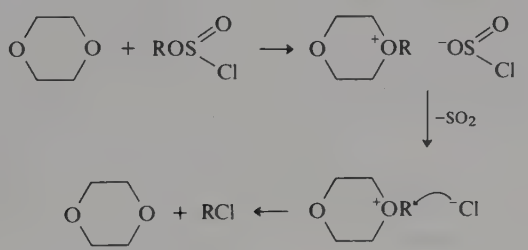
77. T. Cohen, A. D. Botelho, and E. J. Jankowski, *J. Org. Chem.* **45**, 2839 (1980).
76. See p. 285.
78. W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1252 (1937).

Table 5.16. Product Composition from Deamination of Stereoisomeric Amines

	Product composition[a]			
	Alcohol		Ester	
	Ret	Inv	Ret	Inv
cis-4-*t*-Butylcyclohexylamine (ax)[b]	33	8	25	33
trans-4-*t*-Butylcyclohexylamine (eq)[b]	43	2	43	12
trans,trans-2-Decalylamine (ax)[c]	26	2	32	40
trans,cis-2-Decalylamine (eq)[c]	18	1	55	26

a. Composition of total of alcohol and acetate ester. Considerable, and variable, amounts of alkene are also formed.
b. Reference 76.
c. Reference 77.

nucleophilic substitution at carbon. These reactions are now believed to proceed by substitution reactions involving the usual back-side displacement and ion pair processes. Chlorosulfite esters are initially formed by the reaction of the alcohol with thionyl chloride. Nucleophilic attack by chloride ion on the chlorosulfite ester can lead to inverted product. This is the dominant course of the reaction for 2-octanol in the absence of a nucleophilic solvent. In dioxane there is retention to the extent of 84%. This stereochemistry is best described as a double-inversion process. In the first inversion, dioxane displaces chlorosulfite, which then decomposes to sulfur dioxide and chloride ion. Chloride ion then displaces dioxane.[79]



5.9. Secondary Kinetic Isotope Effects in Substitution Mechanisms

The utility of kinetic isotope effects in probing reaction mechanisms was described in the preceding chapter, where it was pointed out that measurable secondary kinetic isotope effects were evident in reactions that do not involve cleavage of the bond to the isotopic nucleus. Measurements of secondary kinetic

79. E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.* **74**, 308 (1952).

isotope effects have proven to be a valuable complement to kinetic and stereochemical studies in characterizing the mechanism of nucleophilic substitution processes. The secondary kinetic isotope effects that have been applied to the study of solvolysis reactions are primarily α- and β-deuterium isotope effects resulting from deuterium substitution for protium at the carbon atom bearing the leaving group or at the β-carbon atom, respectively.

α-deuterium substitution

β-deuterium substitution

In both cases, the observed kinetic isotope effect k_H/k_D is usually greater than 1. The C–D bond has a lower zero-point energy than a C–H bond, and hyperconjugative stabilization of a developing carbonium ion by a β hydrogen involves loss of less zero-point energy than stabilization by a β deuterium and leads to a slightly faster rate. For example, acetolysis of cyclopentyl tosylate at 50°C is 22% faster than that of *cis*-2-deuteriocyclopentyl tosylate and 17% faster than acetolysis of *trans*-2-deuteriocyclopentyl tosylate.[80] The magnitude of the secondary β-isotope effect is dependent on, and can provide information relative to, the nature of the rate-determining step in solvolysis reactions. The value of $k_H/k_{\beta\text{-}D_3}$ for isopropyl brosylate versus its 1,1,1-trideutero analog are 1.46 in trifluoroacetic acid and 1.24 in 70% aqueous trifluoroethanol, respectively.[81] The larger value in CF_3CO_2H is indicative of a greater degree of cationic character and is attributed to the conversion of an intimate ion pair to a solvent-separated ion pair in the rate-determining step. The smaller isotope effect is characteristic of a reaction in which the rate-determining step is formation of an intimate ion pair. In this case C–O heterolysis is incomplete at the transition state, and k_H/k_D is smaller.

Detailed, careful measurements of α-secondary kinetic isotope effects have been carried out with a view toward characterizing the various intermediates and their rates of formation and reaction.[82] An α hydrogen or deuterium substituent will experience a "freeing-up" of its bending mode in the transition state for ionization. Since the amplitude of a C–H bend is greater than that of a C–D bend, there will be a slightly greater drive toward ionization of the hydrogen-substituted compound than its deuterium-substituted counterpart. A direct displacement mechanism would not be expected to exhibit a k_H/k_D of comparable magnitude because the bending mode would be resisted, owing to increased crowding in the pentacoordinate transition state. These studies have led to ranges of k_H/k_D which seem to be characteristic of the various types of rate-determining steps.

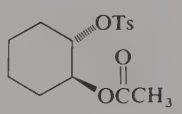
80. A. Streitwieser, Jr., R. H. Jagow, and S. Suzuki, *J. Am. Chem. Soc.* **77**, 6713 (1955).
81. V. J. Shiner, Jr., S. R. Hartshorn, and P. C. Vogel, *J. Org. Chem.* **38**, 3604 (1973).
82. V. J. Shiner, Jr., *Isotope Effects in Chemical Reactions*, C. J. Collins and W. S. Bowman (eds.), Van Nostrand Reinhold Company, New York, 1970, Chap. 2.

α-Isotope effects on direct displacements are, as expected, small. The value of k_H/k_D for hydrolysis of ethyl tosylate is 1.02. A k_H/k_D of 1.00–1.05 is considered to be diagnostic for rate-determining displacement on a covalent substrate. If the rate-determining step is formation of an intimate ion pair, k_H/k_D is about 1.15. Solvolysis of 2-butyl brosylate in 70% aqueous trifluoroethanol, for example, has k_H/k_D of 1.165. If conversion of an intimate ion pair to a solvent-separated ion pair is rate-determining, the α-isotope effect k_H/k_D is larger. As was previously mentioned, solvolysis of isopropyl tosylate in trifluoroacetic acid is an example of this type of mechanism and has $k_H/k_D = 1.22$ for α substitution of deuterium. Rate-determining attack on a solvent-separated ion pair behaves isotopically in a manner similar to rate-determining ion pair formation, and is characterized by α-isotope effects of about 1.15. Dissociation of a solvent-separated ion pair to separated ions has a large $\alpha k_H/k_D$ in the range 1.29–1.35. Although kinetic isotope effects can be used as one of the diagnostic tools for characterizing the nature of nucleophilic displacement processes, they should not be regarded as absolute criteria. The ranges are likely to overlap, particularly in borderline cases.[83]

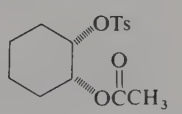
5.10. Neighboring-Group Participation

When a molecule that is a potential substrate for nucleophilic substitution also carries a group that can act as a nucleophile, it is often observed that the kinetics and stereochemistry of substitution are strongly affected. The involvement of nucleophilic substituents in a molecule in a substitution reaction at another point in the same molecule is called *neighboring-group participation*.[84]

A classic example of neighboring-group participation involves the solvolysis of compounds in which an acetoxy substituent is present near a carbon that is undergoing nucleophilic substitution. For example, the rates of solvolysis of the *cis* and *trans* isomers of 2-acetoxycyclohexyl *p*-toluenesulfonate differ by a factor of about 670, the *trans* compound being the more reactive[85]:



$k = 1.9 \times 10^{-4}$ (100°C)

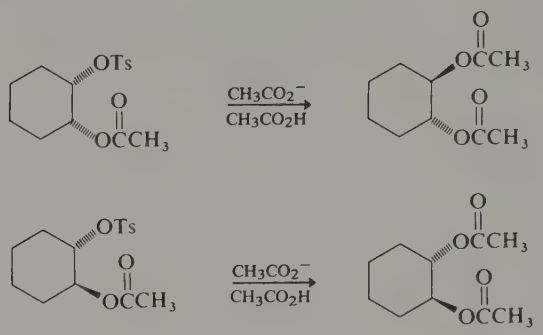


$k = 2.9 \times 10^{-7}$ (100°C)

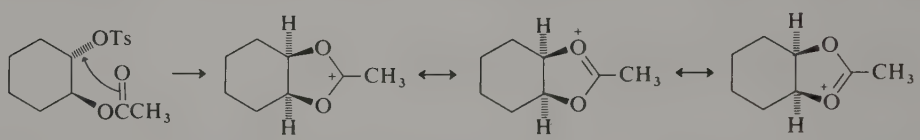
Besides the pronounced difference in rate, the isomeric compounds reveal a marked

83. For some examples of studies where arguments based on kinetic isotope effects have been used to elucidate transition state characteristics, see T. Ando, S.-G. Kim, K. Matsuda, H. Yamataka, Y. Yukawa, A. Fry, D. E. Lewis, K. B. Sims, and J. C. Wilson, *J. Am. Chem. Soc.* **103**, 3505 (1981); T. Ando, H. Yamataka, H. Morisaki, J. Yamawaki, J. Kuramochi and Y. Yukawa, *J. Am. Chem. Soc.* **103**, 430 (1981); V. J. Shiner and J. J. Tai, *J. Am. Chem. Soc.* **103**, 436 (1981).
84. B. Capon, *Q. Rev. Chem. Soc.* **18**, 45 (1964).
85. S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *J. Am. Chem. Soc.* **70**, 816 (1948).

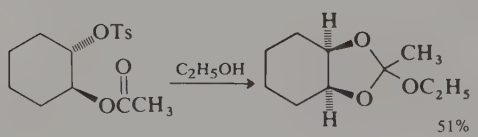
difference in stereochemistry. The diacetate obtained from the *cis* isomer is the *trans* compound (inverted stereochemistry), whereas retention of configuration is observed for the *trans* isomer.



These results are explained by the *participation* of the *trans* acetoxy group in the ionization process. The assistance provided by the acetoxy carbonyl group facilitates the ionization of the tosylate group, accounting for the rate enhancement. The



acetoxonium ion intermediate is subsequently opened by nucleophilic attack with inversion at one of the two equivalent carbons, leading to the observed *trans* product.[86] When optically active *trans*-2-acetoxycyclohexyl tosylate is solvolyzed, the product is racemic *trans*-diacetate. This is consistent with the proposed mechanism, since the acetoxonium intermediate is achiral and can account for the racemization.[87] Additional evidence for this interpretation comes from the isolation of a cyclic *ortho* ester when the solvolysis is carried out in ethanol. In this case the acetoxonium ion is captured by the solvent.



Ref. 88

The hydroxyl group can also act as intramolecular nucleophile. Solvolysis of 4-chlorobutanol in water gives as the product the cyclic ether tetrahydrofuran.[89]

86. S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.* **70**, 812 (1948).
87. S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am. Chem. Soc.* **64**, 2796 (1942).
88. S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.* **65**, 613 (1943).
89. H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Am. Chem. Soc.* **75**, 4778 (1953).

The reaction is much faster than solvolysis of 3-chloropropanol. In basic solution the deprotonated oxygen is a still more effective nucleophile. In ethanol–sodium

$$Cl(CH_2)_4OH \xrightarrow{H_2O} \text{(tetrahydrofuran)} + HCl$$

ethoxide, solvolysis of 2-chloroethanol is about 5000 times as fast as ethyl chloride. The product is ethylene oxide, confirming the involvement of the oxygen atom.

$$HOCH_2CH_2Cl \rightleftharpoons {}^{-}OCH_2CH_2Cl \longrightarrow \text{(ethylene oxide)} + Cl^{-}$$

As the length of the chain separating the reacting groups increases, the rate of cyclization is affected, as shown in Table 5.17. The minimum at the four-membered and maximum at the five-membered ring are quite commonly encountered. The reason is that the free energy of the transition state depends on both enthalpic and entropic factors. A significant contribution to the enthalpy of activation is related to the strain energy that develops in the transition state. This energy will be high in the case of formation of three- and four-membered rings because of angle strain, and lower for the formation of five- and six-membered rings. The entropy of activation depends on the number of atoms that have their rotational degrees of freedom restricted in the transition state. The entropy-of-activation term is more favorable for small rings than for larger rings because the motion of fewer atoms is restricted. Thus, a more favorable entropy-of-activation term is responsible for the rapid formation of three-membered rings, and a more favorable enthalpy-of-activation term for the formation of five-membered rings. Four-membered rings form slowly because angle-strain and torsional-strain contributions to the energy of the transition state are not sufficiently compensated for by a favorable entropy term.

Table 5.17. Solvolysis Rates of ω-Chloroalcohols[a]

ω-Chloroalcohols	Approximate relative rate
$Cl(CH_2)_2OH$	2000
$Cl(CH_2)_3OH$	1
$Cl(CH_2)_4OH$	5700
$Cl(CH_2)_5OH$	20

a. B. Capon, *Q. Rev. Chem. Soc.* **18**, 45 (1964); W. H. Richardson, C. M. Golino, R. H. Wachs, and M. B. Yelvington, *J. Org. Chem.* **36**, 943 (1971).

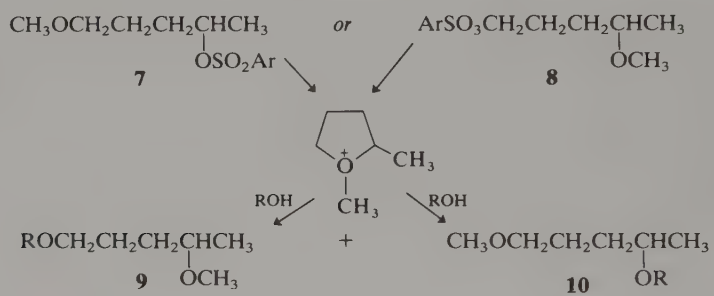
Table 5.18. Solvolysis of Some ω-Methoxyalkyl *p*-Bromobenzenesulfonates in Acetic Acid[a]

$CH_3(CH_2)_2OSO_2Ar$	1.00
$CH_3O(CH_2)_2OSO_2Ar$	0.28
$CH_3O(CH_2)_3OSO_2Ar$	0.67
$CH_3O(CH_2)_4OSO_2Ar$	657
$CH_3O(CH_2)_5OSO_2Ar$	123
$CH_3O(CH_2)_6OSO_2Ar$	1.16

a. From S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron* **3**, 1 (1958).

As a neighboring group becomes farther removed from the reactive site, the strain contribution to the transition state energy becomes less important than the entropy considerations. The entropy term becomes increasingly more unfavorable as the number of atoms between the groups increases, and the effectiveness of neighboring-group participation drops rapidly for rings of seven or more atoms.

Like the un-ionized hydroxyl group, an alkoxy group is a weak nucleophile, but can be involved in neighboring-group participation when steric and other factors are favorable. For example, solvolysis of the isomeric *p*-bromobenzenesulfonate esters **7** and **8** leads to identical product mixtures, suggesting the involvement of a common intermediate, as would be the case if participation of the methoxy group occurred.[90]



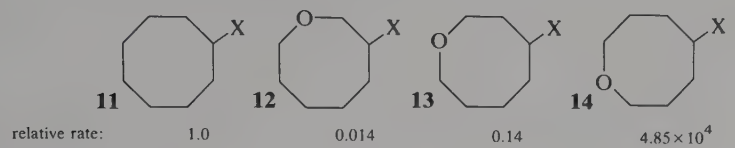
Kinetic data also reveal a substantial increase (~4000) in the rate of solvolysis of **8** relative to *n*-butyl *p*-bromobenzenesulfonate.

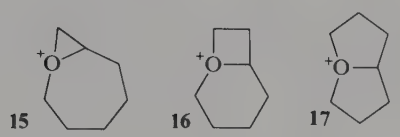
The solvolysis rates of a series of ω-methoxyalkyl *p*-bromobenzenesulfonates have been determined. A maximum in rate is again observed where participation of the methoxy group via a five-membered ring is possible (see Table 5.18).

Transannular participation of ether oxygen has also been identified by kinetic studies of some cyclic ethers. The series **11–14** has been studied, and the data obtained indicate a very large acceleration in the case of replacement of the 5-CH_2 with oxygen in a cyclooctyl ring.[91] The huge difference in rate that results from the

90. E. L. Allred and S. Winstein, *J. Am. Chem. Soc.* **89**, 3991 (1967).
91. L. A. Paquette and M. K. Scott, *J. Am. Chem. Soc.* **94**, 6760 (1972).

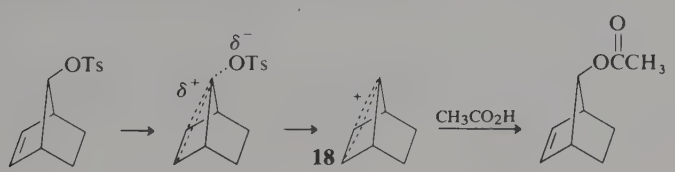
alternative placement of the oxygen atoms reflects the much more favorable geometry of ion **17**, which is derived from **14**, relative to the species **15** and **16**, which would be involved if neighboring-group participation occurred for compounds **12** and **13**. The rate-retarding effect of the oxygen atoms in **12** and **13** presumably reflects unfavorable dipole and inductive effects of the polar C–O bonds which disfavor carbonium ion formation.





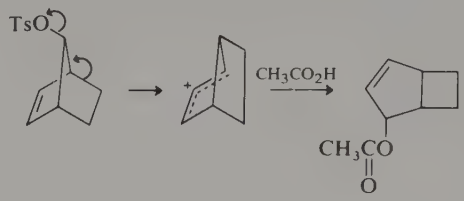
In general, any system that has a potentially nucleophilic substituent group placed properly for back-side displacement of a leaving group at another carbon atom of the molecule can be expected to display neighboring-group participation. The extent of the rate enhancement will depend on how effectively the group acts as a nucleophile. The existence of participation may be immediately obvious from the structure of the product if some derivative of the cyclic intermediate is stable, but in other cases, the demonstration of kinetic acceleration and stereochemical evidence may provide the basis for ascertaining the presence of nucleophilic participation in the rate-determining step.

The π electrons of carbon–carbon double bonds can also become involved in nucleophilic substitution processes. This can result in facilitating the ionization step by leading to a carbonium ion having special stability. Solvolysis reactions of the *syn* and *anti* isomers of 7-substituted norbornenes provide some dramatic examples of the influence of a participating double bond on reaction rates and stereochemistry. The *anti*-tosylate is more reactive by a factor of about 10^{11} toward acetolysis than the saturated analog. The acetolysis product, *anti*-7-acetoxynorbornene, is the product of retention of configuration. These results can be explained by participation of the π electrons of the double bond to give the ion **18**, which would be stabilized by delocalization of the positive charge.[92]

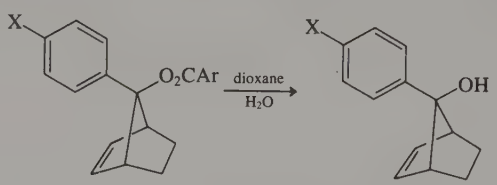


92. S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.* **77**, 4183 (1955); S. Winstein and M. Shatavsky, *J. Am. Chem. Soc.* **78**, 592 (1956); S. Winstein, A. H. Lewin, and K. C. Pande, *J. Am. Chem. Soc.* **85**, 2324 (1963).

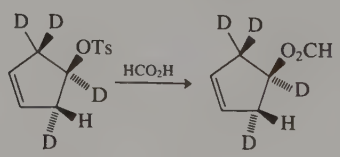
In contrast, the *syn* isomer, in which the double bond is not in a position to participate effectively in the ionization step, reacts 10^7 times slower than the *anti* isomer. The reaction product is derived from a rearranged carbonium ion that is stabilized by virtue of being allylic.[93]



The extent of participation of the carbon–carbon double bond in the ionization process is a function of the substitution at C-7. The placement of an aryl substituent at C-7 diminishes the rate acceleration due to participation by the double bond. The extent of participation by the double bond is a function of the stability of the potential carbonium ion. When an aryl group is present at C-7 the resulting benzyl-type stabilization decreases the importance of participation by the double bond. The extent of stabilization is a function of substituents on the aryl ring. For *p*-methoxyphenyl, phenyl, and *p*-trifluoromethylphenyl, the rate factor for the unsaturated relative to the saturated system are 3, 40, and 3.5×10^4, respectively.[94] This dependence of the extent of participation on other stabilizing features is a general trend and has been observed with other types of carbonium ions.[95]



This same type of π-electron participation controls the stereochemistry of substitution in the case of cyclopent-3-enyl tosylates, even though no strong rate enhancement is observed. This has been demonstrated by solvolysis of a stereospecifically labeled analog.[96] The product is formed with complete retention of



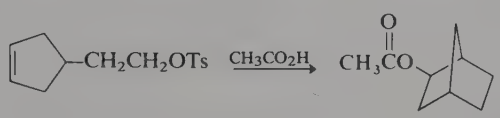
configuration, in contrast to the saturated system which reacts with complete

93. S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.* **79**, 505 (1957).
94. P. G. Gassman and A. F. Fentiman, Jr., *J. Am. Chem. Soc.* **91**, 1545 (1969); **92**, 2549 (1970).
95. H. C. Brown, *The Nonclassical Ion Problem*, Plenum Press, New York, 1977, pp. 163–175.
96. J. B. Lambert, R. B. Finzel and C. A. Belec, *J. Am. Chem. Soc.* **102**, 3281 (1980).

inversion under similar conditions.[97] The retention of configuration is explained by a structure similar to that shown in the case of *anti*-7-norbornenyl cation. Evidently,

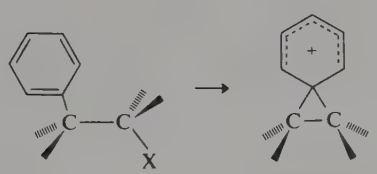
since there is no appreciable rate acceleration, this participation is not very strong at the rate-determining step. Instead, the bridging must arise largely after the transition state is reached. Nevertheless, since the reaction is stereospecific, it is clear that the intermediate formed in the rate-determining step must retain the stereochemical integrity necessary for subsequent stereospecific bridging. If a symmetrically solvated 3-cyclopentenyl cation were formed, this stereochemical information would be lost.

Participation of carbon–carbon double bonds in solvolysis reactions can also be detected in some cases by isolation of products with new carbon–carbon bonds formed as the result of such participation. A particularly significant case is the formation of the bicyclo[2.2.1]heptane system during solvolysis of 2-cyclopent-3-enylethyl tosylate[98]:



In this case, the participation leads to the formation of the norbornyl cation which is captured as the acetate ester. More will be said about this cation in Section 5.12.

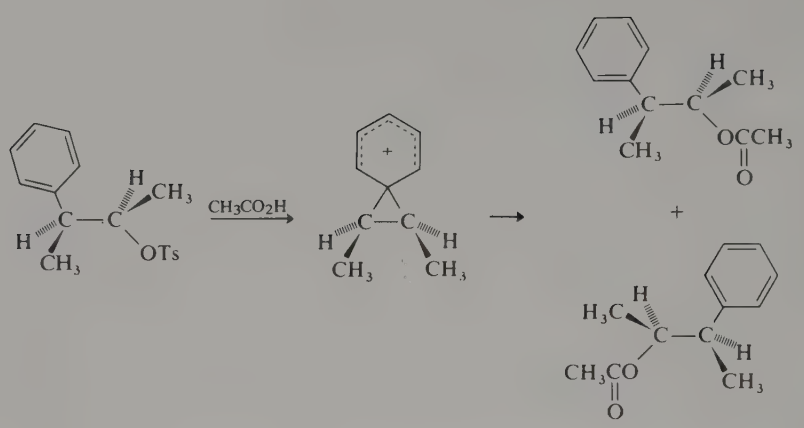
A system in which the details of carbon participation have been thoroughly probed is the case of "phenonium" ions, the species resulting from participation by a β-phenyl group.



"phenonium" ion

Such participation would lead to a bridged species with the positive charge delocalized into the aromatic ring. Evidence for this kind of participation was first obtained in a study in which the stereochemistry of solvolysis of 3-phenyl-2-butyl tosylates was studied. The *erythro* isomer gave largely retention of configuration, a result that could be explained via the bridged ion. The *threo* isomer, where participation leads to an achiral species, gave racemic *threo* product.[99]

97. K. Humski, V. Sendijarević, and V. J. Shiner, Jr., *J. Am. Chem. Soc.* **95**, 7722 (1973).
98. R. G. Lawton, *J. Am. Chem. Soc.* **83**, 2399 (1961).
99. D. J. Cram, *J. Am. Chem. Soc.* **71**, 3863 (1949); **74**, 2129 (1952).



Both primary and secondary carbonium ions with β-phenyl substituents usually give evidence of aryl participation. For example, isotopically labeled carbons are scrambled to some extent during solvolysis of β-phenylethyl tosylates. A bridged-ion intermediate or rapid rearrangement of a primary carbonium ion could account for the rearrangement. The extent of rearrangement increases as solvent nucleophilicity decreases. This increase is attributed to competition between S_N2 displacement by solvent molecules and ionization with participation by the aryl group. The data are summarized in Table 5.19. While substitution in more nucleophilic solvents such as ethanol proceeds almost exclusively by direct displacement, the very nonnucleophilic trifluoroacetic acid leads to complete scrambling of the label.

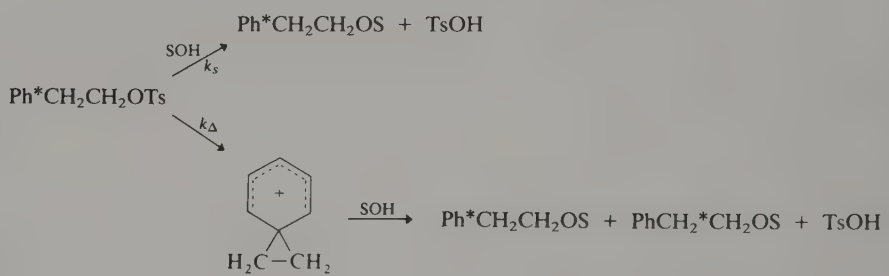


Table 5.19. Extent of Aryl Rearrangement in 2-Phenylethyl Tosylate Solvolysis[a]

Solvent	Rearrangement (%)
C_2H_5OH	0.3
CH_3CO_2H	5.5
$H_2O:HCO_2H$ (10:90)	40
HCO_2H	45
CF_3CO_2H	100

a. C. C. Lee, G. P. Slater, and J. W. T. Spinks, *Can. J. Chem.* **35**, 1417 (1957); J. E. Nordlander and W. G. Deadman, *Tetrahedron Lett.*, 4409 (1967).

Table 5.20. Extent of Solvolysis with Aryl Participation as a Function of Substituent and Solvent for 1-Aryl-2-propyl Tosylates

	Solvent		
X	80% EtOH[a]	CH_3CO_2H[b]	HCO_2H[b]
NO_2	0	—	—
CF_3	0	—	—
Cl	7	—	—
H	21	38	78
CH_3	63	71	94
OCH_3	93	94	99

a. D. J. Raber, J. M. Harris, and P. von R. Schleyer, *J. Am. Chem. Soc.* **93**, 4829 (1971).
b. C. C. Lancelot and P. von R. Schleyer, *J. Am. Chem. Soc.* **91**, 4296 (1969).

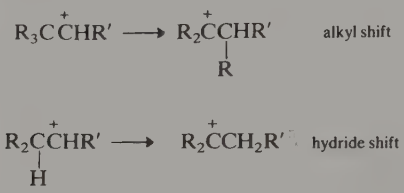
Although there is no large rate enhancement, stereochemical effects attributable to phenyl participation can be observed. The extent of rate enhancement increases as electron-releasing groups are introduced on the ring. The relative importance of aryl participation is a function of the substituents on the aryl ring. The solvent-assisted and aryl-assisted processes have been designated k_s and k_Δ, respectively.[100] The relative contributions to individual solvolyses have been dissected by taking advantage of the higher sensitivity to aryl substituent effects of the assisted mechanism. Phenyl rings with electron-withdrawing substituents do not participate effectively. Only the process described by k_s is important. Such compounds give a Hammett correlation with ρ values (−0.7–0.8) characteristic of weak substituent effects. Compounds with electron-releasing substituents deviate from this correlation line because of aryl participation. The extent of reaction proceeding through the k_s process can be estimated from the correlation line for electron-withdrawing substituents. Table 5.20 gives data indicating the extent of aryl participation under a variety of conditions. This method of analysis also confirms that the relative extent of participation of the β-phenyl groups in ionization processes is highly dependent on solvent.[101] In solvents of good nucleophilicity (e.g., ethanol), the normal solvent displacement mechanism makes the largest contribution. As solvent nucleophilicity decreases, the relative extent of aryl participation increases.

The bridged form of the β-phenylethyl ion can be observed in superacid media, and can be characterized by carbon and proton NMR spectra.[102] The bridged ion subsequently rearranges to the more stable α-methylbenzyl cation with E_a for the rearrangement being 13 kcal/mol. With more substituted cations the rearrangement to benzyl cations occurs too rapidly for the bridged ion to be observed.[103]

100. A. Diaz, I. Lazdins, and S. Winstein, *J. Am. Chem. Soc.* **90**, 6546 (1968).
101. F. L. Schadt, III, C. J. Lancelot, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **100**, 228 (1978).
102. G. A. Olah, R. J. Spear, and D. A. Forsyth, *J. Am. Chem. Soc.* **98**, 6284 (1976).
103. G. A. Olah, R. J. Spear, and D. A. Forsyth, *J. Am. Chem. Soc.* **99**, 2615 (1977).

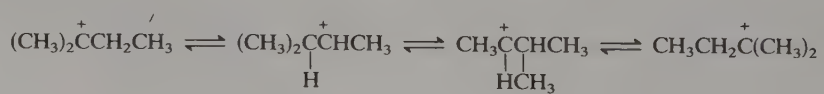
5.11. Carbonium Ion Rearrangements

The discussion of the behavior of carbonium ion intermediates in superacid media and the discussion of neighboring-group participation have already provided examples of skeletal rearrangements. This is a characteristic feature of the chemistry of carbonium ions. Carbonium ion rearrangements occur by shift of an alkyl group, aryl group, or hydrogen with its electron pair. This creates a new carbonium ion site at the carbon atom from which the migration occurred. 1,2 Shifts are the most common type of rearrangement.



A thermodynamic driving force exists for rearrangement of the carbon skeleton in the direction of forming a more stable carbonium ion. Usually, this is the direction in which migrations are observed to occur. Activation energies for skeletal migrations are not large, however, and it is not uncommon to observe rearrangements that must have involved individual steps that have proceeded from a more stable to a less stable species. Thus, while rearrangement of a tertiary cation to a secondary cation is endothermic by at least 10 kcal/mol, the activation barrier is not prohibitive. Formation of primary carbonium ions by rearrangement is much less likely to occur, since the primary ions are ~20 and ~35 kcal/mol higher in energy than secondary and tertiary carbonium ions, respectively.[104] The barriers to alkyl and hydride group shifts when ions of equal or greater stability are formed are apparently very low and the rearrangements occur very rapidly. In superacid media at −160°C, the equilibration of the five methyl groups of the 2,3,3-trimethylbutyl cation is so rapid that the barrier must be less than 5 kcal/mol[105]:

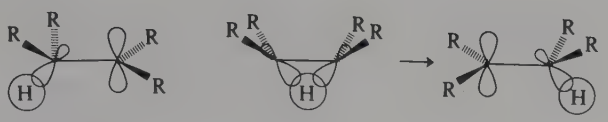
The barrier to the hydride and methyl shifts which interconvert the methyl groups in the *t*-amyl cation is 10–15 kcal/mol. This shift involves the formation of secondary carbonium ions as transient intermediates in the interconversion of the equivalent tertiary carbonium ions[106]:



104. G. J. Karabatsos and F. M. Vane, *J. Am. Chem. Soc.* **85**, 729 (1963).
105. G. A. Olah and A. M. White, *J. Am. Chem. Soc.* **91**, 5801 (1969).
106. M. Saunders and E. L. Hagen, *J. Am. Chem. Soc.* **90**, 2436 (1968).

Although the order of migrating ability H > aryl > alkyl has been suggested, this generalization cannot be depended on.[107] Very often, stereoelectronic factors govern the course of carbonium ion rearrangements. The energy changes associated with structural reorganizations are also affected by molecular strain. In particular, rearrangements that reduce molecular strain are favorable.

The preferred alignment of orbitals for a 1,2-hydride or alkyl shift involves coplanarity of the p orbital at the carbonium ion center and the σ orbital of the migrating group.



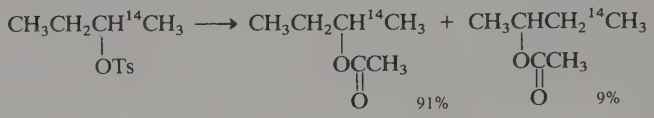
The transition state involves a three-center, two-electron bond. This transition state should be recognized as corresponding in structure to the symmetrically bridged structures and this may be the lowest energy form for some cations. The migration process can be concerted with the formation of the carbonium ion center; that is, the migration can begin before the bond to the leaving group has been completely broken. In that case, the group that will preferentially migrate is that *anti* to the leaving group in the reacting molecule. Conformational factors can also help determine which group migrates in nonconcerted processes if the barrier to migration is lower or comparable in energy to that for conformational equilibration. Structural rearrangements following deamination reactions seem to be particularly likely to be governed by the conformation of the reactant.[108]

The extent to which rearrangement occurs depends on the structure of the cation and the nature of the reaction medium. Capture of carbonium ions by nucleophiles is a process with a low activation energy in general, so that only very rapid rearrangement processes can occur in the presence of nucleophiles. In contrast, in nonnucleophilic media, in which carbonium ions can have long lifetimes, carbonium ions related by structural rearrangements can come to equilibrium. This accounts for the fact that the most stable possible ion is usually observed in superacid systems.

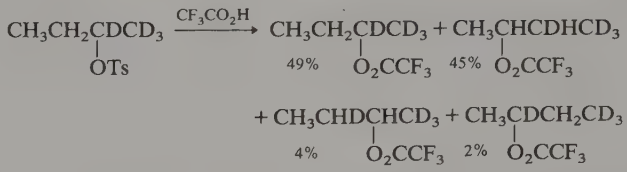
The occurrence and extent of rearrangement in the simpler alkyl carbonium ions has been studied particularly effectively by isotopic labeling. The 2-butyl cation generated by solvolysis of 2-butyl tosylate in acetic acid is converted to 2-butyl acetate. The extent of rearrangement prior to capture by solvent is only 9%.[109] Thus, under these conditions most of the reaction proceeds by direct participation

107. D. J. Cram, in *Steric Effects in Organic Chemistry*, M. S. Newman (ed.), Wiley, New York, 1956, pp. 249–303.
108. J. A. Berson, J. W. Foley, J. M. McKenna, H. Junge, D. S. Donald, R. T. Luibrand, N. G. Kundu, W. J. Libbey, M. S. Poonian, J. J. Gajewski, and J. B. E. Allen, *J. Am. Chem. Soc.* **93**, 1299 (1971).
109. J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, Jr., *J. Am. Chem. Soc.* **74**, 4283 (1952).

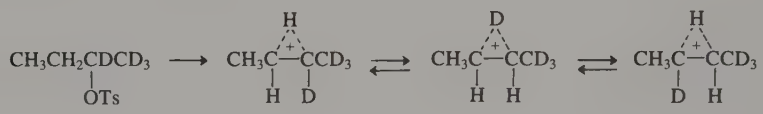
of solvent at the reaction site. When 2-butyl tosylate is solvolyzed in the less



nucleophilic solvent trifluoroacetic acid, a different result emerges. The extent of hydride migration is nearly 50%.[110]

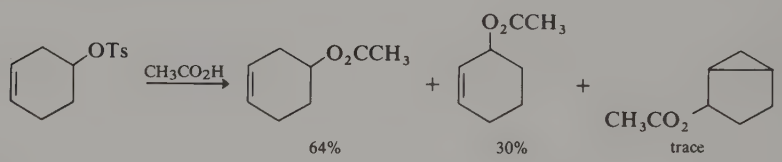


More extensive rearrangement involving interchange of the C-2 and C-3 hydrogens accounts for the two minor products.



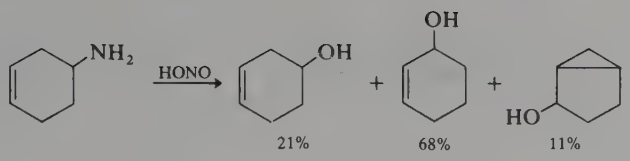
In other cases, the occurrence of rearrangement processes is evident from the structure of the products. Neopentyl systems are very prone to rearrange, since a primary carbonium is converted to a tertiary one by methyl migration. The rearrangement can, however, be avoided by reaction conditions that ensure that the S_N2 mechanism will dominate. One successful approach has been to use aprotic dipolar solvents to enhance the nucleophilicity of anionic nucleophiles.[111]

The 4-cyclohexenyl ion provides an example of the dependence of the extent of rearrangement on reaction conditions. Acetolysis of the tosylate gives considerable hydride shift to the more stable allylic ion as well as a little cyclization to a bicyclo[3.1.0]hexane derivative.[112]

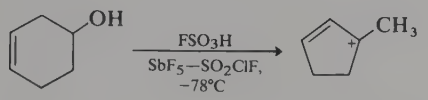


Deamination of the corresponding amine gives the allylic alcohol that results from a hydride shift as the main product, and the extent of cyclization is increased:

110. J. J. Dannenberg, B. J. Goldberg, J. K. Barton, K. Dill, D. H. Weinwurzel, and M. O. Longas, *J. Am. Chem. Soc.* **103**, 7764 (1981); J. J. Dannenberg, J. K. Barton, B. Bunch, B. J. Goldberg, and T. Kowalski, *J. Org. Chem.* **48**, 4524 (1983); A. D. Allen, I. C. Ambridge, and T. T. Tidwell, *J. Org. Chem.* **48**, 4527 (1983).
111. B. Stephenson, G. Solladie, and H. S. Mosher, *J. Am. Chem. Soc.* **94**, 4184 (1972).
112. M. Hanack and W. Keverie, *Chem. Rev.* **96**, 2937 (1963).

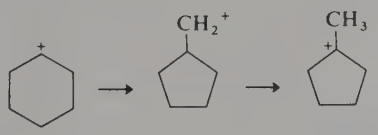


In contrast, formation of 3-cyclohexenyl cation from the alcohol in superacid media is followed by extensive rearrangement, which eventually gives the methylcyclopentenyl ion[113]:

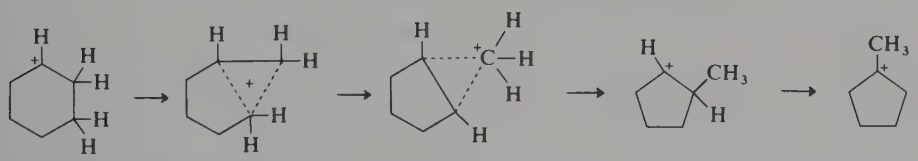


This trend of increasing amount and extent of rearrangement can be readily interpreted. In the acetolysis a large part of the reaction must be occurring via direct nucleophilic participation or rapid ion pair capture so that only a small amount of hydride shift occurs. As is characteristic of deamination, the carbonium ion is somewhat less tightly solvated at formation and as a result the extent of rearrangement is greater. Finally, in the nonnucleophilic fluorosulfonic acid the carbonium ions are sufficiently long lived to undergo several rearrangement steps, leading eventually to the most stable accessible ion.

Not all carbonium ion rearrangements can be adequately accounted for by 1,2 shifts. For example, the ring contraction of a cyclohexyl cation to a methylcyclopentyl cation is thermodynamically favorable, but would require a substantial activation energy if it proceeded through a primary cyclopentylmethyl cation.



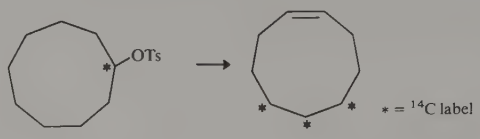
It is believed that a more correct description of the intermediate species involves a pentacoordinate carbon species referred to as a *protonated cyclopropane*.



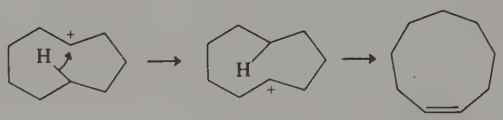
The "corner-protonated cyclopropane" structure corresponds to a methyl-bridged carbonium ion.

113. G. A. Olah, G. Liang, and Y. K. Mo, *J. Am. Chem. Soc.* **94**, 3544 (1972).

Shifts of hydride between carbon atoms separated by still more bonds are also possible, and particularly clear-cut examples have been found in medium-sized rings. For example, solvolysis of cyclononyl-1-^{14}C tosylate followed by degradation of the product cyclononene shows that about 20% of the ^{14}C is located at C(5), C(6), and C(7) in the product.

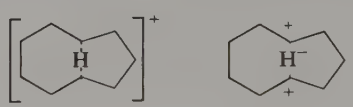


Relatively less ^{14}C is found at C(4). This result can be explained by a "transannular" hydride shift.



Many such processes have been documented.[114] Other examples of transfer of hydride between carbon atoms that are close in space although separated by several bonds have been found in bicylic ring systems.

It is very interesting that unstable cations in which the migrating hydride serves as a bridge can be observed under stable ion conditions.[115] This ion rearranges to the

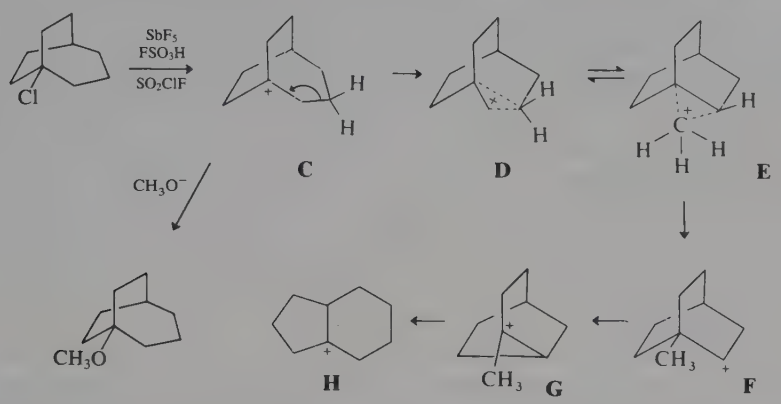


more stable 1-methylcyclooctyl cation, even at −140°C. The observed bridged ion is presumably an intermediate in the transannular hydride shift process which is observed under solvolytic conditions. Similar hydride-bridged ions have been observed for eight- and ten-membered rings.

Insight into successive stages in carbonium ion rearrangements has been gained by NMR studies at successively increasing temperatures in superacid media. The rearrangement of the bridgehead ion **C**, generated by ionization of the corresponding halide, to the tertiary ion **H** is depicted below. The bridgehead ion **C** possesses sufficient flexibility, owing to the size of the rings involved, to permit essentially planar geometry around the sp^2-carbon atom and is stable below −75°C. The unrearranged methyl ether is obtained by addition of sodium methoxide in methanol at −90°C. At −65°C, ion **C** rearranges to **G**. This rearrangement is believed to involve the methyl-bridged ion **E** as an intermediate. Ion **G** is stable below −30°C,

114. V. Prelog and J. G. Traynham, in *Molecular Rearrangements*, P. de Mayo (ed.), Interscience, New York, 1963, p. 593.
115. R. P. Kirchen and T. S. Sorensen, *J. Am. Chem. Soc.* **101**, 3240 (1979).

but above −30°C, the less strained ion **H** is formed. This latter rearrangement involves a sequence of steps again involving methyl-bridged species.[116] This multistep sequence terminating in the most stable $C_9H_{15}^+$ ion is quite typical of carbonium ion processes in superacid media. In the presence of nucleophilic anions or solvent, rearrangement usually does not proceed all the way to the most stable ion, because nucleophilic trapping results in the capture of one or more of the rearranged species.



Carbonium ion rearrangements are particularly facile if a functional group effectively stabilizes the product of rearrangement. Good examples of this are rearrangements of carbonium ions having a hydroxyl substituent on the adjacent carbon. Migration in this case generates a protonated carbonyl compound and is usually very favorable. These rearrangements are referred to as *pinacol rearrangements*.[117] The rearrangement is commonly observed as the result of treatment of 1,2-diols with acid. The structure of the products from unsymmetrical diols such as 1,1-diphenyl-2-methyl-1,2-propanediol can be predicted on the basis of ease of carbonium ion formation. Since the two phenyl groups provide the greater stabilization of the initial carbonium ion, methyl migration is dominant.[118]

$$R_2C(OH)-\overset{+}{C}R_2 \longrightarrow RC(=\overset{+}{O}H)-CR_3 \xrightarrow{-H^+} RC(=O)CR_3$$

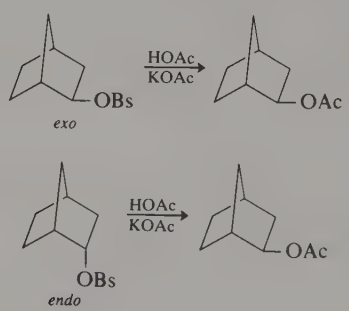
$$Ph_2CC(CH_3)_2(OH)(OH) \xrightarrow{H^+} Ph_2CC(CH_3)_2(OH)(OH_2) \longrightarrow Ph_2\overset{+}{C}C(CH_3)_2(OH) \longrightarrow Ph_2C(CH_3)C(=\overset{+}{O}H) \longrightarrow Ph_2C(CH_3)C(=O) + H^+$$

116. G. A. Olah, G. Liang, J. R. Wiseman, and J. A. Chong, *J. Am. Chem. Soc.* **94**, 4927 (1972).
117. Y. Pocker, in *Molecular Rearrangements*, P. de Mayo (ed.), Interscience, New York, 1963, pp. 15–25.
118. W. M. Schubert and P. H. LeFevre, *J. Am. Chem. Soc.* **94**, 1639 (1972).

5.12. The Norbornyl Cation

Throughout the discussion of carbonium ion structure and reactivity, we have encountered examples of bridged species which require expansion of bonding concepts beyond the two-center, two-electron bonds which suffice for most closed-shell organic molecules. These bridged structures which involve delocalization of σ electrons and formation of three-center two-electron bonds are called "nonclassical carbonium ions." The case for the importance of such bridged structures largely originated with a specific structure, the norbornyl cation and the issue of whether it had a classical or nonclassical (bridged) structure.[119] The special properties of this intermediate were first recognized on the basis of the thorough studies of Saul Winstein and his collaborators. The observed behavior of norbornyl systems in solvolytic displacement reactions was suggestive of neighboring-group participation. The properties of enhanced rate and abnormal stereochemistry characteristic of neighboring-group participation were demonstrated in the acetolysis of *exo*-2-norbornyl brosylate.

The acetolyses of both *exo*-2-norbornyl brosylate and *endo*-2-norbornyl brosylate produce exclusively *exo*-2-norbornyl acetate. The *exo*-brosylate is more reactive than the *endo*-brosylate by a factor of 350, as measured by the solvolysis rate constants.[120] Furthermore, acetolysis of optically active *exo*-brosylate gave completely racemic *exo*-acetate, and *endo*-brosylate gave *exo*-acetate that was at least 93% racemic.

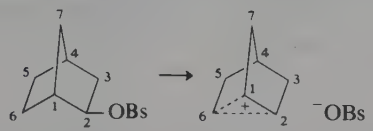


Both acetolyses were considered to proceed by way of rate-determining formation of a carbonium ion. The rate of ionization of the *endo*-brosylate was considered normal, since its reactivity was comparable to that of cyclohexyl brosylate. Elaborating on a suggestion made earlier concerning rearrangement of camphene hydro-

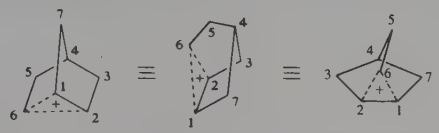
119. H. C. Brown, *The Nonclassical Ion Problem*, Plenum Press, New York, 1977; H. C. Brown, *Tetrahedron* **32**, 179 (1976); P. D. Bartlett, *Nonclassical Ions*, W. A. Benjamin, New York, 1965; S. Winstein, in *Carbonium Ions*, Vol. III, G. A. Olah and P. v. R. Schleyer (eds), Wiley–Interscience, New York, 1972, Chap. 22, G. D. Sargent, *ibid.*, Chap. 24; C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **21**, 87 (1982).

120. S. Winstein and D. S. Trifan, *J. Am. Chem. Soc.* **71**, 2953 (1949); **74**, 1147, 1154 (1952); S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *J. Am. Chem. Soc.* **87**, 376 (1965).

chloride,[121] Winstein proposed that ionization of the *exo*-brosylate was assisted by the C(1)–C(6) bonding electrons and led directly to the formation of a bridged nonclassical ion as an *intermediate*:

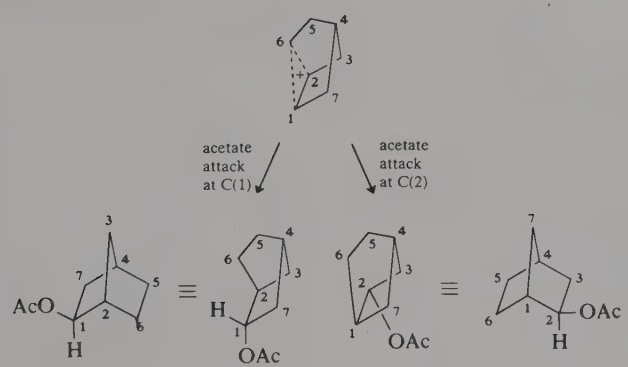


This intermediate serves well to explain the formation of racemic product, since it is achiral. The molecule has a plane of symmetry passing through C(4), C(5), C(6), and the midpoint of the C(1)–C(2) bond. The plane of symmetry is seen more easily in an alternative, but equivalent, representation:



Carbon 6, which bears two hydrogens, is pentacoordinate and serves as the bridging atom in the cation.

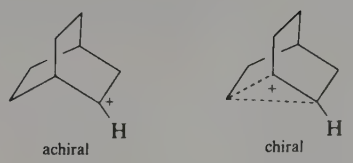
Attack by acetate at C(1) or C(2) is equally likely and produces equal amounts of enantiomeric acetates. The acetate ester produced must be *exo* because capture of the ion by acetate must occur from the direction opposite that of the bridging interaction. The nonclassical ion can be formed directly only from the *exo*-brosylate, not from the *endo*-brosylate, because only the *exo* isomer has the proper *anti* relationship between the C(1)–C(6) bond and the bond to the leaving group at C(2). The bridged ion can be formed from the *endo*-brosylate only after an unassisted rate-determining ionization.



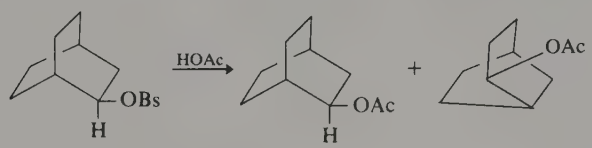
The nonclassical ion concept proved to be an intriguing one, and imaginative tests for the intermediacy of nonclassical ions in other bicylic systems were employed. While the classical ion in the norbonyl system is chiral and the nonclassical ion is achiral, the situation is reversed in the bicyclo[2.2.2] system. Here, the classical ion

121. T. P. Nevell, E. de Salas, and C. L. Wilson, *J. Chem. Soc.* 1188 (1939).

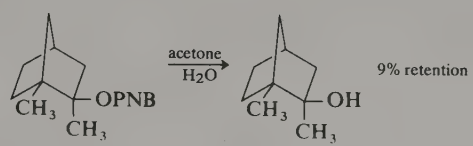
is achiral and the nonclassical ion is chiral:



When bicyclo[2.2.2]octyl brosylate was solvolyzed in acetic acid containing sodium acetate, the products were a mixture of bicyclo[2.2.2]octyl acetate and bicyclo[3.2.1]octyl acetate, each of which was optically active. The stereochemistry of formation of bicyclo[2.2.2]octyl acetate was concluded to be $82 \pm 15\%$ *retention* of configuration, in accord with that expected for a bridged-ion intermediate.[122] The achiral classical structure could not have been a major intermediate. The involvement



of nonclassical ions should not be considered to be universal, by any means. For example, the 1,2-dimethylnorbornyl cation should afford racemic products if it were a nonclassical ion. It has been found, however, that hydrolysis of 1,2-dimethyl-*exo*-2-norbornyl *p*-nitrobenzoate in aqueous acetone gives products of partially retained configuration, and must therefore proceed at least in part through a classical dissymmetric cation[123]:

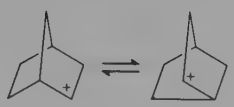


Subsequent studies of other tertiary norbornyl cations have indicated that they are essentially classical structures.

As should be the case with the establishment of any new principle, the concept of σ-bridged nonclassical intermediates was subjected to a searching analysis. An alternative explanation, based on classical carbocations, was put forth by H. C. Brown of Purdue University.[124] Brown pointed out that the evidence in support of the nonclassical formulation for norbornyl cation consisted of (a) rapid solvolysis of *exo*-norbornyl substrates relative to model compounds, (b) high *exo*/*endo* rate ratios, and (c) predominant (99.99%)[125] capture of the cation from the *exo* direction.

122. H. M. Walborsky, M. E. Baum, and A. A. Youssef, *J. Am. Chem. Soc.* **83**, 988 (1961).
123. H. Goering and K. Humski, *J. Am. Chem. Soc.* **90**, 6213 (1968).
124. H. C. Brown, *The Transition State, Chem. Soc. Spec. Publ.* **No. 16**, 140 (1962); *Chem. Br.*, 199 (1966); *Tetrahedron* **32**, 179 (1976).
125. H. L. Goering and C. B. Schewene, *J. Am. Chem. Soc.* **87**, 3516 (1965).

He concluded that all the available data were equally consistent with the intermediacy of rapidly equilibrating classical carbonium ions. The Wagner–Meerwein rearrangement that interconverts the two ions is presumed to be rapid relative to capture by nucleophile, and would lead to racemic product from an optically active norbornyl substrate:



In essence, the question that is raised has to do with the relative energy of the bridged structure. Is it lower in energy than the classical secondary ion and thus an intermediate to which the classical ion would collapse or is it slightly higher in energy and therefore a transition state (or intermediate) in a rapid isomerization between the two classical structures? In either case, the observed rapid isomerization ensures that the energy difference cannot be large. Figure 5.6 illustrates the potential energy diagrams corresponding to the various possibilities.

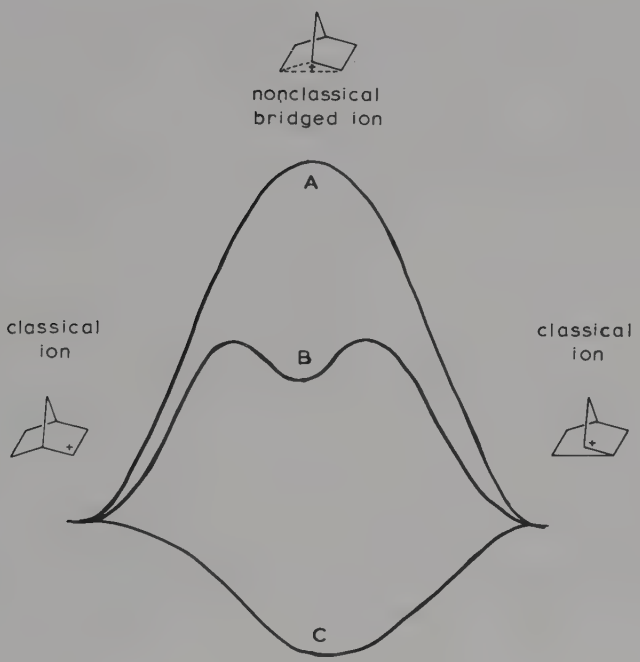
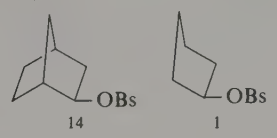
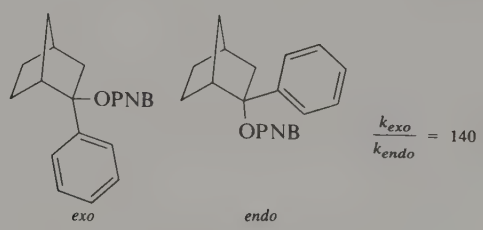


Fig. 5.6. Contrasting potential energy diagrams for stable and unstable bridged norbornyl cation. (A) Bridged ion is a transition state for rearrangement between classical structures. (B) Bridged ion is an intermediate in rearrangement of one classical structure to the other. (C) Bridged nonclassical ion is the only stable structure.

Brown's experimental approach was to show that the observable properties ascribed to σ bridging in the norbornyl cation could be duplicated in systems conceded to involve classical carbonium ions. He argued that the solvolysis of *exo*-norbornyl brosylate was held to be rapid only because it was being compared with inappropriate model compounds. The torsional relationship of the leaving group and adjacent substituents is eclipsed in the ground state, and this strain is relieved on ionization. Cyclohexyl brosylate is completely staggered in its ground state, so no strain relief accompanies its ionization. *exo*-Norbornyl brosylate could therefore be more reactive than cyclohexyl brosylate for reasons that do not require assisted ionization. A better comparison would be between *exo*-norbornyl brosylate and cyclopentyl brosylate. Relief of eclipsing interactions accompanies ionization of cyclopentyl substrates, which should then provide a better basis of comparison than cyclohexyl substrates. When the comparison was made, it was found that acetolysis of *exo*-norbornyl brosylate took place only 14 times faster than acetolysis of cyclopentyl brosylate [126].



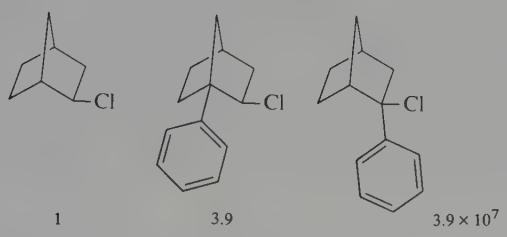
The question of the high *exo*/*endo* rate ratio was examined with *exo*- and *endo*-2-phenyl-2-norbornanol. The tertiary and benzylic 2-phenylnorbornyl cation is classical, as evidenced by its NMR spectrum.[127] Since the relative rates of hydrolysis of *exo*- and *endo*-2-phenylnorbornyl *p*-nitrobenzoate in 60% aqueous dioxane at 50°C are 140 : 1, and the reactions proceed by rate-determining formation of classical carbonium ions, Brown concluded that the *exo-endo* rate ratio of 340 for norbornyl brosylates does not require assisted ionization of *exo*-norbornyl brosylate.[128]



In a similar vein, phenyl substitution at C(1) would be expected to produce a large rate enhancement of *exo*-norbornyl substrates if a nonclassical ion is formed because positive charge develops at this position in the nonclassical ion intermediate. Yet the observed rate increase was only 3.9 for ethanolysis of the chloride. This

126. H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.* **86**, 1247 (1964).
127. D. G. Farnum and G. Mehta, *J. Am. Chem. Soc.* **91**, 3256 (1969).
128. H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.* **86**, 1248 (1964).

was compared to a 3.9×10^7 rate increase for phenyl substitution at C(2). This comparison indicated that little stabilization had been achieved in the transition state for ionization so that the transition state could not have benefitted much from bridging.



Stereoselective capture of the classical 2-phenyl-2-norbornyl cation from the *exo*-direction was also demonstrated. Hydrolysis of 2-phenyl-*exo*-norbornyl chloride in aqueous acetone gave 2-phenyl-*exo*-norborneol as the only isolated product.[129]

Since the kinetic and stereochemical data that were the primary justification for nonclassical σ-bridged carbocations could be mimicked by reactions of classical carbocations, Brown concluded that the involvement of bridged-ion intermediates was not required.

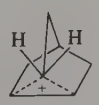
The evidence discussed to this point, both for and against the nonclassical structure, rests on indirect evidence derived from interpretation of kinetic results and stereochemical features of the substitution reactions. With the development of the techniques for directly observing carbonium ions, structural studies on the ion became possible. The norbornyl cation was subjected to intense scrutiny by George Olah at Case Western Reserve University. These spectroscopic investigations constituted a new approach to the problem.

The norbornyl cation was generated as its hexafluoroantimonate salt in SbF_5–SO_2–SO_2F_2 and the temperature dependence of its proton magnetic resonance spectrum examined.[130] It was determined that 3,2- and 6,2-hydride shifts were occurring, with the former having an activation energy of 10.8 kcal/mol, and the latter occurring much more rapidly. The activation energy for the 6,2-hydride shift was estimated as being less than 5.5 kcal/mol. If equilibrating classical ions were produced, the activation energy for Wagner–Meerwein rearrangement, as estimated by the temperature dependence of the spectrum, must also be less than 5.5 kcal/mol.

129. H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.* **86**, 1246 (1964).
130. P. v. R. Schleyer, W. E. Watts, R. C. Fort, Jr., M. B. Comisarow, and G. A. Olah, *J. Am. Chem. Soc.* **86**, 5679 (1964); M. Saunders, P. v. R. Schleyer, and G. A. Olah, *J. Am. Chem. Soc.* **86**, 5680 (1964).

Subsequently, the ^{13}C NMR and Raman spectra were measured for the norbornyl cation under stable ion conditions.[131] The Raman spectrum exhibited similarities to the spectrum of tricyclene, and could be interpreted as indicating that the species under stable ion conditions is a protonated tricyclene. One version of the protonated tricyclene structure is identical to the usual representation of the bridged nonclassical cation. It can be described as a "corner-protonated" cyclopropane structure. A second version of a protonated tricyclene would be an "edge-protonated" cyclopropane. In this structure there are two bridging groups, both the C-6 carbon, as in the usual structure, and the *endo* hydrogen. It is this hydrogen which very rapidly undergoes 2,6 shift. The symmetry of both structures meets the requirement of the earlier stereochemical results.

tricyclene



corner-protonated tricyclene

edge-protonated tricyclene

The ^{13}C NMR spectrum at −150°C exhibited resonances for C(1), C(2), and C(6) at 68.5, 68.5, and 171.4 ppm upfield from $^{13}CS_2$. These resonances are significantly different from the ^{13}C shift of 125 ppm downfield from $^{13}CS_2$ observed for the positive carbon in isopropyl cation. The high field shift of C(6) is attributed to pentacoordination, which, along with the equivalence observed for C(1) and C(2), supports the nonclassical structure for the ion.

Although these NMR studies show with certainty that the *averaged symmetry* of the norbornyl cation under stable ion conditions corresponded to that of a bridged structure, they do not prove that the bridged ion is the most stable, since NMR spectra represent time-averaged measurements and a very rapid equilibration would lead to the same apparent symmetry. However, at temperatures as low as 5°K there is no evidence of separate structures. Thus, if there is a barrier corresponding to the bridged structure it must be exceedingly low, <0.2 kcal/mol.[132] The positions of the chemical shifts relative to model cations and the parent hydrocarbon also tend to support the nonclassical structure.[133]

An NMR technique which does have the ability to distinguish between the case of a static system and a rapidly equilibrating one involves examination of the spectrum of the cation with unsymmetrical deuterium labeling. When this method was applied to the norbornyl cation it gave results which were consistent with a static structure, indicating that the symmetrical bridged structure is the stable one.[134]

131. G. A. Olah, G. Liang, G. D. Mateescu, and J. L. Riemenschneider, *J. Am. Chem. Soc.*, **95**, 8698 (1973); G. A. Olah, *Acc. Chem. Res.* **9**, 41 (1976); G. A. Olah, G. K. Surya Prakash, M. Arvanaghi, and F. A. L. Anet, *J. Am. Chem. Soc.* **104**, 7105 (1982).
132. C. S. Yannoni, V. Macho, and P. C. Myhre, *J. Am. Chem. Soc.* **104**, 7380 (1982).
133. P. v. R. Schleyer, D. Lenoir, P. Mison, G. Liang, G. K. Surya Prakash, and G. A. Olah, *J. Am. Chem. Soc.* **102**, 683 (1980).
134. M. Saunders and M. R. Kates, *J. Am. Chem. Soc.* **102**, 6867 (1980).

X-ray photoelectron spectroscopy revealed significant differences between norbornyl cation and related model cations. The binding energy of electrons in carbon 1*s* orbitals is the property that is measured, and it is sensitive to the charge on carbon. For cyclopentyl cation, two lines separated by 4.3 eV are observed, with the higher binding energy associated with the positively charged carbon and the lower binding energy associated with the neutral methylenes. Similar differences are observed in most carbocations. The spectrum of norbornyl cation, however, does not indicate the presence of a typical cationic carbon but can be analyzed in terms of overlapping absorptions of several types of carbon, which would be consistent with a nonclassical structure.[135]

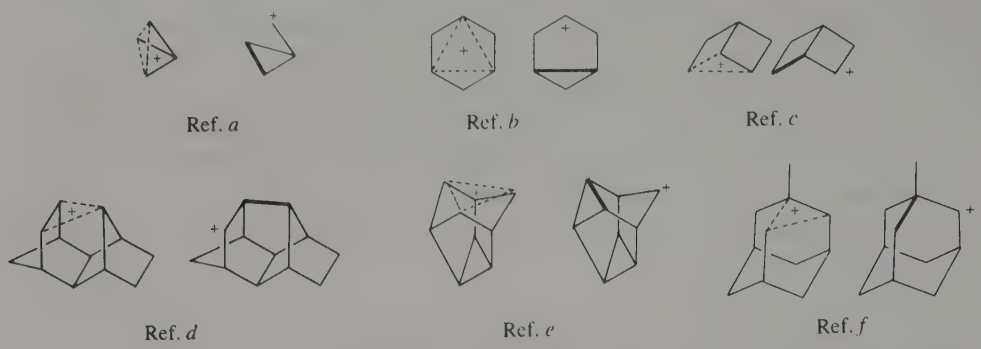
These results, which it should be recalled all pertain to *stable ion conditions*, not solvolysis conditions, provide a strong case that the most stable structure for the norbornyl cation is the bridged nonclassical ion. How much stabilization does the σ bridging provide? An estimate based on molecular mechanics and thermodynamic cycles suggests a stabilization of about 6 ± 1 kcal/mol.[136] Molecular orbital methods suggest a range of 8–15 kcal/mol for the stabilization of the nonclassical structure relative to the classical structure.[137]

Let us now return to the question of solvolysis and how it relates to the structure under stable ion conditions. To relate the structural data to the solvolysis conditions, the primary issues which must be considered are the extent of solvent participation in the transition state and the nature of solvation of the cationic intermediate. The extent of solvent participation has been probed by comparison of solvolysis characteristics in trifluoroacetic acid with the solvolysis in acetic acid. The *exo–endo* reactivity ratio is 1120 in trifluoroacetic acid as compared to 280 in acetic acid. In both cases the product is the *exo* ester. While the *endo* isomer shows solvent sensitivity typical of normal secondary tosylates, the *exo* isomer reveals a reduced sensitivity. This indicates that the transition state for solvolysis of the *exo* isomer possesses a greater charge dispersal, which would be consistent with bridging. This fact, along with the rate enhancement, indicates that the σ participation commences prior to the transition state so that it can be concluded that bridging is a characteristic of the solvolysis intermediate, as well as of the stable ion structure.[138]

Many other cations besides the norbornyl cations have nonclassical structures. Scheme 5.5 shows some examples which have been characterized by structural studies or by evidence derived from solvolysis reactions. To assist in interpretation of the nonclassical structures, the bond representing the bridging electron pair is darkened in a corresponding classical structure. Not surprisingly, the borderline between classical structures and nonclassical structures is blurred. There are two

135. D. T. Clark, B. J. Cromarty, and L. Colling, *J. Am. Chem. Soc.* **99**, 8120 (1977).
136. P. v. R. Schleyer and J. Chandrasekhar, *J. Org. Chem.* **46**, 225 (1981).
137. H.-J. Köhler and H. Lischka, *J. Am. Chem. Soc.* **101**, 3479 (1979); D. W. Goetz, H. B. Schlegel, and L. C. Allen, *J. Am. Chem. Soc.* **99**, 8118 (1977).
138. J. E. Nordlander, R. R. Gruetzmacher, W. J. Kelly, and S. P. Jindal, *J. Am. Chem. Soc.* **96**, 181 (1974).

Scheme 5.5. Other Examples of Nonclassical Carbonium Ions



a. M. Saunders and H.-U. Siehl, *J. Am. Chem. Soc.* **102**, 6868 (1980); J. S. Starat, J. D. Roberts, G. K. Surya Prakash, D. J. Donovan, and G. A. Olah, *J. Am. Chem. Soc.* **100**, 8016, 8018 (1978).
b. G. A. Olah, G. K. Surya Prakash, T. N. Rawdah, D. Whittaker, and J. C. Rees, *J. Am. Chem. Soc.* **101**, 3935 (1979).
c. R. N. McDonald and C. A. Curi, *J. Am. Chem. Soc.* **101**, 7116, 7118 (1979).
d. S. Winstein and R. L. Hansen, *Tetrahedron Lett.*, **No. 25**, 4 (1960).
e. R. M. Coates and E. R. Fretz, *J. Am. Chem. Soc.* **99**, 297 (1977); H. C. Brown and M. Ravindranathan, *J. Am. Chem. Soc.* **99**, 299 (1977).
f. J. E. Nordlander and J. E. Haky, *J. Am. Chem. Soc.* **103**, 1518 (1981).

fundamental factors which prevent an absolute division. (1) The energies of the two (or more) possible structure may be so close as to prevent a clear distinction as to stability. (2) The molecule may adopt a geometry which is intermediate between a classical geometry and a symmetrically bridged geometry.

To summarize, it now appears that nonclassical or bridged structures are either readily attainable intermediates or transition states for many cations and that for others, such as the norbornyl cation, the bridged structure is the most stable. As a broad generalization, tertiary cations are nearly always more stable than related bridged ions and therefore have classical structures. Primary carbonium ions can be expected to undergo rearrangement to more stable secondary or tertiary carbocations, with bridged ions being transition states for the rearrangement. The energy balance between classical secondary structures and bridged structures will depend on the structures of the individual system. Bridging is most likely in cases where a strained bond can participate in bridging or where solvation of the positive charge is difficult. Because of poor solvation, bridged structures are particularly likely to be favored in superacid media and in the gas phase.

General References

Nucleophilic Substitution Mechanisms

A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-Hill, New York, 1962.
C. A. Bunton, *Nucleophilic Substitution at a Saturated Carbon Atom*, Elsevier, New York, 1963.

E. R. Thornton, *Solvolysis Mechanisms*, Ronald Press, New York, 1964.
T. L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, 1977.

Carbonium Ions

G. A. Olah and P. von R. Schleyer (eds.), *Carbonium Ions*, Vols. I–IV, Wiley–Interscience, New York, 1968–1973.
D. Bethell and V. Gold, *Carbonium Ions, an Introduction*, Academic Press, London and New York, 1967.
S. P. McManus and C. U. Pittman, Jr., in *Organic Reactive Intermediates*, S. P. McManus (ed.), Academic Press, New York, 1973, Chap. 4.
G. A. Olah, *Carbocations and Electrophilic Reactions*, John Wiley and Sons, New York, 1974.
M. Saunders, J. Chandrasekhar, and P. v. R. Schleyer, in *Rearrangements in Ground and Excited States*, P. deMayo (ed.), Academic Press, 1980, Chap. 1.

Problems

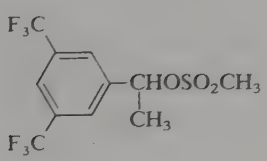
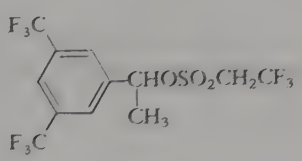
(*References for these problems will be found on page 702.*)

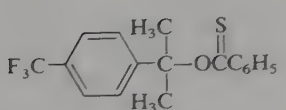
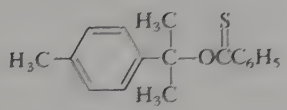
1. From the data in Tables 5.1 (p. 250) and 5.2 (p. 251), estimate the triphenylmethyl cation to triphenylmethanol ratio at equilibrium in

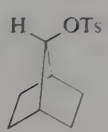
   (a) 75% sulfuric acid
   (b) 25% sulfuric acid

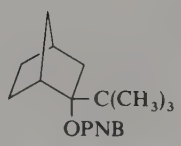
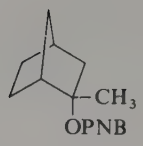
2. A useful thermodynamic measure of gas phase carbonium ion stability is $-\Delta H$ for the reaction $R_3C^+ + H^- \rightarrow R_3CH$. For the cations CH_3^+, CH_2F^+, CHF_2^+, and CF_3^+ this quantity has been determined to be 312, 290, 284, and 299 kcal/mol, respectively. Rationalize these results.

3. Which reaction in each pair would be expected to be faster? Explain.

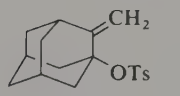
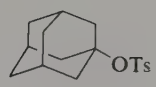
   (a)  *or*  solvolysis in 80% ethanol

   (b)  *or*  solvolysis in 100% ethanol

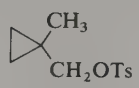
   (c)  *or*  solvolysis in acetic acid

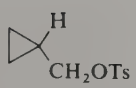
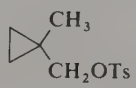
(d)  *or*  solvolysis in aqueous acetone

PNB = *p*-nitrobenzoate

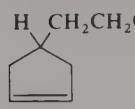
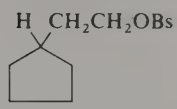
(e)  *or*  solvolysis in acetic acid

(f) $C_6H_5SO_2CH_2CH_2Cl$ *or* $C_6H_5SO_2CH_2Cl$ reaction with KI in acetone

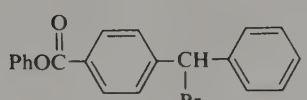
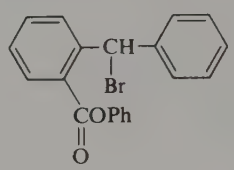
(g) $(CH_3)_3CCH_2OTs$ *or*  solvolysis in aqueous dioxane

(h)  *or*  solvolysis in aqueous dioxane

(i) $H_2C{=}CHCH_2CH_2OTs$ *or* $H_3CCH{=}CHCH_2OTs$ solvolysis in 98% formic acid

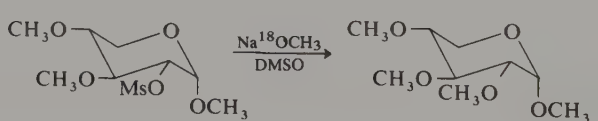
(j)  *or*  solvolysis in acetic acid

(k) $PhS(CH_2)_3Cl$ *or* $PhS(CH_2)_4Cl$ solvolysis in aqueous dioxane

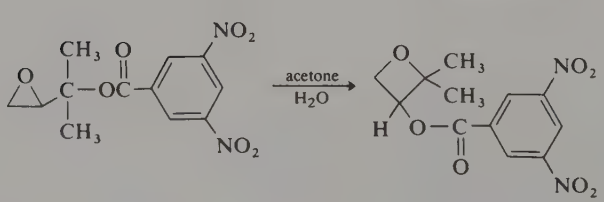
(l)  *or*  solvolysis in acetic acid

4. Suggest reasonable mechanisms for each of the following reactions. The starting materials were the racemic substance, except where noted otherwise.

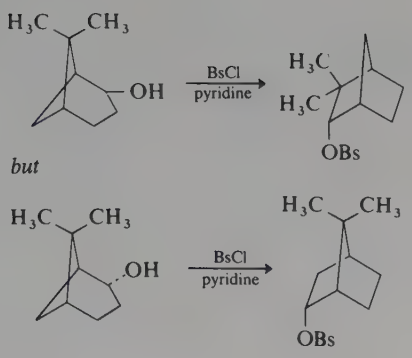
(a) $PhCH_2Cl + P(OCH_3)_3 \longrightarrow PhCH_2P(O)(OCH_3)_2 + CH_3Cl$

(b) 

no ^{18}O label in product

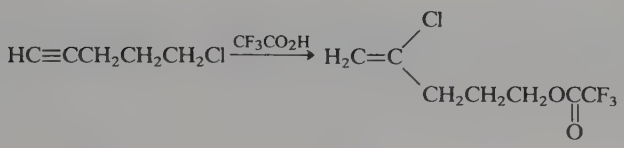
(c) 

(d)

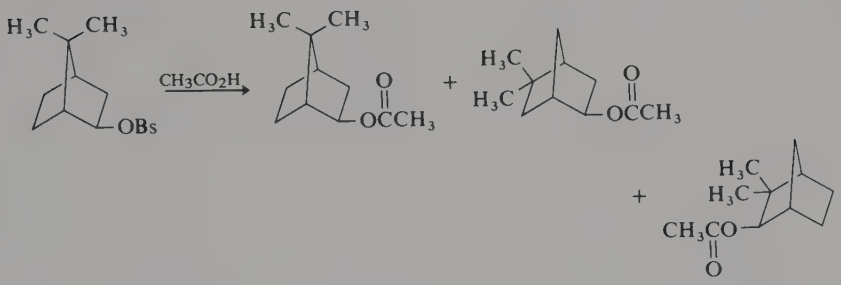


but

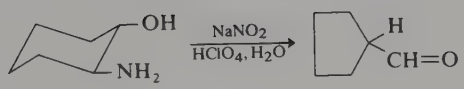
(e)



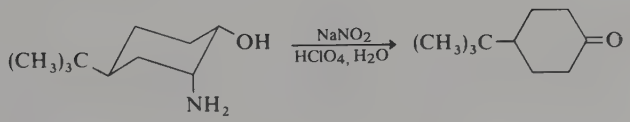
(f)



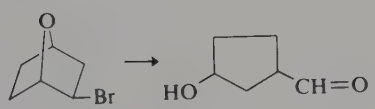
(g)



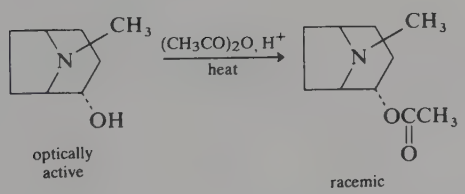
(h)



(i)



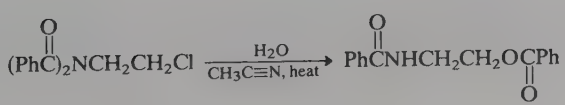
(j)



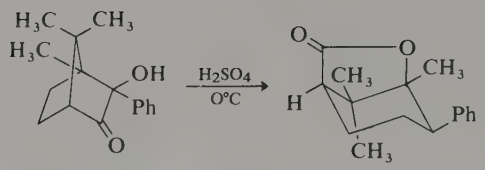
optically active

racemic

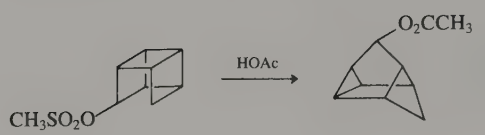
(k)



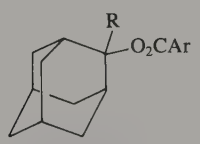
(l)



(m)



5. Explain the trends in the rate data for solvolysis of 2-alkyl-2-adamantyl *p*-nitrobenzoates in 80% aqueous acetone at 25°C.



Ar = *p*-nitrophenyl

R	k
CH_3–	1.4×10^{-10}
CH_3CH_2–	1.1×10^{-9}
$(CH_3)_2CH$–	5.0×10^{-9}
$(CH_3)_3C$–	3.4×10^{-5}
$(CH_3)_3CCH_2$–	1.5×10^{-9}

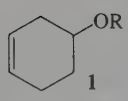
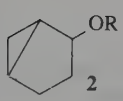
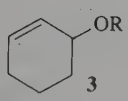
6. The rates of methanolysis of a series of alkyl halides having ω -phenylthio substituents has been reported. The relative rates are as given below. Offer an explanation for the relative reactivity of each compound.

$$PhS(CH_2)_nCl \xrightarrow{CH_3OH} PhS(CH_2)_nOCH_3$$

n	k_{rel}
1	3.3×10^4
2	1.5×10^2
3	1.0
4	1.3×10^2
5	4.3

7. Treatment of 2-*p*-hydroxyphenylethyl bromide with basic alumina produces a white solid: mp, 40–43°C; IR, 1640 cm^{-1}; UV, 282 nm in H_2O, 261 nm in ether; NMR, two singlets of equal intensity at 1.69 and 6.44 ppm from TMS. *Anal.*: C, 79.97; H, 6.71. Suggest a reasonable structure for this product and a rationalization for its formation.

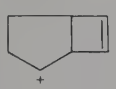
8. The solvolysis of the tosylate of 3-cyclohexenol has been studied in several solvents. The rate of solvolysis is not very solvent sensitive, being within a factor of 5 for all solvents. The product distribution is solvent sensitive, however, as shown below.

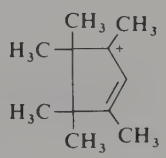
Solvent (ROH)	 1	 2	 3	Cyclohexadienes
H_2O–dioxane	20%	*a*	14%	72%
acetic acid	20%	*a*	10%	70%
formic acid	58%	*a*	*a*	42%
	10%	65%	*a*	25%

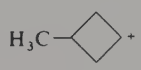
a. Minor product, less than 3% yield.

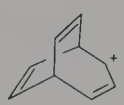
Furthermore, the stereochemistry of the product of structure **1** changes as the solvent is changed. In aqueous dioxane the reaction proceeds with complete inversion but in hexafluoropropanol 100% retention. In acetic acid the reaction occurs mainly with inversion (83%) but in formic acid the amount of retention (40%) is comparable to inversion (60%). Discuss these results, particularly with respect to the change of product composition and stereochemistry as a function of solvent.

9. Each of the following carbonium ions can rearrange to a cation with special stabilization. Indicate likely routes for the rearrangement to a more stable species for each ion.

(a) 

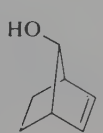
(b) 

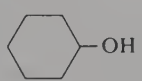
(c) 

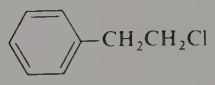
(d) 

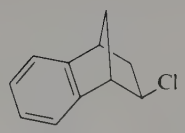
10. In the discussion of the *syn*- and *anti*-7-norbornenyl tosylates, it was pointed out that, relative to 7-norbornyl tosylate, the reactivities of the *syn* and *anti* isomers were 10^4 and 10^{11}, respectively. The high reactivity of the *anti* isomer was attributed to participation of the carbon–carbon double bond. What is the source of the 10^4 factor of acceleration in the *syn* isomer relative to the saturated model?

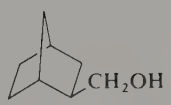
11. Indicate the structure of the ion you expect to be formed as the stable species when each of the following compounds is dissolved in superacid media at −30°C:

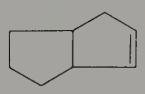
(a) 

(b) 

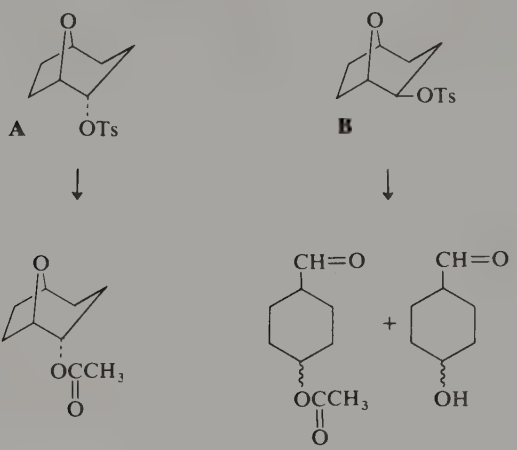
(c) 

(d) 

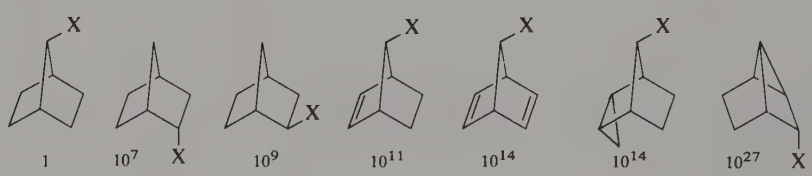
(e) 

(f) 

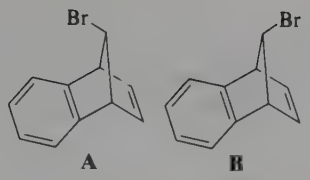
12. The behavior of compounds **A** and **B** on solvolysis in acetic acid containing acetate ion has been studied. The solvolysis of **A** is about 13 times faster than that of **B**. Kinetic studies in the case of **A** show that **A** is racemized competitively with solvolysis. A single product is formed from **A** but **B** gives a mixture. Explain these results.



13. A variety of kinetic data permit the assignment of relative reactivities toward solvolysis of a series of systems related to the norbornane skeleton. Offer a general discussion of the structural effects that are responsible for the observed relative rates.

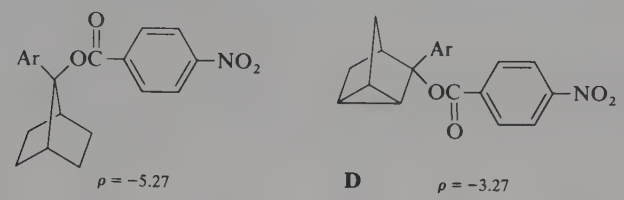


14. Offer a mechanistic interpretation of each of the following phenomena:
    (a) Although there is a substantial difference in the rate at which **A** and **B** solvolyze (**A** reacts 4.4×10^4 times faster in acetic acid), both compounds give products of completely retained configuration.



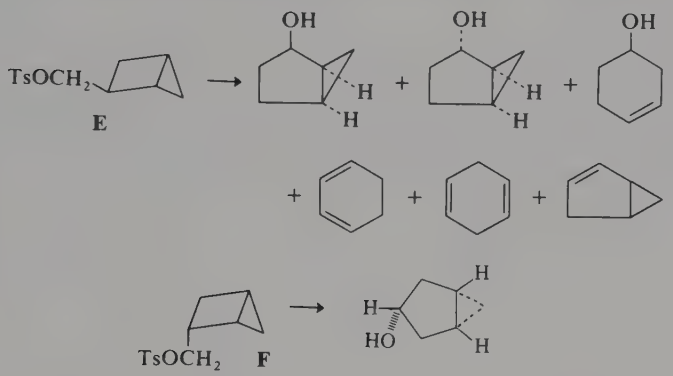
A B

(b) The solvolysis of **C** is much more sensitive to substituent effects than that of **D**.

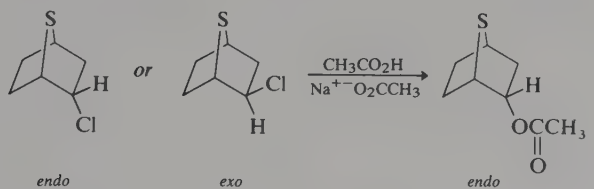


C $\rho = -5.27$ **D** $\rho = -3.27$

(c) Although the stereoisomers **E** and **F** solvolyze in acetone at comparable rates, the products of the solvolysis reactions are very different.



(d) Solvolysis of *endo*-2-chloro-7-thiabicyclo[2.2.1]heptane occurs 4.7×10^9 times faster than the *exo* isomer. The product from either isomer in the presence of sodium acetate is the *endo* acetate.



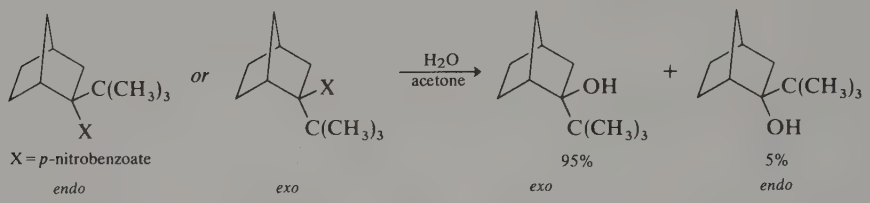
endo *exo* *endo*

(e) Solvolysis of 2-octyl *p*-bromobenzenesulfonate in 80% methanol: 20% acetone gives, in addition to the expected methyl 2-octyl ether, a 15% yield of 2-octanol. The 2-octanol could be shown not to result from the presence of adventitious water in the medium.

(f) Addition of CF_3CHN_2 to fluorosulfonic acid at −78°C gives a solution the ^1H NMR spectrum of which shows a quartet ($J_{HF} = 6.1$ Hz) at δ 6.3 ppm

from external TMS. On warming to −20°C, this quartet disappears and is replaced by another one (J_{HF} = 7.5 Hz) at δ 5.50 ppm.

(g) 2-*t*-Butyl-*exo*-norbornyl *p*-nitrobenzoate is an extremely reactive compound, undergoing solvolysis 2.8×10^6 times faster than *t*-butyl *p*-nitrobenzoate. The *endo* isomer is about 500 times less reactive. In contrast to the unsubstituted norbornyl system, which gives almost exclusively *exo* product, both *t*-butyl isomers give about 5% of the *endo* product.

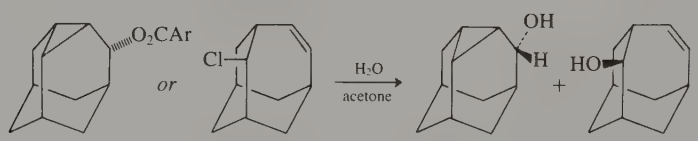


X = *p*-nitrobenzoate — *endo* — *exo* — 95% *exo* — 5% *endo*

(h) Solvolysis of 2,4,6-trimethylbenzyl chloride in 80% aqueous ethanol is characterized by $\Delta S^{\ddagger} = -11.0$ e.u. Solvolysis of 2,4,6-tri-*tert*-butylbenzyl chloride, however, has $\Delta S^{\ddagger} = +0.3$ e.u. Suggest an explanation for the difference in the entropy of activation for solvolysis of these two systems.

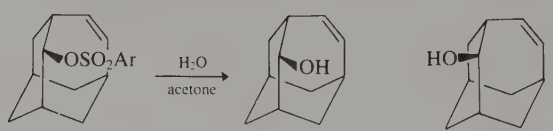
(i) Solvolysis of the *p*-nitrobenzoates of both the *syn* and *anti* isomers of 2-hydroxybicyclo[6.1.0]nonane give as the major solvolysis product the corresponding alcohol of retained stereochemistry when carried out in buffered aqueous acetone.

(j) Solvolysis of compounds **G** and **H** gives a product mixture which is quite similar for both compounds.



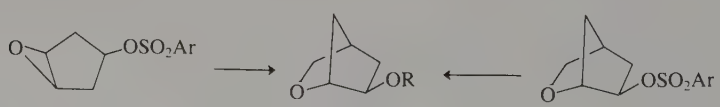
G, Ar = 3,5-dinitrophenyl — **H** — 83% − 85% — 8% − 12%

On the other hand, compound **I** gives a completely different mixture.



I — 39% — 51%

(k) The isomeric tosylates **J** and **K** give an identical product mixture consisting of the alcohol **L** and ether **M** when solvolyzed in aqueous ethanol.



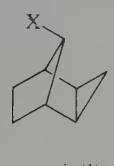
J — **L**, R = H; **M**, R = C_2H_5 — **K**

15. Both experimental studies on gas phase ion stability and MO calculations indicate that the two vinyl cations shown below benefit from special stabilization. Indicate what structural features present in these cations can provide this stabilization.

cyclopropylidenemethyl cation

cyclobutenyl cation

16. The rates of solvolysis of four isomeric tricyclooctane derivatives have been determined. After correction for leaving group and temperature effects the relative reactive reactivities are as shown.



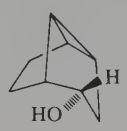
exo–anti (1)

exo–syn (10^4)

endo–anti (10^{12})

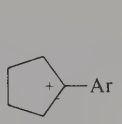
endo–syn (10)

In aqueous dioxane the *endo–anti* isomer gave a product mixture consisting of alcohol **A** and the corresponding ester (derived from capture of the leaving group *p*-nitrobenzoate). The other isomers gave much more complex product mixtures which were not completely characterized. Explain the trend in rates and discuss the structural reason for the stereochemical course of the reaction in the case of the *endo–anti* isomer.

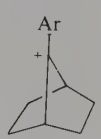


A

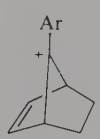
17. The ^{13}C NMR chemical shift of the trivalent carbon is a sensitive indicator of carbonium ion structure. Given below are the data for three carbocations with varying aryl substituents. Generally the greater the chemical shift the lower the electron density at the carbon atom.



A



B



C

Aryl substituent(s)	A	B	C
3,5-di-CF_3	287	283	73
4–CF_3	284	278	81
H	272	264	109
4–CH_3	262	252	165
4–OCH_3	235	230	220

How do you explain the close similarity in the substituent group trends for ions **A** and **B** as contrasted to the opposing trend in **C**?

18. Studies of the solvolysis of 1-phenylethyl chloride and its *p*-substituted derivatives in aqueous trifluorethanol containing azide anion as a potential nucleophile provide details relative to the mechanism of nucleophilic substitution in this system.

    (a) The reaction is independent of the azide ion concentration for *para* substituents that have σ^+ values more negative than -0.3, but is first order in $[N_3^-]$ for substituents with σ^+ more positive than -0.08.

    (b) When other good nucleophiles are present that can compete with azide ion, e.g., $CH_3CH_2CH_2SH$, substrates undergoing solvolysis at rates that are zero order in $[N_3^-]$ show little selectivity between the nucleophiles.

    (c) For substrates that solvolyze at rates independent of $[N_3^-]$ the ratio of 1-arylethyl azide to 1-arylethanol in the product increases as the σ^+ of the substituent becomes more negative.

    (d) The major product in reactions in which the solvolysis is first order in $[N_3^-]$ is the 1-arylethyl azide.

    Consider these results with respect to the three mechanisms outlined in Fig. 5.4 (page 247), i.e., the S_N1, S_N2 (concerted), and S_N2 (intermediate) mechanisms. Delineate the types of substituted 1-arylethyl halides which react with azide ion according to each of these mechanisms on the basis of the data given above.

6

Polar Addition and Elimination Reactions

Addition and elimination processes are the reverse of one another. In general, the two processes follow a similar mechanistic path in opposite directions, the final state of the system depending on the conditions. For example, hydration of alkenes and dehydration of alcohols are both familiar reactions that constitute a related addition–elimination pair.

$$RCH{=}CHR' + H_2O \xrightarrow{H^+} RCHCH_2R' \quad (OH)$$

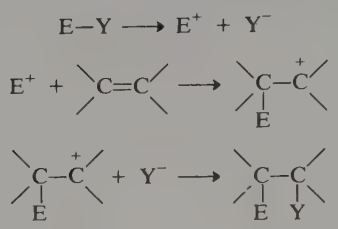
$$RCHCH_2R' \quad (OH) \xrightarrow{H^+} RCH{=}CHR' + H_2O$$

In these circumstances, mechanistic conclusions about the addition reaction are applicable to the elimination reaction and vice versa. The principle of microscopic reversibility states that the mechanism (pathway) traversed in a reversible reaction is the same for the reverse reaction as for the forward one under the same conditions. Thus, if an addition–elimination system proceeds by a reversible mechanism, the intermediates and transition states involved in the addition process are the same as in the elimination reaction.

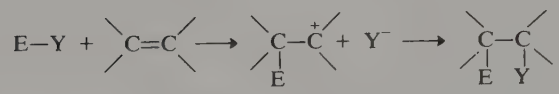
The initial topic here will be addition reactions. The discussion is restricted to reactions that involve polar or ionic mechanisms. There are other important classes of addition reactions, which are discussed elsewhere; these include concerted additions proceeding through nonpolar transition states (Chapter 10), photochemical additions (Chapter 11), radical additions (Chapter 12), and nucleophilic addition to electrophilic alkenes (Part B, Chapter 1, Section 1.10).

Several limiting general mechanisms can be described for polar additions.

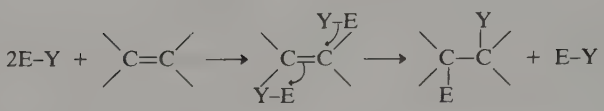
(A)



(B)



(C)



Mechanism A implies that a carbonium ion is generated which is free of the counterion Y^- at its formation. This mechanism involves prior dissociation of the electrophilic reagent. Mechanism B also involves a carbonium ion intermediate but it is generated in the presence of an anion and exists initially as an ion pair. Depending on the mutual reactivity of the two ions, they might or might not become free of one another before combining to give product. Both these mechanisms would be referred to as Ad_E2 reactions; that is, they are *bimolecular electrophilic additions.* Mechanism C is a process that has been established for several electrophilic additions. It implies transfer of the electrophilic and nucleophilic components of the reagent from two separate molecules. It would be described as a *termolecular electrophilic addition,* Ad_E3. Examples of each of these types of processes will be encountered as specific reactions are discussed in the sections that follow. At this point, the discussion will focus on a few reactions that have received the most detailed mechanistic study. There are a number of other synthetically important polar additions, which are described in Part B, Chapter 4.

6.1. Addition of Hydrogen Halides to Alkenes

The addition of hydrogen halides to alkenes has been studied from a mechanistic point of view for many years. One of the first aspects of the mechanism to be established was its regioselectivity, that is, the direction of addition. A reaction is described as *regioselective* if an unsymmetrical alkene gives a predominance of one of the two possible addition products; the term *regiospecific* is used if only one product is formed.[1]

1. A. Hassner, *J. Org. Chem.* **33**, 2684 (1968).

$$RCH{=}CH_2 + X{-}Y \longrightarrow \underset{\displaystyle X}{RCHCH_2Y} + \underset{\displaystyle Y}{RCHCH_2X}$$

(major) (minor)

regioselective reaction

$$RCH{=}CH_2 + X{-}Y \longrightarrow \underset{\displaystyle X}{RCHCH_2Y}$$

regiospecific reaction

In the addition of hydrogen halides, it is generally found that the halogen atom becomes attached to the most-substituted carbon atom of the alkene. The statement of this general observation is called *Markownikoff's rule*. The basis for the regioselectivity lies in the relative ability of the carbon atoms to accept positive charge. The addition of hydrogen halide is initiated by an electrophilic attack involving transfer of a proton to the alkene. The new C–H bond is formed from the π electrons of the carbon–carbon double bond. It is easy to see that if a carbonium ion is formed, the halide would be added to the more-substituted carbon, since addition of the proton at the less-substituted carbon atom provides the more stable carbonium ion intermediate.

$$R_2C{=}CHR \xrightarrow{HX} \underset{\displaystyle +}{R_2CCH_2R} \xrightarrow{X^-} \underset{\displaystyle X}{R_2CCH_2R}$$

more favorable

$$R_2C{=}CHR \xrightarrow{HX} \underset{\displaystyle +}{R_2CHCHR} \xrightarrow{X^-} \underset{\displaystyle X}{R_2CHCHR}$$

less favorable

As will be indicated when the mechanism is discussed in more detail, discrete carbonium ions are not formed in all cases. An unsymmetrical alkene will nevertheless follow the Markownikoff rule, because the partial positive charge that develops will be located primarily at the carbon most able to accommodate the electron deficiency, that is, the more substituted one.

The regioselectivity of addition of hydrogen bromide to alkenes can be complicated if a free radical chain addition occurs in competition with the ionic addition. The free radical reaction is readily initiated by peroxidic impurities or by light and leads to the anti-Markownikoff addition product. The mechanism of this reaction will be considered fully in Chapter 12. Conditions which minimize the competing radical addition include use of very-high-purity materials, exclusion of light, and addition of free radical inhibitors.[2]

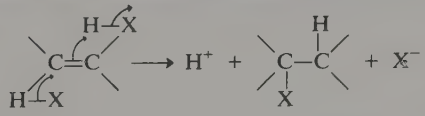
The studies that have been applied to determining mechanistic details concerning addition of hydrogen halides to alkenes have focused on the kinetics and stereochemistry of the reaction and on the effect of added nucleophiles. The kinetic studies have often led to complex rate expressions that demonstrate that more than one elementary process contributes to the overall reaction rate. For addition of

2. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.* **96**, 1858 (1974).

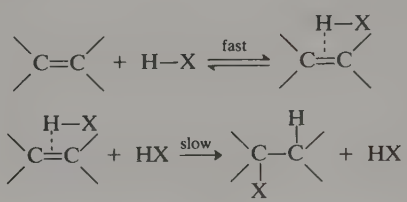
hydrogen bromide or hydrogen chloride to alkenes, an important contribution to the overall rate is often made by a third-order process:

$$\text{rate} = k[\text{alkene}][\text{HX}]^2$$

Among the cases in which this type of kinetics has been observed are the addition of hydrogen chloride to 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene,[3] and cyclohexene.[4] The addition of hydrogen bromide to cyclopentene also follows a third-order rate expression.[2] The transition state usually associated with the third-order rate expression involves proton transfer to the alkene from one hydrogen halide molecule and capture of halide ion from the second:



The reaction probably involves interaction of a complex formed from the alkene and hydrogen halide with a second hydrogen halide molecule, since productive termolecular collisions are rare:

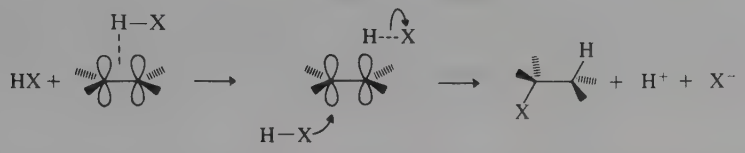


The stereochemistry of addition of hydrogen halides to unconjugated alkenes is predominantly *anti*. This is true for addition of hydrogen bromide to 1,2-dimethylcyclohexene,[5] cyclohexene,[6] 1,2-dimethylcyclopentene,[7] cyclopentene, *cis*- and *trans*-2-butene,[2] and 3-hexene,[2] among others. *Anti* stereochemistry is also dominant for addition of hydrogen chloride to 1,2-dimethylcyclohexene[8] and 1-methylcyclopentene.[3] Temperature and solvent can modify the stereochemistry, however. For example, although the addition of hydrogen chloride to 1,2-dimethylcyclohexene is *anti* near room temperatures, *syn* addition dominates at $-78°C$.[9]

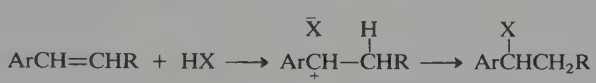
Anti stereochemistry can be explained by a mechanism in which the alkene is interacting simultaneously with the proton-donating hydrogen halide and with a source of halide ion, either a second molecule of hydrogen halide or an added halide

3. (a) Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Am. Chem. Soc.* **91**, 4199 (1969); (b) Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.* **91**, 4205 (1969).
4. R. C. Fahey, M. W. Monahan, and C. A. McPherson, *J. Am. Chem. Soc.* **92**, 2810 (1970).
2. See p. 325.
5. G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.* **76**, 4121 (1954).
6. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.* **86**, 5035 (1964); R. C. Fahey, C. A. McPherson, and R. A. Smith, *J. Am. Chem. Soc.* **96**, 4534 (1974).
7. G. S. Hammond and C. H. Collins, *J. Am. Chem. Soc.* **82**, 4323 (1960).
8. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **93**, 2445 (1971).
9. K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).

salt. The *anti* stereochemistry indicates that the preference is for attack by halide from the opposite side from which proton delivery occurs:

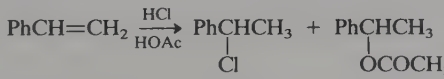


A significant variation in the stereochemistry takes place when the double bond is conjugated with a group that can stabilize a carbonium ion intermediate. Most of the examples that have been studied involve an aryl substituent. Examples of alkenes that give primarily *syn* addition are *cis*- and *trans*-1-phenylpropene,[10] *cis*- and *trans*-β-*t*-butylstyrene,[11] 1-phenyl-4-*t*-butylcyclohexene,[12] and indene.[13] The mechanism proposed for these additions features an ion pair as the key intermediate. Because of the greater stability of the carbonium ion center in these molecules, concerted attack by halide ion is not required for carbon–hydrogen bond formation. If the ion pair formed by alkene protonation collapses to product faster than rotation takes place, the result will be *syn* addition, since the proton and halide ion are

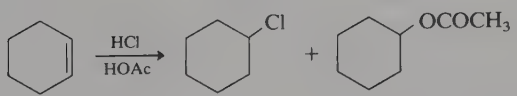


originally on the same side of the molecule. Kinetic studies on the addition of hydrogen chloride to styrene support the conclusion that an ion-pair mechanism operates when aromatic conjugation is present. The reaction is first order in hydrogen chloride, rather than second order, indicating that only one molecule of hydrogen chloride participates in the rate-determining step.[14]

There is usually a competing reaction with solvent when hydrogen halide additions to alkenes are carried out in potentially nucleophilic solvents:



Ref. 14



Ref. 4

It is not difficult to incorporate this observation into the general mechanisms for hydrogen halide additions. These products are formed as the result of solvent competing with halide as the nucleophilic component of the addition reaction.

10. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.* **85**, 3645 (1963).
11. R. J. Abraham and J. R. Monasterios, *J. Chem. Soc. Perkin Trans. II*, 574 (1975).
12. K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *Chem. Commun.* 1246 (1970).
13. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.* **85**, 2248 (1963).
14. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **91**, 3865 (1969).

4. See p. 326.

Solvent addition can occur via the concerted mechanism or through a carbonium ion mechanism. Added halide salts can serve as a halide ion source and increase the likelihood of capture of the carbonium ion intermediate by halide ion. The effect of halide salts can be detected kinetically. For example, the presence of tetramethylammonium chloride increases the rate of addition of hydrogen chloride to cyclohexene.[8] Similarly, lithium bromide increases the rate of addition of hydrogen bromide to cyclopentene.[5]

Skeletal rearrangements have been observed in hydrogen halide additions when hydrogen or carbon migration leading to a more stable carbonium ion can occur.

$$(CH_3)_2CHCH{=}CH_2 \xrightarrow[CH_3NO_2]{HCl} \underset{40\%}{(CH_3)_2CHCHCH_3} + \underset{60\%}{(CH_3)_2CCH_2CH_3} \qquad \text{Ref. 3}$$
$$\qquad\qquad\qquad\qquad\qquad\quad Cl \qquad\qquad\qquad\quad Cl$$

$$(CH_3)_3CCH{=}CH_2 \xrightarrow[CH_3NO_2]{HCl} \underset{83\%}{(CH_3)_2CCH(CH_3)_2} + \underset{17\%}{(CH_3)_3CCHCH_3} \qquad \text{Ref. 3}$$
$$\qquad\qquad\qquad\qquad\qquad\quad Cl \qquad\qquad\qquad\quad Cl$$

Even though the rearrangements suggest that discrete carbonium ion intermediates are involved, these reactions frequently show kinetics consistent with the presence of at least two hydrogen chloride molecules in the rate-determining step. A termolecular mechanism in which the second hydrogen chloride assists in ionization of the electrophile has been suggested.[3]

$$\begin{aligned}
&\overset{H-Cl\cdots H-Cl}{\curvearrowright\ \curvearrowright}\\
&(CH_3)_2CH{=}CH_2 \rightarrow (CH_3)_2CH\overset{+}{C}HCH_3 + [Cl{-}H{-}Cl]^-\\
&(CH_3)_2CH\overset{+}{C}HCH_3 \rightarrow (CH_3)_2\overset{+}{C}CH_2CH_3\\
&(CH_3)_2CH\overset{+}{C}HCH_3 + [Cl{-}H{-}Cl]^- \rightarrow (CH_3)_2CHCHCH_3 + HCl\\
&\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Cl
\end{aligned}$$

and

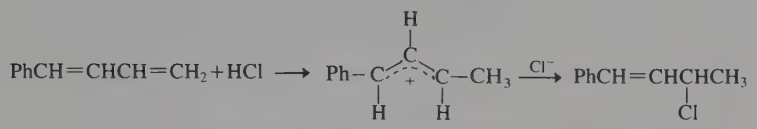
$$(CH_3)_2\overset{+}{C}CH_2CH_3 + [Cl{-}H{-}Cl]^- \rightarrow (CH_3)_2CCH_2CH_3 + HCl$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Cl$$

The addition of the hydrogen halides to dienes can result in either 1,2 or 1,4 addition. The extra stability of the allyl cation which can be formed by proton transfer to a diene makes the ion pair mechanism relatively favorable. 1,3-Pentadiene, for example, gives a mixture of products favoring the 1,2 addition product by a ratio of from 1.5:1 to 3.4:1, depending on the temperature and solvent[15]:

$$CH_3CH{=}CHCH{=}CH_2 \xrightarrow{DCl} \underset{22\text{–}38\%}{CH_3\underset{Cl}{CH}CH{=}CHCH_2D} + \underset{62\text{–}78\%}{CH_3CH{=}CH\underset{Cl}{CH}CHD}$$

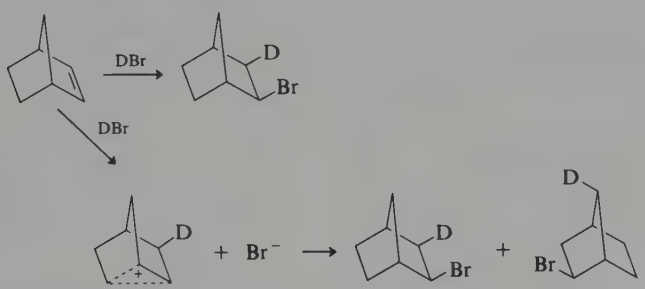
8. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.* **93**, 2445 (1971).
5. See p. 326.
3. See p. 326.
15. J. E. Nordlander, P. O. Owuor, and J. E. Haky, *J. Am. Chem. Soc.* **101**, 1288 (1979).

With 1-phenyl-1,3-butadiene the addition is exclusively at the 3,4 double bond. This reflects the greater stability of this product, which retains a styrene-type conjugation. Initial protonation at C-4 is favored by the fact that the resulting carbonium ion benefits from both allylic- and benzylic-type conjugation:

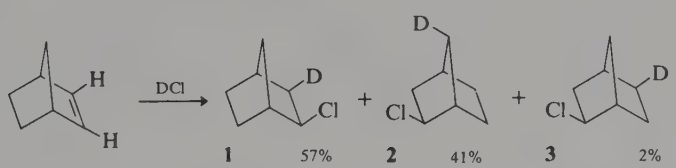


This reaction is second order, as could be expected for the formation of a stable carbocation by an Ad_E2 mechanism.[16]

The addition of hydrogen chloride and hydrogen bromide to norbornene is an interesting case, since such factors as facile rearrangement via a norbornyl cation and steric preference for attack from the *exo* side of the alkene come into consideration. Addition of deuterium bromide to norbornene gives *exo*-norbornyl bromide. Degradation to locate the deuterium atom shows that about half the product has been



formed via the bridged norbornyl cation. The *exo* orientation of the bromine atom and the occurrence of the rearrangement are in accord with a mechanism involving this cationic intermediate. Similar studies have been carried out on the addition of hydrogen chloride to norbornene.[17] Again, the chloride is almost exclusively *exo*:



The distribution of deuterium in the product was examined by NMR methods. The fact that unequal amounts of **1** and **2** are found can rule out a symmetrical nonclassical norbornyl ion as the only cationic species in the reaction. The excess of **1** over **2** indicates that some *syn* addition occurs by ion pair collapse before the bridged

16. K. Izawa, T. Okuyama, T. Sakagami, and T. Fueno, *J. Am. Chem. Soc.* **95**, 6752 (1973).
17. H. Kwart and J. L. Nyce, *J. Am. Chem. Soc.* **86**, 2601 (1964); J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Am. Chem. Soc.* **88**, 4922 (1966).

cation is formed.[18] The small amount of product **3** arises from a 2,6-hydrogen shift, a process that is known to occur rapidly in the norbornyl cation.

6.2. Acid-Catalyzed Hydration and Related Addition Reactions

The synthesis of alcohols by acid-catalyzed addition of water to alkenes is a classic organic reaction. At the most rudimentary mechanistic level, it can be viewed as a carbonium ion reaction. The alkene is protonated and the carbonium ion intermediate is captured by water.

$$RCH{=}CH_2 \xrightarrow{H^+} R\overset{+}{C}HCH_3 \xrightarrow{H_2O} RCH(OH)CH_3 + H^+$$

This mechanism explains the observed formation of the more highly substituted alcohol (Markownikoff's rule). A number of other points must be considered in order to provide a more complete picture of this mechanism. Is the protonation step reversible? Is there a discrete carbonium ion, or does the nucleophile become involved before carbonium ion formation is complete? Can other reactions of carbonium ions, such as rearrangement, compete with capture by water?

Much of the mechanistic work on hydration reactions has been done with conjugated alkenes, particularly styrenes. With styrenes, the rate of hydration is increased by electron-releasing substituents, and there is an excellent correlation with σ^+.[19] A substantial solvent isotope effect $k_{H_2O}/k_{D_2O} = 2$–4 is observed. Both these observations are in accord with a rate-determining protonation to give a carbonium ion intermediate. Capture of the resulting carbonium ion by water is apparently fast relative to deprotonation. This has been demonstrated by showing that in the early stages of hydration of styrene deuterated at C-2, there is no loss of deuterium from the unreacted alkene that is recovered by quenching the reaction.

$$PhCH{=}CD_2 \overset{H^+}{\rightleftharpoons} Ph\overset{+}{C}HCD_2H \overset{-H^+,\ \text{slow}}{\rightleftharpoons} PhCH{=}CHD$$
$$\Big\Updownarrow H_2O,\ \text{fast}$$
$$PhCH(OH)CD_2H$$

The overall process is reversible, however, and some styrene remains in equilibrium with the alcohol, so exchange eventually occurs.

Alkenes lacking the phenyl group are somewhat less convenient to study by kinetic methods, but such data as observation of general acid catalysis[20] and solvent

18. H. C. Brown and K.-T. Liu, *J. Am. Chem. Soc.* **97**, 600 (1975).
19. W. M. Schubert and J. R. Keefe, *J. Am. Chem. Soc.* **94**, 559 (1972); W. M. Schubert and B. Lamm, *J. Am. Chem. Soc.* **88**, 120 (1966); W. K. Chwang, P. Knittel, K. M. Koshy, and T. T. Tidwell, *J. Am. Chem. Soc.* **99**, 3395 (1977).
20. A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald, and G. H. Schmid, *J. Am. Chem. Soc.* **93**, 4907 (1971).

Table 6.1. Rates of Hydration of Some Alkenes in Aqueous Sulfuric Acid[a]

Alkene	$k_2\ (M^{-1}\ s^{-1})$	k_{rel}
$H_2C{=}CH_2$	1.46×10^{-15}	1
$CH_3CH{=}CH_2$	2.38×10^{-8}	1.6×10^7
$CH_3(CH_2)_3CH{=}CH_2$	4.32×10^{-8}	3.0×10^7
$(CH_3)_2C{=}CHCH_3$	2.14×10^{-3}	1.5×10^{12}
$(CH_3)_2C{=}CH_2$	3.71×10^{-3}	2.5×10^{12}
$PhCH{=}CH_2$	2.4×10^{-6}	1.6×10^9

a. W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.* **99**, 7233 (1977).

isotope effects[21] are also consistent with rate-limiting protonation in simple alkenes such as 2-methylpropene and 2,3-dimethyl-2-butene. The observation of general acid catalysis rules out an alternative mechanism for alkene hydration, namely, water attack on an alkene–proton complex. The preequilibrium would be governed by the acidity of the solution, and so this mechanism would exhibit specific acid catalysis.

$$RCH{=}CH_2 + H^+ \rightleftharpoons RCH{-}\overset{+}{C}H_2$$

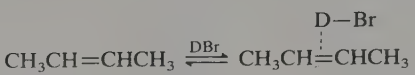
$$RCH{-}\overset{+}{C}H_2 + H_2O \xrightarrow{\text{slow}} RCHCH_3 \quad (OH)$$

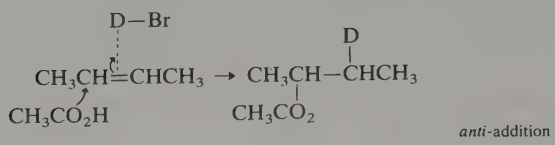
Relative rate data obtained in aqueous sulfuric acid for some simple alkenes reveal that the reaction is accelerated by alkyl substituents. This is as expected since the alkyl groups both increase the alkene electron density and stabilize the intermediate carbonium ion. Table 6.1 gives some representative data. These same reactions show solvent isotope effects consistent with regarding the reactions as proceeding through rate-determining protonation of the alkene to a carbonium ion. The rates of addition give a good correlation with σ^+ over a broad range of alkene structural types.[22]

Other nucleophilic solvents can add to alkenes under the influence of strong acid catalysis. The mechanism is presumably analogous to that for hydration, with the solvent replacing water as the participating nucleophile. The strongest acid catalysts probably react via discrete carbonium ion intermediates, whereas weaker acids may involve reaction of the solvent with an alkene–acid complex. In the addition of acetic acid to *cis*- or *trans*-2-butene, the use of DBr as the catalyst

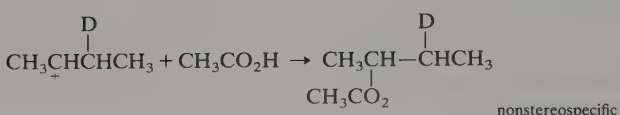
21. V. Gold and M. A. Kessick, *J. Chem. Soc.* 6718 (1965).
22. V. J. Nowlan and T. T. Tidwell, *Acc. Chem. Res.* **10**, 252 (1977).

results in stereospecific *anti* addition, whereas a stronger acid, trifluoromethanesulfonic acid, leads to a loss of stereospecificity. This difference in stereochemistry can be explained by a stereospecific Ad_E3 mechanism in the case of hydrogen bromide and an Ad_E2 mechanism in the case of trifluoromethanesulfonic acid.[23]





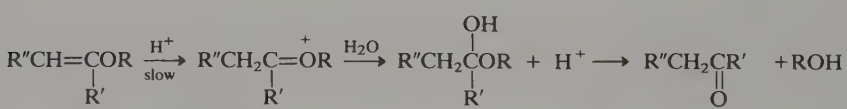
anti-addition



nonstereospecific addition

Strong acids also catalyze the addition of alcohols to alkenes to give ethers and the mechanistic studies which have been done indicate that the reaction closely parallels the hydration process.[24]

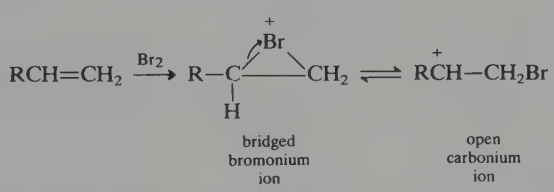
The reactivity of carbon–carbon double bonds toward acid-catalyzed addition of water is greatly increased by electron-releasing substituents and the reaction of vinyl ethers with water in acidic solution has been extensively studied. With these substrates, the initial addition products are unstable hemiacetals which decompose to a ketone and alcohol. Nevertheless, the hydration step is rate determining, and so the kinetic results pertain to this step. The mechanistic features that have been established are similar to the hydration of simple alkenes. Proton transfer is the rate-determining step, as is demonstrated by general acid catalysis and solvent isotope effect data.[25]



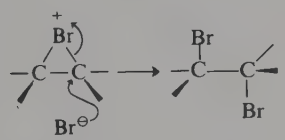
23. D. J. Pasto and J. F. Gadberry, *J. Am. Chem. Soc.* **100**, 1469 (1978).
24. N. C. Deno, F. A. Kish, and H. J. Peterson, *J. Am. Chem. Soc.* **87**, 2157 (1965).
25. A. J. Kresge and H. J. Chen, *J. Am. Chem. Soc.* **94**, 2818 (1972); A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Am. Chem. Soc.* **99**, 7228 (1977).

Alkene chlorinations and brominations are among the most general of organic reactions and mechanistic study of these reactions has provided much insight into addition reactions of alkenes. Two of the principal points at issue in the description of the mechanism for a given reaction are: (1) Is there a discrete positively charged intermediate, or is the addition concerted? (2) If there is a positively charged intermediate, is it a carbonium ion or a cyclic halonium ion? Stereochemical studies have provided much of the data pertaining to these points. The results of numerous stereochemical studies can be generalized as follows: For brominations, *anti* addition is preferred for alkenes that do not contain substituent groups that would strongly stabilize a carbonium ion center. When the alkene is conjugated with an aryl group, the extent of *syn* addition becomes much larger, and can become the dominant pathway. Chlorination is not as stereospecific as bromination, but tends to follow the same pattern. Some specific cases are given in Table 6.2.

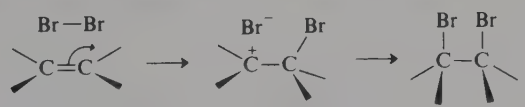
Interpretations of stereochemistry have focused attention on the role played by cyclic halonium ions:



If the addition of Br^+ to the alkene results in a bromonium ion, the *anti* stereochemistry can be readily explained. Nucleophilic ring opening by bromide ion would occur by back-side attack at carbon, with rupture of one of the C–Br bonds, giving overall *anti* addition:



On the other hand, a freely rotating open carbonium ion would be expected to give both *syn* and *anti* addition. If the principal intermediate were an ion pair that collapsed faster than rotation about the C–C bond, *syn* addition could predominate.



Whether a bridged intermediate or a carbonium ion is involved in bromination depends primarily on the stability of the potential carbonium ion. Aliphatic systems normally go through the bridged intermediate but styrenes are a borderline case. When the phenyl ring has electron-releasing substituents there is sufficient stabilization to permit carbonium ion formation, while electron-attracting groups favor the

Table 6.2. Stereochemistry of Halogenation

Alkene	Solvent	Ratio *anti* : *syn*	Ref.
Bromination			
cis-2-Butene	CH_3CO_2H	>100:1	a
trans-2-Butene	CH_3CO_2H	>100:1	a
Cyclohexene	CCl_4	very large	b
Z-1-Phenylpropene	CCl_4	83:17	c
E-1-Phenylpropene	CCl_4	88:12	c
E-2-Phenylbutene	CH_3CO_2H	68:32	a
Z-2-Phenylbutene	CH_3CO_2H	63:37	a
cis-Stilbene	CCl_4	>10:1	d
	CH_3NO_2	1:9	d
Chlorination			
cis-2-Butene	none	>100:1	e
	CH_3CO_2H	>100:1	f
trans-2-Butene	none	>100:1	e
	CH_3CO_2H	>100:1	f
Cyclohexene	none	>100:1	g
E-1-Phenylpropene	CCl_4	45:55	f
	CH_3CO_2H	41:59	f
Z-1-Phenylpropene	CCl_4	32:68	f
	CH_3CO_2H	22:78	f
cis-Stilbene	$ClCH_2CH_2Cl$	92:8	h
trans-Stilbene	$ClCH_2CH_2Cl$	65:35	h

a. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.* **91**, 1469, 1477 (1969).
b. S. Winstein, *J. Am. Chem. Soc.* **64**, 2792 (1942).
c. R. C. Fahey and H.-J. Schneider, *J. Am. Chem. Soc.* **90**, 4429 (1968).
d. R. E. Buckles, J. M. Bader, and R. L. Thurmaier, *J. Org. Chem.* **27**, 4523 (1962).
e. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 2172 (1965).
f. R. C. Fahey and C. Schubert, *J. Am. Chem. Soc.* **87**, 5172 (1965).
g. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 2161 (1965).
h. R. E. Buckles and D. F. Knaack, *J. Org. Chem.* **25**, 20 (1960).

bridged intermediate.[26] There is a correlation with stereochemistry, of course, with electron-attracting groups leading to stereospecific *anti* addition.

The stereochemistry of chlorination can be explained in similar terms. Chlorine would be expected to be a somewhat poorer bridging group than bromine because

26. M. F. Ruasse, A. Argile, and J. E. Dubois, *J. Am. Chem. Soc.* **100**, 7645 (1978).

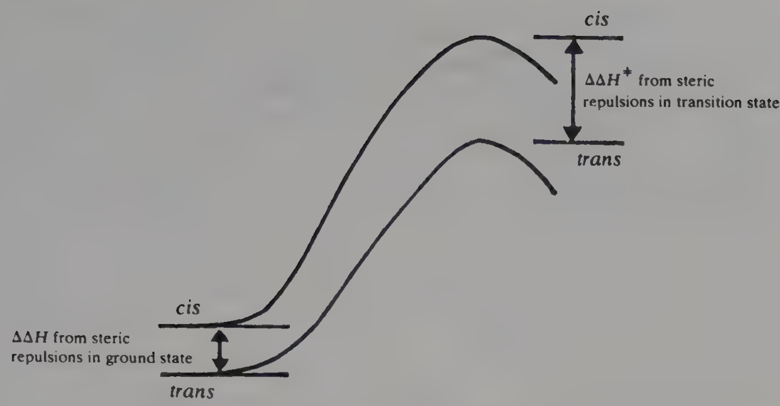
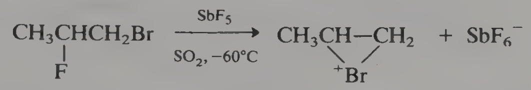


Fig. 6.1. Enthalpy differences of starting alkenes and transition states in bromination.

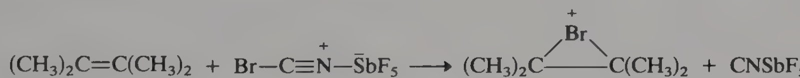
it is less polarizable and more reluctant to become positively charged. Comparison of the data for *E*- and *Z*-1-phenylpropene in bromination and chlorination confirms that this is so. Although *anti* addition is dominant for bromination, *syn* addition is preferred for chlorination. Styrenes generally appear to react with chlorine via ion pair intermediates.[27] For nonconjugated alkenes, however, stereospecific *anti* addition is usually observed with both halogens.

There is direct evidence for the existence of halonium ions such as those that are invoked in bromination and chlorination reactions. They can be formed from dihalides by ionization with neighboring-group participation and can be observed by NMR measurements in nonnucleophilic solvents:



Ref. 28

The same ions can also be produced by electrophilic attack on alkenes by species that should generate positive halogen:



Ref. 29

An interpretation of activation parameters has also led to the conclusion that the bromination transition state resembles a three-membered ring, even in the case of alkenes that eventually proceed via open carbonium ion intermediates. It was found that for *cis–trans* pairs of alkenes the difference in enthalpy of the transition states for bromination was *greater than* the enthalpy difference of the isomeric alkenes (Fig. 6.1). This finding suggests that the steric repulsions between *cis* groups *increase* in the bromination transition state. Such a view is consistent with a cyclic

27. K. Yates and H. W. Leung, *J. Org. Chem.* **45**, 1401 (1980).
28. G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Am. Chem. Soc.* **90**, 2587 (1968).
29. G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.* **96**, 3581 (1974).

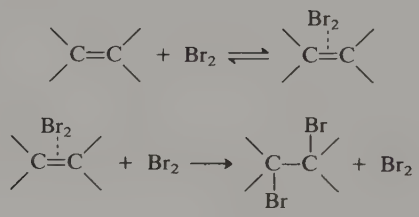
transition state in which the groups would be eclipsed and somewhat closer together than in the alkene.[30]

Comparison of the structure–reactivity relationships for a series of styrene and alkene addition reactions with bromine and with arylsulfenyl halides also supports the idea that a bromonium ion is formed in the rate-determining step.[31] From other evidence the sulfenyl halides are known to add through a bridged intermediate and the similarity between the two reaction series points to a closely similar transition state.

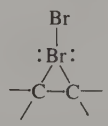
The kinetics of brominations are often complex, with at least three terms making contributions under given conditions:

$$\text{rate} = k_1[\text{alkene}][Br_2] + k_2[\text{alkene}][Br_2]^2 + k_3[\text{alkene}][Br_2][Br^-]$$

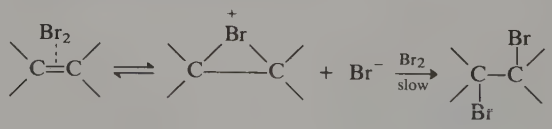
In methanol, pseudo-second-order kinetics are observed when a high concentration of Br^- is present.[32] The dominant contribution to the rate comes from the third term of the general rate expression under these conditions. The occurrence of third-order terms suggests the possibility of a mechanism like that proposed for addition of hydrogen halides to alkenes, namely, attack of nucleophilic halide on an alkene–halogen complex:



As in the case of hydrogen halide additions, this attack should lead to *anti* addition. The initial complex could resemble a bromonium ion structurally. One can account



for the observed third-order kinetics and retain a distinct bromonium ion as an intermediate by postulating that the bromonium ion is in equilibrium with the initial complex.[33] Under these conditions a reaction of the bromonium ion with bromine would be the rate-determining step.



30. K. Yates and R. S. McDonald, *J. Org. Chem.* **38**, 2465 (1973).
31. G. H. Schmid, A. Modro, and K. Yates, *J. Org. Chem.* **42**, 871 (1977).
32. J.-E. Dubois and G. Mouvier, *Tetrahedron Lett.* 1325 (1963); *Bull. Soc. Chim. Fr.* 1426 (1968).
33. C. G. Gebelein and G. D. Frederick, *J. Org. Chem.* **37**, 2211 (1972).

Table 6.3. Relative Reactivity of Alkenes toward Halogenation

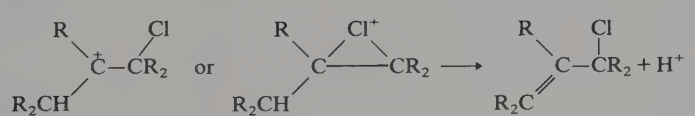
Alkenes	Relative reactivity		
	Chlorination[a]	Bromination[b]	Bromination[c]
Ethylene		0.01	0.0045
1-Butene	1.00	1.00	1.0
3,3-Dimethyl-1-butene	1.15	0.27	1.81
cis-2-Butene	63	27	173
trans-2-Butene	50	17.5	159
2-Methylpropene	58	57	109
2-Methyl-2-butene	11,000	1,380	
2,3-Dimethyl-2-butene	430,000	19,000	

a. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 4285 (1965); solvent is excess alkene.
b. J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.* 1426 (1968); solvent is methanol.
c. A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.* **42**, 3637 (1977); solvent is carbon tetrachloride.

The relative reactivities of some alkenes toward chlorination and bromination are given in Table 6.3. The relative reactivities are solvent dependent.[34] The reaction is faster in the more polar solvents, and in all media, reactivity increases with additional substitution of electron-releasing alkyl groups at the double bond.[35] Quantitative estimation of the solvent effect using the Winstein–Grunwald Y values indicates that the transition state has a high degree of ionic character. The Hammett correlation for bromination of styrenes is best with σ^+ substituent constants, and gives $\rho = -4.8$.[36] All of these features are in accord with an electrophilic mechanism.

Chlorination generally exhibits second-order kinetics, first order in alkene and first order in chlorine.[31] The reaction rate also increases with alkyl substitution, as would be expected for an electrophilic process. The magnitude of the rate increase is quite large, as shown in Table 6.3.

In chlorination, loss of a proton can be a competitive reaction of the cationic intermediate. This process leads to formation of products resulting from net substitution with double-bond migration:



34. F. Garnier and J.-E. Dubois, *Bull. Soc. Chim. Fr.* 3797 (1968); A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.* **42**, 3673 (1977).
35. F. Garnier, R. H. Donnay, and J.-E. Dubois, *Chem. Commun.* 829 (1971); M.-F. Ruasse and J.-E. Dubois, *J. Am. Chem. Soc.* **97**, 1977 (1975).
36. K. Yates, R. S. McDonald, and S. A. Shapiro, *J. Org. Chem.* **38**, 2460 (1973).
31. See p. 336.

Isobutylene and tetramethylethylene give products of this type:

$$(CH_3)_2C{=}CH_2 + Cl_2 \longrightarrow \underset{87\%}{H_2C{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2Cl} \qquad \text{Ref. 37}$$

$$(CH_3)_2C{=}C(CH_3)_2 + Cl_2 \longrightarrow \underset{100\%}{H_2C{=}\overset{\displaystyle CH_3}{\overset{|}{C}}\overset{\displaystyle Cl}{\overset{|}{C}}(CH_3)_2} \qquad \text{Ref. 37}$$

Alkyl migrations can also occur:

$$(CH_3)_3CCH{=}CH_2 + Cl_2 \longrightarrow \underset{\sim 10\%}{H_2C{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CHCH_2Cl} \qquad \text{Ref. 37}$$

$$(CH_3)_3CCH{=}CHC(CH_3)_3 + Cl_2 \longrightarrow \underset{46\%}{CH_2{=}\overset{\displaystyle CH_3}{\overset{|}{C}}\overset{\displaystyle CH_3}{\overset{|}{C}}HCHC(CH_3)_3} \qquad \text{Ref. 38}$$

Considerable less detail is available about the mechanism of fluorination and iodination of alkenes. Elemental fluorine reacts violently with alkenes giving mixtures including products resulting from degradation of the carbon chain. Electrophilic additions of fluorine to alkenes can be achieved with xenon difluoride[39] or fluoroxytrifluoromethane (CF_3OF).[40] These reactions have not been closely studied, but in general the products can be rationalized as occurring through addition of electrophilic fluorine to give a carbonium ion intermediate. Both from stereochemical results and theoretical calculations,[41] it appears unlikely that a bridged fluorine species is involved. There have also been relatively few mechanistic studies of the addition reaction with iodine. One significant feature of iodination is that it is easily reversible, even in the presence of excess alkene.[42] The addition is stereospecifically *anti* but it is not entirely clear whether a polar or a radical mechanism is involved.[43]

$$I_2 + RCH{=}CHR \rightleftharpoons \underset{\displaystyle I\ \ I}{RCHCHR}$$

37. M. L. Poutsma, *J. Am. Chem. Soc.* **87**, 4285 (1965).
38. R. C. Fahey, *J. Am. Chem. Soc.* **88**, 4681 (1966).
39. M. Zupan and A. Pollak, *J. Chem. Soc. Chem. Commun.* 845 (1973); M. Zupan and A. Pollak, *Tetrahedron Lett.* 1015 (1974).
40. D. H. R. Barton, R. H. Hesse, M. M. Pechet, G. Tarzia, H. T. Toh, and N. D. Westcott, *J. Chem. Soc. Chem. Commun.* 122 (1972).
41. W. J. Hehre and P. C. Hiberty, *J. Am. Chem. Soc.* **96**, 2665 (1974).
42. P. W. Robertson, J. B. Butchers, R. A. Durham, W. B. Healy, J. K. Heyes, J. K. Johannesson, and D. A. Tait, *J. Chem. Soc.* 2191 (1950).
43. M. Zanger and J. L. Rabinowitz, *J. Org. Chem.* **40**, 248 (1975); R. L. Ayres, C. J. Michejda, and E. P. Rack, *J. Am. Chem. Soc.* **93**, 1389 (1971); P. S. Skell and R. R. Pavlis, *J. Am. Chem. Soc.* **86**, 2956 (1964).

As with other electrophiles, halogenation can occur to give 1,2- or 1,4-addition product from conjugated dienes. When molecular bromine is used as the brominating agent in chlorinated hydrocarbon solvent, the 1,4-addition product dominates by ~7:1 in the case of butadiene.[44]

$$CH_2{=}CHCH{=}CH_2 \xrightarrow[25°C]{Br_2} \underset{12\%}{BrCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH{=}CH_2} + \underset{88\%}{BrCH_2CH{=}CHCH_2Br}$$

The product distribution can be shifted to favor the 1,2 product by use of such milder brominating agents as the pyridine–bromine complex or the tribromide ion, Br_3^-. It is believed that free bromine reacts through a cationic intermediate, whereas the less reactive brominating agents involve a process more like the ternary Ad_E3 *anti*-addition mechanism.

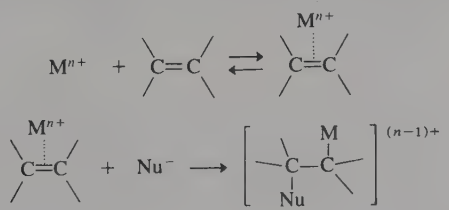
$$CH_2{=}CHCH{=}CH_2 \xrightarrow{Br_2} BrCH_2{-}\overset{\delta+}{C}H\cdots\overset{\delta+}{C}H\cdots CH_2 \xrightarrow{Br^-} \text{products}$$

$$CH_2{=}CHCH{=}CH_2 \xrightleftharpoons{Br_3^-} CH_2{=}CHCH{=}CH_2 \xrightarrow{Br^-} BrCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH{=}CH_2$$

The stereochemistry of both chlorination and bromination of several cyclic and acyclic dienes has been determined. The results show that bromination is often stereospecifically *anti* for the 1,2-addition process, whereas *syn* addition is preferred for 1,4 addition. Comparable results for chlorination show much less stereospecificity.[45] It appears that chlorination proceeds primarily through ion pairs, whereas in bromination a stereospecific *anti*-1,2-addition may compete with a process involving a carbonium ion intermediate. The latter can presumably give *syn* or *anti* product. As a result it must be expected, in general, that halogenation of dienes will not be stereospecific.

6.4. Additions Involving Metal Ions

Certain metal cations are capable of electrophilic attack on alkenes. Addition is completed when a nucleophile, either from the solvent or the metal ion's coordination sphere, acts as a nucleophile toward the alkene–cation complex:



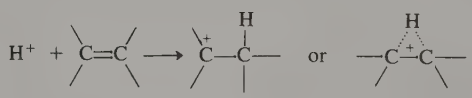
44. G. Bellucci, G. Berti, R. Bianchini, G. Ingrosso, and K. Yates, *J. Org. Chem.* **46**, 2315 (1981).
45. G. E. Heasley, D. C. Hayse, G. R. McClung, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold, and T. L. Ungermann, *J. Org. Chem.* **41**, 334 (1976).

The best studied of these reactions involve the mercuric ion Hg^{2+} as the cation.[46] While the process is feasible for other transition metal cations, the products often go on to react further. The mercuration products are stable and this allows a relatively uncomplicated study of the addition reaction itself. The usual nucleophile is the solvent, either water or an alcohol, but in less nucleophilic solvents other nucleophiles can compete for the complex. The term *oxymercuration* is used to refer to reaction in which water or alcohols are introduced as the nucleophile.

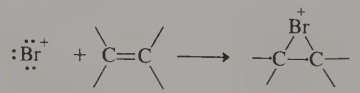
In interesting contrast to the protonation and halogenation reactions which have already been discussed, the mercuration reaction is not accelerated by alkyl substituents on the alkene. For example, 1-pentene is about ten times more reactive than *Z*-2-pentene and 40 times more reactive than *E*-2-pentene.[47] This reversal of reactivity has been attributed to steric effects which evidently outweigh the normal electron-releasing effect of alkyl substituents. When the steric factors are taken into account, the reactivity can be seen to be similar to other electrophilic additions.[48] As expected for an electrophilic reaction, the ρ value is negative.[49] A bridged mercurinium ion is considered to be formed in the rate-determining step. The addition of the nucleophile follows Markownikoff's rule and the regioselectivity of oxymercuration reactions is ordinarily very high.

$$RCH{=}CH_2 \xrightarrow[CH_3OH]{Hg^{II}X_2} \underset{\displaystyle CH_3O}{\overset{\displaystyle |}{RCH{-}CH_2HgX}}$$

A mercurinium ion has both similarities and differences as compared with the intermediates which have been described for other electrophilic additions. The proton which initiates reaction in acid-catalyzed processes is a hard acid and has no unshared electrons. It can form either a carbocation or a hydrogen-bridged cation. Either species is *electron deficient* and highly reactive:



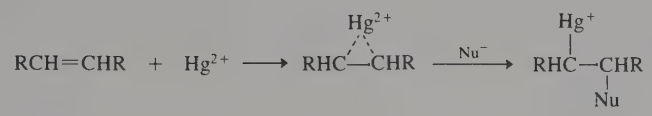
The formal species Br^+ which leads to the bromonium ion intermediate is softer and also has unshared electron pairs which can permit a total of *four* electrons to participate in the bridged bromonium ion intermediate. This would be expected to be more strongly bridged than would be possible for the proton and the bromonium ion can be represented as having two covalent bonds to bromine. This species is electrophilic but not electron deficient.



46. W. Kitching, *Organomet. Chem. Rev.* **3**, 61 (1968).
47. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.* **37**, 1937 (1972).
48. S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.* **103**, 2783 (1981).
49. A. Lewis and J. Arozo, *J. Org. Chem.* **46**, 1764 (1981).

The electrophile in oxymercuration reactions, ^{+}HgX or Hg^{2+}, is a soft acid and strongly polarizing. It polarizes the π-electron distribution of an alkene to the extent that a three-center two-electron bond is formed between mercury and the two carbons of the double bond. A three-center two-electron bond implies weaker bridging in the mercurinium ion than in the three-center four-electron bond of a bromonium ion. Bridging in the mercurinium ion is much more pronounced than is the case for bridging by hydrogen.

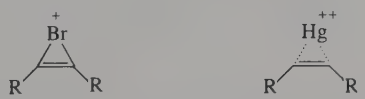
Oxymercuration of simple alkenes is a stereospecific *anti* addition. This result is in agreement with the involvement of a mercurinium intermediate which is opened by nucleophilic attack. The reactivity of the mercury salt is a function both of the



solvent and the counterion in the mercuric salt. Mercuric chloride, for example, is unreactive and usually mercuric acetate is used. When higher reactivity is required salts of electronegatively substituted carboxylic acids such as mercuric trifluoroacetate can be used. Mercuric nitrate and mercuric perchlorate are also suitable. The adducts are often characterized by isolation of the organomercurial as a halide. Organomercury compounds have a number of valuable synthetic applications which will be discussed in Section 4.3 of Part B.

6.5. Additions to Acetylenes

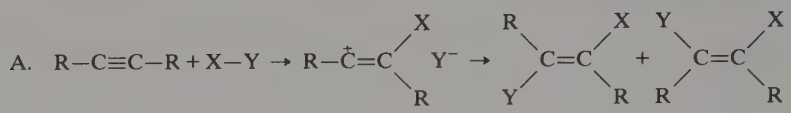
Since acetylenes like alkenes have π electrons which are subject to electrophilic attack, it is not surprising that there is a good deal of similarity between their reactions with such reagents as the hydrogen halides, halogens, and strong acids.[50] The fundamental points of interest for acetylenes include such issues as the following: how reactive are alkynes in comparison with alkenes; what is the stereochemistry of additions to alkynes; and what is the regiochemistry of additions to alkynes? The important role of halonium ions and mercurinium ions also raises the question as to whether similar entities can be involved with acetylenes, where the ring would have to include a double bond:

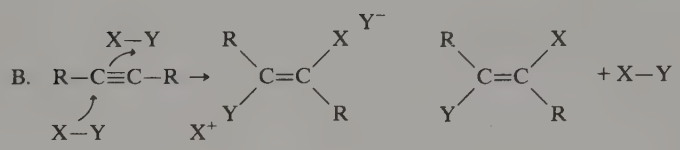


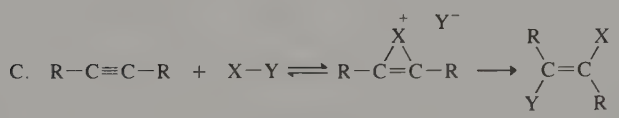
The three basic mechanisms which have been considered to be involved in additions to acetylenes are shown below. The first involves a discrete vinyl cation. In general it could lead to either stereoisomeric addition product. The second is a termolecular process which could be expected to lead to stereospecific *anti* addition.

50. G. H. Schmid, *The Chemistry of the Carbon–Carbon Triple Bond*, Pt. 1, S. Patai (ed.), Wiley, New York, 1978, Chap. 3.

The third mechanism postulates a bridged ion intermediate. Mechanisms A and C are of the Ad_E2 type while mechanism B would be classified as Ad_E3.

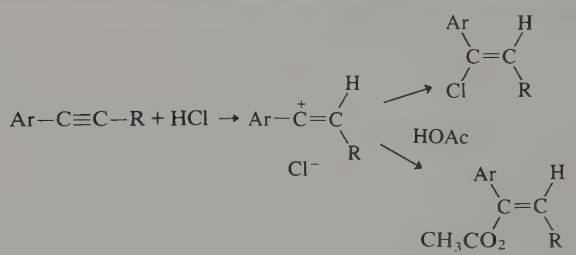




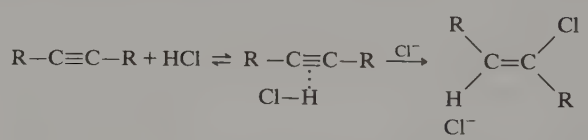


Further details must be added for a complete description but these outlines seem to describe most of the reactions of acetylenes with simple electrophiles.

Hydrogen chloride adds to acetylenes in acetic acid to give mixtures of vinyl halides and vinyl acetates.[51] A vinyl cation is believed to be the intermediate in the rate-determining step when the acetylene carries an aryl substituent. The ion pair



can either collapse or capture the solvent to give product. Aryl-substituted acetylenes give predominantly the *syn* addition product, whereas dialkylacetylenes gives mainly *anti* addition. The presence of added halide ion results in an increasing proportion of *anti* addition. This can be ascribed to an increasing predominance of the Ad_E3 mechanism which leads to *anti*-addition.



Alkyl-substituted acetylenes are believed to be susceptible to reaction by either the Ad_E2 or Ad_E3 process with the precise balance determined by individual structural features and reaction conditions.

51. R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.* **90**, 2124 (1968).

Acetylenes can be hydrated in concentrated aqueous acids. The product is an enol which isomerizes to the stable product.

$$CH_3C{\equiv}CH \xrightarrow{H^+} CH_3\overset{+}{C}{=}CH_2 \xrightarrow{H_2O} CH_3\underset{OH}{C}{=}CH_2 \rightarrow CH_3\underset{O}{C}CH_3$$

Solvent isotope effects are indicative of a rate-determining protonation. Alkyne reactivity increases with addition of electron-donating substituents.[52] Acetylenes are somewhat more strongly affected than alkenes by such substitution, so that whereas simple terminal alkynes are less reactive than alkenes, arylacetylenes with electron donor substituents are more reactive.[53] Kinetic studies on a series of phenylpropiolic acids revealed a strongly negative ρ (−4.8) and showed a solvent isotope effect indicative of rate-determining proton transfer.[54] The hydrogen-bridged version of an ion resulting from protonation is not regarded as a feasible structure.

$$R{-}\overset{+}{\underset{H}{C}}{=}C{-}H \quad \text{less stable than} \quad R{-}\overset{+}{C}{=}CH_2$$

Various MO calculations place the bridged ion 30–45 kcal/mol above the corresponding vinyl cation.[55] Thus additions catalyzed by an initial protonation would be expected to be nonstereospecific.

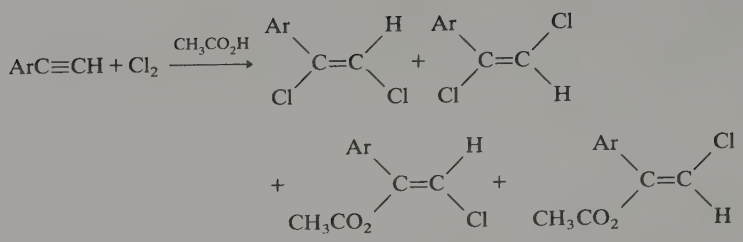
Alkynes react when heated with trifluoroacetic acid to give addition products. Mixtures of *syn* and *anti* addition products are obtained.[56]

$$R{-}C{\equiv}C{-}R + CF_3CO_2H \rightarrow \underset{CF_3CO_2}{\overset{R}{\diagdown}}C{=}C\underset{H}{\overset{R}{\diagup}} + \underset{CF_3CO_2}{\overset{R}{\diagdown}}C{=}C\underset{R}{\overset{H}{\diagup}}$$

These reactions also appear to involve a vinyl cation as the dominant intermediate.

Probably the most thoroughly studied of the addition reactions of acetylene is halogenation. In the presence of excess halogen, acetylenes can yield tetrahaloalkenes but mechanistic studies can be carried out with limited amounts of the halogenating agent so that the initial step can be examined. In general, halogenation of acetylenes is considerably slower than the corresponding reaction of alkenes. We will return to the reason for this shortly. The chlorination of substituted phenylacetylenes follows second-order kinetics in acetic acid. The rates correlate with σ^+ in the Hammett equation with $\rho = -4.2$. The reactions are not stereoselective and considerable acetic acid is incorporated into the addition product.[57]

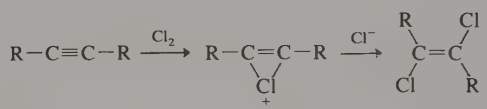
52. P. Cramer and T. T. Tidwell, *J. Org. Chem.* **46**, 2683 (1981).
53. A. D. Allen, Y. Chiang, A. J. Kresge, and T. T. Tidwell, *J. Org. Chem.* **47**, 775 (1982).
54. D. S. Noyce, M. A. Matesich, and P. E. Peterson, *J. Am. Chem. Soc.* **89**, 6225 (1967).
55. H.-J. Köhler and H. Lischka, *J. Am. Chem. Soc.* **101**, 3479 (1979).
56. P. E. Peterson and J. E. Duddey, *J. Am. Chem. Soc.* **88**, 4990 (1966); R. H. Summerville and P. v. R. Schleyer, *J. Am. Chem. Soc.* **96**, 1110 (1974).
57. K. Yates and T. A. Go, *J. Org. Chem.* **45**, 2377 (1980).



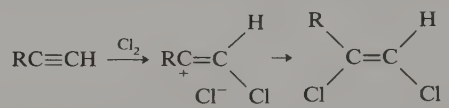
Formation of a vinyl cation intermediate is consistent with these data.

$$ArC{\equiv}CH + Cl_2 \rightarrow Ar\underset{+}{C}{=}CHCl\ (Cl^-) \rightarrow \text{products}$$

For alkyl-substituted acetylenes there is a difference in stereochemistry between mono- and disubstituted acetylenes. The former give *syn* addition while the latter react by *anti* addition. The disubstituted (internal) acetylenes are considerably (~100 times) more reactive. This suggests that the intermediate in the rate-determining step is stabilized by *both* alkyl substituents rather than only one and points to a bridged ion intermediate as does the stereochemistry of the reaction.



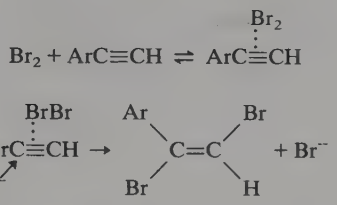
The monosubstituted acetylenes do not seem to be effectively bridged since *syn* addition predominates. It appears that a poorly stabilized and very short-lived vinyl cation is probably the best description of the intermediate in this case.[58]



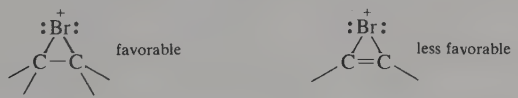
Bromination of acetylenes has been studied quite thoroughly and rates have been measured under conditions that permit comparison with the corresponding alkenes. The rate of bromination of styrene exceeds the rate of bromination of phenylacetylene by about 10^3.[59] For dialkylacetylene-disubstituted alkene pairs, the ratios range upward from 10^3 to 10^7, being greatest in the least nucleophilic solvent.[60] Bromination of alkyl-substituted acetylenes shows rate enhancement by both alkyl substituents and this has been taken to indicate that the bridged ions are probably involved.[61] A termolecular *anti*-addition mechanism generally seems to be involved for alkylacetylenes, whereas aryl-substituted acetylenes give nonstereospecific additions indicative of a vinyl cation intermediate.[62] Arylacetylenes can be caused to

58. K. Yates and T. A. Go, *J. Org. Chem.* **45**, 2385 (1980).
59. M.-F. Ruasse and J.-E. Dubois, *J. Org. Chem.* **42**, 2689 (1977).
60. K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H.-W. Leung, and R. McDonald, *J. Am. Chem. Soc.* **95**, 160 (1973); J. M. Kornprobst and J.-E. Dubois, *Tetrahedron Lett.* 2203 (1974); G. Modena, F. Rivetti, and U. Tonellato, *J. Org. Chem.* **43**, 1521 (1978).
61. G. H. Schmid, A. Modro, and K. Yates, *J. Org. Chem.* **45**, 665 (1980).
62. J. A. Pincock and K. Yates, *Can. J. Chem.* **48**, 3332 (1970).

undergo *anti* addition by including bromide salts in the reaction medium. Under these conditions, a species preceding the vinyl cation is evidently intercepted by bromide ion.



The electrophilic addition reactions of acetylenes can generally be understood by recognizing the possibility for both bridged ions and vinyl cations as intermediates. Reactions proceeding through vinyl cations can be expected to be nonstereospecific with the precise stereochemistry depending upon the lifetime of the vinyl cation and the identity and concentration of potential nucleophiles. Stereospecific anti addition can be expected from processes involving either bridged ions or termolecular mechanisms. These two intermediates can also explain the relative reactivity of alkenes and acetylenes in comparable addition reactions. In general, reactions proceeding through vinyl cations such as those involving rate-determining protonation, are only moderately slower than similar additions to alkenes. This can be attributed to the relatively higher energy of vinyl cations as compared with similar carbocations with sp^2 hybridization. It has been estimated that this difference is about 10 kcal/mol,[63] a significant but not enormous difference which is partially compensated for by the higher ground state energy of the acetylenes. The reactions which proceed through bridged transition states, bromination being the best-studied example, show much larger rate differences. This presumably reflects a greater destabilization of the bridged ion by the strain of the three-membered ring containing



a double bond. The bridged ion may also be considered to be antiaromatic. Thus, while bromonium ions are relatively accessible intermediates for alkenes, the activation energy to reach the corresponding species is much higher for acetylenes. The bromonium ion remains the most accessible intermediate in many cases, but it is energetically relatively less favorable than for alkenes.

6.6. The E2, E1, and E1cb Mechanisms

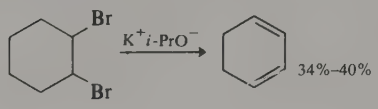
An elimination reaction—the expulsion of another molecule from an organic substrate—can be classified according to the relative placement of the carbon atoms

63. K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H.-W. Leung, and R. McDonald, *J. Am. Chem. Soc.* **95**, 160 (1973).

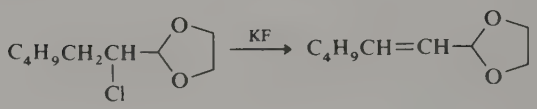
Scheme 6.1. Some Examples

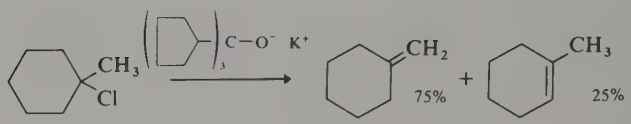
Dehydrohalogenations

1[a] $CH_3(CH_2)_5CH_2CH_2Br \xrightarrow{K^+ t\text{-}BuO^-} CH_3(CH_2)_5CH{=}CH_2$ 85%

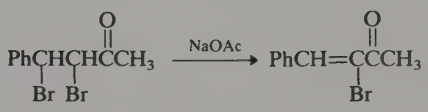
2[b] 

34%–40%

3[c] 

4[d] 

5[e] 

6[f] 

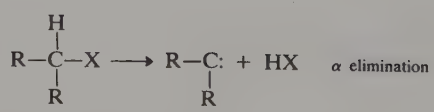
64%–73%

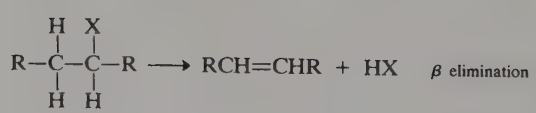
Dehydrohalogenations to acetylenes

7[g] $PhCHCH_2Br \xrightarrow[NH_3]{NaNH_2} PhC{\equiv}CH$ 45%–52%

8[h] $CH_3C(Cl){=}CHCH_2OH \xrightarrow[NH_3]{NaNH_2} \xrightarrow{NH_4Cl} CH_3C{\equiv}CCH_2OH$ 75%–85%

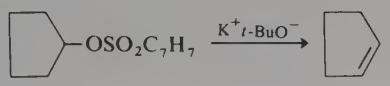
from which elimination occurs.





Eliminations using sulfonates

9[i]



76%

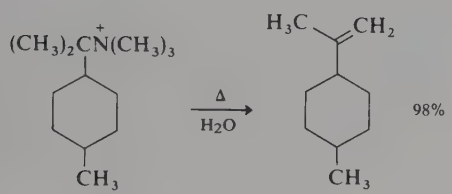
10[j] $Ph_2CHCH_2OSO_2C_7H_7 \xrightarrow{NaOMe} Ph_2C{=}CH_2$ 92%

11[k] $HC{\equiv}CCH_2\underset{\displaystyle OSO_2C_7H_7}{\underset{|}{C}}HCH_3 \xrightarrow[H_2O]{KOH} HC{\equiv}CCH{=}CHCH_3$ 91%

Eliminations involving quaternary ammonium hydroxides

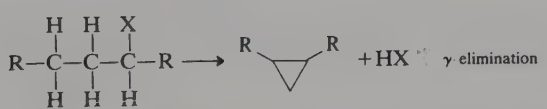
12[l] $(CH_3)_3CCH_2CH_2\overset{+}{N}(CH_3)_3{}^{-}OH \xrightarrow{\Delta} (CH_3)_3CCH{=}CH_2$ 81%

13[m]



98%

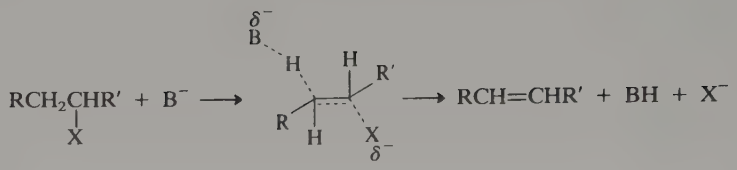
a. P. Veeravagu, R. T. Arnold, and E. W. Eigemann, *J. Am. Chem. Soc.* **86**, 3072 (1964).
b. J. P. Schaeffer and L. Endres, *Org. Synth.* **47**, 31 (1967).
c. E. Elkik, *Bull. Soc. Chim. Fr.*, 283 (1968).
d. S. A. Acharya and H. C. Brown, *Chem. Commun.*, 305 (1968).
e. E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.* **IV**, 162 (1963).
f. N. H. Cromwell, D. J. Cram, and C. E. Harris, *Org. Synth.* **III**, 125 (1953).
g. K. N. Campbell and B. K. Campbell, *Org. Synth.* **IV**, 763 (1963).
h. P. J. Ashworth, G. H. Mansfield, and M. C. Whiting, *Org. Synth.* **IV**, 128 (1963).
i. C. H. Snyder and A. R. Soto, *J. Org. Chem.* **29**, 742 (1964).
j. P. J. Hamrick, Jr., and C. R. Hauser, *J. Org. Chem.* **26**, 4199 (1961).
k. G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).
l. A. C. Cope and D. L. Ross, *J. Am. Chem. Soc.* **83**, 3854 (1961).
m. L. C. King, L. A. Subluskey, and E. W. Stern, *J. Org. Chem.* **21**, 1232 (1956).



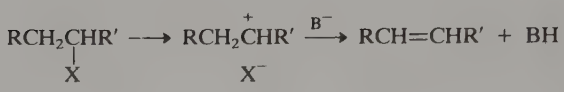
The products of α elimination are unstable divalent carbon species. They will be discussed in Part B, Chapter 9. In the present chapter, attention will be focused on β eliminations, which lead to alkene formation. Scheme 6.1 lists some typical examples of β-elimination reactions.

The β eliminations can be further subdivided by closer examination of the mechanisms involved. The three distinct mechanisms that can operate in such reactions are outlined below:

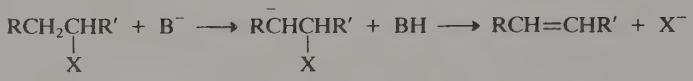
E2 Mechanism



E1 Mechanism



E1cb Mechanism



As depicted, the E2 mechanism involves a bimolecular transition state in which abstraction of a proton β to the leaving group is concerted with departure of the leaving group. In contrast, the rate-determining step in the E1 mechanism is the unimolecular ionization of the substrate. It will be recognized that this is the same process as the rate-determining step in the S_N1 mechanism. Elimination is completed by rapid removal of a β-proton. The E1cb mechanism, like the E1, involves two steps, but the order is reversed. Proton abstraction precedes expulsion of the anionic leaving group. The correlation of many features of β-elimination reactions is greatly aided by recognition that these three mechanisms represent *variations of a continuum of mechanistic possibilities.* Many eliminations occur via mechanisms that are intermediate between the limiting mechanistic types. This idea, called the *variable E2 transition state theory,* is outlined in Fig. 6.2.

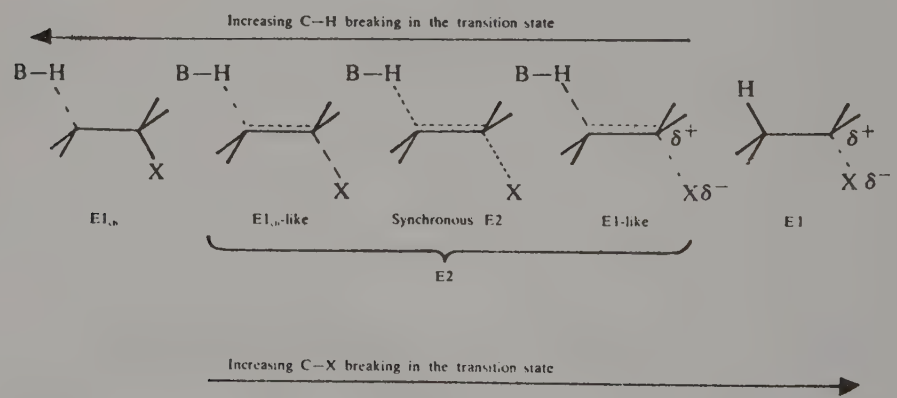


Fig. 6.2. Variable-transition-state theory of elimination reactions. J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.* **1**, 225 (1962); J. F. Bunnett, *Surv. Prog. Chem.* **5**, 53 (1969); W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions,* Wiley, New York, 1973, pp. 48–55; D. J. McLennan, *Tetrahedron* **31**, 2999 (1975); W. H. Saunders, Jr., *Acc. Chem. Res.* **9**, 19 (1976).

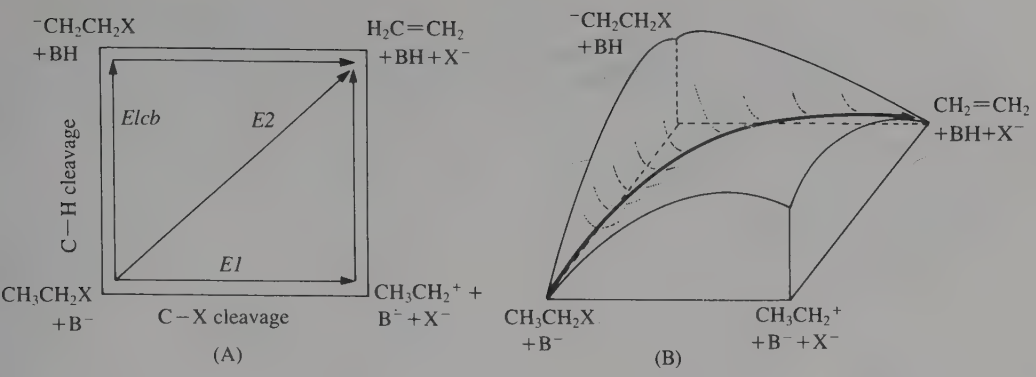


Fig. 6.3. Three-dimensional (More O'Ferrall) diagrams depicting transition state locations for E1, E1cb, and E2 mechanisms.

We will shortly discuss the most important structure–reactivity features of the E2, E1, and E1cb mechanisms. The variable transition state theory allows discussion of reactions proceeding through transition states of intermediate character in terms of the limiting mechanistic types. The most important structural features to be considered in such a discussion are (1) the nature of the leaving group, (2) the nature of the base, (3) electronic and steric effect of substituents in the reactant molecule, and (4) solvent effects.

There is another useful way of depicting the ideas embodied in the variable transition state theory of elimination reactions. This is to construct a *three-dimensional* potential energy diagram.[64] Suppose that we consider the case of an ethyl halide. The two stepwise reaction paths both require the formation of high-energy intermediates. The E1 mechanism requires formation of a carbonium ion, whereas the E1cb proceeds via a carbanion intermediate.

$$CH_3CH_2X \rightarrow CH_3CH_2^+ + X^- \qquad \text{E1 mechanism}$$

$$CH_3CH_2X \xrightarrow{B^-} {}^-CH_2CH_2X + BH \qquad \text{E1cb mechanism}$$

In the absence of other stabilizing substituent groups, both a primary carbonium ion and a primary carbanion are highly unstable intermediates. If we construct a three-dimensional diagram in which progress of C–H bond breaking is one dimension, progress of C–X bond breaking the second, and energy of the reacting system the third, we obtain a diagram such as Fig. 6.3. In Fig. 6.3(A) only the two horizontal (bond-breaking) dimensions are shown. We see that the E1 mechanism corresponds to complete C–X cleavage before C–H cleavage starts. The E1cb mechanism corresponds to complete C–X cleavage before C–H cleavage starts. In Fig. 6.3(B) the energy dimension is added. The front right and back left corners correspond to the E1 and E1cb intermediates, respectively.

64. R. A. More O'Ferrall, *J. Chem. Soc.* ***B***, 274 (1970).

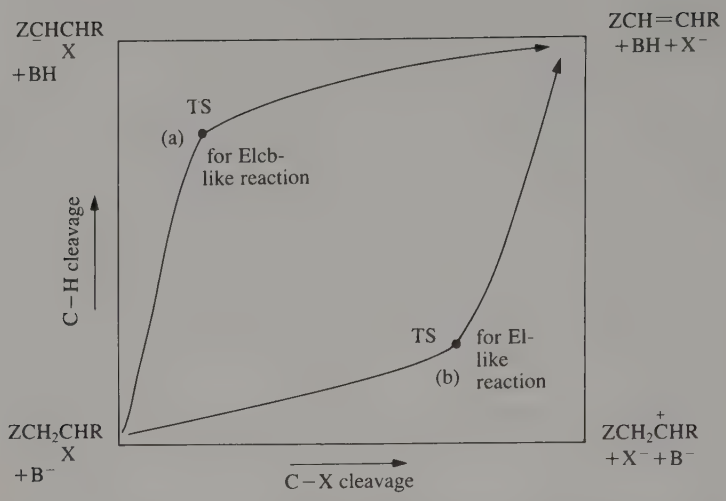


Fig. 6.4. Representation of changes in transition state character in the variable transition state E2 elimination reaction showing displacement of transition state location as a result of substituent effects: (a) substituent Z stabilizes carbanion character of E1cb-like transition state; (b) substituent R stabilizes carbonium ion character of E1-like transition state.

Because of the high energy of both the E1 and E1cb intermediates, the lowest-energy path will be the concerted E2 path, more or less diagonally across the energy surface. If, however, substituents are added to the ethyl group which would stabilize the carbonium ion intermediate, we would expect a lowering of the right front corner of the diagram. Similarly if a substituent is added which would stabilize the carbanion intermediate of the E1cb mechanism, the back left corner of the diagram would be of lower energy. For this reason, substituents which would stabilize carbocation character will move the E2 transition state to a point where it more closely resembles the E1 transition state. A structural change which effects a stabilization of carbanion character would cause the E2 transition state to become more similar to the E1cb transition state. Thus in the E1-like transition state C–X cleavage would be more advanced than C–H cleavage, whereas in the E1cb-like transition state, the C–H bond-breaking would be more advanced. Figure 6.4 illustrates how these changes can be depicted on this type of energy diagram.

We can now use these general ideas to discuss specific structural effects which favor the various possible mechanisms for elimination reactions. We have a background which is pertinent to the structure–reactivity effects in E1 reactions from the discussion of the S_N1 reaction. Ionization is favored by (1) electron-releasing groups that stabilize the positive charge in the carbonium ion; (2) readily ionized, i.e., "good," leaving groups; (3) solvents of high ionizing strength. The base plays no role in the rate-determining step in the E1 mechanism, but its identity cannot be ignored. Once ionization has occurred, the carbonium ion is subject to two competing reactions: nucleophilic capture (S_N1) or proton removal (E1). Stronger bases favor the E1 path over the S_N1 path.

E2 reactions are distinguished from E1 reactions in that the base is present in the transition state for the rate-determining step. The reactions therefore exhibit overall second-order kinetics. The precise nature of the transition state is a function of variables such as the strength of the base, the identity of the leaving group, and the solvent. For example, an elimination reaction proceeding by an E2 transition state will be moved in the E1cb direction by an increase in base strength or by a change to a poorer leaving group. On the other hand, a good leaving group in a highly ionizing solvent will result in an E2 transition state that resembles an E1 process, with significant weakening of the bond to the leaving group.

Reactions that proceed by the E1cb mechanism are limited to reactants having substituent groups that can effectively stabilize the intermediate carbanion. This mechanism is not observed with simple alkyl halides or sulfonates. It is more likely to be involved when the leaving group is β to a carbonyl, nitro, cyano, sulfonyl, or other functional group capable of stabilizing negative charge on carbon.

The nature of the transition state is of great importance, since it controls the direction of β elimination in compounds in which the double bond can be introduced in one of several possible positions. These orientation effects are discussed in the next section.

6.7. Orientation Effects in Elimination Reactions

At present, the most useful generalizations and predictions regarding direction of elimination reactions are drawn from the variable transition state theory. As shown in Fig. 6.2, this theory proposes that the transition states in E2 reactions may vary over a mechanistic range spanning the gap between the E1 and E1cb extremes. As long as the base is present in the transition state, the reactions will exhibit second-order kinetics. In all such cases, the cleavage of the C–H bond and the C–X bond must be concerted. The relative extent of breaking of the two bonds at the transition state may differ a great deal, however, depending on the nature of the leaving group X and the ease of removal of the hydrogen as a proton. If one examines the orientation effects in E1 and E1cb eliminations, it is seen that quite different structural features govern the direction of elimination for these mechanisms. The variable transition state theory of E2 reactions suggests that E2 elimination proceeding through "E1-like" transition states will follow orientation rules of E1 eliminations, and that E2 eliminations proceeding through "E1cb-like" transition states will show directional behavior similar to that found for the E1cb mechanism. It is therefore instructive to consider these mechanisms before discussing the E2 case.

In the E1 mechanism, the leaving group has completely ionized before C–H bond-breaking occurs. The direction of the elimination will then depend on the structure of the carbonium ion and on the identity of the base involved in the rapid proton removal that follows C–X heterolysis. It should be recognized that quite weak bases can suffice to effect proton removal. The solvent may often serve this function. The counterion formed in the ionization step may also act as the proton acceptor:

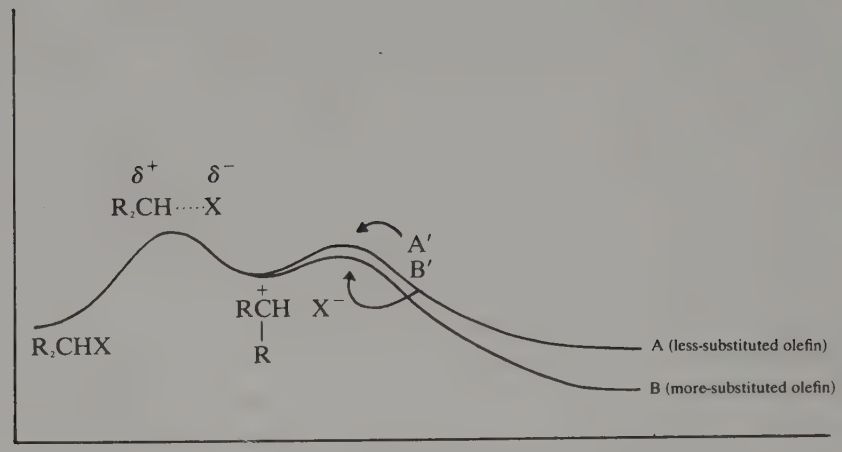
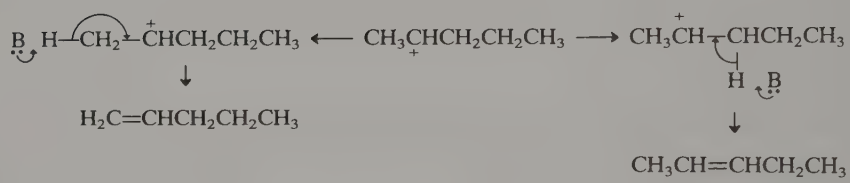


Fig. 6.5. Product-determining step for E1 elimination.



The experimental evidence that has been gathered concerning direction of elimination from substrates reacting by the E1 mechanism indicates that *the relative stability of the product alkene* is a major factor in determining direction of elimination. The direction of elimination will be determined by the relative energies of the transition states A′ and B′ (Fig. 6.5). It is known that the order of stability of the olefins is B more stable than A. The experimental results indicate that the transition states A′ and B′ resemble A and B sufficiently that the same relative order of stability holds. Since the activation energy for proton removal from a carbonium ion is low, the transition states presumably resemble the intermediate carbonium to a great extent; states A′ and B′ should therefore be considerably closer in energy than A and B. Thus, E1 eliminations are often rather low in selectivity, giving rise to a mixture of all possible olefins. The composition, however, roughly reflects the relative thermodynamic stabilities of the olefin, in that the most-substituted olefin is formed in the greatest amount. The precise product composition is governed by a number of factors. In some cases, the product composition is a function of the leaving group, indicating that the carbonium ion cannot be completely free of the counterion when deprotonation occurs. In nondissociating solvents, ion pairs are probably key intermediates, and the counterion may act as the proton acceptor.[65]

65. D. J. Cram and M. R. V. Sahyun, *J. Am. Chem. Soc.* **85**, 1257 (1963); P. S. Skell and W. L. Hall, *J. Am. Chem. Soc.* **85**, 2851 (1963).

In the E1cb mechanism, the direction of elimination is governed by the kinetic acidity of the individual β protons, which in turn is determined by the inductive and resonance effects of nearby substituents and by the degree of steric hindrance to approach of base to the proton. Alkyl substituents will tend to retard proton abstraction both electronically and sterically. Preferential proton abstraction from unhindered positions leads to the formation of less-substituted alkenes.

The preferred direction of elimination via an E2 mechanism depends on the precise nature of the transition state. The two extreme transition states for the E2 elimination will resemble the E1 and E1cb mechanisms in their orientation effects. At the "E1cb-like" end of the E2 spectrum, a highly developed bond is present between the proton being abstracted and the base. The leaving group remains tightly bonded, and there is little development of the carbon–carbon double bonds. At the "E1-like" end of the spectrum, the transition state is characterized by extensive cleavage of the bond to the leaving group and a largely intact C–H bond. In a synchronous E2 reaction, the new double bond is substantially formed at the transition state at the expense of partial cleavage of the C–H and C–X bonds. E2 eliminations that proceed through transition states with high double-bond character give mainly the more substituted alkene because the stability of the alkene is reflected in the transition state. When the transition states have extensive E1cb character, the direction of elimination is governed by ease of proton removal. In this case, the less-substituted alkene usually dominates.

Prior to development of the mechanistic ideas outlined above, it was recognized by experience that some types of elimination reactions gave the more-substituted possible alkene as the major product. Such eliminations were said to follow the "Saytzeff rule." This behavior was observed for eliminations that would now be recognized as proceeding by the E1 mechanism, and for eliminations by the E2 mechanism when halides and sulfonate ions or other good leaving groups were involved. Reactions involving the E2 mechanism, but with poor leaving groups, especially elimination of tertiary amines from quaternary ammonium salts, were observed to give predominantly the less-substituted olefin, and were said to follow the "Hofmann rule." In these reactions, there is little development of the carbon–carbon double bond at the transition state; i.e., the transition state is "E1cb-like."

The data recorded in Table 6.4 for the 2-hexyl system illustrate two general trends that have been recognized in other systems as well. First, poorer leaving groups favor elimination according to the "Hofmann rule," as shown, for example, by the increasing amount of terminal olefin in the halogen series as the leaving group is changed from iodide to fluoride. Poorer leaving groups move the transition state in the E1cb direction. A higher negative charge must be built up on the β carbon to induce loss of the leaving group. This buildup is accomplished by more complete proton abstraction. A more electronegative leaving group, such as fluoride, increases the acidity of the β protons, making the transition state more "E1cb-like" and increasing the proportion of the less-substituted alkene.

Comparison of the data for methoxide with *t*-butoxide in Table 6.4 illustrates the second general trend: Stronger bases favor formation of the less-substituted

Table 6.4. Product Ratios for Some E2 Eliminations

Substrate: $CH_3CH_2CH_2CH_2\underset{\displaystyle X}{\underset{\vert}{C}}HCH_3$[a]	Base, solvent	Percent composition of alkene		
		1-Hexene	2-Hexene	
			trans	*cis*
X = I	MeO^-, MeOH	19	63	18
Cl	MeO^-, MeOH	33	50	17
F	MeO^-, MeOH	69	21	9
$OSO_2C_7H_7$	MeO^-, MeOH	33	44	23
I	*t*-BuO^-, *t*-BuOH	78	15	7
Cl	*t*-BuO^-, *t*-BuOH	91	5	4
F	*t*-BuO^-, *t*-BuOH	97	1	1
$OSO_2C_7H_7$	*t*-BuO^-, *t*-BuOH	83	4	14

a. From R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.* **91**, 1376 (1967).

alkene.[66] A stronger base apparently leads to an increase in the carbanion character at the transition state, and thus shifts it in the E1cb direction. A linear correlation between the strength of the base and the difference in $\Delta G^{\ddagger}$ for formation of 1-butene versus 2-butene has been established.[66b] Some of the data are given in Table 6.5.

The direction of elimination is also affected by steric effects, and if both the base and the reactant are highly branched, steric factors will lead to preferential removal of the less hindered hydrogen.[67] Thus, when 4-methyl-2-pentyl iodide reacts with very hindered bases such as potassium tricyclohexylmethoxide, there is preferential formation of the terminal alkene. In this case potassium *t*-butoxide favors the internal alkene, although by a smaller ratio than for less branched alkoxides.

$$(CH_3)_2CHCH_2\underset{\displaystyle I}{\underset{\vert}{C}}HCH_3 \rightarrow (CH_3)_2CHCH{=}CHCH_3 + (CH_3)_2CHCH_2CH{=}CH_2$$

base		
$K^+{}^-OC(C_6H_{13})_3$	42%	58%
$K^+{}^-OC(CH_3)_3$	61%	39%
$K^+{}^-OCH_2CH_2CH_3$	75%	25%

The leaving group also affects the amount of internal versus terminal alkene that is formed. The poorer the leaving group, the more E1cb-like is the transition state. Thus the trend is toward more of the terminal alkene with poorer leaving groups. This trend is illustrated for the case of the 2-butyl system by the data in Table 6.6. Strongly electronegative leaving groups, such as those of dimethylsul-

66. (a) D. H. Froemsdorf and M. D. Robbins, *J. Am. Chem. Soc.* **89**, 1737 (1967); I. N. Feit and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 5615 (1970); (b) R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.* **95**, 3405 (1973); (c) R. A. Bartsch, K. E. Wiegers, and D. M. Guritz, *J. Am. Chem. Soc.* **96**, 430 (1974).
67. R. A. Bartsch, R. A. Read, D. T. Larsen, D. K. Roberts, K. J. Scott, and B. R. Cho, *J. Am. Chem. Soc.* **101**, 1176 (1979).

Table 6.5. Orientation in E2 Elimination as a Function of Base Strength

Base (potassium salt)	p*K*	% 1-Butene from 2-iodobutane[a]	% 1-butene from 2-butyl tosylate[b]
p-Nitrobenzoate	8.9	5.8	*c*
Benzoate	11.0	7.2	*c*
Acetate	11.6	7.4	*c*
Phenolate	16.4	11.4	30.6
2,2,2-Trifluoroethoxide	21.6	14.3	46.0
Methoxide	29.0	17.0	*c*
Ethoxide	29.8	17.1	56.0
t-Butoxide	32.2	20.7	58.5

a. From R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.* **95**, 3405 (1973). The p*K* values refer to DMSO solution.
b. R. A. Bartsch, R. A. Read, D. T. Larsen, D. K. Roberts, K. J. Scott, and B. R. Cho, *J. Am. Chem. Soc.* **101**, 1176 (1979).
c. Not reported.

Table 6.6. Orientation of Elimination in the 2-Butyl System under Various E2 Conditions

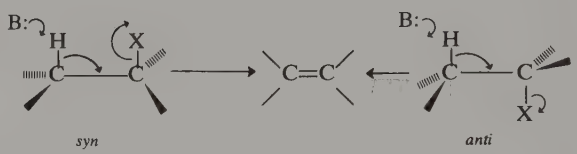
	1-Butene (%)	2-Butene (%)	Ref.
$CH_3\underset{\displaystyle I}{C}HCH_2CH_3 \xrightarrow[DMSO]{PhCO_2^-}$	7	93	a
$CH_3\underset{\displaystyle I}{C}HCH_2CH_3 \xrightarrow[DMSO]{C_2H_5O^-}$	17	83	a
$CH_3\underset{\displaystyle I}{C}HCH_2CH_3 \xrightarrow[DMSO]{(CH_3)_3CO^-}$	21	79	b
$CH_3\underset{\displaystyle Br}{C}HCH_2CH_3 \xrightarrow[DMSO]{(CH_3)_3CO^-}$	33	67	b
$CH_3\underset{\displaystyle Cl}{C}HCH_2CH_3 \xrightarrow[DMSO]{(CH_3)_3CO^-}$	43	57	b
$CH_3\underset{\displaystyle Br}{C}HCH_2CH_3 \xrightarrow[C_2H_5OH]{C_2H_5O^-}$	19	81	c
$CH_3\underset{\displaystyle OSO_2C_7H_7}{C}HCH_2CH_3 \xrightarrow[C_2H_5OH]{C_2H_5O^-}$	35	65	d
$CH_3\underset{\displaystyle OSO_2C_7H_7}{C}HCH_2CH_3 \xrightarrow[DMSO]{(CH_3)_3CO^-}$	61	39	d
$CH_3\underset{\displaystyle +S(CH_3)_2}{C}HCH_2CH_3 \xrightarrow[C_2H_5OH]{C_2H_5O^-}$	74	26	e
$CH_3\underset{\displaystyle +N(CH_3)_3}{C}HCH_2CH_3 \xrightarrow{^-OH}$	95	5	f

a. R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.* **95**, 3405 (1973).
b. D. L. Griffith, D. L. Meges, and H. C. Brown, *Chem. Commun.*, 90 (1968).
c. M. L. Dhar, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2058 (1948).
d. D. H. Froemsdorf and M. D. Robbins, *J. Am. Chem. Soc.* **89**, 1737 (1967).
e. E. D. Hughes, C. K. Ingold, G. A. Maw, and L. I. Woolf, *J. Chem. Soc.*, 2077 (1948).
f. A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Am. Chem. Soc.* **79**, 4720 (1957).

fonium and trimethylammonium salts, also make the orientation of elimination more E1cb-like because their inductive and field effects increase the acidity of the β protons.

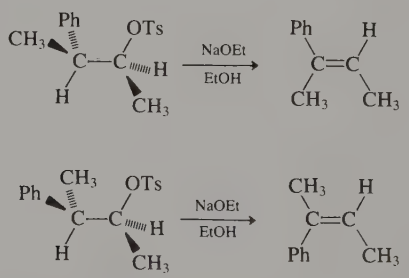
6.8. Stereochemistry of E2 Elimination Reactions

Two elements of stereochemistry enter into determining the ratio of isomeric alkenes formed in E2 reactions. First, elimination may proceed in a *syn* or *anti* fashion:



Second, in many cases, the product alkene may be a mixture of the *cis* and *trans* isomers. The product ratio therefore depends on these stereochemical details of the elimination. These aspects of the elimination reaction have also been of interest because of the insight the data provide into the reaction mechanism.

In most cases, E2 eliminations proceed via a transition state involving the *anti* arrangement. Nevertheless, *syn* elimination is possible, and, when special structural features retard *anti* elimination, *syn* elimination becomes the dominant mode. In acyclic systems the extent of *anti* versus *syn* elimination can be determined by use of stereospecifically deuterated substrates or by use of diastereomeric reactants which will give different product for *syn* and *anti* elimination. The latter approach, for example, showed that elimination from 3-phenyl-2-butyl tosylates is a stereospecific *anti* process[68]:



The occurrence of *syn* elimination in 3-decyl systems has been demonstrated using diastereomeric deuterium-labeled substrates. Stereospecifically labeled 5-substituted decanes were prepared and subjected to appropriate elimination condi-

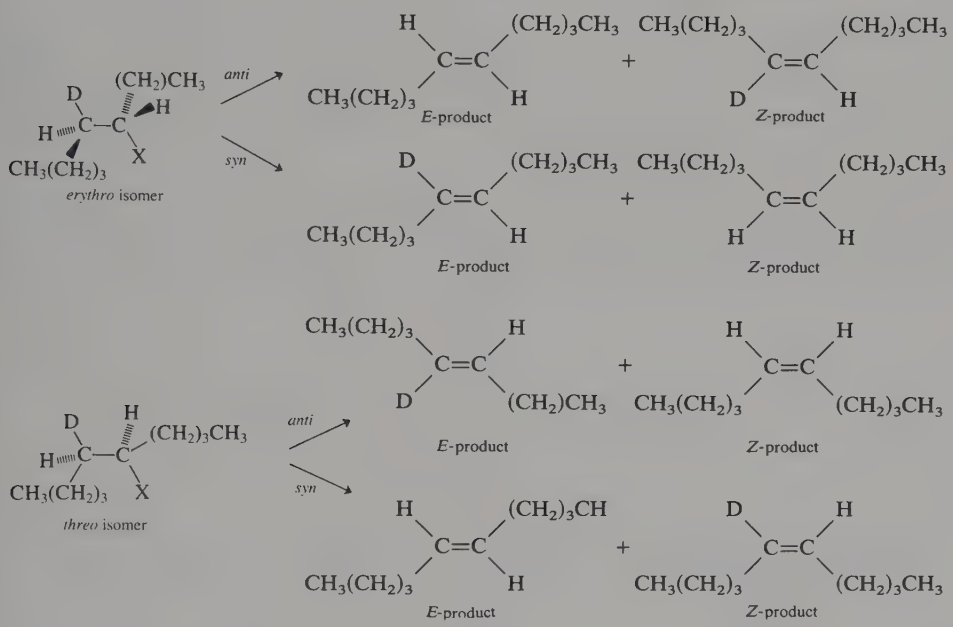
68. W.-B. Chiao and W. H. Saunders, *J. Org. Chem.* **45**, 1319 (1980).

Table 6.7. Extent of *Syn* Elimination as a Function of the Leaving Group in the 5-Decyl System[a]

	Per cent *syn* elimination			
	E product		*Z* product	
Leaving group	DMSO	Benzene	DMSO	Benzene
Cl	6	62	7	39
OTs	4	27	4	16
$^{+}N(CH_3)_3$	93	92	76	84

a. Data from M. Pankova, M. Svoboda, and J. Zavada, *Tetrahedron Lett.* 2465 (1972). The base used was potassium *tert*-butoxide.

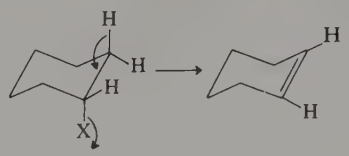
tions. By comparison of the amount of deuterium in the *E* and *Z* isomers of the product, it is possible to determine the extent of *anti* and *syn* elimination[69]:



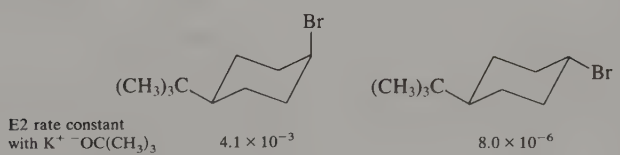
Data obtained for several leaving groups are shown in Table 6.7. The results show that *syn* elimination is extensive for quarternary ammonium salts. With better leaving groups, the extent of *syn* elimination is small in the polar solvent DMSO but quite significant in benzene. The factors which promote *syn* elimination will be discussed shortly.

69. M. Pankova, M. Svoboda, and J. Zavada, *Tetrahedron Lett.* 2465 (1972). The analysis of the data also requires that account be taken of (a) isotope effects and (b) the formation of 4-decene. The method of analysis of the data is described by J. Sicher, J. Zavada, and M. Pankova, *Coll. Czech. Chem. Commun.* **36**, 3140 (1971).

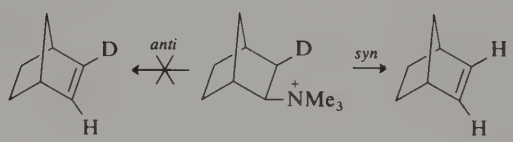
Cyclohexyl systems have a very strong preference for *anti* elimination via conformations in which both the departing proton and the leaving group occupy axial positions. The orientation results in an alignment of the involved orbitals that permits smooth conversion to the π system in the developing double bond:



For example, *cis*-4-*t*-butylcyclohexyl bromide undergoes E2 elimination at a rate about 500 times greater than the *trans* isomer[70]:



Other cyclic systems are not so selective. In the decomposition of *N,N,N*-trimethycyclobutylammonium hydroxide, elimination is 90% *syn*.[71] The cyclobutyl ring resists the conformation required for *anti* elimination. The more flexible five-membered ring analog undergoes about 50% *syn* elimination. Hofmann elimination from the *N,N,N*-trimethylnorbornylammonium ion is exclusively *syn*.[72] Here also, the rigid ring prohibits the conformation required for *anti* elimination; there is also a steric effect operating against removal of an *endo* proton, which is, of course, required for *anti* elimination.



Although there is usually a preference for *anti* elimination in acyclic systems, several studies have shown that *syn* elimination is also competitive in some eliminations.[73] Table 6.8 summarizes some of the available data on *syn* versus *anti* elimination in acyclic systems.

The general trend revealed by these and other data is that *anti* stereochemistry is normally preferred for reactions involving good leaving groups such as bromide and tosylate. With poorer leaving groups (e.g., fluoride, trimethylamine) *syn* elimination becomes important. The amount of *syn* elimination is small in the 2-butyl system but becomes a major pathway with 3-hexyl compounds and with longer

70. J. Zavada, J. Krupicka, and J. Sicher, *Coll. Czech. Chem. Commun.* **33**, 1393 (1968).
71. M. P. Cooke, Jr. and J. L. Coke, *J. Am. Chem. Soc.* **90**, 5556 (1968).
72. J. L. Coke and M. P. Cooke, Jr., *J. Am. Chem. Soc.* **89**, 6701 (1967).
73. R. A. Bartsch, *J. Am. Chem. Soc.* **93**, 3683 (1971); D. S. Bailey and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 6904 (1970).

Table 6.8. Stereochemistry of E2 Eliminations for Some Acyclic Substrates

Substrate	Base, solvent	(%) *anti*	(%) *syn*	Ref.
$CH_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle Br}{\underset{\vert}{C}}HCH_3$	$K^{+-}OC(CH_3)_3$, $(CH_3)_3COH$	100	0	a
$CH_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle OSO_2C_7H_7}{\underset{\vert}{C}}HCH_3$	$K^{+-}OC(CH_3)_3$, $(CH_3)_3COH$	>98	<2	b
$CH_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle {}^{+}N(CH_3)_3}{\underset{\vert}{C}}HCH_3$	$K^{+-}OC(CH_3)_3$, DMSO	100	0	c
$CH_3CH_2\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle {}^{+}N(CH_3)_3}{\underset{\vert}{C}}HCH_2CH_3$	$K^{+-}OC(CH_3)_3$, $(CH_3)_3COH$	20	80	d
$CH_3CH_2\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle F}{\underset{\vert}{C}}HCH_2CH_3$	$K^{+-}OC(CH_3)_3$, $(CH_3)_3COH$	32	68	e
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle {}^{+}N(CH_3)_3}{\underset{\vert}{C}}H(CH_2)_3CH_3$	$K^{+-}OC(CH_3)_3$, DMSO	24	76	f
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle OSO_2C_7H_7}{\underset{\vert}{C}}H(CH_2)_3CH_3$	$K^{+-}OC(CH_3)_3$, $(CH_3)_3COH$	93	7	g
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle Cl}{\underset{\vert}{C}}H(CH_2)_3CH_3$	$K^{+-}OC(CH_3)_3$, benzene	62	38	h
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle F}{\underset{\vert}{C}}H(CH_2)_3CH_3$	$K^{+-}OC(CH_3)_3$, benzene	<20	>80	h
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle Cl}{\underset{\vert}{C}}H(CH_3)_3CH_3$	$K^{+-}OC(CH_3)_3$ DMSO	93	7	h
$CH_3(CH_2)_3\underset{\displaystyle D}{\underset{\vert}{C}}H\underset{\displaystyle F}{\underset{\vert}{C}}H(CH_2)_3CH_3$	$K^{+-}OC(CH_3)_3$ DMSO	80	20	h

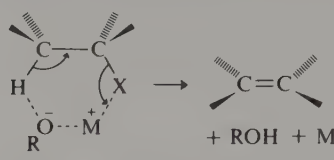
a. R. A. Bartsch, *J. Am. Chem. Soc.* **93**, 3683 (1971).
b. D. H. Froemsdorf, W. Dowd, W. A. Gifford, and S. Meyerson, *Chem. Commun.*, 449 (1968).
c. D. H. Froemsdorf, H. R. Pinnick, Jr., and S. Meyerson, *Chem. Commun.*, 1600 (1968).
d. D. S. Bailey and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 6904 (1970).
e. J. K. Borchardt, J. C. Swanson, and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **96**, 3918 (1974).
f. J. Sicher, J. Závada, and M. Pánková, *Collect. Czech. Chem. Commun.* **36**, 3140 (1971).
g. J. Závada, M. Pánková, and J. Sicher, *Chem. Commun.*, 1145 (1968).
h. M. Pánková, M. Svoboda, and J. Závada, *Tetrahedron Lett.*, 2465 (1972).

chains, and is especially prevalent in the medium-sized alicyclic systems.[74]

The factors that determine whether *syn* or *anti* elimination predominates are still subject to investigation. One factor that is believed to be important is whether

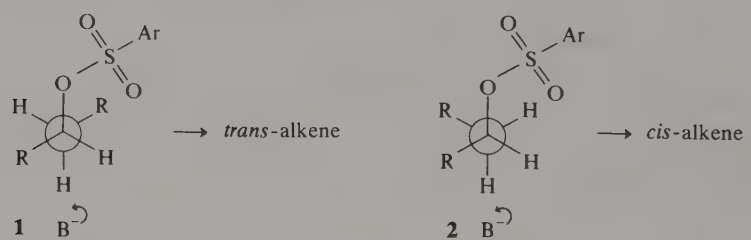
74. J. Sicher, *Angew. Chem. Int. Ed. Engl.* **11**, 200 (1972).

the base is free or present as an ion pair.[75] The evidence is that an ion pair promotes *syn* elimination of anionic leaving groups. This view can be rationalized by proposing a transition state in which the anion functions as a base and the cation assists in the departure of the leaving group:



This interpretation is in agreement with the solvent effect which is evident in the 5-decyl system as revealed in Table 6.7. The extent of *syn* elimination is much higher in the nondissociating solvent benzene than in dimethyl sulfoxide. The ion pair interpretation is also favored by the fact that addition of specific metal ion-complexing agents (crown ethers) that would favor dissociation of the ion pair leads to diminished amounts of *syn* elimination.[76] A theory based on steric effects was also considered, but it suggested that only relatively large leaving groups would show *syn* elimination. Later studies revealed that extensive *syn* elimination occurred even with the small fluoride ion as leaving group.[75] Another factor that affects the *syn* : *anti* ratio is the strength of the base. Strong bases are more likely to exhibit a high proportion of *syn* elimination.[77]

The proportion of *cis* and *trans* isomers of internal alkenes formed during elimination reactions depends on the identity of the leaving group. Halides usually give predominantly the *trans* alkenes.[78] Bulkier groups, particularly arenesulfonates, give higher proportions of the *cis* alkene. Sometimes more *cis* isomer is formed than *trans*. The normal preference for *trans* alkene probably reflects the greater stability of the *trans* alkene; i.e., the unfavorable steric repulsions present in the *cis* alkene are also present in the E2 transition state leading to *cis* alkene. High *cis* : *trans* ratios are attributed to a second steric effect that becomes important only when the leaving group is large. The conformations leading to *cis* and *trans* alkene by *anti* elimination are depicted below:



75. R. A. Bartsch, G. M. Pruss, R. L. Buswell, and B. A. Bushaw, *Tetrahedron Lett.* 2621 (1972); J. K. Borchardt, J. C. Swanson and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **96**, 3918 (1974).
76. R. A. Bartsch, E. A. Mintz, and R. M. Parlman, *J. Am. Chem. Soc.* **96**, 4249 (1974).
77. K. C. Brown and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 4292 (1970); D. S. Bailey and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 6904 (1970).
78. H. C. Brown and R. L. Klimisch, *J. Am. Chem. Soc.* **87**, 5517 (1965); I. N. Feit and W. H. Saunders, Jr., *J. Am. Chem. Soc.* **92**, 1630 (1970).

When the leaving group and base are large, conformation **2** is favored because it permits the bulky leaving group to occupy a position removed from both alkyl substituents. *Anti* elimination through a transition state arising from conformation **2** gives *cis* alkene. *Cis* : *trans* isomer ratios also depend on the amount of *syn versus anti* elimination. The *syn* elimination tends to favor formation of *trans* product.

6.9. Dehydration of Alcohols

The dehydration of alcohols is an important elimination reaction that takes place under acidic rather than basic conditions. It involves an E1 mechanism.[79] The function of the acidic reagent is to convert the hydroxyl group to a better leaving group by protonation:

$$\underset{\text{OH}}{\overset{|}{\text{RCHCH}_2\text{R}'}} \overset{\text{H}^+}{\rightleftharpoons} \underset{{}^+\text{OH}_2}{\overset{|}{\text{RCHCH}_2\text{R}'}} \xrightarrow{-\text{H}_2\text{O}} \underset{+}{\text{RCHCH}_2\text{R}'} \xrightarrow{-\text{H}^+} \text{RCH=CHR}'$$

Since a carbonium ion or closely related species is the intermediate, the elimination step would be expected to favor the most stable alkene. The carbonium ion mechanism also explains the general trend in relative reactivity exhibited in this reaction. Tertiary alcohols are the most reactive, and reactivity decreases on going to secondary and primary alcohols. Also in accord with the cationic mechanism is the fact that rearranged products are found in cases where a carbonium ion intermediate could be expected to rearrange:

$$\underset{\text{OH}}{\overset{|}{\text{R}_3\text{CCHR}'}} + \text{H}^+ \rightleftharpoons \underset{{}^+\text{OH}_2}{\overset{|}{\text{R}_3\text{CCHR}'}} \rightleftharpoons \overset{+}{\text{R}_3\text{C}}\text{CHR}' + \text{H}_2\text{O}$$

$$\overset{+}{\text{R}_3\text{C}}\text{CHR}' \longrightarrow \text{R}_2\overset{+}{\text{C}}\overset{\text{R}}{\overset{|}{\text{C}}}\text{HR}' \longrightarrow \text{R}_2\text{C}=\overset{\text{R}}{\overset{|}{\text{C}}}\text{R}'$$

For many alcohols, exchange of the hydroxyl group with the solvent is faster than dehydration.[80] This indicates reversible formation of the carbonium ion. If the proton removal is rate determining it would be expected that a significant isotope effect would be seen. It should be noted that rate-determining deprotonation corresponds to the rate-controlling protonation step in the reverse reaction, the hydration of an alkene.

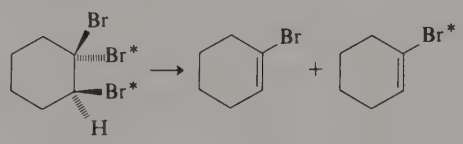
$$\underset{\text{HO}\ \ \text{H}^*}{\overset{|\ \ |}{\text{PhCHCHPh}}} \xrightarrow[\text{H}_2\text{O}]{\text{H}_2\text{SO}_4} \underset{k_\text{H}/k_\text{D} = 1.8}{\text{PhCH=CHPh}} \qquad \text{Ref. 81}$$

79. D. V. Banthorpe, *Elimination Reactions*, Elsevier, New York, 1963, pp. 145–156.
80. C. A. Bunton and D. R. Llewellyn, *J. Chem. Soc.* 3402 (1957); J. Manassen and F. S. Klein, *J. Chem. Soc.* 4203 (1960).
81. D. S. Noyce, D. R. Hartter, and R. M. Pollack, *J. Am. Chem. Soc.* **90**, 3791 (1968).

6.10. Eliminations Not Involving C–H Bonds

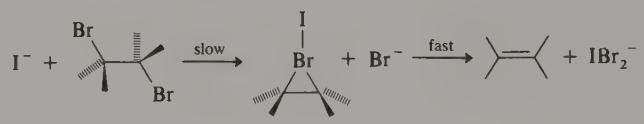
The β elimination processes discussed thus far have focused on those that involve abstraction of a proton bound to carbon. It is the electrons in the C–H σ bond, however, that are primarily involved in the elimination process. Compounds bearing substituents other than protons that are attached to the carbon framework by a σ bond that can be polarized so that carbon becomes electron rich should undergo similar eliminations. A great many such processes are known, and in those instances that lend themselves to mechanistic study, it has been determined that the reactions are usually stereospecific.

Vicinal dibromides may be debrominated by treating them with certain reducing agents, including iodide ion and zinc. The stereochemical features of these reactions were examined using labeled 1,1,2-tribromocyclohexane prepared by *anti* addition of bromine-82 to bromocyclohexene. The radioactivity of ^{82}Br permits determination of the stereochemical course of the reaction, since unlabeled bromocyclohexene would be the exclusive product of *anti* elimination, while ^{82}Br-labeled bromocyclohexene would result from *syn* elimination.[82] Debromination with sodium iodide was found to be cleanly an *anti* elimination, while debromination with zinc gives mainly, but not entirely, *anti* elimination.



Reagent	*anti*	*syn*
Sodium iodide/MeOH	100%	0%
Zinc/EtOH	89%	11%

The iodide-induced reaction may proceed through a bridged intermediate as shown below:



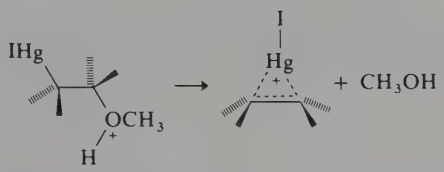
This mechanism is closely related to the reverse of the halogenation of alkenes.[83] The rate-determining transition state leading to the formation of the bridged intermediate requires an *anti* orientation of the two bromines, and is lowered in energy by nucleophilic attack by iodide ion at the bridging bromine. The stereochemical requirements in noncyclic systems are probably similar, as indicated by the fact that

82. C. L. Stevens and J. A. Valicenti, *J. Am. Chem. Soc.* **87**, 838 (1965).
83. C. S. T. Lee, I. M. Mathai, and S. I. Miller, *J. Am. Chem. Soc.* **92**, 4602 (1970).

meso-stilbene dibromide yields *trans*-stilbene, while *d,l*-stilbene dibromide gives mainly *cis*-stilbene under these conditions.[83]

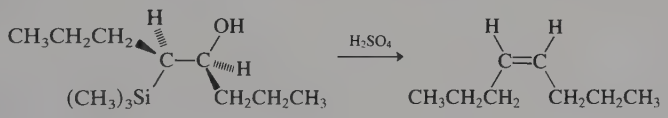
The zinc-induced debromination could proceed by formation of an organozinc intermediate, with the loss in stereospecificity occurring during the formation of the carbon–zinc bond. Similar nonstereospecific debromination has been observed with one-electron donors such as chromium(II) salts, and has been interpreted as resulting from a free-radical intermediate that precedes formation of the chromium–carbon bond.[84] The unstable organozinc and organochromium intermediates suggested are examples of systems that, according to the reasoning cited earlier, should be quite prone to eliminate. Systems of the type M–C–C–X in which M is a metal atom and X is a leaving group usually decompose, yielding olefins via *anti* transition states.

One of the most thoroughly studied of these reactions is acid-catalyzed deoxymercuration.[85] As an example of the great rapidity of this elimination, $CH_3CH(OH)CH_2HgI$ is converted to propylene under conditions of acid catalysis at a rate 10^{11} times faster than dehydration of isopropanol under the same conditions. Substantial bridging must occur in the transition state, since the enthalpy of activation for deoxymercuration of *trans*-2-methoxycyclohexylmercuric iodide is about 8 kcal/mol lower than for the *cis* isomer. The rate-determining step in the reaction may be represented as in the following equation:

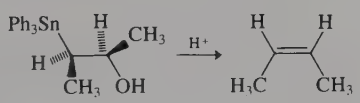


Attack on the intermediate mercurinium ion by some nucleophilic species yields the olefin to complete the elimination. This reaction mechanism is essentially the reverse of oxymercuration.

There are also important elimination processes involving organosilicon[86] and organotin[87] compounds. Treatment of β-hydroxyalkylsilanes or β-hydroxyalkylstannanes with acid results in stereospecific eliminations which are considerably more rapid than for compounds lacking the group IV substituent:



Ref. 87



Ref. 88

84. J. K. Kochi and D. M. Singleton, *J. Am. Chem. Soc.* **90**, 1582 (1968).
85. M. M. Kreevoy and F. R. Kowitt, *J. Am. Chem. Soc.* **82**, 739 (1960).
86. A. W. P. Jarvie, *Organomet. Chem. Rev. Sect. A*, **6**, 153 (1970).
87. P. F. Hudrlick and D. Peterson, *J. Am. Chem. Soc.* **97**, 1464(1975).
88. D. D. Davis and C. E. Gray, *J. Org. Chem.* **35**, 1303 (1970).

β-Halosilanes also undergo facile elimination when treated with reagents such as methoxide ion or fluoride ion which act as nucleophiles at the silicon substituent and promote β elimination[89]:

$$C_4H_9\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HSi(CH_3)_3 \xrightarrow{NaOCH_3} C_4H_9CH{=}CHBr \qquad \text{Ref. 89}$$

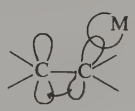
The conversion of β-hydroxyalkylsilanes to the corresponding methanesulfonates leads to rapid elimination[90]:

$$(CH_3)_3SiCH_2\underset{\displaystyle OH}{\underset{|}{C}}R_2 \xrightarrow{CH_3SO_2Cl} H_2C{=}CR_2$$

Tertiary triphenylstannylmethylcarbinols give terminal alkenes on heating.[91]

$$Ph_3SnCH_2\underset{\displaystyle OH}{\underset{|}{C}}R_2 \xrightarrow{\Delta} H_2C{=}CR_2 + Ph_3SnOH$$

Comparing the rates of acid-catalyzed β-elimination of compounds of the type $MCH_2CH_2OH_2$ yields the reactivity order for β substituents $IHg \sim Ph_3Pb \sim Ph_3Sn > Ph_3Si > H$. The relative rates are within one power of ten for the first three, but these are 10^6 greater than for Ph_3Si and 10^{11} greater than for a proton. These large rate accelerations point to a very significant facilitation of the β-elimination process with $Hg \sim R_3Pb \sim R_3Sn > R_3Si > H$.[88,92] Two factors are involved. One is bond energies which are in the order $Hg{-}C = 27 < Pb{-}C = 31 < Sn{-}C = 54 < Si{-}C = 60 < H{-}C = 96$. The transition states for elimination are also favored by the large stabilizing effect that group IV substituents have on generation of carbonium ion character at the β position. This stabilization has been pictured as an interaction in which a relatively electron-rich metal–carbon bond interacts with the vacant p orbital on a carbonium ion, either by hyperconjugation or by formation of a bridged species.



Supportive of the concept of a bridged structure is the fact that trimethylsilyl groups migrate during solvolysis of 2-bromoethyltrimethylsilane, as would be expected if a bridged intermediate were involved[93]:

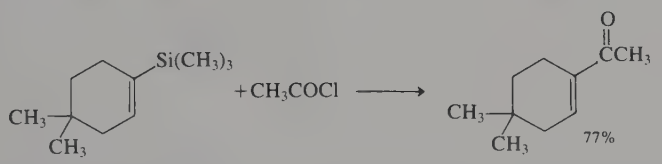
89. A. W. P. Jarvie, A. Holt, and J. Thompson, *J. Chem. Soc. B*, 852 (1969); B. Miller and G. J. McGarvey, *J. Org. Chem.* **43**, 4424 (1978).
90. F. A. Carey and J. R. Toler, *J. Org. Chem.* **41**, 1966 (1976).
91. T. Kauffmann, R. Kriegesmann, and A. Woltermann, *Angew. Chem. Int. Ed. Engl.* **16**, 862 (1977).
88. See p. 363.
92. D. D. Davis and H. M. Jacocks, III, *J. Organomet. Chem.* **206**, 33 (1981).
93. M. A. Cook, C. Eaborn, and D. R. M. Walton, *J. Organomet. Chem.* **24**, 301 (1970).

$$(CH_3)_3SiCH_2CD_2Br \rightleftharpoons (CH_3)_3SiCH_2CD_2^+ \rightleftharpoons {}^+CH_2CD_2Si(CH_3)_3$$
$$\downarrow Br^-$$
$$(CH_3)_3SiCH_2CD_2Br + BrCH_2CD_2Si(CH_3)_3$$

As a result of these facile elimination reactions, silicon and tin compounds are becoming very useful in synthetic chemistry. Vinylsilanes and vinylstannanes, when attacked by electrophilic species, often undergo elimination of the silyl or stannyl substituent:

$$E^+ + RCH{=}CHMR_3 \rightarrow R\overset{+}{C}H{-}\underset{\displaystyle E}{\underset{|}{C}}HMR_3 \rightarrow RCH{=}CHE$$

Both the regiochemistry of the electrophilic addition step and the β-elimination step are strongly directed by the MR_3 substituent and are both more rapid and more selective than would be the case without the substituent. The electrophilic replacement of a trimethylsilyl group by acetyl is an example:



Ref. 94

Further examples of these synthetically useful reactions can be found in Section 9.6 of Part B.

General References

Polar Addition Reactions

P. B. D. de la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, Second Edition, Elsevier, New York, 1982.
R. C. Fahey, in *Topics in Stereochemistry*, Vol. 3, E. L. Eliel and N. L. Allinger (eds.), Interscience, New York, 1968, pp. 237–342.
G. H. Schmid and D. G. Garrat, in *The Chemistry of Double-Bonded Functional Groups*, Part 2, Wiley, New York, 1977, Chap. 9.
G. H. Schmid, in *The Chemistry of the Carbon–Carbon Triple Bond*, Part 1, S. Patai (ed.), Wiley, New York, 1978, Chap. 8.

Elimination Reactions

W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley, New York, 1973.
N. A. LeBel, *Adv. Alicyclic Chem.* **3**, 195 (1971).
J. F. Bunnett, *Surv. Prog. Chem.* **5**, 53 (1969).
A. F. Cockerill and R. G. Harrison, *The Chemistry of Double-Bonded Functional Groups*, Part 1, S. Patai (ed.), Wiley, New York, 1977, Chap. 4.

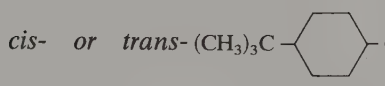
94. I. Fleming and A. Pearce, *J. Chem. Soc. Chem. Commun.* 633 (1975).

Problems

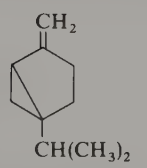
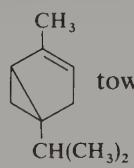
(*References for these problems will be found on page 703.*)

1. Which compound in each of the following pairs will react faster with the indicated reagent?

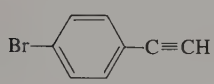
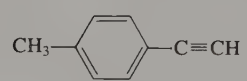
   (a) 1-hexene *or* *trans*-3-hexene with bromine in acetic acid

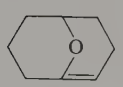
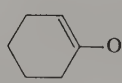
   (b) *cis*- *or* *trans*-  with potassium *tert*-butoxide in *tert*-butyl alcohol

   (c) 2-phenylpropene *or* 4-isopropenylbenzoic acid with sulfuric acid in water

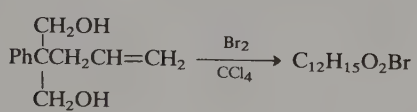
   (d)  *or*  toward acid-catalyzed hydration

   (e) $CH_3CH(CH_2)_3CH_3$ (with $SO_2C_6H_5$) *or* $CH_3CH(CH_2)_3CH_3$ (with $OSO_2C_6H_5$) with potassium *tert*-butoxide in *tert*-butyl alcohol

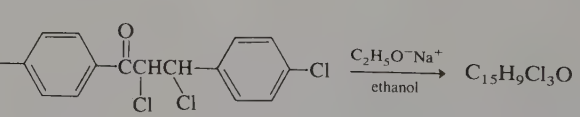
   (f)  *or*  with chlorine in acetic acid

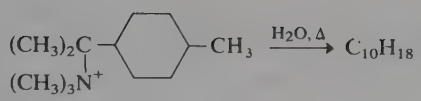
   (g)  *or*  toward acid-catalyzed hydration

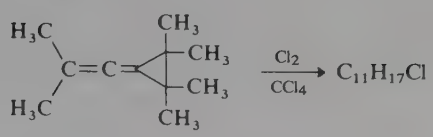
2. Predict the structure, including stereochemistry, of the product(s) of the following reactions. If more than one product is expected, indicate which will be the major product and which the minor product.

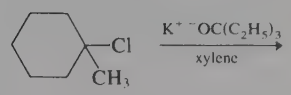
   (a) 

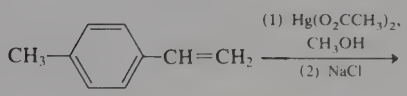
   (b) 

   (c) *erythro* 

(d) 

(e) 

(f) 

(g) 

(h) 

3. The reactions of the *cis* and *trans* isomers of 4-*t*-butylcyclohexyltrimethylammonium chloride with potassium *t*-butoxide in *t*-butanol have been compared. The *cis* isomer gives 90% 4-*t*-butylcyclohexene and 10% *N,N*-dimethyl-4-*t*-butylcyclohexylamine, while the *trans* isomer gives only the latter product in quantitative yield. Explain the different behavior of the two isomers.

4. For E2 eliminations in 2-phenylethyl systems with several different leaving groups, both the primary isotope effect and Hammett ρ values for the reactions are known. Deduce from these data the relationship between the location on the E2 transition state spectrum and the nature of the leaving group; i.e., deduce which system has the most E1-like transition state and which has the most E1cb-like. Explain your reasoning.

$$PhCH_2CH_2X \xrightarrow{C_2H_5O^-} PhCH{=}CH_2$$

X	k_H/k_D	ρ
Br	7.11	2.1
$OSO_2C_7H_7$	5.66	2.3
$^+S(CH_3)_2$	5.07	2.7
$^+N(CH_3)_3$	2.98	3.7

5. When 2-bromo-2-methylpentane is dissolved in DMF, the formation of 2-methyl-1-pentene (**A**) and 2-methyl-2-pentene (**B**) occurs. The ratio of olefins formed is not constant throughout the course of the reaction, however. Initially, the **A** : **B** ratio is about 1 : 1, but this drops to about 1 : 4 by the time the reaction is 25% complete, and then remains fairly constant. In a similar reaction, but

with NaBr present in excess, the **A** : **B** ratio is constant at about 1 : 5 throughout the reaction. Suggest an explanation for this phenomenon?

6. For the reactions given below, predict the effect on the rate of the isotopic substitution which is described. Explain the basis of your prediction.

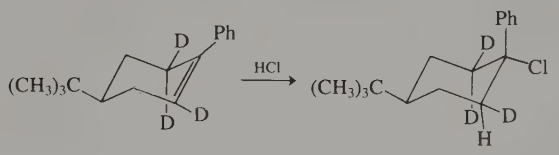
   (a) The effect on the rate of dehydration of 1,2-diphenylethanol of introduction of deuterium at C-2.
   (b) The effect on the rate of dehydration of 1,2-diphenylethanol of using D_2O–D_2SO_4 in place of H_2O–H_2SO_4 as the reaction medium.
   (c) The effect on the rate of bromination of styrene when deuterium is introduced on the α carbon.

7. Predict the effect on the 1-butene : *cis*-2-butene : *trans*-2-butene product ratio when the E2 elimination of *erythro*-3-deuterio-2-bromobutane is compared with 2-bromobutane. Which alkene(s) will increase in relative amount and which will decrease in relative amount? Explain the basis of your prediction.

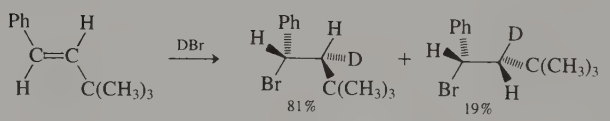
8. Arrange the following compounds in order of increasing rate of acid-catalyzed hydration: ethylene, 2-cyclopropylpropene, 2-methylpropene, propene, 1-cyclopropyl-1-methoxyethene. Explain the basis of your prediction.

9. Discuss the factors which are responsible for the stereochemistry observed for the following reactions.

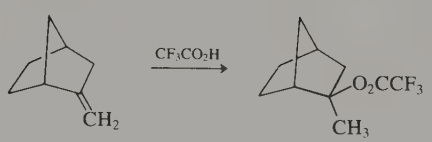
(a)



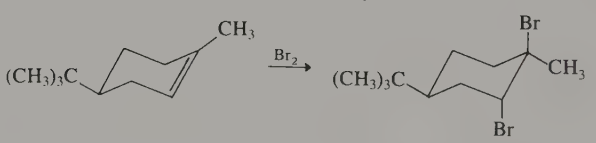
(b)



(c)

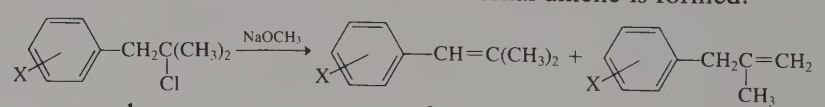


(d)



10. Explain the mechanistic basis of the following observations and discuss how the observation provides information about the reaction mechanism.

    (a) When substituted 1-aryl-2-methyl-2-propyl chlorides react with sodium methoxide, a mixture of terminal and internal alkene is formed:

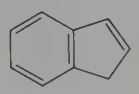


1 2 3

By using the product ratio, the overall rate can be disected into the individual rates for formation of **2** and **3**. These rates are found to be substituent dependent for formation of **2** ($\rho = +1.4$) but substituent independent for formation of **3** ($\rho = -0.1 \pm 0.1$). The reactions are both second order, first order in base, and first order in substrate.

(b) When 1,3-pentadiene reacts with DCl it forms more *E*-4-chloro-5-deuterio-2-pentene than *E*-4-chloro-1-deuterio-2-pentene.

(c) When indene (**4**) is brominated in carbon tetrachloride it gives some *syn* addition (~15%) but indenone (**5**) gives only *anti* addition under the same conditions.



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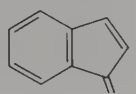


5

(d) The acid-catalyzed hydration of allene gives acetone, not allyl alcohol or propionaldehyde.

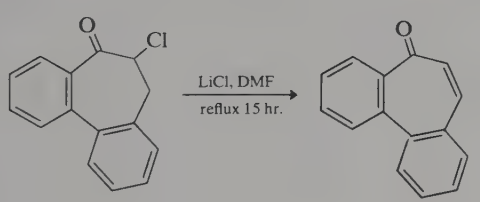
(e) In the addition of hydrogen chloride to cyclohexene in acetic acid, the ratio of cyclohexyl acetate to cyclohexyl chloride drops significantly when tetramethylammonium chloride is added in increasing concentration. This effect is not observed with styrene.

(f) The ρ values for base-catalyzed elimination of HF from a series of 1-aryl-2-fluoroethanes increases from the mono- to the di- and trifluoro compounds as shown by the data below:

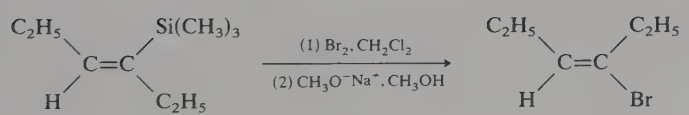
$ArCH_2CF_3$	$ArCH_2CHF_2$	$ArCH_2CH_2F$
$\rho = +4.04$	$\rho = +3.56$	$\rho = +3.24$

11. Suggest reasonable mechanisms for each of the following reactions:

(a)

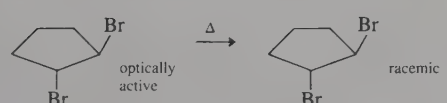


(b)



(c) *threo*-5-trimethylsilyl-4-octanol $\xrightarrow[CH_3CO_2H]{NaO_2CCH_3}$ *cis*-4-octene

(d)



12. The Hammett correlation of the acid-catalyzed dehydration of 1,2-diarylethanols has been studied.

$$\mathrm{ArCHCH_2Ar' \xrightarrow{H^+} ArCH{=}CHAr'}$$
$$\mathrm{\quad\ OH}$$

The equation that correlates the data resulting from substitution in the Ar and Ar′ rings is

$$\log k = -3.78(\sigma^+_{Ar} + 0.23\sigma_{Ar'}) - 3.18$$

Give a rationalization for the form of this correlation equation. What information does it give regarding involvement of the Ar′ ring in the rate-determining step?

13. The addition of hydrogen chloride to olefins in nitromethane follows the rate expression

$$\text{Rate} = k[\mathrm{HCl}]^2[\text{alkene}]$$

Two other features of the reaction that have been established include the following: (1) When DCl is used instead of HCl, unreacted olefin recovered by stopping the reaction at 50% completion contains no deuterium; (2) added chloride salts ($R_4N^+Cl^-$) decrease the reaction rate, but other salts ($R_4N^+ClO_4^-$) do not. Write a mechanism for this reaction that is in accord with the data given.

14. In the bromination of styrene, a $\rho\sigma^+$ plot is noticeably curved. If the extremes of the curves are taken to represent straight lines, the curve can be resolved into two Hammett relationships with $\rho = -2.8$ for electron-attracting substituents and $\rho = -4.4$ for electron-releasing substituents. When the corresponding β-methylstyrenes are examined a similarly curved $\sigma\rho$ plot is obtained. Furthermore, the stereospecificity of the reaction in the case of the β-methylstyrenes varies with the aryl substituents. The reaction is a stereospecific *anti* addition for strongly electron-attracting substituents but becomes only weakly stereoselective for electron-releasing substituents, e.g., 63% *anti*, 37% *syn*, for *p*-methoxy. Discuss the possible mechanistic basis for the Hammett plot curvature and its relationship to the stereochemical results.

15. The second-order rate constants for hydration and the kinetic solvent isotope effect for hydration of several 2-substituted 1,3-butadienes are given below. Discuss the information these data provide about the hydration mechanism.

$$\mathrm{CH_2{=}\overset{R}{\overset{|}{C}}{-}CH{=}CH_2 \xrightarrow[H_2O]{H^+} CH_3\overset{R}{\overset{|}{C}}CH{=}CH_2 + CH_3\overset{R}{\overset{|}{C}}{=}CHCH_2OH}$$
$$\mathrm{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH}$$

R	k_2 (M^{-1} s^{-1}) (25°C)	k_{H^+/D^+}
	1.22×10^{-2}	1.2
CH_3	3.19×10^{-5}	1.8
Cl	2.01×10^{-8}	1.4
H	3.96×10^{-8}	1.8
C_2H_5O	6×10^{1}	—

16. The reaction of both *E* and *Z*-2-butene with acetic acid to give 2-butyl acetate can be catalyzed by various strong acids. Using DBr, DCl, and CH_3SO_3D, in CH_3CO_2D, it was possible to demonstrate that the reaction proceeded largely with *anti* addition (84% ± 2%). If the reaction was stopped short of completion, there was no interconversion of *Z*-2-butene with either *E*-2-butene or 1-butene. When CF_3SO_3D was used as the catalyst, several features of the reaction changed.

    (1) the recovered butene showed small amounts of conversion to 1-butene and partial isomerization to the stereoisomeric 2-butene.
    (2) the recovered 2-butene contains small amounts of deuterium
    (3) the stereoselectivity is somewhat reduced (60%–70% *anti* addition).

    How do you account for the changes which occur when CF_3SO_3D is used as a catalyst, as compared with the other acids?

7

Carbanions and Other Nucleophilic Carbon Species

Introduction

This chapter is concerned with carbanions, which are the conjugate bases (in the Brønsted sense) of organic molecules that are formed by deprotonation of a carbon atom. Carbanions may vary widely in stability, depending on the ability of substituent groups to stabilize negative charge. In the absence of substituents that are effective at delocalizing the charge, proton abstraction from a C–H bond is very difficult.

Carbanions are very useful in synthesis, since formation of new carbon–carbon bonds often requires a nucleophilic carbon species. There has therefore been a good deal of study on methods of generating carbanionic species and on understanding substituent effects on stability and reactivity.

7.1. Acidity of Hydrocarbons

In the discussion of the relative acidity of carboxylic acids in Chapter 1, the thermodynamic acidity, expressed as the acid dissociation constant, was taken as the measure of acidity. It is fairly straightforward to measure dissociation constants of such acids in aqueous media by measurement of pH with a glass electrode (pH meter). Measurement of the relative acidity of most carbon acids is more difficult. Because most are very weak acids, very strong bases are required to cause deprotonation. Water and alcohols are far more acidic than most hydrocarbons, and are

unsuitable solvents for generation of hydrocarbon anions. Any strong base would deprotonate the solvent, rather than the hydrocarbon. For this reason, very weakly acidic solvents such as dimethyl sulfoxide and cyclohexylamine are used in the preparation of strongly basic carbanions. A further feature of dimethyl sulfoxide is its high dielectric constant (45), which facilitates separation of ion pairs so that the equilibrium data obtained refer to the free ions, rather than to ion aggregates.

The basicity of a base–solvent system may be specified by a basicity constant H_-, analogous to the Hammett acidity function H_0. The value of H_- corresponds essentially to the pH of strongly basic nonaqueous solutions. The larger the value of H_-, the greater the proton-abstracting ability of the medium. Use of a series of overlapping indicators permits assignment of H_- values to base–solvent systems, and allows pK's to be determined over a range of 0–30 pK units. The indicators employed include substituted anilines and arylmethanes, which have significantly different electronic (UV-VIS) spectra in their neutral and anionic forms. The assumptions and procedures used to assign H_- are similar to those involved in establishing H_0 scales, as discussed in Section 4.6. Table 7.1 presents H_- values for some representative solvent–base systems.

The acidity of a hydrocarbon can be determined in an analogous way.[1] If the electronic spectra of the neutral and anionic forms are sufficiently different, the concentrations of each can be determined directly, and the equilibrium constant for

$$RH + B^- \rightleftharpoons R^- + BH$$

is related to pK by the equation

$$pK_{RH} = H_- + \log \frac{[RH]}{[R^-]}$$

A measurement of the ratio $[RH]:[R^-]$ at a known H_- yields the pK. If, as is frequently the case, the electronic spectrum of the hydrocarbon and its anion are not sufficiently different, one of the indicators used to determine the basicity of the medium is used and its spectrum monitored. The equilibrium established between the indicator and hydrocarbon in the basic medium

$$RH + In^- \rightleftharpoons R^- + HIn$$

then provides a way to relate concentrations that are not directly measured, [RH] and $[R^-]$, to quantities that are, [HIn] and $[In^-]$.

When the acidities of hydrocarbons are discussed in terms of the relative stabilities of neutral and anionic forms, particularly with respect to the extent of electron delocalization in the anion, it follows that equilibrium measures of acidity are required. We have just seen how such data may be obtained, but in many instances, it is not possible to obtain equilibrium data. In such cases, it may be possible to determine which proton in a molecule is abstracted most easily, or to

1. D. Dolman and R. Stewart, *Can. J. Chem.* **45**, 911 (1967); E. C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.* **87**, 382 (1965); K. Bowden and R. Stewart, *Tetrahedron* **21**, 261 (1965).

Table 7.1. Values of H_- for Some Representative Solvent–Base Systems[a]

Solution	H_-[b]
5 *M* KOH	15.5
10 *M* KOH	17.0
15 *M* KOH	18.5
0.01 *M* NaOMe in 1:1 DMSO–MeOH	15.0
0.01 *M* NaOMe in 10:1 DMSO–MeOH	18.0
0.01 *M* NaOEt in 20:1 DMSO–EtOH	21.0

a. Values are rounded to the nearer 0.5 pH unit; this is typical of the range of disagreement using different indicator series.
b. Selected values from J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York, 1973, Chap. 6.

determine whether a certain molecule is deprotonated faster or slower than a reference molecule, i.e., to determine its *kinetic acidity.* In the presence of a potential source of deuterons, the rate of incorporation of deuterium into an organic molecule is a measure of the rate of carbanion formation[2]:

$$R\text{–}H + B^- \rightleftharpoons R^- + BH$$

$$R^- + S\text{–}D \rightleftharpoons R\text{–}D + S^-$$

$$S^- + BH \rightleftharpoons SH + B^-$$

It has been found that there is often a correlation between the rate of proton abstraction (kinetic acidity) and the thermodynamic stability of the carbanion (thermodynamic acidity). Because of this relationship, kinetic measurements can be used to construct orders of hydrocarbon acidities. These kinetic measurements have the advantage of not requiring the presence of a measurable concentration of the carbanion at any time; instead, the relative ease of carbanion formation is judged from the rate at which exchange occurs. This method is therefore applicable to very weak acids, for which no suitable base will generate a measurable carbanion concentration.

The kinetic method of determining relative acidity suffers from one serious complication, however. This complication has to do with the fate of the ion pair that is formed immediately on abstraction of the proton.[3] If the ion pair separates and diffuses into the solution rapidly, so that each deprotonation results in exchange, the exchange data are an accurate measure of the rate of deprotonation. Under many conditions of solvent and base, however, an ion pair may return to reactants at a rate

2. A. I. Shatenshtein, *Adv. Phys. Org. Chem.* **1**, 155 (1963).
3. W. T. Ford, E. W. Graham, and D. J. Cram, *J. Am. Chem. Soc.* **89**, 4661 (1967); D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.* **83**, 3688 (1961).

exceeding protonation of the carbanion by the solvent. This phenomenon is called *internal return*:

$$R_3C\text{–}H + M^+B^- \underset{\text{internal return}}{\overset{\text{ionization}}{\rightleftharpoons}} [R_3C^-M^+ + BH] \xrightarrow{\text{separation}} R_3C^- + M^+ + BH$$

$$\downarrow \text{exchange, S–D}$$

$$R_3CD + S^-$$

When internal return occurs, a deprotonation has occurred but escaped detection because exchange has not resulted. One experimental test for the occurrence of internal return is racemization at chiral carbanionic sites that is not accompanied by exchange. Even racemization of chiral centers cannot be regarded as an absolute test of deprotonation rates since, under some conditions, hydrogen–deuterium exchange has been shown to occur with retention of configuration. Because of these uncertainties dealing with the fate of ion pairs, it is important that if exchange data are to be used for estimating equilibrium acidity, a linear relationship between the two properties be established for the type of compound in question under the experimental conditions to be used.

In general, the extent of ion pairing is primarily a function of the ability of the solvent to solvate the carbanion and other ionic species present in solution. Ion pairing is generally very significant in nonpolar solvents such as ethers. In dipolar aprotic solvents, especially dimethyl sulfoxide, ion pairing is much less likely to be significant.[4]

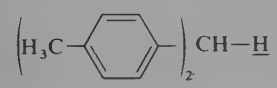
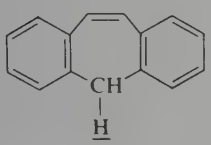
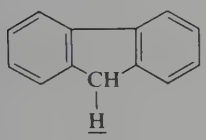
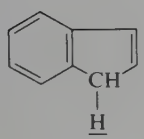
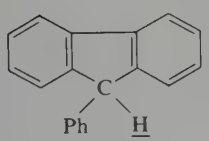
An extensive series of hydrocarbons has been studied in cyclohexylamine, using cesium cyclohexylamide as base. For many, spectroscopic methods were used to determine the extent of deprotonation of two hydrocarbons, and thus to establish relative acidity.[5] For other hydrocarbons, e.g., toluene, the acidity was derived by kinetic measurements. It was also shown that the rate of tritium exchange for a series of related hydrocarbons is linearly related to the measured equilibrium acidities of the same hydrocarbons. While the rate of tritium exchange for toluene can be measured, the equilibrium acidity has not been, but the linear correlation permits calculation of the equilibrium acidity from the rate data.[6] Representative values of some hydrocarbons with pK values ranging from 16 to 40 are given in Table 7.2.

Table 7.2 also lists some hydrocarbon acidities determined in DMSO. Because of the difference in solvent media, it is not expected that these values would be identical. The same trends in relative acidity are generally noted, however, among these hydrocarbons which are all of similar structural type. On the other hand, compounds that are quite different in structural type may show substantial changes in relative acidity when the data refer to different solvents.

Some relative acidities in Table 7.2 can be easily rationalized. The order of decreasing acidity $Ph_3CH > Ph_2CH_2 > PhCH_3$, for example, reflects the ability of

4. E. M. Arnett, T. C. Moriarity, L. E. Small, J. P. Rudolph, and R. P. Quirk, *J. Am. Chem. Soc.* **95**, 1492 (1973); T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.* **88**, 307 (1966).
5. A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *J. Am. Chem. Soc.* **95**, 4248 (1973); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.* **89**, 63 (1967).
6. A. Streitwieser, Jr., M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.* **95**, 4257 (1973).

Table 7.2. Acidities of Some Hydrocarbons

	Hydrocarbon	p*K*	
		(Cyclohexylamine)[a]	(DMSO)[b]
1	$PhCH_2-\underline{H}$	41.2	
2		35.1	
3	$(Ph)_2CH-\underline{H}$	33.4	32.3
4	$(Ph)_3C-\underline{H}$	31.4	30.6
5		31.2	
6		22.7	22.6
7		19.9	20.1
8		18.5	17.9
9		16.6[c]	18.1

a. From A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *J. Am. Chem. Soc.* **95**, 4248 (1973); A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.* **89**, 63 (1967); A. Streitwieser, Jr., and F. Guibe, *J. Am. Chem. Soc.* **100**, 4532 (1978).

b. From C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.* **90**, 2821 (1968); F. G. Bordwell, J. E. Bartmess, G. E. Drucker, Z. Margolin, and W. S. Matthews, *J. Am. Chem. Soc.* **97**, 3226 (1975); W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 7006 (1975); F. G. Bordwell, G. E. Drucker, and H. E. Fried, *J. Org. Chem.* **46**, 632 (1981).

c. A. Streitwieser, Jr., and L. L. Nebenzahl, *J. Am. Chem. Soc.* **98**, 2188 (1976); in water, the pK_a of cyclopentadiene is 16.0.

each successive phenyl group to further delocalize the negative charge on carbon, and thereby stabilize the carbanion. The much greater acidity of fluorene relative to dibenzocycloheptatriene (entries 5 and 6) reflects the aromatic stabilization of the cyclopentadienide ring in the anion of fluorene. Cyclopentadiene itself is similar to alcohols in acidity. This relatively high acidity reflects the aromatic stabilization of the conjugate base.

Allylic conjugation provides some carbanion stabilization, and values of 43 (in cyclohexylamine)[7] and 47–48 (in THF–HMPA)[8] have been determined for propene. On the basis of exchange rates with cesium cyclohexylamide, cyclohexene and cycloheptene have been found to have pK values of about 45 in cyclohexylamine.[9] The hydrogens on the sp^2 carbons in benzene and ethylene would be expected to be more acidic than the hydrogens in saturated hydrocarbons. A pK of 43 has been estimated for benzene on the basis of extrapolation from a series of fluorobenzenes.[10] Electrochemical measurements have been used to establish a lower limit of about 46 for the pK of ethylene.[8]

For saturated hydrocarbons exchange is too slow and reference points are so uncertain that direct determination of pK values by exchange measurements are not feasible. The most useful approach to obtain pK data for such hydrocarbons involves making a measurement of the electrochemical potential for the reaction:

$$R\cdot + e^- \rightleftharpoons R^-$$

From this value and known C–H bond dissociation energies, pK values can be calculated. The electrochemical measurements can be made on halides or alkyllithium compounds. This type of approach has some significant uncertainties but nevertheless can provide at least a semiquantitative estimate of acidities of very weakly acidic hydrocarbons. The pK for isobutane obtained in this way is 71.[11] The appropriate electrochemical measurements cannot be made directly for methane but an extrapolation from toluene and diphenylmethane leads to the range of 52–62 for the pK of methane.[8]

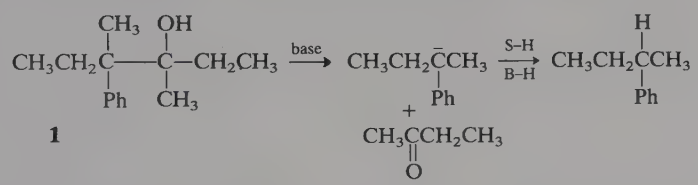
The acetylenes as a group are among the most acidic of the hydrocarbons. For example, in DMSO, phenylacetylene is found to have a pK near 26.5.[12] In cyclohexylamine, the value is given as 23.2.[13] The relatively high acidity of acetylenes is associated with the large degree of s character in the C–H bond. The s character is 50%, as opposed to 25% in sp^3-bonds. The electrons in orbitals with high s-character experience decreased shielding from the nuclear charge. The carbon is therefore effectively more electronegative, as viewed from the proton sharing an sp hybrid orbital, and hydrogens on sp carbons exhibit exceptional acidity. This

7. D. W. Boerth and A. Streitwieser, Jr., *J. Am. Chem. Soc.* **103**, 6443 (1981).
8. B. Jaun, J. Schwarz, and R. Breslow, *J. Am. Chem. Soc.* **102**, 5741 (1980).
9. A. Streitwieser, Jr., and D. W. Boerth, *J. Am. Chem. Soc.* **100**, 755 (1978).
10. A. Stretiwieser, Jr., P. J. Scannon, and H. M. Niemeyer, *J. Am. Chem. Soc.* **94**, 7936 (1972).
11. R. Breslow and R. Goodin, *J. Am. Chem. Soc.* **98**, 6076 (1976).
12. F. G. Bordwell and W. S. Matthews, *J. Am. Chem. Soc.* **96**, 1214 (1974).
13. A. Streitwieser, Jr., and D. M. E. Reuben, *J. Am. Chem. Soc.* **93**, 1794 (1971).

same effect accounts for the relatively high acidity of the hydrogens on cyclopropane rings[14] which have increased *s* character in the C–H bonds.

Knowledge of the structure of carbanions is important to understanding the stereochemistry of their reactions. Theoretical calculations at the *ab initio* level indicate a pyramidal geometry at the carbanionic carbon in methyl anion and ethyl anion. The optimum H–C–H angle in these two carbanions is calculated to be 97–100°. An interesting effect is observed in that the proton affinity of methyl anion decreases in a regular manner as the H–C–H angle is decreased.[15] This increase in acidity with decreasing internuclear angle has a parallel in small-ring compounds, in which the acidity of the hydrogens is substantially greater than in compounds having tetrahedral geometry at carbon. Pyramidal geometry can also be predicted on the basis of qualitative considerations of the orbital occupied by the unshared electron pair. In a planar carbanion, the lone pair would occupy a *p* orbital. In a pyramidal geometry, the orbital would have substantial *s* character. Since the electron pair would be of lower energy in an orbital with some *s* character, it would be predicted that a pyramidal geometry would be favored.

The stereochemistry observed in hydrogen-exchange reactions of carbanions is very dependent on the conditions under which the anion is formed and trapped by proton transfer. The dependence on solvent, counter-ion, and base is the result of the importance of ion-pairing effects. The base-catalyzed cleavage of **1** is noteworthy. The anion of **1** cleaves at elevated temperature to 2-butanone and 2-phenyl-2-butyl anion, which under the conditions of the reaction abstracts a proton from solvent. Use of optically active **1** allows the stereochemical features of the anion to be probed by measuring the enantiomeric purity of the 2-phenylbutane product.



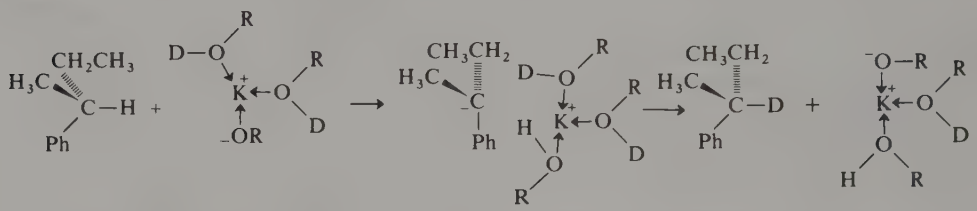
1

Retention of configuration was observed in solvents of low dielectric constant, while increasing amounts of inversion occurred as the proton-donating ability and dielectric constant of the solvent increased. Cleavage of **1** with potassium *tert*-butoxide in benzene ($\varepsilon = 2$) gave 2-phenylbutane with 93% net retention of configuration. The stereochemical course was changed to 48% net inversion of configuration when potassium hydroxide in ethylene glycol ($\varepsilon = 35$) was used. In dimethyl sulfoxide ($\varepsilon = 45$), completely racemic 2-phenylbutane is formed on cleavage of **1** with potassium *tert*-butoxide.[16] The retention in benzene presumably reflects a short lifetime for the carbanion in a tight ion pair. Under these conditions the

14. A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *J. Am. Chem. Soc.* **91**, 529 (1969).
15. A. Streitwieser, Jr., and P. H. Owens, *Tetrahedron Lett.*, 5221 (1973); A. Streitwieser, Jr., P. H. Owens, R. A. Wolf, and J. E. Williams, Jr., *J. Am. Chem. Soc.* **96**, 5448 (1974); E. D. Jemmis, V. Buss, P. v. R. Schleyer, and L. C. Allen, *J. Am. Chem. Soc.* **98**, 6483 (1976).
16. D. J. Cram, A. Langemann, J. Allinger, and K. R. Kopecky, *J. Am. Chem. Soc.* **81**, 5740 (1959).

carbanion may not become symmetrically solvated before proton transfer from either the protonated base or the ketone occurs. The solvent benzene would not be an effective proton donor. In ethylene glycol the solvent provides an additional proton source and since net inversion is observed, the protonation must be occurring on an unsymmetrically solvated species which favors back-side protonation. The racemization that is observed in dimethyl sulfoxide indicates that the carbanion has a sufficient lifetime to become symmetrically solvated.

The stereochemistry of hydrogen–deuterium exchange at the chiral carbon in 2-phenylbutane has also been studied. When potassium *t*-butoxide is used, the exchange occurs with retention of configuration in *t*-butanol, but with racemization in DMSO.[17] The retention of configuration is visualized as occurring through an ion pair in which a solvent molecule coordinated to the metal ion acts as the proton donor:



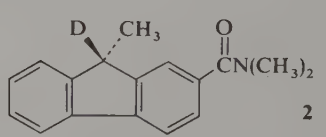
In DMSO, symmetrical solvation is achieved prior to protonation, and complete racemization is observed.

Ion-pair effects have also been implicated in hydrogen–deuterium exchange reactions proceeding through highly delocalized fluorenyl anions. The stereochemical course of exchange of deuterium for protium in the chiral fluorene derivative **2** can be expressed as k_e/k_α, where k_e is the rate constant for exchange and k_α is the rate constant for racemization. The limiting values are

100% retention, $k_e/k_\alpha = \infty$

100% racemization, $k_e/k_\alpha = 1$

100% inversion, $k_e/k_\alpha = 0.5$



2

When ammonia is used as the base, $k_e/k_\alpha = 50$ in *tert*-butanol (high retention) and 1.0 (complete racemization) in DMSO.[18] The high degree of retention observed in *tert*-butanol is explained most simply by postulating that abstraction of deuterium by ammonia to give $\overset{+}{D}NH_3$ is followed by transfer of protium back to the same face of the anion at a rate which is faster than reorientation of the ion pair. There is little doubt that the carbanion is planar in this case, and the stereochemical course is governed by ion pair effects. Again, in the highly polar solvent DMSO, symmetrically solvated ion pairs are dominant, and complete racemization occurs with every act of exchange.

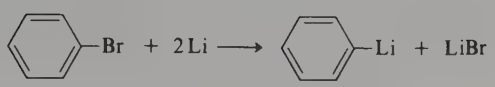
The organometallic compounds are an extremely important group of nucleophilic carbon species. Organolithium and organomagnesium compounds

17. D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Am. Chem. Soc.* **83**, 3688 (1961).
18. D. J. Cram and L. Gosser, *J. Am. Chem. Soc.* **86**, 2950, 5445, 5457 (1964).

(Grignard reagents) are of primary importance. Because of the very weak acidity of most hydrocarbons, the simple organolithium compounds, e.g., methyllithium, butyllithium, phenyllithium, are usually not prepared by proton-transfer reactions. Instead, the most general preparative methods starts with the corresponding halogen compound:

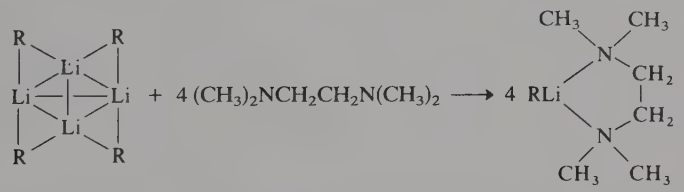
$$CH_3I + 2\,Li \longrightarrow CH_3Li + LiI$$

$$CH_3(CH_2)_3Br + 2\,Li \longrightarrow CH_3(CH_2)_3Li + LiBr$$



There are other preparative methods but we will defer consideration of these until Part B, Chapter 6.

Although these compounds have some covalent character, organolithium compounds react in a manner analogous to what would be expected of the carbanions derived from simple hydrocarbons. Organolithium compounds are rapidly destroyed by any molecule with the more acidic –OH, –NH, or –SH groups with formation of the hydrocarbon. All the organolithium compounds derived from saturated hydrocarbons are extremely strong bases. Accurate pK values are not known, but would range upward from the estimate of ~52–62 for methane. The order of basicity $CH_3Li < CH_3(CH_2)_3Li < (CH_3)_3CLi$ would be predicted on the basis of the electron-releasing effect of alkyl substituents, and appears to be verified by increasing reactivity in proton-abstraction reactions in the order $CH_3Li < CH_3(CH_2)_3Li < (CH_3)_3CLi$. Phenyl-, methyl, *n*-butyl-, and *t*-butyllithium are certainly all stronger bases than the anions of the hydrocarbons listed in Table 7.2. Unlike proton transfers involving oxygen, nitrogen, or sulfur atoms, proton transfer between carbon atoms is usually not a fast reaction. Thus, even though *t*-butyllithium is thermodynamically capable of deprotonating toluene, for example, the reaction is quite slow in a hydrocarbon solvent medium. In part, the reason is that the organolithium compounds exist as tetramers, hexamers and higher aggregates in hydrocarbon and ether solvents.[19] The reactivity of the organolithium compounds is increased by adding molecules capable of solvating the organometallic species. Tetramethylethylenediamine has been commonly used for organolithium systems. This tertiary amine can chelate lithium. These complexes generally are able to effect deprotonation at accelerated rates.[20]



19. G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.* **102**, 3345 (1980).
20. G. G. Eberhardt and W. A. Butte, *J. Org. Chem.* **29**, 2928 (1964); R. West and P. C. Jones, *J. Am. Chem. Soc.* **90**, 2656 (1968).

Another reason for the relative slowness of abstraction of protons from carbon acids is the partial covalent character of the carbon–lithium bond. Alkali metal salts of anions in which the charge is on oxygen or nitrogen are ordinarily ionic, so that only solvation changes are necessary for the anion to act as a reactive base. If the electrons associated with the negatively charged carbon in an organometallic compound are involved in a covalent bond, some activation energy must be expended to break the bond before it can act effectively as a base. This relative sluggishness of organometallic compounds as bases permits important reactions in which the organometallic species acts as a nucleophile in preference to functioning as a strong base. The addition of organolithium and organomagnesium compounds to carbonyl groups in aldehydes, ketones, and esters is an important example. As will be seen in the next section, most carbonyl compounds are much more acidic than hydrocarbons. Nevertheless, in most cases, the proton-transfer reaction is slower than nucleophilic attack at the carbonyl group. It is this feature that permits the very extensive use of organometallic compounds in organic synthesis. These reactions will be discussed specifically in Part B, Chapter 6.

7.2. Carbanions Stabilized by Functional Groups

Functional groups that permit the negative charge of a carbanion to be delocalized to a more electronegative atom such as oxygen cause very large increases in the acidity of C–H bonds. Among the functional groups that exert a strong stabilizing effect on carbanions are carbonyl, nitro, sulfonyl, and cyano groups.

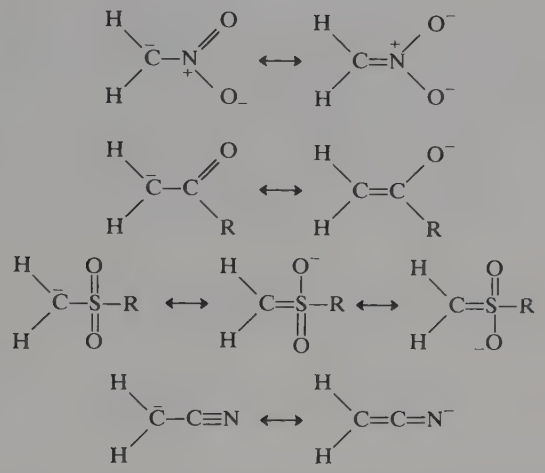
Table 7.3. Equilibrium Acidities of Substituted Methanes in Dimethyl Sulfoxide[a]

Compound	pK
CH_3NO_2	17.2
CH_3COPh	24.7
CH_3COCH_3	26.5
CH_3SO_2Ph	29.0
$CH_3CO_2C_2H_5$	30.5[b]
$CH_3SO_2CH_3$	31.1
CH_3CN	31.3
$CH_3CON(C_2H_5)_2$	34.5[b]

a. Except where noted otherwise, data are from W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 7006 (1975).

b. Accurate to ±0.5, F. G. Bordwell and H. E. Fried, *J. Org. Chem.* **46**, 4327 (1981).

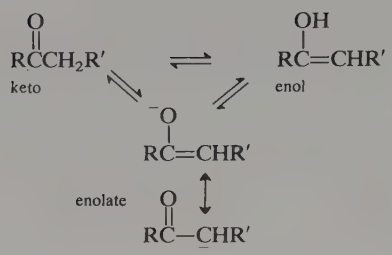
Perhaps the data that provide the best basis for comparison between these groups in terms of internal consistency are those of Bordwell and coworkers.[21] These workers determined relative equilibrium acidities of the substituted methanes with reference to aromatic hydrocarbon indicators in DMSO. The data are given in Table 7.3. The ordering $NO_2 > C{=}O > SO_2 \sim CN$ is established by these data. Both inductive and resonance effects are involved in the ability of these functional groups to stabilize the negative charge.



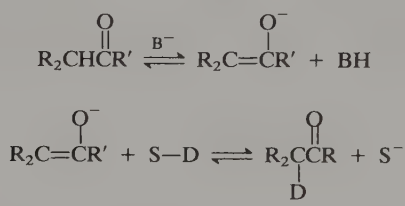
The presence of two such groups further stabilizes the negative charge. Pentane-2,4-dione, for example, has a pK around 9. Most β-diketones are sufficiently acidic that the derived carbanions can be generated in hydroxylic solvents such as water or alcohols, which have pK values in the 15–20 range. This ability to generate carbon anions stabilized by electron-attracting groups is very important from a synthetic point of view, and the synthetic aspects of the chemistry of carbanions will be discussed in Part B, Chapters 1 and 2. Stronger bases are required for compounds that have a single stabilizing carbonyl functional group. Alkali metal salts of ammonia or amines or sodium hydride are sufficiently strong bases to form carbanions from most ketones, aldehydes, and esters. The organometallic reagents, especially the organolithium compounds, are extremely strong bases, and can also be used to generate carbanions in some cases. The anion of DMSO is also a popular strong base for use in synthetic procedures. It is prepared by reaction of sodium hydride with DMSO.

Carbanions derived from carbonyl compounds are often referred to as *enolate* anions. This name is derived from the name for the enol tautomer of carbonyl compounds. The resonance-stabilized enolate anion is the conjugate base of both the keto and the enol forms of carbonyl compounds:

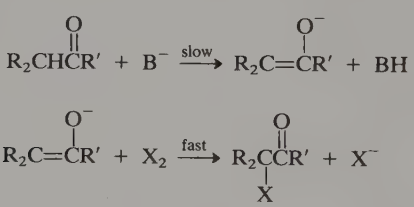
21. F. G. Bordwell and W. S. Matthews, *J. Am. Chem. Soc.* **96**, 1216 (1974); W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum,, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 7006 (1975).



There have been numerous studies of the rates of deprotonation of carbonyl compounds. These data are of interest not only because they define the relationship between thermodynamic and kinetic acidity in these compounds, but also because they are necessary for defining mechanisms of reactions in which enolates are involved as intermediates. Rates of enolate formation can be measured conveniently by following isotopic exchange using either deuterium or tritium:



Another technique is to measure the rate of halogenation of the carbonyl compound. Ketones and aldehydes in their carbonyl forms do not react rapidly with the halogens but the enolate is rapidly attacked. The rate of halogenation is therefore a measure of



the rate of deprotonation. This method has been used extensively, although its reliability has been questioned.[22]

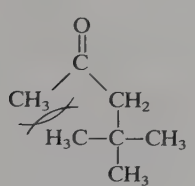
Table 7.4 gives data on the rates of deuteration of some simple alkyl ketones. From these data, the order of reactivity toward deprotonation is $CH_3 > RCH_2 > R_2CH$. Steric hindrance to the approach of the base is probably the major factor in establishing this order. The importance of steric effects can be seen by comparing the CH_2 group in 2-butanone with the more-hindered CH_2 group in 4,4-dimethyl-2-pentanone. The two added methyl groups on the adjacent carbon decrease the rate of proton removal by a factor of about 100. The rather slow rate of exchange at the CH_3 group of 4,4-dimethyl-2-pentanone may also reflect a steric factor arising from the bulky nature of the neopentyl group:

22. C. Rappe, *Acta Chem. Scand.* **21**, 1823 (1967).

Table 7.4. Relative Rates of Base-Catalyzed Deuteration of Some Ketones[a]

Ketone	Relative rate
$CH_3CCH_2-\underline{H}$ (O)	100
CH_3CCHCH_3 (O; $\underline{H}$)	41.5
$\underline{H}-CH_2CCH_2CH_3$ (O)	45
$CH_3CC(CH_3)_2$ (O; $\underline{H}$)	<0.1
$\underline{H}-CH_2CCH(CH_3)_2$ (O)	45
$CH_3CCHC(CH_3)_3$ (O; $\underline{H}$)	0.45
$\underline{H}-CH_2CCH_2C(CH_3)_3$ (O)	5.1

a. In aqueous dioxane with sodium carbonate as base. The data of C. Rappe and W. H. Sachs, *J. Org. Chem.* **32**, 4127 (1967), given on a per-group basis, have been converted to a per-hydrogen basis.

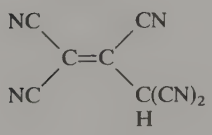
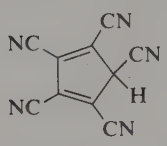


Solvation may also play a role. If bulky groups prohibit effective solvation of the developing negative charge, the rate of proton abstraction will be reduced.

Structural effects on the rates of deprotonation of ketones have also been studied by adding a very strong base, such as triphenylmethyllithium or lithium diisopropylamide, to solutions of unsymmetrical ketones and then determining the composition of the resulting enolate mixture. These data also show that proton abstraction is most rapid at the less-hindered C–H group adjacent to the carbonyl group.[23]

23. H. O. House and B. M. Trost, *J. Org. Chem.* **30**, 1341 (1965).

Table 7.5. Acidities of Some Cyano Compounds[a]

Compound	pK
CH_3CN	>25.0
$NCCH_2CN$	11.2
$(NC)_3CH$	−5.0
	<−8.5
	<−11.0

a. Selected from Tables 5.1 and 5.2 in J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, 1973, pp. 64, 65.

When enolates are allowed to reach equilibrium, the composition of the mixture is usually more closely balanced than under kinetically controlled conditions. In general, the more highly substituted enolate is the preferred isomer, but if the alkyl groups are sufficiently branched as to interfere with the solvation of the enolate, there can be exceptions. Torsional and ring strain effects also come into play with cyclic ketones. The identity of the metal cation and the solvent, which are the major factors in determining the extent of ion pairing, also affect the position of the equilibrium.

The effect of alkyl groups on the kinetic and thermodynamic acidity of nitroalkanes shows opposing trends. Although alkyl groups retard proton abstraction, they stabilize the nitronate anion.[24] These opposing trends can be traced to the fact that

	Kinetic acidity k (M^{-1} min^{-1})	Thermodynamic acidity pK
CH_3NO_2	238	10.2
$CH_3CH_2NO_2$	39.1	8.5
$(CH_3)_2CHNO_2$	2.08	7.7

the transition state for proton abstraction is not very similar to the nitronate product.[25] The alkyl groups have a strong stabilizing effect on the nitronate ion, but

24. D. Turnbull and S. Maron, *J. Am. Chem. Soc.* **65**, 212 (1943), G. W. Wheland and J. Farr, *J. Am. Chem. Soc.* **65**, 1433 (1943).
25. F. G. Bordwell, W. J. Boyle, Jr., and K. C. Yee, *J. Am. Chem. Soc.* **92**, 5926 (1970).

Table 7.6. Acidities of Some Compounds with Sulfur and Phosphorus Substituents

Compound	p*K* (DMSO)	Ref.
$PhCH_2SPh$	30.8	*a*
$PhSO_2CH_3$	29.0	*b*
$PhSO_2CH_2Ph$	23.4	*b*
$PhCH(SPh)_2$	23.0	*a*
$PhSO_2CH_2SPh$	20.3	*b*
$PhSO_2CH_2PPh_2$	20.2	*b*
$H_5C_2O_2CCH_2\overset{+}{P}Ph_3$	9.2[c]	*d*
$PhCOCH_2\overset{+}{P}Ph_3$	6.0[c]	*d*

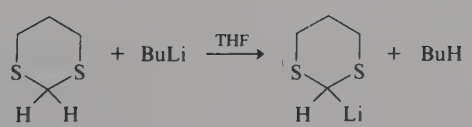
a. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.* **42**, 326 (1977).
b. F. G. Bordwell, W. S. Matthews, and N. R. Vanier, *J. Am. Chem. Soc.* **97**, 442 (1975).
c. In methanol.
d. A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.* **85**, 2790 (1963).

this stabilization is not very significant in the transition state for deprotonation. Instead, steric effects, with alkyl groups retarding deprotonation, are dominant in the transition state.

The cyano group is also effective at stabilizing negative charge on carbon. It has been possible to synthesize a number of hydrocarbon derivatives that are very highly substituted with cyano groups. Some of these compounds are so acidic that they are, like the strong mineral acids, completely dissociated in water. Table 7.5 gives some representative values, ranging from acetonitrile to the exceedingly strong acid pentacyanocyclopentadiene.

Second-row elements, particularly phosphorus and sulfur, are known to stabilize adjacent carbanions. The p*K*'s of some pertinent compounds are given in Table 7.6.

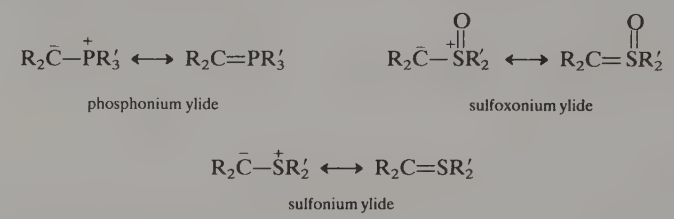
The conjugate base of 1,3-dithiane has proven very valuable in synthetic applications as a nucleophilic carbonyl equivalent (Part B, Chapter 11), and is quantitatively generated by metalation with *n*-butyllithium:



The p*K* of 1,3-dithiane has been determined to be 31 (in cyclohexylamine). There are several factors which might contribute to the anion-stabilizing effect of sulfur substituents. Inductive effects might contribute but cannot be the dominant factor since oxygen substituents do not have a comparable stabilizing effect. Delocalization can be described as involving *d* orbitals on sulfur or the σ^* orbital

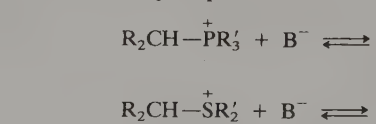
of the adjacent C–S bond.[26] Molecular orbital calculations favor the latter interpretation. Whatever the structural basis is, there is no question that thio substituents enhance the acidity of hydrogens on the adjacent carbon atoms. On hydrocarbons the phenylthio group increases the pK by at least 15 pK units. The stabilizing effect is from 5–10 pK units in compounds with other electron-accepting groups.[27]

Another important group of nucleophilic carbon species are the phosphorus and sulfur ylides. These species have achieved great synthetic importance, and their reactivity will be considered in some detail in Part B, Chapters 1 and 2. Here, we will discuss the structures of a few of the best known ylides. *Ylide* is the name given to molecules for which one of the contributing structures has opposite charges on adjacent atoms when the atoms have octets of electrons. Since we are dealing with nucleophilic carbon species, our interest is in ylides with negative charge on carbon. The three groups of primary importance are phosphonium ylides, sulfoxonium ylides, and sulfonium ylides.



The question of which resonance structure is the principal contributor has been a point of considerable discussion. Since the nonpolar *ylene* resonance structures have ten electrons at the phosphorus or sulfur atom, these structures imply participation of *d* orbitals on the heteroatoms. Structural studies indicate that the dipolar ylide structure is probably the main contributor.[28] Molecular orbital calculations confirm the stabilizing effect that the second row elements phosphorus and sulfur have in ylides, relative to the corresponding first-row elements N and O[29].

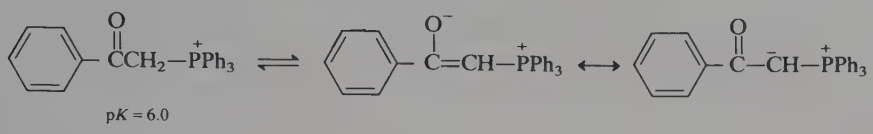
The ylides are formed by deprotonation of the corresponding "onium salts."



The stability of the resulting neutral species is increased by substituent groups that

26. W. T. Borden, E. R. Davidson, N. H. Andersen, A. D. Deniston, and N. D. Epiotis, *J. Am. Chem. Soc.* **100**, 1604 (1978); A. Streitwieser, Jr., and S. P. Ewing, *J. Am. Chem. Soc.* **97**, 190 (1975); A. Streitwieser, Jr., and J. E. Williams, Jr., *J. Am. Chem. Soc.* **97**, 191 (1975); N. D. Epiotis, R. L. Yates, F. Bernardi, and S. Wolfe, *J. Am. Chem. Soc.* **98**, 5435 (1976), J.-M. Lehn and G. Wipff, *J. Am. Chem. Soc.* **98**, 7498 (1976).
27. F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. Van Der Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.* **42**, 326 (1977). F. G. Bordwell, M. Van Der Puy, and N. R. Vanier, *J. Org. Chem.* **41**, 1885 (1976).
28. H. Schmidbaur, W. Buchner, and D. Scheutzow, *Chem. Ber.* **106**, 1251 (1973).
29. F. Bernardi, H. B. Schlegel, H.-H. Whangbo, and S. Wolfe, *J. Am. Chem. Soc.* **99**, 5633 (1977).

can help to stabilize the resulting electron-rich carbon center. Phosphonium salts with acylmethyl substituents, for example, are quite acidic. A series of aroylmethyl phosphonium salts have pK values of 4–7, with the precise value depending on substituents on the aromatic ring[30]:



pK = 6.0

In the absence of the carbonyl or similar stabilizing group, the onium salts are much less acidic. Strong bases such as amide ion or the anion of DMSO are required to deprotonate alkylphosphonium salts:

$$RCH_2\overset{+}{P}R'_3 \xrightarrow[\text{base}]{\text{strong}} R\bar{C}H-\overset{+}{P}R_3$$

Similar structural considerations apply to the sulfoxonium and sulfonium ylides. These ylides are formed by deprotonation of the corresponding positively charged sulfur-containing cations.

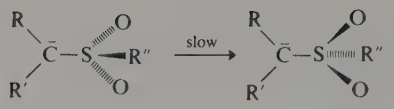
$$\underset{\text{sulfoxonium salt}}{R'_2\overset{O}{\overset{\|}{\overset{+}{S}}}-CH_2R} \xrightarrow{\text{base}} \underset{\text{sulfoxonium ylide}}{R'_2\overset{O}{\overset{\|}{\overset{+}{S}}}-\bar{C}HR}$$

$$\underset{\text{sulfonium salt}}{R'_2\overset{+}{S}CH_2R} \xrightarrow{\text{base}} \underset{\text{sulfonium ylide}}{R_2\overset{+}{S}-\bar{C}HR}$$

The additional electronegative oxygen atom in the sulfoxonium salts stabilizes these ylides considerably, relative to the sulfonium ylides.[31]

Carbanions stabilized by resonance interaction with carbonyl, nitro, or cyano groups would be expected to adopt a planar geometry to permit maximum delocalization of the negative charge. This expectation is confirmed by studies that have compared the rate of racemization at chiral centers adjacent to a carbonyl group with the rate of isotopic exchange at the same site. In general, the rates are identical, implying that the carbanion has a planar geometry.[32] A quite different stereochemical pattern is observed in hydrogen–deuterium exchange reactions involving carbanions stabilized by sulfinyl or sulfonyl substituents. A sulfone substituent, for example, in 2-octyl phenyl sulfone imparts a pronounced tendency for H–D exchange with high retention of configuration (k_e/k_α = 73–1200 using KOt-Bu–t-BuOD).[33] This tendency is not believed to be the result of a rigid pyramidal carbanion; rather, it is attributed to slow rotation about the RCR′–SO_2R″ bond:

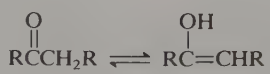
30. S. Fliszár, R. F. Hudson, and G. Salvadori, *Helv. Chim. Acta* **46**, 1580 (1963).
31. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).
32. D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York, 1965, pp. 85–105.
33. D. J. Cram, D. A. Scott, and W. D. Nielsen, *J. Am. Chem. Soc.* **83**, 3696 (1961).



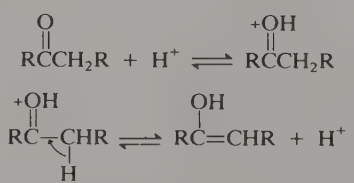
Such slow rotation, coupled with a large preference for proton transfer to the carbon from the side flanked by the two oxygen atoms, accounts for the observed retention of configuration.[34] Similar exchange experiments with 2-octyl phenyl sulfoxide indicate that the sulfinyl group has much less of an effect on the stereochemistry of an adjacent carbanion site, since $k_e/k_\alpha \approx 2$.[33]

7.3. Enols and Enamines

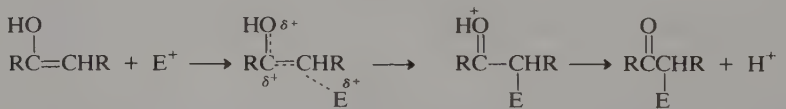
The study of the chemistry of carbonyl compounds has shown that they can act as carbon nucleophiles in the presence of acid catalysts as well as with bases. The nucleophilic reactivity of carbonyl compounds in acidic solution is due to the presence of the enol tautomer:



Enolization in acidic solution is catalyzed by O protonation. Subsequent deprotonation at carbon gives the enol:



Like simple alkenes, enols are nucleophilic by virtue of their π electrons. Enols are much more reactive than simple alkenes, however, because the hydroxyl group can participate as an electron donor during the reaction process:

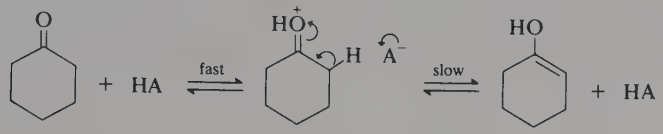


Enols are not as reactive as enolate anions. This lower reactivity simply reflects the presence of the additional proton in the enol, which decreases the nucleophilicity of the enol relative to the enolate.

34. E. J. Corey, H. König, and T. H. Lowry, *Tetrahedron Lett.*, 515 (1962); F. G. Bordwell, D. D. Phillips, and J. M. Williams, Jr., *J. Am. Chem. Soc.* **90**, 426 (1968); F. G. Bordwell and E. Doomes, *J. Org. Chem.* **39**, 2526 (1975).

33. See p. 389.

A number of studies of the acid-catalyzed mechanisms of enolization have been done. We can consider cyclohexanone as a typical case.[35] The reaction is catalyzed by various carboxylic acids and substituted ammonium salts. The effectiveness of the various acids as catalysts correlates with their pK_a values. When plotted according to the Brønsted catalysis law, the value of the slope α is 0.74. When deuterium or tritium is introduced in the α position, there is a marked decrease in the rate of acid-catalyzed enolization: $k_H/k_D \approx 5$. This isotope effect indicates that the C–H bond cleavage is part of the rate-determining step. The generally accepted mechanism for acid-catalyzed enolization pictures the rate-determining step as deprotonation of the protonated ketone:



Rates of enolization have usually been measured in one of two ways. One method involves measuring the rate of halogenation of the ketone. In the presence of a sufficient concentration of bromine or iodine, halogenation is much faster than enolization or its reverse, and therefore serves to measure the rate of enolization:

$$\underset{\text{O}}{\underset{\|}{\text{RCCH}_2\text{R}}} \underset{k_{-1}}{\overset{k_1}{\underset{\text{HA}}{\rightleftharpoons}}} \underset{\text{OH}}{\underset{|}{\text{RC=CHR}}} \xrightarrow[\text{fast}]{\overset{k_2}{\underset{\text{X}_2}{}}} \underset{\text{X}}{\underset{|}{\underset{\text{O}}{\underset{\|}{\text{RCCHR}}}}} + \text{HX}$$

$$k_2 \gg k_1, k_{-1}$$

It is also possible to measure the rate of enolization by isotopic exchange. Much of the early work was done using the halogenation technique, but because proton magnetic resonance spectroscopy provides a very convenient method for following hydrogen–deuterium exchange, this is now the preferred method. Data for several ketones are given in Table 7.7.

A point of contrast with the data for base-catalyzed removal of a proton is the tendency for acid-catalyzed enolization to result in the preferential formation of the more substituted enol. For 2-butanone, the ratio of exchange at CH_2 to that at CH_3 is 4.2, after taking into account the statistical correction for the number of hydrogens. The preference for acid-catalyzed enolization to give the more-substituted enol is usually rationalized in terms of the stabilizing effect that alkyl groups have on carbon–carbon double bonds. To the extent that the transition state resembles product,[36] alkyl groups would be expected to stabilize the more-branched transition state. There is an opposing steric effect that appears to be significant for 4,4-dimethyl-2-pentanone, in which the methylene group that is flanked by a *t*-butyl group is less reactive than the methyl group. The overall range of reactivity is substantially smaller than in base-catalyzed enolate formation, however.

35. G. E. Lienhard and T.-C. Wang, *J. Am. Chem. Soc.* **91**, 1146 (1969).
36. C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.* **80**, 5885 (1958).

Table 7.7. Relative Rates of Acid-Catalyzed Enolization for Some Ketones[a]

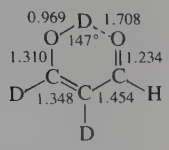
Ketone	Relative rate
$CH_3\overset{\overset{O}{\|}}{C}CH_2-\underline{H}$	100
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underline{H}}{\underset{\|}{C}}HCH_3$	220
$\underline{H}-CH_2\overset{\overset{O}{\|}}{C}CH_2CH_3$	76
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underline{H}}{\underset{\|}{C}}HCH_2CH_3$	171
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underline{H}}{\underset{\|}{C}}(CH_3)_2$	195
$\underline{H}-CH_2\overset{\overset{O}{\|}}{C}CH(CH_3)_2$	80
$CH_3\overset{\overset{O}{\|}}{C}\underset{\underline{H}}{\underset{\|}{C}}HC(CH_3)_3$	46
$\underline{H}-CH_2\overset{\overset{O}{\|}}{C}CH_2C(CH_3)_3$	105

a. In D_2O–dioxane with DCl catalyst. The data of C. Rappe and W. H. Sachs, *J. Org. Chem.* **32**, 3700 (1967), given on a per-group basis, have been converted to a per-hydrogen basis.

The amount of enol present in equilibrium with a carbonyl group is a function of the substituent groups. In the case of compounds containing a single ketone, aldehyde, or ester function, there is very little of the enol present at equilibrium. When two such groups are close to one another in a molecule, however, particularly if they are separated by a single carbon atom, a major amount of enol may be present.

The enol forms of β-diketones and β-ketoesters are stabilized by intramolecular hydrogen bonding and conjugation of the carbon–carbon double bond with the other carbonyl group. For malonaldehyde, for example, a microwave spectroscopy study on a deuterated analog has provided the bond length data which are shown below.[37] An electron diffraction study of 2,4-pentanedione has been completed.[38] These results demonstrated an intramolecularly hydrogen-bonded enol structure. In this case the data pertain to the time-averaged structure resulting from rapid intramolecular transfer of the proton between the two hydrogen-bonded oxygens.

37. S. L. Baughcum, R. W. Duerst, W. F. Rowe, Z. Smith, and E. B. Wilson, *J. Am. Chem. Soc.* **103**, 6296 (1981).
38. A. H. Lowrey, C. George, P. D'Antonio, and J. Karle, *J. Am. Chem. Soc.* **93**, 6399 (1971).



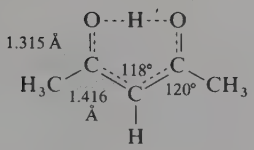
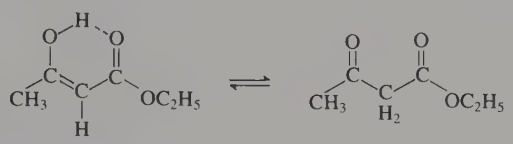
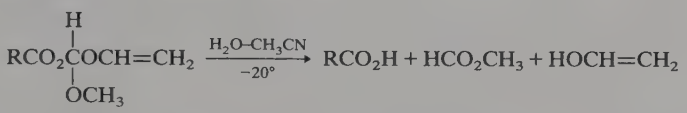


Table 7.8 gives some data on the amount of enol present at equilibrium for some representative compounds. The precise percent of enol present at equilibrium is solvent dependent. For ethyl acetoacetate, for example, the amount of enol is higher in nonpolar solvents (15%–30%) such as carbon tetrachloride and benzene than in polar solvents such as water and acetone (5% in acetone, 1% in water).[39] The strong intramolecular hydrogen bond minimizes the molecular dipole by reducing the negative charge on the oxygen of the carbonyl group. In more polar solvents this stabilization is less important, and in protic solvents such as water hydrogen bonding to solvent is dominant.



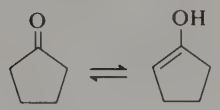
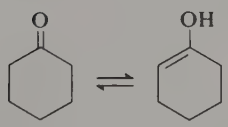
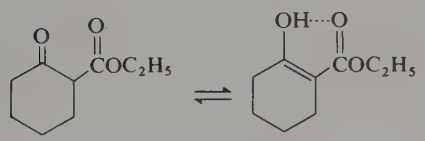
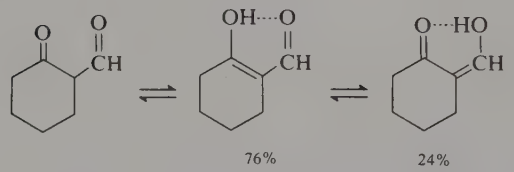
Enols of simple ketones can be generated in high concentration as metastable species by special techniques. Vinyl alcohol, the enol of acetaldehyde, can be generated by hydrolysis of any of several ortho ester derivatives in which the group RCO_2 is acetic acid or a chlorinated acetic acid.



The enol has been observed by NMR and at −20°C has a half-life of several hours. At +20°C the half-life is only 10 min. The presence of base causes rapid isomerization to acetaldehyde via the enolate.[40] Solvents have a significant effect on the lifetimes of such unstable enols. Solvents such as dimethylformamide and dimethyl sulfoxide, which are known from other studies to slow rates of proton exchange by hydrogen bonding, increase the lifetime of unstable enols.[41] Solutions of the unstable enols of simple ketones and aldehydes can be generated in water by addition of a solution of the enolate ion to water.[42] The initial protonation takes place on oxygen, generating the enol which is then ketonized at a rate which depends on the solution pH. The ketonization exhibits both acid and base catalysis. There are some enols which have much longer lifetimes than those of simple aldehydes and ketones, especially among hindered enols of aromatic ketones. Both the conjugation with the aromatic ring and steric effects retard the rate of ketonization in these compounds.[43]

39. K. D. Grande and S. M. Rosenfeld, *J. Org. Chem.* **45**, 1626 (1980).
40. B. Capon, D. S. Rycroft, T. W. Watson, and C. Zucco, *J. Am. Chem. Soc.* **103**, 1761 (1981).
41. E. A. Schmidt and H. M. R. Hoffmann, *J. Am. Chem. Soc.* **94**, 7832 (1972).
42. Y. Chiang, A. J. Kresge, and P. A. Walsh, *J. Am. Chem. Soc.* **104**, 6122 (1982).
43. For a review of metastable enols, see H. Hart, *Chem. Rev.* **79**, 515 (1979).

Table 7.8. Equilibrium Constants for Enolization of Some Organic Compounds[a]

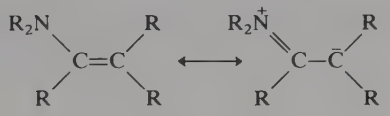
Compound	K = enol/keto	Ref.
$CH_3CH{=}O \rightleftharpoons CH_2{=}CHOH$	10^{-5}	*b*
$CH_3\overset{O}{\overset{\|}{C}}CH_3 \rightleftharpoons H_2C{=}\overset{OH}{\overset{\|}{C}}CH_3$	8×10^{-8} 3×10^{-9}	*b* *c*
$CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3 \rightleftharpoons CH_3CH{=}\overset{OH}{\overset{\|}{C}}CH_2CH_3$	2×10^{-8}	*b, c*
	1×10^{-7} 1×10^{-8}	*b* *c*
	5×10^{-6} 2.5×10^{-7}	*b* *c*
$PhC(O)CH_3 \rightleftharpoons PhC(OH){=}CH_2$	2×10^{-7} 8×10^{-9}	*b* *c*
$CH_3C(O)CH_2C(O)OC_2H_5 \rightleftharpoons CH_3C(OH){=}CHC(O)OC_2H_5$	9×10^{-2}	*d*
$CH_3C(O)CH_2C(O)CH_3 \rightleftharpoons CH_3C(OH){=}CHC(O)CH_3$	3.0	*d*
	1.6	*d*
 76% 24%	>50	*e*

a. In water at 25°C except for references *d* and *e*. Reference *d* refers to the pure substance. Reference *e* refers to CCl_4 solution.

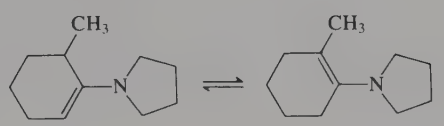
b. J. P. Guthrie and P. A. Cullimore, *Can. J. Chem.* **57**, 240 (1979); J. P. Guthrie, *Can. J. Chem.* **57**, 797 (1979).
c. J. E. Dubois, M. El-Alaoui, and J. Toullec, *J. Am. Chem. Soc.* **103**, 5393 (1981).
d. A. Gero, *J. Org. Chem.* **19**, 1960 (1954).
e. E. W. Garbisch, *J. Am. Chem. Soc.* **85**, 1696 (1963).

The accessibility of enolates and enols in, respectively, basic and acidic solutions of carbonyl compounds makes possible a wide range of reactions that depend on the nucleophilicity of such species. The reactions of enolates as nucleophiles in S_N2-type processes will be discussed in Part B, Chapter 1. Enols and enolates can also act as nucleophiles toward carbonyl centers. These reactions are a major topic in Part B, Chapter 2. Both these classes of reactions are of fundamental importance in the construction of carbon frameworks in organic synthesis.

Amino substituents on a carbon–carbon double bond also enhance the nucleophilicity at the β carbon—even more than enols. Such compounds are called *enamines*. Their preparation and reactions will be discussed in Chapter 8 and in Part B, Chapter 1.

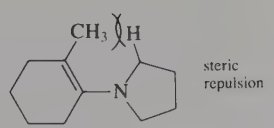


An interesting and useful property of enamines of cyclohexanones is the fact that there is a substantial preference for the less substituted isomer to be preferred. This tendency is especially pronounced for enamines derived from cyclic secondary amines.



strongly favored

This can be traced to a strain effect called $A^{1,3}$ or allylic strain. In order to accommodate conjugate interaction between the nitrogen lone pair and the carbon–carbon double bond the nitrogen substituents must be coplanar with the double bond. This creates a significant steric repulsion when the enamine is disubstituted at the α carbon.



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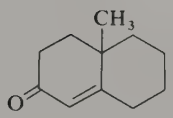
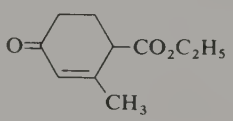
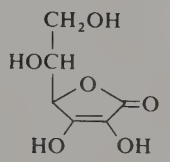
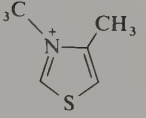
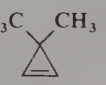
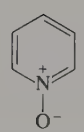
D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York, 1965.
J. R. Jones, *The Ionization of Carbon Acids*, Academic Press, New York, 1973.
E. M. Kaiser and D. W. Slocum, in *Organic Reactive Intermediates*, S. P. McManus (ed.), Academic Press, New York, 1973, Chap. 5.

M. Szwarc, *Ions and Ion Pairs in Organic Reactions*, Wiley, New York, 1972.
H. F. Ebel, *Die Acidität der CH-Säuren*, George Thieme Verlag, Stuttgart, 1969.
E. Buncel, *Carbanions: Mechanistic and Isotopic Aspects*, Elsevier, Amsterdam, 1975.
E. Buncel and T. Durst, *Comprehensive Carbanion Chemistry*, Elsevier, New York, 1981.
J. Toullec, *Adv. Phys. Org. Chem.* **18**, 1 (1982).

Problems

(*References for these problems will be found on page 704.*)

1. Predict the order of increasing thermodynamic acidity in each series of compounds:
   (a) benzene, 1,4-cyclohexadiene, cyclopentadiene, cyclohexane
   (b) CH_3CN, CH_3NO_2, $CH_3\overset{O}{\overset{\|}{C}}CH_3$, $CH_3\overset{O}{\overset{\|}{S}}CH_3$, $CH_3\overset{O}{\overset{\|}{S}}CH_3$ (with $\|O$)
   (c) $PhCH_3$, $PhSiH_3$, $Ph\overset{O}{\overset{\|}{S}}CH_3$ (with $\|O$), $PhCH_2\overset{O}{\overset{\|}{S}}CH_3$ (with $\|O$)
   (d) $CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$, $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$, $Ph\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$, $Ph\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CF_3$
   (e) 9-(*m*-chlorophenyl)fluorene, 9-(*p*-methoxyphenyl)fluorene, 9-phenylfluorene, 9-(*m*-methoxyphenyl)fluorene, 9-(*p*-methylphenyl)fluorene.

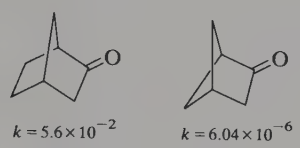
2. Indicate which proton is the most acidic in each of the following molecules. Explain your reasoning.
   (a) $H_3CC{\equiv}CH$
   (b) 
   (c) 
   (d) 
   (e) 
   (f) 
   (g) $CH_3\overset{O}{\overset{\|}{S}}CH_2SCH_3$ (with $\|O$)
   (h) 
   (i) $(CH_3)_2CH\overset{+}{N}(O^-)=NOCH_3$
   (j) 

3. (a) Exchange rates indicate the hydrocarbon cubane to be much more acidic than cyclobutane, and even more acidic than cyclopropane. What structural rationalization can you offer?

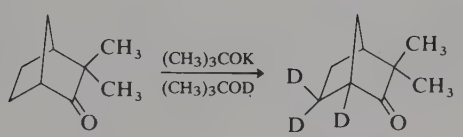

cubane

(b) Although the C–H bonds of cyclopropane are more acidic than those of propane, it has been found that H–D exchange of phenyl cyclopropyl ketone occurs much less readily than that of phenyl isopropyl ketone, using NaOD in aqueous dimethylformamide. Suggest an explanation.

4. (a) The relative rates of hydroxide ion-catalyzed deuterium exchange at C-3 (the CH_2 α to the C=O) has been measured for the bicyclic ketones shown below. Analyze the factors that would be involved in the relative ease of exchange in these compounds.



(b) Treatment of (+)-camphenilone with potassium *t*-butoxide in *tert*-butyl alcohol-O-*d* at 185°C results in H–D exchange accompanied by racemization at an equal rate. Prolonged reaction periods result in the introduction of three deuterium atoms. Suggest a mechanism to account for these observations.



5. Using data from Tables 7.1 (p. 375) and 7.2 (p. 377), estimate the extent of deprotonation for each hydrocarbon–solvent–base combination. Discuss the uncertainties involved in your calculations.
   (a) indene by 0.01 *M* $NaOCH_3$ in 1:1 DMSO–CH_3OH
   (b) fluorene by 0.01 *M* $NaOC_2H_5$ in 20:1 DMSO–C_2H_5OH
   (c) triphenylmethane by 5 *M* $KOCH_3$ in CH_3OH

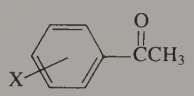
6. The rates of abstraction of axial and equatorial protons from 4-*t*-butylcyclohexanone have been measured by an NMR technique. The rate of removal of an axial proton is 5.5 times faster than for an equatorial proton. What explanation can you offer for this difference?

7. The following table gives exchange rates in methanolic sodium methoxide for a number of hydrocarbons and equilibrium acidities for some. Determine whether

there is a correlation between kinetic and thermodynamic acidity in this series of compounds. If so, predict the thermodynamic acidity of the hydrocarbons for which no values are listed.

Compound	k (exchange) (M^{-1} sec^{-1})	pK
9-Phenylfluorene	173×10^{-4}	18.5
Indene	50×10^{-4}	19.9
3,4-Benzfluorene	90.3×10^{-4}	
1,2-Benzfluorene	31.9×10^{-4}	20.3
2,3-Benzfluorene	2.15×10^{-4}	
Fluorene	3.95×10^{-4}	22.7

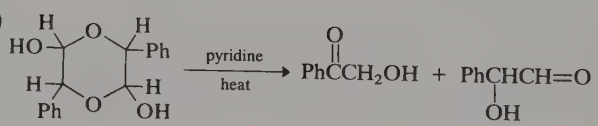
8. The acidity of various substituted acetophenones has been measured in DMSO. Would you expect the ρ value for a Hammett correlation to be positive or negative? Would you expect the best correlation with σ, σ^+, or σ^-? Justify your prediction, considering each of the σ values explicitly. The data are given below. Check your prediction by plotting the pK versus σ, σ^+, and σ^-.



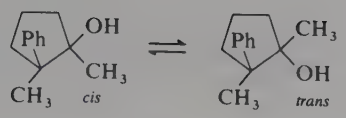
X	pK_{DMSO}	X	pK_{DMSO}	X	pK_{DMSO}
p-$(CH_3)_2$N	27.48	H	24.70	m-Cl	23.18
p-CH_3	25.70	p-F	24.45	m-Br	23.19
m-$(CH_3)_2$N	25.19	m-CH_3O	24.52	m-CF_3	22.76
p-CH_3	25.19	p-Br	23.81	p-CF_3	22.69
m-CH_3	24.95	p-Cl	23.78	p-CN	22.04
p-Ph	24.51	m-F	23.45		

9. Suggest mechanisms for each of the following reactions:

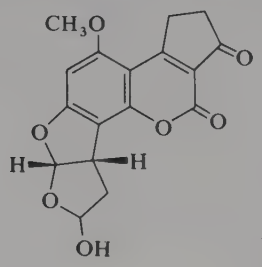
(a) $Ph_3CCPh \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4,\ pyridine} Ph_3CH + PhCH_2OH$

(b) 

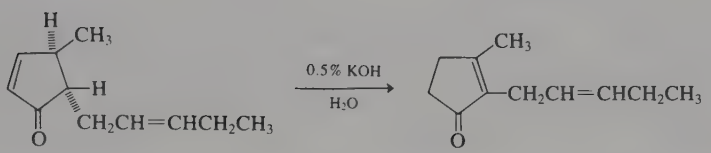
(c) Treatment of either diastereomer shown below with 0.025 M $Na^+\ ^-CH_2SOCH_3$ in DMSO produces the same equilibrium mixture of 72% *trans* and 28% *cis*.



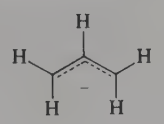
(d) The hemiacetal of aflatoxin B_1 racemizes readily in basic solution.



(e)



10. It is possible to measure the barrier to rotation of the allyl anion in THF solution by observing coalescence of the terminal protons in the NMR spectrum.



M = Li, 10.7 kcal/mol
M = K, 16.7 kcal/mol
M = Cs, 18.0 kcal/mol

As shown by the data, the barrier depends upon the metal ion. Explain the basis for the metal ion dependence. Data on the rotational barrier of the allyl cation (~18 kcal/mol) and allyl radical (≥17 kcal/mol) indicate that the barrier for rotation in all three species is similar. According to simple Hückel MO theory, should the barrier to rotation in the allyl system increase, decrease, or remain the same as electrons are added to the π system in the progression $CH_2{=}CHCH_2^+$, $CH_2{=}CHCH_2^{\cdot}$, and $CH_2{=}CHCH_2^-$?

11. In some solvents, it can be shown that the equilibrium k_1/k_{-1} is fast relative to the process governed by k_2:

$$R_3C{-}H + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [R_3C^- + H{-}B]$$

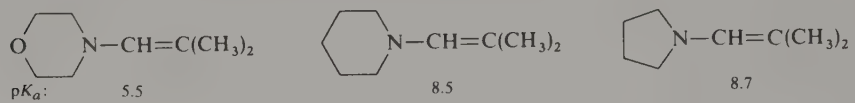
$$[R_3C^- + H{-}B] + D{-}B \xrightarrow{k_2} [R_3C^- + D{-}B] + H{-}B$$

$$[R_3C^- + D{-}B] \longrightarrow R_3CD + B^-$$

This is referred to as *internal return*; i.e., the base returns the proton to the carbanion faster than exchange of the protonated base with other solvent molecules. If internal return is important under a given set of conditions, how

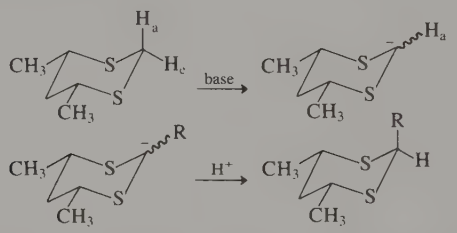
would the correlation between kinetics of exchange and equilibrium acidity be affected? How could the occurrence of internal return be detected experimentally?

12. The pK_a values of the conjugate acids of several enamines derived from isobutyraldehyde have been reported. Rationalize the observed variation with the structure of the amino constituent.



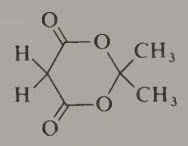
13. Metal ions, in particular Zn^{2+}, Ni^{2+}, and Cu^{2+}, enhance the rate of general base-catalyzed enolization of 2-acetylpyridine by several orders of magnitude. Account for this effect.

14. The C-2 equatorial proton is selectively removed when 1,3-dithianes are deprotonated. Furthermore, if the resulting carbanion is protonated, there is a strong preference for equatorial protonation, even if this leads to a less stable axial orientation for the 2-substituent.



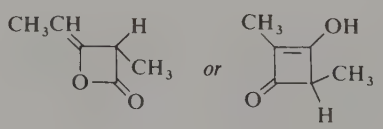
Discuss the relevance of these observations to the structure of sulfur-stabilized carbanions and rationalize your conclusion about the structure of the carbanions in MO terms.

15. The cyclic isopropylidene derivative of malonic acid (**A**), which is known as "Meldrum's acid" is much more acidic (about 7 powers of 10 in K_a) than diethyl malonate. Offer an explanation.

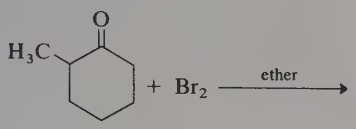


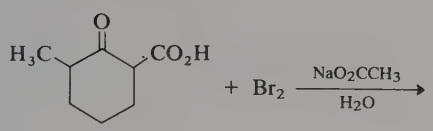
A

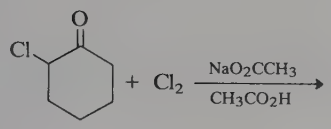
16. Which of the two plausible structures given for methylketene dimer is more consistent with its observed pK_a of 2.8? Why?

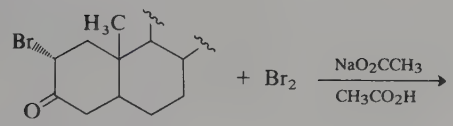


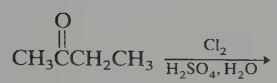
17. Predict the products of each of the following reactions:

(a) 

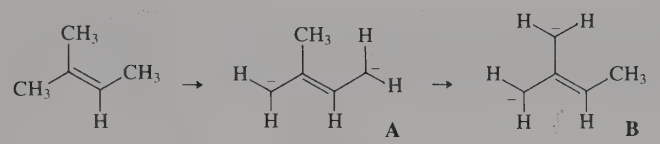
(b) 

(c) 

(d) 

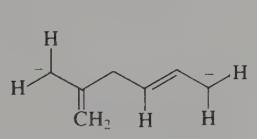
(e) 

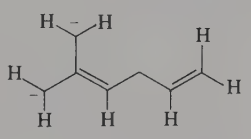
18. (a) It is found that when 2-methyl-2-butene is converted to a dianion it first gives the 2-methylbutadiene dianion **A** but this is converted to the more stable anion **B** which can be referred to as "methyltrimethylene–methane dianion."

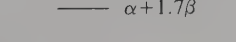


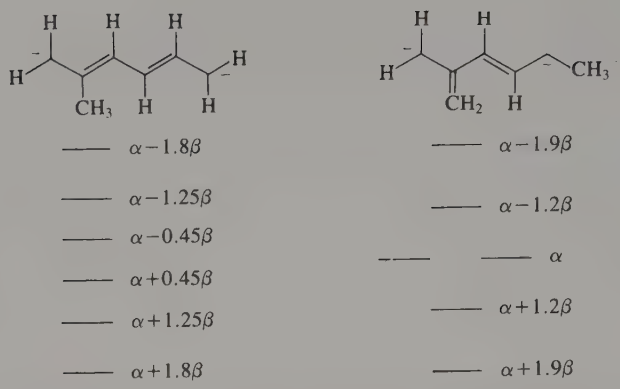
Does simple Hückel MO theory offer an explanation for this result?

(b) The Hückel MO diagrams for several conceivable dianions which might be formed by double deprotonation of 2-methyl-1,5-hexadiene are given. On the basis of these diagrams which of the dianions would be expected to be the most stable species?

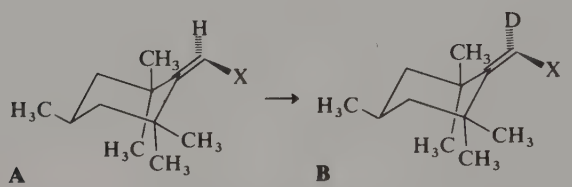






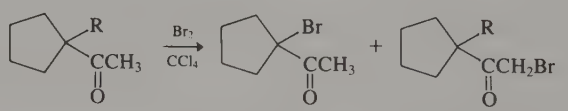


19. The stereochemistry of base-catalyzed deuterium exchange has been examined for **A** where X = CN and X = CPh:
‖
O



When X = CN, the isotopic exchange occurs with 99% retention of configuration, but when X = CPh, only about 30% net retention is observed. Explain.
‖
O

20. The distribution of α-bromoketones formed in the reaction of acetylcyclopentane with bromine was studied as a function of deuterium substitution. On the basis of the data given below, calculate the primary kinetic isotope effect (k_H/k_D) for enolization of acetylcyclopentane.



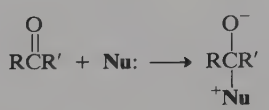
R = H	94%	6%
R = D	80%	20%

8

Reactions of Carbonyl Compounds

The carbonyl group is one of the most prevalent of the functional groups; great importance is therefore attached both to mechanistic studies and synthetic processes involving carbonyl compounds. Reactions involving carbonyl groups are also exceptionally important in biological processes. Most of the reactions of aldehydes, ketones, esters, amides, and other carboxylic acid derivatives are intimately associated with the carbonyl group. In Chapter 7, the role of the carbonyl group in stabilizing carbanion centers was discussed. The first two chapters of Part B deal mainly with the chemistry of carbonyl compounds, reflecting their importance in formation of carbon–carbon bonds in organic synthesis. In this chapter, the primary topic for discussion will be the characteristic mechanistic patterns of reactions at carbonyl centers.

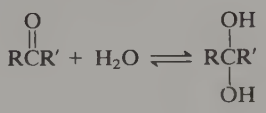
In many reactions at carbonyl groups, a key step is addition of a nucleophile, generating a tetracoordinate carbon atom. The overall course of the reaction is then determined by the fate of this *tetrahedral intermediate*. The reactions of the specific



classes of carbonyl compounds are related by the decisive importance of tetrahedral intermediates, and differences in reactivity can often be traced to structural features present in the intermediate.

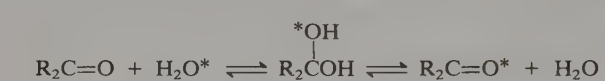
8.1. Hydration and Addition of Alcohols to Aldehydes and Ketones

For most simple carbonyl compounds, the equilibrium constant for addition of water to the carbonyl group is unfavorable:



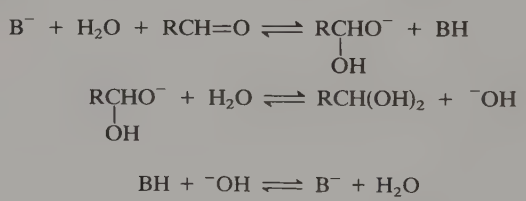
Exceptions are formaldehyde, which is nearly completely hydrated in aqueous solution, and aldehydes and ketones with highly electronegative groups such as trichloroacetaldehyde and hexafluoroacetone, which form particularly stable *gem*-diols. Some data, given in Table 8.1, illustrate that the equilibrium constant for hydration decreases with increasing alkyl substitution. The trend of decreasing K in the order $CH_2{=}O > RCH{=}O > R_2C{=}O$ is very pronounced for R = alkyl.

Although the equilibrium constant for hydration is unfavorable, the equilibrium between an aldehyde or ketone and its hydrate is established rapidly, and can be detected by isotopic exchange, using water labeled with ^{18}O, for example:



For acetaldehyde, the half-life of the exchange reaction is on the order of 1 min under neutral conditions, but is considerably faster in acidic or basic media. The second-order rate constant for acid-catalyzed hydration of acetaldehyde is on the order of $500\ M^{-1}\ \text{sec}^{-1}$.[1] The hydration reaction has been extensively studied because it is the mechanistic prototype for many reactions at carbonyl centers that involve more complex molecules.[2] Hydration is catalyzed by both base and acid. Basic catalysts function by assisting deprotonation of water, giving the more nucleophilic hydroxide ion:

Base-catalyzed hydration



Acid catalysis involves hydrogen-bonding or protonation at the carbonyl oxygen, which makes the carbonyl group a more reactive electrophile:

1. P. Greenzaid, Z. Luz, and D. Samuel, J. *Am. Chem. Soc.* **89**, 756 (1967).
2. R. P. Bell, *Adv. Phys. Org. Chem.* **4**, 1 (1966); W. P. Jencks, *Chem. Rev.* **72**, 705 (1972).

Table 8.1. Hydration of Carbonyl Compounds[a]

$$K = \frac{[\text{hydrate}]^b}{[\text{carbonyl}]}$$

Carbonyl compound	K(in water, 25°C)
CH_2O	2280
CH_3CHO	1.06
CH_3CH_2CHO	0.85
$(CH_3)_2CHCHO$	0.61
$(CH_3)_3CCHO$	0.23
CF_3CHO	2.9×10^{4}
CH_3COCH_3	1.4×10^{-3}
$ClCH_2COCH_3$	0.11
CF_3COCH_3	35
CF_3COCF_3	1.2×10^{6}
$C_6H_5COCF_3$	78

a. From J. P. Guthrie, *Can. J. Chem.* **53**, 898 (1975).
b. $K = K_{eq}[H_2O] = 55.5\,K_{eq}$.

Acid-catalyzed hydration

$$\text{RCH=O} + \text{HA} \rightleftharpoons \text{RCH=O}\cdots\text{HA}$$

$$\text{RCH=O}\cdots\text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{RCHOH} + \text{A}^-$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad {}^{+}\text{OH}_2$$

$$\text{A}^- + \text{RCHOH} \rightleftharpoons \text{RCH(OH)}_2 + \text{HA}$$
$$\qquad\quad {}^{+}\text{OH}_2$$

The effectiveness of many acids as catalysts for the hydration reactions have been determined and there is usually a correlation between acid strength and catalytic efficiency. The existence of such correlations is determined by plotting the catalytic rate constants against dissociation constants for a series of catalysts. The Brønsted correlation generally holds, at least within structurally related series of compounds, and the magnitude of the Brønsted α provides an indication of the sensitivity of the catalysis to the strength of the acid. (See Section 4.6 to review the Brønsted catalysis law.) The Brønsted catalysis law is an empirical free-energy relationship which holds if the free energy of a kinetic process, the proton transfer from the acid catalyst, is proportional to the free-energy change of an equilibrium process, that is, the ionization of the acid in aqueous solution. If the value of α, the proportionality constant in the Brønsted relationship, is close to unity, this implies that structural differences that are responsible for differences in equilibrium acidity are *nearly fully reflected* in the catalytic activity of the series of acids under investigation. This would be expected to be true in a process in which the proton transfer is nearly complete at the transition state. On the other hand, if the value of α is considerably less than unity, the implication is that relatively less of the changes associated with proton transfer have occurred at the transition state and this implies

an early transition state, closer in structure to the reactants. Although the relationship between the magnitude of α and transition state structuure is not necessarily applicable to all reaction systems, it has been found to be generally valid in the description of the proton transfer reactions which are important in the addition reactions of carbonyl groups.

Aldehydes and ketones undergo reversible reactions with alcohols. The product of addition of one mole of alcohol to an aldehyde or ketone is referred to as a *hemiacetal* or *hemiketal*, respectively. Dehydration and addition of a second mole of alcohol gives an *acetal* or *ketal*. This second phase of the process can be catalyzed only by acids, since a necessary step is elimination of hydroxide ion from a tetrahedral intermediate. There is no low-energy mechanism for base assistance of this elimination step. For this reason, acetals and ketals are stable toward hydrolysis in alkaline aqueous solution.

$$R_2C{=}O + R'OH \rightleftharpoons R_2C(OH)OR' \quad \textit{hemiketal}$$

$$R_2C(OH)OR' + H^+ \rightleftharpoons R_2C(^+OH_2)OR'$$

$$R_2C(^+OH_2)OR' \rightleftharpoons R_2C{=}\overset{+}{O}R' + H_2O$$

$$R_2C{=}\overset{+}{O}R' + R'OH \rightleftharpoons R_2C(\overset{+}{O}HR')OR' \rightleftharpoons R_2C(OR')_2 + H^+ \quad \textit{ketal}$$

The equilibrium constants for addition of alcohols to carbonyl compounds to give hemiacetals or hemiketals show the same response to structural features as do those for hydration reactions. The magnitude of the equilibrium constants is slightly smaller than for hydration. For example, whereas K for addition of water to acetaldehyde is 1.06, K's for addition of methanol and ethanol are 0.75 and 0.50 M^{-1}, respectively.[3] The overall equilibrium constants for formation of the acetals are 0.03 and 0.0125 M^{-2}, respectively. Because the position of the equilibrium does not favor product, the formation of acetals and ketals must be carried out in such a way as to compensate for the unfavorable equilibrium. One approach is to use a dehydrating reagent or azeotropic distillation so that the water that is formed is irreversibly removed, driving the reaction to completion:

$$R_2C{=}O + 2R'OH \rightarrow R_2C(OR')_2 + H_2O$$

Acetals are also frequently prepared from orthoesters by an exchange process.

$$R_2C{=}O + RC(OR')_3 \rightarrow R_2C(OR')_2 + RCO_2R'$$

Because of the unfavorable equilibrium constant in aqueous solution and the relative facility of the reverse reactions, acetals and ketals rapidly undergo hydrolysis

3. Data tabulated by J. P. Guthrie, *Can J. Chem.* **53**, 898 (1975).

in contact with water in the presence of acid:

$$R_2C(OR')_2 \xrightarrow[H_2O]{H^+} R_2C{=}O + 2R'OH$$

The mechanism of this hydrolysis reaction has been studied in great detail.[4] The mechanism is the reverse of that for acetal or ketal formation. The evidence that supports this general mechanism includes the following items:

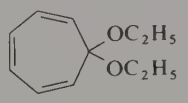
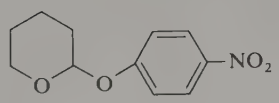
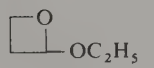
1) Isotopic labeling experiments establish that C–O bond fission occurs between the carbonyl carbon and oxygen; therefore, carbonium ions derived from the alcohol are not involved.
2) The reaction is specific acid catalyzed for most acetals and ketals. This is consistent with the existence of a preequilibrium in which the ketal is protonated. A logical role for the proton is to assist in the departure of one of the alkoxy groups. In essence, this cleavage step is an S_N1 reaction with the ease of formation of the carbonium ion being greatly increased by the stabilization afforded by the remaining alkoxy substituent.
3) Hammett treatments show good correlations with large negative ρ values for hydrolysis of acetals derived from aromatic aldehydes. This is consistent with the development of a positive charge at the carbonyl center in the rate-determining step.
4) Solvent isotope effects are usually in the range $k_{D_3O^+}/k_{H_3O^+} = 2$–3. These values reflect the greater equilibrium acidity of deuterated acids (Chapter 4, Section 4.4), and indicate that the initial protonation is a fast step, as would be expected for a protonation at oxygen.

Acetal and ketal hydrolyses usually exhibit specific acid catalysis, in agreement with a mechanism involving unimolecular cleavage of the conjugate acid of the substrate. General acid catalysis is observed, however, in certain acetals and ketals in which special structural features reduce the energy required for C–O bond cleavage.[5] Thus, hydrolysis of each of the acetals shown in Scheme 8.1 exhibits general acid catalysis, and each acetal has a special structural feature that facilitates C–O bond heterolysis. Easing the energy requirement for C–O bond cleavage permits the proton transfer step to become partially rate determining, which results in the observation of general acid catalysis.

Three-dimensional potential energy diagrams of the type introduced in connection with the variable E2 transition state theory for elimination reactions can be used to consider structural effects on the reactivity of carbonyl compounds and the tetrahedral intermediates involved in carbonyl group reactions. Many of these reactions involve the formation or breaking of two separate bonds. This is the case in the first stage of acetal hydrolysis which involves both a proton transfer and breaking of a C–O bond. The overall reaction might take place in several ways.

4. E. H. Cordes and H. G. Bull, *Chem. Rev.* **74**, 581 (1974).
5. T. H. Fife, *Acc. Chem. Res.* **5**, 264 (1972).

Scheme 8.1. Acetals and Ketals That Exhibit General Acid Catalysis in Hydrolysis

	Acetal or ketal	Special structural feature
1[a]		Very stable carbonium ion (stabilized by both alkoxy function and aromaticity)
2[b]		Good leaving group
3[c]		Ring strain relieved in cleavage step
4[d]	$(Ar)_2C(OC_2H_5)_2$	Aryl substituents stabilize carbonium ion
5[e]	$PhCH[OC(CH_3)_3]_2$	Aryl stabilization and relief of steric strain

a. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.* **91**, 7163 (1969).
b. T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.* **92**, 1681 (1970).
c. R. F. Atkinson and T. C. Bruice, *J. Am. Chem. Soc.* **96**, 819 (1974).
d. R. H. DeWolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.* **34**, 848 (1969).
e. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.* **93**, 1701 (1971).

There are two mechanistic extremes.

1) The proton could be completely transferred and then the departing alcohol molecule leave to form a carbocation in a distinct second step. This is the usual specific H^+-catalyzed mechanism.
2) The acetal might undergo ionization with formation of an alkoxide ion and a carbocation. (This mechanism is rare if not unknown, primarily because an alkoxide ion is a poor leaving group.)

There could be intermediate mechanisms between these extremes. These are the general acid-catalyzed mechanisms in which the proton transfer and the C–O bond rupture occur in a single *concerted* process. This concerted process need not be perfectly synchronous, that is, proton transfer might be more complete at the transition state than C–O rupture, or vice versa. These ideas are represented in the three-dimensional energy diagram in Figure 8.1.

The two paths around the edge of the diagram represent stepwise reactions (1) and (2) described as the mechanistic extremes. We know that (2) is a high-energy process so that the upper-left corner of the diagram would be at high energy. The other two lines represent concerted but nonsynchronous mechanisms in which there is both partial protonation and partial C–O bond rupture at the transition state. If either of these pathways should provide the lowest-energy transition state, the reaction will be a concerted, general-acid-catalyzed process. If it is possible to calculate or estimate the energy of the systems at various stages, the values of the

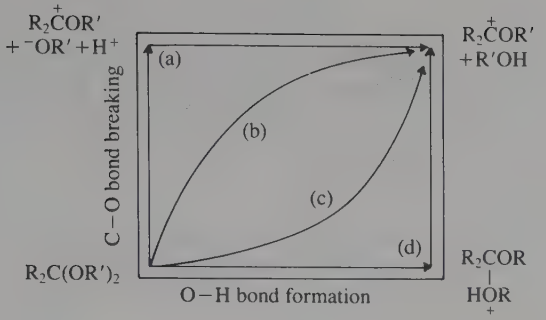


Fig. 8.1. Representation of transition states for the first stage of acetal hydrolysis. (a) initial C–O bond breaking; (b) concerted mechanism with C–O bond breaking leading C–H bond formation; (c) concerted mechanism with proton transfer leading C–O bond breaking; (d) initial proton transfer.

energy dimension will convert the figure into a contour plot. The favored route from reactants to product will be that path with the minimum energy transition state. Figure 8.2 shows such a contour plot for a hypothetical first step in an acetal hydrolysis. The diagram shows that the initial ionization to an alkoxide ion and a carbocation is very high energy. The stepwise path of protonation followed by ionization which proceeds along the bottom and right edge of the diagram encounters barriers of 16 and 14 in the arbitrary units used in the diagram. The preferred mechanism is a concerted process which does not cross the 8 contour. From its position on the diagram the transition state can be recognized as having proton transfer more complete than C–O bond breaking.

Structural effects can now be discussed by asking how they will affect the position of the transition state on the potential energy surface. The stepwise path via the protonated acetal should be followed in the case of alcohols that are poor

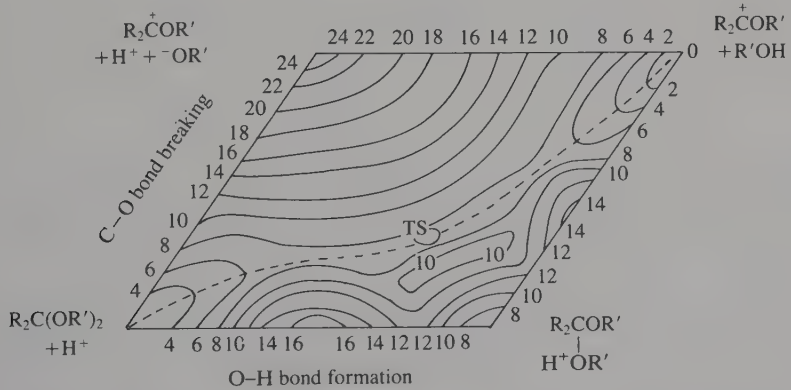
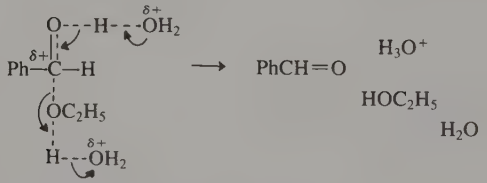


Fig. 8.2. Contour plot showing a favored concerted mechanism for the first step in acetal hydrolysis in which proton transfer is more complete in the transition state than C–O bond breaking. Contours are labeled with arbitrary energy units.

leaving groups. As the alcohol becomes more acidic and its conjugate base is a better leaving group, the transition state could be shifted to a point where C–O bond breaking has begun before proton transfer is complete. This would mean that that mechanism becomes concerted, although the transition state would still have much of the character of a carbocation.

Consideration of the types of acetals shown in Scheme 8.1, which exhibit general acid catalysis, indicated why the concerted mechanism becomes possible in these molecules. The developing aromatic character of the cation formed in the case of entry 1 will lower the energy requirement for carbon–oxygen bond rupture. The bond can begin to break before protonation is complete. Entry 2 represents a case where the good leaving group (a stable phenolate anion) reduces the energy requirement for C–O bond cleavage. In entry 3 the four-membered ring is broken in the reaction. This is facilitated by the release of strain energy, so again the transition state is reached before protonation is complete. Entries 4 and 5 are similar to entry 1 because the aryl groups provide stabilization for developing carbonium ion character. Three-dimensional reaction energy diagrams can provide an indication of how structural changes would be expected to displace the location of the transition state. Just as the two-dimensional diagrams help to visualize the ideas of an "early" or a "late" transition state, the three-dimensional diagrams can give meaning to such phrases as C–O cleavage "is more advanced" than protonation.

The second step in acetal and ketal hydrolysis is conversion of the hemiacetal or hemiketal to the carbonyl compound. The mechanism of this step is similar to that of the first step. Usually the second step is faster than the initial one, although benzaldehydes with electron-releasing groups provide an exception to this generalization. Hammett σ–ρ plots and solvent isotope effects both indicate, however, that the transition state has less carbonium ion character than is the case for the first step. These features of the mechanism suggest that a synchronous removal of the proton at the hydroxyl group occurs as the alcohol molecule is eliminated:

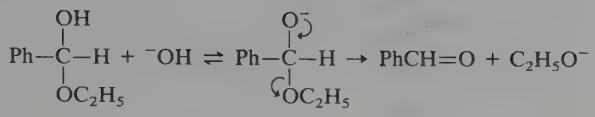


This would disperse the positive charge over several atoms and diminish the sensitivity of the reaction to substituent effects. This is consistent with the ρ values that are observed. While ρ is -3.25 for acetal hydrolysis it is only -1.9 for the hemiacetal hydrolysis.[6]

In contrast to acetals which are base stable, hemiacetals undergo base-catalyzed hydrolysis. In the alkaline pH range the mechanism shifts toward a base-catalyzed

6. T. J. Przystas and T. H. Fife, *J. Am. Chem. Soc.* **103**, 4884 (1981).

elimination:



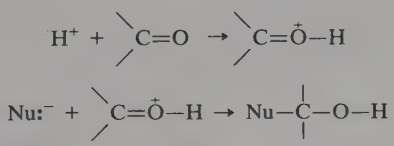
There are two competing substituent effects on this reaction. Electron-attracting groups favor the deprotonation but disfavor the elimination step. The observed substituent effects are small and under some conditions the Hammett plot is nonlinear.[7]

8.2. Addition–Elimination Reactions of Ketones and Aldehydes

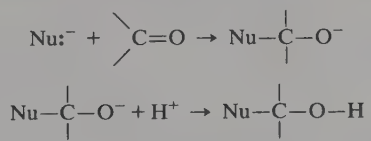
The mechanistic picture established by study of hydration and alcohol addition reactions of ketones and aldehydes sets a pattern that will be evident in a number of other reactions of carbonyl compounds. Reactions at carbonyl centers usually involve a series of addition and elimination steps proceeding through tetrahedral intermediates. These steps can be either acid catalyzed or base catalyzed. The overall result of the reaction is determined by the reactivity of these tetrahedral intermediates.

In general terms, there are three possible mechanisms for addition of a nucleophile and a proton to give a tetrahedral intermediate in a carbonyl addition reaction.

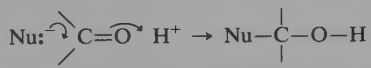
A) Protonation followed by nucleophilic attack on the protonated carbonyl group:



B) Nucleophilic addition at the carbonyl group followed by protonation:



C) Concerted proton transfer and nucleophilic attack:



There are examples of each of these mechanisms and a three-dimensional potential energy diagram can provide a useful general framework within which to consider the specific addition reactions that we will encounter. The breakdown of a tetrahedral intermediate involves the same processes but operates in the opposite direction,

7. R. L. Finley, D. G. Kubler and R. A. McClelland, *J. Org. Chem.* **45**, 644 (1980).

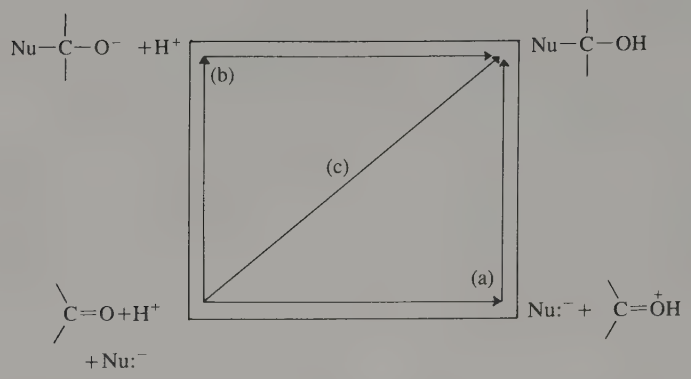


Fig. 8.3. Three-dimensional potential energy diagram for addition of a proton and nucleophile to a carbonyl group. (a) Proton transfer complete before nucleophilic addition begins; (b) nucleophilic addition complete before proton transfer begins; (c) concerted proton transfer and nucleophilic addition.

so the principles that are developed will apply equally well to the reactions of tetrahedral intermediates. Let us examine the three general mechanistic cases in relation to the energy diagram in Figure 8.3.

Case (A) should be favored for weakly basic nucleophiles. The protonated carbonyl compound will be much more highly reactive toward such a nucleophile. Therefore mechanism (A) should be expected in the case of weak nucleophiles. Case (B) should be favored for strongly basic nucleophiles. Species which are more basic than a carbonyl group would be protonated in preference to the carbonyl group. The presence of proton donors would diminish the overall reaction rate by decreasing the amount of unprotonated nucleophile which is available for reaction. The reactions of primary amines are of this type and are not acid catalyzed because these nucleophiles are much more basic than the carbonyl compounds. Less basic nucleophiles can be expected to follow the concerted mechanism. The simultaneous transfer of the proton at the carbonyl oxygen assists in achieving addition by species which are not sufficiently nucleophilic to react by mechanism (B). Among nucleophiles which have been found to exhibit this behavior are urea and semicarbazide.[8] If we consider the reverse process, breakdown of the tetrahedral intermediate, we expect good leaving groups to follow path (A), poor leaving groups to follow path (B), and intermediate cases to react via path (C).

Certain nucleophilic species add to carbonyl groups to give tetrahedral intermediates that are unstable and break down to form a new double bond. An important group of such reactions are those between compounds containing primary amino groups and ketones or aldehydes. Scheme 8.2 lists some of the more familiar classes of such reactions. At one time, a principal interest in these reactions was for the preparation of crystalline derivatives of ketones and aldehydes for characterization,

8. W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969, pp. 490–496.

Scheme 8.2. Some Addition–Elimination Reactions of Aldehydes and Ketones

$$R_2C{=}O + R'NH_2 \rightleftharpoons R_2C{=}NR'$$

imine (also often called Schiff base, especially when the amine is an aniline derivative)

$$R_2C{=}O + HONH_2 \rightleftharpoons R_2C{=}NOH$$

oxime

$$R_2C{=}O + NH_2NHR' \rightleftharpoons R_2C{=}NNHR'$$

hydrazone

$$R_2C{=}O + NH_2NHC(=O)NH_2 \rightleftharpoons R_2C{=}NNHC(=O)NH_2$$

semicarbazone

but more recently, these types of reactions have been studied in detail because they are models of processes that are of importance in biological reactions. In general, these reactions are reversible, and mechanistic information can be obtained by study of either the forward or the reverse process.

The hydrolysis of simple imines occurs readily in aqueous acid, and has been studied in great detail by kinetic methods. The precise mechanism is a function of the reactant structure and the pH of the solution. The overall mechanism consists of an addition of water to the C=N bond, followed by expulsion of the amine from a tetrahedral intermediate.[9]

$$RCH{=}NR' + H^+ \rightleftharpoons RCH{=}\overset{+}{N}HR'$$

$$RCH{=}\overset{+}{N}HR' + H_2O \rightleftharpoons RCH(^+OH_2)NHR' \rightleftharpoons RCH(OH)\overset{+}{N}H_2R'$$

or

$$RCH{=}\overset{+}{N}HR' + {}^-OH \rightleftharpoons RCH(OH)NHR'$$

$$RCH(OH)NHR' + H^+ \rightleftharpoons RCH(OH)\overset{+}{N}H_2R'$$

$$^-OH + RCH(OH)\overset{+}{N}H_2R' \rightleftharpoons H_2O + RCH(\_O)\overset{+}{N}H_2R' \rightleftharpoons RCH(=O) + H_2NR'$$

9. J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, J. *Am. Chem. Soc.* **92**, 5194 (1970); E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.* **85**, 2843 (1963).

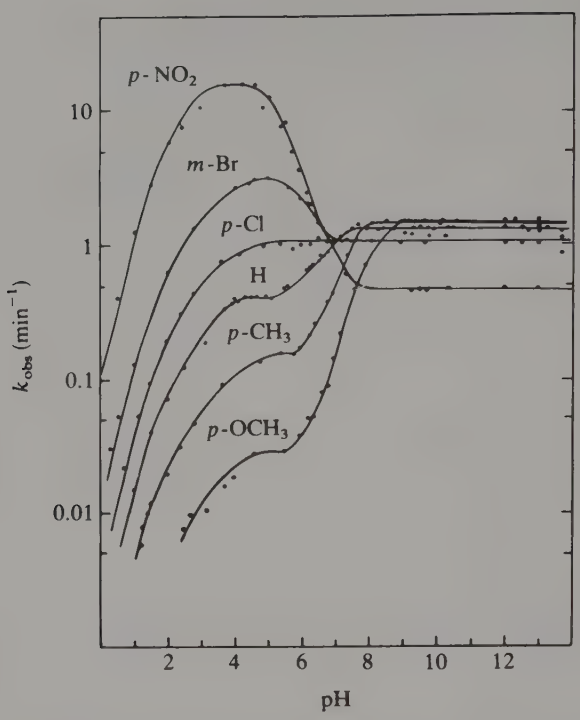


Fig. 8.4. Logarithm of the first-order rate constants for the hydrolysis of substituted benzylidene-1,1-dimethylethylamines as a function of pH. [Reproduced from *J. Am. Chem. Soc.* **85**, 2843 (1963) by permission of the American Chemical Society.]

The relative rates of the various steps are a function of the pH of the solution and the basicity of the imine. In the alkaline range, the rate-determining step is usually nucleophilic attack of hydroxide ion on the protonated C=N bond. At intermediate pH values, water replaces hydroxide ion as the dominant nucleophile. In acidic solution, the rate-determining step becomes the breakdown of the tetrahedral intermediate. A mechanism of this sort, in which the overall rate is sensitive to pH, can be usefully studied by constructing a pH–rate profile, which is a plot of the observed rate constants versus pH. Figure 8.4 is an example of the pH–rate profiles for hydrolysis of a series of imines derived from substituted aromatic aldehydes and *t*-butylamine. The form of pH–rate profiles can be predicted on the basis of the detailed mechanism. The value of the observed rate can be calculated quantitatively as a function of pH, if a sufficient number of the individual rate constants and of the acid dissociation constants of the species involved are known or can be estimated reliably. Agreement between the calculated and observed pH–rate profile can then serve as a sensitive test of the adequacy of the postulated mechanism. Alternatively, one may begin with the experimental pH–rate profile and deduce details of the mechanism from it.

Complete understanding of the shape of the curves in Fig. 8.4 requires a kinetic expression somewhat more complicated than we wish to deal with here. The nature

of the extremities of the curves can be understood, however, on the basis of qualitative arguments. The rate decreases with pH in the acidic region, because formation of the zwitterionic tetrahedral intermediate is required for expulsion of the amine. The concentration of the zwitterionic species decreases with increasing acidity, since its concentration is governed by an acid dissociation constant:

$$K = \frac{[H^+][RCH(O^-)\overset{+}{N}H_2R]}{[RCH(OH)\overset{+}{N}H_2R]}$$

As the hydrogen ion concentration increases, the concentration of the reactive form of the intermediate decreases.

In the alkaline region, the rate is pH independent. In this region the rate-determining step is attack of hydroxide ion on the protonated imine. The concentration of each of these species is pH dependent, but in opposite, compensating, ways, and the overall rate is therefore pH independent in the alkaline range (work problem 6 to establish that this is so).

The formation of imines takes place by a mechanism that is the reverse of the hydrolysis. Preparative procedures often ensure completion of the reaction by removing water as it is formed by azeotropic distillation or by use of a dehydrating agent.

The other C=N systems included in Scheme 8.2 are more stable to aqueous hydrolysis than are the imines. For many cases, the equilibrium constants for product formation are high even in aqueous solution. The additional stability can be attributed to the participation of the atoms adjacent to the nitrogen in delocalized bonding.

$$R_2C{=}N{-}\ddot{O}H \longleftrightarrow R_2\bar{C}{-}N{=}\overset{+}{O}H$$

$$R_2C{=}N{-}\ddot{N}H_2 \longleftrightarrow R_2\bar{C}{-}N{=}\overset{+}{N}H_2$$

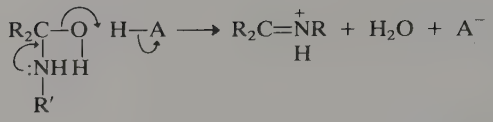
The formation of oximes, hydrazones, and related imine derivatives is catalyzed by both general acids and general bases. General base catalysis of dehydration of the tetrahedral intermediate involves nitrogen deprotonation concerted with elimination of hydroxide ion[10]:

$$R_2C{=}O + NH_2R' \rightleftharpoons R_2C(OH)NHR'$$

$$\ddot{B} + H{-}\overset{R}{\underset{R'}{N}}{-}\overset{R}{\underset{R}{C}}{-}OH \longrightarrow \overset{+}{B}H + R'N{=}CR_2 + \bar{O}H$$

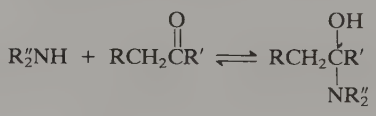
General acid catalysis of the breakdown of the carbinolamine intermediate occurs by assistance of the expulsion of water:

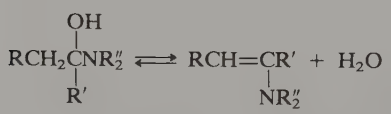
10. W. P. Jencks, *Prog. Phys. Org. Chem.* **2**, 63 (1964); J. M. Sayer, M. Peskin, and W. P. Jencks, *J. Am. Chem. Soc.* **95**, 4277 (1973).



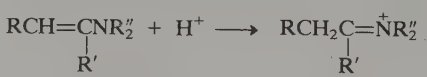
As with simple imines, the identity of the rate-determining step changes with solution pH. As the pH decreases, the rate of the addition step decreases because protonation of the amino compound reduces the concentration of the nucleophilic unprotonated form. Thus, while the dehydration step is normally rate determining in neutral and basic solution, addition becomes rate determining in acidic solutions.

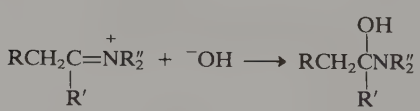
Secondary amines cannot form imines, and dehydration proceeds to give carbon–carbon double bonds bearing amino substituents (enamine). These enamines were mentioned in Chapter 7 as examples of nucleophilic carbon species, and their synthetic utility will be summarized in Part B, Chapter 1, Section 1.9. The equilibrium for this reaction ordinarily lies far to the left in aqueous solution, but the reaction can be driven forward by dehydration techniques. The mechanism of hydrolysis of enamines has been studied kinetically over a range of pH. In alkaline solution,

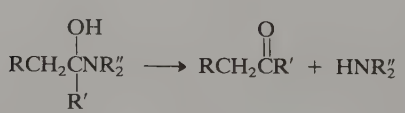




rate-determining C-protonation is followed by attack of hydroxide ion on the resulting iminium ion. The carbinolamine intermediate then breaks down as in imine hydrolysis. In the neutral and weakly acidic pH range, water attack on the C-protonated enamine becomes rate limiting. As in imine hydrolysis, decomposition of the tetrahedral intermediate becomes rate limiting in strongly acidic solution.[11] The pH at which the mechanism changes for any individual compound is a function of its structure and, in particular, of its basicity.







11. P. Y. Sollenberger and R. B. Martin, *J. Am. Chem. Soc.* **92**, 4261 (1970); W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *J. Org. Chem.* **32**, 1111 (1967); E. J. Stamhuis and W. Maas, *J. Org. Chem.* **30**, 2156 (1965).

Certain reactions between carbonyl compounds and nucleophiles are catalyzed by amines. Some of these reactions are of importance for forming carbon–carbon bonds and these are discussed in Section 2.2 of Part B. The mechanistic principle can be illustrated by considering the catalysis of the reaction between ketones and hydroxylamine by aniline derivatives:

$$ArCH{=}O + NH_2OH \xrightarrow{Ar'NH_2} ArCH{=}NOH + H_2O$$

Analysis of the kinetics of this amine catalysis points to the protonated imine as the key species:

$$ArCH{=}O + Ar'NH_2 + H^+ \rightarrow ArCH{=}\overset{+}{N}HAr' + H_2O$$
$$ArCH{=}\overset{+}{N}HAr' + NH_2OH \xrightarrow{fast} ArCH{=}NOH + Ar\overset{+}{N}H_3$$

Because the imine is much more basic than the original carbonyl compound, it is more extensively protonated at any given pH than is the aldehyde. Thus, the equilibrium system presents four distinct electrophiles for consideration:

$$ArCH{=}\overset{+}{O}H > ArCH{=}\overset{+}{N}HAr' > ArCH{=}O > ArCH{=}NAr'$$
$$\xrightarrow[\text{decreasing reactivity}]{}$$

Considering the various equilibrium constants shows that the protonated imine is present in sufficient concentration to be the dominant reactive species. Although the protonated aldehyde would be even more reactive, its concentration is very low. On the other hand, even though the aldehyde may be present in greater concentration than the protonated imine, its reactivity is sufficiently less so that the iminium ion is the major reactant.[12]

8.3. Reactivity of Carbonyl Compounds toward Addition

We would like at this point to consider some general relationships concerning reactivity of carbonyl compounds. The preceding discussion of the addition–elimination reactions indicates that many factors influence the overall rate of a reaction under typical conditions. Among the crucial factors are (1) the role of proton transfer in activating the carbonyl group toward nucleophilic attack, (2) the reactivity of the nucleophilic species and its influence on the mechanism which is followed, and (3) the stability of the tetrahedral intermediate and the extent to which it proceeds to product rather than reverting to starting materials. Since consideration of all these factors complicates the interpretation of the inherent reactivity of the carbonyl compound itself, it has been of interest to study irreversible processes where the addition product is stable. Under these conditions, the relative rate of reaction of different carbonyl compounds can be directly compared. One such reaction is hydride reduction. In particular, reactions with sodium borohydride in

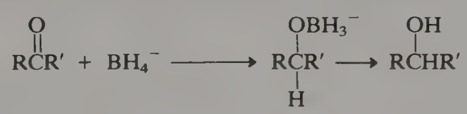
12. E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.* **84**, 826 (1962); J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.* **42**, 1593 (1977).

Table 8.2. Rates of Reduction of Aldehydes and Ketones by Sodium Borohydride

Carbonyl compound	$k_2 \times 10^4$ $(M^{-1}\ \mathrm{sec}^{-1})^a$
Benzaldehyde	12,400[b]
Benzophenone	1.9
Acetophenone	2.0
Acetone	15.1
Cyclobutanone	264
Cyclopentanone	7
Cyclohexanone	161

a. In isopropyl alcohol at 0°C.
b. Extrapolated from data at lower temperatures.

alcoholic solvents are rapid irreversible reactions which have provided a basis for comparing the reactivity of different carbonyl compounds[13]:



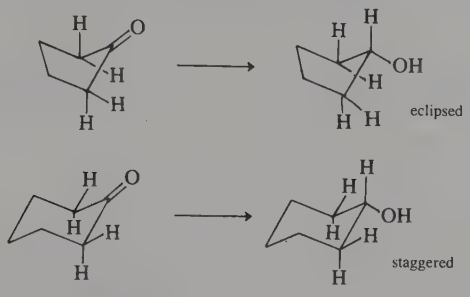
The reaction is second order overall, with rate $= k[\mathrm{R\overset{\overset{O}{\|}}{C}R}][BH_4^-]$, and complicated only slightly by the fact that borohydride ion is converted to alkoxyborohydrides during the course of the reaction. The rate-determining step is addition of hydride to the carbonyl carbon; this allows relative reactivities to be directly determined. Table 8.2 presents some of the rate data obtained from these studies.

The reactions are characterized by low enthalpies of activation (8–13 kcal/mol) and large negative entropies of activation (−28 to −40 eu), as expected for a bimolecular reaction. It can be seen that the only aldehyde (benzaldehyde) reacts much more rapidly than any of the ketones. This behavior is typical for carbonyl addition reactions. The additional alkyl or aryl substituents present in ketones increase the steric repulsion of the attacking nucleophile. There is also a significant contribution from the fact that as the carbon atom undergoes a change from sp^2 hybridization (~120° bond angles) to sp^3 hybridization (~109.5° bond angles) during the rate-determining step; both electron-pair repulsions and van der Waals repulsions between the substituents increase. These effects are minimal for a hydrogen substituent. Acetophenone is less reactive than acetone both because of increased steric compression in the transition state and because conjugation of the carbonyl group with the aromatic ring, which stabilizes the ground state, is lost on going to the transition state.

Among the cyclic ketones, the reactivity of cyclobutanone is enhanced because of the decrease in angle strain in going from the ground state to the transition state.

13. H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron* **1**, 214 (1957); H. C. Brown and K. Ichikawa, *Tetrahedron* **1**, 221 (1957).

The small C–CO–C angle forced on cyclobutanone by the ring geometry deviates more from the trigonal value than from the tetrahedral value. As the transition state is approached, the magnitude of the angle strain is reduced. For cyclopentanone and cyclohexanone, the angle-strain component is not significant. The major factor responsible for the large difference in rate between these two is the difference in torsional strain introduced in the transition state. As the transition state is approached, the hybridization changes from sp^2 to sp^3, and eclipsing interactions develop between the oxygen and vicinal C–H bonds and between the C–H bond being formed and vicinal C–H bonds in the five-membered ring. The analogous torsional interactions are much less in the six-membered ring, in which the chair conformation allows all the bonds to be staggered. Because of this factor, cyclohexanone is much more reactive than cyclopentanone toward addition reactions:



The analysis of borohydride reduction rate data finds parallels in many other carbonyl addition reactions. In fact, for a series of ketones, most of which were cyclic, it was found that a linear free-energy correlation of the form

$$\log k = A \log k_0 + B$$

where $A \approx 1$ exists for nucleophiles such as NH_2OH, CN^-, $HOCH_2CH_2S^-$, and SO_3^{2-}.[14] These nucleophiles span a wide range of reactivity and represent nitrogen, carbon, and sulfur atoms acting as the nucleophile. Since A in the above correlation is approximately unity, the correlation can be further simplified to

$$\log(k/k_0) = B$$

This relationship implies that in this series of ketones the same structural features govern reactivity toward each of the nucleophiles that was studied. That is, the relative reactivity is independent of the specific nucleophile. Table 8.3 lists B for some representative ketones. The parameter B represents the relative reactivity of the various ketones (on a log scale). Cyclohexanone is seen to be a particularly reactive ketone, being almost as reactive as cyclobutanone and more than ten times more reactive than the acyclic ketone acetone.

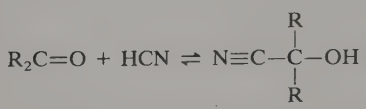
The same structural factors come into play in determining the position of equilibria in reversible additions to carbonyl compounds. The best studied of such equilibrium processes is probably cyanide addition to give cyanohydrins:

14. A. Finiels and P. Geneste, *J. Org. Chem.* **44**, 1577 (1979).

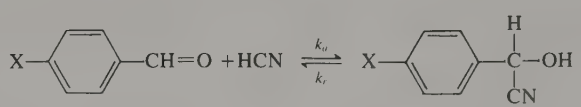
Table 8.3. Relative Reactivity of Some Ketones toward Addition of Nucleophiles

Ketone	B = log relative reactivity[a]
Cyclobutanone	0.09
Cyclohexanone	0.00[a]
4-*tert*-butylcyclohexanone	−0.008
Adamantanone	−0.46
Cycloheptanone	−0.95
Cyclopentanone	−1.18
Acetone	−1.19
Bicyclo[2.2.1]heptan-2-one	−1.48
3,3,5,5-Tetramethylcyclohexanone	−1.92

a. A. Finiels and P. Geneste, *J. Org. Chem.* **44**, 1577 (1979); reactivity relative to cyclohexanone as a standard.



In the case of aromatic aldehydes, electron-releasing substituents such as methoxy and methyl disfavor the addition process by stabilizing the carbonyl group by π-electron donation. The nitro group has the opposite effect:



Ref. 15

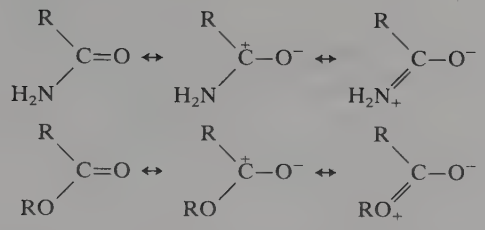
K is correlated by Hammett equation with σ^+, $\rho = 1.01$

k_a is correlated by Hammett equation with σ^+, $\rho = 1.18$

The equilibrium for addition of HCN to the C-6, C-5, and C-7 cyclic ketones have been measured as $K = 10^3$, 48, and $7.8\,M^{-1}$.[16] These data again indicate the especially favorable nature of addition reactions of cyclohexanone.

Comparison of ketones and aldehydes with other types of carbonyl compounds such as esters, amide, and acid chlorides reveals additional factors. The most important is the stabilizing effect which substituents can have on the heteroatom carbonyl group. In esters and amides there is a strong stabilization of the carbonyl group resulting from the π-donor effect of the substituents. Esters and amides are therefore much less reactive than aldehydes and ketones toward nucleophilic addition, because this stabilizing conjugation is destroyed as the tetrahedral intermediate is formed:

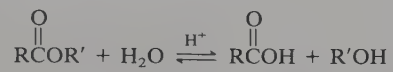
15. W.-M. Ching and R. G. Kallen, *J. Am. Chem. Soc.* **100**, 6119 (1978).
16. V. Prelog and M. Kobelt, *Helv. Chim. Acta* **32**, 1187 (1949).



Acid chlorides, on the other hand, are more reactive toward addition than ketones since the inductive effect of the chlorine substituent increases carbonyl group reactivity and more than compensates for the small π-donor effect of the chlorine.

8.4. Ester Hydrolysis

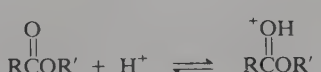
Esters can be hydrolyzed in either basic or acidic solution. In acidic solution the reaction is reversible:

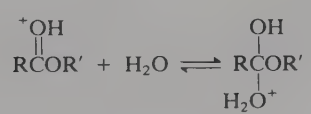


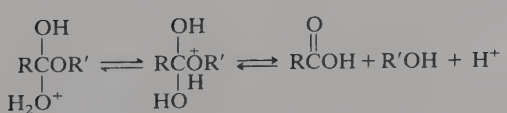
The position of the equilibrium depends on the relative concentrations of water and the alcohol. In aqueous solution, hydrolysis occurs; in alcoholic solution, the equilibrium is shifted in favor of the ester by the mass law effect. In aqueous alkaline solution ester hydrolysis is essentially irreversible:

The carboxylic acid is converted to its anion under these conditions, and the position of the equilibrium lies far to the right. The mechanistic designations $A_{AC}2$ and $B_{AC}2$ have been given to the acid- and base-catalyzed ester hydrolysis mechanisms, respectively. The A denotes acid, the B base, catalysis; AC indicates acyl–oxygen fission. The digit 2 has its usual significance, indicating the bimolecular nature of the rate-determining step.

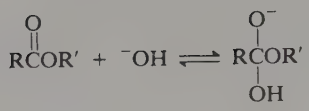
$A_{AC}2$ mechanism

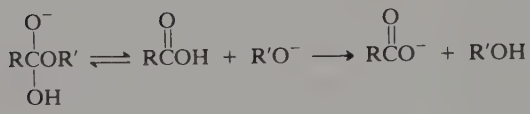




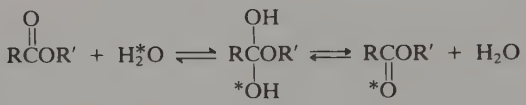


$B_{AC}2$ mechanism





Esters without special structural features hydrolyze by these mechanisms. Among the kinds of evidence supporting these mechanisms are kinetic studies that show the expected dependence on hydrogen ion or hydroxide ion concentration and isotopic labeling studies that prove it is the acyl–oxygen, not the alkyl–oxygen, bond that is cleaved during hydrolysis.[17] Acid-catalyzed hydrolysis of esters is accompanied by some exchange of oxygen from water into the ester. This exchange can occur by way of the tetrahedral intermediate if expulsion of water is competitive with expulsion of the alcohol molecule.



Substituent effects come into play at several points in the ester hydrolysis mechanism. Consider the base-catalyzed reaction, for example. Electron-withdrawing substituents in either the acyl group or the alkoxy group of an ester facilitate hydrolysis. Since the rate-determining tetrahedral intermediate is negatively charged, it, and the transition state leading to it, will be stabilized by electron withdrawal. This stabilization is primarily an inductive effect, which is reduced as the substituent becomes further removed from the carbonyl group. If the carbonyl group is conjugated with an electron-releasing substituent group, for example, *p*-methoxyphenyl, reactivity will be reduced because of increased ground-state stabilization. Additionally, the partitioning of the tetrahedral intermediate between reversion to starting ester by loss of hydroxide and formation of product by loss of alkoxide will be affected by substituents in the alkoxy group. Stabilization of the alkoxide ion by electron-withdrawing substituents shifts the partitioning in the direction favoring products, leading to an increase in the overall rate. For this reason, exchange of carbonyl oxygen with solvent does not occur in basic hydrolyses when the alkoxy group is a good leaving group (weakly basic). This has been demonstrated in particular for esters of phenols. Because phenols are much stronger acids than simple alcohols, their conjugate bases are better leaving groups than the simple alkoxy groups. Aryl esters are hydrolyzed faster than alkyl esters and without observable exchange of carbonyl oxygen with the solvent:

17. M. L. Bender, *Chem. Rev.* **60**, 53 (1960).

$$RCOAr + {}^{-}OH \underset{\text{slow}}{\rightleftharpoons} RC(O^{-})(OH)OAr \xrightarrow{\text{fast}} RCOH + ArO^{-} \xrightarrow{{}^{-}OH} RCO_2^{-} + ArO^{-}$$

These substituent effects can be summarized in a general way for the $B_{AC}2$ mechanism by noting the effect of substituents on each step of the mechanism:

$$RCOR' + {}^{-}OH \rightleftarrows R-C(O^{-})(OH)-OR'$$

favored by electron-attracting substituents in both R and R'

$$R-C(O^{-})(OH)-OR' \rightarrow R-C(=O)-OH + {}^{-}OR'$$

strongly favored by electron-attracting substituents in R'

It is possible to shift ester hydrolyses away from the normal $A_{AC}2$ or $B_{AC}2$ mechanisms by structural changes in the substrate. When the ester is derived from a tertiary alcohol, acid-catalyzed hydrolysis often occurs by a mechanism involving alkyl–oxygen fission. The change in mechanism is due to the stability of the carbonium ion that can be formed by C–O heterolysis, and probably also to a decrease in the rate of nucleophilic attack at the carbonyl group because of steric factors.[18] Alkenes, as well as alcohols may be produced from the carbonium ion, since water can function either as a nucleophile or as a Brønsted base. This mechanism is referred to as $A_{AL}1$, reflecting the fact that the alkyl–oxygen bond is cleaved.

$$RCOCR_3' + H^{+} \rightleftharpoons RC(^{+}OH)OCR_3' \xrightarrow{\text{slow}} RCO_2H + R_3'C^{+}$$

$$R_3'C^{+} + H_2O \longrightarrow R_3'COH$$

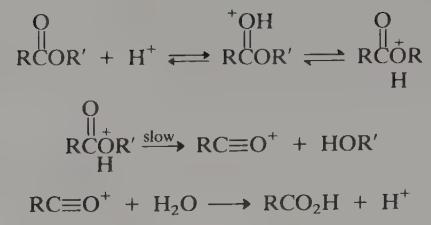
and

$$R_3'C^{+} \longrightarrow \text{alkene} + H^{+}$$

In practical synthetic terms this change of mechanism can be of value since it allows certain types of esters to be converted to the corresponding acids very selectively. The usual situation involves the use of *t*-butyl esters which can be cleaved to acids by the action of acids such as *p*-toluenesulfonic acid or trifluoroacetic acid under conditions where other types of esters are stable.

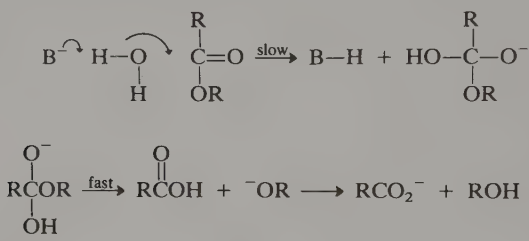
In very strongly acidic solution, a unimolecular mechanism involving acyl–oxygen cleavage of the conjugate acid can operate.[19] This mechanism is the result of decreased availability of nucleophilic water in the strongly acidic medium. The products of heterolysis are the alcohol (which is subsequently protonated) and an acylium ion:

18. A. G. Davies and J. Kenyon, *Q. Rev. Chem. Soc.* **9**, 203 (1955).
19. K. Yates and R. A. McClelland, *J. Am. Chem. Soc.* **89**, 2686 (1967).

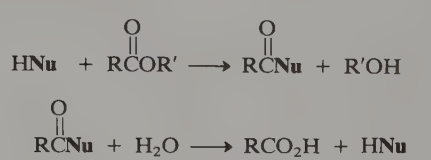


The mechanistic designation is $A_{AC}1$. This mechanism is the basis for a useful method of hydrolyzing esters that are very severely sterically hindered, such as esters of 2,4,6-trimethylbenzoic acid.[20] The ester is dissolved in strong sulfuric acid, and then quenched into water. Hydrolysis occurs via the acylium ion which is formed in the strongly acidic solution.

In the preceding paragraphs, the ester hydrolysis mechanisms discussed pertained to aqueous solutions of strong acids and strong bases. These are conditions in which specific acid catalysis or specific base catalysis would be expected. In media in which other acids or bases are present, the possible occurrence of general-acid- and general-base-catalyzed hydrolysis must be considered. General base catalysis has been observed in the case of esters in which the acyl group carries electron-attracting substituents.[21] The transition state for esters undergoing hydrolysis by a general base-catalyzed mechanism involves partial proton transfer from the attacking water molecule to the general base in the formation of the tetrahedral intermediate:



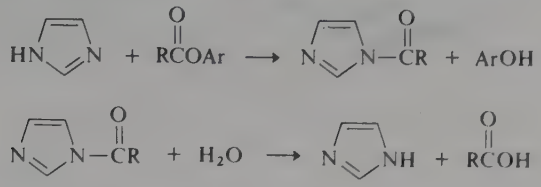
Ester hydrolysis can also be promoted by *nucleophilic catalysis*. If a component of the reaction system is a more effective nucleophile toward the carbonyl group than hydroxide ion or water under a given set of conditions, an acyl transfer reaction can take place to form an intermediate:



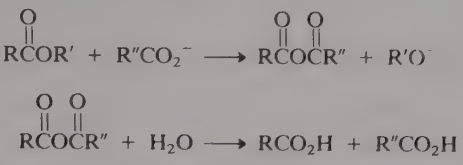
If this intermediate, in turn, is more rapidly attacked by water or hydroxide ion than the original ester, the overall reaction will be faster in the presence of the nucleophile than in its absence. These are the requisite conditions for nucleophilic catalysis. Esters of relatively acidic alcohols (in particular, phenols) are hydrolyzed by the

20. M. S. Newman, *J. Am. Chem. Soc.* **63**, 2431 (1941).
21. W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.* **83**, 1743 (1961).

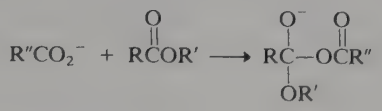
nucleophilic catalysis mechanism in the presence of imidazole[22]:



Carboxylate anions can also serve as nucleophilic catalysts.[23] In this case, an anhydride is the reactive intermediate:



This mechanism is important only for alcohols in which the alkoxy group $^-OR'$ is not much more basic than the nucleophilic catalyst. This relationship can be understood by considering the tetrahedral intermediate generated by attack of the potential catalyst on the ester:

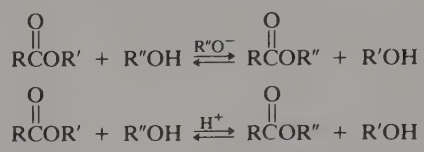


The relative leaving-group abilities of $R'O^-$ and $^-O_2CR''$ are strongly correlated with the basicity of the two anions. If $^-O_2CR''$ is much the better leaving group, no nucleophilic catalysis will be observed. Even if the tetrahedral intermediate is formed, it will be nonproductive in terms of hydrolysis of the ester because $^-O_2CR''$ will be preferentially eliminated, returning starting material.

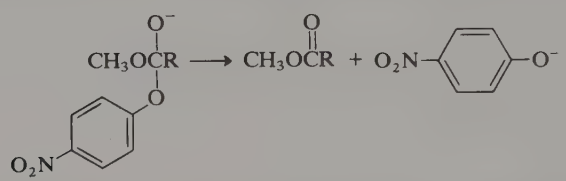
The preceding discussion has touched on the most fundamental aspects of ester hydrolysis mechanisms. Much study has been devoted to establishing some of the finer details, particularly concerning proton transfers during the formation and breakdown of the tetrahedral intermediates. These studies have been undertaken in part because of the fundamental importance of hydrolytic reactions in biological systems. These biological hydrolyses are catalyzed by enzymes. The detailed mechanistic studies of ester hydrolysis have been carried out in part to lay the groundwork for determining the catalytic mechanisms of the hydrolytic enzymes. Many of these studies and their relationship to biological mechanisms have been discussed in detail in books which discuss enzymatic reactions from the point of view of molecular mechanisms.[24]

22. T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.* **79**, 1663 (1967); M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.* **79**, 1652, 1656 (1957).
23. V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968).
24. T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*, Vol. 1, W. A. Benjamin, New York, 1966, pp. 1–258; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969; M. L. Bender, *Mechanism of Homogeneous Catalysis from Protons to Proteins*, Wiley–Interscience, New York, 1971; C. Walsh, *Enzymatic Reaction Mechanisms*, W. H. Freeman, San Francisco, 1979.

Esters react with alcohols in either acidic or basic solution to exchange alkoxy groups (ester interchange) by mechanisms that parallel hydrolysis. The alcohol molecule or alkoxide ion takes the role of the nucleophilic species. As in the case of



hydrolysis, there has been a good deal of careful kinetic work on these reactions to assess the importance of substituent effects, general acid and general base catalysis, solvent effects, and isotope effects.[25] The alcoholysis reaction is reversible in both acidic and basic solution, in contrast to hydrolysis. The key intermediate in these reactions is again the tetrahedral intermediate. Its fate is determined in large part by the relative basicities of the two alkoxy groups. A tetrahedral intermediate generated by addition of methoxide ion to a *p*-nitrophenyl ester, for example, breaks down exclusively by elimination of the much less basic *p*-nitrophenoxide ion:

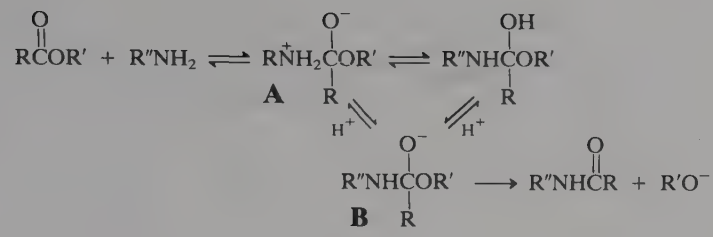


In general, the equilibrium in a base-catalyzed alcohol exchange reaction lies in the direction of incorporating the less acidic alcohol in the ester.

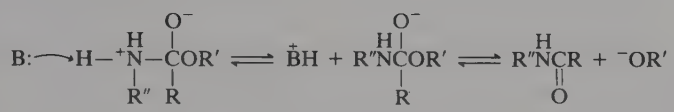
8.5. Aminolysis of Esters

Esters react with ammonia and amines to give amides. The underlying mechanism is similar to hydroxide-ion-catalyzed ester hydrolysis and involves nucleophilic attack of the amine at the carbonyl group, followed by expulsion of alkoxide ion from the tetrahedral intermediate. The identity of the rate-determining step depends primarily on the leaving ability of the alkoxy group.[26] With relatively good leaving groups such as phenolates or acidic alcohols such as trifluoroethanol, the slow step is expulsion of the oxygen leaving group from a zwitterionic tetrahedral intermediate **A**. With poorer leaving groups, breakdown of the tetrahedral intermediate occurs only after formation of the anionic species **B**. For such systems, the deprotonation step is rate determining.

25. C. G. Mitton, R. L. Schowen, M. Gresser, and J. Shapley, *J. Am. Chem. Soc.* **91**, 2036 (1969); C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Am. Chem. Soc.* **91**, 2045 (1969).
26. F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.* **94**, 3824 (1972); A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 7018 (1974).

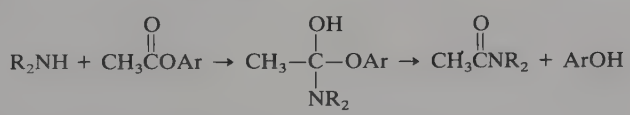


Aminolysis of esters often reveals general base catalysis and in particular a contribution to the reaction from terms that are second order in the amine. The base is believed to function by deprotonating the zwitterionic tetrahedral intermediate.[27] Deprotonation facilitates breakdown of the tetrahedral intermediate, since the increased electron density at nitrogen favors expulsion of an anion:



In aprotic solvents other molecules which can assist proton removal by hydrogen bonding, such as amides, exhibit significant catalysis too.[28]

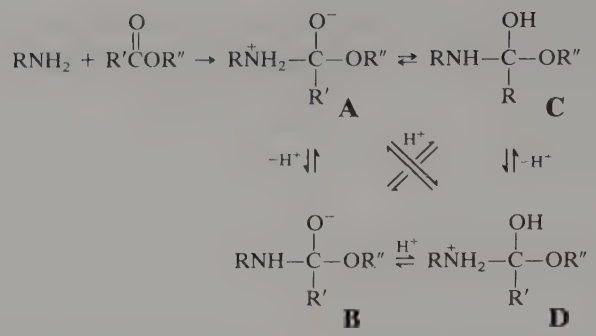
Detailed mechanistic studies have been carried out on aminolysis of substituted aryl acetates and aryl carbonates.[29] Aryl esters are considerably more reactive than alkyl esters because the less basic phenoxide ions are better leaving groups than alkoxide ions. Since a tetrahedral intermediate is involved in these reactions, insight into the factors that determine relative leaving-group ability of nitrogen and oxygen species can be obtained by studying the fate of the tetrahedral intermediate.



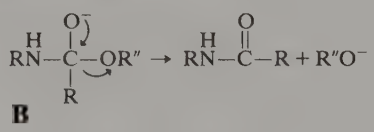
The preference for expulsion of one leaving group over another from a tetrahedral intermediate depends on several factors. Two of the most important are (a) basicity of the leaving group and (b) stabilization of the carbonyl bond in the product by the group which remains.

The tetrahedral intermediate that is formed in aminolysis can exist in several different forms, depending upon the extent and site of protonation:

27. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* **88**, 104 (1966); J. F. Kirsch and A. Kline, *J. Am. Chem. Soc.* **91**, 1841 (1969).
28. C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.* **96**, 1854 (1974).
29. (a) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.* **90**, 2622 (1968).
    (b) A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 7018 (1974).
    (c) A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.* **96**, 7031 (1974).
    (d) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.* **99**, 6970 (1977).

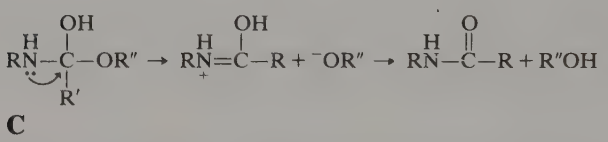


In **A** and **D** the best leaving group at the tetrahedral carbon is the neutral amine, whereas in **B** and **C** the group $^{-}OR''$ would be expected to be a better leaving group than RNH^{-}. Furthermore, in **B** and **C** the lone pair on nitrogen can assist in elimination. In **A** the negatively charged oxygen also has the capacity to assist by "pushing" with reformation of a carbonyl group. Precisely how the intermediate proceeds to product depends upon pH and the identity of the groups RNH_2 and $^{-}OR''$. When $^{-}OR''$ is a relatively poor leaving group, as would be the case for alkyl esters, reaction usually occurs through **B** or **C**.



B

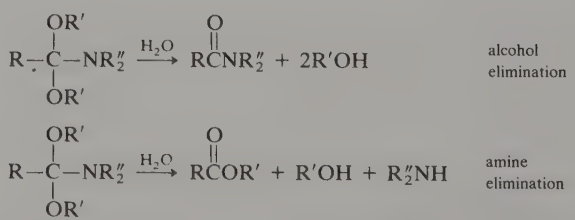
or



C

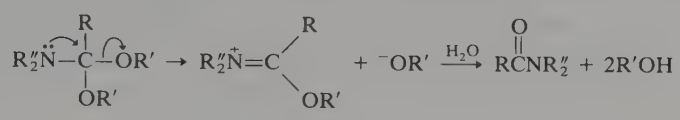
When the leaving group is better, breakdown can occur directly from **A**. This is the case when $-OR''$ is a phenolate anion. It is clear that the presence of acids and bases will be able to affect the mechanism since the overall rate of the reaction will depend upon the position of the equilibria between the four possible tetrahedral intermediates and the rates of the proton transfer processes.

Insight into the factors which govern breakdown of tetrahedral intermediates has also been gained by studying the hydrolysis of amide acetals. If the amino group is expelled an ester is formed, whereas elimination of an alcohol group gives an amide:

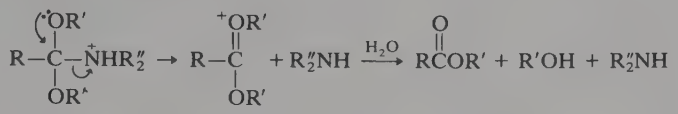


The pH of the solution is of overwhelming importance in determining the course

of these hydrolyses.[30] In basic solution, oxygen elimination is dominant. This is because the unprotonated nitrogen substituent is a poor leaving group and is also more effective at stabilizing the intermediate resulting from alkoxide elimination:

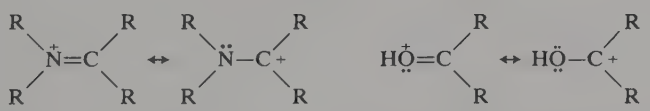


In acidic solution nitrogen is protonated and becomes a better leaving group and also loses its ability to stabilize the resulting intermediate. In these circumstances, oxygen elimination is favored:



In analyzing the behavior of these types of tetrahedral intermediates, it must always be kept in mind that proton transfer reactions are usually fast relative to other steps. This permits the possibility that a minor species, in equilibrium with the major species by proton transfer, may be the active intermediate. Detailed studies of kinetics, solvent isotope effects, and the nature of catalysis are the best tools for investigating the various possibilities.

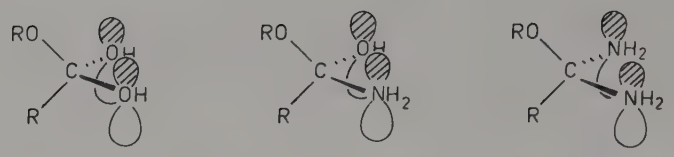
It is useful to recognize that the dissociation of tetrahedral intermediates in carbonyl chemistry bears some broad general relationship to the chemistry of carbocations generated by ionization processes. Thus the question of which substituent on a tetrahedral intermediate is the best leaving group is similar to the issues raised in discussing the ease of generation of a carbocation from related reactants differing only in the identity of the potential *leaving group.* Also the iminium ions and protonated carbonyl compounds which are generated by breakdown of tetrahedral intermediates should be recognized as being stabilized carbocations:



Keeping these relationships in mind can be helpful in understanding the reactivity of tetrahedral intermediates.

Evidence is accumulating that stereoelectronic factors are also of importance in the breakdown of tetrahedral intermediates. The fundamental hypothesis concerning steroelectronic effects is that the preferred conformation involves a leaving group which is oriented *anti*-periplanar to lone-pair electrons on the participating oxygen or nitrogen substituents.[31] Shown below are the stereoelectronically preferred conformations for the elimination of an alkoxide leaving groups from the tetrahedral intermediate involved in three different reaction types:

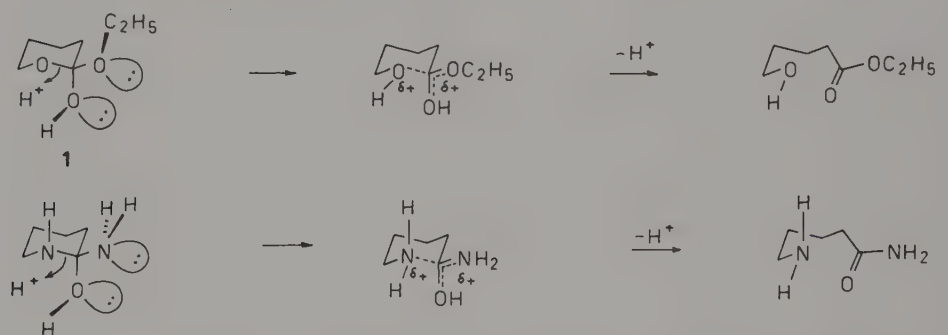
30. R. A. McClelland, *J. Am. Chem. Soc.* **100**, 1844 (1978).
31. P. Deslongchamps, *Heterocycles* **7**, 1271 (1977); *Tetrahedron* **31**, 2463 (1975).



(a) (b) (c)

Preferred stereoelectronic arrangement for participation of lone pairs in expulsion of leaving group –OR from tetrahedral intermediate in (a) ester hydrolysis, (b) ester aminolysis, and (c) imidate aminolysis.

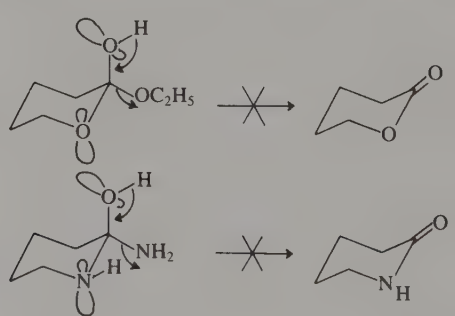
The basis for this preference is that this arrangement permits smooth transformation to the stabilizing π-molecular orbital which is present in the trigonal product. In general, acyclic systems can adopt conformations corresponding to this preferred geometry. In cyclic systems, however, only limited conformations permit this interaction and clear evidence for a stereoelectronic effect has been obtained. Analysis of rates of conformational change and overall reaction rates has led to the conclusion that compounds such as **1** and **2** undergo stereospecific elimination faster than conformational interconversion. The reacting conformers possess the preferred structure with the potential leaving group aligned *anti*periplanar to lone pairs of the remaining stabilizing groups.[32,33]



1

2

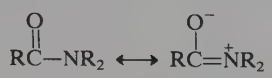
Notice that in each case an alternative breakdown of the tetrahedral intermediate which cannot achieve an *anti*periplanar arrangement with both stabilizing groups is avoided:



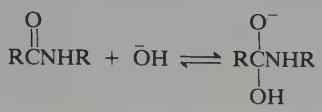
32. P. Deslongchamps, P. Atlani, D. Frehel, A. Malaval, and C. Moreau, *Can. J. Chem.* **52**, 3651 (1974); P. Deslongchamps, R. Chenevert, R. J. Taillefer, C. Moreau, and J. K. Saunders, *Can. J. Chem.* **53**, 1601 (1975).

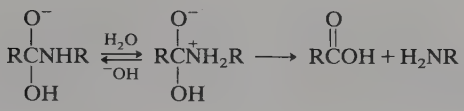
33. C. L. Perrin and G. M. L. Arrhenius, *J. Am. Chem. Soc.* **104**, 2839 (1982).

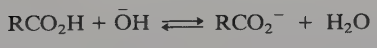
The hydrolysis of amides to carboxylic acids and amines requires considerably more vigorous conditions than ester hydrolysis.[34] The reason is that the electron-releasing nitrogen substitutent imparts a very significant ground state stabilization to the carbonyl group, which is lost in the transition state leading to the tetrahedral intermediate:



In basic solution, a mechanism similar to the $B_{AC}2$ mechanism for ester hydrolysis is believed to operate[35]:

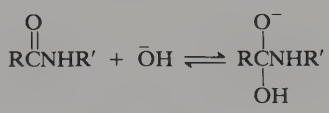


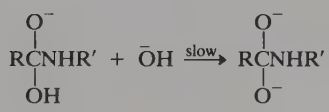


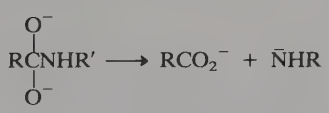


The principal difference lies in the poorer ability of amide ions to act as leaving groups, compared to alkoxides. As a result, protonation at nitrogen is required for breakdown of the tetrahedral intermediate. Also, exchange between the carbonyl oxygen and water is extensive because reversal of the tetrahedral intermediate to reactants is faster than decomposition to products.

In some amide hydrolyses, the breakdown of the tetrahedral intermediate in the forward direction may proceed through formation of a dianion[36]:



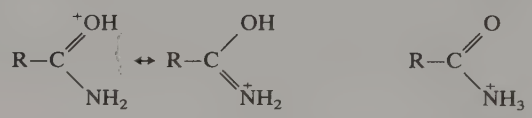




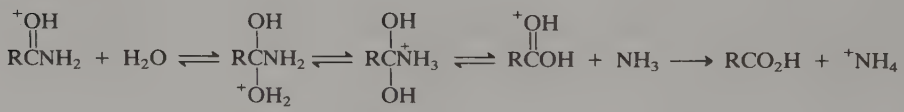
34. C. O'Connor, *Q. Rev. Chem. Soc.* **24**, 553 (1970).
35. M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.* **83**, 4183 (1961).
36. R. M. Pollack and M. L. Bender, *J. Am. Chem. Soc.* **92**, 7190 (1970).

This variation from the ester hydrolysis mechanism also reflects the poorer leaving ability of the amide ions compared to alkoxide ions. The evidence for the involvement of the dianion comes from kinetic studies, and from solvent isotope effects which suggest that a rate-determining proton transfer is occurring.[37] The reaction is also higher than first-order in hydroxide ion under these circumstances, which is consistent with the dianion mechanism.

The mechanism for acid-catalyzed hydrolysis of amides involves attack by water on the protonated amide. An important feature of the chemistry of amides is that the most basic site in an amide is the carbonyl oxygen. Very little of the *N*-protonated form is present.[38] By using *N*-acyltrialkylammonium ions as models of the *N*-protonated amide it has been possible to show that it would be kinetically impossible for acid-catalyzed hydrolysis to proceed via the *N*-protonated form.[39] The major factor that contributes to the stability of the O-protonated form is its π electron delocalization over the O–C–N system. This permits delocalization of the positive charge. No such delocalization is possible in the *N*-protonated form:



The usual hydrolysis mechanism in strongly acidic solution involves addition of water to the O-protonated amide followed by breakdown of the tetrahedral intermediate:



There is almost no exchange of oxygen with water during acid-catalyzed hydrolysis of amides.[40] Since a tetrahedral intermediate is involved, the lack of exchange requires that it must dissociate almost exclusively by elimination of the nitrogen substituent. This requirement is not unreasonable, since the amino group is the most basic site, and therefore the preferred site of protonation in the tetrahedral intermediate. Protonation on nitrogen means that neutral ammonia rather than the amide ion is the leaving group, and its expulsion in preference to hydroxide ion is to be expected.

37. R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *J. Am. Chem. Soc.* **88**, 4008 (1966).
38. R. J. Gillespie and T. Birchall, *Can. J. Chem.* **41**, 148, 2642 (1963); A. J. Kresge, P. H. Fitzgerald, and Y. Chiang, *J. Am. Chem. Soc.* **96**, 4698 (1974); R. B. Martin, *Chem. Commun.*, 793 (1972).
39. A. Williams, *J. Am. Chem. Soc.* **98**, 5645 (1976).
40. R. A. McClelland, *J. Am. Chem. Soc.* **97**, 5281 (1975).

The conversion of alcohols to esters by O-acylation and of amines to amides by N-acylation are fundamental organic reactions. These reactions are the reverse of the hydrolytic procedures discussed in the preceding sections. Section 3.4 in Part B discusses these reactions from the point of view of synthetic applications and methods.

Although the previous two sections of this chapter emphasized hydrolytic processes, two mechanisms that lead to O or N acylation were discussed. In the discussion of acid-catalyzed ester hydrolysis, it was pointed out that this reaction is reversible. Thus it is possible to acylate alcohols by reaction with a carboxylic acid. To drive the reaction forward, the alcohol is usually used in large excess, and it may also be necessary to remove water as it is formed. This can be done by azeotropic distillation in some cases:

$$RCOH + R'OH \overset{H^+}{\rightleftharpoons} RCOR'' + H_2O$$

The second reaction discussed earlier that should be recalled in a discussion of acylation procedures is the aminolysis of esters. This reaction leads to the formation of amides by N-acylation:

$$RCOR' + R''NH_2 \longrightarrow RCNHR'' + R'OH$$

The equilibrium constant for this reaction is ordinarily favorable but the reactions are rather slow.

The most common O- and N-acylation procedures use acylating agents that are more reactive than esters or carboxylic acids. In particular, acid chlorides and acid anhydrides react rapidly with most unhindered hydroxy or amino groups to give alcohols and amides, respectively:

$$R'OH + RCCl \longrightarrow RCOR' + HCl$$

$$R'OH + (RCO)_2O \longrightarrow RCOR' + RCO_2H$$

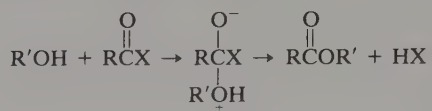
$$R'NH_2 + RCCl \longrightarrow RCNHR' + HCl$$

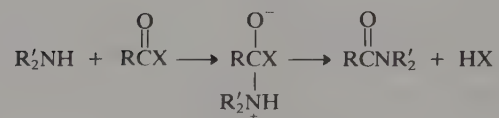
$$R'NH_2 + (RCO)_2O \longrightarrow RCNHR' + RCO_2H$$

The overall mechanisms are well known.[41] The nucleophilic species undergoes addition at the carbonyl group, followed by elimination of the halide or carboxylate group. Acid halides and anhydrides are reactive acylating reagents because of a

41. D. P. N. Satchell, *Q. Rev. Chem. Soc.* **17**, 160 (1963).

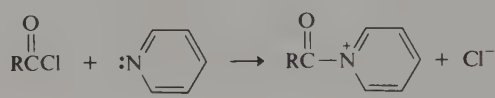
combination of the inductive effect of the halogen or oxygen substituent, which facilitates nucleophilic attack, and the ease with which the tetrahedral intermediate can expel such relatively good leaving groups:

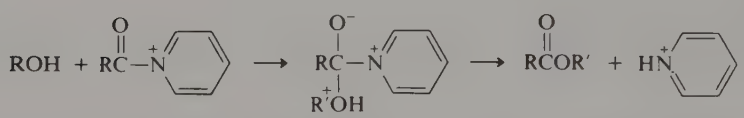




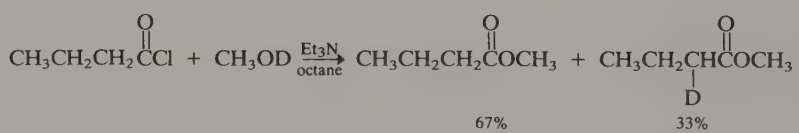
X = halogen or carboxylate

Acylation of alcohols is usually performed in the presence of an organic base such as pyridine. The base can serve two purposes. It reacts with the protons generated in the reaction and prevents the development of high acid concentration. Pyridine also becomes directly involved in the reaction as a *nucleophilic catalyst*:



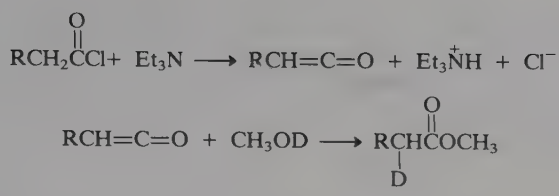


Pyridine is more nucleophilic than an alcohol toward the carbonyl center of an acid chloride. The product that results, an acylpyridinium ion, is, in turn, more reactive toward an alcohol than the original acid chloride. The conditions required for nucleophilic catalysis therefore exist, and acylation of the alcohol by acid chloride is faster in the presence of pyridine than in its absence. Among the evidence that supports this mechanism is spectroscopic observation of the acetylpyridinium ion.[42] With more strongly basic tertiary aliphatic amines such as triethylamine, another mechanism also comes into play. It has been found that when methanol deuterated on oxygen reacts with acid chlorides in the presence of triethylamine, some deuterium is found α to the carbonyl group in the ester:



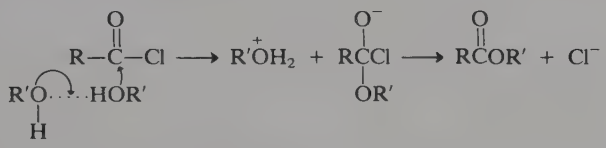
This finding suggests that some of the ester is formed via a ketene intermediate[43]:

42. A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.* **92**, 5432, 5442 (1970).
43. W. E. Truce and P. S. Bailey, Jr., *J. Org. Chem.* **34**, 1341 (1969).

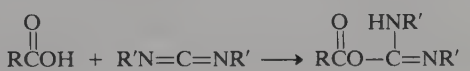


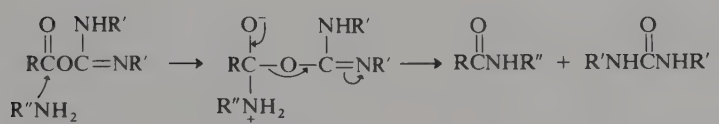
Ketenes undergo rapid addition by nucleophilic attack at the *sp*-carbon atom. The reaction of tertiary amines and acid halides, in the absence of nucleophiles, is a general preparation for ketenes.[44]

Kinetic studies of the reaction of alcohols with acid chlorides in polar solvents in the absence of basic catalysts generally reveal terms both first order and second order in alcohol.[45] Transition states in which the second alcohol molecule acts as a proton acceptor have been proposed:



In addition to acid chlorides and acid anhydrides, there are a number of other types of compounds that are reactive acylating agents. Many have been developed to facilitate the synthesis of polypeptides, in which mild acylation conditions and high selectivity are required. An important group of reagents for converting carboxylic acids to active acylating agents are the carbodiimides. The most frequently used compound is dicyclohexylcarbodiimide. The mechanism for carbodiimide-promoted amide bond formation is shown below:

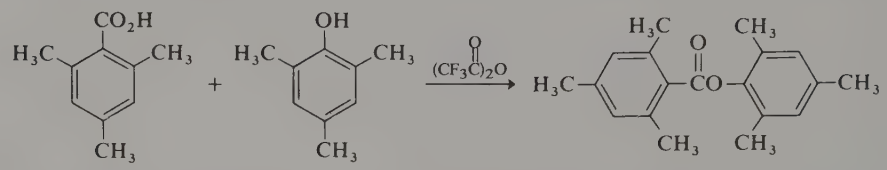




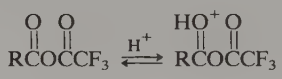
The first step is addition of the carboxylic acid to a C=N bond of the carbodiimide to generate an O-acylated urea derivative. This is a reactive acylating agent because there is a strong driving force for elimination of the urea unit, with formation of the very stable amide carbonyl group.[46] The amine reacts with the active acylating agent. In the absence of an amine, the acid would be converted to the anhydride, with a second molecule of carboxylic acid serving as the nucleophile.

44. R. N. Lacey, in *The Chemistry of Alkenes*, S. Patai (ed.), Interscience Publishers, New York, 1964, pp. 1168–1170; W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 108 (1947).
45. D. N. Kevill and F. D. Foss, *J. Am. Chem. Soc.* **91**, 5054 (1969); S. D. Ross, *J. Am. Chem. Soc.* **92**, 5998 (1970).
46. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.* **88**, 1013, 1020 (1966).

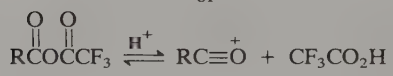
Carboxylic acids react with trifluoroacetic anhydride to give reactive acylating agents that are especially useful for the acylation of hindered alcohols and phenols:



The active acylating agent may be the protonated mixed anhydride,[47] or, alternatively, the anhydride may dissociate to the acylium ion and trifluoroacetate[48]:

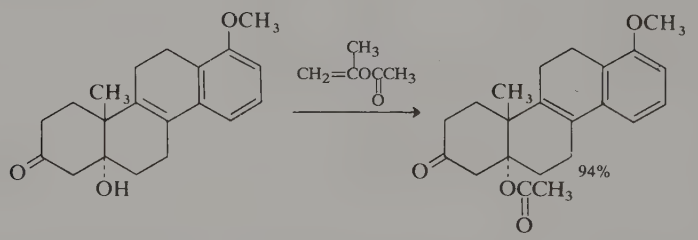


or



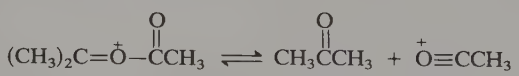
Either mechanism explains why trifluoroacetylation of the nucleophile does not occur. Protonation of the anhydride would occur selectively at the more electron-rich carbonyl oxygen, rather than at the carbonyl flanked by the very electron-withdrawing trifluoromethyl group. Similarly, cleavage of the unsymmetrical anhydride would occur to give the more stable acylium ion. The trifluoroacetylium ion would be highly unstable. In either case the more reactive acylating site is derived from the carboxylic acid which is being activated by trifluoracetic anhydride.

Another useful family of acylating agents are the enol esters. The acetate of the enol form of acetone, isopropenyl acetate, is the most commonly used member of this group of compounds. They act as acylating agents in the presence of a trace amount of acid catalyst, and are reactive toward poor nucleophiles such as hindered hydroxyl groups:



Ref.49

The active acylating agent is presumably the C-protonated enol ester:



This species would be highly reactive owing to the presence of a positively charged

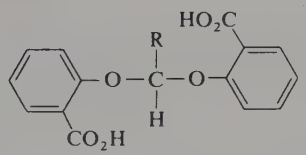
47. R. C. Parish and L. M. Stock, *J. Org. Chem.* **30**, 927 (1965).
48. J. M. Tedder, *Chem. Rev.* **55**, 787 (1955).
49. W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Am. Chem. Soc.* **78**, 6302 (1956).

oxygen. An alternative possibility is that the protonated enol ester decomposes to acetone and an acylium ion, which then acts as the acylating agent. Section 3.4 of Part B gives additional examples of synthetically useful acylation reagents.

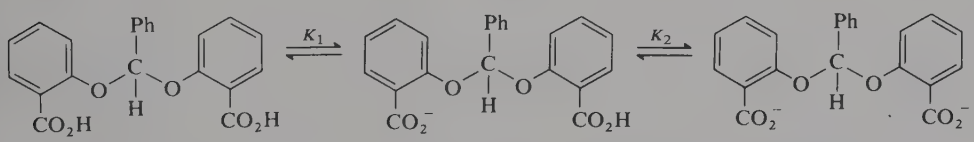
8.8. Intramolecular Catalysis

The fundamental reactions of carbonyl compounds have provided the testing ground for developing the facts and theories of intramolecular catalysis. Studies in intramolecular catalysis have been designed to determine how much more efficiently a given functional group acts as a catalyst when it is part of the reacting molecule and in such a geometry that encounter between the catalytic group and the reacting group is facilitated. These studies are important to understanding biological mechanisms because the enzymes are believed to act as exceedingly efficient catalysts, at least in part, by bringing together at the "active site" the various basic, nucleophilic, or acidic groups in a very favorable orientation of a particular reaction. The next several paragraphs illustrate some of the facts that have emerged from these studies and the mechanistic conclusions that have been drawn.

It was pointed out in the mechanistic discussion concerning acetals and ketals that general acid catalyzed hydrolysis occurs only for acetals and ketals having special structural features. Usually, specific acid catalysis operates. The question of whether general acid catalysis could be observed in intramolecular reactions has been of interest because intramolecular general acid catalysis is thought to play a part in the mechanism of action postulated for the enzyme lysozyme, which hydrolyzes the acetal linkage present in certain polysaccarides. One group of molecules that has been examined as a model system are acetals derived from *o*-hydroxybenzoic acid (salicylic acid):



The pH–rate profile (see Figure 8.5) indicates that of the species which are available, the monoanion of the acetal is most reactive. The concentration of this species is at a maximum in the intermediate pH range. The neutral molecule decreases in concentration with increasing pH; the converse is true of the dianion.



The transition state for the rapid hydrolysis of the monoanion has been depicted as involving an intramolecular general acid catalysis by the carboxylic acid group,

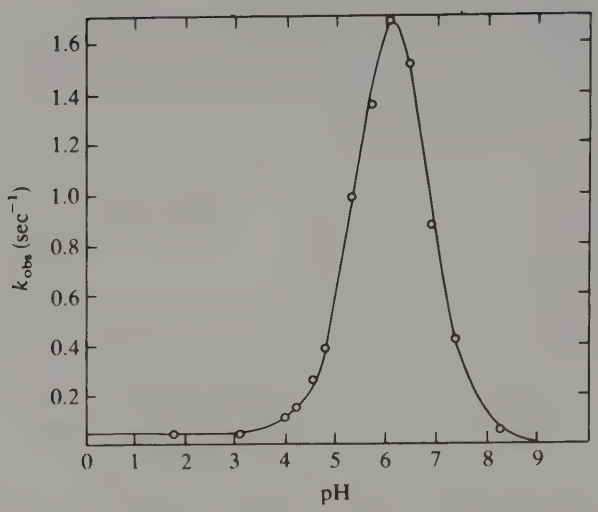
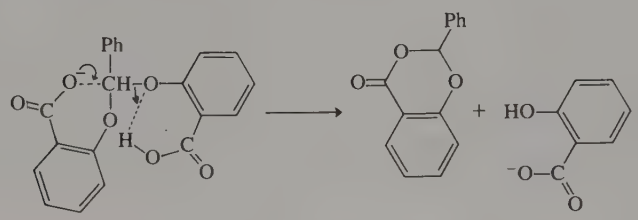
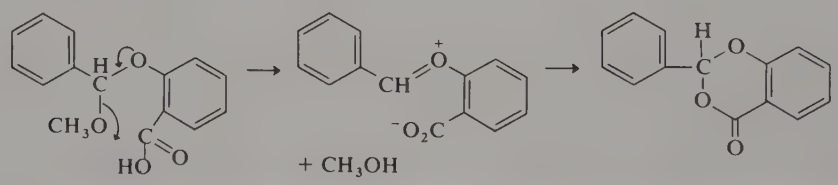


Fig. 8.5. pH–Rate profile for release of salicylic acid from benzaldehyde disalicyl acetal. [From E. Anderson and T. H. Fife, *J. Am. Chem. Soc.* **95**, 6437 (1973). Reproduced by permission of the American Chemical Society.]

with participation by the anionic carboxylate group, which can serve to stabilize the developing carbonium ion center:



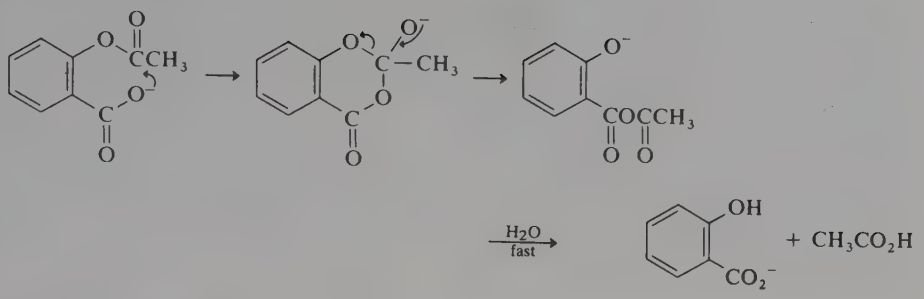
A mixed acetal of benzaldehyde, methanol, and salicylic acid has also been studied.[50] It, too, shows a marked rate enhancement attributable to intramolecular general acid catalysis:



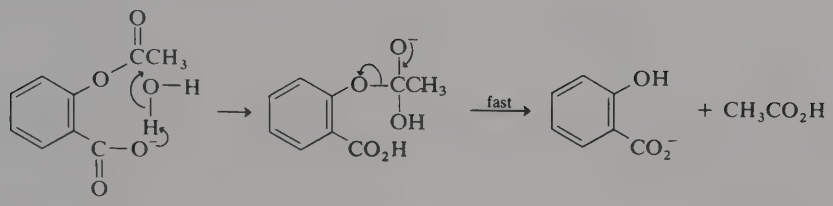
The case of intramolecular participation in ester hydrolysis has been extensively studied using acetylsalicylic acid (aspirin) and its derivatives. The kinetic data show that the anion is hydrolyzed more rapidly than the neutral species, indicating that the carboxylate group becomes involved in the reaction in some way. Three mechanisms can be considered:

50. T. H. Fife and E. Anderson, *J. Am. Chem. Soc.* **93**, 6610 (1971).

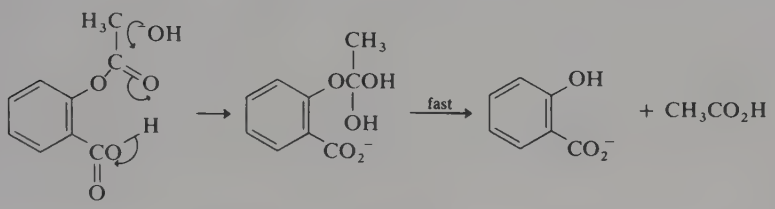
I. Nucleophilic catalysis



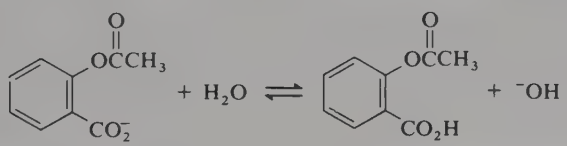
II. General base catalysis



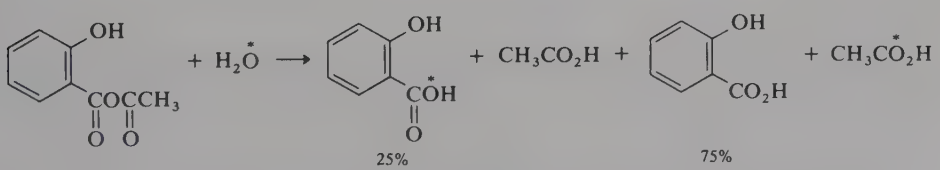
III. General acid catalysis of hydroxide ion attack



Mechanism III cannot be immediately distinguished from the first two because of the kinetic equivalence of the reagents involved, which are in rapid equilibrium:



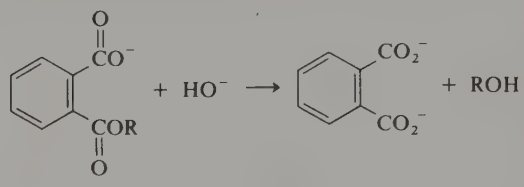
Mechanism I has been ruled out by an isotopic labeling experiment. The mixed anhydride of salicylic acid and acetic acid is an intermediate if nucleophilic catalysis occurs. This molecule is known to hydrolyze in water with about 25% incorporation



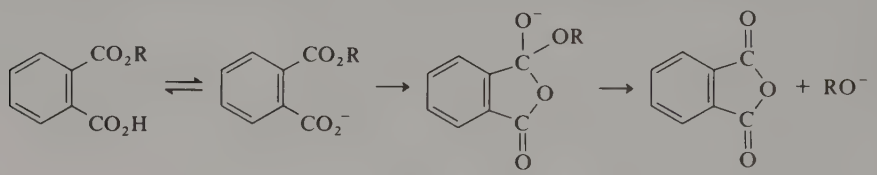
of solvent water into the salicyclic acid. Hydrolysis of aspirin in $H_2{}^{18}O$ leads to no incorporation of ^{18}O into the product salicyclic acid, ruling out the nucleophilic

catalysis mechanism.[51] The general acid catalysis mechanism (III) can be ruled out on arguments based on the failure of addition of other nucleophiles to show evidence for general acid catalysis by the neighboring carboxylic acid group. Thus mechanism II, general acid catalysis of hydroxide ion attack, is believed to be the correct description of the hydrolysis of aspirin.

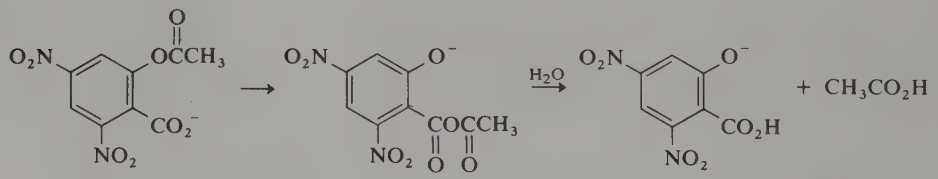
The extent to which intramolecular nucleophilic catalysis of the type depicted in mechanism I is important is a function of the leaving ability of the alkoxy group, as is demonstrated by a study of a series of phthalate monoesters:



Nucleophilic participation is important only for esters of alcohols that have $pK_a \leq 13$; i.e., the alcohol must be rather acidic. Specifically, phenyl and trifluoroethyl esters showed nucleophilic catalysis, but methyl and 2-chloroethyl esters did not.[52] This result reflects the fate of the tetrahedral intermediates that result from nucleophilic participation. For relatively acidic alcohols, the alkoxide group can be eliminated, leading to hydrolysis via nucleophilic catalysis:



For less acidic alcohols, nucleophilic participation is ineffective because of the decreased tendency for such alcohols to function as leaving groups. The tetrahedral intermediate formed by intramolecular addition simply returns to starting material. This leaving-group effect has been demonstrated to occur also in the case of salicylate esters. Phenyl esters with good leaving groups (those substituted with nitro groups *ortho* and *para* to the phenolic oxygen, in particular) hydrolyze via the nucleophilic catalysis mechanism[53]:



Intramolecular catalysis of ester hydrolysis by nitrogen nucleophiles is also important. The role of imidazole rings in intramolecular catalysis has received

51. A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.* **89**, 4857 (1967).
52. J. W. Thanassi and T. C. Bruice, *J. Am. Chem. Soc.* **88**, 747 (1966).
53. A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.* **89**, 5960 (1967); **90**, 5818 (1968).

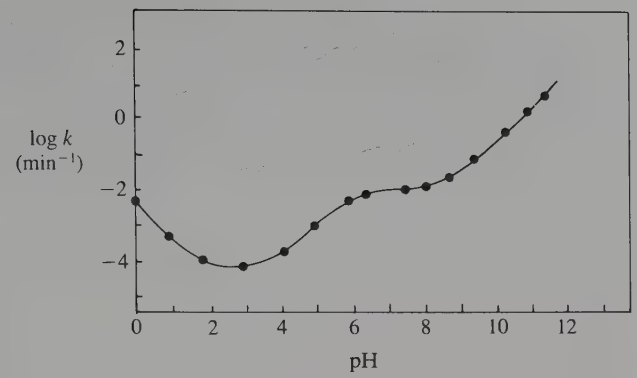
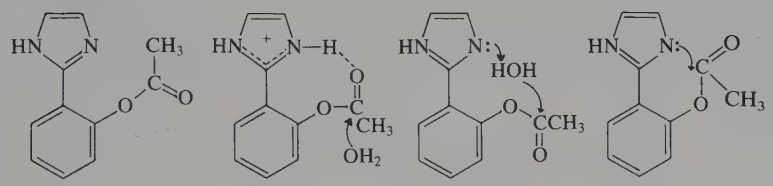


Fig. 8.6. pH–Rate profile for compound **3**. Reproduced with permission from Ref. 54.

particularly close scrutiny. There are at least two reasons for this. One is that the imidazole ring of the histidine residue in proteins is believed to frequently be involved in enzyme-catalyzed hydrolyses. Secondly, this ring has several possible catalytic functions which include action as a general acid catalyst in the protonated form, action as a general base in the neutral form, and action as a nucleophilic catalyst in the neutral form. A study of a number of derivatives of compound **3** was undertaken to distinguish between the importance of these various possible mechanisms as a function of pH.[54]



3 general acid catalysis general base catalysis nucleophilic catalysis

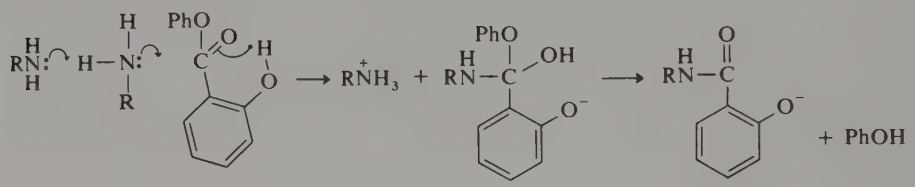
The relative importance of the potential catalytic mechanisms depends on pH, which also determines the concentration of other participating species such as water, hydronium ion, and hydroxide ion. At low pH the general acid catalysis mechanism dominates and comparison with analogous systems where the intramolecular proton transfer process is not available suggests that the intramolecular catalysis results in a 25–100-fold rate enhancement. At neutral pH the intramolecular general base mechanism begins to operate. It is estimated that the catalytic effect for this mechanism is a factor of about 10^4. Although nucleophilic catalysis was not observed in the parent compound, it was observed in certain substituted derivatives. The change in mechanism with pH for compound **3** gives rise to the pH–rate profile shown in Fig. 8.6.

The rates at the extremities pH < 2 and pH > 9 are proportional to $[H^+]$ and $[^-OH]$, respectively, and represent the specific proton-catalyzed and hydroxide-catalyzed mechanisms. The region pH 2–4 represents the area where intramolecular

54. G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.* **96**, 2463 (1974).

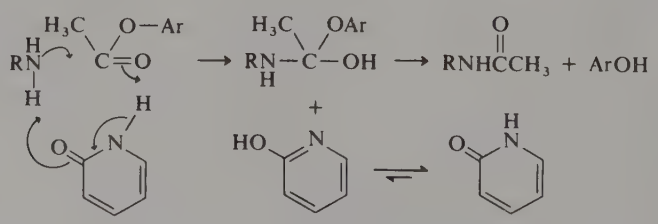
general acid-catalyzed mechanism operates, whereas at pH 6–8 the intramolecular general base mechanism is operative. In the absence of the intramolecular catalysis the H^+- and ^-OH-catalyzed reactions would decrease in proportion to the concentration of the catalytic species to a minimum value representing the "uncatalyzed hydrolysis by water." An estimate of the effectiveness of the intramolecular mechanism can be made by extrapolating the lines which are proportional to $[H^+]$ and $[^-OH]$. The extent to which the actual rate lies above these extrapolated lines in the pH range 2–7 represents the contribution from the intramolecular catalysis.

Intramolecular participation of the *o*-hydroxy group in the aminolysis of phenyl salicylate has been established by showing that such compounds are more reactive than analogs lacking the hydroxyl substituent. This reaction exhibits overall third-order kinetics, second order in the reacting amine. This is similar to aminolysis of simple esters. Both intermolecular general base catalysis (by the second amine molecule) and intramolecular general acid catalysis (by the hydroxyl group) apparently occur.[55]



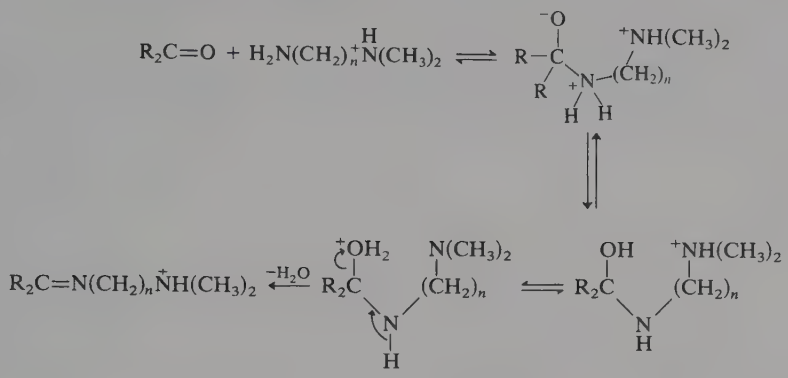
Such a mechanism can reduce the activation energy of the reaction in at least two ways. The partial transfer of a proton to the carbonyl oxygen increases the electrophilicity of the carbonyl. Likewise, partial deprotonation of the amino group increases its nucleophilicity.

Certain molecules that can permit concerted proton transfers are efficient catalysts for reactions at carbonyl centers. An example that can be cited is the catalytic effect that 2-pyridone has on the aminolysis of esters. Although neither a strong base ($pK_{a_{H^+}}$ 0.75) nor a strong acid (pK_a 11.62), 2-pyridone is an effective catalyst of the reaction of *n*-butylamine with 4-nitrophenyl acetate.[56] The overall rate is more than 500 times greater when 2-pyridone acts as the catalyst than when a second molecule of butylamine (acting as a general base) is present in the transition state. 2-Pyridone has been called a *tautomeric catalyst* to emphasize its role in proton transfer. Such molecules are also called *bifunctional catalysts*, since two atoms in the molecule are involved in the proton transfer process.

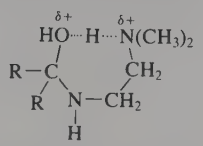


55. F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.* **91**, 5346 (1969).
56. P. R. Rony, *J. Am. Chem. Soc.* **91**, 6090 (1969).

Another type of bifunctional catalysis has been noted with α,ω-diamines in which one of the amino groups is primary and the other tertiary. These substituted diamines are from several times to as much as 100 times more reactive toward imine formation than similar monofunctional amines.[57] This is attributed to a catalytic intramolecular proton transfer.



The rate enhancement is greatest for $n = 2$ (1000) and still significant for $n = 3$ (10). As the chain is lengthened to $n = 4$ and $n = 5$, any rate enhancement is minor. This reflects the fact that when $n = 4$ or 5, the transition state for the intramolecular proton transfer would have to contain rings of nine and ten atoms, respectively, and such cyclic transition states are not favorable. The particularly rapid reaction when $n = 2$ corresponds to the possibility for a proton transfer via a seven-membered cyclic transition state. Assuming that the proton is transferred in a colinear fashion, this represents a favorable transition state geometry.



These examples serve to introduce the idea of intramolecular catalysis and the fact that favorable juxtaposition of acidic, nucleophilic, or basic sites can markedly accelerate some of the common reactions of carbonyl compounds. It is widely believed that nature has evolved a similar strategy of optimal placement of functional groups to achieve the catalytic activity of enzymes. The functional groups employed are the substituents present on many of the amino acid residues found in proteins. The acidic sites available include phenolic groups or carboxyl groups (from tyrosine and glutamic acid or aspartic acid, respectively). Basic sites include an amidine group in arginine, the imidazole ring in histidine, and the ε-amino group of lysine. Thiol (cysteine) and hydroxyl (threonine and serine) groups are also available to participate in enzyme-catalyzed processes. The student interested in further examining the mechanisms of enzymatic reactions will find these topics covered in considerably more detail in several of the texts listed as general references.

57. J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.* **42**, 1593 (1977); J. Hine and Y. Chou, *J. Org. Chem.* **46**, 649 (1981).

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T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*, Benjamin, New York, 1966.
A. J. Kirby and A. R. Fersht, in *Progress in Bioorganic Chemistry*, Vol. 1, E. T. Kaiser and F. J. Kezdy (eds.), Wiley–Interscience, New York, 1971, pp. 1–82.
S. Patai (ed.), *The Chemistry of the Carbonyl Group*, Wiley–Interscience, New York, 1974.
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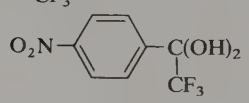
J. E. Zabicky (ed.), *The Chemistry of Amides*, Wiley–Interscience, New York, 1970.

Problems

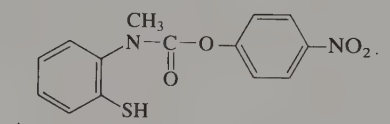
(*References for these problems will be found on page 705.*)

1. The hydrates of aldehydes and ketones are considerably more acidic than normal alcohols (p$K \approx 16$–19). How would you account for this fact? Some reported values are shown below. Explain the order of relative acidity.

Hydrate	pK
$H_2C(OH)_2$	13.4
$Cl_3CCH(OH)_2$	10.0
$PhC(OH)_2$ CF_3	10.0
	9.2

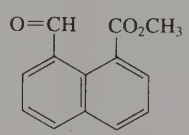
2. Suggest explanations for each of the following observations.

   (a) The equilibrium constant for cyanohydrin formation from 3,3-dimethyl-2-butanone is 40 times larger than that for acetophenone.
   (b) The rate of release of *p*-nitrophenoxide from compound **A** is independent of pH in aqueous solution of pH > 10.

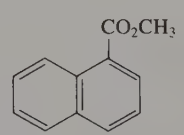


A

   (c) Ester **B** undergoes alkaline hydrolysis 8300 times faster than ester **C** in aqueous dioxane.

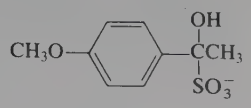


B

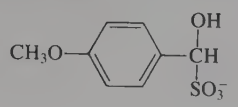


C

(d) Under comparable conditions the general base-catalyzed elimination of bisulfite ion from **D** is about ten times greater than from **E**.



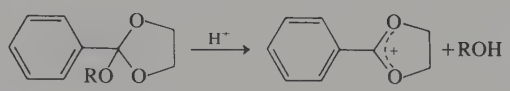
D



E

3. Arrange the carbonyl compounds in each group in order of decreasing rate of hydrolysis of their respective diethyl acetals or ketals. Explain your reasoning.
   (a) acetaldehyde, chloroacetaldehyde, crotonaldehyde
   (b) acetaldehyde, formaldehyde, acetone
   (c) cyclopentanone, cyclohexanone, camphor
   (d) acetone, methyl *tert*-butyl ketone, methyl neopentyl ketone
   (e) benzaldehyde, *p*-methoxybenzaldehyde, butyraldehyde.

4. The acid-catalyzed hydrolysis of 2-alkoxy-2-phenyl-1,3-dioxolanes has been studied. The initial step is rate determining under certain conditions and is described by the rate law given below, which reveals general acid catalysis.



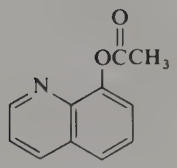
$$k_{obs} = k_{H^+}k_{H_2O}[H_2O] + k_{HA}[HA]$$

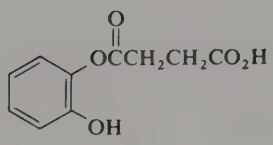
By determining k_{HA} for several different buffer catalysts and each of several alkoxy leaving groups it was determined that there was a relationship between the Brønsted coefficient α and the structure of the alkoxy leaving group. The data are given and show that α decreases as the alkoxy group becomes less basic.

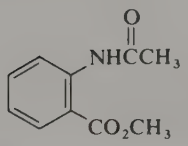
RO–	α
Cl_2CHCH_2O–	0.69
$ClCH_2CH_2$–	0.80
$CH_3OCH_2CH_2O$–	0.85
CH_3O–	0.90

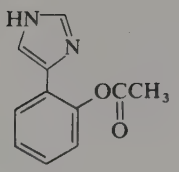
What information is provided by the fact that the Brønsted α decreases as the acidity of the alcohol increases? Discuss these results in terms of a three-dimensional potential energy diagram with the extent of O–H bond formation and the extent of C–O bond breaking taken as the reaction progress coordinates.

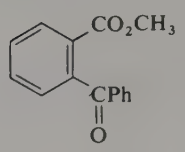
5. Each of the following molecules has been considered to be capable of some form of intramolecular catalysis of ester hydrolysis. For each substrate indicate one or more mechanisms by which intramolecular catalysis might occur. Depict a transition state arrangement that shows this catalysis.

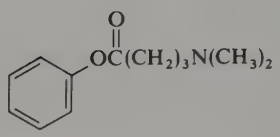
(a) 

(b) 

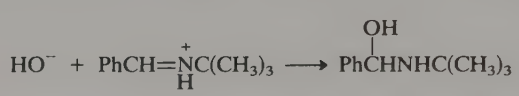
(c) 

(d) 

(e) 

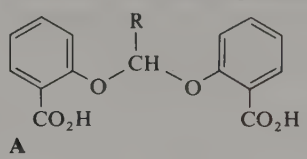
(f) 

6. Consider the alkaline pH region of the pH–rate profile in Fig. 8.4 (p. 414), which indicates a rate independent of pH. The rate-controlling reaction in this region is



Show that the rate of this reaction is pH independent, despite the involvement of two species, the concentrations of which are pH dependent.

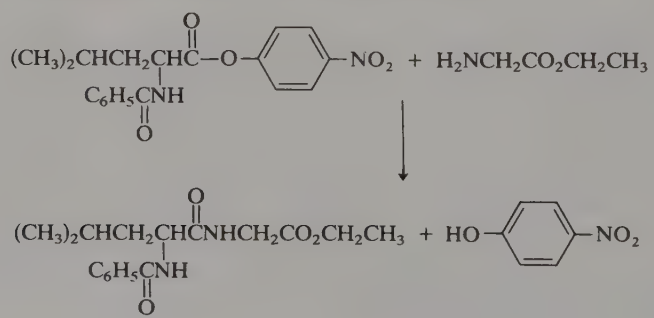
7. Derive the general expression for the observed rate constant for hydrolysis of **A** as a function of pH. Assume, as is the case experimentally, that intramolecular



A

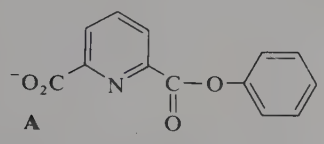
general acid catalysis completely outweighs intermolecular catalysis by hydronium ion in the pH range of interest. Does the form of your expression agree with the pH–rate profile given for this reaction in Fig. 8.5 (p. 438)?

8. Optically pure dipeptide is obtained when the *p*-nitrophenyl ester of *N*-benzoyl-L-leucine is coupled with glycine ethyl ester in ethyl acetate:



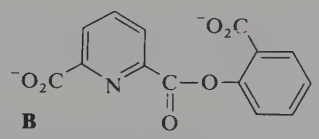
If, however, the *p*-nitrophenyl ester of *N*-benzoyl-L-leucine is treated with 1-methylpiperidine in chloroform for 30 min, then coupled with glycine ethyl ester, the dipeptide isolated is almost completely racemic. Furthermore, treatment of the *p*-nitrophenyl ester of *N*-benzoyl-L-leucine with 1-methylpiperidine alone leads to the formation of a crystalline material, $C_{13}H_{15}NO_2$, having strong IR bands at 1832 and 1664 cm^{-1}. Explain these observations, and suggest a reasonable structure for the crystalline product.

9. The rates of hydrolysis of the ester group in compounds **A** and **B** have been compared. The effect of an added metal ion (Ni^{2+}) on the rate of hydrolysis has been studied, and the observed rate constants for attack by ^-OH are tabulated. Suggest the most favorable transition state structure for the addition step of the hydrolysis reaction with each substrate under each set of conditions. Discuss the relationship between the structures of these transition states and the relative rates of attack by hydroxide ion.



A

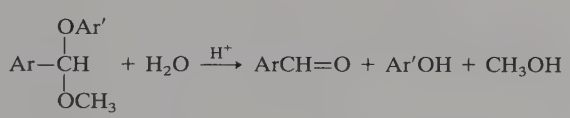
k_{HO^-}: $3.0 \times 10^2\ M^{-1}\ sec^{-1}$
k_{HO^-} in presence of excess Ni^{2+}:
$2.8 \times 10^6\ M^{-1}\ sec^{-1}$



B

k_{HO^-}: $7.1 \times 10^1\ M^{-1}\ sec^{-1}$
k_{HO^-} at pH values where salicylic acid group is not ionized:
$2.7 \times 10^5\ M^{-1}\ sec^{-1}$
k_{HO^-} when salicylic acid group is not ionized and excess Ni^{2+} is present:
$2.7 \times 10^7\ M^{-1}\ sec^{-1}$

10. Data pertaining to substituent effects on the acid-catalyzed hydrolysis of mixed methyl aryl acetals of benzaldehyde are given below. The reactions exhibited general acid catalysis and the Brønsted α values are tabulated. Discuss the information provided by these data about the transition state for the first hydrolysis step, making reference to a diagram showing the location of the transition state as a function of O–H bond formation and C–O bond breaking.



$$\mathrm{Ar{-}CH(OAr')(OCH_3) + H_2O \xrightarrow{H^+} ArCH{=}O + Ar'OH + CH_3OH}$$

Series I, substituent in Ar			Series II, substituent in Ar'		
X	k_{cat}[a]	α	X	k_{cat}[a]	α
m-NO_2	2.7×10^{-4}	1.05	m-NO_2	8.85×10^{-2}	0.49
m-F	2.2×10^{-3}	0.92	*m*-Br	4.7×10^{-2}	0.65
m-CH_3O	9.6×10^{-3}	0.78	*m*-F	2.45×10^{-2}	0.67
H	1.3×10^{-2}	0.77	*m*-CH_3O	2.55×10^{-2}	0.71
p-CH_3	1.1×10^{-1}	0.72	H	1.3×10^{-2}	0.77
p-CH_3O	2.8×10^{-1}	0.68	*p*-CH_3	1.3×10^{-2}	0.88
			p-CH_3O	1.65×10^{-2}	0.96

a. Rate constant for catalysis by acetic acid.

11. Indicate which compound in each of the following pairs will have the more negative standard free-energy change for hydrolysis at pH 7:

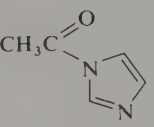
(a) $CH_3CO_2CH_3$ *or* $Ch_3\overset{\overset{O}{\|}}{C}SCH_3$

(b) $CH_3CO_2CH_3$ *or* $CH_3CO_2PO_3H_2$

(c) $CH_3CO_2CH_3$ *or* $H_2NCH_2CO_2CH_3$

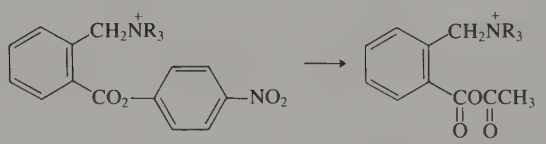
(d) $CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}SCH_3$ *or* $CH_3\overset{\overset{O}{\|}}{C}SCH_3$

(e) $CH_3CO_2CH_3$ *or*



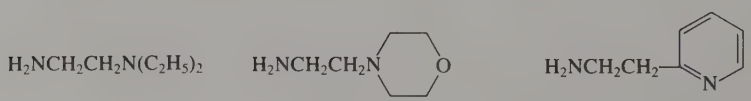
(f) $CH_3CO_2CH_3$ *or* $CH_3\overset{\overset{O}{\|}}{C}N(CH_3)_2$

12. Sodium acetate reacts with *p*-nitrophenyl benzoates to give mixed anhydrides if the reaction is conducted in a polar aprotic solvent in the presence of a crown ether. The reaction is strongly accelerated by quaternary nitrogen groups substituted at the *ortho* position. Explain the basis for the enhanced reactivity of these compounds.



Introduction of $^+NR_3$ for H accelerates the reaction by a factor of $> 10^3$

13. The kinetics of the hydrolysis of some imines derived from benzophenone and primary amines revealed the normal dependence of mechanism on pH with rate-determining nucleophilic attack at high pH and rate-determining decomposition of the tetrahedral intermediate at low pH. The simple primary amines show a linear correlation between the rate of nucleophilic addition and the basicity of the amine. Several diamines which were included in the study, in particular **A**, **B**, and **C**, all showed a positive (more reactive) deviation from the correlation line for the simple amines. Why might these amines be more reactive than predicted on the basis of their basicity?



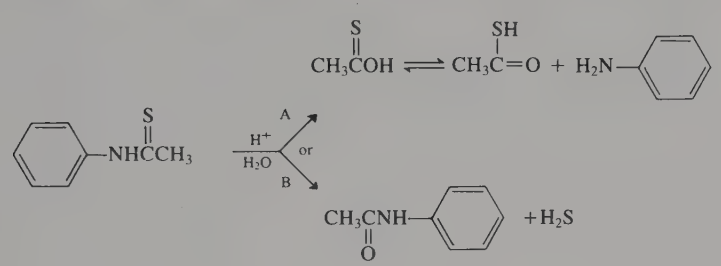
A **B** **C**

14. The following data give the dissociation constants for several acids that catalyze hydration of acetaldehyde. Also given are the rate constants for the hydration reaction catalyzed by each acid. Treat the data according to the Brønsted equation, and comment on the mechanistic significance of the result.

Acid	K	k_{hydr}
Formic	1.77×10^{-4}	1.74
Phenylacetic	4.9×10^{-5}	0.91
Acetic	1.75×10^{-5}	0.47
Pivalic	9.4×10^{-6}	0.33

15. The rates of imine formation of simple aliphatic amines with acetone have been compared with those of 2-dimethylaminoethylamine, 3-diethylaminopropylamine, and 4-dimethylaminobutylamine at pH values where the tertiary amino group is protonated. The bifunctional amines show rate enhancements of 1000, 12, and 3, respectively. Suggest one or more mechanisms by which the additional tertiary amino substituents might catalyze imine formation.

16. The acid-catalyzed hydrolysis of thioacetanilide can follow two courses.

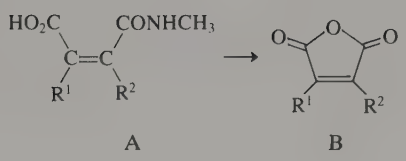


The product analysis permits determination of the amount of product formed by each path, as a function of the acidity of the solution. The results are as shown:

H_2SO_4 (% by weight)	3.2	6.1	12	18	36	48
% following path A	50	55	65	75	96	100

Provide a mechanism in sufficient detail to account for the change in product ratio with acid strength.

17. Figure 8. P17 gives the pH–rate profile for conversion of the acid A to the anhydride B in aqueous solution. The reaction shows no sensitivity to buffer concentration. Notice that the reaction rate increases with the size of the alkyl substituent, and in fact the derivative with $R^1 = R^2 = CH_3$ is still more reactive. Propose a mechanism which is consistent with the pH–rate profile and the structure of the initially formed product (which is subsequently hydrolyzed to the diacid). How do you account for the effect of the alkyl substituents on the rate?



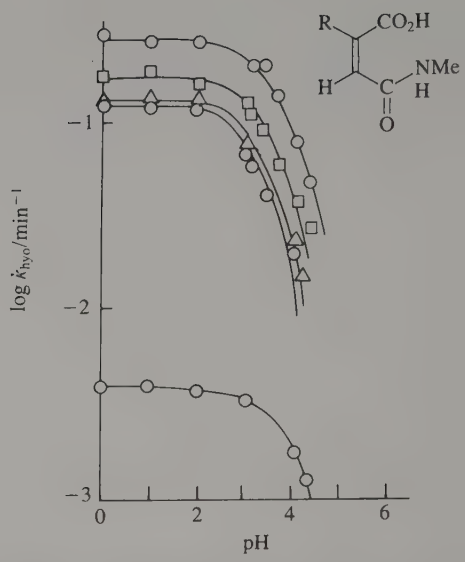


Fig. 8.P17. pH–Rate profiles for the hydrolysis of alkyl-*N*-methylmaleamic acids at 39°C and ionic strength 1.0. In increasing order of reactivity R = H, Me, Et, *i*-Pr, and *t*-Bu.

18. Examine the structure of the reactants given and the pH–rate profiles (Figs. 8.P18a–d) of the reactions in question. Offer explanations for the response of the observed reaction rate to the pH for each case.

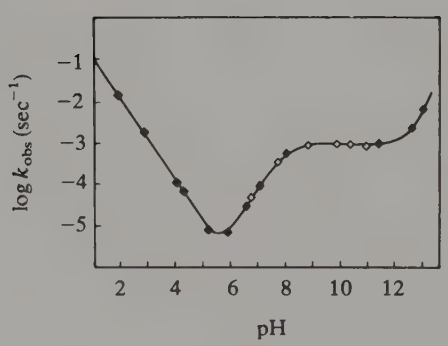


Fig. 8.P18a. (Reproduced from problem reference 18a by permission of the American Chemical Society.)

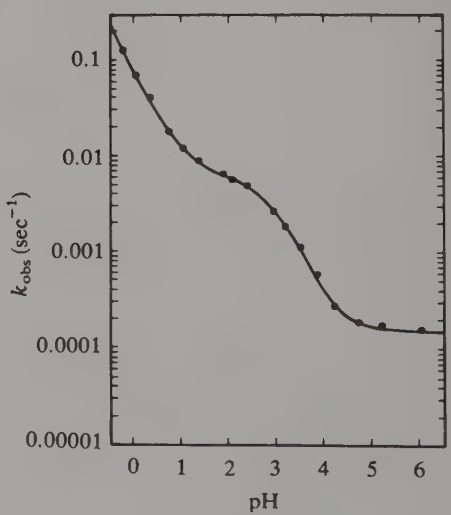


Fig. 8.P18b. (Reproduced from problem reference 18b by permission of the American Chemical Society.)

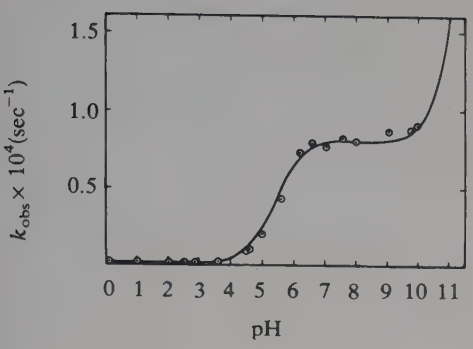


Fig. 8.P18c. (Reproduced from problem reference 18c by permission of the American Chemical Society.)

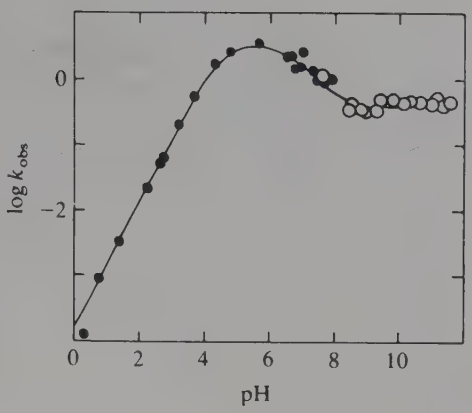
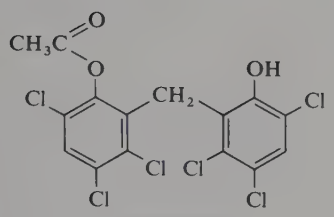


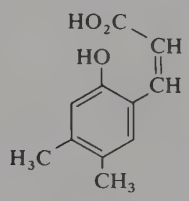
Fig. 8.P18d. (Reproduced from problem reference 18d by permission of the American Chemical Society.)

(a)



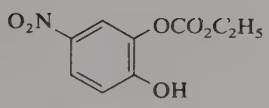
ester hydrolysis

(b)



lactonization

(c)



ester hydrolysis

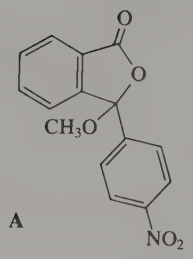
(d) $(CH_3)_2CHCH{=}NCH_3$

hydrolysis

19. The hydrolysis of the lactone **A** shows a significant catalysis by acetate ion in acetate buffer, with the rate expression being

$$k_{obs} = 1.6 \times 10^{-6} + 6.4 \times 10^{-4}[H^+] + 2.08 \times 10^{-5}[OAc^-] + 49[^-OH]$$

This results in a pH rate profile as shown in Fig. 8P19, with the acetate catalysis being significant in the pH range 3–6. Discuss how this catalysis by acetate ion might occur. What are the most likely mechanisms for hydrolysis at pH < 2 and pH > 7, where the rates are linear in $[H^+]$ and $[^-OH]$, respectively?



A

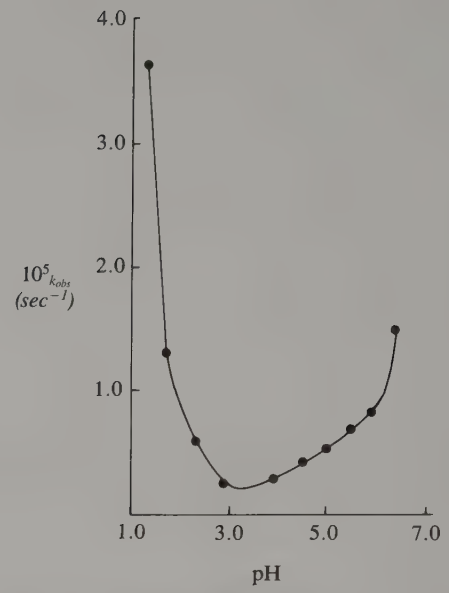
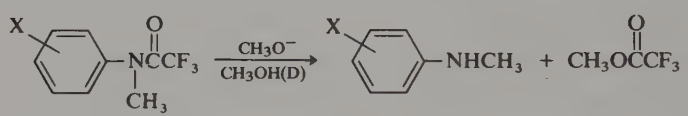


Fig. 8.P19. pH–Rate profile for hydrolysis of A in buffered aqueous solution at 70°C.

20. Some data on substituent effects for the reaction of trifluoroacetanilides with methoxide ion in methanol and methanol-O-*d* are given below. Calculate the isotope effect for each system. Plot the rate data against appropriate Hammett substituent constants. What facets of the data are in agreement with a normal addition–elimination sequence passing through a tetrahedral intermediate? What facets of the data indicate additional complications? Can you propose a mechanism that is consistent with all the data given?

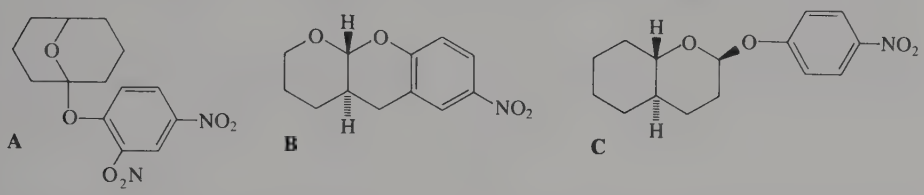


X	k_{CH_3OH} [a]	k_{CH_3OD} [a]
m-NO_2	5.75	8.13
m-Br	0.524	0.464
p-Cl	0.265	0.274
p-Br	0.349	0.346
m-Cl	0.513	0.430
m-OCH_3	0.110	0.101
H	0.104	0.0899
m-CH_3	0.0833	0.0595
p-CH_3	0.0729	0.0451
p-OCH_3	0.0564	0.0321

a. Second-order rate constants in M^{-1} sec^{-1}

21. The halogenation of simple ketones such as acetone can proceed through the enol or enolate. By applying the steady state condition to the enolate, derive a kinetic expression for reaction of acetone with any halogenating agent X–Y in a buffered solution where both C-protonation and O-protonation of the enolate can compete with halogenation. Show that this rate expression predicts that halogenation will be zero order in halogenating agent under some conditions but first order in halogenating agent under other conditions.

22. The order of reactivity toward hydrolysis of the cyclic acetals shown below is A ≪ B ≪ C. Offer an explanation for this difference in reactivity.



23. Assume that the usual mechanism for hydrolysis of an imine, Im, is operative, i.e., that the hydrolysis occurs through a tetrahedral intermediate, TI:

$$\mathrm{Im} + \mathrm{H^+} \rightleftharpoons \mathrm{HIm^+}$$
$$\mathrm{HIm^+} + \mathrm{H_2O} \rightleftharpoons \mathrm{TI} + \mathrm{H^+}$$
and
$$\mathrm{HIm^+} + {}^{-}\mathrm{OH} \rightleftharpoons \mathrm{TI}$$
$$\mathrm{TI} \longrightarrow \text{products}$$

Assume that the steady state approximation can be applied to the intermediate TI. Derive the kinetic expression for hydrolysis of the imine. How many variables must be determined to construct the pH–rate profile? What simplifying assumptions are justified at very high and very low pH values? What are the kinetic expressions that result from these assumptions?

24. The rates of both formation and hydrolysis of dimethyl acetals of *p*-substituted benzaldehydes are substituent dependent. Do you expect k_{form} to increase or decrease with increasing electron-attracting capacity of the *para* substituent? Do you expect the k_{hydrol} to increase or decrease with the electron-attracting power of the substituent? How do you expect K, the equilibrium constant for acetal formation, to vary with the nature of the substituent?

25. Consider the kinetic isotope effect that would be observed in the reaction of semicarbazide with benzaldehyde:

$$\mathrm{PhC\overset{*}{H}{=}O} + \mathrm{H_2NNHC(=O)NH_2} \longrightarrow \mathrm{PhC\overset{*}{H}{=}NNHC(=O)NH_2}$$

Would you expect to find $k_{\mathrm{H}}/k_{\mathrm{D}}$ to be normal or inverse? Would you expect $k_{\mathrm{H}}/k_{\mathrm{D}}$ to be constant, or would it vary with pH?

9

Aromaticity and Electrophilic Aromatic Substitution

9.1. Aromaticity

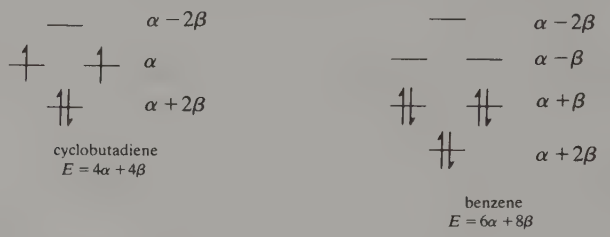
9.1.1. The Concept of Aromaticity

The meaning of the word *aromaticity* has evolved as understanding of the reason for the special properties of benzene and other aromatic molecules has deepened. Originally, aromaticity was associated with a special chemical reactivity.[1] The aromatic hydrocarbons were considered to be those unsaturated systems that underwent substitution reactions in preference to addition. Later, the idea of special stability came to play a larger role. Benzene can be shown to be much lower in enthalpy than predicted by summation of the normal bond energies for the C=C, C–C, and C–H bonds present in the Kekulé representation of benzene. Aromaticity is now generally associated with this property of lowered molecular energy. A major contribution to the stability of the aromatic systems is recognized as being due to the delocalization of the electrons in these molecules.

Currently, aromaticity is usually described in MO terminology. Structures that have a particularly stable arrangement of occupied π-molecular orbitals are called aromatic. A simple expression of the relationship between a MO description of structure and aromaticity is known as the *Hückel rule.* It is derived from simple Hückel molecular orbital (HMO) theory, and states that *planar monocyclic completely conjugated hydrocarbons will be aromatic when the ring contains* $(4n + 2)\pi$

1. For a historical account of early considerations of aromaticity, see J. P. Snyder, *Nonbenzenoid Aromatics*, Vol. 1, Academic Press, New York, 1969, Chap. 1.

electrons. HMO calculations assign the π-orbital energies of the cyclic unsaturated systems of ring size 3–9 as shown in Fig. 9.1. (See Chapter 1, Section 1.5, p. 37, to review the basis of HMO theory.) Orbitals below the dotted reference line are bonding orbitals; when they are filled, the molecule is stabilized. The orbitals that fall on the reference line are nonbonding; placing electrons in these orbitals has no effect on the total bonding energy of the molecule. The orbitals above these are antibonding; the presence of electrons in these orbitals destabilizes the molecule. The dramatic difference in properties of cyclobutadiene (extremely unstable) and benzene (very stable) are explicable in terms of these energy level diagrams:



Cyclobutadiene has two bonding electrons, but the other two electrons are unpaired because of the degeneracy of the two nonbonding orbitals. The two electrons in the

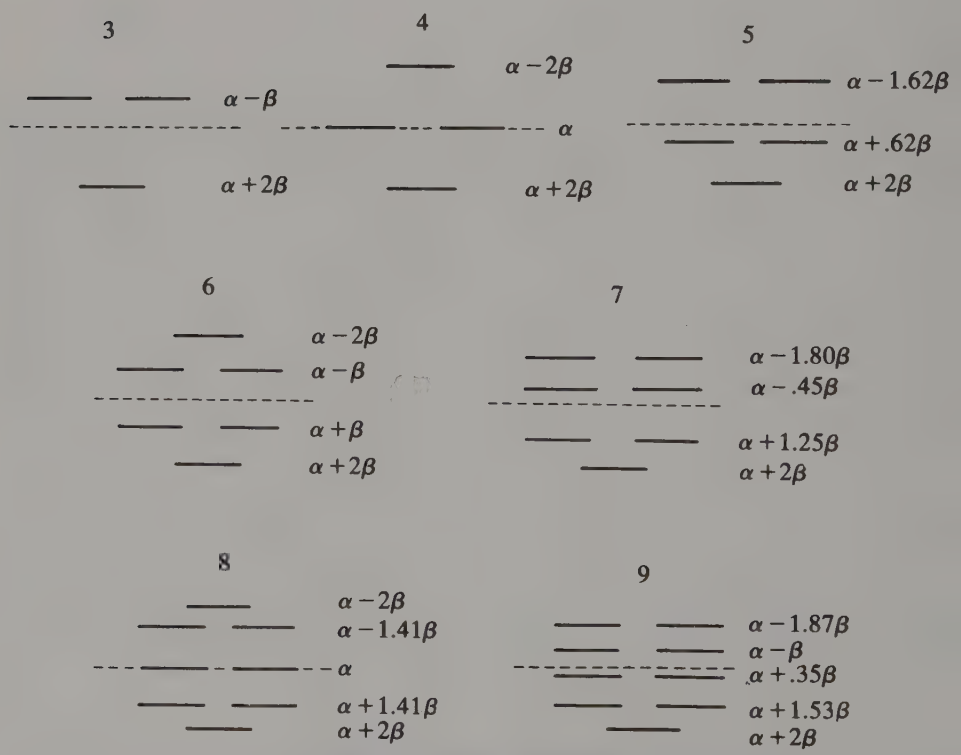


Fig. 9.1. Orbital energies for conjugated ring systems of 3–9 carbon atoms.

nonbonding levels do not contribute to the stabilization of the molecule. Furthermore, these electrons, since they occupy a high-energy orbital, are particularly available for chemical reactions. As we shall see in a moment, current evidence indicates that cyclobutadiene is rectangular rather than square. This distorts the orbital picture from the simple Hückel pattern, which assumes a square geometry. This distortion still leaves the two frontier electrons in a high-energy orbital, but permits them to be paired.

Simple Hückel calculations on benzene, in contrast, place all the π electrons in bonding MO's. The π electron energy of the benzene molecule is calculated by summing the energies of the six π electrons, which is $6\alpha + 8\beta$, lower by 2β than the value $6\alpha + 6\beta$ for three isolated double bonds. Thus the HMO method predicts a special stabilization for benzene.

The pattern of two half-filled degenerate levels persists for larger rings containing $4n$ π electrons. In contrast, all $4n + 2$ systems are predicted to have all electrons paired in bonding MO's. This provides the theoretical basis of the Hückel rule. Figure 9.1 gives the orbital energies for conjugated rings of up to nine carbon atoms.

As indicated in Chapter 1, the simple HMO theory is based on rather drastic assumptions. More elaborate MO treatments indicate that the most stable geometry for cyclobutadiene is rectangular.[2] Although several derivatives of cyclobutadiene are known and will be discussed shortly, cyclobutadiene itself has been observed only as a "matrix-isolated" species. Several compounds when photolyzed at very low temperature (~10 K) in solid argon release cyclobutadiene. Analysis of the infrared spectrum of the product and the tetradeutero analog generated from deuterated compounds is consistent with the theoretical conclusion that cyclobutadiene is a rectangular molecule.[3]

Attempts to describe just how stable a given aromatic molecule is in terms of simple HMO calculations have centered on the *delocalization energy*. The total π-electron energy of a molecule is expressed in terms of the energy parameters α and β, which arise in simple HMO calculations. This energy value can be compared to that for a hypothetical localized version of the same molecule. The HMO energy for the π electrons of benzene is $6\alpha + 8\beta$. The same quantity for the hypothetical localized model cyclohexatriene is $6\alpha + 6\beta$, the sum of three isolated C=C bonds. The difference of 2β is called the *delocalization energy* or *resonance energy*. Although this quantity is often useful for comparing related systems, it should be remembered that it is not a real, measurable physical quantity; rather, it is a comparison between a real molecule and a nonexistent one. Most estimates of the stabilization of benzene are in the range 20–40 kcal/mol.

2. J. A. Jafri and M. D. Newton, *J. Am. Chem. Soc.* **100**, 5012 (1978); W. T. Borden, E. R. Davidson, and P. Hart, *J. Am. Chem. Soc.* **100**, 388 (1978); H. Kollmar and V. Staemmler, *J. Am. Chem. Soc.* **99**, 3583 (1977); M. J. S. Dewar and A. Komornicki, *J. Am. Chem. Soc.* **99**, 6174 (1977).
3. S. Masamune, F. A. Souto-Bachiller, T. Machiguchi, and J. E. Bertie, *J. Am. Chem. Soc.* **100**, 4889 (1978); B. A. Hess, Jr., P. Carsky and L. J. Schaad, *J. Am. Chem. Soc.* **105**, 695 (1983).

There have been two general approaches to determining the amount of stabilization that results from aromatic delocalization. One is to use experimental thermodynamic measurements. Bond energies, as was mentioned in Chapter 1, are nearly additive when there are no special interactions between the various bond types. Thus it is possible to calculate such quantities as the heat of combustion or heat of hydrogenation of "cyclohexatriene" by assuming that it is a compound with no interaction between the three conjugated double bonds. For example, a very simple calculation of the heat of hydrogenation for cyclohexatriene would be to multiply the heat of hydrogenation of cyclohexene by 3, i.e., 3×28.6 kcal/mol = 85.8 kcal/mol. The actual heat of hydrogenation of benzene is 49.8 kcal/mol, suggesting a total stabilization or delocalization energy of 36.0 kcal/mol. There are other, more elaborate, ways of approximating the thermodynamic characteristics of the hypothetical cyclohexatriene. The difference between the calculated and corresponding measured thermodynamic property of benzene is taken to be the aromatic stabilization. For benzene, these values are usually around 30 kcal/mol, but they cannot be determined in an absolute sense since the value is in effect established by the properties assigned to the model cyclohexatriene.

The second general approach is to use molecular orbital methods. This has, in essence, already been illustrated by the discussion of HMO theory and the stabilization in terms of β units. More advanced MO methods can attempt to assign the stabilization energy in a more quantitative way. One MO method assigns resonance energy as the difference between the calculated energy of the cyclic conjugated polyene and a linear conjugated polyene with the same number of double bonds.[4] This definition assigns a resonance stabilization of 0 to the polyene, although it is known by thermodynamic criteria that conjugated polyenes do have some stabilization relative to isomeric compounds with isolated double bonds. Using this definition and semiempirical SCF calculations, the resonance energy of benzene has been assigned a value of 20 kcal/mol, relative to 1,3,5-hexatriene.

Another molecular orbital approach is to calculate the energy of a model in which the π bonds are constrained to be localized double bonds by the definition of the wave function. The calculated energy of this model can then be compared with the computed energy of the molecule in which delocalization is permitted.[5] By this definition, butadiene has a resonance stabilization of about 9.3 kcal/mol, while benzene has a resonance energy of about 56 kcal/mol. To compare this with the polyene definition one must subtract a correction for the butadiene resonance energy (3×9.3) which gives a value of about 28 kcal/mol as the resonance stabilization of benzene.[5]

The isodesmic reaction approach has also been applied to calculation of the resonance stabilization of benzene.

4. M. J. S. Dewar and C. deLlano, *J. Am. Chem. Soc.* **91**, 789 (1969).
5. H. Kollmar, *J. Am. Chem. Soc.* **101**, 4832 (1979).

$$+ 3\ CH_2{=}CH_2 \rightarrow 3\ CH_2{=}CH{-}CH{=}CH_2$$

This approach can be taken using either experimental thermochemical data or energies obtained by MO calculations.[6] If the resonance energy of butadiene is assigned as 0, the above reaction gives the resonance energy of benzene directly as 21.2 kcal/mol. If butadiene is considered to have a resonance energy, the computation must be modified to reflect that fact. Using 7.2 kcal/mol as the butadiene resonance energy gives a value of 42.8 kcal/mol as the benzene resonance energy.

Both thermochemical and molecular orbital approaches agree that benzene is an especially stable molecule and are reasonably consistent with one another in the stabilization energy which is assigned. It is very significant that MO calculations also show a destabilization of certain conjugated cyclic polyenes, cyclobutadiene in particular. In this case the instability of cyclobutadiene has precluded any thermochemical evaluation of the extent of destabilization. Compounds which are destabilized relative to conjugated but noncyclic models are called *antiaromatic.*[7]

There are also physical measurements that can give direct evidence of aromaticity. The determination of the bond lengths in benzene by electron diffraction is a classic example of use of the bond length criterion of aromaticity. Spectroscopic methods and electron or X-ray diffraction can also provide bond length data. Aromatic molecules consistently show bond lengths in the range 1.38–1.40 Å, and the bond lengths are quite uniform around the ring. In contrast, localized polyenes show alteration between typical sp^2-sp^2 single-bond and sp^2-sp^2 double-bond lengths along the conjugated chain.

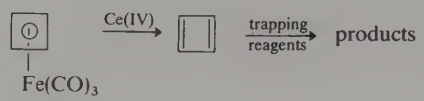
NMR spectroscopy also provides an experimental tool capable of assessing aromaticity. Aromatic compounds are characterized by their capability of exhibiting a *diamagnetic ring current.* Qualitatively, this ring current can be viewed as the migration of the electrons in a delocalized π system under the influence of the magnetic field in an NMR spectrometer. The ring current is responsible for a large magnetic anisotropy in aromatic compounds. The induced ring current gives rise to a local magnetic field perpendicular to the ring that is opposed to the direction of the applied magnetic field. Nuclei in a cone above and below the plane of an aromatic ring are shielded by the induced field and appear at relatively high field in the NMR spectrum, while nuclei in the plane of the ring—i.e., the atoms bound directly to the ring—occur relatively downfield. The occurrence of these chemical shift phenomena can be taken as evidence for aromaticity. This criterion must be applied with some care, and recent discussions of the relationship between ring current and aromaticity can be consulted to pursue this topic in more depth.[8]

6. P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *J. Chem. Soc. Perkin Trans. II*, 1222 (1976); P. George, M. Trachtman, C. W. Bock, and A. M. Brett, *Tetrahedron* **32**, 1357 (1976).
7. R. Breslow, *Acc. Chem. Res.* **6**, 393 (1973).
8. R. C. Haddon, *J. Am. Chem. Soc.* **101**, 1722 (1979); J. Aihara, *J. Am. Chem. Soc.* **103**, 5704 (1981).

9.1.2. The Annulenes

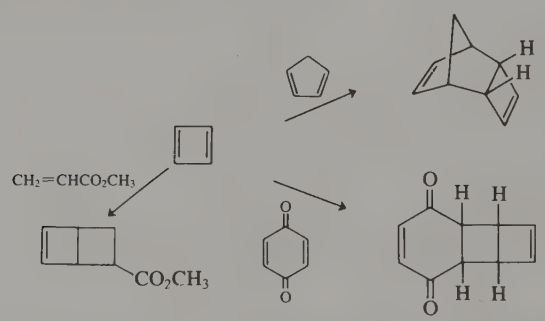
The term *annulene* has been coined to refer to the completely conjugated monocyclic polyenes.[9] The synthesis of annulenes has now been extended well beyond the first two members of the series, [4]annulene (cyclobutadiene) and [6]annulene (benzene). The generality of the Hückel rule can be tested by considering the properties of the members of the annulene series.

The smallest member, cyclobutadiene, has been the objective of synthetic efforts for many years, but success was achieved only relatively recently. It was first detected by trapping with various reagents after release from an iron complex[10]:



Dehalogenation of *trans*-3,4-dibromocyclobutene was shown to generate a species with similar behavior[11]:

Cyclobutadiene is trapped as Diels–Alder adducts by molecules such as quinone, cyclopentadiene, and methyl acrylate[12]:



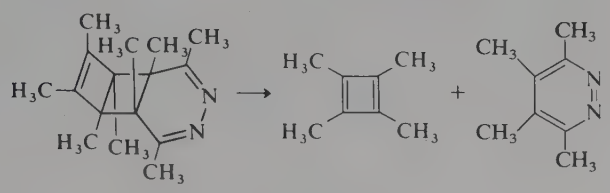
In the absence of trapping agents, a characteristic dimer is produced.

This is an extremely facile reaction and limits the lifetime of cyclobutadiene, except at extremely low temperatures. When cyclobutadiene is prepared by photolytic

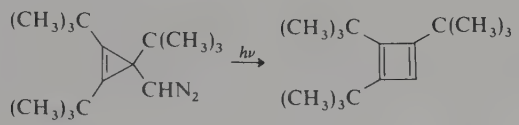
9. F. Sondheimer, *Pure Appl. Chem.* **28**, 331 (1971); *Acc. Chem. Res.* **5**, 81 (1972).
10. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.* **87**, 3253 (1965).
11. E. K. G. Schmidt, L. Brener, and R. Pettit, *J. Am. Chem. Soc.* **92**, 3240 (1970).
12. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.* **88**, 623 (1966); J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.* **88**, 1328 (1966); D. W. Whitman and B. K. Carpenter, *J. Am. Chem. Soc.* **102**, 4272 (1980).

procedures at very low temperatures in solid inert gases it is found that at 35 K, the molecule begins to react to give the dimer.

Some substituted derivatives of cyclobutadiene have also been reported. Tetramethylcyclobutadiene is obtained by a photochemical reaction at 25–196°C[13]:



1,2,3-Tri-*t*-butylcyclobutadiene is reported to be obtained in solution at −70°C by a photolytic ring expansion[14]:



It is not stable at higher temperatures, and is highly reactive toward oxygen. Increasing alkyl substitution increases the stability of cyclobutadienes toward dimerization. The tetra-*t*-butyl compound has been prepared and is thermally stable (at ~150°C at least) but remains very sensitive to oxygen.[15] Quite a number of functionally substituted cyclobutadienes have now been prepared by various routes. Although special conjugation can lead to stabilized systems, most of the compounds are highly reactive, especially toward oxygen. This chemical behavior is in excellent accord with that which would be expected from the theoretical picture of the structure of these compounds.[16]

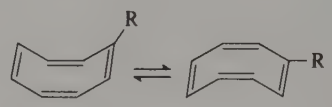
[6]Annulene is benzene. Its properties are sufficiently familiar to students of organic chemistry that not much need be said here. It is the parent of a vast series of compounds. The ring exhibits exceptional stability, both with regard to chemical reactivity and as measured by thermodynamic stability. It is much less reactive toward electrophilic reagents than acyclic conjugated trienes of similar size. Thermodynamic measurements such as combustion data and heats of hydrogenation point to a stabilization of ~30 kcal/mol relative to hypothetical models.

The next higher annulene, cyclooctatetraene, is readily determined to be nonaromatic. The bond lengths around the ring alternate as expected for a polyene,[17]

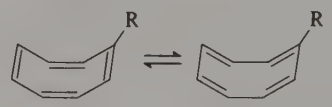
13. G. Maier and M. Schneider, *Angew. Chem. Int. Ed. Engl.* **10**, 809 (1971).
14. S. Masamune, N. Nakamura, M. Suda, and H. Ona, *J. Am. Chem. Soc.* **95**, 8481 (1973).
15. G. Maier, S. Pfriem, U. Schäfer, and R. Matusch, *Angew. Chem. Int. Ed. Engl.* **17**, 520 (1978).
16. For reviews of the preparation and reactions of cyclobutadiene derivatives, see G. Maier, *Angew. Chem. Int. Ed. Engl.* **13**, 425 (1974) and T. Bally and S. Masamune, *Tetrahedron* **36**, 343 (1980).
17. M. Traetteberg, *Acta Chem. Scand.* **20**, 1724 (1966).

and thermochemical data provide no evidence of special thermodynamic stability.[18] Neither is the molecule antiaromatic. It is readily isolated and has the chemical behavior of a polyene.[19] The molecule has a tub shape[17] and therefore is not a planar system of the type to which the Hückel rule applies. The molecule exhibits markedly alternating bond lengths, with C=C being 1.334 Å and C–C being 1.462 Å.[19]

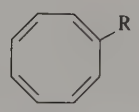
NMR studies have revealed that two dynamic processes occur in cyclooctatetraenes. One is a conformational flip:



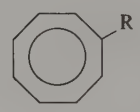
The other involves π-bond migration:



The transition states for these processes are believed to correspond to the localized and delocalized planar forms, respectively, of cyclooctatetraene. Therefore, comparison of the energy of these two transition states might shed some light on the extent of stabilization or destabilization of the planar [8]annulene system[20]:



planar localized transition state for conformational flip

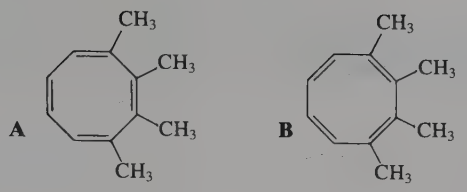


planar delocalized transition state for bond reorganization

Using alkoxy-substituted cyclooctatetraenes, $\Delta H^{\ddagger}$ for the ring flip and bond switch have been placed in the range 10.9–12.1 kcal/mol and 14.9–15.8 kcal/mol, respectively.[21] These data imply an unfavorable delocalization energy of about 4 kcal/mol in planar [8]annulenes and support the notion that planar cyclooctatetraene is antiaromatic.

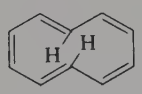
It has been possible to isolate two *different* tetramethylcyclooctatetraenes with four adjacent methyl groups.[22a] These correspond to the isomers differing in double-bond positions:

18. R. B. Turner, B. J. Mallon, M. Tichy, W. v. E. Doering, W. R. Roth, and G. Schröder, *J. Am. Chem. Soc.* **95**, 8605 (1973).
19. G. Schröder, *Cyclooctatetraene*, Verlag Chemie, Weinheim, 1965.
20. F. A. L. Anet, A. J. R. Bourn, and Y. S. Lin, *J. Am. Chem. Soc.* **86**, 3576 (1964).
21. J. F. M. Oth, *Pure Appl. Chem.* **25**, 573 (1971).
22. (a) L. A. Paquette and J. M. Photis, *J. Am. Chem. Soc.* **98**, 4936 (1976);



These compounds are not easily interconverted, but at 160°C after 6 hr a 7:3 mixture favoring **A** is obtained starting with either isomer. The primary cause for the retardation of the bond-shifting process which would interconvert the two isomers is steric interference which develops between adjacent methyl groups in the planar transition state for the bond-shifting process. The activation energy for isomerization has been found to be 33 kcal/mol.[22b] This includes the steric repulsion energy and the aromatic destabilization of the planar structure.

Larger annulenes permit the incorporation of *trans* double bonds into the rings; hence, isomeric annulenes warrant consideration beginning with the cyclodecapentaenes [23] [10]Annulene should, by the Hückel rule, possess aromatic stabilization if it were planar. All the isomeric cyclodecapentaenes suffer serious strain that prevents the planar geometry from being adopted. The *trans,cis,trans,cis,cis*-isomer, which has minimal angle strain, suffers a severe nonbonded repulsion between the two internal hydrogens.

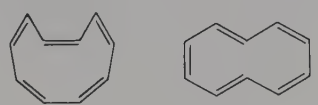


The all-*cis* isomer is required by geometry to have ring angles of 144° in a planar geometry, and is therefore destabilized enormously by the angle strain associated with a distortion of 24° from the normal trigonal geometry at each of ten carbon atoms.

Molecular orbital calculations give a value of about 30 kcal/mol for the difference between planar all-*cis* delocalized molecular and the most stable nonplanar form, which is a *trans, cis, cis, cis, cis* isomer[24]:

1

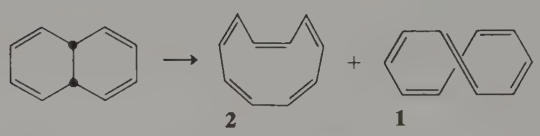
Structures **2** and **3** are calculated to be about 2.4 kcal/mol higher in energy:



2 **3**

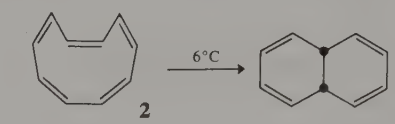
22. (b) L. A. Paquette and J. M. Gardlik, *J. Am. Chem. Soc.* **102**, 5033 (1980).
23. T. L. Burkoth and E. E. van Tamelen, in *Nonbenzenoid Aromatics*, J. P. Snyder (ed.), Vol. 1, Academic Press, New York, 1969, Chap. 3.
24. L. Farnell, J. Kao, L. Radom, and H. F. Schaefer, III, *J. Am. Chem. Soc.* **103**, 2147 (1981).

Two isomeric [10]annulenes, as well as other products, are formed by photolysis of *cis*-9,10-dihydronaphthalene[25]:

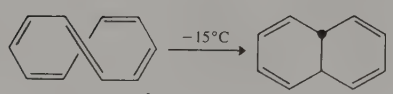


2 1

Neither compound exhibits properties that would suggest aromaticity. The NMR spectra are consistent with polyene structures. Both compounds are thermally unstable and rapidly undergo cyclization back to dihydronaphthalenes:

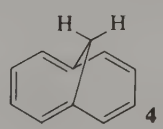


2



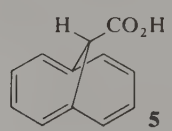
1

That this nonaromaticity is a consequence of nonplanarity, not of a breakdown of the Hückel rule, can be demonstrated by study of a ten-π-electron ring in which the steric problems associated with the cyclodeca-1,3,5,7,9-pentaenes are avoided. Compound **4** avoids these steric problems with only slight loss of planarity in the



4

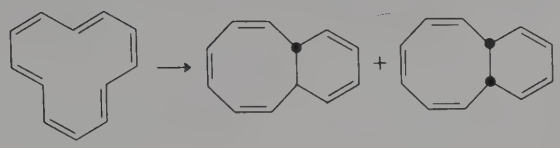
π system.[26] The NMR spectrum of this compound shows a diamagnetic ring current of the type expected in an aromatic system. An X-ray structure determination on the carboxylic acid **5** reveals no significant alternation in the C–C bond lengths around the ring, providing further support of aromatic character.[27]



5

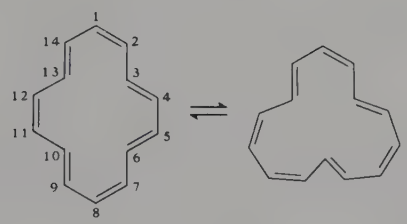
25. S. Masamune, K. Hojo, G. Bigam, and D. L. Rabenstein, *J. Am. Chem. Soc.* **93**, 4966 (1971); S. Masamune and N. Darby, *Acc. Chem. Res.* **5**, 272 (1972).
26. E. Vogel and H. D. Roth, *Angew. Chem. Int. Ed. Engl.* **3**, 228 (1964).
27. M. Dobler and J. D. Dunitz, *Helv. Chim. Acta* **48**, 1429 (1965).

[12]Annulene is a very unstable compound that undergoes cyclization to bicyclic isomers and can be kept only at very low temperature.[28] The NMR spectrum has been studied at low temperature.[29] Besides indicating the molecular configura-



tion shown, it reveals that the molecule has a *paramagnetic* ring current, which is opposite to that expected for an aromatic compound. This feature is quite characteristic of the $4n$ annulenes, and has been useful in characterizing the aromaticity or lack of it in the larger ring annulenes.[30]

[14]Annulene was first reported in 1960.[31] The molecule is not particularly stable. Its NMR spectrum has been investigated, and this work has established that two structures are in equilibrium:

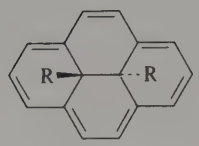


The spectrum also reveals a significant diamagnetic ring current. The four internal hydrogens are very far upfield ($\delta = -0.61$ ppm).[32] The interconversion of these forms involves a configurational change at one of the double bonds. The activation energy for this process is about 10 kcal/mol, which implies a greatly reduced barrier to rotation relative to a nonconjugated system. The crystal structure of [14]annulene has been determined.[33] The *cis,trans,trans,cis,trans,cis,trans* form is present. The bond lengths around the ring range from 1.35 to 1.41 Å, but do not show a pattern of alternating long and short bonds. There is some distortion from planarity, particularly at carbon atoms 3, 6, 10, and 13. This nonplanarity is caused by nonbonded repulsion between the internal hydrogen atoms.

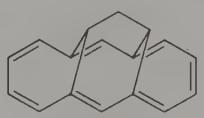
A 14-electron π system can be generated in a circumstance in which the steric problem associated with the internal hydrogens of [14]annulene can be avoided. This goal was achieved by synthesizing a system in which the annulene ring is built around

28. J. F. M. Oth, H. Röttele, and G. Schröder, *Tetrahedron Lett.*, 61 (1970).
29. J. F. M. Oth, J.-M. Gilles, and G. Schröder, *Tetrahedron Lett.*, 67 (1970).
30. R. C. Haddon, *Tetrahedron* **28**, 3613, 3635 (1972).
31. F. Sondheimer and Y. Gaoni, *J. Am. Chem. Soc.* **82**, 5765 (1960).
32. J. F. M. Oth, *Pure Appl. Chem.* **25**, 573 (1971).
33. C. C. Chiang and I. C. Paul, *J. Am. Chem. Soc.* **94**, 4741 (1972).

a saturated core:



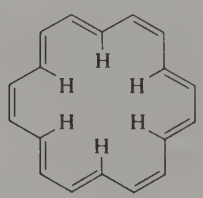
Several such compounds have been synthesized.[34] These compounds exhibit properties indicating they are aromatic. They exhibit NMR shifts characteristic of an aromatic-type ring current. Typical aromatic substitution reactions can be carried out.[35] An X-ray structure ($R = C_2H_5$) shows that the bond lengths are in the aromatic range (1.39–1.40 Å), and that there is no strong alternation around the ring.[36] The peripheral atoms are not precisely planar, with maximum deviation from the average plane being 0.23 Å. A number of 14-π-electron systems have also been prepared in which the internal steric repulsions have been removed by using the same bridging approach discussed for the 10-π-electron ring system.[37] Compound **6** is an example.



6

The Hückel rule would predict nonaromaticity for [16]annulene. The compound has been synthesized and thoroughly characterized.[38] The bond lengths show significant alternation (C=C, 1.34 Å; C–C, 1.46 Å), and the molecule is significantly less planar than [14]annulene.[39] These structural data are consistent with regarding [16]annulene as being nonaromatic.

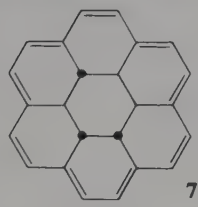
[18]Annulene offers a particularly significant test of the Hückel rule. The internal cavity in [18]annulene is large enough to minimize steric interactions between the internal hydrogens in a conformation that is free of angle strain. The properties of the molecule are consistent with regarding it as being aromatic. The



34. R. H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.* **96**, 1547 (1974);V. Boekelheide and T. A. Hylton, *J. Am. Chem. Soc.* **92**, 3669 (1970); H. Blaschke, C. E. Ramey, I. Calder, and V. Boekelheide, *J. Am. Chem. Soc.* **92**, 3675 (1970); V. Boekelheide and J. B. Phillips, *J. Am. Chem. Soc.* **89**, 1695 (1967).
35. J. B. Phillips, R. J. Molyneux, E. Sturm, and V. Boekelheide, *J. Am. Chem. Soc.* **89**, 1704 (1967).
36. A. W. Hanson, *Acta Crystallogr.* **23**, 476 (1967).
37. E. Vogel, *Pure Appl. Chem.* **28**, 355 (1971).
38. I. C. Calder, Y. Gaoni, and F. Sondheimer, *J. Am. Chem. Soc.* **90**, 4946 (1968); G. Schröder and J. F. M. Oth, *Tetrahedron Lett.*, 4083 (1966).
39. S. M. Johnson and I. C. Paul, *J. Am. Chem. Soc.* **90**, 6555 (1968).

X-ray structure shows the molecule to be close to planarity, with the maximum deviation of carbon from the plane being 0.085 Å.[40] The bond lengths are in the range 1.38–1.42 Å, and in the pattern short, short, long, rather than alternating. The NMR spectrum is indicative of an aromatic ring current.[41] The chemical properties of the molecule would also justify its classification as aromatic.[42]

There are also examples of [18]annulenes constructed around a saturated central core such as compound **7**.[43] The internal protons are at very high field (−6 to −8 ppm), whereas the external protons are far downfield (~9.5 ppm). The chemical



7

shift data can be used as the basis for calculating the diamagnetic ring current and then comparing that with the maximum ring current expected for complete delocalization. By this criterion the flexible [18]annulene maintains only about half (0.56) of the maximum ring current, whereas the more rigid ring gives a value of 0.88, indicating a much more effective conjugation.

The synthesis of annulenes has been carried forward successfully to larger rings as well. [20]Annulene,[44] [22]annulene,[45] and [24]annulene[46] have all been reported. The NMR spectra of these compounds are consistent with regarding [22]annulene as aromatic, while the [20] and [24] analogs are not. In each case, there is some ambiguity as to the preferred conformation in solution, and the NMR spectra are temperature dependent. While the properties of these molecules have not been studied as completely as the smaller systems, they are consistent with the predictions of the Hückel rule.

It has been pointed out that a different array of atomic orbitals might be conceived of in large conjugated rings. The array, called a *Möbius twist*, results in there being one point on the rings at which the atomic orbitals would show a phase

40. J. Bregman, F. L. Hirshfeld, D. Rabinovich, and G. M. J. Schmidt, *Acta Crystallogr.* **19**, 227 (1965); F. L. Hirshfeld and D. Rabinovich, *Acta Crystallogr.* **19**, 235 (1965).
41. Y. Gaoni, A. Melera, F. Sondheimer, and R. Wolovsky, *Proc. Chem. Soc.*, 397 (1964).
42. I. C. Calder, P. J. Garratt, H. C. Longuet-Higgins, F. Sondheimer, and R. Wolovsky, *J. Chem. Soc. C*, 1041 (1967).
43. T. Otsubo, R. Gray, and V. Boekelheide, *J. Am. Chem. Soc.* **100**, 2449 (1978).
44. B. W. Metcalf and F. Sondheimer, *J. Am. Chem. Soc.* **93**, 6675 (1971).
45. R. M. McQuilkin, B. W. Metcalf, and F. Sondheimer, *Chem. Commun.*, 338 (1971).
46. I. C. Calder and F. Sondheimer, *Chem. Commun.*, 904 (1966).

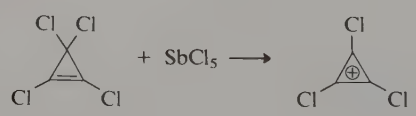
reversal.[47] If the ring were sufficiently large that the twist between individual atomic orbitals were small, such a system would not necessarily be less stable than the normal array of atomic orbitals. This same analysis points out that in such an array, the Hückel rule is reversed, and aromaticity is predicted for the $4n$ π-electron systems. So far, no ground state molecule in which the twisted conjugation would exist has been made, so the prediction remains to be tested. Its correctness is strongly suggested, however, by the fact that transition states with twisted orbital arrays appear to be perfectly acceptable in many organic reactions.[48] We will return to this topic in the next chapter. The rules for aromaticity can be generalized to include Möbius orbital arrays:

Hückel orbital array	Möbius orbital array
$4n+2$ aromatic	$4n$ aromatic
$4n$ antiaromatic	$4n+2$ antiaromatic

9.1.3. Aromaticity in Charged Rings

There are also striking examples of stability relationships due to aromaticity in the charged small and common ring systems. The HMO energy levels that apply to the fully conjugated planar 3–9-membered rings were given in Fig. 9.1 (p. 456). These energy levels are applicable to charged species as well as to the neutral annulenes. A number of cations and anions that could exist as completely conjugated planar systems are indicated in Fig. 9.2. Of these species, the Hückel rule would predict aromatic stability for cyclopropenium ion (**A**), cyclobutadiene dication (**C**), cyclobutadiene dianion (**D**), cyclopentadienide anion (**F**), cycloheptatrienyl cation (tropylium ion, **G**), the dications and dianion derived from cyclooctatetraene (**I**, **J**), and the cyclononatetraenide ion (**K**). The other species shown, having $4n$ π-electrons, would be expected to be very unstable. Let us examine what is known about the chemistry of some of these species.

The cyclopropenium ion and a number of derivatives have been generated by ionization procedures:



Ref. 49

47. E. Heilbronner, *Tetrahedron Lett.*, 1923 (1964).
48. H. E. Zimmerman, *Acc. Chem. Res.* **4**, 272 (1971).
49. S. W. Tobey and R. West, *J. Am. Chem. Soc.* **86**, 1459 (1964); R. West, A. Sado, and S. W. Tobey, *J. Am. Chem. Soc.* **88**, 2488 (1966).

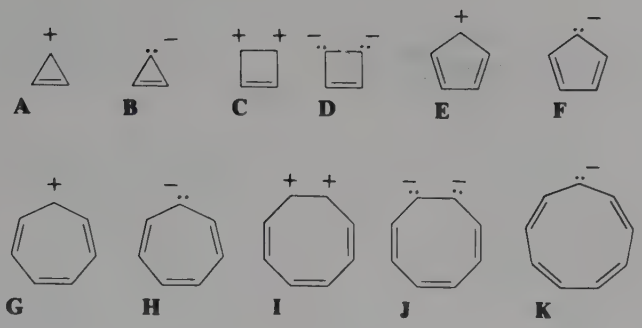
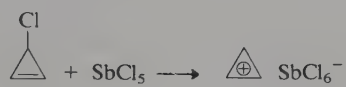
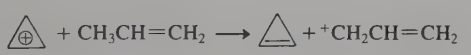


Fig. 9.2. Some fully conjugated monocyclic organic ions.



Ref. 50

The carbonium ion salt 1,2,3-tri-*t*-butylcyclopropenium perchlorate is so stable that it can be recrystallized from water.[51] An X-ray study of triphenylcyclopropenium perchlorate has verified the existence of the carbonium ion as a discrete species.[52] Quantitative estimation of the stability of the unsubstituted ion can be made in terms of its pK_{R^+} value of -7.4, which is intermediate between such highly stabilized carbonium ions as triphenylmethyl and *p*-methoxybenzhydryl.[53] A calculation of the isodesmic reaction



yields a ΔH of +38.2 kcal/mol, while experimental data on the heats of formation of the various species indicate $\Delta H = +31$ kcal/mol. Since the allyl cation is estimated to have a resonance energy of ~30 kcal/mol, this indicates that the total resonance stabilization of the cyclopropenyl cation is about 60 kcal/mol.[54]

In contrast, the less-strained four-π-electron cyclopentadienyl cation is very unstable. Its pK_{R^+} has been estimated as -40, using an electrochemical cycle.[55] Solvolysis of cyclopentadienyl halides assisted by silver ion is extremely slow, even though the halide is doubly allylic.[56] When the bromide and antimony pentafluoride

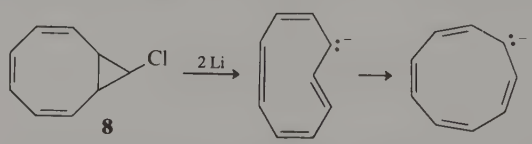
50. R. Breslow, J. T. Groves, and G. Ryan, *J. Am. Chem. Soc.* **89**, 5048 (1967).
51. J. Ciabattoni and E. C. Nathan, III, *J. Am. Chem. Soc.* **91**, 4766 (1969).
52. M. Sundaralingam and L. H. Jensen, *J. Am. Chem. Soc.* **88**, 198 (1966).
53. R. Breslow and J. T. Groves, *J. Am. Chem. Soc.* **92**, 984 (1970).
54. L. Radom, P. C. Hariharan, J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **98**, 10 (1976).
55. R. Breslow and S. Mazur, *J. Am. Chem. Soc.* **95**, 584 (1975).
56. R. Breslow and J. M. Hoffman, Jr., *J. Am. Chem. Soc.* **94**, 2110 (1972).

react at −78°C, the product has an EPR spectrum indicating that the cyclopentadienyl cation is a triplet, in agreement with both HMO and more sophisticated MO calculations.[57] The pentachloro derivative is also a triplet, but the pentaphenylcyclopentadienyl cation is a singlet.

The relative stability of the anions derived from cyclopropene and cyclopentadiene by deprotonation is just the reverse of the situation for the cations. Cyclopentadiene is one of the most acidic hydrocarbons known, with a pK_a of 16.0.[58] The pK's of triphenylcyclopropene and trimethylcyclopropene have been estimated as 50 and 62, respectively, using electrochemical cycles.[59] The unsubstituted compound would be expected to be somewhere between, and thus must be roughly 40 powers of 10 less acidic than cyclopentadiene.

The Hückel rule predicts aromaticity for the cation derived from cycloheptatriene by hydride abstraction and antiaromaticity for the planar eight-π-electron anion that would be formed by deprotonation. The cation is very stable, with a pK_{R^+}, of +4.7,[60] and salts containing the ion can be characterized and isolated as the result of a variety of preparative procedures.[61] On the other hand, the pK_a of cycloheptatriene has been estimated as 36.[59] This value is indicative of nonaromaticity but does not suggest strong destabilization. Thus the seven-membered ring in the anion may be nonplanar, as in cyclooctatetraene, and avoid the destabilization associated with a planar ring.

The cyclononatetraenide anion is generated by treatment of the halide **8** with lithium metal[62]:



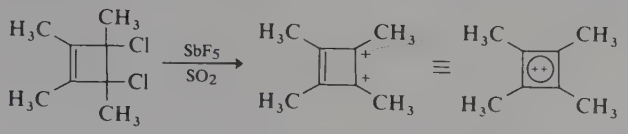
8

An isomeric form of the anion that is initially formed is converted to the all-*cis* system rapidly at room temperature.[63] Data on the equilibrium acidity of the parent hydrocarbon are not available, so the stability of the anion cannot be judged quantitatively. The NMR spectrum of the anion, however, is indicative of aromatic character.

Several doubly charged ions are included in Fig. 9.2; some have been observed experimentally. Ionization of 3,4-dichloro-1,2,3,4-tetramethylcyclobutene in SbF_5–

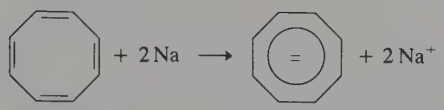
57. M. Saunders, R. Berger, A. Jaffe, J. M. McBride, J. O'Neill, R. Breslow, J. M. Hoffman, Jr., C. Perchonock, E. Wasserman, R. S. Hutton, and V. J. Kuck, *J. Am. Chem. Soc.* **95**, 3017 (1973).
58. A. Streitwieser, Jr., and L. L. Nebenzahl, *J. Am. Chem. Soc.* **98**, 2188 (1976).
59. R. Breslow and W. Chu, *J. Am. Chem. Soc.* **95**, 411 (1973).
60. W. v. E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **76**, 3203 (1954).
61. T. Nozoe, *Prog. Org. Chem.* **5**, 132 (1961); K. M. Harmon, in *Carbonium Ions*, Vol. IV, G. A. Olah and P. v. R. Schleyer (eds.), Wiley–Interscience, New York, 1973, Chap. 2.
62. T. J. Katz and P. J. Garratt, *J. Am. Chem. Soc.* **86**, 5194 (1964); E. A. LaLancette and R. E. Benson, *J. Am. Chem. Soc.* **87**, 1941 (1965).
63. G. Boche, D. Martens, and W. Danzer, *Angew. Chem. Int. Ed. Engl.* **8**, 984 (1969).

SO_2 at −75°C results in an NMR spectrum attributed to the tetramethyl derivative of the cyclobutadienyl dication[64]:

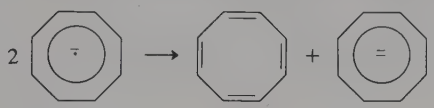


It is difficult to choose a reference compound against which to characterize the stability of the dication. That it can be formed at all, however, is suggestive of special stabilization associated with the two-electron π system. Aromaticity would also be predicted for the dianion of cyclobutadiene. There is some evidence that this species may have a finite existence.[65] Reaction of 3,4-dichlorocyclobutadiene with sodium naphthalenide followed in a few minutes by methanol-O-*d* gives a low yield of 3,4-di-*deuterio*-cyclobutene. As yet, however, no direct structural characterization of this species has been accomplished.

Cyclooctatetraene is reduced by alkali metals to a dianion:



The NMR spectrum of this dianion is indicative of a planar aromatic structure.[66] It has been demonstrated that the dianion is more stable than the radical anion formed by one-electron reduction, since the radical anion disproportionates to cyclooctatetraene and the dianion:

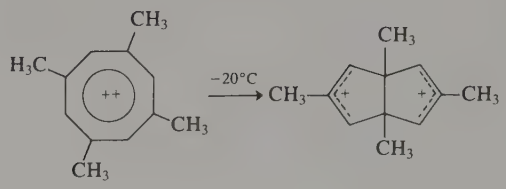


The crystal structure of the potassium salt of 1,3,5,7-tetramethylcyclooctatetraene dianion has been determined by X-ray diffraction.[67] The eight-membered ring is planar, with "aromatic" C–C bond lengths of about 1.41 Å. There is no significant bond alternation. These findings lead to the conclusion that the cyclooctatetraene dianion is delocalized and stabilized.

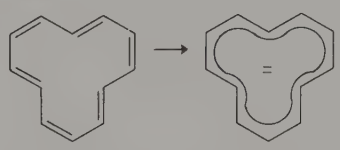
A dication derived from 1,3,5,7-tetramethylcyclooctatetraene is formed at −78°C in SO_2ClF by reaction with SbF_5. Both the proton and carbon NMR spectra indicate that the ion is a symmetrical, diamagnetic species and the chemical shifts are consistent with an aromatic ring current. At about −20°C this dication undergoes

64. G. A. Olah, J. M. Bollinger, and A. M. White, *J. Am. Chem. Soc.* **91**, 3667 (1969): G. A. Olah and G. D. Mateescu, *J. Am. Chem. Soc.* **92**, 1430 (1970).
65. J. S. McKennis, L. Brener, J. R. Schweiger, and R. Pettit, *J. Chem. Soc. Chem. Commun.*, 365 (1972).
66. T. J. Katz, *J. Am. Chem. Soc.* **82**, 3784 (1960).
67. S. Z. Goldberg, K. N. Raymond, C. A. Harmon, and D. H. Templeton, *J. Am. Chem. Soc.* **96**, 1348 (1974).

a chemical transformation, indicating that there is at least one more stable form for the dication[68]:



Reduction of [12]annulene, either electrochemically or with lithium metal, generates a 14-π-electron dianion[69]:



The NMR spectrum of the resulting dianion shows a diamagnetic ring current indicative of aromatic character, even though steric interactions among the internal hydrogens must prevent complete coplanarity. In contrast to the neutral [12]annulene, which is thermally unstable above −50°C, the dianion remains stable at 30°C. The dianion of [16]annulene has also been prepared, and shows properties consistent with regarding it as being aromatic.[70]

The pattern of experimental results on charged species with cyclic conjugated systems as summarized in Table 9.1 is consistent with the Hückel rule.

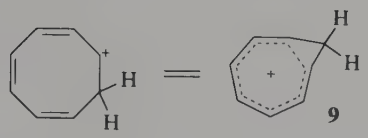
9.1.4. Homoaromaticity

Homoaromaticity is a term coined to describe systems in which a stabilized cyclic conjugated system is formed by bypassing one saturated atom.[71] The resulting stabilization would in general be expected to be reduced but the properties of several cationic species suggest that substantial stabilization does result. The cyclooctatrienyl cation is an example[72]:

68. G. A. Olah, J. S. Staral, G. Liang, L. A. Paquette, W. P. Melega, and M. J. Carmody, *J. Am. Chem. Soc.* **99**, 3349 (1977).
69. J. F. M. Oth and G. Schröder, *J. Chem. Soc. B*, 904 (1971).
70. J. F. M. Oth, G. Anthoine, and J.-M. Gilles, *Tetrahedron Lett.*, 6265 (1968).
71. S. Winstein, *Q. Rev. Chem. Soc.* **23**, 141 (1969).
72. P. Warner, D. L. Harris, C. H. Bradley, and S. Winstein, *Tetrahedron Lett.* 4013 (1970); C. E. Keller and R. Pettit, *J. Am. Chem. Soc.* **88**, 604, 606 (1966).

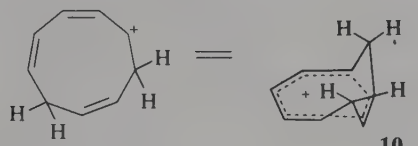
Table 9.1. Hückel's Rule Relationships for Charged Species

Compound	π-Electrons
Aromatic species	
Cyclopropenium cation	2
Cyclopentadienide anion	6
Cycloheptatrienyl cation	6
Cyclooctatetraene dianion	10
Cyclononatetraenide anion	10
[12]Annulene dianion	14
Antiaromatic species	
Cyclopropenide anion	4
Cyclopentadienyl cation	4
Nonaromatic species	
Cycloheptatrienyl anion	8



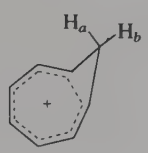
9

If two saturated atoms were present, the term *bishomoaromatic* would be applied[73]:



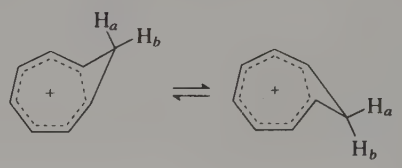
10

Clearly, stabilization in such systems will depend not only on the presence of a favorable electronic system, but also on the ability of the molecule to adopt a geometry favorable for overlap of the π system. Ions such as **9** and **10** do appear, however, to gain considerable stability from such conjugation and to have other aromatic characteristics. For example, protons *a* and *b* exhibit sharply different chemical shifts:



73. P. Warner and S. Winstein, *J. Am. Chem. Soc.* **93**, 1284 (1971).

Proton *a* is 5.8 ppm upfield of *b*, indicating the existence of an aromatic ring current. The π system also apparently contributes to imposing a high barrier to conformational inversion:

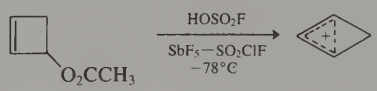


$\Delta G^{\ddagger} = 22.3$ kcal

Perhaps the simplest example of a homoaromatic cation is the ion $C_4H_5^+$, **11**.

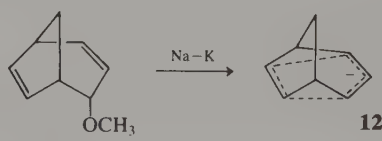
11

This is the homoaromatic analog of the very stable cyclopropenium cation. This ion can be prepared for spectroscopic work from 3-acetoxycyclobutene using typical "superacid" conditions[74]:



The temperature-dependent NMR spectrum can be analyzed to show that there is a barrier (8.4 kcal/mol) for ring flip which interchanges the hydrogens of the methylene group. The C-13 chemical shifts are also compatible with the homoaromatic structure.

The existence of stabilizing homoconjugation in anions has been more difficult to establish. Much of the discussion has revolved about anion **12**. The six-electron anion **12** is formed by a reductive process.[75] The species was proposed to have



12

homoaromatic stabilization on the basis of a large upfield shift in the CH_2 group that would lie in the shielding region generated by a diamagnetic ring current. However, in contrast to the cations **9** and **11**, MO calculations fail to reveal any stabilization of anion **12**.[76] The reason that homoconjugation is not as favorable in anionic systems may be that electron–electron repulsions outweigh the stabilization due to delocalization.

74. G. A. Olah, J. S. Staral, R. J. Spear, and G. Liang, *J. Am. Chem. Soc.* **97**, 5489 (1975).
75. S. Winstein, M. Ogliaruso, M. Sakai, and J. M. Nicholson, *J. Am. Chem. Soc.* **89**, 3656 (1967).
76. J. B. Grutzner and W. L. Jorgenson, *J. Am. Chem. Soc.* **103**, 1372 (1981); E. Kaufmann, H. Mayr, J. Chandrasekhar, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **103**, 1375 (1981).

9.1.5. Fused-Ring Systems

Many completely conjugated hydrocarbons can be built up from the annulenes and related structural fragments. Scheme 9.1 gives the structures, names, and stabilization energies of a variety of such hydrocarbons. Derivatives of these hydrocarbons having substituent groups or with heteroatoms in place of one or more carbon atoms constitute another important class of organic molecules.

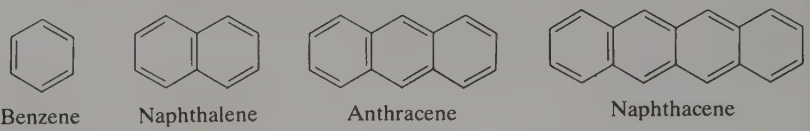
It is of substantial interest to be able to make at least qualitative predictions about the stability of such fused-ring compounds and many efforts to do so have been made. In Scheme 9.1 the results of some of these approaches are given. Because of the relative simplicity of the calculations, many of the approaches are based on the Hückel molecular orbital (HMO) approach outlined in Chapter 1. In the simplest application, the stabilization energy can be taken as the difference between the energy obtained by a HMO calculation and the energy of an equivalent number of isolated π bonds, which is $n(2\alpha + 2\beta)$. This approach is not very satisfactory because it suggests increasing stabilization for larger fused-ring systems and implies substantial stabilization for many nonbenzenoid hydrocarbons which are, in fact, very unstable. By choosing an alternate reference state, the HMO results can be brought into much better agreement with fact. This approach takes the reference compound to be a hypothetical localized molecule made up from the same structural units as the delocalized molecule which is being considered. Each of these structural units can be assigned a certain energy value on the basis of empirical studies. The difference between the calculated HMO energy and the hypothetical reference compound gives the aromatic stabilization. The results from a procedure of this type developed by Hess and Schaad[77] are given in Scheme 9.1 as the HMO′ stabilization energies. In this procedure the calculations on the aromatic molecule are the same as in the classical HMO method. The reference energy is a value obtained by summing empirically determined resonance energies for each of the structural entities in the molecule. These values are given below:

Component	E (in β)
$H_2C{=}CH$	2.000
$CH{=}CH$	2.070
$H_2C{=}C$	2.000
$HC{=}C$	2.108
$C{=}C$	2.172
$HC{-}CH$	0.466
$HC{-}C$	0.436
$C{-}C$	0.436

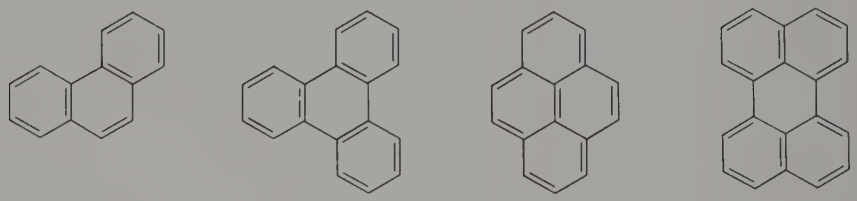
The sum of these values corresponds to the energy that would be assigned to a hypothetical model in which the double bonds act as a conjugated, but not aromatic,

77. B. A. Hess, Jr. and L. J. Schaad, *J. Am. Chem. Soc.* **93**, 305, 2413 (1971); *J. Org. Chem.* **36**, 3418 (1971); **37**, 4179 (1972).

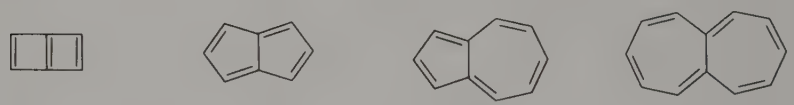
Scheme 9.1. Stabilization Energies of



	Benzene	Naphthalene	Anthracene	Naphthacene
HMO	2.00 β	3.68 β	5.31 β	6.93 β
HMO′	0.39 β	0.55 β	0 66 β	0.76 β
SCF–MO	0.869 eV	1.323 eV	1.600 eV	1.822 eV



	Phenanthrene	Triphenylene	Pyrene	Perylene
HMO	5.44 β	7.27 β	6.50 β	8.24 β
HMO′	0.77 β	1.01 β	0.82 β	0.96 β
SCF–MO	1.933 eV	2.654 eV	2.10 eV	2.619 eV



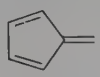
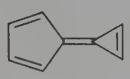
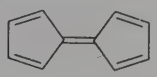
	Butalene	Pentalene	Azulene	Heptalene
HMO	1.66 β	2.45 β	3.36 β	3.61 β
HMO′	−0.48 β	−0.14 β	0.23 β	−0.048 β
SCF–MO	−0.28 eV	−0.006 eV	0.169 eV	−0.004 eV

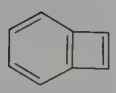
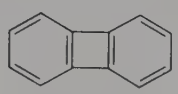
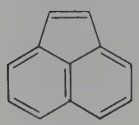
polyene. For azulene, for example, the tabulated HMO energy is 13.36β. The energy for a localized model is obtained by summing contributions for the component carbon–carbon bonds: 3CH=CH + 2HC=C + 3HC–CH + C–C = 13.13β. The difference, 0.23β, is the resonance energy assigned to azulene. For comparison between nonisomeric molecules, the Hess–Schaad treatment uses the resonance energy per electron (REPE), which is obtained by dividing the calculated stabilization energy by the number of π electrons. Although based on a rudimentary MO method, both the HMO′ and REPE values obtained in this way have proven to have a good qualitative correlation with observed chemical stability.

More sophisticated MO methods can be applied to the problem of aromatic stabilization. The values listed in Scheme 9.1 as SCF were obtained from SCF–MO calculations which treated all valence electrons.[78] The reference state for comparison is again taken to be a hypothetical localized polyene derived from the same structural units as the cyclic hydrocarbon. Notice that in a few cases, butalene and pentalene,

78. M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.* **91**, 789 (1969).

Some Conjugated Hydrocarbons[a,b]

	 Methylene-cyclopropene	 Fulvene	 Triafulvene	 Fulvalene
HMO	0.96β	1.46β	———	2.80β
HMO′	0.02β	-0.012β	0.34β	-0.33β
SCF–MO	———	———	———	———

	 Benzocyclo-butadiene	 Biphenylene	 Acenaphthylene	
HMO	2.38β	4.50β	4.61β	—
HMO′	-0.22β	0.32β	0.47β	-0.22β
SCF–MO	—	1.346 eV	1.335 eV	—

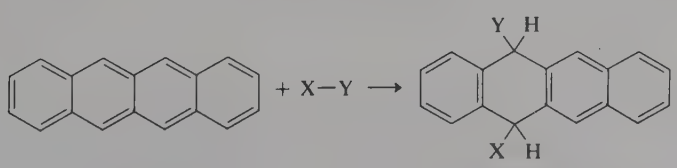
a. Stabilization energies given are from the following sources:

HMO: C. A. Coulson, A. Streitwieser, Jr., M. D. Poole, and J. I. Brauman, *Dictionary of π-Electron Calculations*, W. H. Freeman, San Francisco, 1965.
HMO′: B. A. Hess, Jr., and L. J. Schaad, Jr., *J. Am. Chem. Soc.* **93**, 305, 2413 (1971); *J. Org. Chem.* **36**, 3418 (1971); **37**, 4179 (1972).
SCF–MO: M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.* **91**, 789 (1969).

b. For comparison of stabilization energies in β with those in eV, a rough approximation is $1\beta = 2.5$ eV. This value is derived from an approximate correlation line, restricted to passing through the origin, between the HMO′ and SCF stabilization energies.

for example, both the HMO′ and SCF methods indicate that cyclic conjugation results in destabilization, as indicated by negative resonance energies.

All these approaches agree that benzene and the numerous structures that can be built up simply by fusing together benzenoid rings are strongly stabilized relative to localized structures. The larger rings tend to have lower resonance energies per π electron than does benzene. This feature of the results is in agreement with a well-established chemical fact. Large rings such as naphthacene undergo addition reactions very readily in the center rings. The reason is that the smaller separated aromatic rings may have nearly as much, or even more, aromatic stabilization than the larger fused ring system in the reactant.



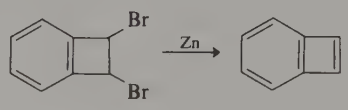
SCF stabilization energy = 1.822 eV

SCF stabilization energy = 0.869 + 1.323 = 2.192 eV

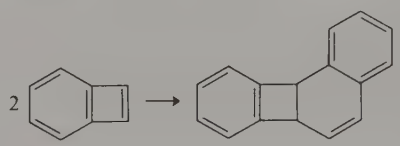
The predictions of the various approaches diverge more widely when nonbenzenoid conjugated systems are considered. The simple Hückel method using total π delocalization energies fails. It predicts delocalization energies of the same order of magnitude for such unstable systems as pentalene and fulvalene as it does for the much more stable aromatics. The HMO′, and SCF–MO methods do much better. They show drastically reduced stabilization for such systems and, in fact, indicate destabilization in some cases.

It is of interest at this point to consider some of the molecules included in Scheme 9.1 and compare the calculated stabilization with experimental data on the properties of these compounds.

Benzocyclobutadiene has been generated in a number of ways, including dehalogenation of dibromobenzocyclobutene[79]:

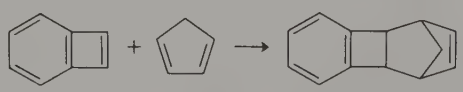


The compound is highly reactive, dimerizing or polymerizing readily[80]:



Ref. 80b

Benzocyclobutadiene is very reactive as a dienophile in the Diels–Alder reaction:



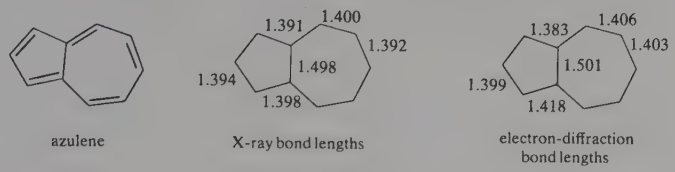
Ref. 80c

The high reactivity of benzocyclobutadiene has precluded detailed structural studies, but the reactivity confirms the prediction that the presence of the cyclobutadiene moiety is strongly destabilizing, since the compound is much more reactive than the noncyclic analog styrene.

Azulene is one of the few completely conjugated nonbenzenoid hydrocarbons that appears to have appreciable aromatic stabilization. There is some divergence on this point between the SCF–MO and HMO′ treatments. The latter estimates a resonance energy about half that for the isomeric naphthalene, whereas the SCF–MO method assigns a resonance energy which is only about one seventh that of naphthalene. The parent hydrocarbon and many of its derivatives have been well characterized and are stable compounds. The structure of azulene itself has been

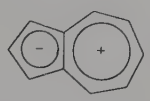
79. M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.* **78**, 500 (1956); **79**, 1701 (1957).
80. (a) M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, pp. 192–216. (b) M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.* **80**, 2255 (1958). (c) M. P. Cava and M. J. Mitchell, *J. Am. Chem. Soc.* **81**, 5409 (1959).

determined by both X-ray and electron-diffraction measurements.[81] The peripheral bond lengths are in the aromatic range and show no regular alternation. The bond shared by the two rings is significantly longer, indicating dominant single-bond character:



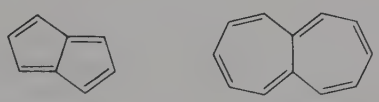
azulene | X-ray bond lengths | electron-diffraction bond lengths

An interesting structural question revolves around the contribution of a dipolar structure that pictures the molecule as



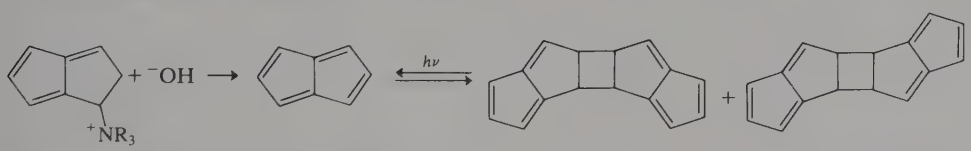
This structure is a fusion of a cyclopentadienide anion and a tropylium cation. The molecule does have an appreciable dipole moment (0.8 D).[82] The essentially single-bond nature of the shared bond indicates, however, that the conjugation is principally around the periphery of the molecule.

The modest resonance stabilization of azulene can be contrasted with pentalene and heptalene, both of which are indicated to be destabilized relative to a reference polyene:



pentalene | heptalene

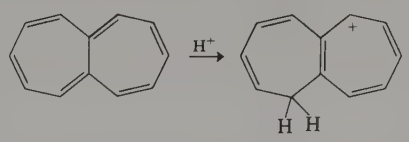
Preparation of pentalene by a Hofmann elimination at 20°C is followed by dimerization. Low-temperature photolysis produces a new species believed to be pentalene but dimerization occurs at ~−100°C[83]:



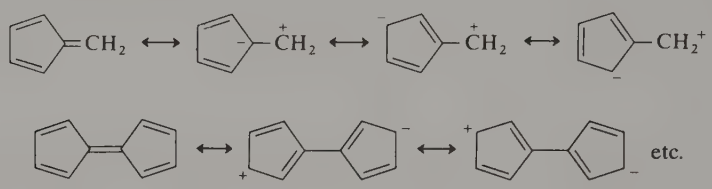
Heptalene readily polymerizes and is sensitive to oxygen. The NMR spectrum does not indicate the presence of an aromatic ring current. The conjugate acid of

81. A. W. Hanson, *Acta Crystallogr.* **19**, 19 (1965); O. Bastiansen and J. L. Derissen, *Acta Chem. Scand.* **20**, 1319 (1966).
82. H. J. Tobler, A. Bauder, and H. H. Günthard, *J. Mol. Spectrosc.* **18**, 239 (1965); G. W. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 264 (1949).
83. K. Hafner, R. Dönges, E. Goedecke, and R. Kaiser, *Angew. Chem. Int. Ed. Engl.* **12**, 337 (1973).

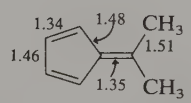
heptalene, however, is very stable (even at pH 7 in aqueous solution) reflecting the stability of the cation, which is a tropylium ion[84]:



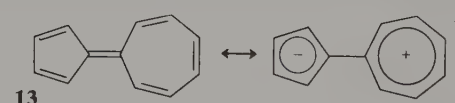
The fulvene and fulvalene systems are not predicted to be aromatic by any of the quantitative estimates of stability. Even simple resonance considerations would suggest polyene behavior, since only dipolar resonance structures can be drawn in addition to the single nonpolar structure:



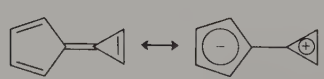
A substantial number of fulvene and fulvalene derivatives have been prepared.[85] The chemical properties of these molecules are those of reactive polyenes. The molecular geometry of dimethylfulvene has been examined by electron diffraction methods. Strong bond-length alternation indicative of a localized structure is found[86]:



Because the five-membered ring is a substituted cyclopentadienide anion in some dipolar resonance structures, it might be expected that exocyclic groups that could strongly stabilize a positive charge might lead to a large contribution from dipolar structures and enhanced stability. The heptafulvene (**13**) and triafulvene (**14**)



13

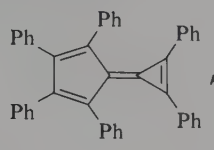


14

molecules would appear to be cases in which a large dipolar contribution would be

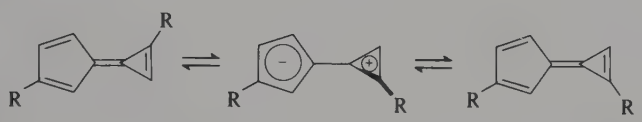
84. H. J. Dauben, Jr., and D. J. Bertelli, *J. Am. Chem. Soc.* **83**, 4657, 4659 (1961).
85. E. D. Bergmann, *Chem. Rev.* **68**, 41 (1968).
86. J. F. Chiang and S. H. Bauer, *J. Am. Chem. Soc.* **92**, 261 (1970).

feasible. The stability of such systems depends on the balance between the increase in energy required to separate unlike charges and the aromaticity associated with Hückel $4n+2$ systems. Neither of the parent molecules has yet been well studied. Phenyl-substituted analogs are known, and the large measured dipole moments suggest considerable charge separation:



$\mu = 6.3$ D Ref. 87

Some alkyl derivatives have been prepared. Their chemical behavior is that of highly reactive polyenes.[88] One interesting property does appear in the NMR spectra, which reveal a very low barrier to rotation about the double bond between the two rings. This property suggests that rotation about this bond takes place easily through a transition state in which the two charged aromatic rings are twisted out of conjugation:



In general conclusion, the HMO′ and SCF methods both appear able to make reasonably accurate predictions about the stabilization in conjugated molecules. The stabilization is general for benzenoid compounds, but quite restricted in nonbenzenoid systems. Since the HMO′ method of estimating stability is based on the ideas of HMO theory, its general success vindicates the ability of this very simplified MO approach to provide some insight into the structural nature of the annulenes and other conjugated polyenes. More sophisticated MO methods, of course, are now accessible and should be applied for more detailed analysis of the structures of these molecules.

9.2. Electrophilic Aromatic Substitution Reactions

Electrophilic aromatic substitution reactions are important for synthetic purposes and because they represent one of the most thoroughly studied classes of organic reactions from a mechanistic point of view. The synthetic aspects of these reactions are discussed in Part B. The discussion here will emphasize the mechanisms

87. E. D. Bergmann and I. Agranat, *Chem. Commun.* 512 (1965).
88. H. Prinzbach, *Pure Appl. Chem.* **28**, 281 (1971).

of several of the well-studied reactions. These mechanistic ideas lay the groundwork for the extensive study that has been done on structure–reactivity relationships in aromatic electrophilic substitution. This topic will be considered in Section 9.3.

A wide variety of electrophilic species can attack aromatic rings and effect substitution. Usually, it is a substitution of some other group for hydrogen that is observed, but this is not always the case. Scheme 9.2 lists some of the specific electrophilic species that are capable of carrying out substitution for hydrogen. Some indication of the relative reactivity of the various electrophiles is given as well. Most of these electrophiles will not be treated in detail until Part B, since not all have been studied thoroughly from a mechanistic point of view. Nevertheless, it is important to recognize that the scope of electrophilic aromatic substitution is very broad.

The reactivity of a particular electrophile determines which aromatic compounds can be successfully substituted. Those electrophiles grouped in the first category are sufficiently reactive to attack almost all aromatic compounds, even those containing strongly electron-attracting substituents. Those in the second group react readily with benzene and derivatives having electron-releasing substituents, but are not generally reactive toward aromatic rings having electron-withdrawing substituents. Those classified in the third group are reactive only toward aromatic compounds that are much more reactive than benzene, specifically those with strong electron-releasing substituent groups. These broad groupings can provide a general guide to the feasibility of successfully carrying out a given electrophilic aromatic substitution.

Despite the wide range of electrophilic species and the variety of aromatic ring systems that can undergo substitution, a single broad mechanistic picture encompasses the large majority of electrophilic aromatic substitution reactions. As would be expected, the identity of the rate-determining step and the shape of the potential energy surface are governed by the identity of the specific reagents, but the series of steps involved appear to be very similar aross the wide range of reactivity. This permits discussion of the fundamental mechanism in terms of a generalized electrophile, E^+ (Scheme 9.3).

A nonspecific complexation of the electrophile with the π-electron system of the aromatic ring can occur. This complex may or may not be involved directly in the substitution mechanism, since π complexes can also be formed under conditions that result in no further reaction. π-Complex formation is, in general, a rapidly reversible reaction. In order for a substitution reaction to occur, a σ-complex must be formed. This intermediate necessarily involves a bond to a specific carbon atom of the aromatic ring. It is at this stage that the site of the substitution, relative to substituents already on the ring, is established. The term *σ complex* is used extensively in discussion of electrophilic aromatic substitution. It should be recognized that this name implies no special bonding properties. The σ complex is a carbocation; more specifically it is a delocalized cyclohexadienyl cation in which the positive charge is located primarily at the positions *ortho* and *para* to the site of substitution. Formation of the σ complex can be reversible. The partitioning of the σ-complex intermediate

forward to product or back to reactants depends on the ease with which the electrophile can be eliminated relative to a proton. For most electrophiles, it is much easier to eliminate the proton, in which case the formation of the σ complex is essentially irreversible. Formation of the σ-complex is usually, but not always, the rate-determining step in electrophilic aromatic substitution. Finally, there may be a π-complex involving the aromatic ring and the departing electrophile. The crucial intermediate for interpretation of relative reactivity and orientation effects is the σ complex.[89]

Let us now consider some of the evidence for this general mechanism. Such evidence has, of course, been gathered by study of specific reaction mechanisms. Only some of the most clear-cut examples are cited here. Additional cases will be mentioned when individual mechanisms are discussed in Section 9.5. A good example of studies that have focused on the identity and mode of generation of the electrophile is aromatic nitration. Primarily on the basis of kinetic studies, it has been possible to show that the active electrophile in nitrations is the nitronium ion, NO_2^+, and that the generation of this active electrophile can be the rate-determining step under some conditions. The existence of the nitronium ion in solutions capable of nitrating aromatic substrates has been established both by cryoscopic measurements and by spectroscopic data. In concentrated sulfuric acid, nitric acid gives rise to four ions, as determined by freezing-point depression:

$$2\,H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + H_3O^+ + 2\,HSO_4^-$$

The NO_2^+ ion can be detected in such solutions by the observation of characteristic Raman absorption bands. Two kinds of rate laws have been found to describe the kinetics of most aromatic nitration reactions. With relatively unreactive aromatic substrates, second-order kinetics, first order in nitrating reagent and first order in aromatic compound, are observed. This finding corresponds to the rate-limiting step being the attack of the electrophile on the aromatic substrate. With more reactive aromatics, this step becomes faster than formation of the nitronium ion, and the concentration of the aromatic no longer appears in the rate expression. Under these conditions, different aromatic substrates suffer nitration *at the same rate*, since the rate-determining step does not directly involve the aromatic substrate. (Review Chapter 4, Section 4.2, p. 169, where the kinetic expressions for nitration under these conditions were discussed.)

The general point that should be drawn from this example is that the actual electrophile in aromatic substitution is usually a highly reactive intermediate formed under the conditions of the reaction. The formation of the true electrophile may or may not be the rate-determining step. Scheme 9.2 indicates the structure of some of

89. For additional discussion of the roles of σ and π complexes, see G. A. Olah, *Acc. Chem. Res.* **4**, 240 (1971), and J. H. Ridd, *Acc. Chem. Res.* **4**, 248 (1971).

Scheme 9.2. Electrophilic Species

Electrophile	Typical mode of generation	Ref.
A. Electrophiles capable of substituting both activated and deactivated aromatic rings		
$O{=}\overset{+}{N}{=}O$	$2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + 2HSO_4^- + H_3O^+$	a
Br_2 or Br_2–MX_n	$Br_2 + MX_n \rightleftharpoons Br_2$–$MX_n$	b
$Br\overset{+}{O}H_2$	$BrOH + H_3O^+ \rightleftharpoons Br\overset{+}{O}H_2 + H_2O$	b
Cl_2 or Cl_2–MX_n	$Cl_2 + MX_n \rightleftharpoons Cl_2$–$MX_n$	b
$Cl\overset{+}{O}H_2$	$ClOH + H_3O^+ \rightleftharpoons Cl\overset{+}{O}H_2 + H_2O$	b
SO_3	$H_2S_2O_7 \rightleftharpoons H_2SO_4 + SO_3$	c
RSO_2^+	$RSO_2Cl + AlCl_3 \rightleftharpoons RSO_2^+ + AlCl_4^-$	d
B. Electrophiles capable of substituting activated but not deactivated aromatic rings		
R_3C^+	$R_3CX + MX_n \rightleftharpoons R_3C^+ + [MX_{n+1}]^-$	e
	$R_3COH + H^+ \rightleftharpoons R_3C^+ + H_2O$	f
	$R_2C{=}CR_2' + H^+ \rightleftharpoons R_2\overset{+}{C}CHR_2'$	g

a. G. A. Olah and S. J. Kuhn, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XLIII.
b. H. P. Braendlin and E. T. McBee, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XLVI.
c. K. L. Nelson, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XLII.
d. F. R. Jensen and G. Goldman, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chapter XL.
e. F. A. Drahowzal, in *Friedel–Crafts and Related Reactions*, Vol. II, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XVII.
f. A. Schreisheim, in *Freidel–Crafts and Related Reactions*, Vol. II, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XVIII.

the electrophilic species involved in typical electrophilic aromatic substitution processes and the reactions involved in their formation.

The evidence for a σ-complex intermediate is based on several lines of investigation. One particularly informative approach involves measurement of isotope effects on the rate of aromatic substitution. If removal of the proton at the site of substitution were concerted with introduction of the electrophile, a primary isotope effect would be observed in reactions in which electrophilic attack on the ring is rate determining. This is not the case for nitration nor for several other types of aromatic substitution reactions. Nitration of aromatic substrates partially labeled by tritium showed no selectivity between protium- and tritium-substituted sites.[90] Similarly, the rate of nitration of nitrobenzene is identical to that of penta-*deuterio*-

90. L. Melander, *Acta. Chem. Scand.* **3**, 95 (1949); *Ark. Kemi* **2**, 211 (1950).

Electrophile	Typical mode of generation	Ref.
$RCH_2X\text{–}MX_n$	$RCH_2X + MX_n \rightleftharpoons RCH_2X\text{–}MX_n$	e
$RC{\equiv}O^+$	$RCX + MX_n \rightleftharpoons RC{\equiv}O^+ + [MX_{n+1}]^-$	h
$RCX\text{–}MX_n$	$RCX + MX_n \rightleftharpoons RCX\text{–}MX_n$	h
H^+	$HX \rightleftharpoons H^+ + X^-$	i
$R_2C{=}\overset{+}{O}H$	$R_2C{=}O + H^+ \rightleftharpoons R_2C{=}\overset{+}{O}H$	j
$R_2C{=}\overset{+}{O}\text{–}\bar{M}X_n$	$R_2C{=}O + MX_n \rightleftharpoons R_2C{=}\overset{+}{O}\text{–}\bar{M}X_n$	j

C. Electrophiles capable of substituting only strongly activated aromatic rings

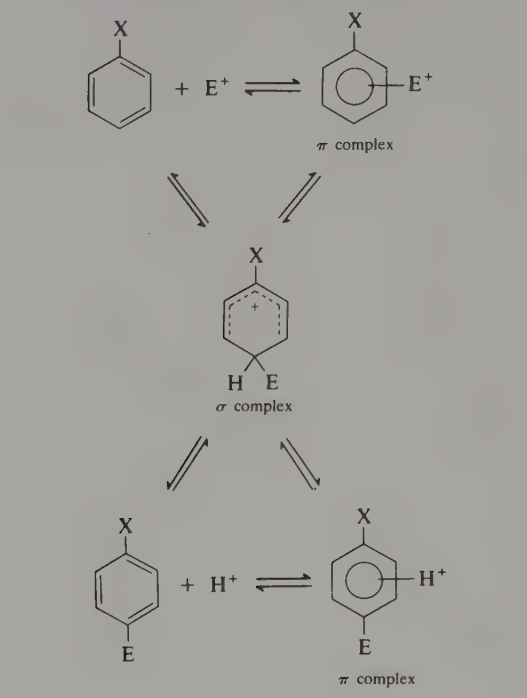
$HC{\equiv}\overset{+}{N}H$	$HC{\equiv}N + HX \rightleftharpoons HC{\equiv}\overset{+}{N}H + X^-$	k
$N{\equiv}O^+$	$HNO_2 + H^+ \longrightarrow N{\equiv}O^+ + H_2O$	l
$Ar\overset{+}{N}{\equiv}N$	$ArNH_2 + HNO_2 + H^+ \longrightarrow Ar\overset{+}{N}{\equiv}N + 2H_2O$	m

g. S. H. Patinkin and B. S. Friedman, in *Freidel–Crafts and Related Reactions*, Vol. II, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XIV.
h. P. H. Gore, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XXXI.
i. R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, New York, 1965, Chap. 8.
j. J. E. Hofmann and A. Schriesheim, in *Friedel–Crafts and Related Reactions*, G. A. Olah (ed.), Interscience, New York, 1964, Vol. II, Chap. XIX.
k. W. Ruske, in *Friedel–Crafts and Related Reactions*, Vol. III, G. A. Olah (ed.), Interscience, New York, 1964, Chap. XXXII.
l. B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc. Perkin Trans. II*, 1831 (1972).
m. H. Zollinger, *Azo and Diazo Chemistry*, translated by H. E. Nursten, Interscience, New York, 1961, Chap. 10.

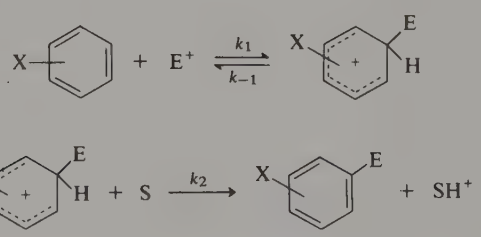
nitrobenzene.[91] The lack of an isotope effect suggests that the proton is lost in a fast step subsequent to the rate-determining step, and implies the involvement of an intermediate. The absence of a primary isotope effect at the site of substitution is not always the case, however. There are some aromatic substitution reactions that show k_H/k_D values between 1 and 2, and a few that are clearly in the range indicating a primary isotope effect.[92] The existence of these isotope effects is compatible with the σ-complex mechanism if the proton-removal (aromatization) step is rate determining. Many of the modest kinetic isotope effects ($k_H/k_D = 1.2\text{–}2.0$) that have been observed have been interpreted in terms of comparable rates for formation and destruction of the σ complex.

91. T. G. Bonner, F. Bowyer, and G. Williams, *J. Chem. Soc.* 2650 (1953).
92. H. Zollinger, *Adv. Phys. Org. Chem.* **2**, 163 (1964).

Scheme 9.3. Generalized Mechanism for Electrophilic Aromatic Substitution

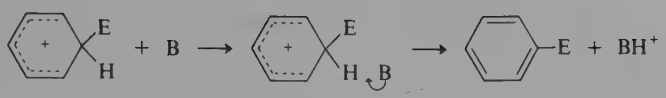


In general terms, the observation of an isotope effect will depend on the relative rate constants k_1, k_{-1}, and k_2. When formation of the σ-complex is rate-determining

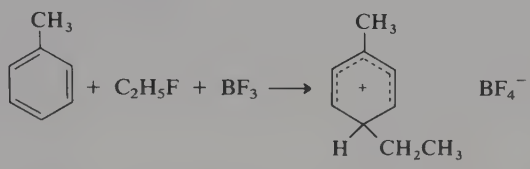


no isotope effect will be observed. If the second step is rate-determining an isotope effect would be expected. Some of the largest isotope effects that have been observed are in substitutions involving the weakly electrophilic diazonium ions. In these cases, the first step is reversible, and the deprotonation can be shown to be rate determining, not only by the existence of the isotope effect, but also by kinetic studies that demonstrate general base catalysis. The general bases participate in the deproton-

ation step:

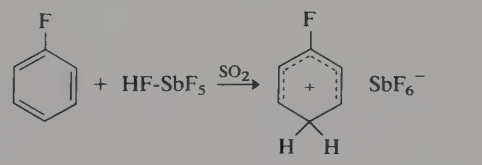


The case for the generality of the σ-complex mechanism is further strengthened by numerous studies showing that such compounds can exist as stable entities under suitable conditions. Salts of substituted benzenium ions (an alternative name for the σ complex) can be isolated as crystalline materials or observed by spectroscopic techniques (especially NMR) in nonnucleophilic solvents:

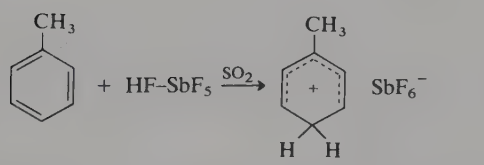


Ref. 93

At low temperatures in nonnucleophilic solvents, aromatic compounds can be protonated to give stable ions that can be characterized on the basis of their proton and carbon NMR spectra as being substituted benzenium ions[94]:



Ref. 95

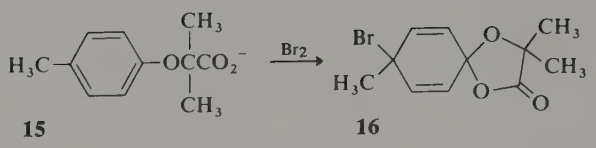


Ref. 96

Under the normal conditions of electrophilic substitution, such species are short-lived and not detectable because of rapid deprotonation. Nevertheless, the direct evidence attained in nonnucleophilic solvent media clearly demonstrated the feasibility of such intermediates.

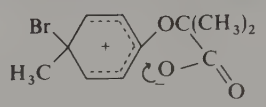
Finally, the existence of σ-complex intermediates can be inferred from the ability of nucleophiles to capture the carbonium ion under certain special circumstances. For example, treatment of the acid **15** with bromine gives the cyclohexadienyl lactone **16**.

93. G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.* **80**, 6541 (1958).
94. G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. Mateescu, *J. Am. Chem. Soc.* **94**, 2034 (1972).
95. G. A. Olah and T. E. Kiovsky, *J. Am. Chem. Soc.* **89**, 5692 (1967).
96. G. A. Olah, *J. Am. Chem. Soc.* **87**, 1103 (1965).

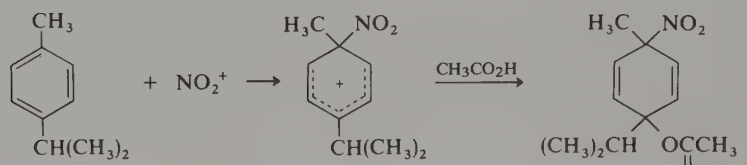


15 16 Ref. 97

This reaction represents capture of the intermediate σ complex as the result of intramolecular nucleophilic attack by the carboxylate group:



A number of examples of nucleophilic capture of cyclohexadienyl cations have been uncovered in the study of nitration of alkylated benzenes in acetic acid. Nitration of *p*-cymene at 0°C leads to the formation of **17** by capture of an intermediate nitrocyclohexadienyl cation.[98]



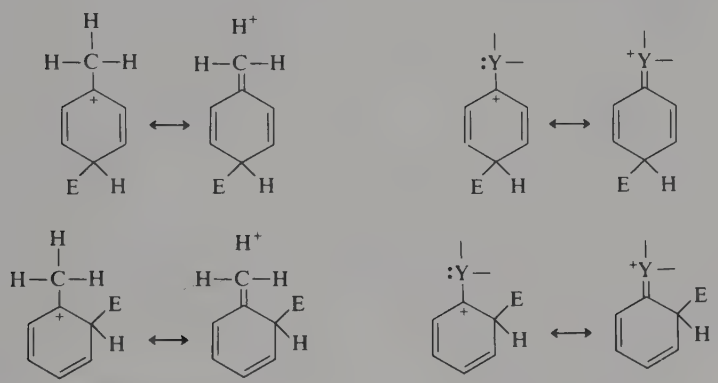
17

This type of addition process is particularly likely to be observed when the electrophile attacks a position that is already substituted, since facile rearomatization by deprotonation is then blocked. Such attack at a substituted position is called *ipso* attack. Addition products have also been isolated, however, when initial electrophilic attack has occurred at an unsubstituted position. The extent of addition occurring in competition with substitution increases on going to naphthalene and the larger polycyclic aromatic ring systems.[99]

The general mechanistic framework outlined in the preceding paragraphs must be further elaborated by other details to fully describe the mechanisms of the individual electrophilic substitutions. The question of the identity of the active electrophile in each reaction is important. We have discussed the case of nitration, in which, under many circumstances, the electrophile has been established to be the nitronium ion. Similar questions arise in many of the other substitution processes. Other matters that are important include the ability of the electrophile to select among alternative positions on a substituted aromatic ring. The relative reactivity of different substituted benzenes toward various electrophiles has also been important in developing a firm understanding of electrophilic aromatic substitution. The next section considers some of the structure–reactivity relationships that have proven to be informative.

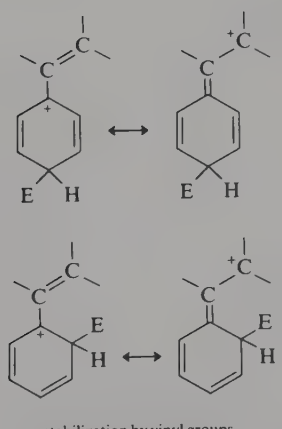
97. E. J. Corey, S. Barcza, and G. Klotmann, *J. Am. Chem. Soc.* **91**, 4782 (1969).
98. R. C. Hahn and D. L. Strack, *J. Am. Chem. Soc.* **96**, 4335 (1974).
99. P. B. D. de La Mare, *Acc. Chem. Res.* **7**, 361 (1974).

The effect that substituents already on the ring have on electrophilic aromatic substitution reactions represents an area of structure–reactivity relationships that has been studied since about 1870. The classification of substituents as activating and *ortho–para*-directing or deactivating and *meta*-directing has been known since those early studies. A basic understanding of these substituent effects became possible when ideas about electronic interactions and resonance theory were developed. Activating, *ortho–para*-directing substituents are those that can serve as electron donors and stabilize the electron-deficient transition state leading to σ-complex formation. Alkyl groups and substituent groups with unshared electron pairs on the atom directly attached to the ring can selectively stabilize the transition states leading to *o*- and *p*-substitution products. This effect is the result of electron donation by the substituents, and can be qualitatively expressed in terms of resonance structures showing electron release to the ring:



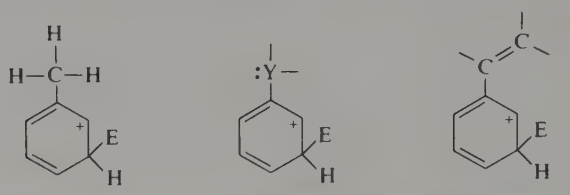
stabilization by alkyl groups

stabilization by heteroatoms with unshared pairs



stabilization by vinyl groups

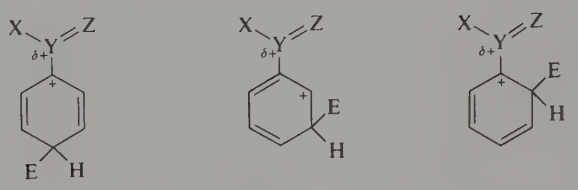
Direct resonance interaction with the substituent group cannot occur in the σ-complex for *meta* substitution. As a result, the transition state leading to this σ-complex is relatively less favored than those for the *ortho* and *para* cases. Because



absence of direct conjugation of electron-donor substituents in *meta* σ-complex

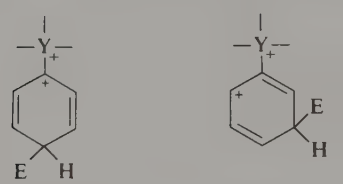
the positive charge can interact directly with the substituent group, the substituent effects in electrophilic aromatic substitution are characterized by a very large resonance component. The σ^+ values[100] given in Table 4.3 (p. 183) are the best numerical indicators of the relative stabilizing abilities of the various common substituent groups.

Electron-attracting groups retard electrophilic substitution. Since deactivation of the *ortho* and *para* positions is greatest, electrophilic substitution occurs primarily at the *meta* position:



strongly destabilized | less destabilized | strongly destabilized

destabilization by electron-attracting multiple bonds



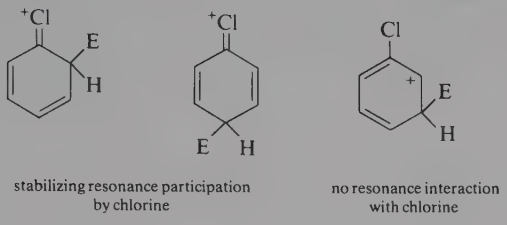
strongly destabilized | less destabilized

destabilization by electronegative heteroatoms with no unshared pairs

A few substituent groups, most notably chlorine and bromine, decrease the rate of reaction, but nevertheless direct incoming electrophiles to the *ortho* and *para* positions. This is the result of competition between field and resonance effects. The halogens are more electronegative than carbon, and as a result of their electron withdrawal, the electron density in the rings is diminished and reactivity toward

100. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.* **80**, 4979 (1958).

electrophiles is reduced. Since unshared electrons are available on the heteroatom, however, the *ortho* and *para* σ complexes are stabilized relative to the *meta* complex, and the halogens act as *ortho–para*-directing groups:



stabilizing resonance participation by chlorine

no resonance interaction with chlorine

The *ortho–para*- versus *meta*-directing and activating versus deactivating effects of substituents can also be described in terms of PMO theory. The discussion can focus either on the structure of the σ complex or on the aromatic substrate. According to the Hammond postulate, it would be most appropriate to focus on the intermediate in the case of reactions which are relatively endothermic. The transition state should then resemble the σ complex in reactions when the initial step has an appreciable activation energy. For more highly reactive electrophiles the transition state may be more reactant-like, in which case consideration of the reactant and application of frontier orbital theory would be more appropriate. Let us examine the effect of substituents from both perspectives.

If we look at the structure of the intermediate, assuming that it accurately reflects transition state structure, we see that we are dealing with a pentadienyl cation system. The electrophile has localized one pair of electrons from the π system to form the new σ bond. The pentadienyl orbitals, according to HMO theory, are shown in Fig. 9.3. The principal mode of stabilization which is available to this π system will be electron donation into ψ_3. This is the LUMO and will best accommodate electron density from substituent groups. Notice that ψ_3 has its highest coefficient at carbons 1,3, and 5 of the pentadienyl system. These are the positions which are *ortho* and *para* to the incoming electrophile. We can conclude that a π-donor substituent at these positions should strongly stabilize the intermediate. This stabilization will be reflected in a lower energy for the corresponding transition state. A substituent at C-2 or C-4 of the pentadienyl system (the *meta* positions) will have much less of an effect on the transition state because of the nodes of ψ_3

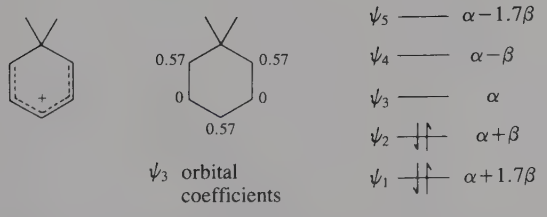


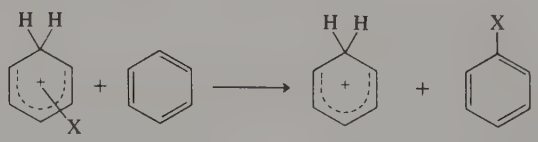
Fig. 9.3. π-Molecular orbitals of the pentadienyl cation.

at these positions. We can therefore expect that a *meta* substituent will have a relatively small effect on the energy of the transition state, even if it is capable of acting as a π donor, because there can be no strong interaction with the LUMO. If we look at the effect of a π-acceptor substituent we see that such a substituent should be strongly destabilizing in the *ortho* or *para* position, but should have a relatively smaller effect in the *meta* position. This interpretation of substituent effects in PMO terminology leads to the same conclusion as resonance theory. Substituent groups which are capable of π-electron donation should be activating and *ortho, para*-directing, whereas substituents which are π acceptors should be *meta* directing and deactivating.

An additional factor which would not be directly revealed by Hückel-type MO calculations has to do with electrostatic effects. Since the electron distribution of the pentadienyl cation is such as to place the positive charge primarily at C-1, C-3, and C-5, there will be an electrostatic repulsion for substituents which have a positive charge on the atom directly bound to the aromatic ring. This factor contributes to the deactivating effect of electron-attracting substituents such as carbonyl, cyano, and nitro groups.

The same factor is responsible for the deactivating effect of the halides. Although their π-donor capability makes them *o, p* directors, the unfavorable electrostatic factor retards the overall rate of reaction. This factor is also present with oxygen and nitrogen substituents, but is overwhelmed by the strong π-donating ability of these substituents. In MO treatments which consider all valence electrons, this factor would appear as increase in energy of orbitals associated with the σ-bonds.

More detailed calculations can provide some indication of the magnitude of such substituent effects. Calculations were carried out at the STO-3G level for the proton transfer from a substituted σ complex to benzene[101]:



This isodesmic process should reflect the stabilization (or destabilization) of the σ complex by the substituent. The results are given in Table 9.2. These calculated energy differences give a good correlation with σ^+. The correlation indicates a somewhat greater substituent dependence ($\rho = -17$) than is observed in experimental proton exchange studies in solution ($\rho = \sim -8$). A physical interpretation of this trend would be that the theoretical results pertain to the gas phase where substituent effects would be maximized because of the absence of any leveling by solvation.

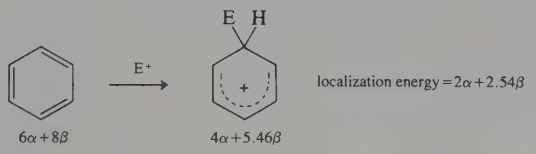
101. J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. J. Hehre, *J. Am. Chem. Soc.* **98**, 244 (1976).

Table 9.2. Energy Changes for Isodesmic Proton Transfer Reactions of Substituted Benzenes[a]

Substituent	ΔE (kcal/mol)	
	meta	*para*
NO_2	−17.9	−22.1
CN	−14.0	−13.8
CF_3	−7.5	−8.4
F	−7.5	3.7
CH_3	2.0	8.5
OCH_3		15.7
OH	−5.3	16.0
NH_2	0.6	27.2

a. From STO-3G calculations reported by J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. J. Hehre, *J. Am. Chem. Soc.* **98**, 244 (1976).

Both HMO calculations and more elaborate MO methods can be applied to the issue of the position of electrophilic substitution in polycyclic conjugated molecules. The most direct approach is to calculate the localization energy. This is the energy difference between the aromatic molecule and the σ-complex intermediate. In simple Hückel calculations, the localization energy is just the difference between the energy calculated for the initial π system and that remaining after two electrons and one carbon atom have been removed from the conjugated system:



This type of approach has frequently been applied to the prediction of relative positional reactivity in polycyclic aromatic hydrocarbons. Simple HMO calculations have only marginal success. More complete treatments such as all-electron SCF and CNDO/2 calculations do give results which show good correlation with experimental proton exchange data.[102]

Now let us turn to the case of a highly reactive electrophile, where we expect an early transition state. In this case the total charge density and the coefficient of the HOMO at each atom would be expected to be the features governing the orientation of electrophilic attack. The transition state should resemble the reactants and, according to frontier MO theory, the electrophile should attack the positions with the largest coefficients for the HOMO. The case of anisole can be taken as a

102. A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.* **92**, 6529 (1970).

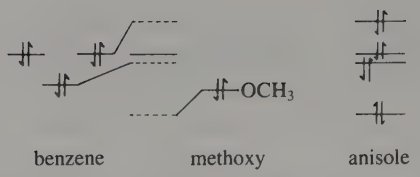


Fig. 9.4. MO diagram for anisole by application of perturbation for a methoxy substituent.

reactive molecule with a π-donor substituent. MO calculations indicate that the lone-pair oxygen orbital is lower than the aromatic π orbitals, leading to the MO diagram in Fig. 9.4 for anisole. According to this analysis, the degeneracy of the two highest-lying occupied π orbitals is broken. To predict the reactivity on the basis of the HOMO distribution, we need to know the coefficients of this orbital at the various ring positions. Figure 9.5 gives these coefficients for the two highest-lying π-type orbitals as calculated by the CNDO method. We see that the HOMO has its highest coefficients on the *ipso*, *ortho* and *para* positions. However, the situation is not entirely satisfactory since the calculations for strongly *meta*-directing substituents have a similar distribution of the HOMO. Another factor which should enter the picture for reactions with an early transition state is the total charge density at the various positions. The distribution of π electrons from all orbitals, as calculated by STO-3G computations, is shown in Fig. 9.6. They show that electron donor substituents increase π-electron density at the *ortho* and *para* positions, whereas π-acceptor substituents cause a slight decrease in π-electron density at the *ortho* and *para* positions.

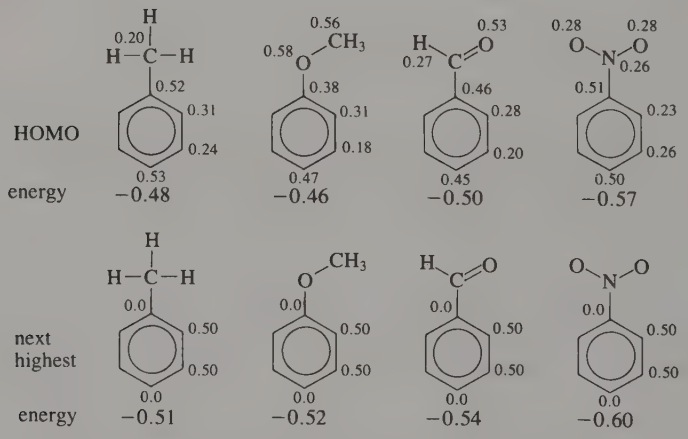


Fig. 9.5. Orbital coefficients for HOMO and next highest π orbital for some substituted benzenes. (From CNDO/2 calculations. *Ortho* and *meta* coefficients have been averaged in the case of the unsymmetrical methoxy and formyl substituents. Orbital energies are given in atomic units.)

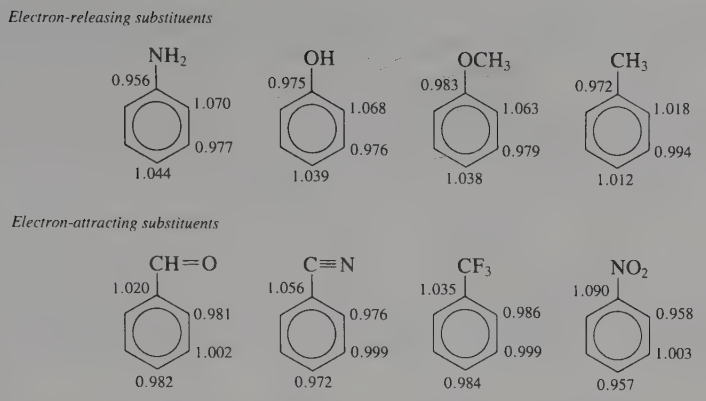


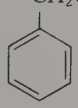
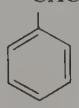
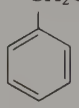
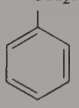
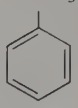
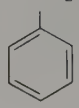
Fig. 9.6. Total π-electron density for some substituted benzenes. [From STO-3G calculations as reported by W. J. Hehre, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.* **94**, 1496 (1972).]

Taken together, these results can provide a satisfactory description of the substituent effects on aromatic substitution involving an early transition state. The energy of the HOMO is raised by π-donor substituents and its distribution is such that the largest coefficients are on the *ortho* and *para* positions. This effect is reinforced by the total π-electron density which is also highest at the *ortho* and *para* positions. In the case of π-acceptor substituents the energy of the HOMO is lowered, in agreement with decreased reactivity. The interpretation of the directional effect is less straightforward because the HOMO distribution and total π-electron density make contradictory predictions. Two aspects of the assumption made when applying the frontier MO approach to deactivating substituents should be recognized. First, for deactivating substituents we expect a relatively late or product-like transition state. Thus the HOMO distribution may be a relatively minor factor in determining orientation in this series. (It should be recalled that considerations based on intermediate stability correctly predict *meta* substitution for π-acceptor groups.) The second problem arises in assuming that the orientation is controlled by a single HOMO. The second π orbital lies close to the HOMO and has a high coefficient on the *meta* carbon (see Fig. 9.5 for benzaldehyde and nitrobenzene). More elaborate frontier orbital theory goes on to consider the contribution of this orbital and leads to the prediction of dominant *meta* substitution.[103]

Substituent groups which are not directly bound to the aromatic ring can also influence the course of electrophilic aromatic substitution. Several alkyl groups bearing electron-attracting substituents are *meta* directing and deactivating, as indicated in Table 9.3, with nitration as the electrophilic substitution reaction. In these molecules, stabilization of the *ortho* or *para* σ complex involving electron

103. K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).

Table 9.3. Percent *meta* Nitration for Some Alkyl Groups with Electron-Withdrawing Substituents[a]

$CH_2CO_2C_2H_5$	$CHCl_2$	CH_2CCl_3	CH_2NO_2	CCl_3	$CH_2\overset{+}{N}(CH_3)_3$
					
11%	34%	37%	55%	64%	85%

a. From C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Second Edition, Cornell University Press, Ithaca, New York, 1969, pp. 275, 281; F. DeSarlo, G. Grynkiewicz, A. Rici, and J. H. Ridd, *J. Chem. Soc. B*, 719 (1971).

release by the alkyl group is counteracted by the electron-withdrawing effect of the electronegative substituents on the alkyl group.

With this general background, and on the basis of extensive accumulation of experimental results, we can recognize some general relationships between aromatic substituents and the scope of the reactions listed in Scheme 9.2.

1) The hydroxyl (phenols) and amino (anilines) groups are highly activating *ortho, para*-directing groups. Such compounds are attacked by all the electrophilic reagents tabulated in Scheme 9.2 (p. 484). With some electrophilic reagents, all available *ortho* and *para* positions are rapidly substituted.
2) The alkyl, acylamino (anilides), and alkoxy groups are activating and *ortho, para*-directing, but are not so strongly activating as hydroxyl or amino groups. Synthetically useful conditions for selective substitution are available for essentially all the electrophilic reactions except those involving very weak electrophiles such as NO^+ or PhN_2^+.
3) The carbonyl group (aromatic aldehydes, ketones, acids, and esters) is deactivating and *meta* directing. There are distinct limitations on the types of substitutions that are satisfactory with carbonyl-substituted aromatics. In general, only those electrophiles in category A in Scheme 9.2 react readily.
4) The halobenzenes, as mentioned earlier, are a somewhat unique group, being deactivating but *ortho–para* directing. In general, halogenated aromatics will react successfully with electrophiles listed in categories A and B in Scheme 9.2.
5) The cyano, nitro, and quaternary ammonium groups are strongly deactivating and *meta* directing. Electrophilic substitution involving reactants having these substituents usually requires especially vigorous conditions, and fails completely with all but strong electrophiles.

Since nitration has been studied over such a wide variety of compounds, this reaction is useful to illustrate the directing effect of substituent groups. Table 9.4 presents some of the data. A variety of reaction conditions are represented in the table, so direct comparison is not always valid, but the trends are nevertheless clear.

Table 9.4. Isomer Proportions in the Nitration of Some Substituted Benzenes[a]

Substituent	Product (%)		
	o	*m*	*p*
$\overset{+}{N}H_3$	3–5	35–50	50–60
$\overset{+}{N}(CH_3)_3$	0	89	11
$CH_2\overset{+}{N}(CH_3)_3$	0	85	15
$\overset{+}{S}(CH_3)_2$	4	90	6
NO_2	5–8	91–93	0–2
CO_2H	15–20	75–85	~1
$C{\equiv}N$	15–17	81–83	~2
$CO_2C_2H_5$	24–28	66–73	1–6
$COCH_3$	26	72	0–2
F	9–13	0–1	86–91
Cl	30–35	~1	64–70
Br	36–43	1	56–62
I	38–45	1–2	54–60
CCl_3	7	64	29
CF_3	6	91	3
$CH_2C{\equiv}N$	24	20	56
CH_2NO_2	22	55	23
CH_2OCH_3	51	7	42
CH_3	56–63	2–4	34–41
CH_2CH_3	46–50	2–4	46–51
OCH_3	30–40	0–2	60–70

a. Data are from Tables 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6 in J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971.

It is important to remember that other electrophiles, while showing the same qualitative trends, will reveal large quantitative differences in position selectivity.

The directing or orienting effect of substituents can be placed on a quantitative basis by use of *partial rate factors*. The reactivity of each position in an aromatic ring can be compared with benzene by measuring the overall rate relative to benzene and then dissecting that rate by multiplying the total relative rate by the fraction of product resulting from *ortho*, *meta*, and *para* substitution. Corrections for the statistical factor arising from the relative number of available positions permit the partial rate factors to provide meaningful comparisons of the reactivity at each ring position with a single position on the benzene ring:

$$\text{partial rate factor} = f = \frac{(6)\,(k_{\text{subs}})\,(\text{fraction } z \text{ product})}{(y)\,(k_{\text{benz}})}$$

where y is the number of equivalent z positions. A partial rate factor calculation is illustrated for the specific case of nitration of toluene in Example 9.1.

Example 9.1. The nitration of toluene is 23 times as fast as for benzene in nitric acid–acetic anhydride. The product ratio is 63% *ortho*, 34% *para*, and 3% *meta*. Calculate the partial rate factor at each position.

$$f_{ortho} = \frac{(6)}{(2)} \times \frac{(23)}{(1)} \times (0.63) = 43.5$$

$$f_{meta} = \frac{(6)}{(2)} \times \frac{(23)}{(1)} \times (0.03) = 2.1$$

$$f_{para} = \frac{(6)}{(1)} \times \frac{(23)}{(1)} \times (0.34) = 46.9$$

Partial rate factors give insight into two related aspects of reactivity. They reveal the selectivity of a given electrophile for different substrates. Some reactions exhibit high *substrate selectivity*; that is, there are large differences in rate of reaction, depending on the identity of ring substituents. In general, low substrate selectivity is taken as evidence of high reactivity in the electrophile and vice versa. Clearly, when substrate selectivity is high, the partial rate factor for the substituted aromatic will be very different from unity. The partial rate factors also reveal *positional selectivity* within individual substituted aromatics. This selectivity also varies for different reactions, and provides insight into the details of the mechanism. In general, there is a correlation between position and substrate selectivity. Electrophiles that show high substrate selectivities generally exhibit low *ortho* : *para* ratios and negligible amounts of *meta* substitution. Very reactive, unselective electrophiles tend to show low substrate and low position selectivity. Table 9.5 gives some data on the selectivity of some representative aromatic substitution reactions. The most informative datum in terms of substrate selectivity is f_p, since the partial rate factors for *ortho* substitution contain a variable steric component. Using f_p as the criterion, halogenation and Friedel–Crafts acylation exhibit high selectivity, protonation and nitration are intermediate, and Friedel–Crafts alkylation shows low selectivity.

A quantitative measurement of selectivity, the selectivity factor S_f, has been proposed and is defined as[104]

$$S_f = \log \frac{f_p \text{ for toluene}}{f_m \text{ for toluene}}$$

The experimental measurement of S_f then requires an accurate determination of the $m:p$ product ratio as well as the toluene:benzene rate ratio for the reaction under question. It was shown that this selectivity factor correlated very strongly with f_p for the reaction. Reactions where f_p is large also show a large S_f. That is, reactions which are selective between substrates (toluene versus benzene) are also selective with respect to position (*para* versus *meta*). The majority of electrophilic

104. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.* **1**, 35 (1963).

Table 9.5. Selectivity in Some Electrophilic Aromatic Substitution Reactions[a]

Reaction	Partial rate factors for toluene		
	f_o	f_m	f_p
Nitration			
$HNO_3(CH_3NO_2)$	38.9	1.3	45.7
Halogenation			
$Cl_2(CH_3CO_2H)$	617	5	820
$Br_2(CH_3CO_2H–H_2O)$	600	5.5	2420
Protonation			
$H_2O–H_2SO_4$	83	1.9	83
$H_2O–CF_3CO_2H–H_2SO_4$	330	7.2	313
Acylation			
$PhCOCl(AlCl_3, PhNO_2)$	32.6	5.0	831
$CH_3COCl(AlCl_3, ClCH_2CH_2Cl)$	4.5	4.8	749
Alkylation			
$CH_3Br(GaBr_3)$	9.5	1.7	11.8
$(CH_3)_2CHBr(GaBr_3)$	1.5	1.4	5.0
$PhCH_2Cl(AlCl_3)$	4.2	0.4	10.0

a. From L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.* **1**, 35 (1963).

substitutions which have been studied in this way (over 100 specific reactions) obey this selectivity relationship with a statistical correlation of about 0.95.[104,105]

Reactivity and selectivity are believed to be largely determined by the position of the transition state on the reaction coordinate. With highly reactive electrophiles the shape of the reaction coordinate would be expected to be as in Fig. 9.7A. The transition state then resembles the reactants more closely than the σ complex. The positive charge on the ring is small, and the interaction with the substituent group resulting in preferential stabilization of a specific σ complex is weak. With a less reactive electrophile, the transition state comes later, as in Fig. 9.7B. The new bond to the electrophile is more completely formed, and, as a result, a substantial positive charge is present on the ring. This situation results in strong substituent effects. These arguments follow the general lines of Hammond's postulate (Chapter 4, Section 4.8). Molecular orbital calculations at the STO-3G level reproduce these qualitative expectations by revealing greater stabilization of the *ortho* and *para* positions in toluene with a closer approach of an electrophile.[105]

Hammett correlations also permit some insight into the reactivity and selectivity of electrophiles in aromatic substitution reactions. In general, the standard Hammett σ substituent constants give poor correlations with reactions involving electrophilic aromatic substitution. The σ^+ values, which reflect an increased importance of direct

104. See p. 498.
105. C. Santiago, K. N. Houk, and C. L. Perrin, *J. Am. Chem. Soc.* **101**, 1337 (1979).

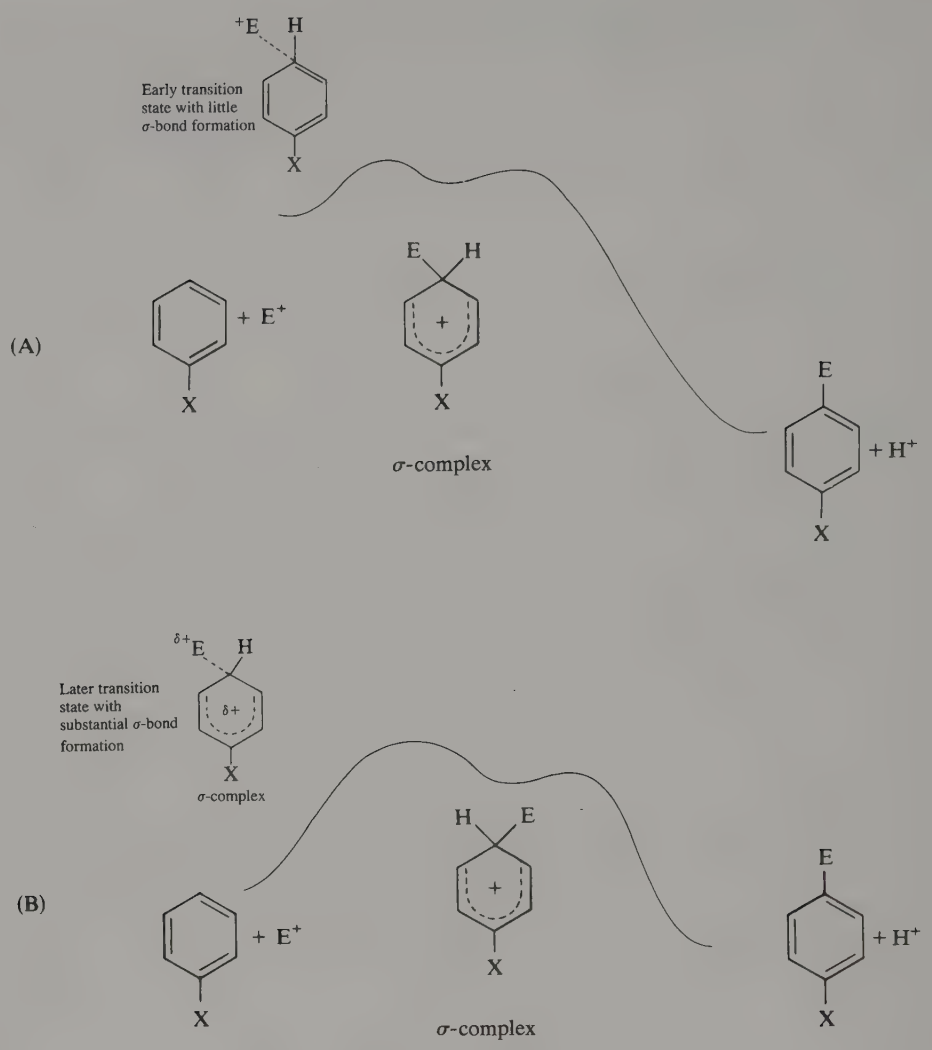


Fig. 9.7. Transition states for highly reactive (A) and less reactive (B) electrophiles.

resonance interaction, give better correlations and, indeed, were developed as a result of the poor correlations observed with σ in electrophilic aromatic substitution. It has been suggested that one could judge the position of a transition state on the reaction coordinate by examining the slope (ρ) of the correlation line between rate of substitution and the substituent constant σ^+, the rationale for this being as follows: A numerically large value for the slope suggests a strong substituent effect, i.e., a late transition state resembling the σ complex. A small value indicates a weak substituent effect and implies an early transition state.[106] Some of the data are given

106. P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.* **11**, 874 (1972).

Table 9.6. Values of ρ for Some Electrophilic Aromatic Substitution Reactions[a]

Reaction	ρ
Bromination (CH_3CO_2H)	−13.1
Chlorination (CH_3NO_2)	−13.0
Chlorination (CH_3CO_2H–H_2O)	−8.8
Proton exchange (H_2SO_4–CF_3CO_2H–H_2O)	−8.6
Acetylation (CH_3COCl, $AlCl_3$, $C_2H_4Cl_2$)	−8.6
Nitration (H_2SO_4–HNO_3)	−6.4
Chlorination ($HOCl$, H^+)	−6.1
Alkylation (C_2H_5Br, $GaBr_3$)	−2.4

a. From P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.* **11**, 874 (1972).

in Table 9.6. The data indicate that halogenation reactions show the characteristics of a highly selective electrophile, nitration and Friedel–Crafts acylation represent reactions of modest selectivity, and Friedel–Crafts alkylation is an example of low

Table 9.7. Kinetic Isotope Effects in Some Electrophilic Aromatic Substitution Reactions

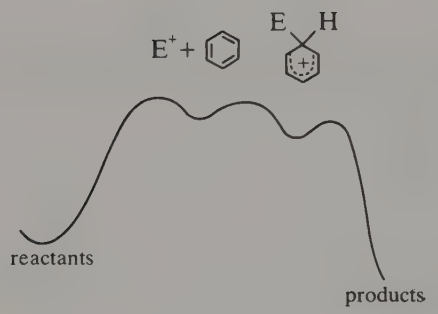
Reaction and substrates	Electrophilic reagents	k_H/k_D or k_H/k_T	Ref.
Nitration			
Benzene-*t*	HNO_3–H_2SO_4	<1.2	a
Toluene-*t*	HNO_3–H_2SO_4	<1.2	a
Nitrobenzene-d_5	HNO_3–H_2SO_4	1	a
Halogenation			
Benzene-d_6	$HOBr$, $HClO_4$	1	a
Anisole-*d*	Br_2	1.05	a
Acylation			
Benzene-d_6	$CH_3C{\equiv}O^+SbF_6^-$, CH_3NO_2	2.25	b
Benzene-d_6	$PhC{\equiv}O^+SbF_6^-$, CH_3NO_2	1.58	b
Sulfonation			
Benzene-d_6	$ClSO_3H$, CH_3NO_2	1.7	c
Benzene-d_6	$ClSO_3H$, CH_2Cl_2	1.6	c
Nitrobenzene-d_5	H_2SO_4–SO_3	1.6-1.7	a
Nitrosation			
Benzene-d_6	HNO_2, D_2SO_4	8.5	d
Diazo coupling			
1-Naphthol-4-sulfonic acid-2-*d*	PhN_2^+	1.0	a
2-Naphthol-8-sulfonic acid-1-*d*	PhN_2^+	6.2	a

a. From a more extensive compilation by H. Zollinger, *Adv. Phys. Org. Chem.* **2**, 163 (1964).
b. From G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.* **91**, 5319 (1969).
c. From M. P. van Albada and H. Cerfontain, *Rec. Trav. Chim.* **91**, 499 (1972).
d. From B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc. Perkin Trans. II*, 1831 (1972).

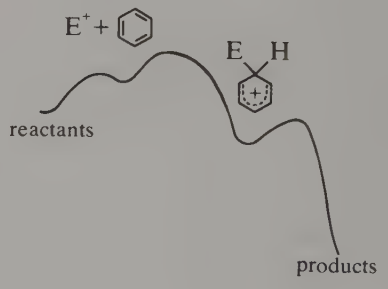
selectivity. This is in general agreement with the selectivity as measured by f_p as shown in Table 9.5, p. 499.

Isotope effects are also useful in providing insight into other aspects of the mechanisms of individual electrophilic aromatic substitution processes. In particular, since primary isotope effects are expected only when the breakdown of the σ complex is rate determining, the observation of a substantial k_H/k_D points to rate-determining deprotonation. Some typical isotope effects are summarized in Table 9.7. While isotope effects are rarely observed for nitration and halogenation, Friedel–Crafts acylation, sulfonation, nitrosation, and diazo coupling provide examples in which the rate of proton abstraction can affect the rate of substitution. However, only nitrosation and diazo coupling are in the range expected for fully rate-controlling deprotonation.

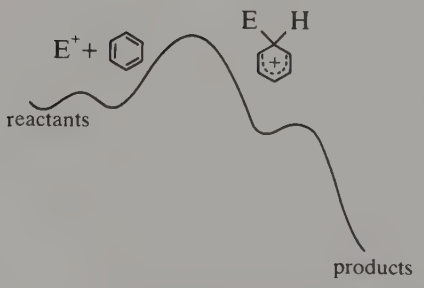
Figure 9.8 summarizes the general ideas presented in Sections 9.2 and 9.3. At least four types of energy profiles have been recognized for individual electrophilic aromatic substitution reactions. Case A is the case of rate-determining generation of the electrophile. It is most readily identified by kinetics. A rate law independent of



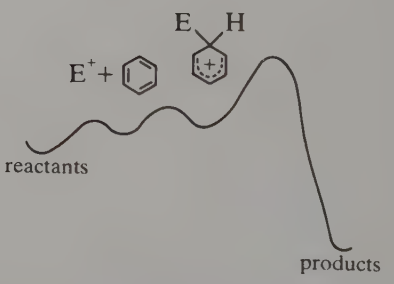
(A) rate-controlling formation of the electrophile



(B) rate-controlling σ-complex formation (nonselective electrophile)



(C) rate-controlling σ-complex formation (selective electrophile)



(D) rate-controlling deprotonation

Fig. 9.8. Various potential energy profiles for electrophilic aromatic substitution.

the concentration of the aromatic is diagnostic of this case. Case B represents rate-determining σ-complex formation, with an electrophile of low selectivity. The rate law in such a case should have terms in both the electrophile and the aromatic. Furthermore, low selectivity, as indicated by low ρ values and low partial rate factors, is expected when this potential energy profile is applicable. Case C is rate-determining σ-complex formation with a more selective electrophile, and, therefore, a later transition state. Finally, there is case D, in which the proton removal and rearomatization are rate limiting. This case can be recognized by the observation of a primary kinetic isotope effect at the site of substitution.

9.4. Specific Substitution Mechanisms

At this point, attention can be given to specific electrophilic aromatic substitution reactions. The kinds of data that have been especially pertinent to elucidating mechanistic detail include linear free-energy relationships, kinetic studies, isotope effects, and selectivity patterns. In general, the basic questions that need to be asked about each mechanism are (1) What is the active electrophile? (2) Which step in the general mechanism for electrophilic aromatic substitution is rate determining? (3) What are the orientation and selectivity patterns?

9.4.1. Nitration

A substantial body of data including reaction kinetics, isotope effects, and structure–reactivity relationships has permitted a quite thorough understanding of the steps in aromatic nitration.[107] As indicated by the general mechanism for electrophilic substitution, there are three distinct steps:

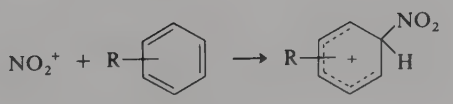
1. Generation of the Electrophile

$$2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + 2HSO_4^- + H_3O^+$$

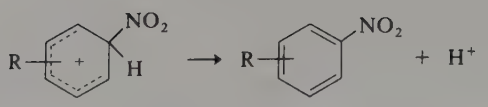
or

$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

2. Attack on the Aromatic Ring



107. L. M. Stock, *Prog. Phys. Org. Chem.* **12**, 21 (1976).



Conditions under which each of the first two steps is rate determining have been recognized. The third step is usually very rapid and has not been amenable to direct kinetic investigation.

The existence of the nitronium ion in sulfuric acid–nitric acid mixtures can be demonstrated by cryoscopic measurements and by spectroscopy. An increase in the strong acid concentration increases the rate of the reaction by shifting the equilibrium of step 1 to the right. Addition of nitrate ion to nitric acid has the opposite effect of suppressing the preequilibrium dissociation of nitric acid. It is possible to prepare crystalline salts of nitronium ions such as nitronium tetrafluoroborate. Solutions of these salts in organic solvents rapidly nitrate aromatic compounds.[108]

These are three types of general kinetic situations which have been observed in aromatic nitrations. Aromatics of modest reactivity exhibit second-order kinetics in mixtures of nitric acid with the stronger acids sulfuric or perchloric acid.[109] Under these conditions the formation of the nitronium ion is a rapid pre-equilibrium and step 2 of the nitration mechanism becomes rate-controlling. If the nitration is conducted in inert organic solvents such as nitromethane or carbon tetrachloride the rate of the first step is slowed and can become rate-controlling.[110] Finally, very reactive aromatics, including alkylated benzenes, can react so rapidly that the rate of nitration becomes governed by encounter rates. Under these circumstances mixing factors enter into the kinetics and the differences in reactivity between different aromatic substrates disappear.

With very few exceptions, the final step in the nitration mechanism, the deprotonation of the σ complex, is fast and therefore has no effect on the observed kinetics. The fast deprotonation can be confirmed by the absence of an isotope effect when deuterium or tritium is introduced at the substitution site. Several compounds such as benzene, toluene, bromobenzene, and fluorobenzene have been found not to exhibit isotope effects.[111] The only case where a primary isotope effect indicating rate-controlling deprotonation has been seen is with 1,3,5-tri-*t*-butylbenzene where steric hindrance evidently makes deprotonation the slow step.[112]

108. S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.* **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.* **84**, 3684 (1962).

109. J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971, Chap. 2.

110. E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); R. G. Coombes, *J. Chem. Soc. B*, 1256 (1969).

111. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.* **83**, 4571, 4581 (1961); H. Suhr and H. Zollinger, *Helv. Chim. Acta* **44**, 1011 (1961); L. Melander, *Acta Chem. Scand.* **3**, 95 (1949); *Arkiv Kemi*, **2**, 211 (1950).

112. P. C. Myhre, M. Beug, and L. L. James, *J. Am. Chem. Soc.* **90**, 2105 (1968).

The question of other species acting as electrophiles in nitration reactions arises principally in the case of nitration using solutions prepared by dissolving nitric acid in acetic anhydride. Acetyl nitrate is formed in such solutions, and so the question arises as to whether it is the nitrating species. Such solutions are very potent nitrating

$$HNO_3 + (CH_3CO)_2O \longrightarrow CH_3\overset{\overset{O}{\|}}{C}ONO_2 + CH_3CO_2H$$

mixtures and effect nitrations at higher rates than solutions of nitric acid in inert organic solvents.

The question of the identity of the nitrating species can be approached by comparing selectivity with that of nitrations known to involve the nitronium ion. Examination of part B of Table 9.8 shows that the position selectivity exhibited by acetyl nitrate toward toluene and ethylbenzene is not dramatically different from that observed with nitronium ion. The data for 2-propylbenzene suggest a higher *o* : *p* ratio for nitronium ion nitrations, however. Several substituted aromatic compounds—for example, anisole[113a] and acetanilide[113b]—give much higher *o* : *p* ratios when nitrated by acetyl nitrate than when nitronium ion conditions are used, suggesting the involvement of a different electrophile.[113]

The selectivity data for nitration must be treated with special caution since there are some conditions where encounter control of reaction rates is present. Under these conditions substrate selectivity disappears. An example of this can be seen in Table 9.8 where no difference in reactivity of mesitylene and xylene can be seen in H_2SO_4–HNO_3, whereas in HNO_3–CH_3NO_2 a factor of about 2 exists. Encounter control prevails in the former case. In general, nitration is a relatively unselective reaction with toluene partial rate factors ranging from about 50–60, as shown in Table 9.8. When the aromatic compound carries an electron-attracting group, the selectivity increases since the transition state occurs later on the reaction coordinate. For example, while toluene is ~20 times more reactive than benzene, *p*-nitrotoluene is ~200 times more reactive than nitrobenzene. Because of the later transition state, the effect of the methyl substituent is magnified.

9.4.2. Halogenation

Substitution for hydrogen by halogen is an important electrophilic aromatic substitution reaction. The reactivity of the halogen molecules decreases in the order $Cl_2 > Br_2 > I_2$. The molecular halogens are not the only species that can effect halogenation, however. Many reactions are run in the presence of Lewis acids, in

113. (a) J. G. Hoggett, R. B. Moodie, and K. Schofield, *Chem. Commun.*, 605 (1969); (b) B. M. Lynch, C. M. Chen, and Y.-Y. Wigfield, *Can. J. Chem.* **46**, 1141 (1969); (c) S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 2454 (1971); R. G. Coombes and L. W. Russell, *J. Chem. Soc. B*, 2443 (1971).

Table 9.8. Relative Reactivity and Position Selectivity for Nitration of Some Aromatic Compounds

A. Relative reactivity of some hydrocarbons

Substrate	H_2SO_4–HNO_3–H_2O[a]	HNO_3–CH_3NO_2[b]	HNO_3–$(CH_3CO)_2O$[c]
Benzene	1	1	1
Toluene	17	25	27
p-Xylene	38	139	92
m-Xylene	38	146	—
o-Xylene	38	139	—
Mesitylene	36	400	1750

B. Partial rate factors for some monoalkylbenzenes

	H_2SO_4–HNO_3 in sulfolane[d]			HNO_3–CH_3NO_2[e,f]			HNO_3–$(CH_3CO)_2O$[g]		
Substrate	f_o	f_m	f_p	f_o	f_m	f_p	f_o	f_m	f_p
Toluene	52.1	2.8	58.1	49	2.5	56	49.7	1.3	60.0
Ethylbenzene	36.2	2.6	66.4	32.7	1.6	67.1	31.4	2.3	69.5
2-Propylbenzene	17.9	1.9	43.3	—	—	—	14.8	2.4	71.6
t-Butylbenzene	—	—	—	5.5	3.7	71.4	4.5	3.0	75.5

C. Relative reactivity and isomer distribution for nitrobenzene and the nitrotoluenes[h]

Substrate	Relative reactivity	Product %		
		o	*m*	*p*
Nitrobenzene	1	7	92	1
o-Nitrotoluene	545	29	1	70
m-Nitrotoluene	138	38	1	60
p-Nitrotoluene	217	100	0	—

a. From R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968).
b. From J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1 (1969).
c. From A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron* **26**, 5101 (1970).
d. From G. A. Olah, S. J. Kuhn, S. H. Flood, and J. C. Evans, *J. Am. Chem. Soc.* **84**, 3687 (1962).
e. From L. M. Stock, *J. Org. Chem.* **26**, 4120 (1961).
f. From G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.* **96**, 549 (1974); *o*, *m*, *p* designations refer to the methyl substituent.
g. From J. R. Knowles, R. O. C. Norman, and G. K. Radda, *J. Chem. Soc.*, 4885 (1960).
h. From G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.* **96**, 549 (1974); *o*, *m*, *p* designations for the nitrotoluenes are relative to the methyl groups.

which case a complex of the halogen and Lewis acid may be the active agent. The hypohalous acids, ClOH, BrOH, and IOH, are weak halogenating agents, which, however, become much more reactive in acidic solution.

Bromine and especially iodine form complexes with the corresponding halide ion. These anions are far less reactive than the free halogens, but are capable of

$$Br_2 + Br^- \rightleftharpoons Br_3^-$$
$$I_2 + I^- \rightleftharpoons I_3^-$$

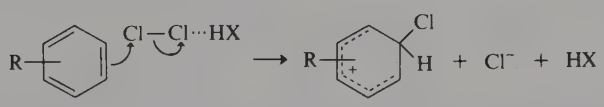
substituting certain highly reactive molecules. In any case, they can present a complication in kinetic studies, since the concentration of halide ion increases during the course of a halogenation, and successively more of the halogen will be present as the complex ion. Finally, there are a number of other molecular species that can effect halogenation, including the hypohalites of carboxylic acids such as acetyl hypochlorite[114a] and trifluoroacetyl hypobromite[114b]:

$$Cl_2 + Hg(OAc)_2 \rightleftharpoons HgClOAc + CH_3CO_2Cl$$
$$Br_2 + Hg(O_2CCF_3)_2 \rightleftharpoons HgBr(O_2CCF_3) + CF_3CO_2Br$$

The latter is an extremely reactive species. The inductive effect of the trifluoroacetyl group makes it a good leaving group, and facilitates cleavage of the O–Br bond during reaction with an aromatic compound. The acyl hypohalites are also the active halogenating species in solutions of the hypohalites in carboxylic acids, where they exist in equilibrium with the hypohalous acid.

$$HOCl + RCO_2H \rightleftharpoons RC(=O)Cl + H_2O$$
$$HOBr + RCO_2H \rightleftharpoons RC(=O)Br + H_2O$$

Molecular chlorine is believed to be the active electrophile in uncatalyzed chlorination of aromatic compounds. Simple second-order kinetics are observed in acetic acid.[115] The reaction is much slower in nonpolar solvents such as dichloroethane and carbon tetrachloride. Chlorination in nonpolar solvents is catalyzed by added acids, and it is believed that this catalysis is the result of assistance in the cleavage of the Cl–Cl bond[116]:



There is no evidence of prior dissociation of the chlorine to give Cl^+ as a distinct chemical entity.

Chlorination in acetic acid is characterized by a large ρ value (~ -9 to -10) and a partial rate factor for toluene ($f_p = 820$) indicating high substrate selectivity.[117] The transition state can be regarded as being similar to the σ-complex intermediate.

Often, for preparative purposes, a Lewis acid such as $AlCl_3$ is added to catalyze chlorination. Chlorination of benzene under these conditions is overall third order,

114. (a) P. B. D. de la Mare, I. C. Hilton, and S. Varma, *J. Chem. Soc.*, 4044 (1960); (b) J. R. Barnett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.* **94**, 6129 (1972).
115. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.* **84**, 1661 (1962).
116. L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.* **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.* **82**, 4547 (1960).
117. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.* **79**, 5175 (1957).

first order in aromatic, chlorine, and catalyst[118]:

$$\text{rate} = k[\text{ArH}][\text{Cl}_2][\text{AlCl}_3]$$

These kinetics could be associated with formation of a complex Cl_2–$AlCl_3$ that acts as the active halogenating agent, but are also consistent with a rapid equilibrium involving formation of Cl^+:

$$\text{Cl}_2 + \text{AlCl}_3 \rightleftharpoons \text{Cl}_2\text{–AlCl}_3 \rightleftharpoons \text{Cl}^+ + \text{AlCl}_4^-$$

There is, however, no direct evidence for the formation of Cl^+, and it is much more likely that the complex is the active electrophile. The substrate selectivity ($k_{tol} = 160\, k_{benz}$) is lower than in uncatalyzed chlorinations. This lower selectivity indicates that the transition state is reached earlier than in the uncatalyzed reaction. This conclusion is reasonable, since the catalyst presumably acts to weaken the Cl–Cl bond, which should lower the activation energy for the electrophilic attack.

Hypochlorous acid is a weak chlorinating agent. In acidic solution, however, it is converted to a much more active chlorinating species. Although early mechanistic studies suggested that Cl^+ was formed under these conditions, it has been shown that this is not the case. Detailed kinetic analysis of the chlorination of anisole has revealed a rather complex rate expression[119]:

$$\text{rate} = k_1[\text{HOCl}]^2 + k_2[\text{H}_3\text{O}^+][\text{HOCl}]^2 + k_3[\text{ArH}][\text{H}_3\text{O}^+][\text{HOCl}]$$

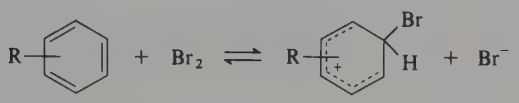
Some of the terms are independent of the concentration of the aromatic species. This complex rate law can be explained in terms of the formation of Cl_2O, an anhydride of hypochlorous acid:

$$2\text{HOCl} \longrightarrow \text{Cl}_2\text{O} + \text{H}_2\text{O}$$
$$2\text{HOCl} + \text{H}_3\text{O}^+ \longrightarrow \text{Cl}_2\text{O} + \text{H}_3\text{O}^+ + \text{H}_2\text{O}$$

The active chlorinating species apparently include both Cl_2O and $H_2\overset{+}{O}Cl$. The terms involving chlorination by Cl_2O are zero order in aromatic substrate, since formation of Cl_2O is slower than subsequent reaction with the aromatic. For some time, the occurrence of these zero-order terms was puzzling, since it suggested that chlorination might be proceeding via rate-determining cleavage of $H_2\overset{+}{O}Cl$ to Cl^+. Thermodynamic considerations argued strongly against this possibility. It can be estimated that the equilibrium concentration of $Cl^+ = 10^{-40}\, M$, far too low to account for the observed reaction rate.[120] The implication of Cl_2O as the active chlorinating species permits an alternative explanation of the established fact that chlorination proceeds in part by a process that is independent of the concentration of the aromatic reagent.

118. S. Y. Caille and R. J. P. Corriu, *Tetrahedron* **25**, 2005 (1969).
119. C. G. Swain and D. R. Crist, *J. Am. Chem. Soc.* **94**, 3195 (1972).
120. E. Berliner, *J. Chem. Ed.* **43**, 124 (1966).

Molecular bromine is believed to be the reactive brominating species in uncatalyzed brominations. The brominations of benzene and toluene are first order in bromine and first order in substrate in trifluoroacetic acid solutions,[121] but become more complicated in the presence of water.[122] The bromination of benzene in aqueous acetic acid exhibits a first-order dependence on bromine concentration when bromide ion is present. The observed rate is, however, dependent on bromide ion concentration, decreasing with increasing bromide ion concentration. The bromine concentration appears as a higher power in the absence of bromide ion. These data are consistent with a rate-determining formation of the σ complex when bromide ion concentration is low, but with a shift to reversible formation of the σ complex and rate-determining deprotonation at higher bromide ion concentration[123]:



Bromination is characterized by high substrate selectivity.[104] The data in Table 9.5 (p. 499) show that for toluene, f_p is around 2.5×10^3, as compared to about 50 for nitration. The very large stabilizing effect of electron donor substituents is also evident in the large negative ρ value (-12) that is observed.[124] That substituents can strongly influence both the rate and the orientation implies that the transition state comes late in the reaction and resembles the σ complex. Especially high partial rate factors for bromination are found in solutions consisting largely of trifluoroacetic acid,[121,122] so that the solvent also plays a significant role in determining selectivity.

Bromination has been shown not to exhibit a primary isotope effect in the case of benzene,[125] bromobenzene,[90] toluene,[126] or anisole.[127] On the other hand, several substituted anisoles[127] and derivatives of *N,N*-dimethylaniline[128] and 1,3,5-trialkylaromatics[129] show isotope effects. The observation of isotope effects in highly substituted systems generally seems to be the result of steric factors that can operate in two ways. There may be resistance to the large bromine taking up a position coplanar with adjacent substituents, as is required in the aromatization step. In addition, the bulk of several substituent groups may hinder solvent or another base from assisting in proton removal.

121. H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.* **88**, 1447 (1966).
122. W. M. Schubert and D. F. Gurka, *J. Am. Chem. Soc.* **91**, 1443 (1969).
123. E. Berliner and J. C. Powers, *J. Am. Chem. Soc.* **83**, 905 (1961); W. M. Schubert and J. L. Dial, *J. Am. Chem. Soc.* **97**, 3877 (1975).
104. See p. 498.
124. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.* **79**, 1421 (1957).
125. P. B. D. de la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).
90. See p. 484.
126. R. Josephson, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.* **83**, 3562 (1961).
127. J.-J. Aaron and J.-E. Dubois, *Bull. Soc. Chim. Fr.*, 603 (1971).
128. J.-E. Dubois and R. Uzan, *Bull. Soc. Chim. Fr.*, 3534 (1968); A. Nilsson, *Acta Chem. Scand.* **21**, 2423 (1967); A. Nilsson and K. Olsson, *Acta Chem. Scand.* **23**, 7 (1969).
129. P. C. Myhre, *Acta Chem. Scand.* **14**, 219 (1960).

Bromination is catalyzed by Lewis acids, and a study of the kinetics of bromination of benzene and toluene in the presence of aluminum chloride has been reported.[118] Toluene is found to be about 35 times more reactive than benzene under these conditions. Thus, the catalyzed reaction shows a good deal less substrate selectivity than the uncatalyzed reaction in acidic solution. The active electrophile is presumably a complex of Br_2 with the Lewis acid.

Bromination can also be carried out using solutions of acetyl hypobromite or trifluoroacetyl hypobromite.[130,131] Acetyl hypobromite is the active halogenating species present in solutions of hypobromous acid in acetic acid:

$$CH_3CO_2H + HOBr \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}OBr + H_2O$$

The reagent can also be formed by reaction of bromine with mercuric acetate:

$$Hg(OAc)_2 + Br_2 \rightleftharpoons Hg(OAc)Br + CH_3CO_2Br$$

Both equilibria lie to the left, but acetyl hypobromite is sufficiently reactive that it is the principal halogenating reagent in both solutions. The reactivity of these molecules as halogenating agents increases with the ability of the carboxylate group to function as a leaving group on reaction with an aromatic substrate, as is demonstrated by the very high reactivity of trifluoroacetyl hypobromite.[114] The estimated relative rates of Br_2, CH_3CO_2Br, and CF_3CO_2Br are $1 : 10^6 : 10^{10}$. It is these high reactivities of the hypobromites that permit them to be the reactive halogenating species in solutions where they are present in relatively low equilibrium concentrations.

Molecular iodine is not a very powerful halogenating agent. Only very reactive aromatics such as anilines or phenolate anions are reactive toward iodine. Iodine monochloride can be used as an iodinating reagent. The greater electronegativity of chlorine assures that iodine will be the electrophilic entity in substitution reactions. As with the simple halogens, the kinetics of reactions of aromatic hydrocarbons with iodine monochloride show terms higher than first order in the halogenating agent.[132] The reactions are catalyzed by the Lewis acids, such as $ZnCl_2$. Iodinations can also be carried out with acetyl hypoiodite[133] and trifluoroacetyl hypoiodite. The methods of formation of these reagents and the mechanism of substitution are similar to those for the corresponding hypobromites.

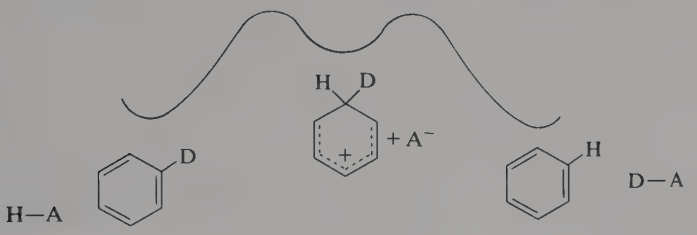
Direct fluorination of aromatics is not a preparatively important reaction because it can occur with explosive violence. Mechanistic studies have been done

118. See p. 508.
130. P. B. D. de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 4829 (1962).
131. Y. Hatanaka, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.* **87**, 4280 (1965).
114. See p. 507.
132. R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.* **78**, 5623 (1956).
133. E. M. Chen, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.* **89**, 428 (1967).

at very low temperatures and with low fluorine concentrations. For toluene the f_p and f_m are 8.2 and 1.55, respectively, indicating a very unselective electrophile. The ρ value in a Hammett correlation with σ^+ is -2.45. Thus, so far as conclusions are possible, fluorination seems to fit the pattern of the other halogens by being by far the most reactive and least selective electrophilic species among them.[134]

9.4.3. Protonation and Hydrogen Exchange

Hydrogen exchange brought about by attack on the aromatic ring by protonation can be followed by the use of isotopic labels. Both deuterium and tritium have been used, and the experiments can be performed in such a way that the isotope enters or is displaced from the aromatic molecule. The study of the mechanism of hydrogen exchange is simplified by the fact that there is no question about the identity of the electrophile. It is the solvated proton. Furthermore, the principle of microscopic reversibility guarantees a nearly symmetrical potential energy diagram for the reaction. The product and reactant differ in energy only by the zero-point energy of the isotopically substituted C–H bond, and the transition states differ only by some fraction of the zero-point energy. The transition states involve a partial transfer of the proton to and from the proton donor. Cyclohexadienyl cations (the



σ complex) are intermediates. As mentioned earlier, such species have been shown to be stable in strongly acidic nonnucleophilic media.

Partial rate factors for a number of substituted aromatic compounds have been measured. They reveal activation of *o* and *p* positions by electron-releasing groups. Some typical data are given in Table 9.9. The k_{tol}/k_{benz} ratio of around 300 indicates considerable substrate selectivity. The f_p value for toluene varies somewhat depending on the reaction medium, but generally is about 10^2.[104] The ρ value for hydrogen exchange in H_2SO_4–CF_3CO_2H–H_2O is -8.6.[106] A similarly large ρ value of -7.5 has been observed in aqueous sulfuric acid.[135] As expected for an electrophilic aromatic substitution, the best correlation is with σ^+.

134. F. Cacace, P. Giacomello, and A. P. Wolff, *J. Am. Chem. Soc.* **102**, 3511 (1980).
104. See p. 499.
106. See p. 500.
135. S. Clementi and A. R. Katritzky, *J. Chem. Soc. Perkin Trans. II*, 1077 (1973).

Table 9.9. Partial Rate Factors for Hydrogen Exchange in Some Substituted Aromatic Compounds

X	f_o	f_m	f_p	Ref.
CH_3	330	7.2	313	a
F	0.136	—	1.79	b
Cl	0.035	—	0.161	b
OPh	6900	~0.1	31,000	c
Ph	133	<1	143	d

a. From C. Eaborn and R. Taylor, *J. Chem. Soc.*, 247 (1961).
b. From C. Eaborn and R. Taylor, *J. Chem. Soc.*, 2388 (1961).
c. From R. Baker and C. Eaborn, *J. Chem. Soc.*, 5077 (1961).
d. From C. Eaborn and R. Taylor, *J. Chem. Soc.*, 1012 (1961).

Among the experimental results that have been reported regarding hydrogen exchange, a most important one is that general acid catalysis has been demonstrated.[136] This finding is in accord with a rate-limiting step involving proton transfer. Since the two steps in hydrogen exchange are the reverse of one another, except for the isotopic differences, the two steps must have very similar activation energies, and neither protonation nor proton loss would be entirely rate determining. Since proton removal is partially rate determining, hydrogen exchange exhibits an isotope effect. A series of experiments using both deuterium and tritium labels arrived at $k_H/k_D = 9.0$ for the proton-loss step in exchange of 1,3,5-trimethoxybenzene.[137] Substantial isotope effects have also been reported for the exchange process with azulene.[138]

Data on hydrogen exchange have been of particular interest for comparison with theoretical predictions of aromatic reactivity. Because the electrophile is well defined and small, calculation of the stability of various competing intermediates by MO methods is feasible.

9.4.4. Friedel–Crafts Alkylation and Related Reactions

The Friedel–Crafts reaction is a very important method for introducing alkyl substituents on an aromatic ring. It involves generation of a carbonium ion intermediate or a related electrophilic carbon species. The most general method for generating these electrophiles involves reaction between an alkyl halide and a Lewis acid. The most common Lewis acid for preparative work is aluminum chloride. Alternative routes to the alkylating species include protonation (followed by dehydration) of alcohols and protonation of alkenes.

136. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.* **83**, 2877 (1961); A. J. Kresge, S. Slae, and D. W. Taylor, *J. Am. Chem. Soc.* **92**, 6309 (1970).
137. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.* **89**, 4411 (1967).
138. L. C. Gruen and F. A. Long, *J. Am. Chem. Soc.* **89**, 1287 (1967).

There are relatively few kinetic data on the Friedel–Crafts reaction. Alkylation of benzene or toluene with methyl bromide or ethyl bromide with gallium bromide as catalyst is first order in each reactant and in catalyst.[139] With aluminum bromide as catalyst, the rate of reaction changes with time, apparently because of heterogeneity. The initial rate data fit the following kinetic expression[140]:

$$\text{rate} = k[\text{EtBr}][\text{benzene}][\text{AlBr}_3]^2$$

Good kinetic results, in general, have been difficult to come by in the Friedel–Crafts reaction. With the common catalysts, the reactions are very fast and often complicated by other problems, including heterogeneity. For this reason, most studies of structure–reactivity trends have been done using competitive reactivity data, rather than direct rate measurements.

A study of alkylations with a group of substituted benzyl halides and a variety of Friedel–Crafts catalysts has provided insight into the trends in selectivity and orientation that accompany changes in both the alkyl group and the catalyst.[141] There is a marked increase in substrate selectivity on going from *p*-nitrobenzyl chloride to *p*-methoxybenzyl chloride. For example, with titanium tetrachloride as the catalyst, $k_{\text{tol}}/k_{\text{benz}}$ increases from 2.5 to 97. This increase in substrate selectivity is accompanied by an increasing preference for *para* substitution. With *p*-nitrobenzyl chloride, the *o* : *p* ratio is 2 : 1 (the statistically expected ratio), whereas with the *p*-methoxy compound, the *para* product dominates by 2.3 : 1. There is a clear trend within the family of substituted benzyl chlorides of increasing selectivity with increasing electron release by the substituent. All the reactions, however, remain in a region that constitutes rather low selectivity. Thus, the position of the transition state for a benzyl halide carrying no electron-releasing substituent must come quite early. The substituents present on the ring undergoing substitution are able to exert only weak effects in orienting the incoming alkyl group. With benzyl halides having electron-releasing groups, the transition state comes somewhat later, permitting the substituents present on the ring to exert a greater directing influence. Toluene–benzene reactivity ratios under a number of Friedel–Crafts conditions are recorded in Table 9.10. As would be expected on the basis of the relatively low substrate selectivity, position selectivity is quite modest. The amount of *ortho* substitution is often comparable to the amount of *para* substitution. Isomer ratio data are included in Table 9.10.

139. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.* **85**, 2596 (1963).
140. B. J. Carter, W. D. Covey, and F. P. DeHaan, *J. Am. Chem. Soc.* **97**, 4783 (1975); cf. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.* **81**, 3315 (1959); F. P. DeHaan and H. C. Brown, *J. Am. Chem. Soc.* **91**, 4844 (1969); H. Jungk, C. R. Smoot, and H. C. Brown. *J. Am. Chem. Soc.* **78**, 2185 (1956).
141. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.* **94**, 7448 (1972).

Table 9.10. Toluene–Benzene Reactivity Ratios in Friedel–Crafts Alkylation Reactions

Electrophilic reagents	$\frac{k_{tol}}{k_{benz}}$	Toluene $o:p$ ratio	Ref.
CH_3Br–$AlBr_3$	2.5–4.1	1.9	a
C_2H_5Br–$GaBr_3$	6.5	—	b
$PhCH_2Cl$–$AlCl_3$	3.2	0.82	c
$(CH_3)_2CHBr$–$AlCl_3$	2.0	1.2	d
$(CH_3)_3CBr$–$AlCl_3$	1.9	0	e
$(CH_3)_3CBr$–$SnCl_4$	16.6	0	e
$PhCH_2Cl$–$TiCl_4$	6.3	0.74	f
p-Methoxybenzyl chloride–$TiCl_4$	97	0.40	f

a. From H. C. Brown and H. Jungk, *J. Am. Chem. Soc.* **77**, 5584 (1955).
b. From S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.* **85**, 2596 (1963).
c. From G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.* **84**, 1688 (1962).
d. G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuck, *J. Am. Chem. Soc.* **86**, 1046 (1964).
e. From G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.* **86**, 1060 (1964).
f. From G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.* **94**, 7448 (1972).

Steric effects also play a major role in determining the $o:p$ ratio in Friedel–Crafts alkylations. The amount of *ortho* substitution of toluene decreases as the size of the entering alkyl group increases along the series methyl, ethyl, 2-propyl.[142] No *ortho*-substitution product is found when the entering group is *t*-butyl.[143]

A good deal of experimental care is often required to ensure that the product mixture at the end of a Friedel–Crafts reaction is the composition determined by *kinetic control.* The strong Lewis acid catalysts can catalyze the isomerization of alkylbenzenes, and if isomerism takes place, the product composition is not informative about position selectivity. Isomerization of the reaction product usually favors formation of the *meta* isomer in the case of dialkylbenzenes, since this isomer is thermodynamically the most stable.[144]

Alcohols and alkenes can also serve as sources of electrophiles in Friedel–Crafts reactions in the presence of strong acids:

$$R_3COH + H^+ \longrightarrow R_3C\overset{+}{O}H_2 \longrightarrow R_3C^+$$

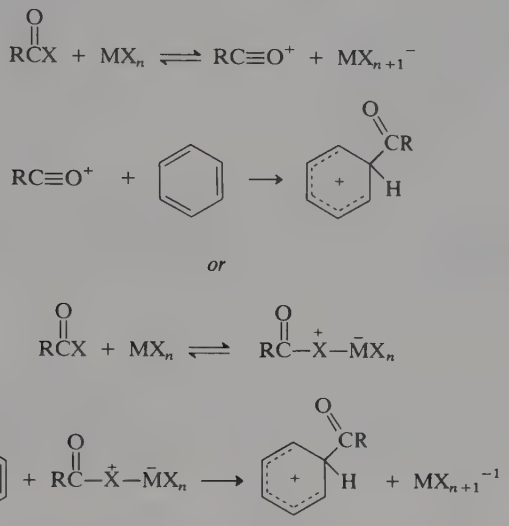
$$R_2C{=}CHR' + H^+ \longrightarrow R_2\overset{+}{C}CH_2R'$$

The generation of carbonium ions from these sources is well documented. The reaction of aromatics with alkenes in the presence of Lewis acid catalysts is the basis for the industrial production of many alkylated aromatic compounds. Styrene, for example, is prepared by dehydrogenation of ethylbenzene made from benzene and ethylene.

142. R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.* **83**, 2799 (1961).
143. G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.* **86**, 1060 (1964).
144. D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.* **74**, 6246 (1952).

9.4.5. Friedel–Crafts Acylation and Related Reactions

Friedel–Crafts acylation usually involves the reaction of an acyl halide, a Lewis acid catalyst, and the aromatic substrate. Two possible electrophiles can be envisaged. A discrete positively charged acylium (or oxocarbonium) ion can be formed and act as the electrophile, or the active electrophile could be a complex formed by the acid halide and Lewis acid catalyst.



As is the case with Friedel–Crafts alkylations, direct kinetic measurements are difficult, and not many data are available. Rate equations of the form

$$\text{rate} = k_1[\text{RCOCl–AlCl}_3][\text{ArH}] + k_2[\text{RCOCl–AlCl}_3]^2[\text{ArH}]$$

have been reported for reaction of benzene and toluene with both acetyl and benzoyl chloride.[145] The kinetic data available to date do not permit any unambiguous conclusions about the identity of the reactive electrophile. Most mechanistic discussions have depended on competitive rate data and on structure–reactivity relationships.

The existence of acylium ions has been demonstrated by X-ray diffraction studies on crystalline salts. For example, crystal structure determinations have been reported for *p*-methylphenyloxocarbonium ($SbCl_6^-$ salt)[146] and acetylium (SbF_6^- salt) species.[147] There is also a good deal of evidence from NMR measurements demonstrating that acylium ions can exist in nonnucleophilic solvents.[148] The

145. R. Corriu, M. Dore, and R. Thomassin, *Tetrahedron* **27**, 5601, 5819 (1971).
146. B. Chevrier, J.-M. LeCarpentier, and R. Weiss, *J. Am. Chem. Soc.* **94**, 5718 (1972).
147. F. P. Boer, *J. Am. Chem. Soc.* **90**, 6706 (1968).
148. N. C. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Am. Chem. Soc.* **86**, 4370 (1964); G. A. Olah and M. B. Comisarow, *J. Am. Chem. Soc.* **88**, 4442 (1966).

Table 9.11. Substrate and Position Selectivity in Friedel–Crafts Acylation Reactions

	Electrophilic reagents	$\frac{k_{tol}}{k_{benz}}$	Toluene $o:p$ ratio
1[a]	Acetyl chloride–$AlCl_3$	134	0.012
2[b]	Propionyl chloride–$AlCl_3$	106	0.033
3[c]	$CH_3C{\equiv}O^+SbF_6^-$	125	0.014
4[d]	Formyl fluoride–BF_3	35	0.82
5[d]	2,4-Dinitrobenzoyl chloride–$AlCl_3$	29	0.78
6[d]	Pentafluorobenzoyl chloride–$AlCl_3$	16	0.61
7[d]	Benzoyl chloride–$AlCl_3$	153	0.09
8[d]	*p*-Methylbenzoyl chloride–$AlCl_3$	164	0.08
9[d]	*p*-Methoxybenzoyl chloride–$AlCl_3$	233	0.2

a. From G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.* **86**, 2198 (1964).
b. From G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.* **91**, 5319 (1969).
c. From G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.* **86**, 2203 (1964).
d. From G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.* **93**, 6964 (1971).

positive charge on acylium ions is delocalized onto the oxygen atom. This delocalization is demonstrated in particular by the short C–O bond lengths in acylium ions which imply a major contribution from the structure having a C–O triple-bond:

$$R\overset{+}{C}{=}O \longleftrightarrow RC{\equiv}O^+$$

Selectively in Friedel–Crafts acylation reactions, with regard to both substrate selectivity and position selectivity, is moderate. Some typical data are collected in Table 9.11. It can be seen that the toluene:benzene reactivity ratio is generally between 100 and 200. A progression from low substrate selectivity (entries 5 and 6) to higher substrate selectivity (entries 8 and 9) has been demonstrated for a series of aroyl halides.[149] Electron-attracting groups on the aroyl chloride lead to low selectivity, presumably because of the increased reactivity of such electrophiles. Electron-releasing groups diminish reactivity and increase selectivity. The *p*-methoxy compound is somewhat anomalous. Although substrate selectivity increases as expected, the $o:p$ ratio is higher than the unsubstituted system.

In general, Friedel–Crafts acylation shows a preference for *para* over *ortho* substitution, although highly reactive acylating reagents such as perfluorobenzoyl chloride are an exception.

One other feature of the data in Table 9.11 is worthy of further comment. Notice that alkyl(acetyl, propionyl)-substituted acylium ions exhibit a smaller $o:p$ ratio than the various aroyl systems. If steric factors were dominating the position selectivity, one would expect the opposite result. A possible explanation for this

149. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.* **93**, 6964 (1971).

feature of the data could be that the aryl compounds are reacting via free acylium ions, whereas the alkyl systems may involve the more bulky acid chloride–catalyst complex.

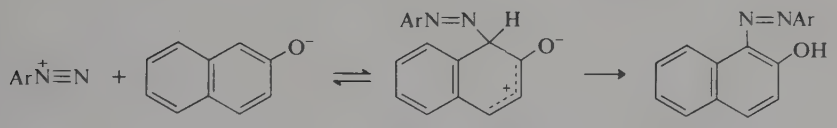
Steric factors also enter into determining the $o:p$ ratio. The hindered 2,4,6-trimethylbenzoyl group is introduced with a 50 : 1 preference for the *para* position.[149] Similarly, in the benzoylation of alkylbenzenes by benzoyl chloride–aluminum chloride, the amount of *ortho* product decreases (10.3%, 6.0%, 3.1%, 0.6%, respectively) as the branching of the alkyl group is increased along the series methyl, ethyl, 2-propyl, *t*-butyl.[150]

Friedel–Crafts acylation sometimes shows a modest kinetic isotope effect.[151] This effect suggests that the proton removal is not much faster than the formation of the σ complex, and that the formation of the σ complex may be reversible under some conditions.

A number of variations of the Friedel–Crafts acylation reaction are possible. Acid anhydrides can serve as the acylating agent in place of acid halides. Also, the carboxylic acids can be used, particularly along with polyphosphoric acid. A mixed carboxylic–phosphoric anhydride is probably the active acylating reagent. In these systems, the leaving group differs, but other facets of the reaction mechanism are probably similar to the more standard Friedel–Crafts conditions involving acyl halides. Synthetic applications of some of these modified procedures are discussed in Part B, Chapter 8.

9.4.6. Coupling with Diazonium Compounds

Among the reagents that would be classified as weakly electrophilic, the best studied are the aromatic diazonium ions. These reagents react only with aromatic substrates having strong electron donor substituents. The products are azo compounds. The aryl diazonium ions are generated by diazotization of aromatic amines.

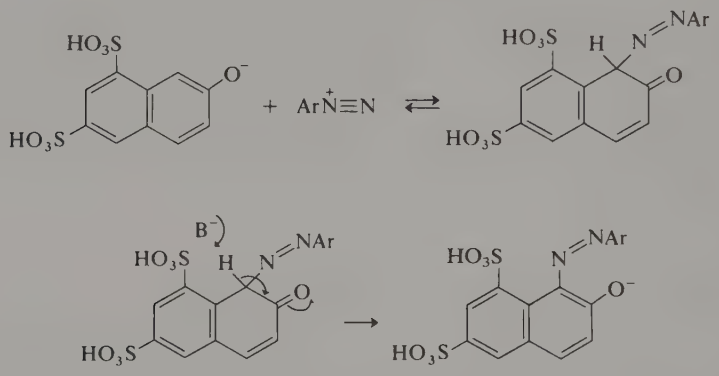


They are stable in solution only near room temperature or below, and this limits the range of compounds that can be successfully coupled with diazonium ions. The mechanism of diazonium ion formation is discussed more completely in Part B, Chapter 8, Section 8.2.1.

150. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.* **91**, 5319 (1969).
151. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.* **86**, 2203 (1964); D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.* **80**, 3285, 6014 (1958).

Kinetic investigations have revealed second-order kinetic behavior for diazonium coupling reactions in a number of instances. They have further revealed that in the case of phenols, it is the conjugate base that is attacked.[152] This finding is entirely reasonable, since the deprotonated oxy group is a better electron donor than the neutral hydroxyl substituent. The reactivity of the diazonium ion depends on substituent groups present. Reactivity is increased by electron attracting groups and decreased by electron donor substituents.

The most unique feature of the mechanism for diazonium coupling is that proton loss can clearly be demonstrated to be the rate-determining step in certain cases. This feature is revealed in two ways. First, diazonium couplings of several naphthosulfonate ions exhibit primary isotope effects in the range of 4–6 when deuterium is present at the site of substitution, clearly indicating that cleavage of the C–H bond is occurring in the rate-determining step. Second, these diazonium coupling reactions can be shown to be general base catalyzed. This, too, implies that proton removal is rate-determining[153]:



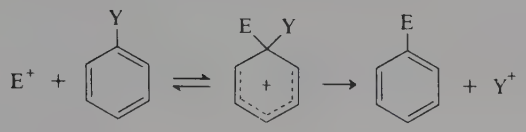
Because of the limited range of aromatic compounds that react with diazonium ions, selectivity data comparable to those discussed for other electrophilic substitutions are not available. Presumably, diazotization, since it involves a weak electrophile, would reveal high substrate and position selectivity.

9.4.7. Substitution of Groups Other Than Hydrogen

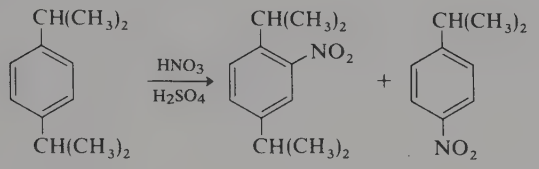
The general mechanism for electrophilic substitution suggests that groups other than hydrogen could be displaced, provided the electrophile attacked at a substituted

152. R. Wistar and P. D. Bartlett, *J. Am. Chem. Soc.* **63**, 413 (1941).
153. H. Zollinger, *Azo and Diazo Chemistry*, translated by H. E. Nursten, Interscience, New York, 1961, Chap. 10; H. Zollinger, *Adv. Phys. Org. Chem.* **2**, 163 (1964); H. Zollinger, *Helv. Chim. Acta* **38**, 1597 (1955).

carbon. Substitution at a site already carrying a substituent has been called *ipso* substitution and has been observed in a number of situations. The ease of removal of a substituent depends on its ability to accommodate a positive charge. This factor will determine whether the newly attached electrophile or the substituent will be eliminated from the σ complex or rearomatization:

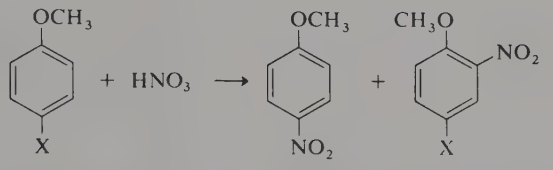


One of the most frequently encountered examples of substituent replacement involves the cleavage of highly branched aliphatic groups. The alkyl group is expelled as a carbonium ion, and for this reason, cleavage occurs most readily with *tert*-alkyl groups. Nitrations of isopropyl- and *t*-butyl-substituted aromatics frequently give products resulting from dealkylation:



Ref. 154

The replacement of bromine and iodine during aromatic nitration has also been observed. *p*-Bromoanisole and *p*-iodoanisole, for example, give 30%–40% of *p*-nitroanisole, a product resulting from displacement of halogen, on nitration[155]:



Because of greater resistance to elimination of chlorine as a positively charged species, *p*-chloroanisole does not undergo dechlorination under similar conditions.

Cleavage of *t*-butyl groups has also been observed in halogenation reactions. Minor amounts of dealkylated products are formed during chlorination and bromination of *t*-butylbenzene.[156] The amount of dealkylation increases greatly in the case of 1,3,5-tri-*t*-butylbenzene, and the principal product of bromination is 3,5-dibromo-*t*-butylbenzene.[157]

154. G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.* **86**, 1067 (1964).
155. C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.* **93**, 3389 (1971).
156. P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 131 (1957); P. B. D. de la Mare, J. T. Harvey, M. Hassan, and S. Varma, *J. Chem. Soc.*, 2756 (1958).
157. P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.* **76**, 2349 (1954).

The most thoroughly studied group of aromatic substitutions involving replacement of a substituent group in preference to a hydrogen are electrophilic substitutions of arylsilanes:

$$Ar\text{–}SiR_3 + E^+ + X^- \longrightarrow Ar\text{–}E + R_3SiX$$

The silyl group directs attacking electrophiles such as the proton or bromine to the substituted position. It is thus a strongly *ipso*-directing group. Structure–reactivity relationships indicate that the mechanism is similar to an aromatic substitution

involving a σ complex. The reaction shows a strong dependence on *para* substituents, as would be expected for an electrophilic substitution.[158] Protonation and halogenation have been studied most thoroughly.[159] Electrophilic replacement by acyl,[160] nitro,[161] and sulfonyl groups[162] have also been reported.

Trialkyltin substituents are also powerful *ipso*-directing groups. As the substituent atom becomes more metallic and less electronegative, electron density at carbon increases. Acidic cleavage of trimethylphenylstannane and tributylphenylstannane is a reaction that can be formulated as an electrophilic aromatic substitution.[163]

General References

Aromaticity, Special Publication No. 21, The Chemical Society, London, 1967.
P. J. Garratt, *Aromaticity*, McGraw-Hill, London, 1971.
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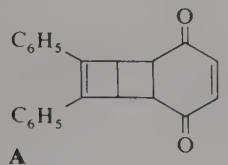
G. A. Olah, *Friedel–Crafts Chemistry*, Wiley, New York, 1973.
C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, New York, 1969, Chap. VI.
R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, Amsterdam, 1965.
E. Berliner, *Prog. Phys. Org. Chem.* **2**, 253 (1964).

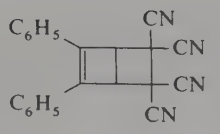
158. F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 2299 (1959).
159. F. B. Deans, C. Eaborn, and D. E. Webster, *J. Chem. Soc.*, 3031 (1959); C. Eaborn, Z. Lasocki, and D. E. Webster, *J. Chem. Soc.*, 3034 (1959); C. Eaborn, *J. Organomet. Chem.* **100**, 43 (1975).
160. J. D. Austin, C. Eaborn, and J. D. Smith, *J. Chem. Soc.*, 4744 (1963).
161. F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 498 (1957).
162. R. W. Bott, C. Eaborn, and T. Hashimoto, *J. Chem. Soc.*, 3906 (1963).
163. C. Eaborn, I. D. Jenkins, and D. R. M. Walton, *J. Chem. Soc. Perkin Trans. II*, 596 (1974).

(*References for these problems will be found on page 706.*)

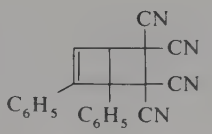
1. The reaction of *o*-diphenylcyclobutadiene (generated *in situ* by oxidation of its iron tricarbonyl complex) with *p*-benzoquinone yields **A** as the exclusive product. With tetracyanoethylene, however, **B** and **C** are formed in a 1 : 7 ratio. Discuss these results, and explain how they relate to the question of the square versus rectangular shape of cyclobutadiene.



A



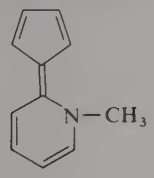
B



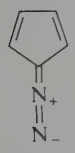
C

2. A single resonance structure is shown below for each of several molecules. Consider other resonance structures. Comment on those that would be expected to make a major stabilizing contribution to the molecule in question.

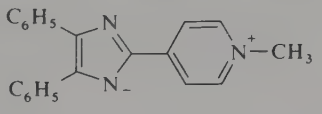
(a)



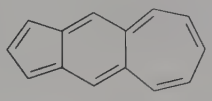
(b)



(c)

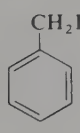


(d)

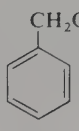


3. Predict qualitatively the isomer ratio for the nitration of each of the following compounds.

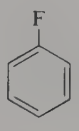
(a)



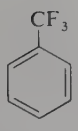
(c)



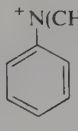
(e)



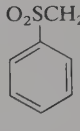
(b)



(d)



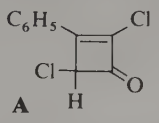
(f)



4. While *N,N*-dimethylaniline is an extremely reactive aromatic substrate and is readily attacked by such weak electrophiles as aryl diazonium ions and nitrosyl ion, this reactivity is greatly diminished by introduction of an alkyl substituent in the *ortho* position. Explain.

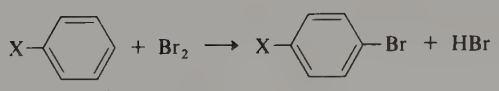
5. (a) A synthesis of tropone (cycloheptatrienone) entails treating 1-methoxycycloheptatriene with bromine. A salt is produced that yields tropone on treatment with aqueous sodium bicarbonate. What is the salt? Write a mechanism for its formation.

   (b) The optically active dichlorophenylcyclobutenone **A** undergoes racemization in acetic acid at 100°C. Suggest an experiment to determine if the enol (a hydroxycyclobutadiene) is an intermediate.



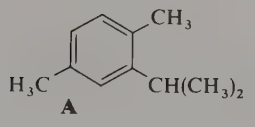
A

6. Some bromination rate constants are summarized below. Compare the correlation of the rate data with σ and σ^+ substituent constants. What is the value of ρ? What is the mechanistic significance of these results?

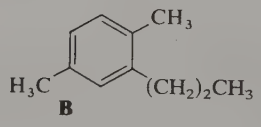


X	k (M^{-1} sec^{-1})
H	2.7×10^{-6}
CH_3	1.5×10^{-2}
OCH_3	9.8×10^{3}
OH	4.0×10^{4}
$N(CH_3)_2$	2.2×10^{8}

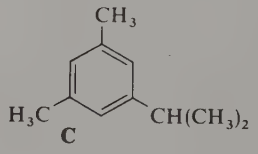
7. Compare the results given below for the alkylation of *p*-xylene under a variety of conditions. Explain the reasons for the variation in product composition with temperature and with the use of 1- versus 2-propyl chloride.



A



B

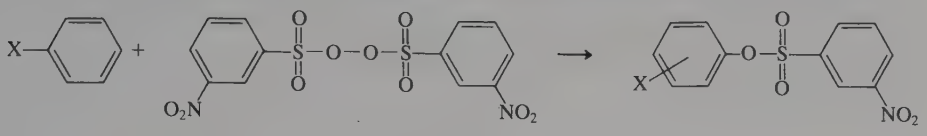


C

		A	**B**	**C**
1-propyl chloride	0°C	27%	73%	0%
1-propyl chloride	50°C	31%	53%	16%
2-propyl chloride	0°C	100%	0%	0%
2-propyl chloride	50°C	62%	0%	38%

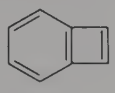
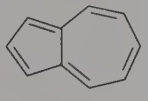
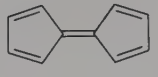
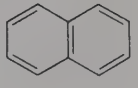
8. Toluene is 17 times times more reactive than benzene and isopropylbenzene is 14 times more reactive than benzene when nitration is carried out in the organic solvent sulfolane. The $o:m:p$ ratio for toluene is 62:3:35, and isopropylbenzene it is 43 : 5 : 52. Calculate the partial rate factors for each position in toluene and isopropylbenzene. Discuss the significance of the partial rate factors. Compare the reactivity at the various positions of each molecule, and explain any differences you consider to be significant.

9. The table below gives first-order rate constants for reaction of substituted benzenes with *m*-nitrobenzenesulfonyl peroxide. From these data calculate the overall relative reactivity and partial rate factors. Does this reaction fit the pattern of an electrophilic aromatic substitution? If so, does the active electrophile exhibit low, moderate, or high substrate and position selectivity?

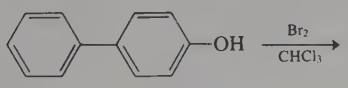


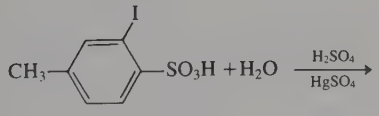
		Product composition		
X	k (sec^{-1})	*o*	*m*	*p*
H	8.6×10^{-5}	—	—	—
Br	4.8×10^{-5}	21	3	76
CH_3	1.7×10^{-3}	32	3	65
CH_3O	4.3×10^{-2}	14	0	86
CH_3O_2C	9.1×10^{-6}	24	67	9

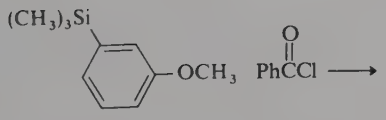
10. Using the empirically chosen energy equivalents for contributing bond types given on p. 475 and a standard compilation of simple HMO calculations, calculate resonance energies for the following molecules according to the modified procedure of Hess and Schaad. Do you find any discrepancies between predicted and observed stability?

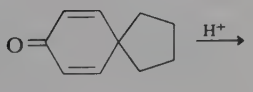
(a)  (b)  (c)  (d) 

11. Give the products to be expected from each of the following reactions:

(a) 

(b) 

(c) 

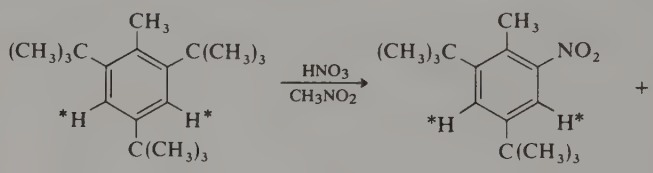
(d) 

12. *Ipso* substitution, in which the electrophile attacks a position already carrying a substituent, is relatively rare in electrophilic aromatic substitution and was not explicitly covered in Section 9.3 in the discussion of substituent effects on reactivity and selectivity. Using qualitative MO concepts, discuss the effect of the following type of substituents on the energy of the transition state for *ipso* substitution.

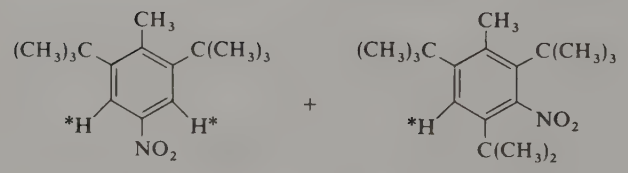
    (a) A π-donor substituent which is more electronegative than carbon, e.g., F or CH_3O.
    (b) A π-acceptor substituent which is more electronegative than carbon, e.g., NO_2 or CN.
    (c) A group without a strong π-conjugating capacity which is more electronegative than carbon, e.g., $^{+}N(CH_3)_3$.
    (d) A group without a strong π-conjugating capacity which is less electronegative than carbon, e.g., $(CH_3)_3Si$.

    According to this analysis, which types of groups will most favor *ipso* substitution? Can you cite any experimental evidence to support this conclusion?

13. The nitration of 2,4,6-tri-*t*-butyltoluene gives rise to three products. The distribution is changed when the 3 and 5 positions are deuterated:



*H = H 40.3%
*H = D 42.4%



*H = H 51.0%
*H = D 54.6%

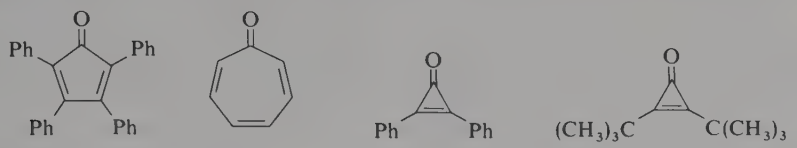
*H = H 8.7%
*H = D 2.7%

    Indicate mechanisms that would account for the formation of each product. Show how the isotopic substitution could cause a change in product composition. Does your mechanism predict that the isotopic substitution would give rise to a primary or secondary deuterium kinetic isotope effect? Calculate the magnitude of the kinetic isotope effect from the data given.

14. Consider an electrophilic aromatic substitution reaction in which a base, B, other than solvent is required in the rate-determining deprotonation. Write down the rate expression in terms of the electrophile E, base B, and aromatic

ArH. What relationship would one expect between the concentration of B and the observed primary kinetic isotope effect in such a system?

15. The relative basicity of carbonyl oxygen atoms can be measured by studying the strength of hydrogen bonding with the carbonyl compound to a hydrogen donor such as phenol. In carbon tetrachloride, the K_{eq} for 1:1 complex formation for the compounds shown have been measured. Rationalize the observed order of basicity.



16. The complex kinetic expression for chlorination of anisole by hypochlorous acid (p. 508) becomes simpler for both less reactive and more reactive substrates. For benzene the expression is

$$\text{Rate} = k[\text{benzene}][\text{ClOH}][\text{H}^+]$$

For *p*-dimethyoxybenzene, it is

$$\text{Rate} = k[\text{ClOH}][\text{H}^+]$$

What is the reason for this dependence of the form of the rate expression on the reactivity of the aromatic compound?

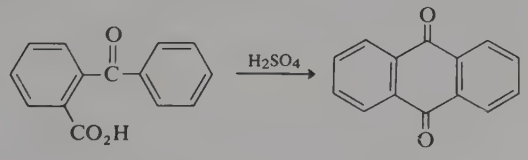
17. The reactivities of chlorobenzene and bromobenzene relative to benzene are 0.033 and 0.030, respectively, using acetyl nitrate as the nitration reagent. The product ratios are: chlorobenzene, *o* : *m* : *p*, 30%, 1%, 69%; bromobenzene, *o* : *m* : *p*, 37%, 1%, 62%. Calculate the partial rate factors.

18. The chlorination of a series of compounds having electron-withdrawing substituents has been studied. The relative rates of chlorination and the isomer distribution are known. The data give a satisfactory correlation with the Hammett equation using σ^+, but no rate measurement for benzene under precisely comparable conditions is possible. How could you estimate f_o, f_m, and f_p for chlorination from the available data?

$$\rho = -6.6$$

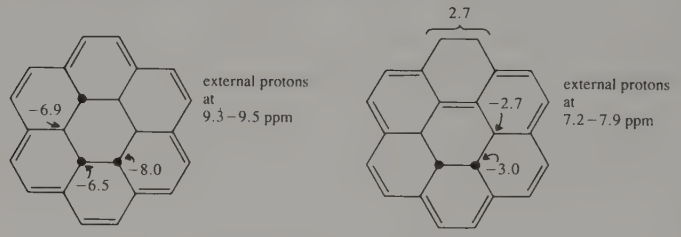
$$o:m:p \text{ ratio for benzonitrile} = 34:55:11$$

19. In 100% sulfuric acid, the cyclization shown below occurs:



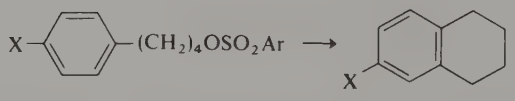
When one of the *ortho* hydrogens is replaced by deuterium, the rate drops from 1.53×10^{-4} sec^{-1} to 1.38×10^{-4} sec^{-1}. What is the kinetic isotope effect? The product from such a reaction contains 60% of the original deuterium in the product. Give a mechanism for this reaction that is consistent with both the kinetic isotope effect and the deuterium retention data.

20. One criterion of aromaticity is the "ring current" which is revealed by a chemical shift difference between protons in the plane of the conjugated system and those above or below the plane. The chemical shifts of two isomeric hydrocarbons are given below. In qualitative terms, which appears to be more aromatic? (Because the chemical shift is a sensitive function of the geometric relationship to the ring current a quantitative calculation would be necessary to confirm the correctness of this qualitative impression.) Does Hückel MO theory predict a difference in the aromaticity of these two compounds?

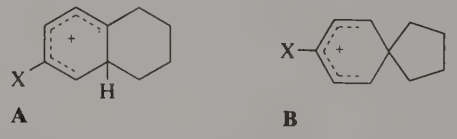


chemical shift in ppm from tetramethylsilane

21. The solvolysis of 4-arylbutyl arenesulfonates in nonnucleophilic media leads to the formation of tetralins:



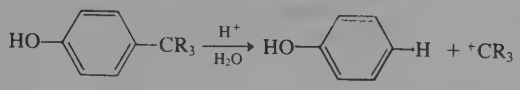
Two σ intermediates are conceivable. **A** would lead directly to product on deprotonation, while **B** could give product by rearrangement to **A**, followed by deprotonation:



Devise an experiment that would permit one to determine how much product formed via **A** and how much via **B**. How would you expect the relative importance of the alternate routes to be related to the identity of the substituent group X?

22. Alkyl groups which are *para* to strong π-donor substituents such as hydroxy or methoxy can be removed from aromatic rings under acidic conditions, if the

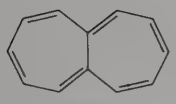
alkyl group is capable of forming a stable carbonium ion:



For the equation above, when R = CH_3, the solvent isotope effect is $k_H/k_D = 0.1$. When R = Ph, $k_H/k_D = 4.3$. How do you account for the difference in the isotope effect for the two systems, and particularly, what is the probable cause of the inverse isotope effect in the case of R = CH_3?

23. Acylation of 1,4-dimethoxynaphthalene with acetic anhydride (1.2 equiv.) and aluminum chloride (2.2 equiv.) in ethylene dichloride (60°C, 3 hr) gives two products, 6-acetyl-1,4-dimethoxynaphthalene (30%) and 1-hydroxy-2-acetyl-4-methoxynaphthalene (50%). Suggest a rationalization for the formation of these two products and in particular for the differing site of substitution in the two products.

24. The proton and carbon NMR spectra of heptalene (**A**) and octalene (**B**) are described below. Discuss these spectra with reference to the question: Are heptalene and octalene aromatic, antiaromatic or nonaromatic?



heptalene **A**

^{1}H NMR: Two two-proton multiplets at 6 and 6.2 ppm and a four-proton multiplet at 7.0 ppm.

^{13}C NMR: Four-line spectrum at room temperature. Three of the peaks broaden at −160°C but further resolution is precluded because of temperature limitations. The fourth peak remains sharp at this temperature.

octalene **B**

^{1}H NMR: Two proton multiplets centered near 5.8, 5.6, 5.7, and 6.3 ppm and a four-proton multiplet at 5.7 ppm.

^{13}C NMR: Seven-line spectrum at room temperature which changes to a 14-line spectrum at −150°C.

25. (a) The heats of combustion, ΔH_c, the heats of hydrogenation for addition of one mole of H_2, ΔH_{H_2}, and the estimated stabilization energies (S.E.) for benzene and cyclooctatetraene are given below. The heat of combustion of [16]annulene is also given. Estimate the stabilization energy of [16]annulene. Does this value agree with the prediction of simple Hückel MO theory?

	Benzene	Cyclooctatetraene	[16]Annulene
ΔH_c (kcal/mol)	781	1086	2182
ΔH_{H_2} (kcal/mol)	−5.6	25.6	28
S.E.[a] (kcal/mol)	36	4	?

a. Estimated stabilization resulting from conjugation in kcal/mole.

(b) The enthalpy of the reaction of the cyclooctatetraene and [16]annulene dianions (HC^{2-}) with water have been measured.

$$2Na^+ + (C_nH_n)^{2-} + 2H_2O_{(l)} \rightarrow C_nH_{n+2} + 2NaOH$$

$\Delta H = -33.3$ kcal/mol for cyclooctatetraene

$\Delta H = -81.1$ kcal/mol [16]annulene

Using these data and the enthalpy value for the reaction

$$2Na_{(s)} + H_2O_{(l)} \rightarrow 2NaOH_{(aq)} + H_2, \qquad \Delta H = -88.2 \text{ kcal/mol}$$

calculate ΔH for the reaction

$$2Na_{(s)} + C_nH_n \rightarrow 2Na^+ + (C_nH_n)^{2-}$$

How do you interpret the difference in the heat of reaction for the two hydrocarbons in the reaction to form the respective dianions?

10

Concerted Reactions

There are many reactions in organic chemistry that give no evidence of involving intermediates when they are subjected to the usual probes employed for studying reaction mechanisms. Highly polar transition states do not seem to be involved either, since the rates of such reactions are insensitive to solvent polarity. Efforts to detect free-radical intermediates by physical or chemical means have not been successful, and the reaction rates are neither increased by initiators nor decreased by free-radical inhibitors. This lack of evidence of intermediates leads to the conclusion that the reactions are concerted processes in which bond making and bond breaking both contribute to the structure at the transition state, although not necessarily to the same degree. There are numerous examples of both unimolecular and bimolecular concerted processes.

An important class of concerted reactions are the *pericyclic reactions.*[1] A pericyclic reaction is characterized as a change in bonding relationship which takes place as a continuous concerted reorganization of electrons. The word "concerted" specifies that there is a single transition state and thus no intermediate in the process. To maintain continuous smooth electron flow, pericyclic reactions occur through *cyclic transition states.* Furthermore, the cyclic transition state must correspond to an arrangement of the participating orbitals that can maintain a bonding interaction between the reaction components throughout the course of the reaction. We shall see shortly that these requirements make pericyclic reactions highly predictable, in terms of such features as relative reactivity, stereospecificity, and regioselectivity.

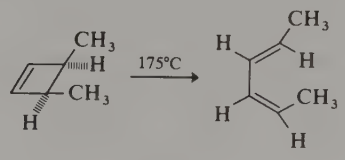
The key to understanding the mechanisms of the pericyclic reactions was the recognition by Woodward and Hoffmann[2] that the pathway of the reaction was determined by the symmetry properties of the orbitals involved in the reaction.

1. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry,* Academic Press, NewYork, 1970.
2. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965).

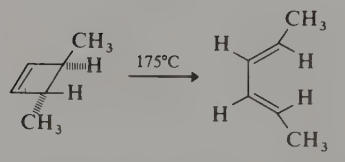
Their recognition that the symmetry of each participating orbital must be conserved during the concerted process dramatically transformed the understanding of this family of reactions and stimulated much experimental work to test and extend their theories.[3] The success of the theory emphasized the potential which systematic analysis of orbital properties had for deepening the understanding of organic reaction mechanisms. Woodward and Hoffmann's approach led to other related interpretations of orbital properties which are also successful in predicting and explaining the course of concerted thermal reactions.[4–9] It was also recognized that many photochemical reactions were subject to analysis by the application of the same principles.

10.1. Electrocyclic Reactions

There are several general classes of pericyclic reactions for which the orbital symmetry factors determine both the stereochemistry and relative reactivity. The first class that we will consider are the *electrocyclic reactions.* An electrocyclic reaction is defined as the formation of a single bond between the ends of a linear system of π electrons and the reverse process. It is exemplified by the thermal ring opening of cyclobutenes to butadienes:



Ref. 10

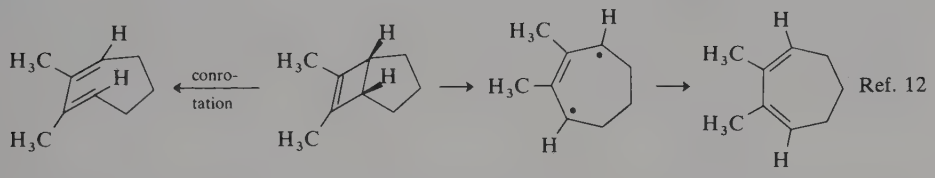


It is not surprising that thermolysis of cyclobutenes leads to ring opening since the strain in the four-membered ring is relieved. What is particularly significant about these reactions is that they are stereospecific; *cis*-3,4-dimethylcyclobutene is

3. For a recent review of several reactions within the general theory of pericyclic reactions, see A. P. Marchand and R. E. Lehr (eds.), *Pericyclic Reactions*, Vols. I and II, Academic Press, New York, 1977.
4. H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.* **87**, 2045 (1965).
5. M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969; *Angew. Chem. Int. Ed. Engl.* **10**, 761 (1971).
6. H. E. Zimmerman, *Acc. Chem. Res.* **4**, 272 (1971).
7. C. Trindle, *J. Am. Chem. Soc.* **92**, 3251, 3255 (1970).
8. A. C. Day, *J. Am. Chem. Soc.* **97**, 2431 (1975).
9. N. D. Epiotis, *J. Am. Chem. Soc.* **95**, 1191, 1200, 1206 (1973).
10. R. E. K. Winter, *Tetrahedron Lett.*, 1207 (1965).

converted to *trans,cis*-2,4-hexadiene, while *trans*-3,4-dimethylcyclobutene yields the *trans,trans* isomer. The stereospecificity of such processes is very high. In the ring opening of *cis*-3,4-dimethylcyclobutene, for example, only 0.005% of the minor product *trans,trans*-2,4-hexadiene is formed.[11]

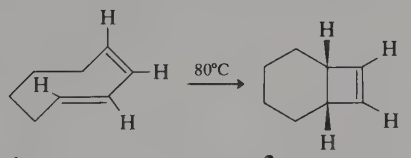
Moreover, notice that the reason for the observed stereospecificity is that the groups bonded to the termini of the final diene system all rotate in the same direction during the ring-opening process. Such motion, either all substituents rotating clockwise or all counterclockwise, is known as the *conrotatory* mode, and has been demonstrated to hold for all cyclobutene–butadiene concerted thermal interconversions. A reasonable expectation would be that a nonconcerted process would be nonstereospecific and would occur only at a higher temperature, since bond breaking would be considerably more advanced than bond making. An example of a cyclobutene that undergoes thermal ring opening by a nonconcerted mechanism is the bicycloheptene shown below, which reacts slowly even at 400°C:



Ref. 12

The conrotatory process is unfavorable, since the product of such a reaction would incorporate a *trans*-double bond in a seven-membered ring and be of very high energy. Thus, reaction takes place only under more forcing conditions, probably through a diradical intermediate.

The principle of microscopic reversibility requires that the reverse process, ring closure of butadienes to cyclobutenes, must also be a conrotatory process. Because the free-energy change for this reaction is usually unfavorable, few examples of this reverse process are known. A case in which the thermodynamic situation is favorable and in which the stereochemistry of ring closure is consistent with a conrotatory motion is seen in *trans,cis*-2,3-cyclooctadiene (**1**), which undergoes quantitative conversion to bicyclo[4.2.0]octene (**2**) in refluxing benzene.[13] The ring closure is



1 **2**

favored by the strain present in the *trans* double bond. Electrocyclic reactions which

11. J. I. Brauman and W. C. Archie, Jr., *J. Am. Chem. Soc.* **94**, 4262 (1972).
12. R. Criegee and H. Furrer, *Chem. Ber.* **97**, 2949 (1964).
13. K. M. Schumate, P. N. Neuman, and G. J. Fonken, *J. Am. Chem. Soc.* **87**, 3996 (1965); R. S. H. Liu, *J. Am. Chem. Soc.* **89**, 112 (1967).

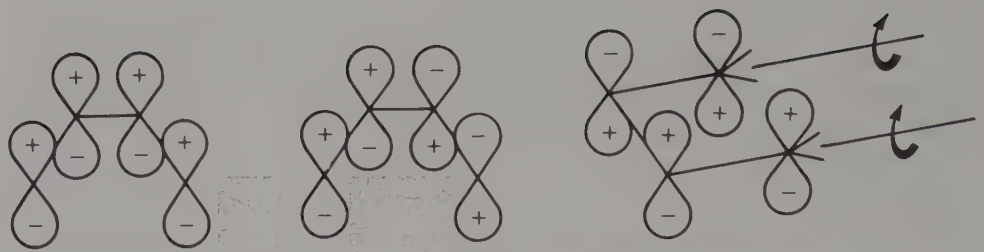
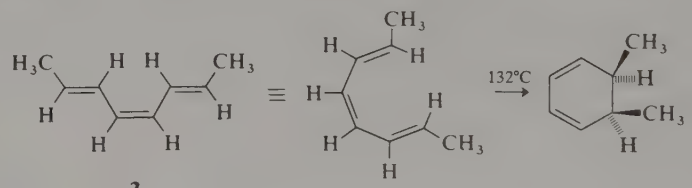


Fig. 10.1 Symmetry properties for the π system of a conjugated diene.

interconvert hexatrienes and cyclohexadienes also exhibit a high degree of stereospecificity. In this case the reaction generally proceeds in the direction of ring closure of the triene because of the greater thermodynamic stability of a system with six σ bonds and two π bonds as compared to one with five σ bonds and three π bonds. Like cyclobutene ring openings, these cyclizations are highly stereospecific.



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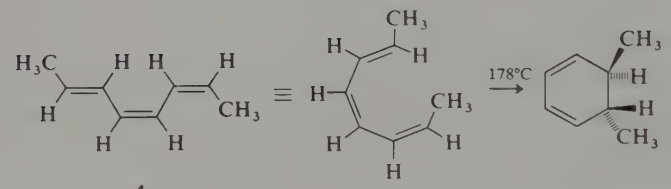


4

trans,cis,trans-2,4,6-Octatriene (**3**) cyclizes only to *cis*-dimethylcyclohexadiene, while *trans,cis,cis*-2,4,6-octatriene (**4**) affords exclusively the *trans* isomer.[14,15] A point of particular importance regarding the stereochemical features of this reaction is that the groups at the termini of the triene system rotate in opposite directions during the cyclization process. This mode of electrocyclic reaction is called *disrotatory.*

A complete mechanistic description of these reactions must explain not only their high degree of stereospecificity, but also why four-π-electron systems undergo conrotatory reactions, while six-π-electron systems undergo disrotatory reactions. Woodward and Hoffmann[2] suggested that the stereochemistry of these reactions is controlled by the symmetry properties of the highest occupied molecular orbital

14. E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965).
15. E. Vogel, W. Grimme, and E. Dinné, *Tetrahedron Lett.*, 391 (1965).
2. See p. 529.

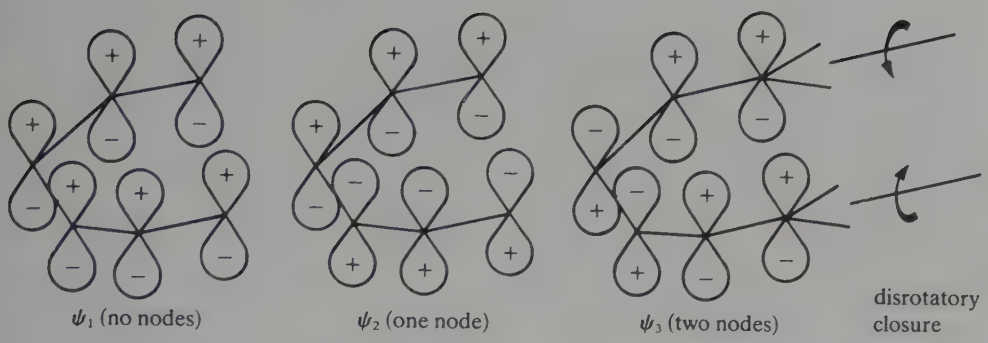


Fig. 10.2. Symmetry properties of hexatriene molecular orbitals.

(HOMO) of the open-chain partner. This suggestion was based on the idea that in processes involving transfer of electron density, it is the electrons of highest energy, i.e., those occupying the HOMO, that are of prime importance.[16] This is an application of the ideas of frontier orbital theory which state that the orbitals of highest energy will control the course of the reaction. In the case of butadiene, the HOMO is ψ_2, which is depicted in Figure 10.1.

How do the symmetry properties of ψ_2 influence electrocyclic reactions? For convenience, let us examine the microscopic reverse of the ring opening of a cyclobutene to a butadiene, realizing that any factors that appear on this reaction path also appear on the forward reaction path. For bonding to occur between the carbon atoms at the end of the π system, the positive lobe on C(1) must overlap with the positive lobe on C(4) (or negative with negative). This overlap can be accomplished only by conrotatory motion. Disrotatory motion causes overlap of orbitals of opposite sign, and precludes bond formation. Since similar symmetry properties of the HOMO exist for other $4n$ π systems, the conrotatory mode will also be preferred for all thermal electrocyclic reactions in these systems.

Analysis of the symmetry properties of hexatriene MO's (Fig. 10.2) follows the same reasoning and leads to a strikingly different conclusion, which is in complete agreement with the experimental observations. Since there are six π electrons, ψ_3 is the HOMO, and a bonding interaction will occur only for disrotatory closure. Consideration of orbital symmetries for other π systems leads to the conclusion that concerted electrocyclic reactions in systems containing $4n + 2$ π electrons should be disrotatory.

An additional dimension was introduced into the analysis of concerted reactions with the suggestion that orbital correlation diagrams be used.[4,17] This approach

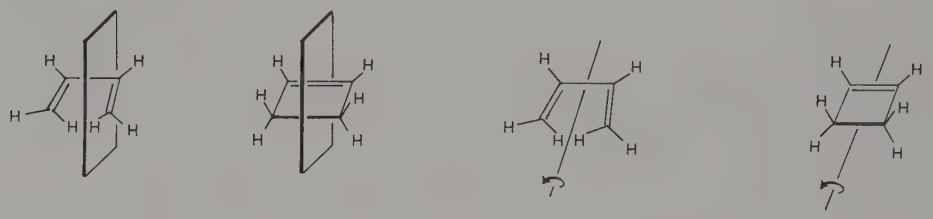
16. K. Fukui and H. Fujimoto, in *Mechanisms of Molecular Migrations*, Vol. 2, B. S. Thyagarajan (ed.), Interscience, New York, 1968, p. 113; K. Fukui, *Acc. Chem. Res.* **4**, 57 (1971).
4. See p. 530.
17. R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.* **87**, 2046 (1965).

focuses attention on the orbital symmetries of both reactants and products, and considers the symmetry properties of all the orbitals. In any concerted process, the orbitals of starting material must be transformed into orbitals of product that have the same symmetry; i.e., orbital symmetries are conserved in concerted reactions. If, during a concerted process, bonding orbitals of starting material are transformed into bonding orbitals of product of the same symmetry, the reaction will proceed with a low activation energy, and is said to be *allowed.* If, on the other hand, bonding orbitals of the reactant correlate with antibonding orbitals of the product, the reaction will be energetically unfavorable, since it would produce an excited state molecule, and is said to be *forbidden.*

The cyclobutene–butadiene interconversion can serve as an example of the reasoning employed in constructing a correlation diagram. For this reaction, four π orbitals of butadiene are converted smoothly to two π-molecular orbitals and two σ-molecular orbitals of cyclobutene. The bonding orbitals of butadiene are ψ_1 and ψ_2, and the antibonding orbitals are ψ_3 and ψ_4. For cyclobutene, the bonding orbitals are σ and π, while the antibonding orbitals are σ^* and π^*. In order to determine whether the conrotatory or disrotatory mode is allowed, the symmetry properties of the orbitals are examined with respect to the symmetry elements of the reacting molecule.

The symmetry properties of the orbitals are defined with respect to those elements of symmetry that exist throughout the course of the reaction process. The most common elements of symmetry are planes of symmetry and rotation axes. An orbital is classified as symmetric (S) if it is unchanged by reflection in a plane of symmetry or by rotation about an axis of symmetry. If the orbital changes phase as the result of a reflection or rotation it is called antisymmetric (A). Proper molecular orbitals must be either symmetric or antisymmetric. Local orbitals which are neither symmetric nor antisymmetric must be combined to give combinations which are either symmetric or antisymmetric with respect to all elements of symmetry which are maintained in the reaction.

Figure 10.3 illustrates the classification of the MO's of butadiene and cyclobutene. We will use (+) and (−) to specify orbital phase when we are considering individual molecular orbitals. There are two elements of symmetry which are common both to the *s*-cis conformation of butadiene and cyclobutene. These are a plane of symmetry and a two-fold rotation axis.



plane of symmetry

axis of symmetry

There are two different ways in which butadiene and cyclobutene might be interconverted. These are the conrotatory and disrotatory processes. The symmetry

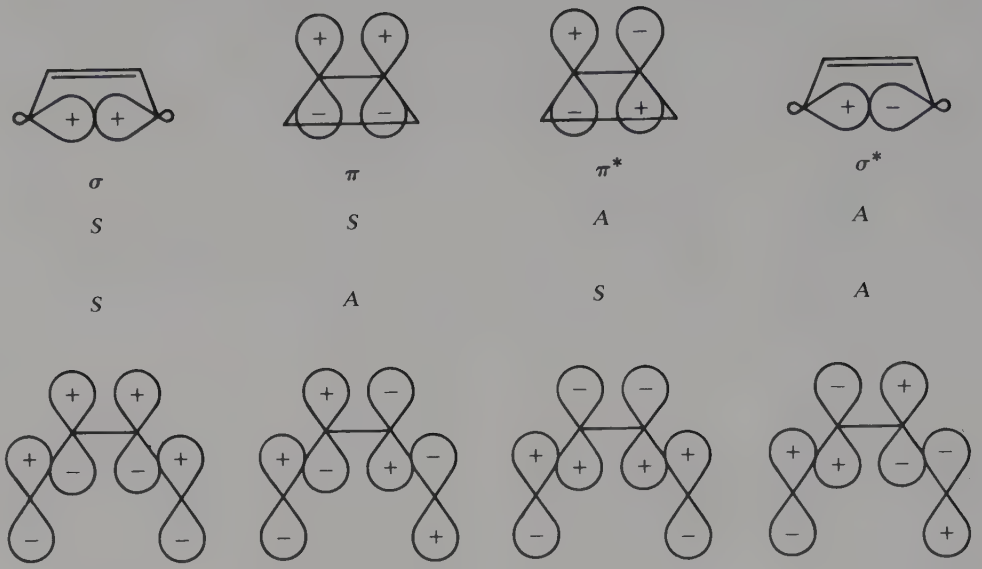


Fig. 10.3. Symmetry properties of cyclobutene and butadiene orbitals.

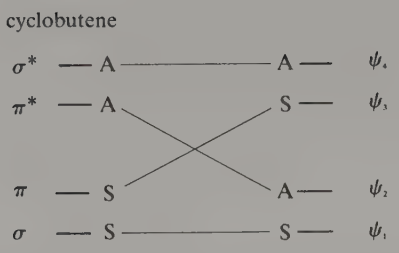
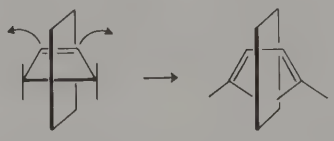


Fig. 10.4. Correlation diagram for cyclobutene and butadiene orbitals (symmetry-forbidden disrotatory reaction).

elements that are maintained in these two processes are different. During the disrotary opening of cyclobutene to butadiene, a plane of symmetry is maintained throughout the reaction:



This process must then be analyzed using the symmetry designations which apply to the plane of symmetry (Fig. 10.3) The orbitals are arranged according to energy in Fig. 10.4 and the states of like symmetry are connected. It is evident that not all ground state orbitals of cyclobutene correlate with ground state orbitals of butadiene. The bonding orbital of cyclobutene designated π is transformed into an antibonding orbital of butadiene (ψ_3), while ψ_2 of butadiene is transformed into an antibonding orbital of cyclobutene (π^*). A reaction incorporating these processes would have to attain a very high energy transition state, and the reaction is said to be *symmetry forbidden.*

Analysis of the conrotatory process is carried out in exactly the same fashion. In this case the element of symmetry that is maintained throughout the reaction process is the twofold axis of symmetry so that the symmetry designations appropriate for that symmetry operation apply:

The resulting correlation diagram is shown in Fig. 10.5. This reaction is symmetry allowed, since the bonding orbitals of butadiene correlate with the bonding orbitals of cyclobutene and vice versa.

Correlation diagrams can be constructed in an analogous fashion for the disrotatory and conrotatory closure of a hexatriene to a cyclohexadiene. They lead to the prediction that the disrotatory mode is an allowed process, while the conrotatory mode is forbidden.

Still another useful viewpoint of concerted reactions is based on the idea that transition states can be classified as aromatic or antiaromatic, just as is the case for

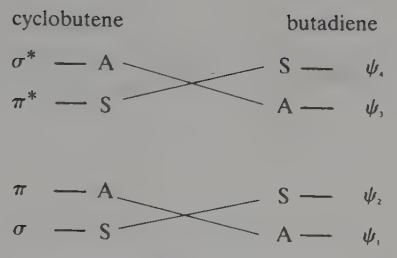


Fig. 10.5. Correlation diagram for cyclobutene and butadiene orbitals (symmetry-allowed conrotatory reaction).

ground state molecules.[5] A stabilized or aromatic transition state will result in a low activation energy, i.e., an allowed reaction. An antiaromatic transition state will mean that a high energy barrier exists, and the reaction will be unfavorable or forbidden. With this idea as a basis, it is possible to analyze potential transition states for concerted reactions and draw conclusions about their stability. This analysis directly parallels that used in deciding on the aromaticity or antiaromaticity of ground state molecules.

For the butadiene–cyclobutene interconversion, this analysis involves drawing the array of interacting *basis set orbitals*, i.e., the carbon $2p$ orbitals that form the molecular orbitals of the reacting system. Notice that this approach is different from the two earlier approahces, in which the *molecular orbitals* were considered. We have used shaded and unshaded lobes to indicate orbital phase when discussing basis set orbitals.

basis set orbitals
for conrotatory closure

basis set orbitals
for disrotatory closure

We consistently assign phases to the orbitals in such a way as to minimize the number of sign changes, although it has been shown that this convention is not necessary, and the correct conclusion as to the stability of the transition state will be reached, no matter what array of individual atomic orbitals is drawn.[6,8] Once the array of interacting orbitals has been drawn, two features of the system must be established in order to determine whether the corresponding transition state will be aromatic or antiaromatic; these features are the topology of the orbital array and the number of electrons involved. There are two classes of orbital systems, referred to as the *Hückel type* and the *Möbius type*. A Hückel system has zero (or some even number) of phase changes around the orbital array. A Möbius system has one (or some other odd number) of phase changes. For the cyclobutene–butadiene interconversion, a

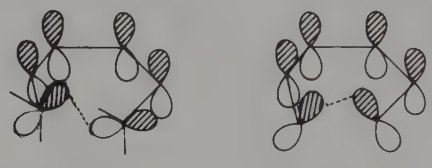
5. See p. 530.
6. See p. 530.
8. See p. 530.

conrotatory closure results in a Möbius system, while a disrotatory closure gives a Hückel system. The second important feature of the transition state is the number of participating electrons; in this case, it is four. The same rules of aromaticity and antiaromaticity apply as for ground state molecules:

Electrons	Hückel (disrotatory)	Möbius (conrotatory)
2	aromatic	antiaromatic
4	antiaromatic	aromatic
6	aromatic	antiaromatic
8	antiaromatic	aromatic

It is therefore the Möbius system involving conrotation that leads to a stabilized transition state in the cyclobutene–butadiene interconversion.

The basis set orbitals for conrotatory and disrotatory transition states for cyclohexadiene–hexatriene derivatives are shown below:



conrotatory:
Möbius system

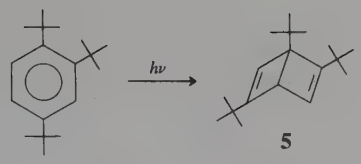
disrotatory:
Hückel system

Here, with six electrons involved, it is the disrotatory mode (Hückel system) in which the transition state is stabilized.

Generalization of either the frontier orbital, the orbital symmetry, or the transition-state aromaticity analysis leads to the same conclusion about the preferred stereochemistry for concerted *thermal* electrocyclic reactions: The stereochemistry is a function of the number of electrons involved. *Processes involving 4n + 2 electrons will be disrotatory and involve a Hückel-type transition state, whereas those involving 4n electrons will be conrotatory and the orbital array will be of the Möbius type.*

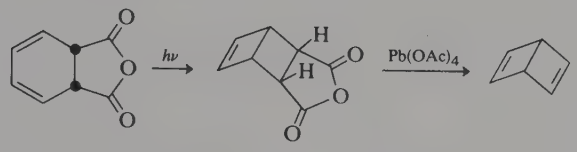
These principles serve to explain many specific observations in organic chemistry that would otherwise be difficult to understand. The bicyclo[2.2.0]hexa-2,5-diene ring system is a valence isomer of the benzene ring and is known as *Dewar benzene.* After many attempts to prepare Dewar benzene failed, there was a widespread feeling that all efforts would be fruitless and that Dewar benzene would not be isolable but would revert to benzene. The situation changed abruptly in 1962, when van Tamelen and Pappas reported the first stable Dewar benzene derivative. They prepared a tri-*tert*-butyl derivative by photolysis of 1,2,4-tri-*tert*-butylbenzene.[18]

18. E. E. van Tamelen, S. P. Pappas, and K. L. Kirk, *J. Am. Chem. Soc.* **93**, 6092 (1971); this paper contains references to the earlier work, and describes it and subsequent studies in greater detail.

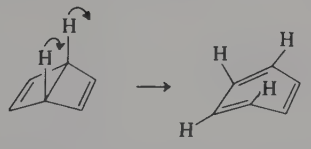


5

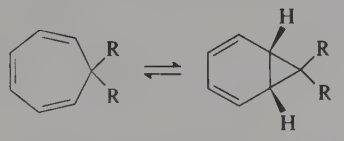
The compound was reasonably stable, reverting to the aromatic starting material only on heating. The *tert*-butyl groups contribute to the stability of **5** since they are somewhat farther apart than in the aromatic structure, so that rearomatization is resisted by a steric factor. The parent unsubstituted compound was obtained by van Tamelen and Pappas in 1963:



This compound is less stable than **5** and reverts to benzene with a half-life of about two days at 25°C, with $\Delta H^{\ddagger} = 23.0$ kcal/mol.[19] The observed kinetic stability of Dewar benzene is surprisingly high when one considers that its conversion to benzene is exothermic by 71 kcal/mol. The stability of Dewar benzene is intimately related to the orbital symmetry requirements for concerted electrocyclic transformations. The concerted, thermal pathway should be conrotatory, since the reaction is the ring opening of a cyclobutene and therefore leads not to benzene, but to a highly strained *cis,cis,trans*-cyclohexatriene, with the result that the activation energy for a concerted ring opening would be very high:



An especially interesting case of hexatriene–cyclohexadiene interconversion is the case of the rapid equilibrium between cycloheptatrienes and bicyclo[4.1.0]hepta-2,4-dienes[20]:

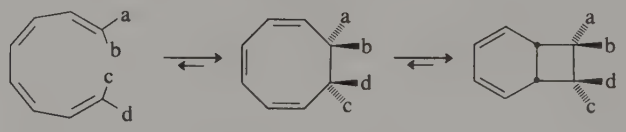


The energy requirement for this electrocyclic transformation is so low that the process is very rapid at room temperature. Low-temperature NMR measurements have given a value of about 7 kcal/mol for the activation energy in the case where R = CO_2CH_3.[21] The transformation is an example of a *valence tautomerism*, i.e., a

19. M. J. Goldstein and R. S. Leight, *J. Am. Chem. Soc.* **99**, 8112 (1977).
20. G. Maier, *Angew. Chem. Int. Ed. Engl.* **6**, 402 (1967).
21. M. Görlitz and H. Günther, *Tetrahedron* **25**, 4467 (1969).

rapid process involving reorganization of bonding electrons. The reason the process is much more rapid than electrocyclization of acyclic trienes is that the ring holds the reacting termini together, reducing the unfavorable negative entropy of activation. In contrast to the ring opening of Dewar benzene, the opening of bicyclo[4.1.0]hepta-2,4-diene is disrotatory and easily accommodated by the ring geometry. The equilibrium constant for most cycloheptatriene-bicyclo[4.1.0]hepta-2,4-diene pairs favors the cycloheptatriene. The equilibrium constant is about 3×10^{-3} at 100°C for the unsubstituted system.[22a] Alkyl groups do not affect this much but electron-withdrawing groups such as cyano and trifluoromethyl shift the equilibrium in the direction of the bicyclic system.[22b]

The prediction of conrotation in the cyclization of eight-π-electron systems has been confirmed by the study of a series of stereoisomeric 2,4,6,8-decatetraenes. Electrocyclic reaction occurs near room temperature and establishes an equilibrium favoring the cyclooctatriene product. At slightly more elevated temperatures, the hexatriene system produced undergoes a subsequent disrotatory cyclization, establishing equilibrium with the corresponding bicyclo[4.2.0]octa-2,4-diene[23]:

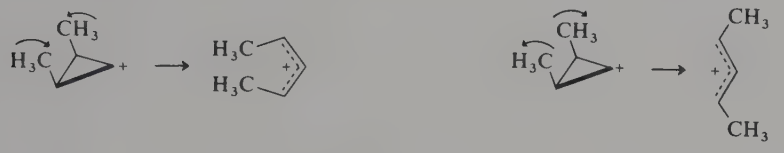


a = d = CH_3; b = c = H
b = c = CH_3; a = d = H
b = d = CH_3; a = c = H

The Woodward–Hoffmann rules are not limited in application to the neutral systems that have been discussed up to this point. They also apply to charged systems. The conversion of cyclopropyl cation to allyl cation has been thoroughly studied[24] and represents the simplest possible case of an electrocyclic transformation, since it involves only two π electrons. Because of the restrictions imposed on the internuclear angles in cyclopropyl rings, carbonium ions do not form readily, and cyclopropyl halides and arenesulfonates are quite unreactive under ordinary solvolytic conditions. For example, it was found that temperatures of 180°C were necessary for cyclopropyl tosylate to react in acetic acid, and the product was allyl acetate, rather than cyclopropyl acetate. A mechanism was considered in which cyclopropyl cation was formed in the rate-determining step, followed by rapid conversion to allyl cation[25]:

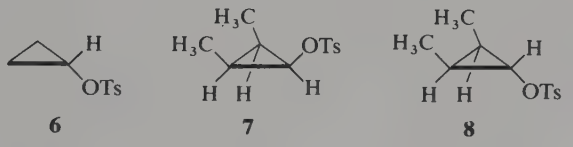
22. a. P. Warner and S.-L. Lu, *J. Am. Chem. Soc.* **95**, 5099 (1973).
    b. P. M. Warner and S.-L. Lu, *J. Am. Chem. Soc.* **102**, 331 (1980).
23. R. Huisgen, A. Dahmen, and H. Huber, *Tetrahedron Lett.*, 1461 (1969); *J. Am. Chem. Soc.* **89**, 7130 (1967); A. Dahmen and R. Huisgen, *Tetrahedron Lett.*, 1465 (1969).
24. P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, J. Paust, and K. Fellenberger, *J. Am. Chem. Soc.* **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 133 (1972).
25. J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.* **73**, 5034 (1951).

Formation of allylic products is characteristic of solvolysis reactions of cyclopropyl halides and arenesulfonates. Similarly, diazotization of cyclopropylamine in aqueous media gives only allyl alcohol.[26] The ring opening of the cyclopropyl cation is an electrocyclic reaction of the $4n + 2$ type, where n is equal to zero and should be disrotatory. Another facet of stereochemistry arises in substituted cyclopropyl systems. Note that for a *cis*-2,3-dimethylcyclopropyl cation, two nonequivalent disrotatory modes are possible, leading to conformationally distinct allyl cations:



The disrotatory mode in which the methyl groups move away from each other would be more favorable for steric reasons, and would be the expected pathway if a cyclopropyl cation were formed in the rate-determining step.

By comparing the rates of acetolysis of cyclopropyl tosylates **6–8** at 100°C, some remarkable conclusions can be drawn:

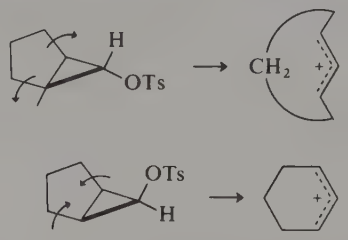


	6	**7**	**8**
relative rate:	1	4	41,000

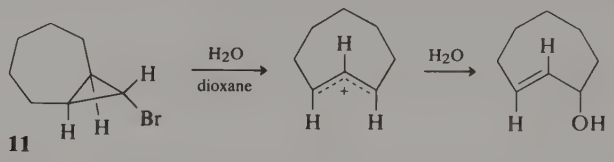
If formation of the cyclopropyl cation were rate-determining, **7** should be more reactive than **8**, since the eclipsing interaction between the tosylate leaving group and the two methyl groups is reduced in the transition state for ionization. Since **7** is 10,000 times less reactive than **8**, it follows that a free cyclopropyl cation is not involved in these solvolyses. A reasonable explanation, first suggested by De Puy,[27] involves concerted ring opening and ionization, and assumes that loss of the leaving group is assisted by the electron density that becomes available on cleavage of the ring carbon–carbon bond. Maximum interaction of these electrons with the developing p orbital occurs when the substituents that are *trans* to the leaving group move outward during the ionization process and only this disrotatory mode is allowed. In **7**, the allowed disrotatory mode results in methyl groups moving toward each other in the transition state, and is unfavorable relative to **8**, in which the methyl groups move away from each other.

26. P. Lipp, J. Buchkremer, and H. Seeles, *Justus Liebigs Ann. Chem.* **499**, 1 (1932); E. J. Corey and R. F. Atkinson, *J. Org. Chem.* **29**, 3703 (1964).
27. C. H. De Puy, *Acc. Chem. Res.* **1**, 33 (1968).

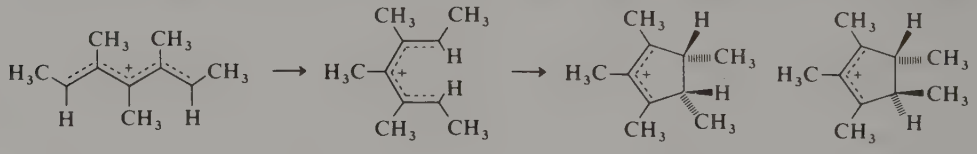
A similar rate effect occurs in the acetolysis of bicyclic tosylates **9** and **10**. With **9** after three months in acetic acid at 150°C, 90% of the starting material was recovered. Here, the allyl cation that would be produced by the preferred disrotatory process would be extremely strained, since it is a *trans*-cyclohexenyl cation. In

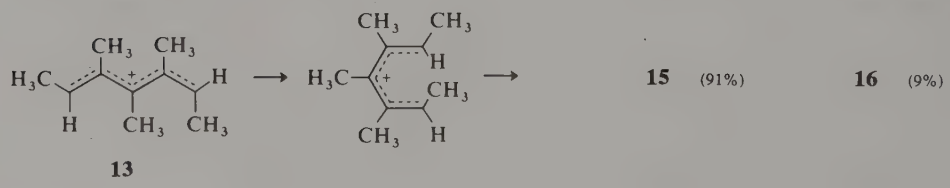


contrast, the epimer **10** reacts at least 2×10^6 times faster,[24] since it can proceed to the stable cyclohexenyl cation. An increase in the size of the fused ring, as in the case of **11**, permits ring opening to a *trans*-allyl cation. In agreement with expectation, the product of hydrolysis of the bromide **11** is *trans*-cycloocten-3-ol[28]:

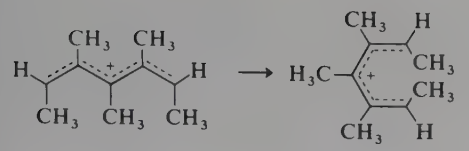


Orbital symmetry considerations predict that ring closure of pentadienyl cations, which are $4n$ systems, should be controtatory. While some pentadienyl cations are sufficiently stable to be observed by NMR in acidic media, they do tend to cyclize to cyclopentenyl cations. The stereospecificity of cyclization of pentadienyl cations **12–14** to the cyclopentenyl cations **15** and **16** in a variety of acidic media has been determined. The data are shown for 99% sulfuric acid at −5°C.[29] The observed stereochemical course is predominantly conrotatory, but the reactions are not as stereospecific as the others we have seen. This is attributed to the fact that





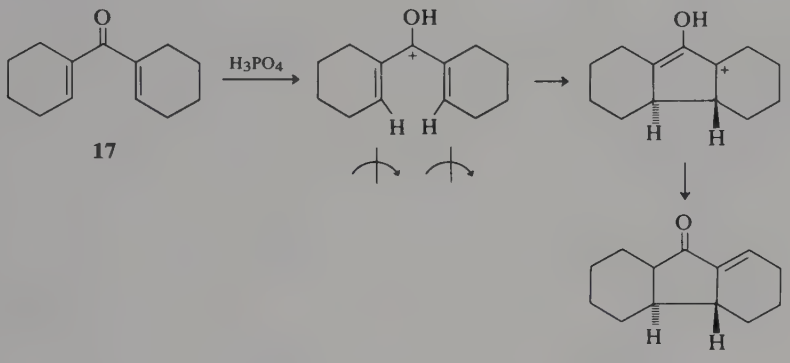
24. See p. 540.
28. G. H. Whitham and M. Wright, *J. Chem. Soc. C*, 883 (1971).
29. P. H. Campbell, N. W. K. Chiu, K. Deugau, I. J. Miller, and T. S. Sorenson, *J. Am. Chem. Soc.* **91**, 6404 (1969).



14 → **15** (21%) **16** (79%)

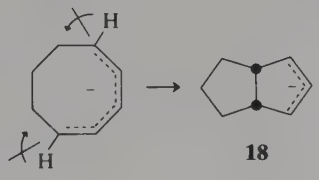
in order to cyclize, the ion must achieve a U geometry by rotation about the carbon–carbon bonds in a W-shaped pentadienyl cation. The barrier to rotation about these bonds is not much less than the barrier to interconversion of the ions, which leads to a partial loss of stereochemical integrity in **12**, **13**, and **14**.

Another example of the preference for controtatory cyclization can be seen in the acid-catalyzed cyclization of the divinyl ketone **17**. This occurs via a 3-hydroxypentadienyl cation and the stereochemistry of the product is as expected for a conrotatory process[30]:



17

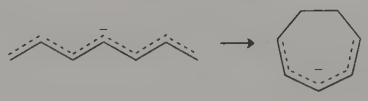
There are also examples of electrocyclic processes involving anionic species. Since pentadienyl anion is a six-π-electron system, its thermal cyclization to a cyclopentenyl anion should be disrotatory. Examples typifying this electrocyclic reaction are rare, and NMR studies of pentadienyl anions indicate that they are rather stable and do not tend to cyclize.[31] Cyclooctadienyllithium is exceptional in this respect, in that it does undergo cyclization to **18**, with a first-order rate constant of 8.7×10^{-3} min^{-1} at 35°C. The stereochemistry of the ring fusion is consistent with the disrotatory nature of the cyclization. Examination of a model of cyclooctadienyl anion reveals that it is quite highly strained, a fact that explains its ready conversion to **18**.



18

30. R. B. Woodward, in *Aromaticity*, Special Publication No. 21, the Chemical Society, London, 1969, p. 217.
31. R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 199, 205 (1967); R. B. Bates and D. A. McCombs, *Tetrahedron Lett.*, 977 (1969).

In contrast to pentadienyl anions, heptatrienyl anions have been found to cyclize readily to cycloheptadienyl anions.[32] The transformation of heptatrienyl anion to cycloheptadienyl anion proceeds with a half-life of 13 min at −13°C in tetrahydrofuran containing hexane. While the Woodward–Hoffmann rules predict this to be a conrotatory closure, no data confirming this point are available as yet.[33]



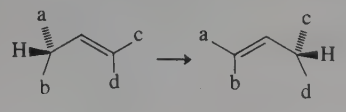
10.2. Sigmatropic Rearrangements

A group of reactions called *sigmatropic rearrangements* are closely related to electrocyclic transformations in being concerted processes governed by orbital symmetry.[34] Sigmatropic processes involve a concerted reorganization of electrons during which a group attached by a σ-bond migrates to a more distant terminus of an adjacent π-electron system. There is a simultaneous shift of the π electrons. Sigmatropic rearrangements are further described by noting the relationship between the reacting centers in the migrating fragment and the π system. The order $[i, j]$ specifies the number of atoms in the migrating fragment and the number of atoms in the π system which are directly involved in the bonding changes. This classification system is illustrated by the examples in Scheme 10.1. As with other electrocyclic reactions, the topological properties of the interacting orbitals dictate the facility of the various sigmatropic rearrangements and their stereochemistry. First, it must be recognized that there are two topologically distinct processes by which a sigmatropic migration can occur. If the migrating group remains associated with the same face of the conjugated π system throughout the process, the migration is termed *suprafacial.* The alternative mode involves a process in which the migrating group moves to the opposite face of the π system during the course of the migration and is called *antarafacial.*

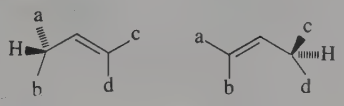
The orbital symmetry requirements of sigmatropic reactions are analyzed by considering the interactions between the orbitals of the π system and the migrating fragment. A frontier orbital analysis of the 1,3-sigmatropic shift of hydrogen is treated as the interaction of a hydrogen atom with an allyl radical. The frontier orbitals are the hydrogen $1s$ and the allyl ψ_2 orbitals, respectively. The suprafacial and antarafacial modes are illustrated as

32. E. A. Zuech, D. L. Crain, and R. F. Kleinschmidt, *J. Org. Chem.* **33**, 771 (1968); R. B. Bates, W. H. Deines, D. A. McCombs, and D. E. Potter, *J. Am. Chem. Soc.* **91**, 4608 (1969).
33. S. W. Staley, in *Pericyclic Reactions*, Vol. 1, A. P. Marchand and R. E. Lehr (eds.), Academic Press, New York, 1977, Chap. 4.
34. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 2511 (1965).

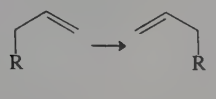
Scheme 10.1. Examples of Sigmatropic Rearrangements



1,3-suprafacial shift of hydrogen

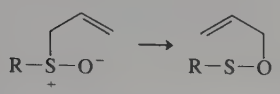


1,3-antarafacial shift of hydrogen

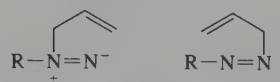


1,3-shift of alkyl group

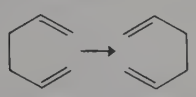
1,5-shift of alkyl group



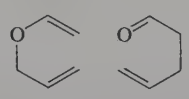
2,3-sigmatropic rearrangement of an allyl sulfoxide



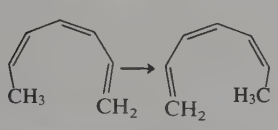
2,3-sigmatropic rearrangement of an allyl diazene



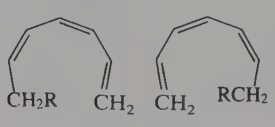
3,3-sigmatropic rearrangement of a 1,5-hexadiene



3,3-sigmatropic rearrangement of an allyl vinyl ether



1,7-sigmatropic shift of hydrogen

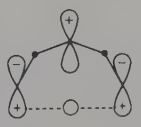


1,7-sigmatropic shift of an alkyl group

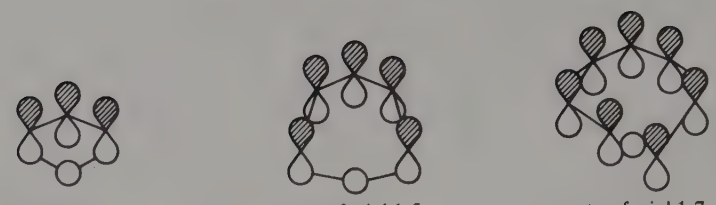
suprafacial antarafacial

A bonding interaction can be maintained only in the antarafacial mode; therefore, the 1,3-sigmatropic suprafacial hydrogen shift is considered *forbidden*. Since the geometry required for the orbital symmetry-allowed antarafacial shift is very contorted, this shift, too, is of high energy, and the concerted process in unlikely under conditions of thermal activation.

A similar analysis of the 1,5-sigmatropic hydrogen shift leads to the opposite conclusion: the suprafacial mode is allowed; the antarafacial mode is forbidden. The relevant orbitals are the hydrogen 1*s* orbital and ψ_3 of pentadienyl radical.



thermally allowed 1,5-suprafacial hydrogen shift in 1,3-pentadiene



suprafacial 1,3
Hückel system
4 electrons
antiaromatic
forbidden

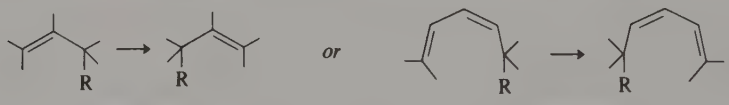
suprafacial 1,5
Hückel system
6 electrons
aromatic
allowed

antarafacial 1,7
Möbius system
8 electrons
aromatic
allowed

Fig. 10.6. Classification of sigmatropic hydrogen shifts with respect to basis set orbitals.

An alternative analysis involves drawing the basis set atomic orbitals and classifying the resulting system as Hückel or Möbius in character. Once this classification is complete and the electrons involved in the process are counted, the transition state can be recognized as aromatic or antiaromatic. This analysis is illustrated in Fig. 10.6.

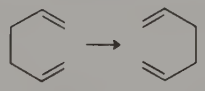
Sigmatropic rearrangements involving alkyl group shifts can also occur:



1,3 alkyl shift 1,5 alkyl shift

When a carbon migration occurs, there is an additional feature to consider. Migration might occur with retention or inversion of configuration at the migrating center. An analysis of sigmatropic shifts of alkyl groups is illustrated in Fig. 10.7.

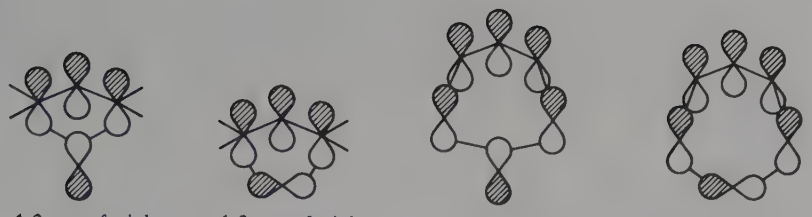
Sigmatropic rearrangements of order [3,3] are also very common:



The transition states for such processes can be considered as two interacting allyl fragments and are aromatic, and the reactions are therefore allowed thermally:

Generalization of these analyses leads to the Woodward–Hoffmann rules for sigmatropic processes.[34] For sigmatropic shifts of order $[i, j]$ where $i > 1$, the

34. See p. 544.



1,3 suprafacial retention Hückel system 4 electrons antiaromatic forbidden

1,3 suprafacial inversion Möbius system 4 electrons aromatic allowed

1,5 suprafacial retention Hückel system 6 electrons aromatic allowed

1,5 suprafacial inversion Möbius system 6 electrons antiaromatic forbidden

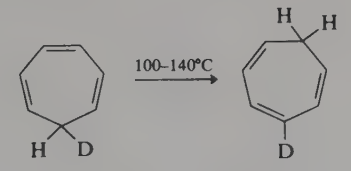
Fig. 10.7. Classification of sigmatropic shifts of alkyl groups with respect to basis set orbitals.

antarafacial or suprafacial nature of the migration must be specified for both components.

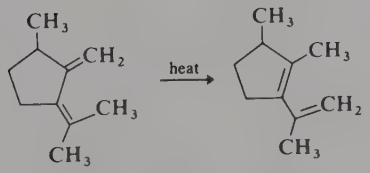
Selection rules for sigmatropic shifts of order [*i*, *j*]

A. Order [i,j]				
i+j	supra/retention	supra/inversion	antara/retention	antara/inversion
4*n*	forbidden	allowed	allowed	forbidden
4*n*+2	allowed	forbidden	forbidden	allowed
B. Order [i,j]				
i+j	supra/supra	supra/antara	antara/antara	
4*n*	forbidden	allowed	forbidden	
4*n*+2	allowed	forbidden	allowed	

With these rules as a unifying theoretical framework, we can consider specific examples of sigmatropic rearrangements. In accord with the theoretical concepts, there are many examples of sigmatropic 1,5-hydrogen migration in molecules which incorporate the pentadienyl fragment:



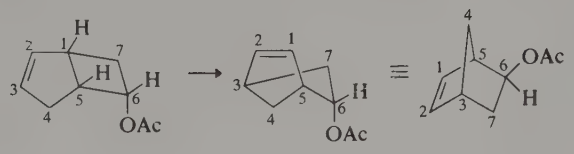
Ref. 35



Ref. 36

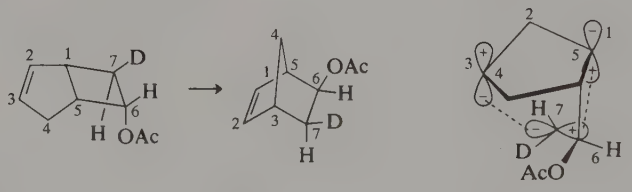
35. A. P. ter Borg, H. Kloosterziel, and N. Van Meurs, *Proc. Chem. Soc.*, 359 (1962).
36. J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.* **84**, 2775 (1962).

Confirmation of the prediction that 1,3-suprafacial 1,3-alkyl shifts would occur with inversion has been obtained by studying the stereochemistry of the rearrangement of **19** to **20** [37].

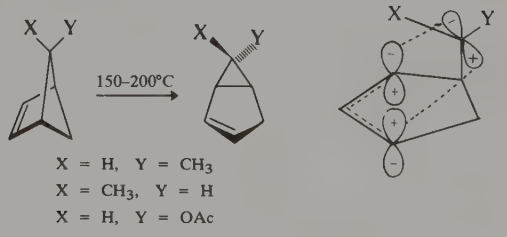


19 **20**

According to orbital symmetry considerations, the reaction should proceed with inversion of configuration at C(7), the migrating group. In the absence of any notions about the importance of orbital symmetry in controlling organic reactions, one might assume that in a concerted process, the C(3)–C(7) bond would form as the C(1)–C(7) bond was breaking and from the same side, i.e., with retention of configuration, but this would be in violation of the orbital symmetry rules. The experiment that was performed used deuterium-labeled **19**. In starting material, the deuterium was *trans* to the acetoxy group, while in the product, it was found to be exclusively *cis*, thereby establishing conclusively that inversion of configuration at C(7) had occurred during rearrangement in accord with the stereochemistry required by the Woodward–Hoffmann rules.

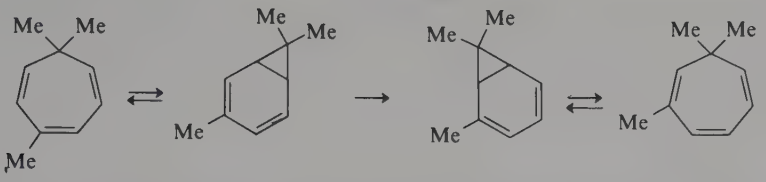


Suprafacial 1,3-shifts with inversion of configuration at the migrating carbon have also been observed in the thermal conversion of bicyclo[2.1.1]hexenes to bicyclo[3.1.0]hexenes.[38] Kinetic studies of this system are consistent with a concerted unimolecular rearrangement[39]:

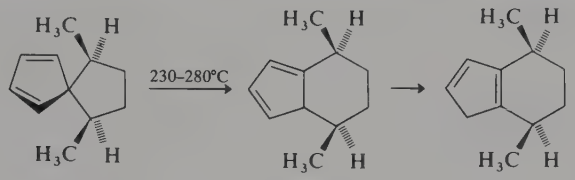


37. J. A. Berson, *Acc. Chem. Res.* **1**, 152 (1968); J. A. Berson and G. L. Nelson, *J. Am. Chem. Soc.* **89**, 5503 (1967).
38. W. R. Roth and A. Friedrich, *Tetrahedron Lett.*, 2607 (1969); S. Masamune, S. Takada, N. Nakatasuka, R. Vukov, and E. N. Cain, *J. Am. Chem. Soc.* **91**, 4322 (1969).
39. H. M. Frey, R. G. Hopkins, H. E. O'Neal, and F. T. Bond, *Chem. Commun.*, 1069 (1969).

The thermal rearrangements of methyl-substituted cycloheptatrienes have been proposed to proceed by sigmatropic migrations of the norcaradiene valence tautomer[40]:

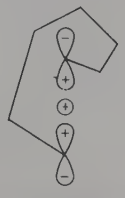


These are suprafacial sigmatropic shifts of the 1,5 type, and should therefore occur with retention of configuration at the migrating carbon. This stereochemical prediction has been established as being correct for the 1,5-thermal sigmatropic shift responsible for formation of **22** from **21**.[41] The stereochemistry of this step was determined by analysis of **23**, which is formed from **22** by a 1,5-hydrogen shift subsequent to the formation of **22**. This step does not alter the stereochemistry at the migrating carbon. The configuration of the migrating carbon is retained, as predicted.



21 **22** **23**

Like the thermal 1,3-hydrogen shift, a 1,7-hydrogen shift will be allowed when antarafacial and forbidden when suprafacial. Because a π system involving seven carbon atoms may adopt a helical shape more readily than one involving three carbon atoms, the geometrical limitations on the antarafacial sigmatropic shift are not as restrictive and 1,7-hydrogen shifts have been observed in a number of reactions. Among these reactions is the important thermal equilibrium established

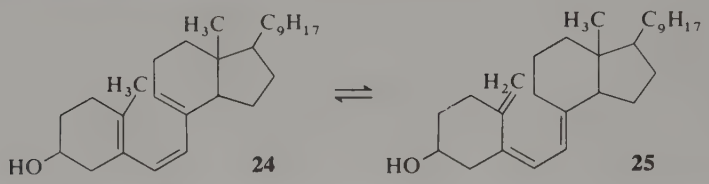


antarafacial 1,7-hydrogen shift

between precalciferol (pre-Vitamin D_2, **24**) and calciferol (Vitamin D_2, **25**).[42] It is of interest here that this reaction was clearly represented as proceeding by way of a concerted antarafacial 1,7 migration of hydrogen before the enunciation of the

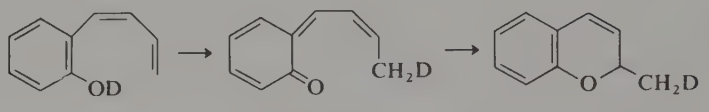
40. J. A. Berson and M. R. Willcott, III, *Rec. Chem. Prog.* **27**, 139 (1966); *J. Am. Chem. Soc.* **88**, 2494 (1966).
41. M. A. M. Boersma, J. W. de Haan, H. Kloosterziel, and L. J. M. van de Ven, *Chem. Commun.*, 1168 (1970).
42. For a historical review, see L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, Chap. 4.

concepts of orbital symmetry control on the basis of geometrical considerations derived from inspection of models.[43]



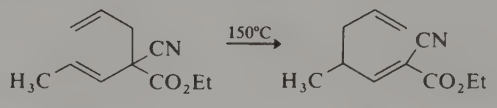
24 **25**

A thermal 1,7-hydrogen shift provides a reasonable explanation for the conversion of **26** to **27** which occurs at 110°C.[44]



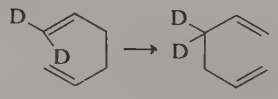
26 **27**

The most important sigmatropic rearrangements from the synthetic point of view are the [3,3] processes.[45] Sigmatropic rearrangements of order [3,3] are typified by the thermal reorganizations of 1,5-dienes known as *Cope rearrangements.* The reaction is simply a conversion of one 1,5-diene into another, and was first detected in reactions such as the formation of **29** from **28**.[46] The position of equilibrium is favorable for this transformation because of the gain in stability associated with conjugation of the double bond with the cyano and carbethoxy groups.



28 **29**

As we shall see later in this section, some extremely interesting Cope rearrangements have been detected in systems in which no gross structural change is apparent. The rearrangement of the parent system, 1,5-hexadiene, has been studied using deuterium-labeled diene and found to occur with an activation energy of 33.5 kcal/mol and an entropy of activation of −13.8 eu.[47] The relatively low

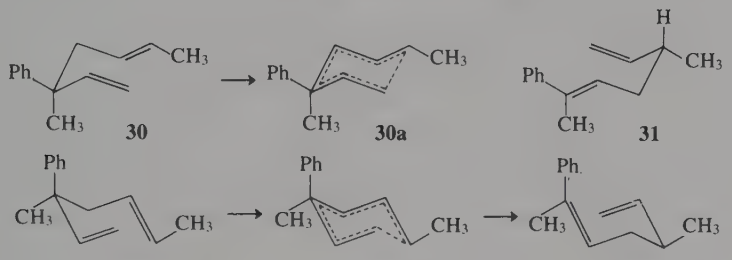


activation energy and negative entropy of activation are reasonable for a concerted

43. J. L. M. A. Schlatmann, J. Pot, and E. Havinga, *Rec. Trav. Chim.* **83**, 1173 (1964).
44. E. E. Schweizer, D. M. Crouse, and D. I. Dalrymple, *Chem. Commun.*, 354 (1969).
45. A review of synthetically important [3,3] rearrangements is available: S. J. Rhoads and N. R. Raulins, *Org. React.* **22**, 1 (1975).
46. A. C. Cope and E. M. Hardy, *J. Am. Chem. Soc.* **62**, 441 (1940).
47. W. v. E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron* **27**, 5299 (1971).

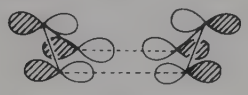
process. A mechanism involving dissociation to two allyl radicals is excluded by the data, since it would require a larger ΔH (estimated as 57 kcal/mol) and a *positive* entropy of activation.

The Cope rearrangement usually proceeds through a chair-like transition state, and when stereochemical features need to be considered they can usually be analyzed and predicted in terms of a preference for the chair transition state which minimizes unfavorable steric interactions. Thus compound **30** reacts primarily through transition state **30a** to give **31** as the major product, while **32**, the minor product, is formed through the less favorable transition state **30b**. When optically pure **30** is

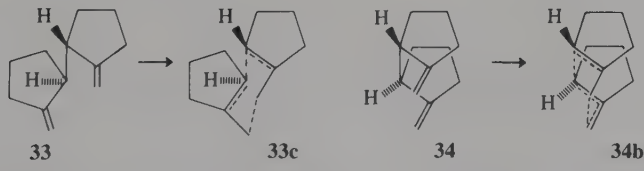


used the newly formed chiral center in **31** has an optical purity of at least 95%, establishing that chirality is maintained throughout the reaction.[48]

There is a second possible transition state for the Cope rearrangement in which the geometry of the transition state is boatlike:



It has been generally assumed that this transition state is higher in energy than the chair transition state. It has been possible to make an estimate of the difference in energy requirements of the boat and chair transition states by determining the activation parameters for the rearrangement of the iomeric alkenes **33** and **34**.[49]

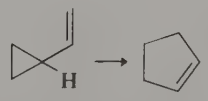


While **33** can attain a chair-like transition state, **34** can achieve overlap of the 1,6 carbons only in a boat-like transition state **34b**. Comparison of the rate of rearrangement of **33** and **34** showed **33** to react faster by a factor of 18,000. This corresponds to about 14 kcal/mol in the measured $\Delta H^{\ddagger}$, but is partially compensated for by a more favorable $\Delta S^{\ddagger}$ for compound **34**. The corresponding compounds containing six-membered rings gave similar results with $\Delta H^{\ddagger}$ favoring the chair-like transition

48. R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).
49. K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.* **102**, 3156 (1980).

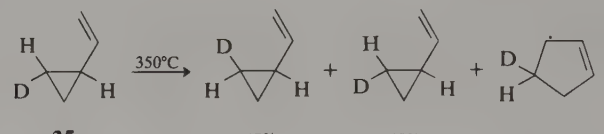
state by about 16 kcal/mol. These results are in accord with a separate study which estimated a $\Delta H^{\ddagger}$ for the rearrangement of the parent compound, 1,5-hexadiene, to be less favorable by about 11.2 kcal/mol when it proceeded through a boat transition state.[50]

Some particularly striking examples of Cope rearrangements can be found in the rearrangement reactions of *cis*-divinylcyclopropanes. But before we go into these, let us examine vinylcyclopropane itself, which is known to rearrange thermally to cyclopentene[51]:



The activation energy for this process is 50 kcal/mol, which is about what would be expected for a stepwise reaction from a rough bond energy calculation. A reasonable sequence of events would be cleavage of one of the C–C bonds of the cyclopropane ring to give a diradical, one end of which is allylic. An estimate of the energy required for this step is obtained by subtracting the resonance stabilization energy of allyl radical (13 kcal/mol) from the activation energy for isomerization of *cis*-di-*deuterio*-cyclopropane to *trans*-di-*deuterio*-cyclopropane (63 kcal/mol), since this latter reaction serves as a model for a process in which cleavage of a cyclopropane C–C bond occurs in the rate-limiting step.

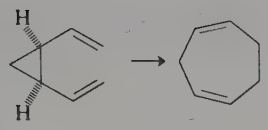
Additional experimental evidence in support of a two-step nonconcerted sequence can be found in the observation that *cis–trans* isomerization of **35** occurs faster than rearrangement. This isomerization results from C–C bond cleavage without any involvement by the vinyl substituent.[52]



35 47% 47% 6%

A dramatic change in reactivity is evident when *cis*-divinylcyclopropane is compared with vinylcyclopropane. The presence of the *cis*-divinyl groups causes rearrangement to occur with great ease. *cis*-Divinylcyclopropane can only be isolated at low temperature because it rapidly undergoes Cope rearrangement to give 1,4-cycloheptatriene.[53] The enthalpy of activation at 0°C is 18.8 kcal/mol with $\Delta S^{\ddagger} = -9.4$ eu:

50. M. J. Goldstein and M. S. Benzon, *J. Am. Chem. Soc.* **94**, 7147 (1972).
51. C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.* **82**, 1007 (1960).
52. M. R. Willcott and V. H. Cargle, *J. Am. Chem. Soc.* **89**, 723 (1967).
53. J. M. Brown, B. T. Golding, and J. F. Stofko, Jr., *Chem. Commun.*, 319 (1973); M. Schneider, *Angew. Chem. Int. Ed. Engl.* **14**, 707 (1975); M. P. Schneider and A. Rau, *J. Am. Chem. Soc.* **101**, 4426 (1979).

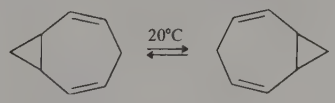


Because of unfavorable molecular geometry, the corresponding rearrangement of *trans*-divinylcyclopropane to cycloheptadiene cannot be concerted, and it requires temperatures on the order of 190°C to occur at a significant rate. *cis*-Divinylcyclopropanes offer almost ideal circumstances for rapid Cope rearrangements. The 1,5-diene system required for the [3,3]-sigmatropic shift, by virtue of the proximity of the termini fixed by the *cis* relationship on the ring, is oriented in the ground state in such a way that the loss in entropy in going to the transition state is not large. Moreover, the bond that is broken in the rate-determining step is significantly strained. Qualitative correlations with ring strain in analogous systems are in accord with expectation. Thus, *cis*-divinylcyclopropane rearranges to cycloheptadiene below 20°C,[53] while rearrangement of *cis*-divinyloxirane requires temperatures of about 60°C and *cis*-divinylthiirane about 100°C.[54] This order of reactivity parallels inversely the degree of ring strain in the three-membered rings. *cis*-Divinylcyclobutane rearranges to cyclooctadiene rather readily, with an enthalpy of activation of 23 kcal/mol and an entropy of activation of −11.7 eu, but is stable enough to be isolated.[54] The rearrangement of *cis*-divinylcyclopentane does not occur even at 250°C.[55]

Divinylcyclopropane rearrangements can proceed with even greater ease if the entropy of activation is made still less negative by incorporating both vinyl groups into a ring. An example of such an arrangement is found in the degenerate homotropilidene rearrangement. A *degenerate rearrangement* is a reaction process in which no overall change in structure has occurred. The product of rearrangement is structurally identical to starting material. Depending on the rate at which the reaction occurs, the existence of a degenerate rearrangement can be detected by use of isotopic labels or by interpretation of the temperature dependence and chemical shift behavior of the NMR spectrum. In the case of homotropilidene, **36**, the occurrence of a dynamic equilibrium is evident from the NMR spectrum. At low temperature, the rate of equilibrium is slow enough that the spectrum is consistent with the presence of four olefinic protons, two allylic protons, and four cyclopropyl ring protons. As the temperature is raised and the rate of equilibration increases, it is observed that two of the olefinic protons remain substantially unchanged with respect to their chemical shift, while two of the olefinic protons and two of the cyclopropane ring protons coalesce. Coalescence is also observed between the allylic protons and two of the cyclopropane ring protons.[56] This means

54. E. Vogel, *Justus Liebigs Ann. Chem.* **615**, 1 (1958); G. S. Hammond and C. D. De Boer, *J. Am. Chem. Soc.* **86**, 899 (1964).
55. E. Vogel, W. Grimme, and E. Dinné, *Angew. Chem.* **75**, 1103 (1963).
56. G. Schröder, J. F. M. Oth, and R. Merényi, *Angew. Int. Ed. Engl.* **4**, 752 (1965); H. Günther, J. B. Pawliczek, J. Ulmen, and W. Grimme, *Angew. Chem. Int. Ed. Engl.* **11**, 517 (1972); W. v. E. Doering and W. R. Roth, *Tetrahedron* **19**, 715 (1963).

that the protons whose signals coalesce are undergoing a sufficiently rapid interchange with one another to result in an averaged signal. Many other examples of



homotropilidene

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this type of rearrangement are known, one of the most interesting being the case of bullvalene, which is converted into itself with a first-order rate constant of 3440 sec^{-1} at 25°C.[57] At 100°C, the NMR spectrum of bullvalene exhibits a single peak at 4.22 ppm. This result indicates the "fluxional" nature of the molecule. Because of the threefold axis of symmetry present in bullvalene, the degenerate rearrangement results in all of the carbons having an identical averaged environment. The free energy of activation for the rearrangement has been determined to be 12.6 kcal/mol, a very low value indeed.[58]

structures indicating changing environment of carbons in bullvalene

As rapid as the Cope rearrangement of bullvalene is, and blessed as it is with an esthetically pleasing level of symmetry, other degenerate rearrangements have been discovered that are even faster. Barbaralane (**37**), for example, rearranges to itself with a rate constant of 17,300,000 sec^{-1} at 25°C.[59] The free energy of activation of this rearrangement is 7.6 kcal/mol. The lowered energy requirement has been attributed to an increase in ground state energy due to strain.[60] Barbaralane is less symmetrical than bullvalene. There are four different kinds of carbons and protons in the averaged structure and only the methylene group labelled d is not affected by the degenerate rearrangement.

37

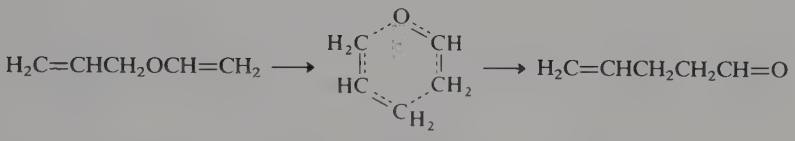
A further reduction in the barrier and increase in rate is seen with semibullvalene (**38**) in which the strain is increased still more. The $\Delta G^{\ddagger}$ for this degenerate

57. G. Schröder and J. F. M. Oth, *Angew. Chem. Int. Ed. Engl.* **6**, 414 (1967).
58. A. Allerhand and H. S. Gutowsky, *J. Am. Chem. Soc.* **87**, 4092 (1965).
59. W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron* **23**, 3943 (1967).
60. For an interesting theoretical discussion of Cope rearrangements dealing with the possibility of designing a compound capable of rearranging with a negative (or very small) activation energy, see R. Hoffmann and W.-D. Stohrer, *J. Am. Chem. Soc.* **93**, 6941 (1971).

38

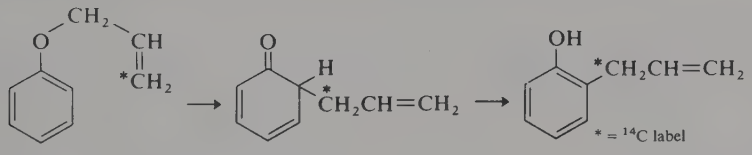
rearrangement is 5.5 kcal/mol at −143°C.[61] This means that the degenerate rearrangement is much more rapid than the conformational inversion of cyclohexane, for example.

The [3,3]-sigmatropic reaction pattern is quite general for other systems which incorporate one or more heteroatoms in place of carbon in the 1,5-hexadiene unit. The most useful and widely studied of these reactions is the Claisen rearrangement in which an oxygen atom is present in the reacting system. The simplest example of a Claisen rearrangement is the thermal conversion of allyl vinyl ether to 4-pentenal:



This reaction occurs with an energy of activation of 30.6 kcal/mol and an entropy of activation of −7.7 eu at 180°C.[62]

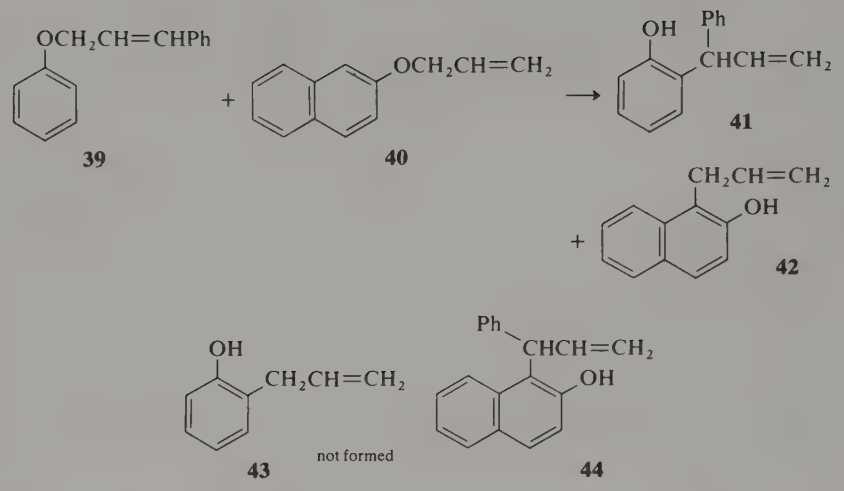
Extensive studies on Claisen rearrangements of allyl ethers of phenols have provided further evidence bearing on [3,3]-sigmatropic rearrangements.[63] For example, an important clue as to the mechanism of the Claisen rearrangement was obtained by use of ^{14}C-labeled allyl phenyl ether. It was found that the rearrangement was specific with respect to which carbon atom of the allyl group became bonded to the ring and led to the proposal of the following mechanism[64]:



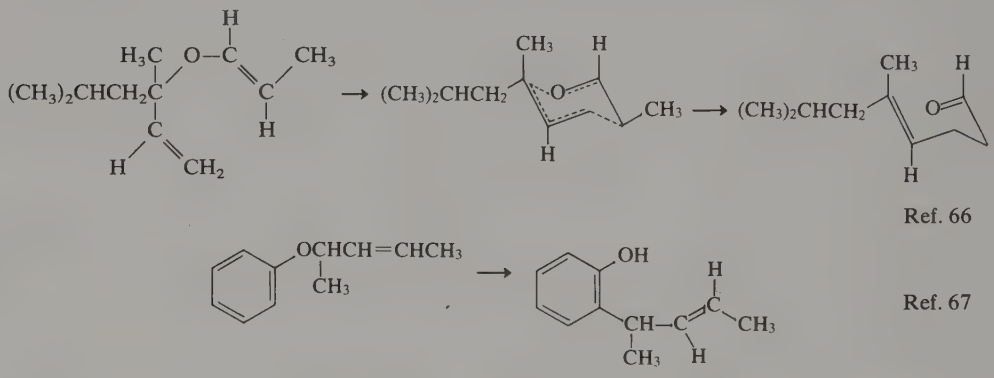
It was also found that if both *ortho* positions were substituted with alkyl groups, thereby blocking the step in which the dienone tautomerizes to the phenol, the intermediate dienone can be trapped as a Diels–Alder adduct with maleic anhydride.

The intramolecular nature of the rearrangement was firmly established by a crossover experiment in which **39** and **40** were heated simultaneously and found to yield the same products as when they were heated separately, there being no evidence whatsoever for the formation of the cross products **43** and **44**.[65]

61. A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *J. Am. Chem. Soc.* **96**, 2887 (1974).
62. F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.* **72**, 3155 (1950).
63. For a review, see D. S. Tarbell, *Org. React.* **2**, 1 (1944).
64. J. P. Ryan and P. R. O'Connor, *J. Am. Chem. Soc.* **74**, 5866 (1952).
65. C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.* **59**, 107 (1937).



The stereochemical features of the Claisen rearrangement are very similar to those described for the Cope rearrangement and reliable stereochemical predictions can be made on the basis of the preference for a chair-like transition state. The major product will have the *E* configuration at the newly formed double bond because of the preference for placing the larger substituent in the pseudoequatorial position in the transition state.[66,67] Studies of chiral substrates have also demonstrated that chirality is maintained in the reaction.[68] Several very important synthetic



Ref. 66

Ref. 67

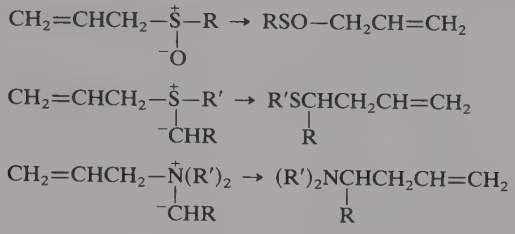
transformations have been developed on the basis of the Claisen rearrangement. These reactions are considered in Section 7.3 of Part B.

Another significant concerted rearrangement exhibits the [2,3]-sigmatropic reactivity pattern. The most well-developed of these reactions are rearrangements of nitrogen[69] and sulfur[70] ylides and rearrangements of allyl sulfoxides.[71] One requirement for a [2,3]-sigmatropic process is that the atom at the allylic position

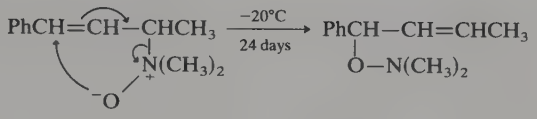
66. R. Marbet and G. Saucy, *Helv. Chim. Acta* **50**, 2095 (1967).
67. A. W. Burgstahler, *J. Am. Chem. Soc.* **82**, 4681 (1960).
68. H. L. Goering and W. I. Kimoto, *J. Am. Chem. Soc.* **87**, 1748 (1965).
69. E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.* **43**, 1185 (1978).
70. B. M. Trost and R. LaRochelle, *Tetrahedron Lett.*, 3327 (1968).
71. D. A. Evans and G. C. Andrews, *Acc. Chem. Res.* **7**, 147 (1974).

be able to act as a leaving group when the adjacent atom begins bonding to the allyl system:

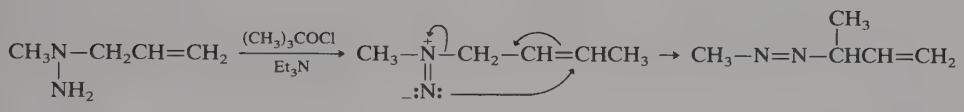
This reaction is most facile in systems where the atoms X and Y bear formal charges, as in the case of ylides and sulfoxides:



Other examples of [2,3]-sigmatropic rearrangements involve amine oxides and diazenes:

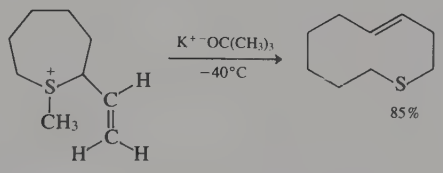


Ref. 72



Ref. 73

Some of the most useful synthetic applications of these reactions are for ring expansion:



Ref. 74

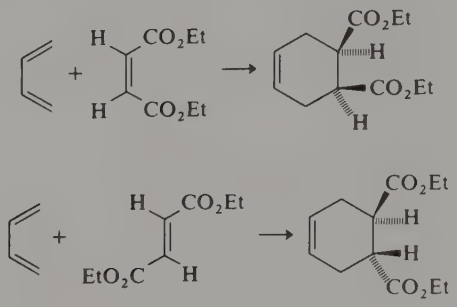
Further examples of synthesis using [2,3]-sigmatropic reactions are given in Section 7.4 of Part B.

10.3. Cycloaddition Reactions

The principles of conservation of orbital symmetry can be applied to intermolecular cycloaddition reactions and to what can be thought of as their reverse, the

72. Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.* **41**, 303 (1976).
73. J. E. Baldwin, J. E. Brown, and G. Höfle, *J. Am. Chem. Soc.* **93**, 788 (1971).
74. V. Ceré, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.* **43**, 4826 (1978).

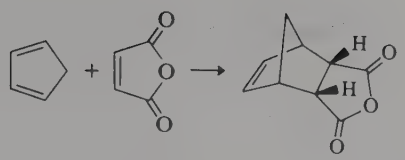
fragmentation of one molecule into two or more smaller fragments. Let us consider first the *Diels–Alder reaction*, a reaction of great synthetic usefulness as well as the subject of many theoretical and mechanistic speculations and studies.[75] In its simplest form, this reaction is the addition of an olefin to a conjugated diene to give a cyclohexene. It is termed a [4 + 2]-cycloaddition reaction, since it involves a four-π-electron system and a two-π-electron system. All available data indicate that the reaction is a concerted one that proceeds stereospecifically by *syn* addition to the double bond. This stereospecificity is exemplified by the formation of stereoisomeric products from the reaction of butadiene with ethyl maleate and ethyl fumarate:

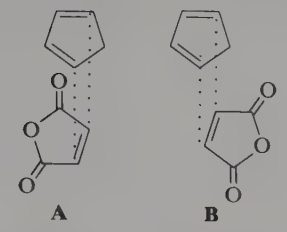


The high degree of stereospecificity indicates either that the reaction is concerted or that if the process involves two discrete bond-making steps, the second must occur much faster than rotation about a carbon–carbon bond in the intermediate. The most widely held view is that the Diels–Alder reaction is a concerted process, but it is recognized that there is the possibility that the extent of bond making at the two sites may be different at the transition state.

Another stereochemical feature of the Diels–Alder reaction is considered by the *Alder rule* or as it is also called, the rule of *maximum accumulation of unsaturation.* The empirical observation is that if two isomeric adducts are possible, the one that has the conjugated unsaturated units aligned over one another in the transition state will be the preferred product. For example, the addition of dienophiles to cyclopentadiene usually is stereoselective in favor of the *endo* isomer, even though this is the more sterically conjested isomer and is usually thermodynamically less stable than the *exo* isomer. This behavior is illustrated by the addition reaction of maleic anhydride with cyclopentadiene. The transition state geometries which lead to the formation of the *endo* and *exo* adducts, respectively, can be approximated by the structures **A** and **B**. In **A**, the π electrons of the carbonyl group are aligned to permit interaction with the diene unit and **A** would be the favored transition state according to the Alder rule. Similarly, the Alder rule provides a basis for

75. M. C. Kloetzel, *Org. React.* **4**, 1 (1948); H. L. Holmes, *Org. React.* **4**, 60 (1958); S. Seltzer, *Adv. Alicyclic Chem.* **2**, 1 (1968); J. G. Martin and R. K. Hill, *Chem. Rev.* **61**, 537 (1961); A. Wassermann, *Diels–Alder Reactions*, Elsevier, London, 1965; *1,4-Cycloaddition Reactions*—The *Diels–Alder Reaction in Heterocyclic Syntheses*, J. Hamer (ed.), Academic Press, New York, 1967; J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **19**, 779 (1980).

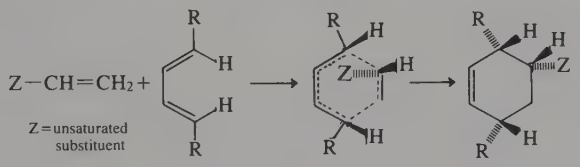




A transition state for *endo* product

B transition state for *exo* product

prediction of stereochemistry in the adducts from Diels–Alder reactions of acylic dienes. By using deuterium labels it has been found that the addition of 1,3-butadiene and maleic anhydride gave 85% of the product resulting from an *endo* transition state.[76] Stereochemical predictions can be made by assuming that the preferred diene conformation will react via a transition state which achieves maximum overlap of the dienophile substituent with the conjugated diene system:



Z = unsaturated substituent

The physical basis of the Alder rule is not entirely understood and there are undoubtedly several factors which make a contribution to determining the actual product ratio in any specific case. These include steric effects, dipole–dipole interactions, and London dispersion forces. Molecular orbital interpretations emphasize the interactions between the various orbitals. The orientation which aligns the reacting π systems provides for interaction not only between the frontier orbitals but also other orbitals, so that the term *secondary orbital interactions* is often used to describe stabilizing features arising by a particular alignment. Whatever the contributing factors are, the Alder rule is far from absolute. Both isomeric products may form and sometimes the rule is broken. For example, while cyclopentadiene reacts with methyl acrylate in decalin solution to give mainly the *endo* adduct (75%) the ratio of *endo* to *exo* product is solvent sensitive and ranges up to 90% *endo* in methanol. Methyl methacrylate gives mainly *exo* product (2:1) in decalin but in methanol the *endo* product is favored.[77]

How do orbital symmetry requirements relate to cycloaddition reactions of the [4+2] type? Let us construct a simple correlation diagram for the addition of

76. L. M. Stephenson, D. E. Smith, and S. P. Current, *J. Org. Chem.* **47**, 4170 (1982).
77. J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.* **84**, 297 (1962).

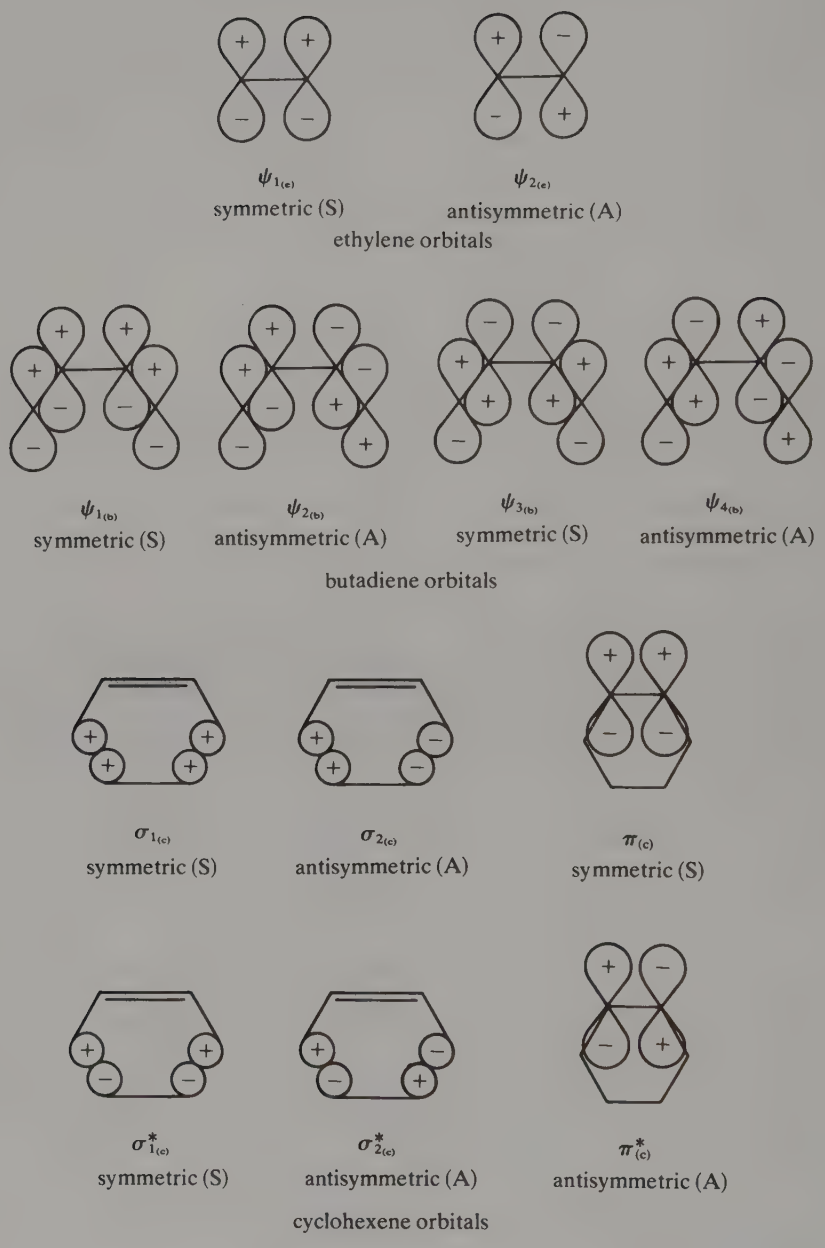
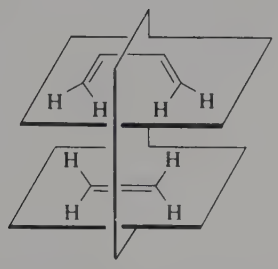


Fig. 10.8. Symmetry properties of ethylene, butadiene, and cyclohexene orbitals with respect to cycloaddition.

butadiene and ethylene to give cyclohexene. For concerted cycloaddition to occur, it may be assumed that the diene reacts in the *s-cis* conformation, and that the diene and dienophile approach each other in parallel planes. It can be seen from such a description that a plane of symmetry perpendicular to the two parallel planes is maintained at all stages of the cycloaddition. The reaction is suprafacial for both components:



An orbital correlation diagram can be constructed by examining the orbital symmetries with respect to this symmetry plane. The orbitals are either symmetric or antisymmetric with respect to this plane, and are shown in Fig. 10.8 for ethylene, butadiene, and cyclohexene. The relevant orbitals for butadiene are the four π levels, each designated by the sub-subscript (b); those for ethylene are designated by the sub-subscript (e) and consist of two π levels; those for cyclohexene are a bonding and an antibonding π level and two bonding and two antibonding σ levels, all designated by the sub-subscript (c). The cyclohexene orbitals σ_1, σ_2, σ_1^*, and σ_2^* are linear combinations of the localized σ and σ^* orbitals. These *symmetry-adapted orbitals*, which are equivalent to the localized σ and σ^* orbitals, are used, since the individual localized orbitals are neither symmetric nor antisymmetric with respect to the mirror plane.

Arranging these orbitals in relative order of energy and connecting orbitals of like symmetry leads to the diagram shown in Fig. 10.9 and to the conclusion that the thermal concerted reaction between butadiene and ethylene is allowed, since bonding levels of starting materials and products correlate. The extension of these

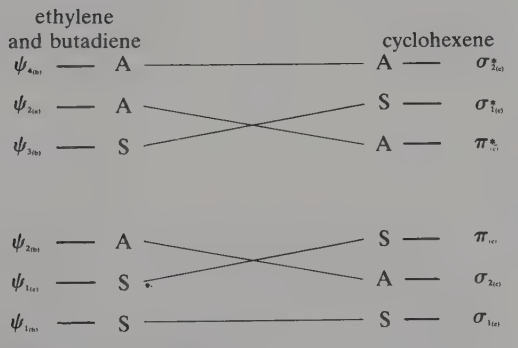
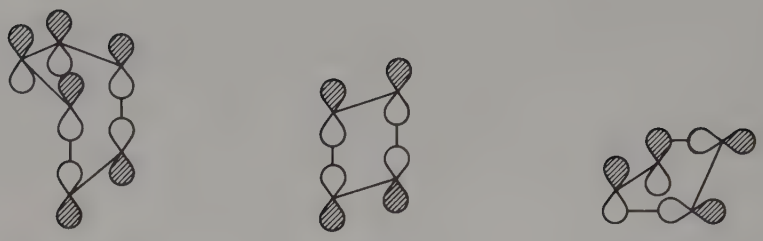


Fig. 10.9. Correlation diagram for ethylene, butadiene, and cyclohexene orbitals.



supra/supra
Hückel system
6 electrons
aromatic
allowed

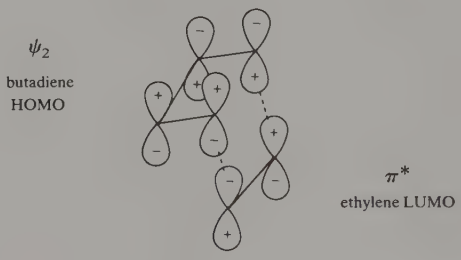
supra/supra
Hückel system
4 electrons
antiaromatic
forbidden

supra/antara
Möbius system
4 electrons
aromatic
allowed

Fig. 10.10. Classification of cycloaddition reactions with respect to basis set orbitals.

ideas to other cycloadditions leads to the conclusion that the reaction is allowed for systems with $4n + 2\pi$ electrons and forbidden for systems with $4n\ \pi$ electrons.

Equivalent conclusions are drawn by analysis of the frontier orbitals involved in the cycloaddition. For most combinations of reactants, the appropriate orbitals are the highest occupied molecular orbital (HOMO) of the diene (ψ_2 of butadiene) and the lowest unoccupied molecular orbital (LUMO) of the olefin (ψ_2 of ethylene). Reaction then occurs by interaction of the HOMO and the LUMO, which can be seen from the illustration below to be symmetry allowed, since the orbitals have the appropriate symmetry:



The selection rules for cycloaddition reactions can also be derived from consideration of the basis set orbitals from which the transition state for the cycloadditions would arise (Fig. 10.10). For [4+2]-suprafacial addition, the transition state is aromatic; for [2+2]-suprafacial addition, it is antiaromatic. On the other hand, a [2+2]-addition that is antarafacial in one component is an allowed process.

The generalized Woodward–Hoffmann rules for concerted cycloaddition can be summarized as follows:

Selection rules for $m + n$ cycloadditions			
$m+n$	supra/supra	supra/antara	antara/antara
$4n$	forbidden	allowed	forbidden
$4n+2$	allowed	forbidden	allowed

Table 10.1. Relative Reactivity toward Cyclopentadiene in the Diels–Alder Reaction

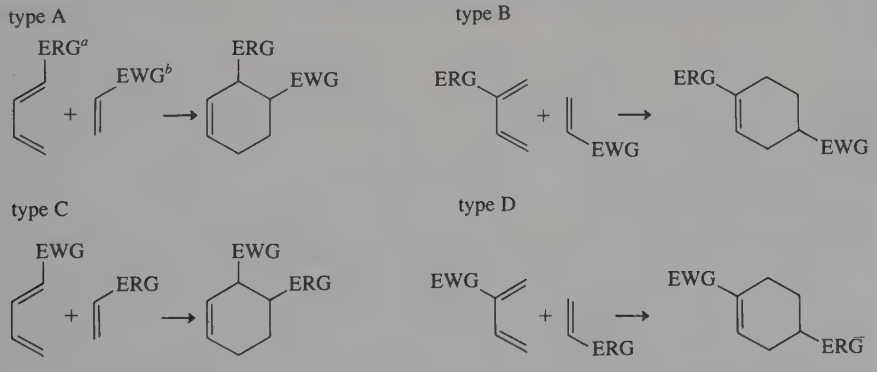
Dienophile	Relative rate[a]
Tetracyanoethylene	4.3×10^7
1,1-Dicyanoethylene	4.5×10^5
Maleic anhydride	5.6×10^4
p-Benzoquinone	9.0×10^3
Maleonitrile	91
Fumaronitrile	81
Dimethyl fumarate	74
Dimethyl maleate	0.6
Methyl acrylate	1.2
Acrylonitrile	1.0

a. From second-order rate constants in dioxane at 20°C as reported by J. Sauer, H. Wuest, and A. Mielert, *Chem. Ber.* **97**, 3183 (1964).

Cycloaddition processes can be described by a symbolism which describes the type and number of electrons involved in the reaction and the topology of the reaction. Thus a Diels–Alder reaction is a $[4\pi_s + 2\pi_s]$ process, signifying addition of a four-π-electron and a two-π-electron system, with both sets of orbitals reacting in a suprafacial mode. The allowed 2 + 2 addition would be described as $[2\pi_s + 2\pi_a]$.

It has long been known that the Diels–Alder reaction is particularly efficient and rapid when the dienophile contains one or more electron-attracting groups and is enhanced still more if the diene also contains electron-releasing groups. The effect of electron-attracting substituents on dienophile reactivity is illustrated by the data in Table 10.1.

Scheme 10.2. Regioselectivity of the Diels–Alder Reaction



a. ERG, electron-releasing group.
b. EWG, electron-withdrawing group.

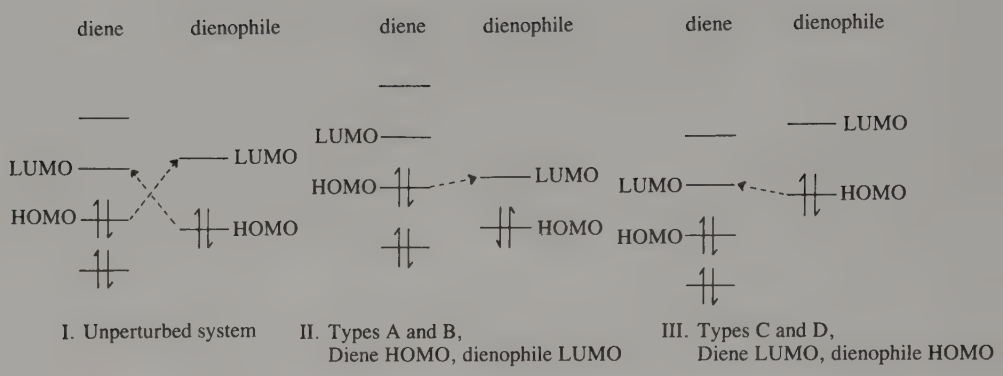


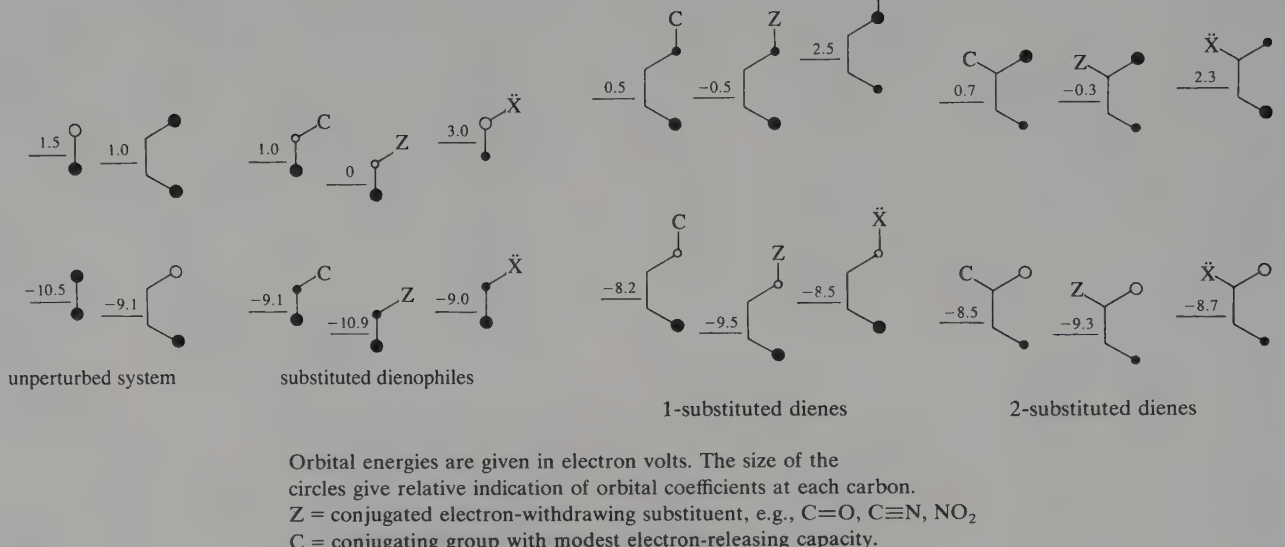
Fig. 10.11. Frontier orbital interactions in Diels–Alder reactions.

The basis for these relative reactivity relationships and also the regioselectivity of the Diels–Alder reaction can be interpreted very satisfactorily in terms of frontier molecular orbital theory. The pattern of regioselectivity of the Diels–Alder reaction is summarized in Scheme 10.2.

The interpretation of these regiochemical effects is based on the frontier orbital approach and the coefficients of the frontier orbitals at the reaction centers. In reactions of type A illustrated in Scheme 10.2, it is expected that the frontier orbitals will be the diene HOMO and the dienophile LUMO. This is because an electron-releasing group will raise the energy of the diene HOMO and an electron-attracting group will lower the energy of the dienophile LUMO. These two orbitals should therefore be quite close in energy and will provide the frontier orbital interaction. In types C and D, the opposite pairing of LUMO and HOMO would be expected, since the diene will now possess an orbital lowered in energy by the electron-withdrawing group, while the orbitals of the dienophile will have been raised by the electron-releasing group. These relationships are illustrated in Fig. 10.11.

Figure 10.12 gives the approximate values of the orbital coefficients for various substituted dienes and dienophiles. Relative orbital energies are also estimated in the figure.

As shown in Figure 10.12, the LUMO of dienophiles with electron-withdrawing groups has a large coefficient at the carbon which is β to the substituent. For dienes with electron-releasing groups, the HOMO has its largest coefficient at C-4. The strongest frontier orbital interaction therefore occurs between C-4 of the diene and C-2 of the dienophile and leads to the regioselectivity shown in case A of Scheme 10.2. A similar analysis of each of the other combinations in Scheme 10.2 by using the diagrams in Fig. 10.12 leads to the regioselectivity indicated. Any specific system can be analyzed by first identifying the frontier orbitals and then determining the orientation which leads to the strongest interaction between these two orbitals. The data in Fig. 10.12 are generalized and are therefore rather approximate for any specific system. More detailed analysis would apply these same concepts to the

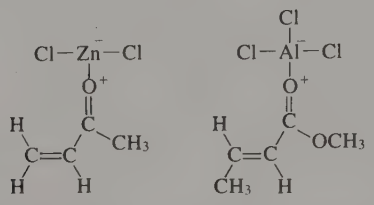


Orbital energies are given in electron volts. The size of the circles give relative indication of orbital coefficients at each carbon.
Z = conjugated electron-withdrawing substituent, e.g., C=O, C≡N, NO_2
C = conjugating group with modest electron-releasing capacity.
X = electron donating substituent, e.g., OCH_3, NH_2.

Fig. 10.12. Coefficients and relative energies of dienophile and diene molecular orbitals. Reproduced from K. N. Houk, *J. Am. Chem. Soc.* **95**, 4092 (1973).

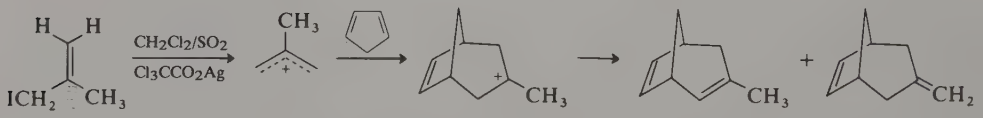
individual system with more accurate energy and orbital coefficient information.[78]

Frontier orbital concepts can also serve to explain the very strong catalysis of certain Diels–Alder reactions by Lewis acid catalysts. The catalysis is most evident in reactions involving dienophiles with electron-attracting substituents when the reactions are carried out in the presence of Lewis acids such as $AlCl_3$, $SnCl_4$, and $ZnCl_2$. The types of dienophiles which are subject to catalysis are typically those with carbonyl activating groups. Lewis acid catalysts are known to form complexes at carbonyl oxygen and this has the effect of increasing the electron-withdrawing capacity of the substituent group:

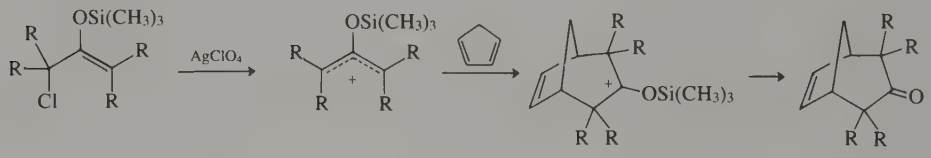


This complexation accentuates both the energy and orbital distortion effects of the substituent and therefore enhances both the selectivity and reactivity of the dienophile, relative to the uncomplexed compound.[79]

Cycloadditions of the [4+2] type are not restricted to the reactions of neutral materials such as the diene–olefin additions most commonly encountered, but have been detected in ionic systems as well. The addition of 2-methylallyl cation to cyclopentadiene is an example[80]:



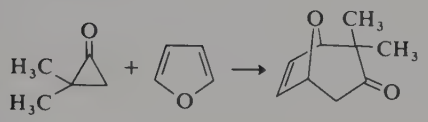
A similar transformation results when trimethylsilyloxy-substituted allylic halides react with silver perchlorate in nitromethane. The resulting allylic cation gives cycloaddition reactions with dienes such as cyclopentadiene. The isolated products result from desilylation of the initial adduct[81]:



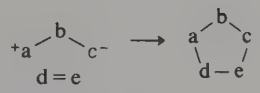
78. For discussion of the development of frontier orbital control of cycloaddition regiochemistry, see K. N. Houk, *Acc. Chem. Res.* **8**, 361 (1975); K. N. Houk, *J. Am. Chem. Soc.* **95**, 4092 (1973); R. Sustmann and R. Schubert, *Angew. Chem. Int. Ed. Engl.* **11**, 840 (1972); K. N. Houk, *Topics Current Chem.* **79**, 1 (1979).
79. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.* **95**, 4094 (1973).
80. H. M. R. Hoffmann, D. R. Joy, and A. K. Suter, *J. Chem. Soc. B*, 57 (1968); H. M. R. Hoffmann and D. R. Joy, *J. Chem. Soc. B*, 1182 (1968).
81. N. Shimizu, M. Tanaka, and Y. Tsuno, *J. Am. Chem. Soc.* **104**, 1330 (1982).

While cyclopropanone has been shown to possess the closed structure by microwave spectroscopy,[82] many of its reactions appear to proceed by way of the zwitterionic "oxyallyl cation" intermediate **C**. The addition of 2,2-dimethylcyclopropanone to furan is analogous to the [4 + 2]-cycloaddition just described, and yields a product consistent with this rationalization[83]:

C



There also exists a large class of reactions known as *1,3-dipolar cycloaddition reactions* that are analogous to the Diels–Alder reaction in that they are concerted additions of the [4+2] type.[84] These reactions are customarily represented as in the following diagram, in which *a–b–c* is termed the 1,3-*dipolar molecule* and *d–e* the *dipolarophile*:



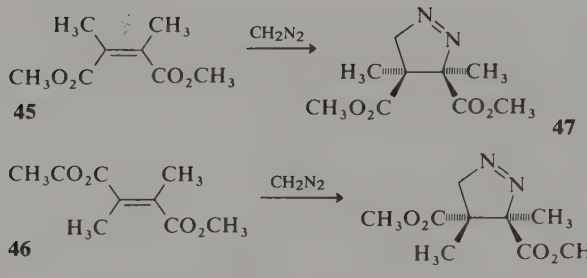
The dipolarophile typically is an alkene, but diversity in the structure of the dipolarophile is one of the synthetically important features of 1,3-dipolar cycloaddition reactions. Many different types of unsaturated compounds have been employed as dipolarophiles.[85] Likewise, quite a range of structures are possible for compounds capable of acting as 1,3 dipoles. Variability in structure in both the 1,3 dipole and dipolarophile makes this a very versatile and useful reaction, particularly in the synthesis of heterocyclic compounds. The most significant structural feature of 1,3-dipolar compounds is that they possess a π system containing four electrons over three atoms, and are isoelectronic with the allyl anion. Some typical 1,3-dipolar species are shown in Scheme 10.3.

Stereochemically, the reactions of 1,3-dipoles with alkenes strongly resemble the Diels–Alder reaction in being stereospecific *syn* additions. Diazomethane, for example, adds stereospecifically to alkenes **45** and **46** to yield the corresponding pyrazolines **47** and **48**, respectively.

82. J. M. Pochan, J. E. Bladwin, and W. H. Flygare, *J. Am. Chem. Soc.* **90**, 1072 (1968).
83. N. J. Turro, S. S. Edelson, J. R. Williams, T. R. Darling, and W. B. Hammond, *J. Am. Chem. Soc.* **91**, 2283 (1969); S. S. Edelson and N. J. Turro, *J. Am. Chem. Soc.* **92**, 2770 (1970); N. J. Turro, *Acc. Chem. Res.* **2**, 25 (1969).
84. R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **2**, 565 (1963); R. Huisgen, R. Grashey, and J. Sauer, in *The Chemistry of the Alkenes*, S. Patai (ed.), Interscience Publishers, London, 1965, pp. 806–878.
85. H. Ulrich, *Cycloaddition Reactions of Heterocumulenes*, Academic Press, New York, 1967.

Scheme 10.3. Some 1,3-Dipoles

Nitrile oxide	$R-C\equiv\overset{+}{N}-\ddot{O}:^{-} \longleftrightarrow R-\overset{+}{C}=\underset{\cdot\cdot}{N}-\ddot{O}:^{-}$
Azides	$R-\overset{-}{\ddot{N}}-\underset{\cdot\cdot}{N}=\overset{+}{N}: \longleftrightarrow R-\overset{-}{\ddot{N}}-\overset{+}{N}\equiv N:$
Diazomethane	$\overset{-}{:}CH_2-\underset{\cdot\cdot}{N}=\overset{+}{N}: \longleftrightarrow \overset{-}{:}CH_2-\overset{+}{N}\equiv N:$
Nitrones	$R_2C=\overset{+}{N}(R)-\ddot{O}: \longleftrightarrow R_2\overset{+}{C}-\ddot{N}(R)-\ddot{O}:$
Nitrilimines	$R-\overset{+}{C}=\underset{\cdot\cdot}{N}-\overset{-}{\ddot{N}}-R \longleftrightarrow R-C\equiv\overset{+}{N}-\overset{-}{\ddot{N}}-R$



The regiochemistry of the 1,3-dipolar cycloaddition reaction is an interesting topic that brings both electronic and steric factors into consideration. The most generally satisfactory interpretation of the regiochemical results has been based on frontier orbital concepts. As with the Diels–Alder reaction, the most favorable reactions are those which involve complementary substituent effects in the dipolarophile and the 1,3 dipole. Although most dipolar cycloadditions are of the type in which the LUMO of the dipolarophile interacts with the HOMO of the 1,3 dipole, there are also a significant number of systems where the relationship is reversed and also some in which the two possible HOMO–LUMO interactions between the dipolarophile and 1,3 dipole are of a comparable magnitude.

Molecular orbital calculations which provide the coefficients of the HOMO and LUMO orbitals of the more important 1,3 dipoles have been reported. Some of these, as obtained by CNDO/2 calculations, are shown in Fig. 10.13. By using these orbital coefficients and by calculation or estimation of the relative energy of the interacting orbitals, it is possible to make predictions of the regiochemistry of 1,3-dipolar cycloaddition reactions.[86] Since the most important dipolarophiles are the same types of compounds which are the dienophiles shown in Figure 10.12, these data can be applied in the analysis of 1,3-dipolar cycloadditions. Figure 10.14 gives estimates of the HOMO and LUMO energies of the orbitals which participate in

86. K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973); R. Sustmann and H. Trill, *Angew. Chem. Int. Ed. Engl.* **11**, 838 (1972).

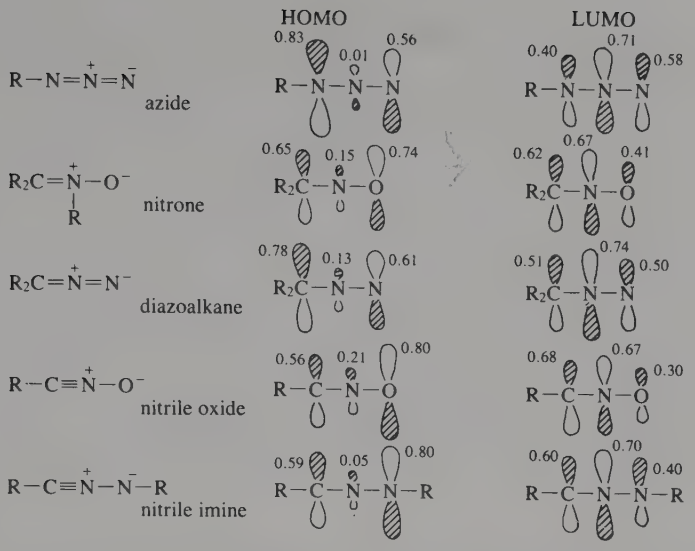


Fig. 10.13. Orbital coefficients for HOMO and LUMO π MO's of some common 1,3 dipoles. [From K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973).]

1,3-dipolar cycloaddition reactions. The energy scale given is compatible with that used in Fig. 10.12.

[2 + 2] Additions are less common than [4 + 2] cycloadditions because they are allowed only when one component reacts in the antarafacial mode. Most examples of [2 + 2] additions that are antarafacial in one component have been observed with

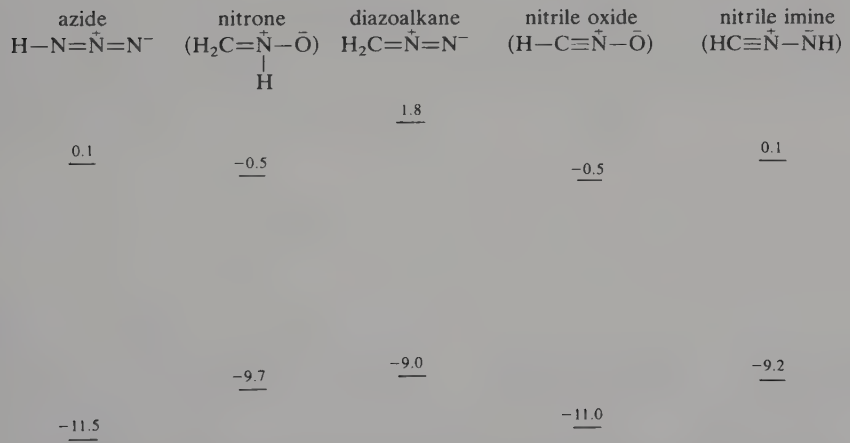


Fig. 10.14. Estimated energy of frontier π orbitals for some common 1,3 dipoles. [From K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.* **95**, 7287 (1973).]

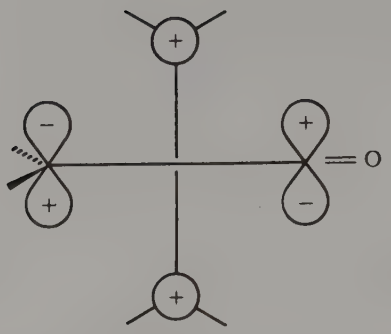
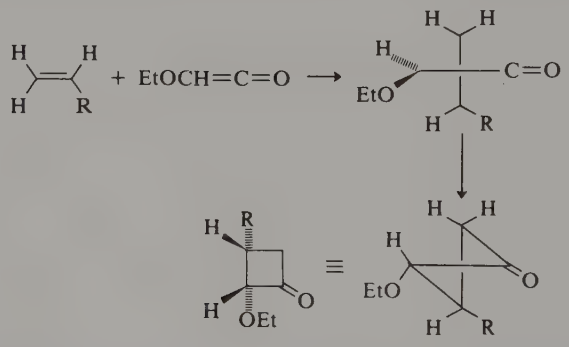


Fig. 10.15. Concerted cycloaddition of a ketene and an olefin. The orbitals represented are the HOMO of the olefin and the LUMO of the ethylenic portion of the ketene.

ketenes.[87] Ketenes are ideal antarafacial components in reactions of this type, since they offer a minimum of steric hindrance to antarafacial addition because one of the carbon atoms involved is *sp* hybridized. This results in a substantial decrease in the degree of crowding in the transition state.

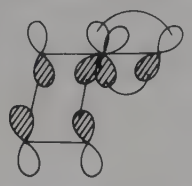
The experimental observations relative to the cycloaddition of ethoxyketene to olefins are in accord with stereochemical predictions that can be made from analysis of Fig. 10.15.[88] Isomeric products are obtained from *cis*- and *trans*-2-butene, indicating that the addition is stereospecific and consistent with a concerted reaction. The substituent on the olefin always becomes vicinal and *cis* to the ethoxy group in the cyclobutanone product. This is exactly the stereochemistry predicted from the geometry shown in Fig. 10.15 if the ethoxy group on the ketene and the largest substituent on the alkene are placed as far apart as possible:



There is an alternative description of the 2 + 2 cycloaddition process involving ketenes. This formulation is $[2\pi_s + (2\pi_s + 2\pi_s)]$. The basis set orbital array is shown below and it can be seen that this array presents a Hückel-type topology with $4n + 2$

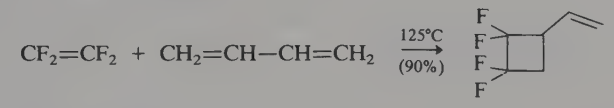
87. W. T. Brady and R. Roe, Jr., *J. Am. Chem. Soc.* **93**, 1662 (1971).
88. T. DoMinh and O. P. Strausz, *J. Am. Chem. Soc.* **92**, 1766 (1970).

electrons and would therefore be an allowed process:



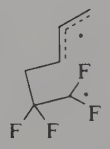
This analysis is equally compatible with available data, and some predictions of stereoselectivity and reactivity based on this model are in better accord with experimental results than similar predictions derived from the $[2\pi_s + 2\pi_a]$ transition state.[89]

Halogenated alkenes—tetrafluoroethylene in particular—exhibit a great tendency to react with other alkenes to afford cyclobutanes.[90] With dienes, tetrafluoroethylene reacts by this route even to the exclusion of the [4+2] process, as shown in the following equation:

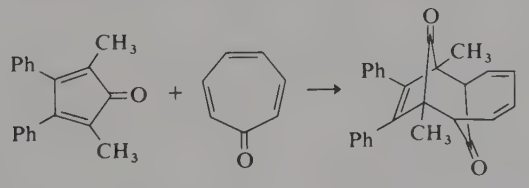


Ref. 91

The reason for this anomalous behavior of halogenated olefins lies not in antarafacial cycloaddition, but rather in the fact that these reactions are not concerted.[92] They are stepwise processes that proceed by way of a diradical intermediate stabilized by the halogen substituents:



The predictions of Woodward and Hoffmann that thermal concerted cycloaddition reactions are allowed when the number of π electrons is equal to $4n+2$ has stimulated experimentation along the lines of higher-order cycloadditions, with the result that a number of interesting and novel examples of this type are now known. A representative example is the [6+4] cycloaddition of tropone and 2,5-dimethyl-3,4-diphenylcyclopentadienone to yield the adduct in 95% yield[93]:



89. D. J. Pasto, *J. Am. Chem. Soc.* **101**, 37 (1979).
90. See P. D. Bartlett, *Q. Rev. Chem. Soc.* **24**, 473 (1970); J. D. Roberts and C. M. Sharts, *Org. React.* **12**, 1 (1962).
91. D. D. Coffman, P. L. Barrick, R. D. Cramer, and M. S. Raasch, *J. Am. Chem. Soc.* **71**, 490 (1949).
92. L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Am. Chem. Soc.* **86**, 622 (1964).
93. K. N. Houk and R. B. Woodward, *J. Am. Chem. Soc.* **92**, 4145 (1970).

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Problems

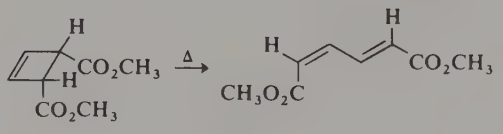
(*References for these problems will be found on page 707.*)

1. Show, by constructing a correlation diagram, whether each of the following disrotatory cyclizations is symmetry allowed:

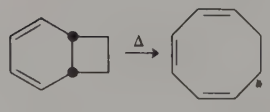
   (a) pentadienyl cation to cyclopentenyl cation
   (b) pentadienyl anion to cyclopentenyl anion

2. Which of the following reactions are allowed according to the orbital symmetry conservation rules? Explain.

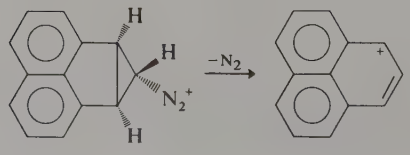
(a)



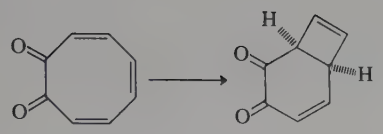
(b)



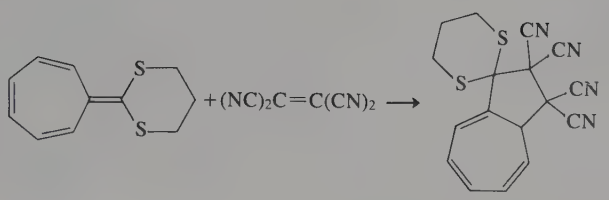
(c)



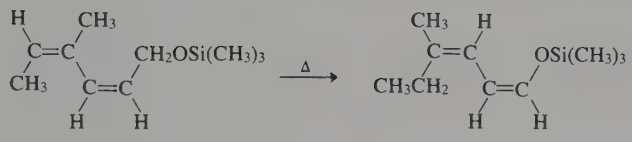
(d)



(e)

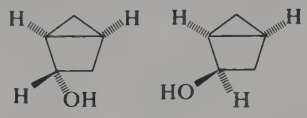


(f)

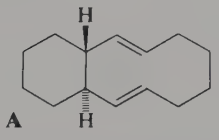


3. All *cis*-cyclononatetraene undergoes a spontaneous electrocyclic ring closure at 25°C to afford a single product. Suggest a structure for this product. Also, describe an alternative symmetry-allowed electrocyclic reaction that would lead to an isomeric bicyclononatriene. Explain why the product of this alternative reaction pathway is not formed.

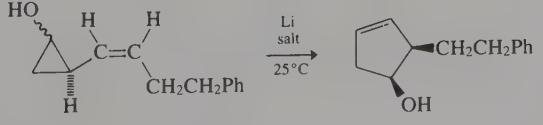
4. Offer a mechanistic explanation of the following observations.
   (a) The 3,5-dinitrobenzoate esters of the epimers shown below both yield 3-cyclopenten-1-ol on hydrolysis in dioxane–water. The relative rates, however, differ by a factor of ten million! Which is more reactive and why?

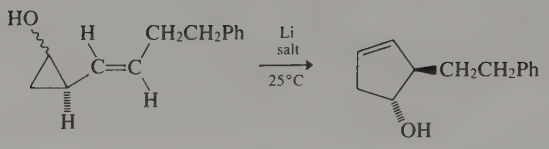


   (b) Optically active **A** racemizes on heating at 50°C with a half-life of 24 h.



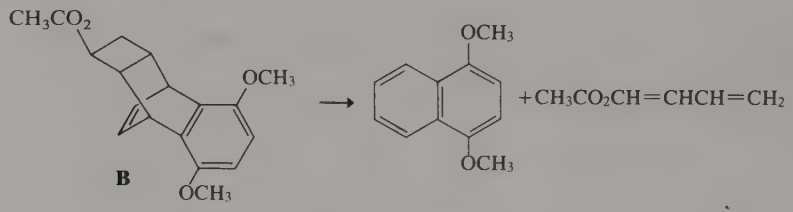
   (c) The anions of various 2-vinylcyclopropanols undergo very facile vinylcyclopropane rearrangement to give cyclopent-3-enols. For example:



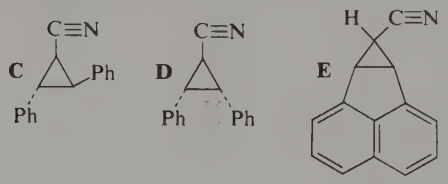


Offer an explanation for the facility of the reaction, as compared to the vinylcyclopropane rearrangement of hydrocarbons which requires a temperature above 200°C. Consider concerted reaction pathways which would account for the observed stereospecificity of the reaction.

(d) On being heated at 320–340°C, compound **B** produces 1,4-dimethoxynaphthalene and 1-acetoxybutadiene.

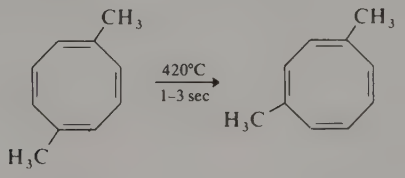


(e) It has been found that compounds **C** and **D** are opened at −25°C to allylic anions in the presence of strong bases such as lithium di-*t*-butylamide. In contrast, **E** opens only slowly at 25°C.

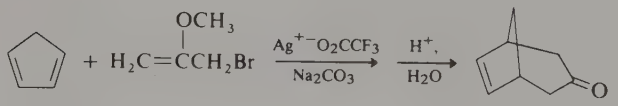


5. Suggest mechanisms by which each transformation could occur. More than one step is involved in each case.

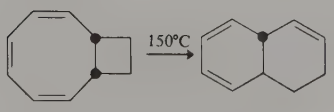
(a)



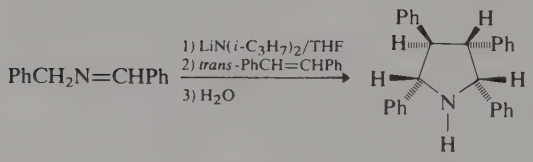
(b)

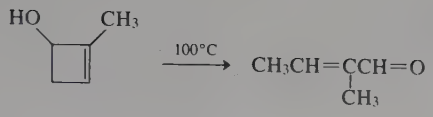


(c)

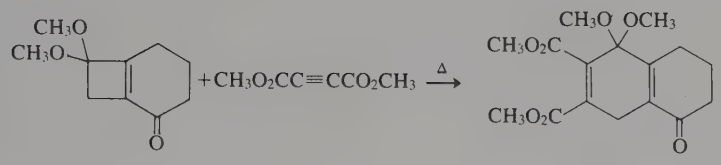


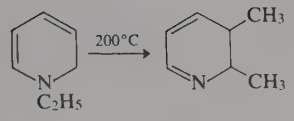
(d)

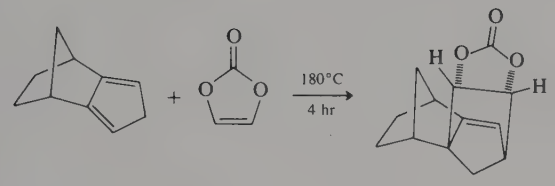


(e) 

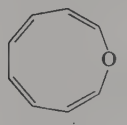
(f) 

(g) 

(h) 

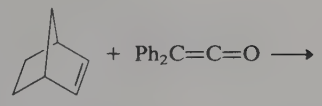
(i) 

6. Predict which is the more likely mode of ring closure for oxonin:
   (a) cyclization of the tetraene unit to a bicyclo[6.1.0] system, or;
   (b) cyclization of a triene unit to a bicyclo[4.3.0] system.

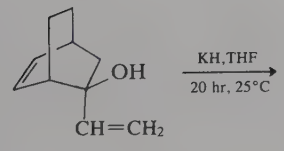


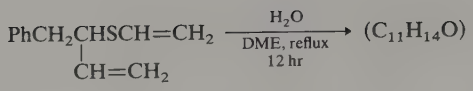
oxonin

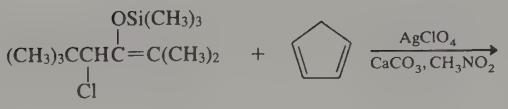
7. Give the structure, including stereochemistry, of the products expected for the following reactions.

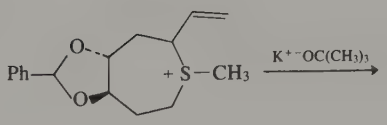
(a) 

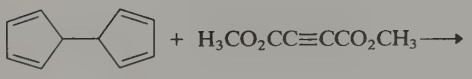
(b) $(CH_3)_2C{=}C{=}O + C_2H_5OC{\equiv}CH \xrightarrow{0°C}$

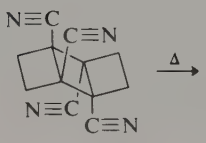
(c) 

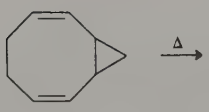
(d) 

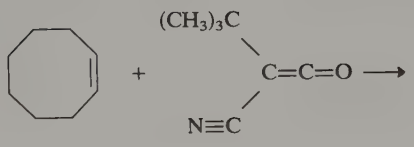
(e) 

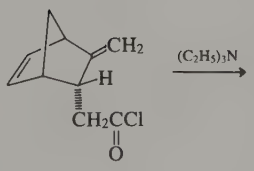
(f) 

(g) 

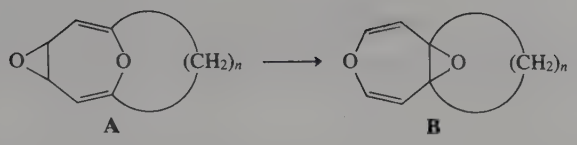
(h) 

(i) 

(j) 

(k) 

8. In the series of oxepins **A** ($n = 3$, 4, and 5), only the compound with $n = 5$ undergoes rearrangement (at 60°C) to the isomeric oxepin **B**. The other two compounds ($n = 3$ or 4) are stable even at much higher temperature. When **B** ($n = 3$) was synthesized by an alternate route it showed no tendency to revert to **A** ($n = 3$). Explain these observations.

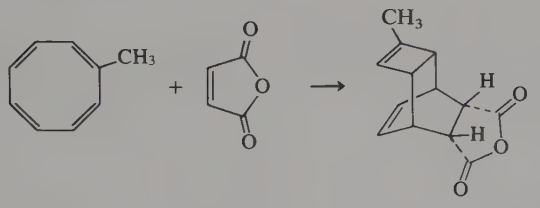


A B

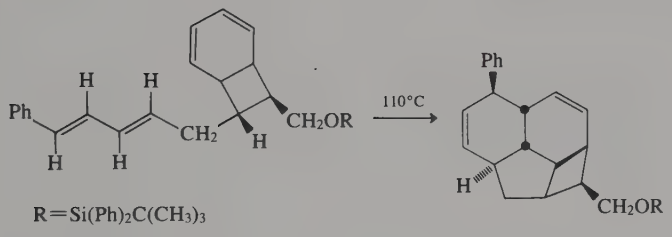
9. Bromocyclooctatetraene rearranges to *trans*-β-bromostyrene. The rate of the rearrangement is solvent dependent, the first-order rate constant increasing from $\sim 10^{-7}\ sec^{-1}$ in cyclohexane to $\sim 10^{-3}$ in acetonitrile at 80°C. In the presence of lithium iodide, the product is *trans*-β-iodostyrene, although *trans*-β-bromostyrene is unaffected by lithium iodide under the conditions of the reaction. Suggest a mechanism for this rearrangement.

10. Classify the following reactions as electrocyclizations, sigmatropic rearrangements, cycloadditions, etc. and give the correct symbolism for the electrons involved in each concerted process. Some of the reactions proceed by two sequential processes.

(a)

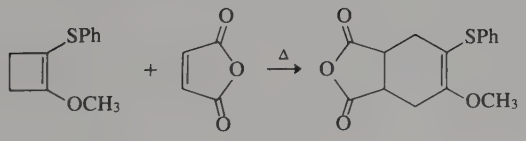


(b)

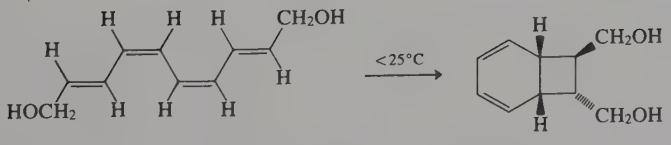


R=Si(Ph)$_2$C(CH$_3$)$_3$

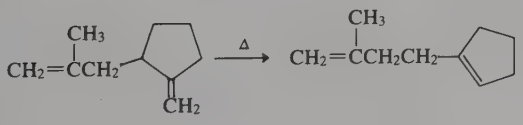
(c)



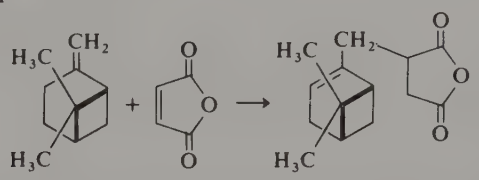
(d)



(e)



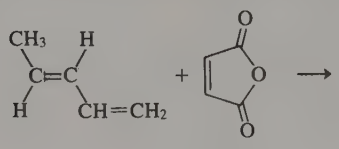
11. The "ene" reaction is a concerted reaction in which addition of an alkene to an electrophilic olefin occurs with migration of a hydrogen and the alkene double bond. For example:



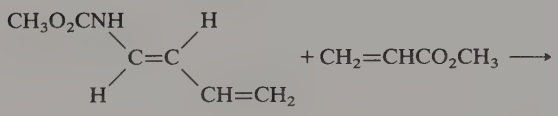
Depict the orbital array through which this process could occur in a concerted manner.

12. Predict the regiochemistry and stereochemistry of the following cycloaddition reactions and indicate the basis for your prediction.

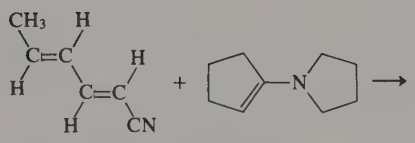
(a)



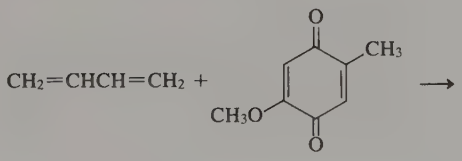
(b)



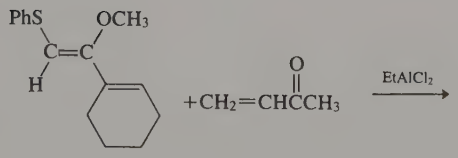
(c)



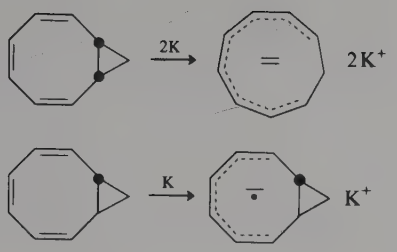
(d)



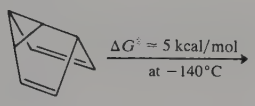
(e)



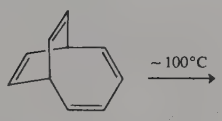
13. On treatment with potassium metal, *cis*-bicyclo[6.1.0]nona-2,4,6-triene gives a monocyclic dianion. The *trans* isomer under similar conditions gives only a bicyclic monoanion (radical anion). Explain how the stereochemistry of the ring junction can control the course of these chemical reductions.

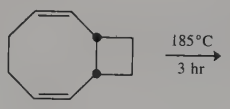


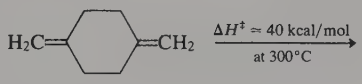
14. The following compounds are capable of degenerate rearrangement at the temperature given. Identify chemical processes which are consistent with the temperature and which would lead to degenerate rearrangement. Indicate by an appropriate labeling scheme the carbons and hydrogens which become equivalent as a result of the rearrangement process you have suggested.

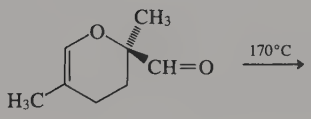
(a) 

(b) 

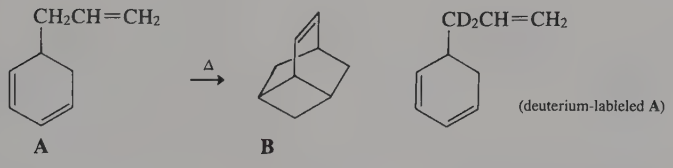
(c) 

(d) 

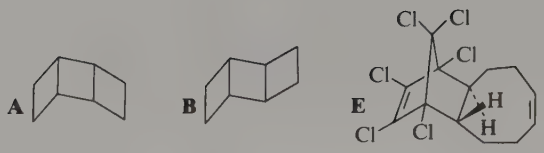
(e) 

(f) 

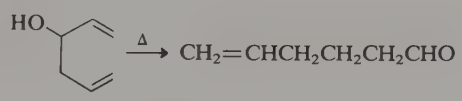
15. On heating at 225°C, 5-allylcyclohexa-1,3-diene, **A**, undergoes intramolecular cycloaddition to give the tricyclic nonene **B**. The mechanism of formation of **B** was probed using the deuterium-labeled sample of **A** which is shown. Indicate the position of deuterium labels in product **B** if the reaction proceeds by (a) a 2 + 2 cycloaddition or (b) a 4 + 2 cycloaddition.

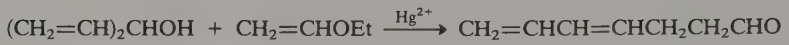


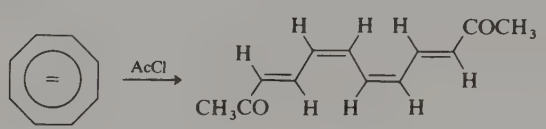
16. The thermal behavior of **A** and **B** above 150°C has been studied. Both in the gas phase and in solution, each compound yields a 3:5 mixture of *trans,cis*-1,5-cyclooctadiene (**C**) and *cis,cis*-1,5-cyclooctadiene (**D**). When hexachlorocyclopentadiene is present, compound **E** is found in place of **C**, but the amount of **D** formed is about the same as in its absence. Formulate a description of the thermolysis mechanism that is consistent with these facts and the general theory of thermal reactions.

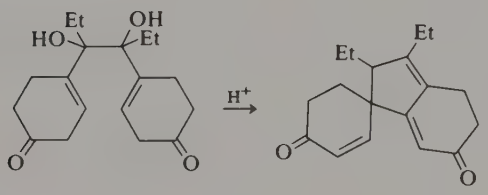


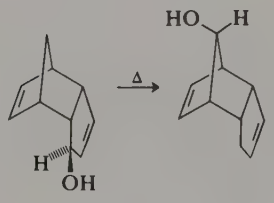
17. Suggest mechanisms for the following reactions. Classify the symmetry-controlled process as clearly as you can with respect to type.

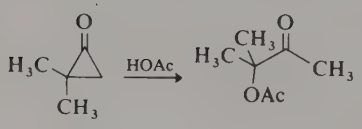
(a) 

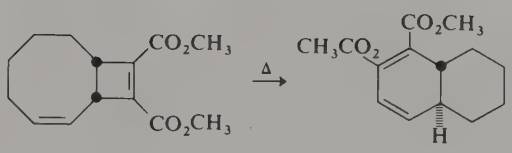
(b) 

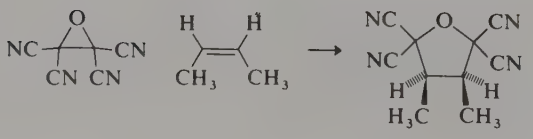
(c) 

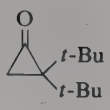
(d) 

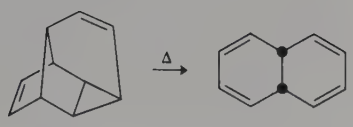
(e) 

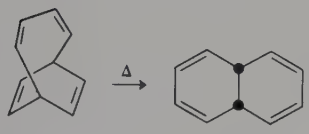
(f) 

(g) 

(h) 

(i) $(t\text{-Bu})_2C{=}C{=}CH_2 + CH_3CO_3H \longrightarrow$ 

(j) 

(k) 

11

Photochemistry

It is a relatively recent development that photochemical reactions of organic compounds have been systematically explored. The area attracted great interest in the 1960's, and, as a result of the many useful and fascinating reactions that were uncovered, photochemistry is now a useful synthetic tool for organic chemists. There is also a firm basis for mechanistic discussion of many photochemical reactions. Some general principles of photochemical reactions will be discussed in this section. In Section 11.2, the relationship of photochemical reactions to the principles of orbital symmetry will be considered. In the remaining sections, some of the photoreactions that have been subjected to mechanistic study will be considered. Synthetic applications of photochemical reactions are covered in Part B, Chapter 7.

11.1. General Principles

The general description of a photochemical reaction is not difficult. The first condition that must be met is that the compound absorb the light emitted by the irradiation source. For light to be absorbed, of course, the molecule must have an electronic transition between orbitals corresponding in energy to that of light emitted by the source. The electronic absorption spectra of organic compounds usually consist of rather broad bands. Table 11.1 lists the general regions of absorption of some of the kinds of organic molecules that have been used most frequently in photochemical reactions. A number of light sources can be used. The most common are mercury vapor lamps which emit mainly at 254, 313, and 366 nm. The composition of the radiation reaching the sample can be controlled by use of filters. For example, if the system is constructed so that light must pass through borosilicate glass, only wavelengths longer than 300–310 nm will reach the sample, because the higher-energy radiation is absorbed by the glass. Pure fused quartz,

Table 11.1. General Wavelength Ranges for Lowest Energy-Absorption Band of Some Classes of Photochemical Substrates

Substrates	Absorption maxima (nm)
Simple alkenes	190–200
Acyclic dienes	220–250
Cyclic dienes	250–270
Styrenes	270–300
Saturated ketones	270–280
α,β-Unsaturated ketones	310–330
Aromatic ketones and aldehydes	280–300
Aromatic compounds	250–280

which transmits down to 2000 Å, must be used if the 254-nm radiation is required. Other materials have cutoff points between those of quartz and Pyrex. Filter solutions that absorb in specific wavelength ranges can also be used to control the wavelength of light reaching the sample.[1]

When a quantum of light is absorbed, the molecule is promoted to an excited electronic state. Two general points about this process should be emphasized:

1) At the instant of excitation, only electrons are reorganized; the heavier nuclei retain their ground state geometry. The statement of this condition is referred to as the *Franck–Condon principle.*
2) The electrons do not undergo spin inversion at the instant of excitation. Inversion is forbidden by quantum mechanical selection rules, which require that the absorption process not involve a change in the spin of an electron.

Thus, in the very short time (10^{-15} sec) required for excitation, the molecule does not undergo changes in nuclear position or a spin change of the promoted electron. After the excitation, however, these changes can occur very rapidly. A new minimum-energy molecular geometry is associated with the excited-state structure, and this geometry is rapidly achieved by vibrational processes. The excited-state molecules come to thermal equilibrium with the solvent. Sometimes, chemical reactions of the excited molecule are fast relative to this vibrational relaxation, but this circumstance is rare in solution. When reaction proceeds faster than vibrational relaxation, the reaction is said to involve a "hot excited state," i.e., one with excess vibrational energy.

The excited state can also undergo *intersystem crossing*, that is, one of the electrons in a half-filled orbital can undergo spin inversion, giving a *triplet* in which

1. Detailed information on the emission characteristics of lamps and the transmission properties of glasses and filter solutions can be found in A. J. Gordon and R. A. Ford, *The Chemists' Companion*, Wiley–Interscience, New York, 1972, pp. 348–368, or in S. L. Murov, *Handbook of Photochemistry*, Marcel Dekker, New York, 1973.

the unpaired electrons both have the same spin. The triplet state will adopt a new minimum-energy molecular geometry.

The general situation can be represented for a hypothetical molecule using a potential energy diagram. The designations S and T are used for singlet and triplet states, respectively. The excitation is a "vertical transition," that is, it involves no distortion of the molecular geometry. Horizontal displacement on the diagram corresponds to motion of the atoms relative to one another. Since the potential energy curves are displaced from one another, the species formed after energy absorption are excited both electronically and vibrationally. The same is true for the triplet state formed by intersystem crossing. Vibrational relaxation converts the excited state, either singlet or triplet, to the lowest vibrational state. One of the central issues in the description of any photochemical reaction is the question of whether the singlet or triplet excited state is involved. Which state is involved depends on the relative rate of intersystem crossing versus chemical reaction of the excited singlet state. If intersystem crossing is fast relative to photochemical reaction, the triplet state will be reached. If it is not, the reaction will occur via the singlet state.

Photosensitization is an important alternative to direct excitation of molecules, and it usually results in reactions via triplet excited states. If a reaction is to be carried out by photosensitization, a substance, the *sensitizer*, is present in the system, in addition to the desired reactant(s). This substance is chosen to meet the following criteria:

1) It must be excited by the irradiation to be used.
2) It should be present in sufficient concentration and absorb more strongly than the reactant molecule under the conditions of the experiment.
3) It should be capable of exciting the reactant molecule by transfer of energy.

The most usual case and the one that will be emphasized here is triplet sensitization. In this case, the intersystem crossing of the sensitizer must be faster than energy transfer to the reactant.

The transfer of energy must proceed with net conservation of spin. In the usual cases, the acceptor molecule is a ground state singlet, and its reaction with the triplet state of the sensitizer will produce the triplet state of the acceptor. The mechanism for triplet photosensitization is outlined below:

$\text{Sens} \longrightarrow {}^1\text{Sens}^*$	Sensitizer singlet formed
${}^1\text{Sens}^* \longrightarrow {}^3\text{Sens}^*$	Intersystem crossing of sensitizer
${}^3\text{Sens}^* + \text{React} \longrightarrow \text{Sens} + {}^3\text{React}^*$	Energy transfer to reactant molecule

A corollary of requirement 3 is that the triplet excited state of the sensitizer be of the same energy or of higher energy than that of the reactant. If this condition is not met, step 3 of the mechanism above becomes endothermic and loses out in competition with other means for deactivation of ${}^3\text{Sens}^*$.

Once the excited state of the reactant has been formed, either by direct or sensitized energy transfer, the stage is set for a photochemical reaction. There are

still, however, competitive processes that can occur and result in the return of unreacted starting material. The excited state can decay to the ground state by emission of light, a *radiative transition*. The rate of emission is very high ($k = 10^5$–10^9 sec^{-1}) for radiative transitions between electronic states of the same multiplicity, and somewhat lower ($k = 10^3$–10^5 sec^{-1}) between states of different multiplicity. The two processes are known as *fluorescence* and *phosphorescence*, respectively. Once energy has been emitted as light, the reactant is no longer excited, of course, and a photochemical reaction will not occur.

Excited states can also be *quenched*. Quenching is essentially the same physical process as sensitization, but the word "quenched" is applied when a photoexcited state of the reactant is deactivated by transferring its energy to another molecule in solution. This substance is called a *quencher*.

Finally, *nonradiative decay* can occur. This name is given to the process by which the energy of the excited state is transferred to the surrounding molecules as vibrational (thermal) energy without light emission.

The kinds of processes that can occur after photochemical excitation are summarized in Fig. 11.1.

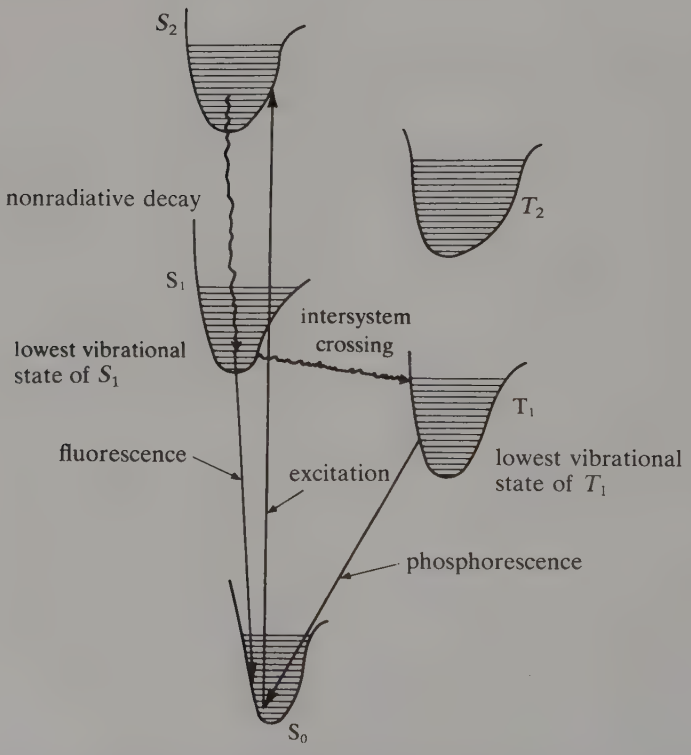


Fig. 11.1. Energy level diagram and summary of photochemical processes.

Because of the existence of these competing processes, not every molecule that is excited undergoes a photochemical reaction. The fraction of molecules that react, relative to those that are excited, is called the *quantum yield*. This yield is a simple measure of the efficiency of the absorbtion of light in producing reaction product. A quantum yield of 1 means that each molecule excited (which equals the number of quanta of light absorbed) goes to product. If the quantum yield is 0.01, then only one one-hundredth of the molecules that are excited undergo photochemical reaction. This yield can vary widely, depending on the structure of the reactants and the reaction conditions. Quantum yields larger than 1 are encountered when a mechanism exists by which one photoexcitation can produce more than one molecule of product. Quantum yields, for example, can be very large in chain reactions, in which a single photoexcitation initiates a repeating series of reactions leading to many molecules of product per initiation step.

Because photochemical processes are very fast, special techniques are required to obtain rate measurements of photochemical reactions. One method is flash photolysis. The irradiation is effected by a short pulse of light in an apparatus designed for exceedingly rapid monitoring of spectroscopic changes. The spectral changes are recorded electronically or photographically, and rate constants can be derived from these data. Another useful technique for measuring the rates of certain reactions involves measuring the quantum yield as a function of quencher concentration. A plot of the inverse of the quantum yield versus quencher concentration is then made (*Stern–Volmer plot*). Since the quantum yield indicates the fraction of excited molecules that go on to product, it is a function of the rates of the processes that result in other fates for the excited molecule. These processes are described by the rate constants k_q (quenching) and k_n (other nonproductive decay to ground state):

$$\Phi = \frac{k_r}{k_r + k_q[Q] + k_n}$$

A plot of $1/\Phi$ versus $[Q]$ then gives a line with the slope k_q/k_r. It is usually possible to assume that quenching is diffusion controlled, permitting assignment of a value to k_q. The rate of photoreaction, k_r, for the excited intermediate can then be calculated.

In this chapter, the discussion will center on the reactions of excited states, rather than on the other routes available to them for dissipation of their excess energy. The chemical reactions of photoexcited molecules are of interest primarily for three reasons:

1) Excited states have a great deal of energy, and can therefore undergo reactions that would be highly endothermic if initiated from the ground state.
2) The population of an antibonding orbital in the excited state allows the occurrence of chemical transformations that are electronically not available to ground state species.
3) Either the singlet or the triplet state may be involved in a photochemical reaction, while only singlet species are involved in most thermal processes. This permits the formation of intermediates that are unavailable under conditions of thermal activation.

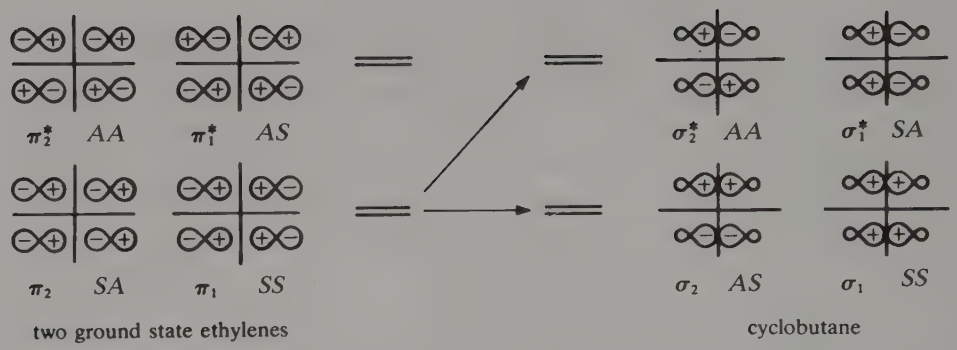


Fig. 11.2. Orbital correlation diagram for two ground state ethylenes and cyclobutane. The symmetry designations apply, respectively, to the horizontal and vertical planes for two ethylene molecules approaching one another in parallel planes.

11.2. Orbital Symmetry Considerations Related to Photochemical Reactions

The complementary relationship between thermal and photochemical reactions can be illustrated by considering some of the same reaction types discussed in the preceding chapter and examining the application of orbital symmetry considerations to the photochemical mode of reaction.

The case of 2 + 2 cycloaddition of two alkene units can serve as an example. This reaction was classified as a forbidden thermal reaction on the basis of an orbital correlation diagram (Fig. 11.2) that showed that the ground state molecules would lead to an excited cyclobutane, and would therefore involve a prohibitive energy requirement.

How does the situation change when a photochemical reaction involving one ground state alkene and one excited alkene is to be considered? We can assume the

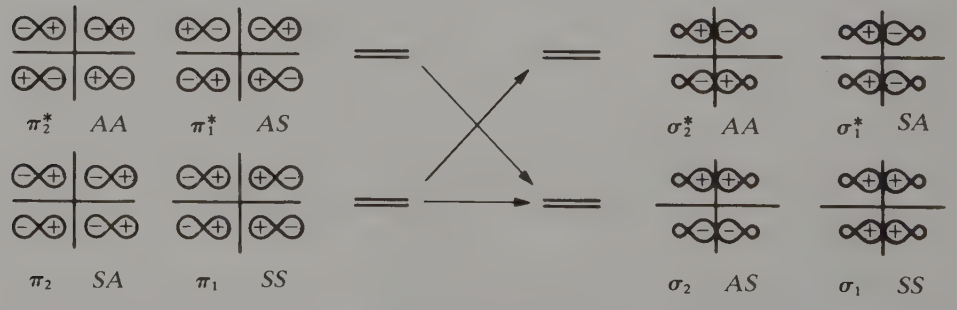
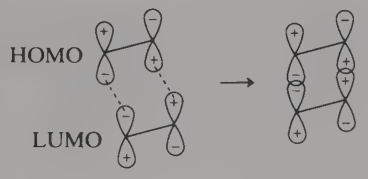


Fig. 11.3. Orbital correlation diagrams for one ground-state alkene and one excited alkene. The symmetry designations apply, respectively, to the horizontal and vertical planes for two ethylene molecules approaching one another in parallel planes.

same symmetrical approach as in the thermal reaction, so the same array of orbitals is involved. The occupation of the orbitals is different however; the π_1, (*SS*) orbital is doubly occupied, but π_2 (*SA*) and π_1^* (*AS*) are singly occupied. The reaction is therefore allowed. Although the correlation diagram illustrated in Fig. 11.3 might suggest that the product would initially be formed in an excited state, this is not necessarily the case. The concerted process can involve a transformation of the reactant excited state to ground state product. This transformation will be discussed shortly.

Consideration of the HOMO–LUMO interactions also indicates that the 2+2 additions would be allowed photochemically. The HOMO in this case is the excited alkene π^* orbital. The LUMO is the π^* of the ground state alkene, and a bonding interaction is present between the carbons where new bonds must be formed:



A striking illustration of the relationship between orbital symmetry considerations and the outcome of photochemical reactions can be found in the stereochemistry of electrocyclic reactions. In Chapter 10, the distinction between the conrotatory and disrotatory modes of reaction as a function of the number of electrons in the system was described. Orbital symmetry considerations predict, and it has been verified experimentally, that photochemical electrocyclic reactions show a reversal of stereochemistry[2]:

Number of π-electrons	Thermal	Photochemical
2	disrotatory	conrotatory
4	conrotatory	disrotatory
6	disrotatory	conrotatory
8	conrotatory	disrotatory

The most fundamental way of making this prediction is to construct an electronic energy state diagram for the reactant and product molecule and observe the correlation between the states.[3] Those reactions will be permitted in which the reacting state correlates with a state of the product that is not appreciably higher in energy.[4]

2. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965).
3. H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.* **87**, 2045 (1965).
4. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.

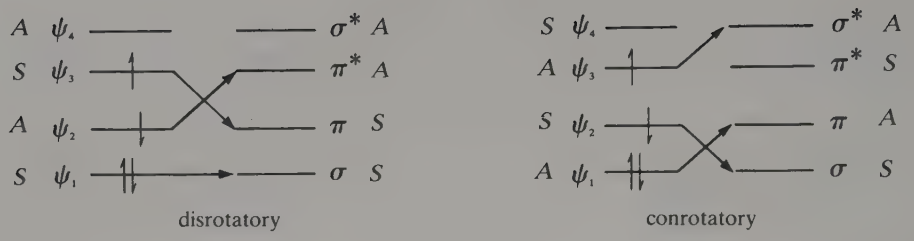
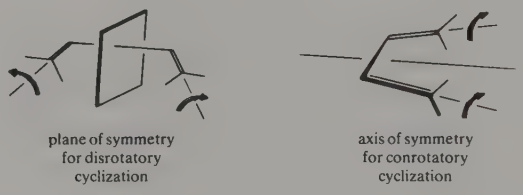
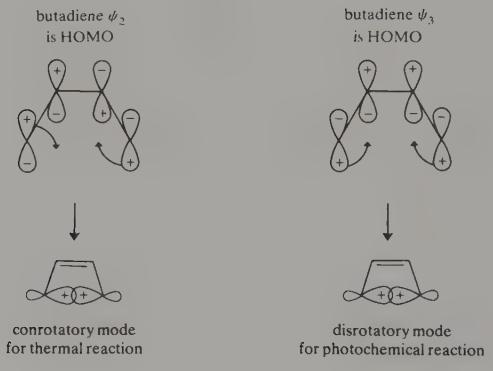


Fig. 11.4. Correlation of energy states involved in the photochemical butadiene-to-cyclobutene conversion.

The states involved in the photochemical butadiene-to-cyclobutene conversion are ψ_1, ψ_2, and ψ_3 of the first excited state of butadiene, and σ, π, and π^* for the lowest excited state of cyclobutene. The correlation diagram for this reaction is shown in Fig. 11.4. The appropriate elements of symmetry are the plane of symmetry and the axis of symmetry corresponding to conrotatory and disrotatory rotation:



This analysis shows that disrotatory cyclization is allowed, while conrotation would lead to a highly excited σ^1, π^2, σ^{*1} configuration of cyclobutene. The same conclusion is reached if it is assumed that the frontier orbital will govern reaction stereochemistry[2]:



2. See p. 589.

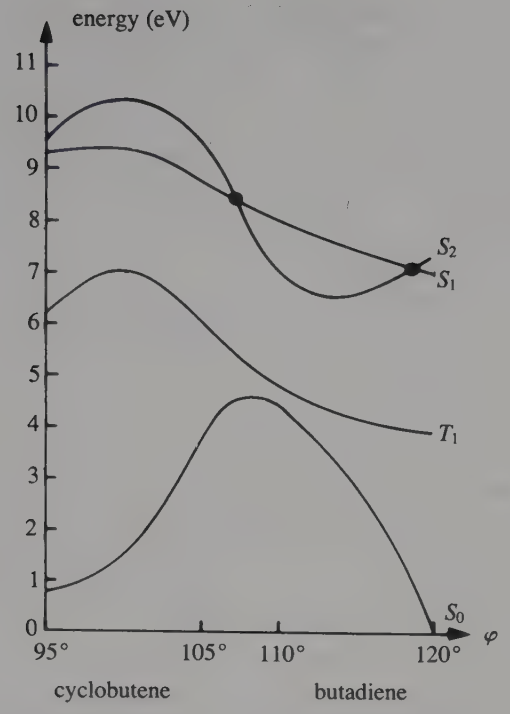


Fig. 11.5. Energy diagram showing potential energy curves for interconversion of ground (S_0), first and second singlet (S_1 and S_2), and first triplet (T_1) excited states. The angle φ is the C–C–C bond angle at C-2 and C-3. [From D. Grimbert, G. Segal, and A. Devaquet, *J. Am. Chem. Soc.* **97**, 6629 (1975).]

In fact, it is a general result that the Woodward–Hoffmann rules predict that photochemical reactions will be precisely complementary to thermal reactions: What is allowed photochemically is forbidden thermally, and vice versa. The physical basis for this complementary relationship is that the high barrier associated with forbidden thermal reactions provides a point for strong interaction of the ground state and excited-state species, and this interaction is necessary for efficient photochemical reaction.[5,6] An energy diagram illustrating this relationship is shown in Fig. 11.5.

This diagram, which is based on quantum chemical calculations of the butadiene and cyclobutene molecules in the geometries traversed during interconversion, shows a minimum in the S_2 excited state.[7] It also shows that with a small activation energy (this is calculated to be about 5 kcal/mol), the molecules in the S_1 state can

5. W. Th. A. M. van der Lugt and L. J. Oosterhoff, *Chem. Commun.*, 1235 (1968); *J. Am. Chem. Soc.* **91**, 6042 (1969).
6. R. C. Dougherty, *J. Am. Chem. Soc.* **93**, 7187 (1971); J. Michl, *Top. Current Chem.*, **46**, 1 (1974); J. Michl, *Photochem. Photobiol.* **25**, 141 (1977).
7. D. Grimbert, G. Segal, and A. Devaquet, *J. Am. Chem. Soc.* **97**, 6629 (1975).

reach points where the S_1 and S_2 energy surfaces cross. The excited molecules, whether generated from cyclobutene or butadiene, would be expected to follow the S_2 surface to the minimum located above the S_0 transition state. By loss of energy to the surrounding medium the excited-state molecules will drop to the S_0 surface and then be transformed to butadiene or cyclobutene. This diagram also provides an explanation of how the excited state shown in Fig. 11.4, which has one singly occupied antisymmetric orbital, returns to ground state cyclobutene, in which only symmetric orbitals are occupied. The S_2 state has the same symmetry as the ground state and can therefore decay directly to the ground state.

Mention should be made of several pitfalls that can render the mechanistic interpretation of photochemical reactions subject to some uncertainties:

1) *What is the geometry of the excited state*? In contrast to the well-defined information about ground state geometries for most organic molecules, the case of excited-state geometries is much less certain. Incorrect assumptions about the molecular geometry may lead to an erroneous basis for assignment of elements of molecular symmetry and orbital symmetry.
2) *Is the reaction concerted*? As was emphasized in the preceding chapter, orbital symmetry considerations apply only to concerted reactions. The possible involvement of triplet excited states and, as a result, a nonconcerted process is much more common in photochemical reactions than in thermal processes. A concerted mechanism must be established before the orbital symmetry rules can be applied.

Scheme 11.1 lists some examples of cycloaddition reactions and electrocyclic processes of the type that are allowed on the basis of orbital symmetry considerations.

11.3. Photochemistry of Carbonyl Groups

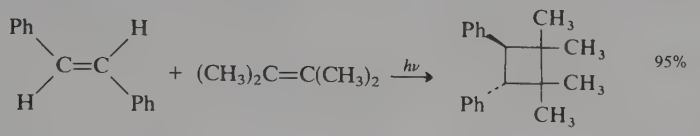
The photochemistry of carbonyl compounds has been extensively studied both in solution and in the gas phase. It is not surprising that there are major differences between the two phases. In the gas phase, the energy transferred by excitation cannot be lost rapidly by collisions, whereas in the liquid phase the energy is rapidly transferred to the solvent or to other components of the solutions. Solution photochemistry will be emphasized here, since most organic chemists interested in either mechanistic studies or preparative photochemistry have studied this aspect of the problem.

The reactive excited state of saturated ketones is the $n-\pi^*$ state. On excitation, an electron from the oxygen nonbonding orbital is transferred to the π-antibonding orbital of the carbonyl group. The singlet is initially formed, but intersystem crossing to the triplet can occur. For saturated ketones, the singlet lies about 80–85 kcal/mol above the ground state. The triplet state is about 75–80 kcal/mol above the ground state. The first excited singlet, S_1, and triplet, T_1, can be described structurally from

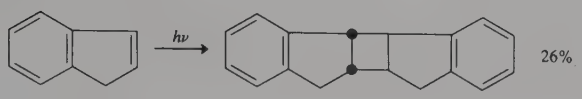
Scheme 11.1. Some Examples of Photochemical Cycloaddition and Electrocyclic Reactions

Cycloaddition reactions

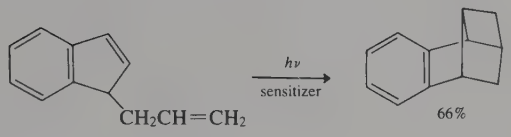
1[a]



2[b]

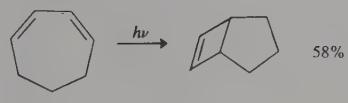


3[c]

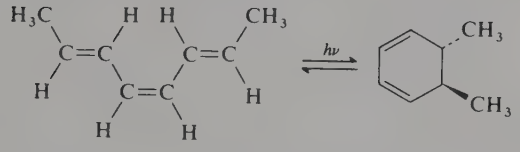


Electrocyclic reactions

4[d]



5[e]



a. O. L. Chapman and W. R. Adams, *J. Am. Chem. Soc.* **90**, 2333 (1968).
b. A. G. Anastassiou, F. L. Setliff, and G. W. Griffin, *J. Org. Chem.* **31**, 2705 (1966).
c. A. Padwa, S. Goldstein, and M. Pulwer, *J. Org. Chem.* **47**, 3893 (1982).
d. O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.* **84**, 1220 (1962).
e. G. J. Fonken, *Tetrahedron Lett.*, 549 (1962).

spectroscopic data in the case of formaldehyde. In both excited states, the molecule is pyramidal, the C–O bond is stretched, and, relative to the ground state, the dipole moment is reduced from 2.34 D to 1.56 D.[8] The reduction in dipole moment corresponds to transfer of electron density from an orbital that is localized on oxygen to one that also encompasses the carbon atom.

An alternative excited state available to carbonyl compounds involves promotion of a bonding π electron to the antibonding π^* orbital. This is called a π–π^*

8. J. C. D. Brand and D. G. Williamson, *Adv. Phys. Org. Chem.* **1**, 365 (1963); D. E. Freeman and W. Klemperer, *J. Chem. Phys.* **45**, 52 (1966).

transition, and is most likely to occur when the ketone group is conjugated with an extensive π-bonding system.

It is not possible to draw unambiguous Lewis structures of excited states of the sort that are so useful for depicting ground state chemistry. Instead, it is common to asterisk the normal carbonyl structure and provide information about the multiplicity of the excited state if it is available:

$[H_2C{=}O]^*$	$^3[H_2C{=}O]^*$	$^1[H_2C{=}O]^*$
excited state, multiplicity unspecified	excited-state triplet	excited-state singlet

One of the most common reactions of photoexcited carbonyl groups is hydrogen abstraction from solvent or some other hydrogen atom donor by the oxygen of the carbonyl group. A second common reaction is cleavage of the carbon–carbon bond adjacent to the carbonyl group:

$$R_2C{=}O \xrightarrow{h\nu} [R_2C{=}O]^* \begin{cases} \xrightarrow{X\text{-}H} R_2\dot{C}{-}OH \\ \xrightarrow{or} R\dot{C}{=}O + R\cdot \end{cases}$$

The hydrogen atom abstraction can be either intramolecular or intermolecular. Many aromatic ketones undergo hydrogen abstraction from solvent or some other hydrogen donor, followed by coupling of the resulting α-hydroxy radicals. Such reactions go best in solvents that have easily abstractable hydrogens:

$$\underset{\underset{O^*}{\|}}{ArCR} + S{-}H \longrightarrow \underset{\underset{OH}{|}}{Ar\dot{C}R} + S\cdot$$

$$2\,\underset{\underset{OH}{|}}{Ar\dot{C}R} \longrightarrow \underset{\underset{HO}{|}}{\overset{\overset{R}{|}}{Ar}C}{-}\underset{\underset{OH}{|}}{\overset{\overset{R}{|}}{C}}Ar$$

These reactions usually occur via the triplet excited state T_1. The intersystem crossing of the initially formed singlet is so fast ($k \approx 10^{10}$ sec^{-1}) that reactions of the singlet state of aromatic ketones are usually not observed. The reaction of benzophenone has been particularly closely studied. Some of the facts that have been established which are in agreement with the general mechanism outlined above are as follows:

1) For a given hydrogen donor S–H, replacement by S–D leads to a decreased rate of reduction relative to nonproductive decay to the ground state.[9] This decreased rate indicates the existence of a primary isotope effect in the abstraction step.

9. W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.* **83**, 2789 (1961); G. S. Hammond, W. P. Baker, and W. M. Moore, *J. Am. Chem. Soc.* **83**, 2795 (1961).

2) The photoreduction can be prevented (quenched) by known triplet quenchers. The effective quenchers are those the T_1 states of which are ≤ 69 kcal/mol above S_0. Quenchers with higher triplet energies are ineffective because the benzophenone $\pi-\pi^*$ triplet is then not sufficiently energetic to transfer energy.
3) The intermediate diphenylhydroxymethyl radical has been detected after generation by flash photolysis.[10] Photolysis of benzophenone in benzene solution containing hydrogen donors results in the formation of two intermediates that are detectable, and their rates of decay have been measured. One intermediate is the $Ph_2\dot{C}OH$ radical. It disappears by combination with another radical in a second-order process. A much shorter-lived species disappears with first-order kinetics in the presence of excess amounts of various hydrogen atom donors. The pseudo-first-order rate constants vary with the structure of the donor; for 2,2-diphenylethanol, for example, $k = 2 \times 10^6\ \text{sec}^{-1}$. The rate is much less with poorer donors. The rapidly disappearing intermediate is the triplet excited state of benzophenone.
4) In 2-propanol, the quantum yield for photolytic conversion of benzophenone to the coupled reduction product is 2.0,[11] the reason being that the radical remaining after abstraction of a hydrogen atom from 2-propanol transfers a hydrogen atom to ground state benzophenone in a nonphotochemical reaction. Because of this transfer, two molecules of benzophenone are reduced for each one that is photoexcited.

$$Ph_2C{=}O \xrightarrow{h\nu} [Ph_2C{=}O]^*$$

$$[Ph_2C{=}O]^* + (CH_3)_2CHOH \longrightarrow Ph_2\dot{C}OH + (CH_3)_2\dot{C}OH$$

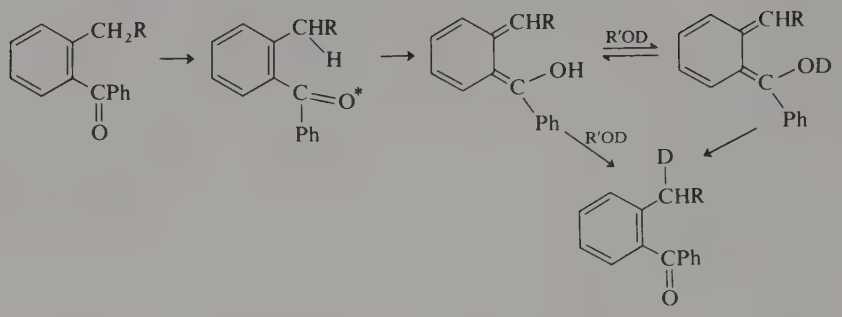
$$(CH_3)_2\dot{C}OH + Ph_2C{=}O \longrightarrow Ph_2\dot{C}OH + (CH_3)_2C{=}O$$

$$2\,Ph_2\dot{C}OH \longrightarrow Ph_2C(OH)-C(OH)Ph_2$$

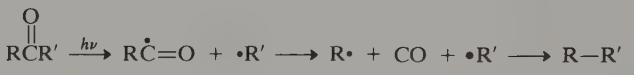
The efficiency of reduction of benzophenones is greatly reduced when an *ortho* alkyl substituent is present because a new photoreaction, intramolecular hydrogen abstraction, becomes the dominant process. The abstraction takes place from the benzylic position on the adjacent alkyl chain, giving an unstable enol that can revert to the original benzophenone without photoreduction. This process is known as *photoenolization.*[12] It can be detected, even though no net reaction occurs, by photolysis in deuterated hydroxylic solvents. The proton of the enolic hydroxyl is rapidly exchanged with solvent molecules, so when a deuterated solvent is used, deuterium is introduced at the benzylic position. Deuterium is also introduced if the

10. J. A. Bell and H. Linschitz, *J. Am. Chem. Soc.* **85**, 528 (1963).
11. N. J. Turro, *Molecular Photochemistry*, W. A. Benjamin, New York, 1965, pp. 143, 144.
12. P. G. Sammes, *Tetrahedron*, **32**, 405 (1976).

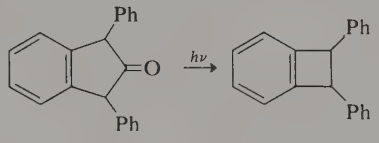
enol is protonated at the benzyl carbon by solvent:



The dominant photochemical reaction of ketones in the gas phase is cleavage of one of the carbonyl substituents, which is followed by decarbonylation and subsequent reactions of the alkyl free radicals that result. This reaction is frequently

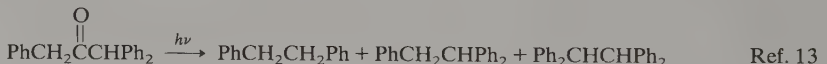


referred to as the *type-I* reaction of carbonyl compounds. This type of reactivity is not so common in solution, although some cyclic ketones do undergo decarbonylation:

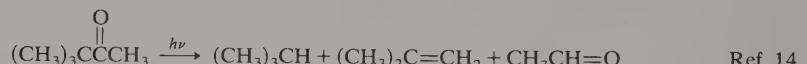


Ref. 13

The facility with which this reaction occurs in solution depends on the stability of the radical fragments that can be ejected. Dibenzyl ketone, for example, is readily cleaved photolytically.[13] Similarly, *t*-butyl ketones undergo α-cleavage quite readily on photolysis in solution.[14]



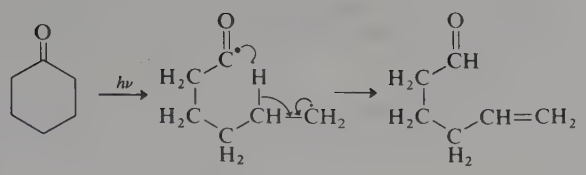
Ref. 13



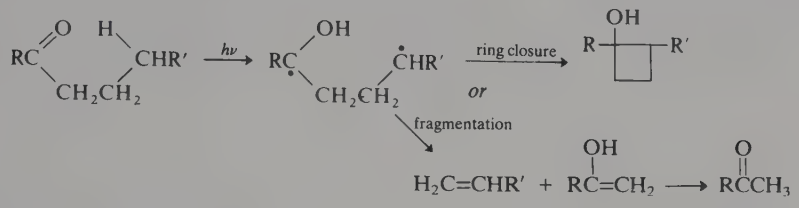
Ref. 14

With cyclic ketones, the α cleavage can also be followed by an intramolecular hydrogen atom abstraction that leads eventually to an unsaturated ring-opened aldehyde[15]:

13. G. Quinkert, K. Opitz, W. W. Wiersdorff, and J. Weinlich, *Tetrahedron Lett.*, 1863 (1963).
14. N. C. Yang and E. D. Feit, *J. Am. Chem. Soc.* **90**, 504 (1968).
15. W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.* **93**, 3947 (1971); P. J. Wagner and R. W. Spoerke, *J. Am. Chem. Soc.* **91**, 4437 (1969).

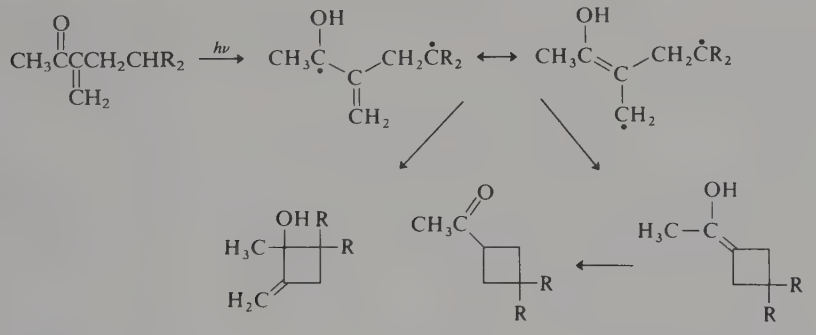


In ketones having a propyl or larger alkyl group as a carbonyl substituent, intramolecular hydrogen atom abstraction can be followed either by cleavage or by formation of a cyclobutanol:



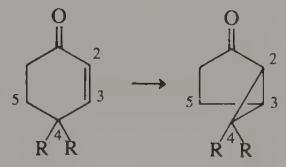
Cleavage between C_α and C_β is often referred to as *type-II* photoelimination to distinguish it from reactions involving rupture of the bond between the carbonyl carbon and C_α.[16] Type-II photoelimination is observed for both aromatic and aliphatic ketones. Studies aimed at establishing the identity of the reactive excited state indicate that both S_1 and T_1 are involved for aliphatic ketones, but when one of the carbonyl substituents is aryl, intersystem crossing is very fast, and T_1 is the reactive state. Usually, cleavage is the dominant reaction, with the cyclobutanol yields being below 20%, but there are exceptions. The 1,4-diradical intermediate generated by intramolecular hydrogen abstraction is very short-lived, probably not more than 10^{-7}–10^{-9} sec.

Intramolecular hydrogen abstraction is also the dominant process for acyclic α,β-unsaturated ketones.[17] The intermediate diradical then cyclizes, giving the enol of a cyclobutyl ketone. Among the by-products of such photolyses are cyclobutanols resulting from alternative modes of cyclization of the diradical intermediate:

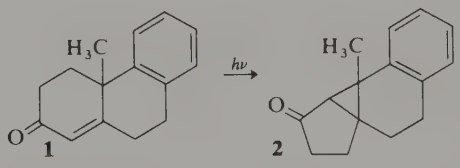


16. P. J. Wagner, *Acc. Chem. Res.* **4**, 168 (1971).
17. R. A. Cormier, W. L. Schreiber, and W. C. Agosta, *J. Am. Chem. Soc.* **95**, 4873 (1973); R. A. Cormier and W. C. Agosta, *J. Am. Chem. Soc.* **96**, 618 (1974).

4,4-Dialkylcyclohexenones undergo a photochemical rearrangement which involves a formal shift of the C-4–C-5 bond to C-3 and formation of a new bond between C-2 and C-4[18]:

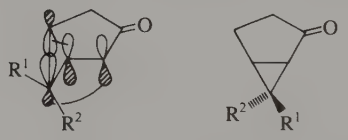


This reaction is quite general and also proceeds in the case of 4-alkyl-4-arylcyclohexenones:

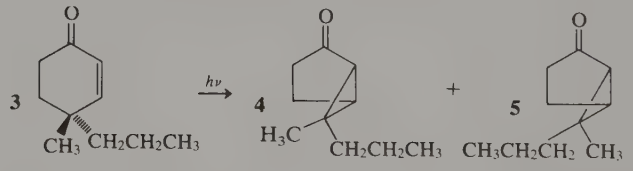


Ref. 19

The reaction is stereospecific and can be described as a $[\pi 2_a + \sigma 2_a]$ cycloaddition. This mechanism requires that inversion of configuration occur at C-4 as the new σ bond is formed at the back lobe of the reacting C-4–C-5 σ bond:



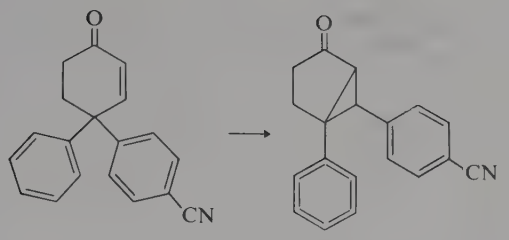
It has been demonstrated in several systems that the reaction is in fact stereospecific with the expected inversion occurring at C-4. The ketone **3** provides a specific example. The stereoisomeric products **4** and **5** are both formed but in each product inversion has occurred at C-4.



Ref. 20

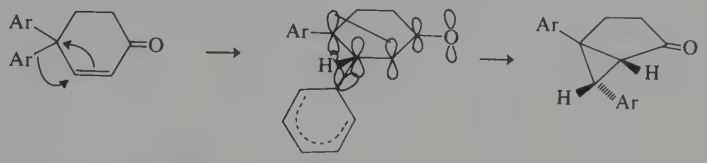
With 4,4-diarylcyclohexenones, the reaction takes a slightly different course involving aryl migration. In compounds in which the two aryl groups are substituted differently, it is found that the substituents which stabilize radical character favor rearrangement. Thus the *p*-cyanophenyl substituent migrates in preference to the

18. For a review, see D. I. Schuster in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo (ed.), Academic Press, New York, 1980, Chap. 17.
19. O. L. Chapman, J. B. Sieja, and W. J. Welstead, Jr., *J. Am. Chem. Soc.* **88**, 161 (1966).
20. D. I. Schuster and J. M. Rao, *J. Org. Chem.* **46**, 1515 (1981); D. I. Schuster, R. H. Brown, and B. M. Resnick, *J. Am. Chem. Soc.* **100**, 4504 (1978).

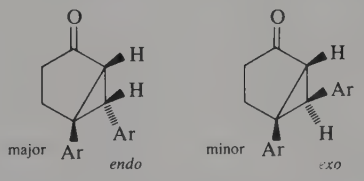


Ref. 21

phenyl substituent in **6**. This rearrangement can be considered to occur via a transition state in which 2–4 bridging is accompanied by a 4 → 3 aryl migration[22]:

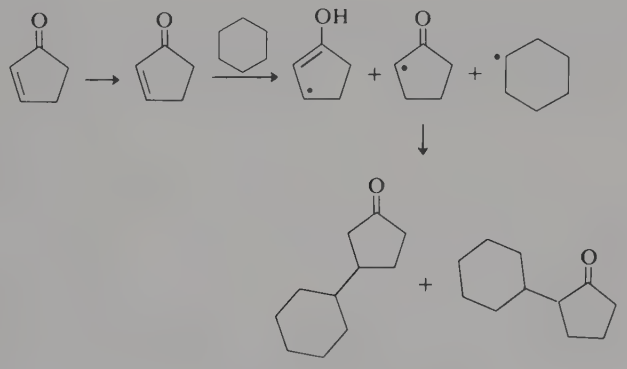


In contrast to the rearrangement described for 4,4-dialkylcyclohexenones, this reaction is not entirely stereospecific and a minor stereoisomer is obtained:



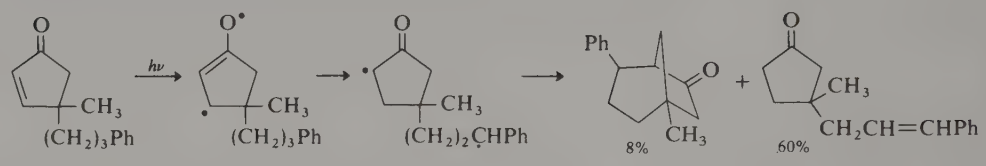
This suggests the existence of a competitive reaction pathway which is not concerted. Note that the *endo* product is predicted by the concerted mechanism. It is the major product although it is sterically more congested than the *exo* isomer.

With other ring sizes the photochemistry of unsaturated cyclic ketones takes different courses. For cyclopentenones the principal products result from hydrogen abstraction processes. Irradiation of cyclopentenone in cyclohexane gives a mixture of 2- and 3-cyclohexylcyclopentanone.[23] These products can be formed by intermolecular hydrogen abstraction, followed by recombination of the product radicals:



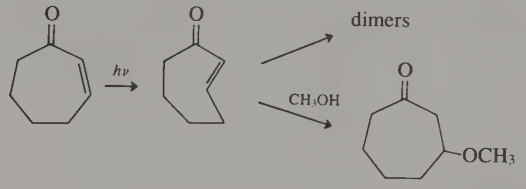
21. H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *J. Am. Chem. Soc.* **89**, 2033 (1967).
22. H. E. Zimmerman, *Tetrahedron*, **30**, 1617 (1974).
23. S. Wolff, W. L. Schreiber, A. B. Smith, III, and W. C. Agosta, *J. Am. Chem. Soc.* **94**, 7797 (1972).

If a substituent chain is present on the cyclopentenone ring, an intramolecular hydrogen abstraction can take place:

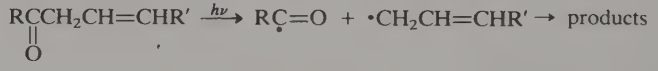


The bicyclic product is formed by coupling of the two radical sites, while the alkene results from a second intramolecular hydrogen abstraction. These reactions can be sensitized by aromatic ketones and quenched by typical triplet quenchers, and are therefore believed to proceed via triplet excited states.

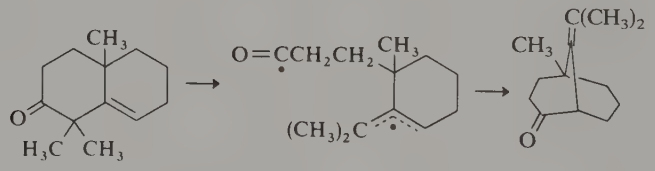
In the case of cycloheptenone and larger rings, the main initial photoproducts are the *trans*-cycloalkenones produced by photoisomerization. In the case of the seven- and eight-membered rings, the *trans* double bonds are sufficiently strained that rapid reactions follow. In nonnucleophilic solvents dimerization occurs, whereas in nucleophilic solvents addition occurs[24]:



Ketones in which the double bond is located in the β,γ positions are likely candidates for α cleavage because of the stability of the allyl radical that is formed. This is an important process on direct irradiation. Products then arise by recombination of the radicals or by recombination after decarbonylation:

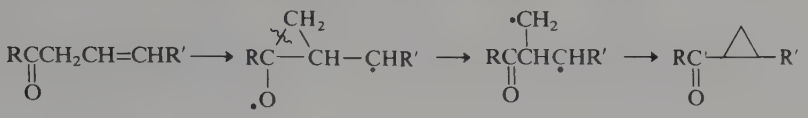


In cyclic ketones, the diradical intermediates usually recombine, leading to isomerized ketones[25]:

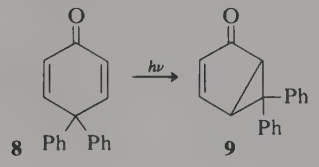


24. H. Hart, B. Chen, and M. Jeffares, *J. Org. Chem.* **44**, 2722 (1979).
25. H. Sato, N. Furutachi, and K. Nakanishi, *J. Am. Chem. Soc.* **94**, 2150 (1972); L. A. Paquette, R. F. Eizember, and O. Cox, *J. Am. Chem. Soc.* **90**, 5153 (1968).

Excitation of acyclic β,γ-unsaturated ketones can give cyclopropyl ketones[26]:

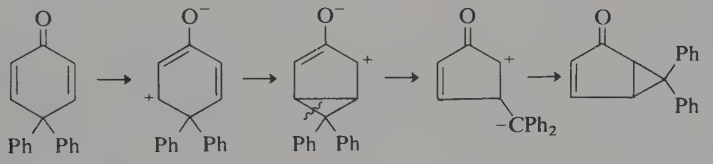


Another class of carbonyl compounds that has received much attention are the cyclohexadienones.[27] The primary photolysis product of 4,4-diphenylcyclohexadienone, for example, is **9**. Quenching and photosensitization experiments on representative examples have indicated that the reaction proceeds through a triplet

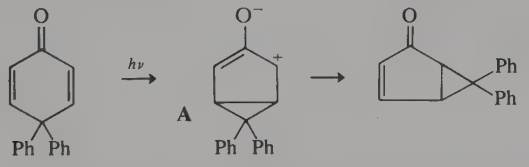


8 **9** Ref. 28

excited state. A hypothetical scheme that delineates the bonding changes is outlined below:

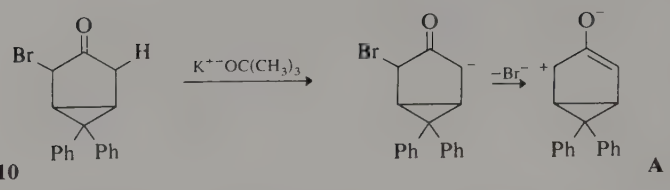


It is believed that a reactive ground state species, the zwitterion **A**, is the initial photoproduct and that it rearranges to the observed product.[29]



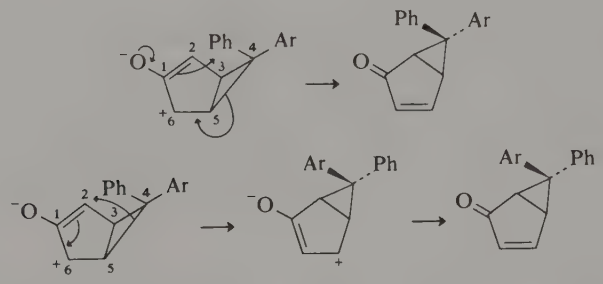
To test this mechanism, a synthesis of species **A** by nonphotochemical means was undertaken.[30] α-Haloketones, when treated with strong base, ionize to such dipolar intermediates. Thus, the bromoketone **10** is a possible precursor of **A**.

26. W. G. Dauben, M. S. Kellogg, J. I. Seeman, and W. A. Spitzer, *J. Am. Chem. Soc.* **92**, 1786 (1970).
27. H. E. Zimmerman, *Angew. Chem. Int. Ed. Engl.* **8**, 1 (1969). K. Schaffner and M. Demuth, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo (ed.), Academic Press, New York, 1980, Chap. 18; D. I. Schuster, *Acc. Chem. Res.* **11**, 65 (1978).
28. H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.* **83**, 4486 (1961).
29. H. E. Zimmerman and J. S. Swenton, *J. Am. Chem. Soc.* **89**, 906 (1967).
30. H. E. Zimmerman, D. Döpp, and P. S. Huyffer, *J. Am. Chem. Soc.* **88**, 5352 (1966).

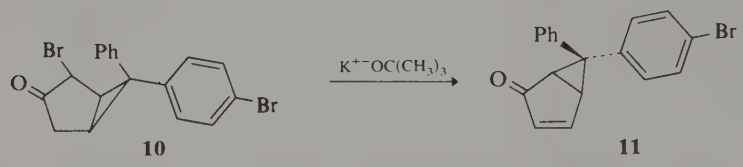


10 **A**

The zwitterion prepared by the nonphotochemical route did lead to **9**, as required if it is an intermediate in the photochemical reaction. Further study of this process established another aspect of the reaction mechanism. The product could be formed by a process involving inversion at C(4) or by one involving a pivot about the bond C(3)–C(4):



The two mechanisms require the formation of stereochemically different products when the aryl groups at C(4) are different. When the experiment was carried out on **10** only the product corresponding to that formed by inversion of configuration at C(4) was observed[31]:

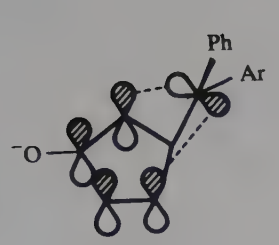


10 **11**

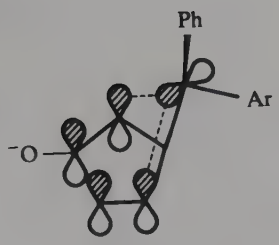
The rearrangement step is a ground state thermal process, and may be classified as a [1,4]-sigmatropic shift of carbon across the face of a 2-oxybutenyl cation. The Woodward–Hoffmann rules require a sigmatropic shift in this system to proceed with inversion of configuration. The symmetry properties for 1,4 shifts with inversion and retention are shown in Fig. 11.6.

As is clear from the preceding examples, there are a variety of overall reactions that can be initiated by photolysis of ketones. The course of photochemical reactions of ketones is very dependent on the structure of the reactant. We have been able to discuss only some of the best-studied reactions. Many other examples can be found in the literature. This variation in reaction path with reactant structure may make photochemical reactions seem somewhat more complex and capricious than ground

31. H. E. Zimmerman and D. S. Crumrine, *J. Am. Chem. Soc.* **90**, 5612 (1968).



1,4 shift with inversion
allowed
4 electrons
Möbius system



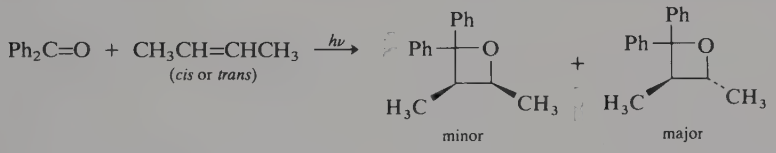
1,4 shift with retention
forbidden
4 electrons
Hückel system

Fig. 11.6. Symmetry properties for 1,4-sigmatropic shifts with inversion and retention.

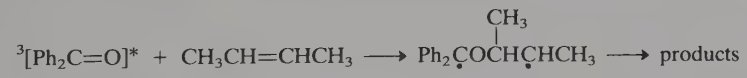
state reactions. The real problem is that structure-reactivity relationships in excited states are not so well established as in ground-state chemistry. Continued study of photochemical reactions will no doubt lead to a general understanding of structure–reactivity effects in excited states.

Despite the variety of overall processes that can be carried out photochemically, the number of individual types of steps involved is limited. For ketones, the most important are inter- and intramolecular hydrogen abstraction, cleavage α to the carbonyl group, and substituent migration to the β-carbon atom of α,β-unsaturated ketones. Reexamination of the mechanisms illustrated in this section will reveal that most of the reactions of carbonyl compounds that have been described involve combinations of these fundamental processes. The final products usually result by rebonding of the reactive intermediates generated by these steps.

Some ketones undergo cycloaddition reactions with alkenes to form oxetanes:



The reaction is ordinarily stereoselective, favoring the more stable adduct, and a long-lived triplet diradical intermediate is implicated[32]:



This diradical is believed to be preceded on the reaction path by a complex of the alkene with excited-triplet benzophenone. This reaction, particularly its stereochemistry and regioselectivity, will be considered in more detail in Part B, Chapter 7.

32. R. A. Caldwell, G. W. Sovocool, and R. P. Gajewski, *J. Am. Chem. Soc.* **95**, 2549 (1973).

11.4. Photochemistry of Alkenes and Dienes

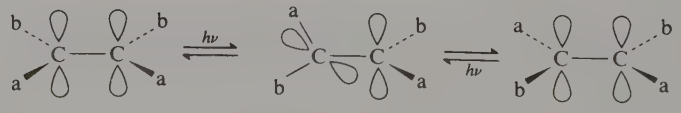
The photochemistry of alkenes and dienes has already been examined in part, since these compounds are particularly illustrative of the principles of orbital symmetry control in electrocyclic processes. The orbital symmetry rules for cycloadditions and electrocyclic processes were covered in Section 11.2. Cycloadditions are also considered, from a synthetic viewpoint, in Part B, Chapter 7, Section 7.2. This section will emphasize unimolecular photoreactions of alkenes and dienes.

A classic reaction in olefin photochemistry is the photochemical interconversion of *cis* and *trans* isomers. Usually, the *trans* isomer of a disubstituted olefin is the more thermodynamically stable form. A photochemical steady state is established on irradiation that is usually richer in the *cis* isomer than is the ground state equilibrium mixture. As a result, irradiation provides a means of converting *trans* alkenes to the *cis* isomers.

The composition of the photostationary state depends on the absorption spectra of the two olefins. Take the hypothetical case in Fig. 11.7. Assume that the vertical line at 265 nm is the lower-wavelength limit of the light impinging on the system. This wavelength can be controlled experimentally by use of appropriate filters. Because of its longer-wavelength maximum and higher extinction coefficient, the *trans* isomer will be absorbing most of the light. If monochromatic light were being used, the amount absorbed by the two isomers would be proportional to their extinction coefficients at that wavelength. Assuming that the quantum yield for conversion *cis* → *trans* ≈ *trans* → *cis*, the conversion of *trans* compound to *cis* will occur faster than the reverse process when the two compounds are in equal concentration. The photostationary state (the composition at which no further net conversion occurs) will occur when [*cis*] > [*trans*]. More quantitatively, for monochromatic light, the composition of the photostationary state for a *cis–trans* isomerism will be given by

$$\frac{[t]_s}{[c]_s} = \left(\frac{\varepsilon_c}{\varepsilon_t}\right)\left(\frac{\phi_{c\to t}}{\phi_{t\to c}}\right)$$

The isomerization of olefins is believed to take place via an excited state in which the two sp^2 carbons have been twisted 90° relative to the ground state. This state is referred to as the *p* (perpendicular) geometry. This twisted geometry is believed to be the minimum energy geometry for both the singlet and triplet excited states:



It is easy to see that if this twisted geometry were attained, there would be a possibility of returning to either *cis* or *trans* ground state compound.

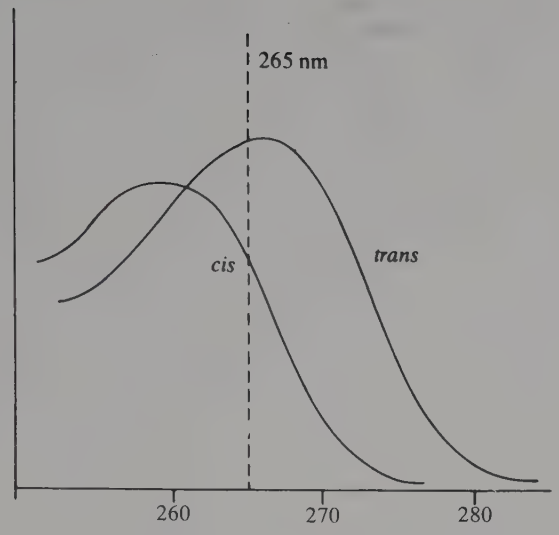


Fig. 11.7. Absorption spectra of a *cis*–*trans* isomer pair.

Especially detailed study of the mechanism of configurational isomerism has been made with *cis*- and *trans*-stilbene.[33] Spectroscopic data have established the energies of the singlet and triplet states of both *cis*- and *trans*-stilbene and of the twisted excited state that is formed from both isomers. This information is summarized in Fig. 11.8. As might be deduced from their similarity in energy, it is believed that the geometry of the species ^3t and ^3p are very similar. The state ^3c is believed to vibrationally convert rapidly to ^3p. Excited states from either the *cis*- or *trans*-stilbene can readily attain the common *p* states.

Direct irradiation leads to isomerization via singlet state intermediates.[34] The isomerization presumably involves a twisted singlet state that can be achieved from either the *cis* or the *trans* isomer. The temperature dependence of the isomerization further reveals that the process of formation of the twisted state involves a small activation energy. This energy is required for conversion of the initial excited state to the perpendicular geometry associated with the ^1S state. Among the pieces of evidence indicating that a triplet intermediate is not involved in direct irradiation experiments is the fact that azulene, which is known to intercept stilbene triplets, has only a minor effect on the efficiency of the direct photoisomerization.[35]

33. J. Saltiel, J. T. D'Agostino, E. D. Megarity, L. Metts, K. R. Neuberger, M. Wrighton, and O. C. Zafiriow, *Org. Photochem.* **3**, 1 (1973); J. Saltiel and J. L. Charlton, in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo (ed.), Academic Press, New York, 1980, Chap. 14.
34. J. Saltiel, *J. Am. Chem. Soc.* **89**, 1036 (1967); **90**, 6394 (1968).
35. J. Saltiel, E. D. Megarity, and K. G. Kneipp, *J. Am. Chem. Soc.* **88**, 2336 (1966); J. Saltiel and E. D. Megarity, *J. Am. Chem. Soc.* **91**, 1265 (1969).

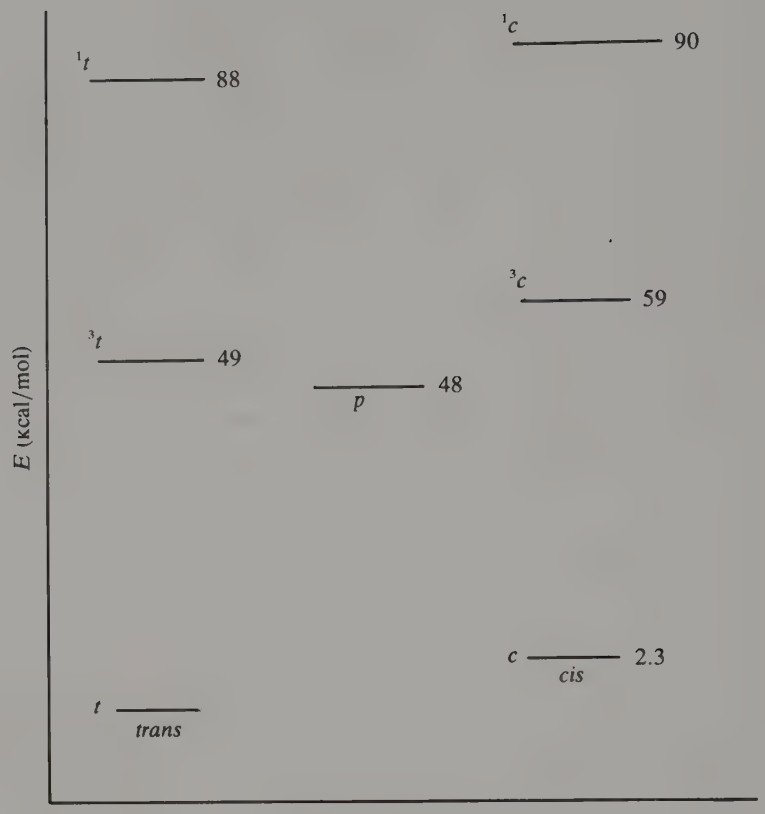


Fig. 11.8. Energy of excited states involved in *cis–trans* isomerization of stilbene. [From J. Saltiel and J. L. Charlton, *Rearrangements in Ground and Excited States*, P. de Mayo (ed.), Academic Press, 1980, Chap. 14.]

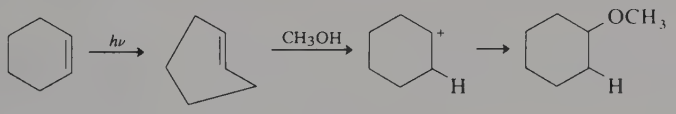
Still more detailed study has been given to photosensitized stilbene isomerization. One of the interesting features of the photosensitized system is that the composition of the photostationary state depends on the triplet energy of the sensitizer. With sensitizers having triplet energies above 60 kcal/mol, $[c]/[t]$ is slightly more than 1, but a range of sensitizers having triplet energies of 52–58 kcal/mol affords much higher *cis* : *trans* ratios in the photostationary state.[36] The high *cis* : *trans* ratio in this region results from the fact that the energy required for excitation of *trans*-stilbene is less than for *cis*-stilbene (see Fig. 11.8). Thus, sensitizers in the range 52–58 kcal/mol selectively excite the *trans* isomer. Since the rate of conversion of *trans* → *cis* is increased, the composition of the photostationary

36. G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Am. Chem. Soc.* **86**, 3197 (1964).

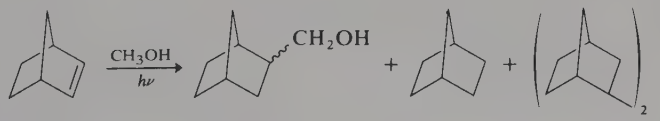
state is then enriched in *cis*-isomer. The reaction also exhibits a curious effect in that the photostationary *cis* : *trans* ratio drops again with sensitizers of still lower energy. The explanation for the effect is still under investigation.[33,37]

Direct photochemical excitation of unconjugated alkenes requires light with $\lambda \leq \sim 230$ nm. There have been relatively few studies of direct photolysis of alkenes in solution. A study of *cis*- and *trans*-2-butene diluted with neopentane demonstrated that *cis–trans* isomerization was competitive with the photochemically allowed 2 + 2 cycloaddition in pure liquid alkene.[38] The cycloaddition is completely stereospecific, which proves that the excited intermediate retains a geometry characteristic of the reactant alkene. As the ratio of neopentane to butene is increased, the amount of cycloaddition diminishes relative to *cis–trans* isomerization. This decrease presumably occurs because the lifetime of the species responsible for cycloaddition is very short. When the alkene is diluted by inert hydrocarbon, the rate of encounter of a second alkene is reduced, and isomerization dominates over cycloaddition.

The reaction course taken by photoexcited cycloalkenes in hydroxylic solvent is somewhat different and depends very much on ring size. 1-Methylcyclohexene, 1-methylcycloheptene, and 1-methylcyclooctene all add methanol, but neither 1-methylcyclopentene nor norbornene does so. The key intermediates in the addition reaction are believed to be highly reactive *trans* isomers of the cycloalkene,



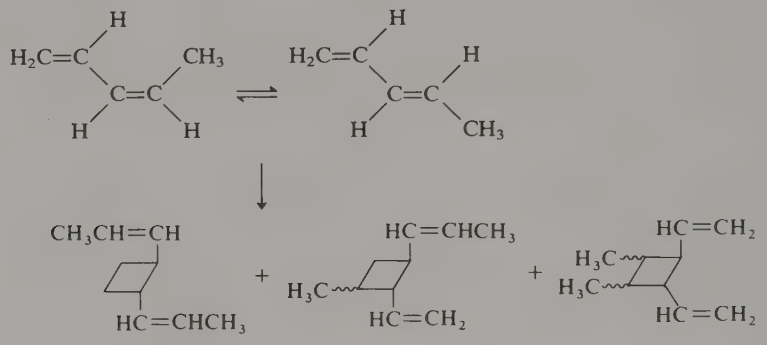
species that are too strained to be formed in a five-membered ring. The *trans*-cycloalkene intermediates can be protonated exceptionally easily because of the enormous relief of strain that accompanies protonation.[39,40] Cyclopentene and norbornene give products that are the result of hydrogen abstraction processes.[41] The reactivity of the excited state resembles that of a diradical species:



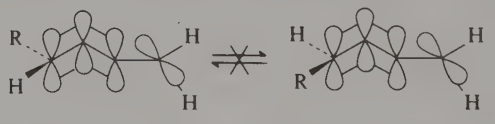
33. See p. 605.
37. S. Yamauchi and T. Azumi, *J. Am. Chem. Soc.* **95**, 2709 (1973).
38. H. Yamazaki and R. J. Cventanović, *J. Am. Chem. Soc.* **91**, 520 (1969); H. Yamazaki, R. J. Cventanović, and R. S. Irwin, *J. Am. Chem. Soc.* **98**, 2198 (1976).
39. J. A. Marshall, *Acc. Chem. Res.* **2**, 33 (1969).
40. P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, Jr., *J. Am. Chem. Soc.* **95**, 7058 (1973).
41. P. J. Kropp, *J. Am. Chem. Soc.* **91**, 5783 (1969).

As was mentioned in Section 11.2, the [2+2] photocycloaddition of alkenes is an allowed reaction according to orbital symmetry considerations. Among the most useful reactions in this category, from a synthetic point of view, are intramolecular [2+2] of dienes and intermolecular [2+2] cycloadditions of alkenes with cyclic α,γ-unsaturated carbonyl compounds. These reactions will be discussed in more detail in Part B, Section 7.2.

Conjugated dienes can undergo a variety of photoreactions, depending on whether excitation is direct or photosensitized. The benzophenone-sensitized excitation of 1,3-pentadiene, for example, results in stereochemical isomerization and dimerization[42]:



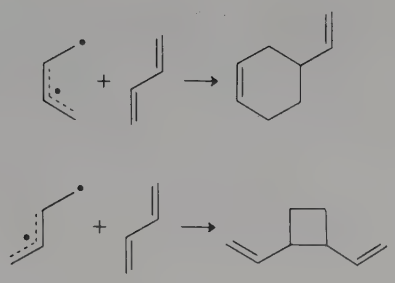
Alkyl derivatives of 1,3-butadiene, in general, undergo photosensitized *cis–trans* isomerism when photosensitizers that can supply at least 60 kcal/mol are used. An additional structural feature must be considered in treatment of their spectroscopy and photochemistry: two conformers of the diene, the *s-cis* and *s-trans*, exist in equilibrium, and there are therefore two nonidentical ground states from which excitation can occur. Two triplet excited states that do not readily interconvert are derived from the *s-trans* and *s-cis* conformers. Theoretical calculations suggest that the minimum energy for the excited state of conjugated dienes involves essentially an alkyl radical and an orthogonal allyl system (allylmethylene diradical):



Such a structure can explain the retention of a barrier to rotation about the C(2)–C(3) bond of a diene system.[43]

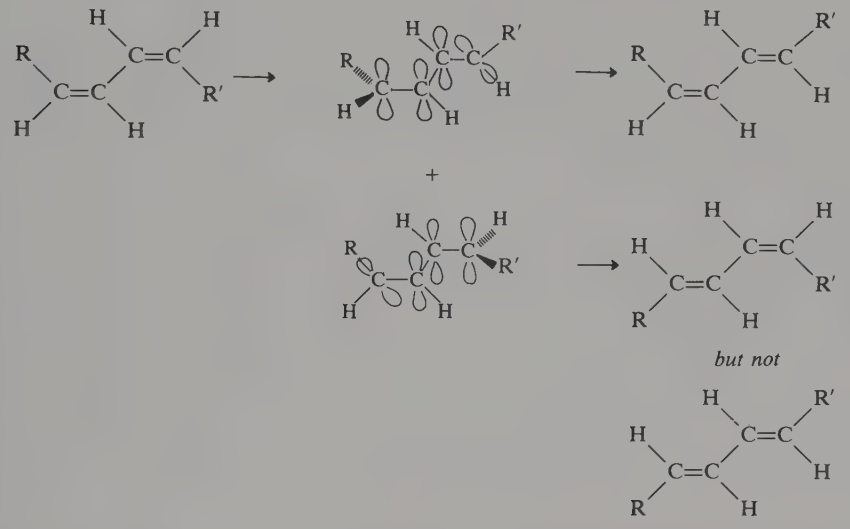
Another result that can be explained in terms of the two noninterconverting excited states is the dependence of the ratio of 2+2 and 2+4 addition products on sensitizer energy. The *s-cis* geometry is suitable for cyclohexene formation; the

42. J. Saltiel, D. E. Townsend, and A. Sykes, *J. Am. Chem. Soc.* **95**, 5968 (1973).
43. R. Hoffmann, *Tetrahedron* **22**, 521 (1966); N. C. Baird and R. M. West, *J. Am. Chem. Soc.* **93**, 4427 (1971).



s-trans is not. The excitation energy for the *s-cis* state is slightly lower than that for the *s-trans*. With low-energy sensitizers, the *s-cis* excited state is formed most readily, and the ratio of cyclohexene to cyclobutane product increases.[44]

The structure of the excited state of 1,3-dienes is also significant with respect to *cis–trans* isomerization. If the excited state is an allylmethylene biradical, only one of the two double bonds would be isomerized in any single excitation event:



On the other hand, if the two possible allylmethylene radicals interconvert rapidly, isomerization could take place at both double bonds without interconverting the excited states derived from *s-cis* and *s-trans* conformers. That is, there could conceivably be rapid rotation at the C_1–C_2 and C_3–C_4 bonds, but not at the C_2–C_3 bond. In this case, excitation could lead to isomerization at either or both the double bonds.

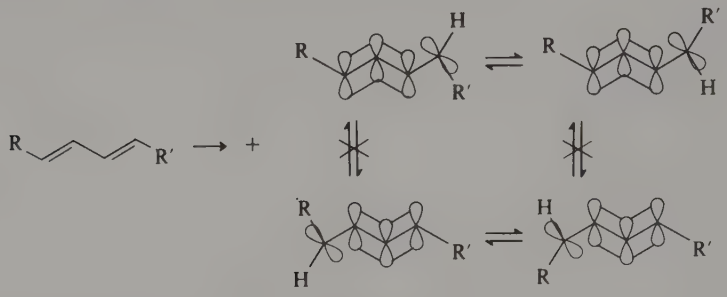
This is apparently the situation that exists in the triplet state. The triplet state has a high bond order between C(2) and C(3) and resists rotation at the center, but the barrier to rotation at either of the terminal carbons is low.[42,45] In contrast, it

44. R. S. H. Liu, N. J. Turro, Jr., and G. S. Hammond, *J. Am. Chem. Soc.* **87**, 3406 (1965); W. L. Dilling, R. D. Kroening, and J. C. Little, *J. Am. Chem. Soc.* **92**, 928 (1970).

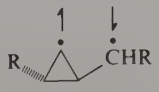
42. See p. 608.

45. J. Saltiel, A. D. Rousseau, and A. Sykes, *J. Am. Chem. Soc.* **94**, 5903 (1972).

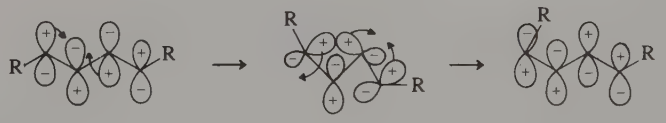
has been shown that in direct irradiation of 2,4-hexadiene, only one of the double bonds isomerizes on excitation.[46] The singlet state apparently retains a substantial barrier to rotation about the bonds in the allyl system:



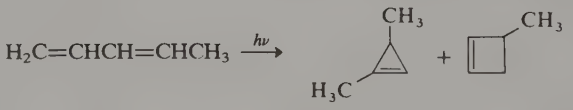
An alternative description of the excited singlet state is the cyclopropylmethyl singlet diradical:



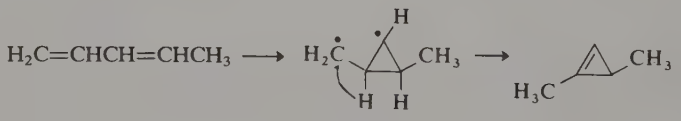
Orbital symmetry control of subsequent ring opening could account for isomerization at only one of the double bonds if the reaction is considered to involve the ψ_3 orbital which is the HOMO in excited butadiene:



On direct irradiation of 1,3-pentadiene, *cis–trans* interconversion is accompanied by cyclization to 1,3-dimethylcyclopropene and 3-methylcyclobutene:



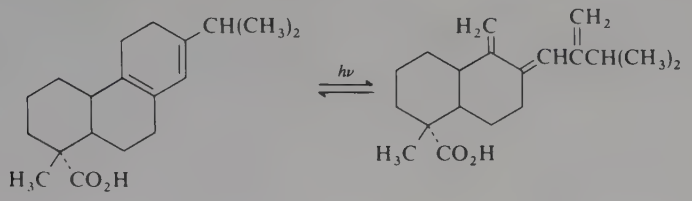
The latter product is an example of a concerted, photochemically allowed, electrocyclic reaction. A hydrogen atom migration from the cyclopropyldimethyl radical can account for the cyclopropene formation.[47] This product, then, is suggestive of a ring structure in the excited state:



Cyclohexadienes represent a somewhat special case among conjugated dienes. The occurrence of *cis-trans* isomerization is precluded by the ring geometry.

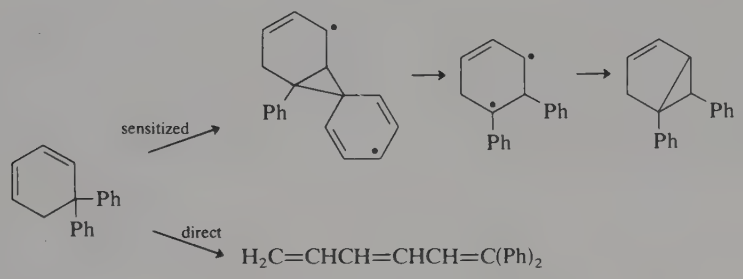
46. J. Saltiel, L. Metts, and M. Wrighton, *J. Am. Chem. Soc.* **92**, 3227 (1970).
47. S. Boué and R. Srinivasan, *J. Am. Chem. Soc.* **92**, 3226 (1970).

Electrocyclic ring-opening (see Section 11.2) can occur on irradiation of cyclohexadienes:

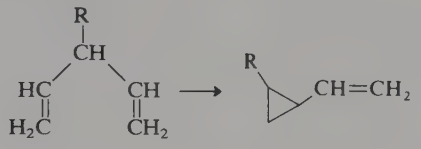


Ref. 48

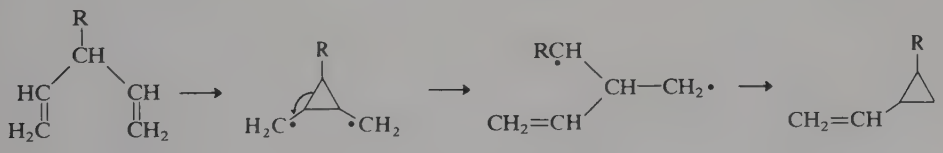
5,5-Diphenylcyclohexadiene shows divergent photochemical behavior, depending on whether the reaction is induced by direct irradiation or by photosensitization. On direct irradiation, the electrocyclic conversion to 1,1-diphenylhexatriene is dominant, whereas a rearrangement involving one of the aromatic rings is the major reaction of the triplet excited state formed by photosensitization[49]:



The latter reaction is an example of the *di-π-methane* rearrangement.[50] This rearrangement is a very general reaction for 1,4-dienes and other systems that have two π systems separated by an sp^3-carbon atom:

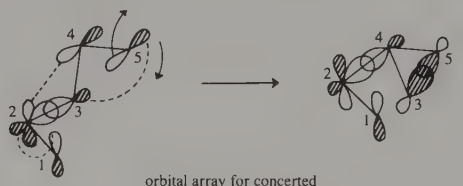


This transformation can be rationalized in terms of a diradical species formed by bonding between C-2 and C-4:



48. W. G. Dauben and R. M. Coates, *J. Org. Chem.* **29**, 2761 (1964).
49. H. E. Zimmerman and G. A. Epling, *J. Am. Chem. Soc.* **94**, 8749 (1972); J. S. Swenton, J. A. Hyatt, T. J. Walker, and A. L. Crumrine, *J. Am. Chem. Soc.* **93**, 4808 (1971).
50. For a review of the di-π-methane rearrangement, see H. E. Zimmerman in *Rearrangements in Ground and Excited States*, Vol. 3, P. de Mayo (ed.), Academic Press, New York, 1980, Chap. 16.

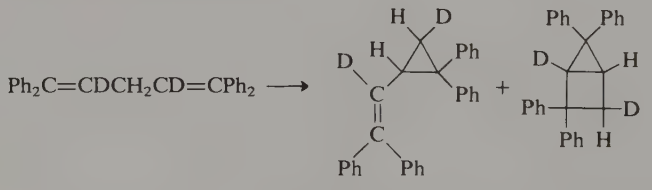
It has been found that this reaction can proceed through either a singlet or a triplet excited state.[51] The reaction can be formulated as a concerted process, and this mechanism appears to be followed in the case of some acyclic dienes and for cyclic systems in which a concerted process is sterically feasible. Notice that the orbital



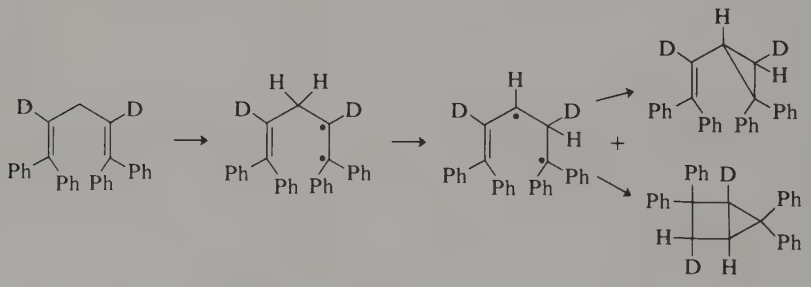
orbital array for concerted
di-π-methane rearrangement

array is of the Möbius topology with a phase change depicted between the C-1 and C-2 positions. This corresponds to an allowed photochemical process since there are six electrons involved in bonding changes.

The di-π-methane rearrangement has been studied in a sufficient number of molecules to develop some of the patterns regarding substituent effects. When the central sp^3 carbon is unsubstituted, the di-π-methane mechanism becomes less favorable. The case of 1,1,5,5-tetraphenyl-1,4-pentadiene is illustrative. Although one of the products has the expected structure, labeling with deuterium proves that an alternative mechanism operates:



The cyclopropane bridge is formed only after hydrogen atom migration. The driving force for this migration may be the fact that a more stable allylic radical results:

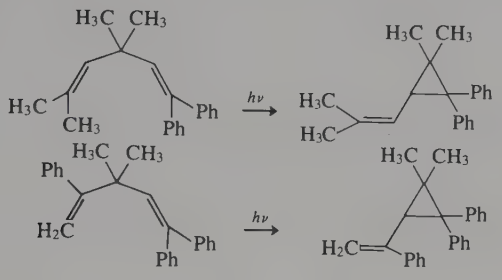


The resistance of the unsubstituted system to the di-π-methane rearrangement probably occurs at the second step of the rearrangement.[52] If the central carbon is

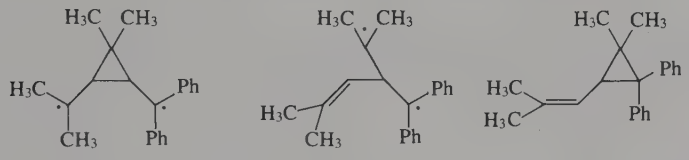
51. H. E. Zimmerman and P. S. Mariano, *J. Am. Chem. Soc.* **91**, 1718 (1969); P. S. Mariano, R. B. Steitle, D. G. Watson, M. J. Peters, and E. Bay, *J. Am. Chem. Soc.*, **98**, 5899 (1976).
52. H. E. Zimmerman and J. O. Pincock, *J. Am. Chem. Soc.* **95**, 2957 (1973).

unsubstituted this step results in the formation of a primary radical and would be energetically unfavorable.

The groups at the termini of the 1,4-pentadiene system also affect the efficiency and direction of the reaction. The general trend is that cyclization will tend to occur at the diene terminus which best stabilizes radical character. Thus, a terminus substituted with aryl groups will cyclize in preference to an unsubstituted or alkyl-substituted terminus:

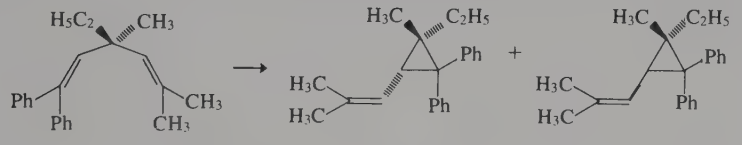


This result can be rationalized in terms of a diradical structure by noting that the bond cleavage will occur to give the more stable of the two possible 1,3 diradicals.[55] The cyclopropane ring in the final product will then incorporate this terminus:



This interpretation can be expressed in terms of the concerted mechanism by regarding the "diradical" to be a contributing structure at the transition state of the concerted process.

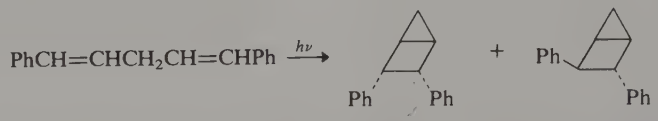
The di-π-methane rearrangement is a stereospecific reaction. There are several elements of stereochemistry to be considered. It is known that the double bond which remains uncyclized retains the *E* or *Z* configuration present in the starting material. This result immediately excludes any intermediate with a freely rotating terminal radical. The concerted transition state implies that C-3 would undergo inversion of configuration since the new C-3–C-5 bond is formed using the back lobe of the C-2–C-3 σ-bond. This inversion of configuration has been confirmed[56]:



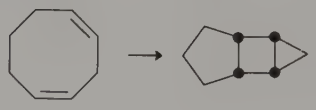
53. H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.* **92**, 1409 (1970).
54. H. E. Zimmerman and A. A. Baum, *J. Am. Chem. Soc.* **93**, 3646 (1971).
55. H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.* **92**, 6259, 6267 (1970).
56. H. E. Zimmerman, J. D. Robbins, R. D. McKelvey, C. J. Samuel, and L. R. Sousa, *J. Am. Chem. Soc.* **96**, 1974, 4630 (1974).

Thus the concerted transition state correctly predicts the stereochemical course of the di-π-methane rearrangement.

An alternative pathway for reaction of 1,4-dienes is intramolecular cycloaddition giving bicyclo[2.1.0]pentanes. This pathway is usually not observed, but photolysis of 1,5-diphenyl-1,4-pentadiene is an example of a compound that takes this course[57]:

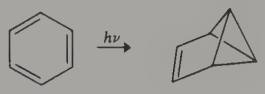


The structural explanation that has been offered to rationalize this altered reaction course is that the phenyl substituents may stabilize the diradical formed by 2,4 bridging, permitting it to exist long enough for closure to occur in preference to the concerted di-π-methane rearrangement. Intramolecular cycloaddition is also observed for 1,4-cyclooctadiene[58]:



11.5. Photochemistry of Aromatic Compounds

Irradiation of benzene and certain of its derivatives results in valence isomerism, leading to nonaromatic products.[59] Irradiation of liquid benzene with light of 254-nm wavelength results in the accumulation of a very small amount of tricyclo[3.1.0.0^{2,6}]hex-3-ene, also known as benzvalene[60]:

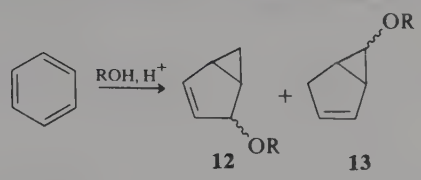


The maximum conversion to this product in liquid benzene is only 0.01%. A higher concentration (~1%) is achieved in solutions diluted with saturated hydrocarbons.

Because of benzvalene's low photostationary concentration, photolysis of benzene is not an efficient way of accumulating it. The highly reactive molecule can be trapped, however, if it is generated in the presence of other molecules with which it reacts. Irradiation of benzene in acidic hydroxylic solvents gives products formally

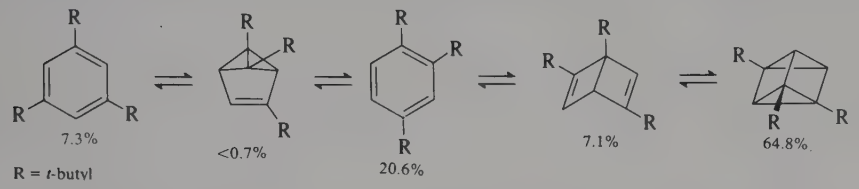
57. E. Block and H. W. Orf, *J. Am. Chem. Soc.* **94**, 8438 (1972).
58. S. Moon and C. R. Ganz, *Tetrahedron Lett.*, 6275 (1968).
59. D. Bryce-Smith and A. Gilbert, *Tetrahedron* **32**, 1309 (1976).
60. K. E. Wilzbach, J. S. Ritscher, and L. Kaplan, *J. Am. Chem. Soc.* **89**, 1031 (1967).

resulting from 1,3 bonding in the benzene ring and addition of a molecule of solvent:



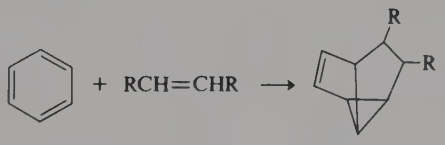
These compounds are not photoproducts as such, however. The products of structure **12** arise by solvolysis of benzvalene, the initial photoproduct. Products of type **13** are secondary photoproducts derived from **12**.[61]

The photoisomerization of benzene rings has also been studied, using 1,3,5-tri-*t*-butyl benzene. The composition of the photostationary state is shown below[62]:



These various photoproducts are all valence isomers of the normal benzenoid structure. These alternative bonding patterns are reached from the excited state, but it is difficult to specify a precise mechanism. The presence of the *t*-butyl groups introduces a steric factor that works in favor of the photochemical valence isomerism. Whereas the *t*-butyl groups are coplanar in the aromatic system, the geometry of the bicyclic products results in reduced steric interactions between adjacent *t*-butyl groups.

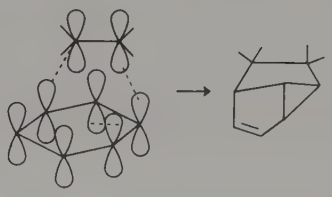
Irradiation of solutions of alkenes in benzene or substituted benzenes gives primarily 1:1 adducts in which the alkene bridges *meta* positions on the aromatic ring[63]:



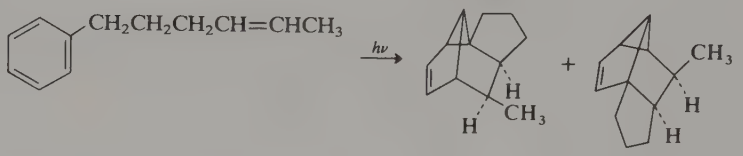
These reactions are believed to proceed through a complex of the alkene with the singlet excited state of the aromatic (an exciplex). The alkene and aromatic ring are presumed to be oriented in such a manner that the alkene π system reacts with

61. L. Kaplan, D. J. Rausch, and K. E. Wilzbach, *J. Am. Chem. Soc.* **94**, 8638 (1972).
62. K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.* **87**, 4004 (1965).
63. K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.* **88**, 2066 (1966); J. Cornelisse, V. Y. Merritt, and R. Srinivasan, *J. Am. Chem. Soc.* **95**, 6197 (1973); A. Gilbert and P. Yianni, *Tetrahedron* **37**, 3275 (1981); D. Bryce-Smith and A. Gilbert, *Tetrahedron* **33**, 2459 (1977).

p orbitals on 1,3 carbons of the aromatic:



This addition to the aromatic ring is believed to be concerted since the relative geometry of the substituents on the alkene is retained in the product. Lesser amounts of products involving addition to 1,2 or 1,4 positions on the aromatic ring are also formed in such photolyses.[64] This type of addition reaction has also been realized intramolecularly when the distance between the alkene and phenyl substituent is sufficient to permit interaction of the alkene group and the aromatic ring[65]:



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N. J. Turro, *Molecular Photochemistry*, W. A. Benjamin, New York, 1967.
D. Neckers, *Mechanistic Organic Photochemistry*, Reinhold, New York, 1967.
J. C. Dalton and N. J. Turro, *Ann. Rev. Phys. Chem.* **21**, 499 (1970).
W. L. Dilling, *Chem. Rev.* **66**, 373 (1966).
D. R. Arnold, *Adv. Photochem.* **6**, 301 (1968).
D. R. Arnold, N. C. Baird, J. R. Bolton, J. C. D. Brand, P. W. M. Jacobs, P. de Mayo, and W. R. Ware, *Photochemistry: An Introduction*, Academic Press, New York, 1974.
J. M. Coxon and B. Halton, *Organic Photochemistry*, Cambridge University Press, London, 1974.
D. O. Cowan and R. L. Drisko, *Elements of Organic Photochemistry*, Plenum, New York, 1976.
P. deMayo (ed.), *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, New York, 1980.
N. J. Turro, *Modern Molecular Photochemistry*, Benjamin–Cummings, 1978.
H. E. Zimmerman, *Top. Current Chem.* **100**, 45 (1982).

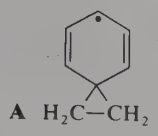
Problems

(*References for these problems will be found on page 708.*)

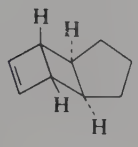
1. The bridged radical **A** has been suggested as a possible intermediate in the

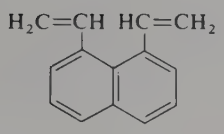
64. K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.* **93**, 2073 (1971).
65. W. Ferree, Jr., J. B. Grutzner and H. Morrison, *J. Am. Chem. Soc.* **93**, 5502 (1971).

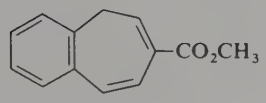
photochemical decarbonylation of 3-phenylpropanal. Suggest an experiment to test this hypothesis.

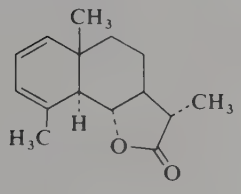


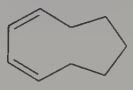
2. Predict the structure, including all aspects of stereochemistry, for the product expected to result from direct irradiation of each compound:

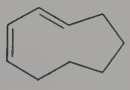
(a) 

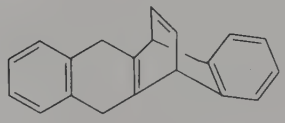
(b) 

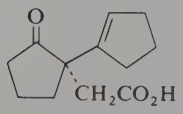
(c) 

(d) 

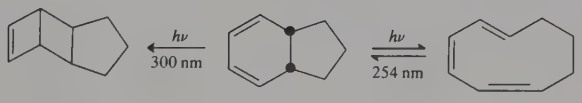
(e) 

(f) 

(g) 

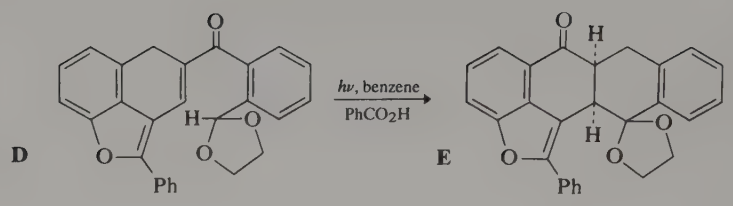
(h) 

3. Suggest reasonable explanations for the following observations:
   (a) Optically active 2,3-pentadiene is racemized rapidly under conditions of toluene-sensitized photolysis.
   (b) Direct photolysis of diene **A** at 254 nm produces a photochemical stationary state containing 40% **A** and 60% triene **B**. When the irradiation is carried out at 300 nm, no **B** is produced, and **C** is the observed product.



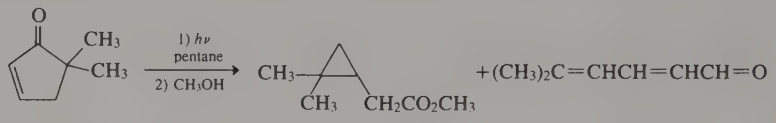
C **A** **B**

   (c) Photochemical cyclization of the acetal **D** to **E** in benzene is efficiently catalyzed by benzoic acid.

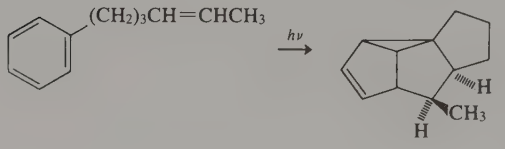


4. Provide a mechanistic rationalization for each of the following reactions.

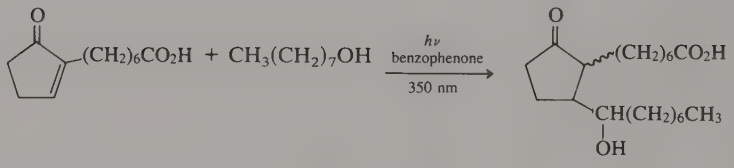
(a)



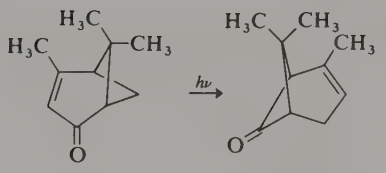
(b)



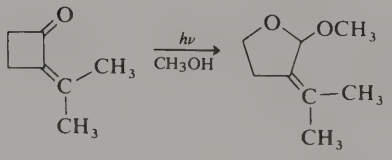
(c)



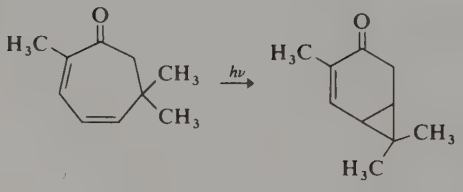
(d)



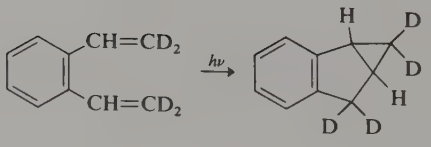
(e)

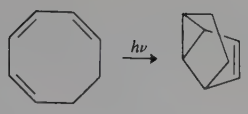


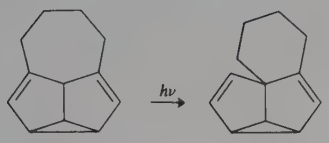
(f)

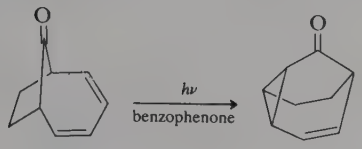


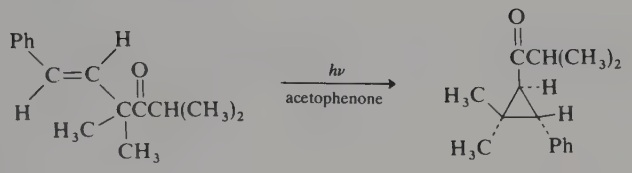
(g)

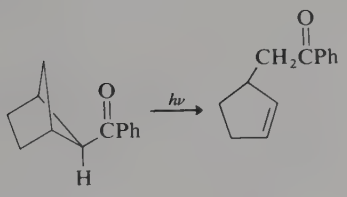


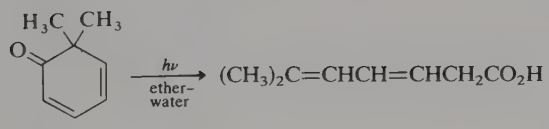
(h) 
hν

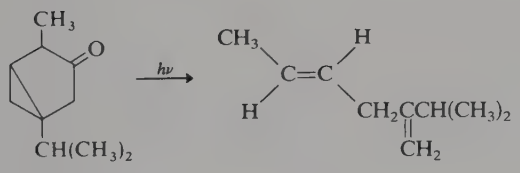
(i) 
hν

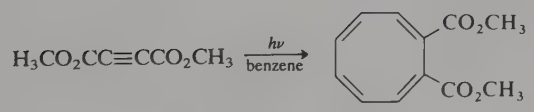
(j) 
O
hν
benzophenone
O

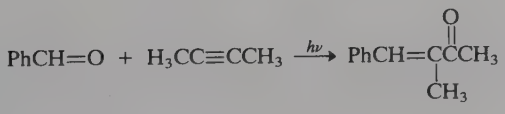
(k) 
Ph
H
C=C
H
O
CCCH(CH3)2
H3C
CH3
hν
acetophenone
O
CCH(CH3)2
H3C
H
H
H3C
Ph

(l) 
O
CPh
H
hν
O
CH2CPh

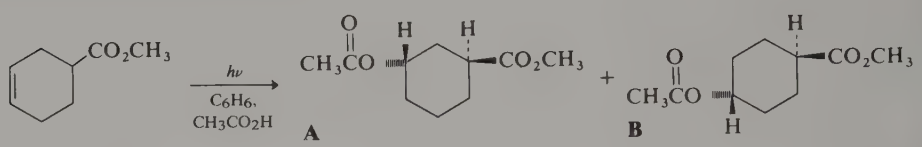
(m) 
H3C CH3
O
hν
ether–
water
(CH3)2C=CHCH=CHCH2CO2H

(n) 
CH3
O
CH(CH3)2
hν
CH3
H
C=C
H
CH2CCH(CH3)2
CH2

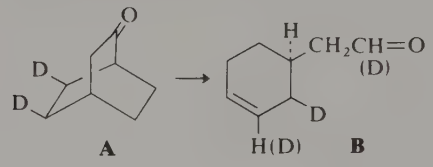
(o) 
H3CO2CC≡CCO2CH3
hν
benzene
CO2CH3
CO2CH3

(p) 
PhCH=O + H3CC≡CCH3
hν
PhCH=CCCH3
O
CH3

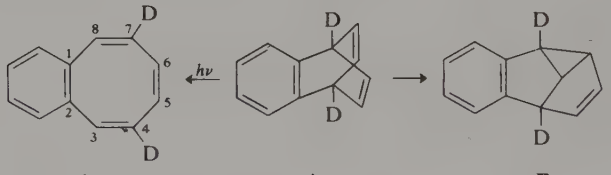
5. Benzene-sensitized photolysis of methyl 3-cyclohexene-1-carboxylate in acetic acid leads to addition of acetic acid to the double bond. Only the *trans* adducts are formed. What factor(s) is (are) responsible for the reaction stereochemistry? Which of the two possible addition products, **A** or **B**, do you expect to be the major product?



6. Photolysis of bicyclo[2.2.2]octan-2-one (**A**) gives **B** in good yield. When **A** labeled as shown is used, the aldehyde group carries deuterium to the extent of 51.7%. Write a mechanism to account for the overall transformation. Calculate the isotope effect for the step in which hydrogen atom transfer occurs. What mechanistic conclusion do you draw from the magnitude of the isotope effect?



7. The photolysis of benzobarrelene, **A**, has been studied in considerable detail. Direct photolysis gives **C**, but when acetone is used as a photosensitizer, the di-π-methane rearrangement product **B** is formed.



(A small amount of D is at C-3,8.)

A deuterium labeling study has been performed with the results shown. Discuss the details of the mechanism that are revealed by these results. Is there a feasible mechanism that would have led to **B** having an alternative label distribution?

8. Quantum yield data for several processes that occur on photolysis of *S*-4-methyl-1-phenyl-1-hexanone have been determined. The results are tabulated below for benzene as solvent:

Process	Quantum yield
Type-II elimination	0.23
Cyclobutanol formation	0.03
Racemization	0.78

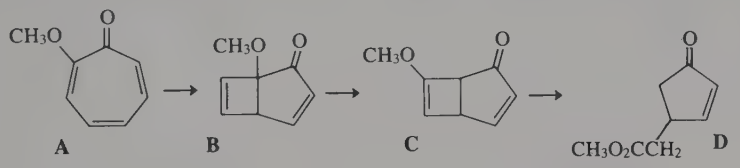
What information about the mechanism operating under these conditions can be drawn from these data?

9. Show by a diagram why the energy of radiation emitted from an excited electronic state (by fluorescence or phosphorescence) is of lower energy than the exciting radiation. Would you expect the shift to lower energy to be more pronounced for fluorescence or phosphorescence? Explain.

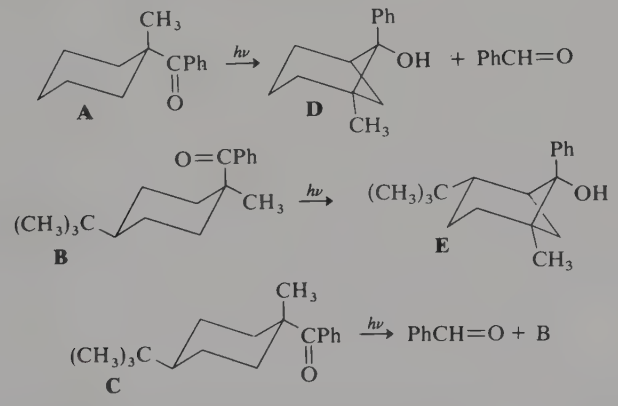
10. *cis*-2-Propyl-4-*t*-butylcyclohexanone is photolyzed to 4-*t*-butylcyclohexanone. The *trans* isomer is converted to the *cis* isomer, which then undergoes cleavage. Offer a rationale for this pronounced stereochemical effect.

11. The quantum yield for formation of 3-methylcyclobutene from *trans*-1,3-pentadiene is ten times greater than for the cyclization of *cis*-1,3-pentadiene. Can you offer an explanation?

12. The irradiation of 2-methoxytropone (**A**) leads to methyl (4-oxo-2-cyclopentenyl) acetate (**D**). The reaction can be followed by analytical gas chromatography and two intermediates are observed which have the structures **B** and **C**. Indicate a mechanism by which each of the three successive reactions might occur. The first two steps are photochemical, while the third is probably an acid-catalyzed reaction which occurs under the photolysis conditions.

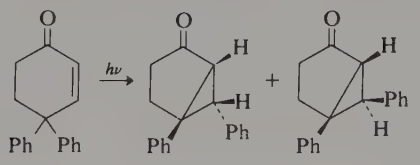


13. A study of the photolysis of **A**, **B**, and **C** has been reported. **A** gives both **D** and the cleavage product benzaldehyde. **B** gives only **E**. **C** gives benzaldehyde and the stereoisomer **B**. Discuss the ways in which the presence and configuration of the remote *t*-butyl group can control the product composition and account for the formation of the observed products.

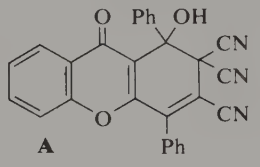


14. In the rearrangement of 4,4-diphenylcyclohexenone to 5,6-diphenylbicyclo-[3.1.0]hexan-2-one, there is a strong preference for formation of the *endo*

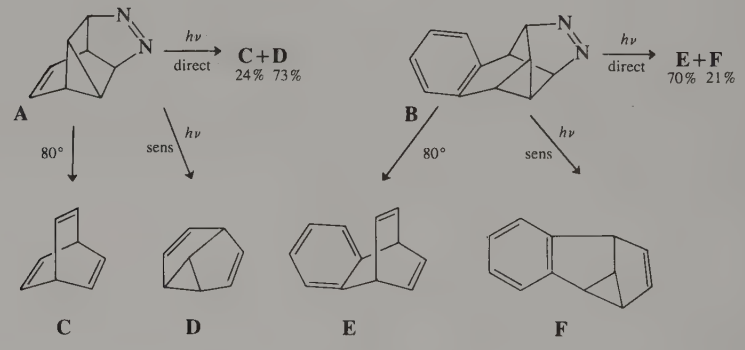
phenyl stereoisomer. Offer an explanation.



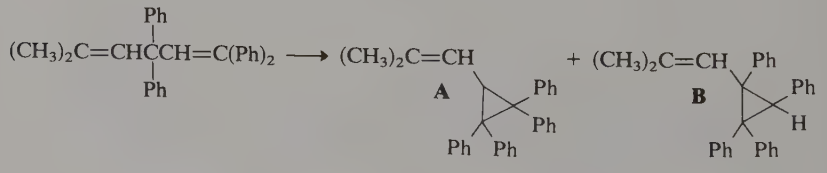
15. Compound **A** is photochromic; that is, it becomes colored on exposure to light. The process is reversible, giving back the starting material in the dark. Suggest a structure for the colored photoisomer.



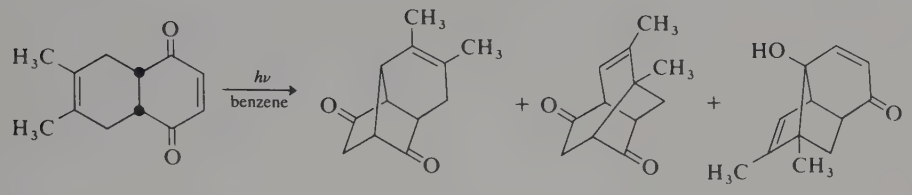
16. The azo compounds **A** and **B** were prepared and the thermal and photochemical behavior of these materials was investigated. The results are summarized in the equations below. Discuss how these results may relate to the photochemical di-π-methane rearrangement. (See Section 12.1.4 for some indications of the reactivity of azo compounds.)



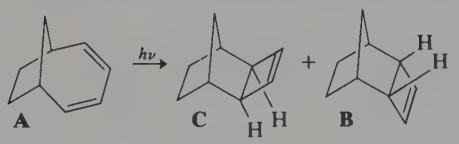
17. Irradiation of 1,1,3,3-tetraphenyl-5-methyl-1,4-hexadiene gives the two products shown below. When the reaction is carried out by photosensitization, **B** is not formed. Suggest mechanisms for the formation of **A** and **B**. What other products might have been expected? Can you rationalize their absence?



18. Suggest a reasonable pathway for the formation of each of the photoproducts formed on irradiation of the Diels–Alder adduct of 2,3-dimethylbutadiene and quinone:



19. The direct irradiation of **A** gives predominantly **B**, but the photosensitized reaction gives more **C**. Explain.



Direct:	28%	72%
Sensitized:	68%	32%

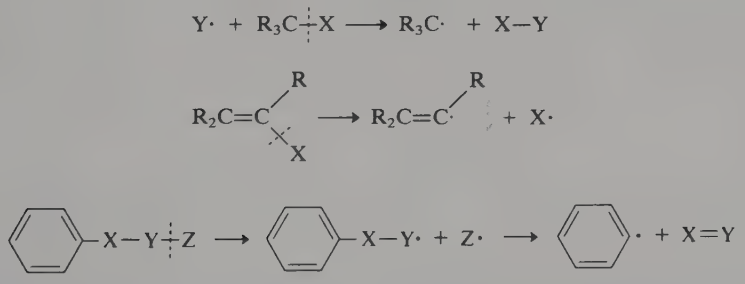
12

Free-Radical Reactions

12.1. Generation and Characterization of Free Radicals

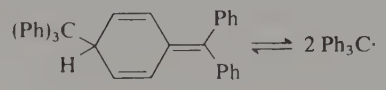
12.1.1. Background

A free-radical reaction is a chemical process in which molecules having unpaired electrons are involved. The radical species could be a starting compound or a product, but in organic chemistry, the most common cases are reactions that involve radicals as intermediates. Most of the reactions discussed to this point have been heterolytic processes involving polar intermediates or transition states in which all electrons remain paired throughout the course of the reaction. In radical reactions, homolytic bond cleavages occur. The generalized reactions shown below illustrate the formation of alkyl, vinyl, and aryl free radicals by hypothetical homolytic processes:



The idea that carbon atoms with seven valence electrons could be involved in organic reactions took firm hold in the 1930's. Two experimental studies stand out with historical significance in the development of the concept of free radical chemistry. The work of Gomberg around 1900 provided evidence that when triphenylmethyl chloride was treated with silver metal, the resulting solution contained $Ph_3C\cdot$ in equilibrium with a less reactive dimeric molecule. It was generally

assumed that the triphenylmethyl radical was in equilibrium with hexaphenylethane. Only recently has a reinvestigation of the structure of the dimeric compound shown that it is not hexaphenylethane, but is instead a cyclohexadiene derivative[1]:



The extent of dissociation is small, with $K = 2 \times 10^{-4}\,M$ in benzene at room temperature. Gomberg deduced the existence of the radical from the fact that the solution exhibited reactions that could not be acceptably explained in terms of the properties expected for a normal organic molecule.

In 1929, Paneth studied the decomposition of tetramethyllead and came to the conclusion that methyl radicals generated in one area of an apparatus could move with inert carrier gas to another region of the system, where their presence was indicated by disappearance of a metal film by the reverse of the cleavage reaction:

$$Pb(CH_3)_{4(g)} \xrightarrow{450°C} Pb_{(s)} + 4\,CH_3{}^{\bullet}{}_{(g)}$$

$$4\,CH_3{}^{\bullet}{}_{(g)} + Pb_{(s)} \xrightarrow{100°C} Pb(CH_3)_{4(g)}$$

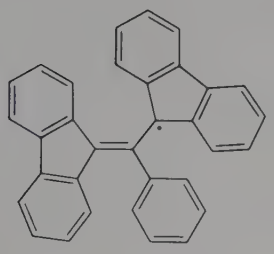
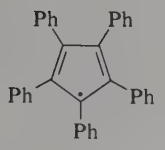
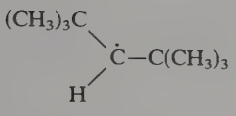
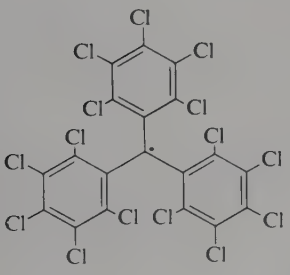
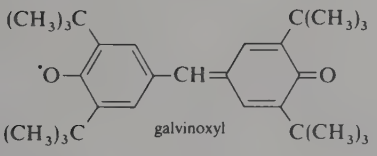
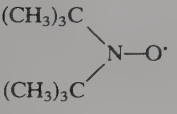
Since these early experiments, much additional evidence for the existence of radical intermediates and of their importance in many reactions has accumulated. In the first section of this chapter, we will discuss some of the radicals that have been studied directly and indicate the structural conclusions that have been reached. Free radicals have some special properties that are associated with the existence of an unpaired electron. Because species with an unpaired electron are attracted by a magnetic field, they are said to be *paramagnetic*. This property itself is not used directly in the study of organic free radicals; however, the existence of the unpaired electron does give rise to special spectroscopic properties for free radicals, which will be discussed more fully in Section 12.1.3.

12.1.2. Stable and Persistent Free Radicals

Most organic free radicals have very short lifetimes, but various structural features enhance stability. A few free radicals are indefinitely stable. Entries 1, 4, and 5 in Scheme 12.1 are examples. These molecules are just as stable to ordinary conditions of temperature and atmosphere as typical closed shell molecules. Entry 2 is somewhat less stable to oxygen, although it can exist indefinitely in the absence

1. H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); for a historical account of the "hexaphenylethane riddle," see J. M. McBride, *Tetrahedron* **30**, 2009 (1974).

Scheme 12.1. Stability of Some Free Radicals

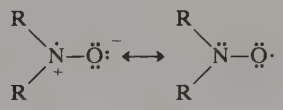
Structure	Conditions for stability
1[a] 	Indefinitely stable as a solid, even in the presence of air.
2[b] 	Crystalline substance is not rapidly attacked by oxygen, although solutions are air sensitive; the compound is stable to high temperature in the absence of oxygen.
3[c] 	Stable in dilute solution ($<10^{-5}$ M) below −30°C in the absence of oxygen, $t_{1/2}$ of 50 sec at 25°C.
4[d] 	Stable in solution for days, even in the presence of air. Indefinitely stable in solid state. Thermally stable up to 300°C.
5[e] 	Stable to oxygen; stable to extended storage as a solid. Slowly decomposes in solution.
6[f] 	Stable to oxygen even above 100°C.

a. C. F. Koelsch, *J. Am. Chem. Soc.* **79**, 4439 (1957).
b. K. Ziegler and B. Schnell, *Justus Liebigs Ann. Chem.* **445**, 266 (1925).
c. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.* **96**, 2441 (1974).
d. M. Ballester, J. Riera, J. Castañer, C. Badía, and J. M. Monsó, *J. Am. Chem. Soc.* **93**, 2215 (1971).
e. G. M. Coppinger, *J. Am. Chem. Soc.* **79**, 501 (1957); P. D. Bartlett and T. Funahashi, *J. Am. Chem. Soc.* **84**, 2596 (1962).
f. A. K. Hoffmann and A. T. Henderson, *J. Am. Chem. Soc.* **83**, 4671 (1961).

of oxygen. The structures shown in entries 1, 2, and 4 all permit extensive delocalization of the unpaired electron into aromatic rings. These highly delocalized radicals show no tendency toward disproportionation or dimerization. Radicals which have long lifetimes and are resistant to dimerization or other routes for bimolecular self-annihilation can be called *stable free radicals.*

Entry 3 has only alkyl substituents and yet has a significant lifetime in the absence of oxygen. The tris(*tert*-butyl)methyl radical has an even longer lifetime with a half-life of about 20 min at 25°C.[2] The steric hindrance provided by the *tert*-butyl substituents greatly retards the rates of dimerization and disproportionation reactions of these radicals. They remain highly reactive toward oxygen, however. The term *persistent radicals* is preferable to the term *stable radicals* in discussing these species, since their extended lifetimes have more to do with kinetic factors than inherent stability.[3]

There are only a few functional groups which contain an unpaired electron and are stable in a wide variety of molecular environments. The best examples are the nitroxide radicals and there are numerous specific nitroxides which have been characterized.



Many of these compounds are very stable under normal conditions, and heterolytic reactions can be carried out on other functional groups in the molecule without destroying the paramagnetic nitroxide group.[4]

Although the existence of the stable and persistent free radicals we have discussed is of significance in establishing that free radicals can have extended lifetimes, most free radical reactions involve highly reactive intermediates that have relatively fleeting lifetimes and can only be studied at very low concentrations. The techniques for study of radicals under these conditions are the subject of the next section.

12.1.3. Direct Detection of Radical Intermediates

A spectroscopic method that is uniquely applicable to the study of free radicals exists, and is known as *electron paramagnetic resonance* (EPR) spectroscopy. *Electron spin resonance* (ESR) spectroscopy is synonymous. Very simply stated, EPR

2. G. D. Mendenhall, D. Griller, D. Lindsay, T. T. Tidwell, and K. U. Ingold, *J. Am. Chem. Soc.* **96**, 2441 (1974).
3. For a review of various types of persistent radicals, see D. Griller and K. U. Ingold, *Acc. Chem. Res.* **9**, 13 (1976).
4. For a review of the preparation, reactions, and uses of nitroxide radicals, see J. F. W. Keana, *Chem. Rev.* **78**, 37 (1978), and L. J. Berliner ed., *Spin-Labelling*, Vol. 2, Academic Press, New York, 1979.

spectroscopy detects transitions between energy levels of unpaired electrons in a magnetic field. A magnetic moment is associated with the spinning electron, and this magnetic moment can have only one of two orientations in a magnetic field. The orientation is specified by the quantum numbers $m_s = \pm 1/2$. An EPR spectrometer records the absorption of energy that occurs when an electron is excited from the lower to the higher state. The energy separation is very small, and microwaves are used for excitation. The detection of a signal constitutes proof that a radical species is present, since molecules having no unpaired electrons give no EPR absorption. Thus, EPR spectroscopy is a highly specific tool for detecting radical species. EPR spectroscopy can also give information well beyond the mere detection of paramagnetic species. As with most other spectroscopic methods, structural information can be deduced by a detailed analysis of the absorption signal. One feature that is determined is the g value. This quantity is determined by the energy separation between the two spin states and the strength of the magnetic field in the spectrometer:

$$h\nu = E = g\mu_B H$$

where μ_B is a constant, the Bohr magneton ($= 9.273$ ergs/gauss), and H is the magnetic field in gauss. The measured value of g is characteristic of the particular type of radical, just as band positions in IR or NMR spectra are characteristic of the absorbing species.

A second type of structural information can be deduced from the hyperfine splitting in EPR spectra. The origin of hyperfine splitting is closely related to the factors that cause spin–spin splitting in NMR spectra. Certain nuclei—in particular, ^{1}H, ^{13}C, and ^{31}P—have a magnetic moment. This relatively small nuclear magnetic moment splits the signal arising from the unpaired electron. The number of lines is given by the equation

$$\text{number of lines} = 2nI + 1$$

where I is the nuclear spin quantum number and n is the number of equivalent interacting nuclei. For ^{1}H, ^{13}C, and ^{31}P, $I = 1/2$. Thus, a single hydrogen splits each level into a doublet. Three equivalent hydrogens, as in a methyl group, give rise to splitting that produces four lines. This splitting is illustrated in Fig. 12.1. Nitrogen (^{14}N) with $I = 1$ splits each energy level into three lines. Neither ^{12}C or ^{16}O has a nuclear magnetic moment, and just as they cause no splitting in NMR spectra, they have no effect on the multiplicity of EPR signals.

A great deal of structural information can be obtained by analysis of the hyperfine splitting pattern of a free radical. If we limit our discussion for the moment to carbon radicals without heteroatoms, the number of lines indicates the number of interacting protons, and the magnitude of the splitting, given by the hyperfine splitting constant a, is a measure of the unpaired-electron density in the hydrogen $1s$ orbital. For planar systems in which the unpaired electron resides in a π-orbital system, the relationship between electron spin density and the splitting constant is

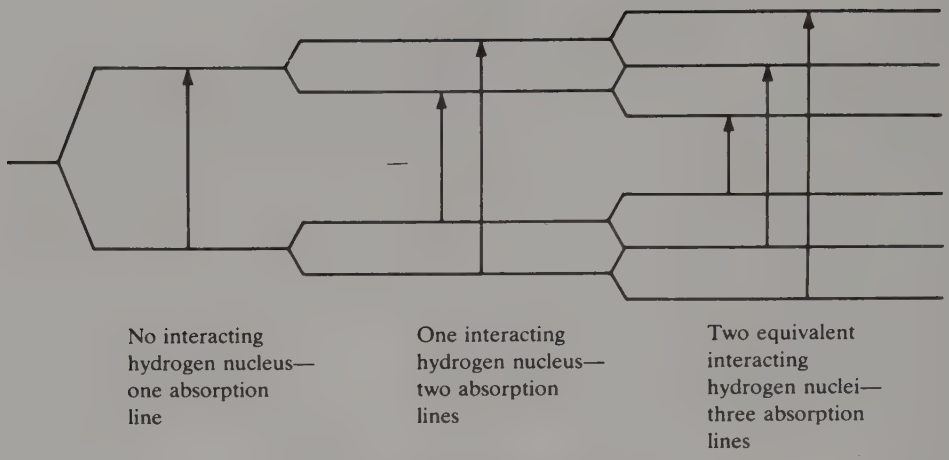


Fig. 12.1. Hyperfine splitting in EPR spectra.

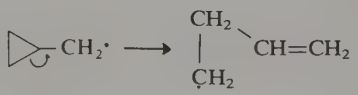
given by the McConnell equation[5]:

$$a = \rho Q$$

where a is the hyperfine coupling constant for a proton, Q a proportionality constant (approximately 23 G), and ρ the spin density on the carbon to which the proton is attached. For example, taking $Q = 23.0$ G, the hyperfine splitting in the benzene radical anion may be readily calculated taking $\rho = 1/6$, since the one unpaired electron is distributed equally among the six carbon atoms. The calculated value of a is 3.83, in good agreement with the observed value. The spectrum (Fig. 12.2a) consists of seven lines separated by a coupling constant of 3.75 G.

The EPR spectrum of the ethyl radical presented in Fig. 12.2b is readily interpreted, and the results are of interest with respect to the distribution of unpaired spin density in the molecule. The 12-line spectrum is a triplet of quartets resulting from unequal coupling of the electron spin to the α and β protons. The two coupling constants are $a_\alpha = 22.38$ G and $a_\beta = 26.87$ G, and imply extensive delocalization of spin density through the σ bonds.

EPR spectra have been widely used in the study of free radical reactions to detect radical intermediates. An interesting example of the direct study of a radical involves the cyclopropylmethyl radical. Much chemical experience has indicated that this radical is exceedingly unstable, giving rise to 3-butenyl radical very rapidly after being generated:



5. H. M. McConnell, *J. Chem. Phys.* **24**, 764 (1956).

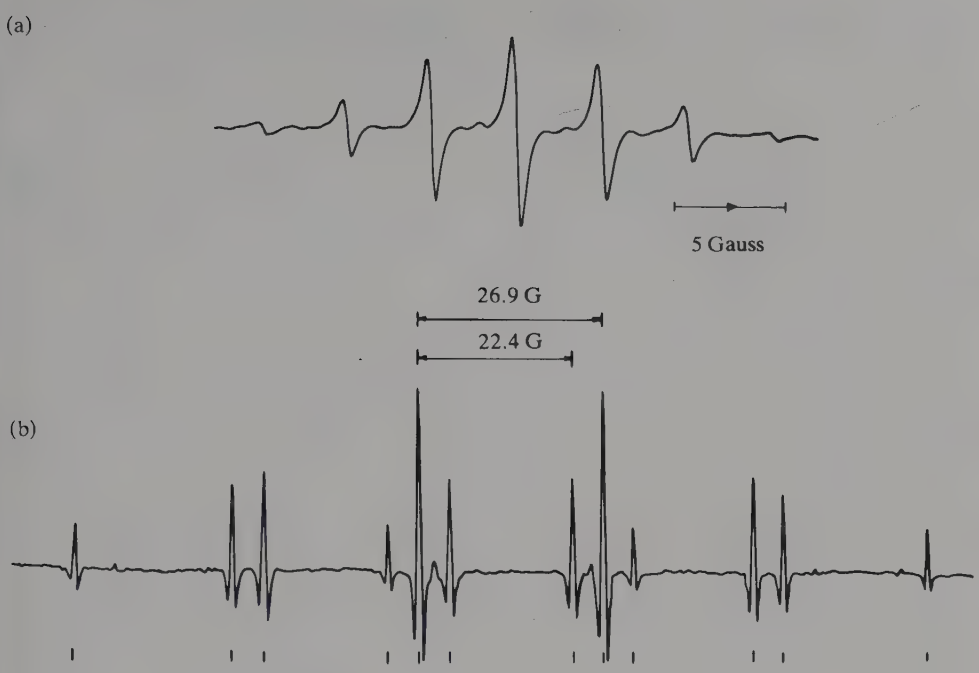


Fig. 12.2. Some EPR spectra of small organic free radicals: (a) Spectrum of the benzene radical anion. [From J. R. Bolton, *Mol. Phys.* **6**, 219 (1963). Reproduced by permission of Taylor and Francis, Ltd.] (b) Spectrum of the ethyl radical. [From R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **33**, 935 (1960); **39**, 2147 (1963). Reproduced by permission of the American Institute of Physics.]

The radical was generated by photolytic decomposition of di-*t*-butyl peroxide in methylcyclopropane, a process that leads to selective abstraction of a methyl hydrogen from methylcyclopropane:

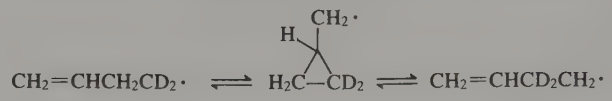
$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2\,(CH_3)_3C{-}O\cdot$$

$$(CH_3)_3C{-}O\cdot + \triangleright\!\!-CH_3 \longrightarrow \triangleright\!\!-CH_2\cdot + (CH_3)_3COH$$

Below −140°C, the EPR spectrum observed was that of the cyclopropylmethyl radical. If the photolysis was done above −140°C, however, the spectrum of a second species was seen, and above −100°C, this was the only spectrum observed. This spectrum could be shown to be that of the 3-butenyl radical.[6] This study also established that the 3-butenyl radical did not revert to the cyclopropylmethyl radical on being cooled back to −140°C. The conclusion is that the ring opening of the cyclopropylmethyl radical is a very facile process, so that its lifetime above −100°C is very short. The reversal of the ring opening can be detected by isotopic labeling

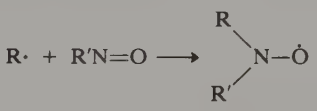
6. J. K. Kochi, P. J. Krusic, and D. R. Eaton, *J. Am. Chem. Soc.* **91**, 1877 (1969).

experiments which reveal the occurrence of deuterium migration:



The rates of both the ring opening ($k \approx 2 \times 10^7\ sec^{-1}$ at 25°C) and the ring closure ($k \approx 3 \times 10^3\ sec^{-1}$) have been measured and show that only a very small amount of the cyclopropylmethyl radical is present at equilibrium, in agreement with the EPR results.[7]

It is important to emphasize that direct studies such as those carried out on the cyclopropylmethyl radical can be done with low steady state concentrations of the radical. In the case of the study of the cyclopropylmethyl radical, removal of the source of irradiation would lead to rapid disappearance of the signal, since the radicals would react rapidly and not be replaced. Under many conditions, the steady state concentration of the radical may be too low to permit detection. Failure to observe an EPR signal therefore cannot be taken as conclusive evidence against a radical intermediate. A technique called *spin trapping* has been developed that can permit EPR studies in such situations. A diamagnetic molecule that has the property of reacting rapidly with radicals to give a stable radical is added to the reaction mixture being studied. Under these conditions, long-lived radicals derived from the intermediate may be formed and can be studied by EPR techniques. The most useful molecules for such studies are nitroso compounds because they react rapidly with radicals to give disubstituted nitroxide radicals[8]:



Analysis of the EPR spectrum of the nitroxide radical can usually provide information about the structure of the original radical.

Another technique for the study of reactions that is highly specific for radical processes is known as CIDNP, an abbreviation for *chemically induced dynamic nuclear polarization*.[9] The instrumentation required for such studies is a normal NMR spectrometer. CIDNP is observed as a strong perturbation of the intensity of NMR signals in products formed in certain types of free radical reactions. CIDNP is observed when the normal population of nuclear spin states dictated by the Boltzmann distribution is disturbed by the presence of an unpaired electron. The intense magnetic moment associated with an electron causes a polarization of nuclear spin states, which is manifested by enhanced absorption or emission, or both, in the NMR spectrum of the diamagnetic product of a free radical reaction. The technique is less general than EPR spectroscopy because not all free radicals can be expected to exhibit the phenomenon.

7. A. Effio, D. Griller, K. U. Ingold, A. L. J. Beckwith, and A. K. Serelis, *J. Am. Chem. Soc.* **102**, 1734 (1980).
8. E. G. Janzen, *Acc. Chem. Res.* **4**, 31 (1971).
9. H. R. Ward, *Acc. Chem. Res.* **5**, 18 (1972); R. G. Lawler, *Acc. Chem. Res.* **5**, 25 (1972).

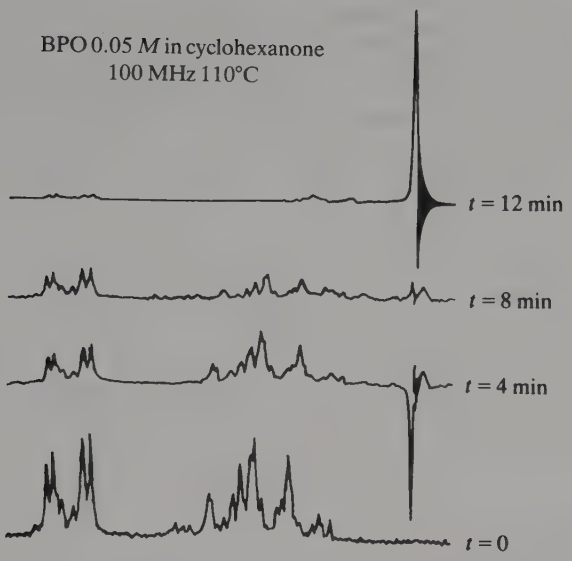


Fig. 12.3. NMR spectra recorded during thermal decomposition of dibenzoyl peroxide. Singlet at high field is due to benzene; other signals are due to dibenzoyl peroxide. [From H. Fischer and J. Bargon, *Acc. Chem. Res.* **4**, 110 (1969). Reproduced by permission of the American Chemical Society.]

The NMR spectra obtained in a typical CIDNP experiment are shown in Fig. 12.3 for the decomposition of benzoyl peroxide in cyclohexanone:

$$\mathrm{PhC(=O)OC(=O)Ph} \longrightarrow 2\,\mathrm{Ph}\cdot + 2\,\mathrm{CO_2}$$

$$\mathrm{Ph}\cdot + \mathrm{S{-}H} \longrightarrow \mathrm{C_6H_6} + \mathrm{S}\cdot$$

The emission signal corresponding to benzene confirms that it is formed by a free-radical reaction. The enhanced absorption or emission signals are observed only as long as the reaction is proceeding. When the reaction is complete or is stopped in some way, the signals rapidly return to their normal intensity.

The origin of the modified signal intensities is understood to arise from interaction of two radicals at close range; the theory used to explain the system is known as the *radical-pair model.* It must be remembered that the energy separation between the two nuclear spin states of a proton is very small (about 4×10^{-3} cal/mol at 10,000 G), and therefore at normal temperatures there are nearly as many molecules in the excited as in the ground state. This places a limit on the intensity of the absorption line in a normal NMR spectrum. In the CIDNP phenomena, the interaction of radicals at close range results in more of the excited state or more of the ground state of the product being populated than in the equilibrium distribution.

If the excited state is populated in excess of that required by the Boltzmann distribution, energy is emitted on relaxation to the normal distribution, and an emission signal (negative peak) is observed. If it is the ground state that is populated in excess, the probability for energy absorption is increased, and enhanced absorption is observed. Several discussions are available that provide a detailed account of the mechanism by which interacting radical pairs affect the population of the nuclear spin states of product.[10]

One aspect of both EPR and CIDNP studies that should be kept in mind is that either is capable of detecting relatively small amounts of radical intermediates. This aspect makes both techniques quite sensitive, but can also present a pitfall. The most prominent features of either EPR or CIDNP spectra may actually be due to radicals that account for only minor amounts of the total reaction process. An example of this was found in a study of the decomposition of trichloroacetyl peroxide in alkenes:

$$Cl_3C\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}CCl_3 \longrightarrow 2\,Cl_3C\cdot + 2\,CO_2$$

$$Cl_3C\cdot + CH_2{=}C(CH_3)_2 \longrightarrow Cl_3CCH_2\dot{C}(CH_3)_2$$

$$Cl_3C\cdot + Cl_3CCH_2\dot{C}(CH_3)_2 \longrightarrow Cl_3CH + Cl_3CCH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}CH_2$$

In addition to the emission signals of $CHCl_3$ and $Cl_3CCH_2\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}{=}CH_2$, the major reaction products, a strong emission line for Cl_3CCHCl_2 was identified. However, Cl_3CCHCl_2 appears to play no major role in the overall reaction, for once the radical reaction is complete and the signals have returned to their normal intensity, so little Cl_3CCHCl_2 is present that its normal spectrum cannot be detected.[11]

12.1.4. Sources of Free Radicals

There are several reactions that are quite commonly used as sources of free radicals, both for the study of radical structure and in synthetic processes. Some of the most general methods are outlined here. Examples of many of these will be encountered again when specific reactions are discussed. For the most part, we will defer discussion of the reactions of the radicals until then.

Peroxides are a common source of radical intermediates. An advantage of the generation of radicals from peroxides is that reaction generally occurs at relatively

10. R. G. Lawler and H. R. Ward, in *Determination of Organic Structures by Physical Methods*, Vol. 5, F. C. Nachod and J. J. Zuckerman (eds.), Academic Press, New York, 1973, Chap. 3; H. R. Ward, in *Free Radicals*, J. Kochi (ed.), Interscience, New York, 1973, Chap. 6. A. R. Lepley and G. L. Closs, *Chemically Induced Magnetic Polarization*, Wiley, New York, 1973; G. L. Closs, *Adv. Mag. Res.* **7**, 157 (1974); R. Kaptein, *Adv. Free Radical Chem.* **5**, 318 (1975); J. Bargon, *J. Am. Chem. Soc.* **99**, 8350 (1977); G. L. Closs and M. S. Czeropski, *J. Am. Chem. Soc.* **99**, 6127 (1977).
11. H. Y. Loken, R. G. Lawler, and H. R. Ward, *J. Org. Chem.* **38**, 106 (1973).

low temperature because the bond energy of the oxygen–oxygen bond in these compounds (~30 kcal/mol) is quite low. Several kinds of peroxide compounds have been employed. Diacyl peroxides are sources of alkyl radicals because the carboxyl radicals that are initially formed lose CO_2 very rapidly[12]:

$$CH_3COOCCH_3 \xrightarrow{80\text{–}100^\circ C} 2\,CH_3CO\cdot \longrightarrow 2\,CH_3\cdot + 2\,CO_2$$

$$PhCOOCPh \xrightarrow{80\text{–}100^\circ C} 2\,PhCO\cdot \longrightarrow 2\,Ph\cdot + 2\,CO_2$$

In the case of aryl analogs, products may be derived either from the carboxyl radical or the radical formed by decarboxylation.[13] Alkyl hydroperoxides give alkoxy radicals and the hydroxyl radical. *t*-Butyl hydroperoxide is easily available, and has often been used as a radical source. Detailed studies have been reported on the mechanism of the decomposition, which is somewhat more complicated than simple unimolecular decomposition.[14] Dialkyl peroxides give two alkoxy radicals[15]:

$$C_2H_5OOC_2H_5 \xrightarrow{80^\circ C} 2\,C_2H_5O\cdot$$

Peroxyesters are also sources of radicals. The acyloxy portion normally loses carbon dioxide, so peroxyesters yield an alkyl (or aryl) and alkoxy radical

$$RCOOC(CH_3)_3 \longrightarrow R\cdot + CO_2 + \cdot OC(CH_3)_3$$

The decomposition of peroxides, which occurs thermally in the examples cited above, can also be readily accomplished by photochemical excitation. The alkyl hydroperoxides are also sometimes used in conjunction with a transition metal ion. Under these conditions, an alkoxy radical is produced, but the hydroxyl portion appears as hydroxide as a result of one-electron reduction by the metal ion.[17]

$$(CH_3)_3COOH + M^{2+} \longrightarrow (CH_3)_3CO\cdot + {}^-OH + M^{3+}$$

The thermal decompositions described above are unimolecular reactions that should exhibit first-order kinetics. Under many conditions, peroxides decompose at rates faster than expected for unimolecular thermal decomposition, and with more

12. J. C. Martin, J. W. Taylor, and E. H. Drew, *J. Am. Chem. Soc.* **89**, 129 (1967); F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *J. Am. Chem. Soc.* **86**, 2080 (1964).
13. D. F. De Tar, R. A. J. Long, J. Rendleman, J. Bradley, and P. Duncan, *J. Am. Chem. Soc.* **89**, 4051 (1967).
14. R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.* **33**, 1416 (1968), and accompanying papers.
15. W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.* **86**, 4237 (1964).
16. P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.* **80**, 1398 (1958).
17. W. H. Richardson, *J. Am. Chem. Soc.* **87**, 247 (1965).

complicated kinetics. This behavior is known as *induced decomposition*, and occurs when at least part of the peroxide decomposition is the result of bimolecular reactions with radicals present in solution, as illustrated specifically for diethyl peroxide:

$$X\cdot + CH_3CH_2OOCH_2CH_3 \longrightarrow CH_3\dot{C}HOOCH_2CH_3 + H{-}X$$

$$CH_3\dot{C}HOOCH_2CH_3 \longrightarrow CH_3CH{=}O + \cdot OCH_2CH_3$$

The amount of induced decomposition that occurs depends on the concentration and reactivity of the radicals generated and the susceptibility of the substrate to radical attack. The attacking radical X· may be one of those formed from the peroxide, but it can also be derived from other sources, such as the solvent. Thus, both the structure of the peroxide and the nature of the reaction medium are important in determining the extent of induced decomposition relative to unimolecular homolysis.

Another quite general source of free radicals is the decomposition of azo compounds. The products are molecular nitrogen and the radicals derived from the alkyl groups:

$$R{-}N{=}N{-}R' \xrightarrow[h\nu]{\Delta \text{ or}} R\cdot + N{\equiv}N + \cdot R'$$

Both symmetrical and unsymmetrical azo compounds can be made so that a single radical or two different ones may be generated. The energy for the decomposition can be either thermal or photochemical.[18] In the thermal decomposition, it has been established that the temperature at which decomposition occurs depends on the nature of the substituent groups. If the radical that will be formed is a very stable one, temperatures only slightly in excess of room temperature may be sufficient. Azomethane, however, does not decompose to methyl radicals and nitrogen until temperatures above 400°C are reached. In Section 12.2.2, a discussion of the structural features that stabilize radicals will be given. The allyl radical is particularly stable, and azo compounds with allyl substituents decompose at much lower temperatures than saturated alkyl azo compounds:

$$CH_3CH_2CH_2N{=}NCH_2CH{=}CH_2 \xrightarrow{130°C} CH_3CH_2CH_2\cdot + N_2 + CH_2{=}CHCH_2\cdot$$

Ref. 19a

Unsymmetrical azo compounds must be used to generate phenyl radicals because azobenzene is very stable thermally. Phenylazotriphenylmethane decomposes quite readily because of the stability of the triphenylmethyl radical:

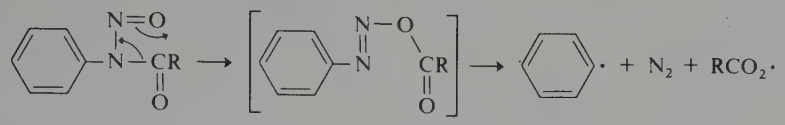
$$PhN{=}NC(Ph)_3 \xrightarrow{60°C} Ph\cdot + Ph_3C\cdot + N_2$$

Ref. 19b

N-Nitrosoanilides are an alternative source of aryl radicals. Although a first glance at

18. P. S. Engel, *Chem. Rev.* **80**, 99 (1980).
19. (a) K. Takagi and R. J. Crawford, *J. Am. Chem. Soc.* **93**, 5910 (1971).
    (b) R. F. Bridger and G. A. Russell, *J. Am. Chem. Soc.* **85**, 3754 (1963).

the substrate would probably not suggest a relationship to azo compound decomposition, there is in fact a fairly close one. Mechanistic studies have shown that the *N*-nitrosoanilides rearrange to species that contain a nitrogen–nitrogen double



bond. This intermediate then decomposes by a relatively complex process that will be discussed more fully in Section 12.3.3.[20]

A technique that is a convenient source of radicals for study by EPR involves photolysis of a mixture of di-*t*-butyl peroxide, triethylsilane, and the alkyl bromide corresponding to the radical to be studied.[21] Photolysis of the peroxide gives *t*-butoxy radicals, which selectively abstract hydrogen from the silane. This reactive silicon radical in turn abstracts bromine from the alkyl halide, generating the alkyl radical at steady state concentrations suitable for EPR study:

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2\,(CH_3)_3CO\cdot$$

$$(CH_3)_3CO\cdot + (C_2H_5)_3SiH \longrightarrow (CH_3)_3COH + (C_2H_5)_3Si\cdot$$

$$(C_2H_5)_3Si\cdot + RBr \longrightarrow (C_2H_5)_3SiBr + R\cdot$$

12.1.5. Structural and Stereochemical Properties of Radical Intermediates

EPR studies and other physical methods have provided the basis for some insight into the detailed geometry of radical species.[22] Deductions about structure can also be drawn from the study of the stereochemistry of reactions involving radical intermediates. Several structural possibilities must be considered. If discussion is limited to alkyl radicals, the possibilities include a rigid pyramidal structure, rapidly inverting pyramidal structures, or a planar trigonal structure.

rigid pyramidal flexible pyramidal planar

Precise description of the pyramidal structures would also require that the bond angles be specified. The EPR spectrum of the methyl radical leads to the conclusion

20. C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); J. I. G. Cadogan, *Acc. Chem. Res.* **4**, 186 (1971).
21. A. Hudson and R. A. Jackson, *Chem. Commun.*, 1323 (1969); D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 7695 (1972).
22. For a review see J. K. Kochi, *Adv. Free Radicals*, **5**, 189 (1975).

that its structure could be either planar or a very shallow pyramid.[23a] The IR spectrum of methyl radical has been recorded at very low temperatures in frozen argon.[23b] Under these conditions, a relatively high concentration of reactive species can be obtained, since chemical reactions are prevented by the inertness of the surrounding matrix. The IR spectrum puts a maximum of ~5° on the deviation from planarity.

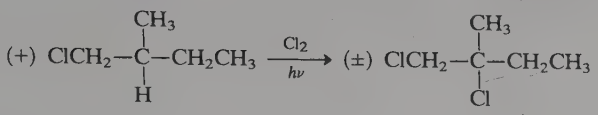
Alkyl substituents apparently cause carbon radicals to adopt a pyramidal geometry. The *tert*-butyl radical has been studied particularly extensively, and while experimental results have been interpreted both in terms of planar and slightly pyramidal structures, theoretical results favor the pyramidal structure.[24] Both theory and experiment agree that the barrier to inversion is very low, leading to rapid inversion.

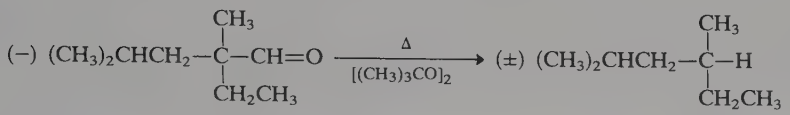
Radical geometry is significantly affected by substituent groups which can act as π donors. Addition of fluorine or oxygen substituents, in particular, favors a pyramidal structure. Analysis of the EPR spectra of the mono-, di-, and trifluoromethyl radicals indicates a progressive distortion from planarity.[25] Both EPR and IR studies of the trifluoromethyl radical show it to be pyramidal.[26] The basis of this structural effect has been probed by molecular orbital calculations and is considered to result from interactions of both the σ and π type. There is a repulsive interaction between the singly occupied p orbital and the filled orbitals occupied by "lone-pair" electrons on the fluorine or oxygen substituents. This repulsive interaction is minimized by adoption of a pyramidal geometry. The tendency for pyramidal geometry is reinforced by an interaction between the p-orbital on carbon and the σ^* antibonding orbitals associated with the C–F or C–O bonds. The energy of the p orbital can be lowered by interaction with the σ^* orbital which increases electron density on the more electronegative fluorine or oxygen atom. This p–σ^* interaction is increased by pyramidal geometry.[25b]

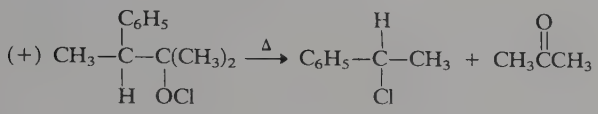
stabilizing interaction with σ^*

23. (a) M. Karplus and G. K. Fraenkel, *J. Chem. Phys.* **35**, 1312 (1961).
(b) L. Andrews and G. C. Pimentel, *J. Chem. Phys.* **47**, 3637 (1967).
24. D. E. Wood, L. F. Williams, R. F. Sprecher, and W. A. Lathan, *J. Am. Chem. Soc.* **94**, 6241 (1972); J. B. Lisle, L. F. Williams, and D. E. Wood, *J. Am. Chem. Soc.* **98**, 227 (1976); P. J. Krusic and P. Meakin, *J. Am. Chem. Soc.* **98**, 228 (1976); L. Bonazzola, N. Leray, and J. Roncin, *J. Am. Chem. Soc.* **99**, 8348 (1977); M. N. Paddon-Row and K. N. Houk, *J. Am. Chem. Soc.* **103**, 5046 (1981).
25. P. J. Krusic and R. C. Bingham, *J. Am. Chem. Soc.* **98**, 230 (1976); F. Bernardi, W. Cherry, S. Shaik, and N. D. Epiotis, *J. Am. Chem. Soc.* **100**, 1352 (1978).
26. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **43**, 2704 (1965); G. A. Carlson and G. C. Pimentel, *J. Chem. Phys.* **44**, 4053 (1966).

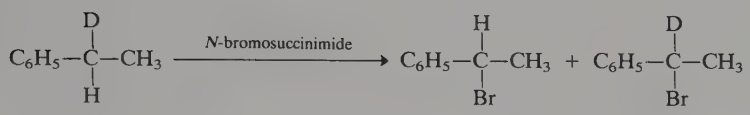
Scheme 12.2. Stereochemistry of Radical Reactions at Chiral Carbon Atoms

1[a] 

2[b] 

3[c] 

99% racemization

4[d] 

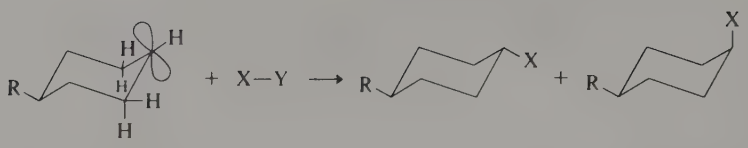
>99.7% racemization

a. H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Am. Chem. Soc.* **62**, 3435 (1940).
b. W. von E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.* **74**, 3000 (1952).
c. F. D. Greene, *J. Am. Chem. Soc.* **81**, 2688 (1959); D. B. Denney and W. F. Beach, *J. Org. Chem.* **24**, 108 (1959).
d. H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.* **81**, 5404 (1959).

There have been many studies aimed at deducing the geometry at radical sites by examining the stereochemistry of reactions known to involve radical intermediates. The most direct kind of study involves the generation of a radical at an asymmetric carbon. A planar or rapidly inverting radical would lead to racemization, whereas a rigid pyramidal structure would be expected to give optically active product. Some reactions that have been subjected to this kind of study are shown in Scheme 12.2. In each case, the product was racemic, indicating that alkyl radicals do not retain the tetrahedral geometry of their precursors.

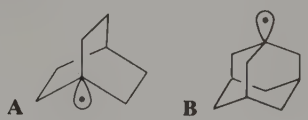
Cyclic molecules also permit deductions about stereochemistry without the necessity for optically active compounds, and the stereochemistry of a number of reactions of 4-substituted cyclohexyl radicals has been investigated.[27] These reactions give mixtures of *cis* and *trans* isomers, indicating that the radical intermediates in these reactions do not retain the stereochemistry of the radical precursor. Such reactions are not usually very stereoselective, but some show a preference for

27. A summary is available in F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Am. Chem. Soc.* **90**, 5793 (1968).

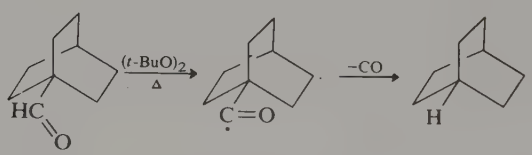


formation of the *cis* product. This has been explained in terms of a torsional effect. If the cyclohexyl radical is planar or a shallow pyramid, equatorial attack leading to *trans* product causes the hydrogen at the radical site to become eclipsed with the two neighboring equatorial hydrogens. Axial attack does not suffer from this strain, since the hydrogen at the radical site moves away from the equatorial hydrogens to the staggered conformation that is present in the chair conformation of the ring.

Another approach to obtaining information about the geometric requirements of free radicals has been to examine bridgehead systems. It will be recalled that the small bicyclic rings strongly resist formation of carbonium ions at bridgehead carbon atoms because the skeletal geometry prevents attainment of the preferred planar geometry at the carbonium ion site. EPR spectra of the bridgehead radicals **A** and **B** are consistent with pyramidal geometry at the bridgehead carbon atoms.[28]



Studies of chemical reactivity have revealed no particularly strong resistance to formation of bridgehead radicals. In an early study, the decarbonylation of bridgehead aldehydes was found to proceed without difficulty[29]:

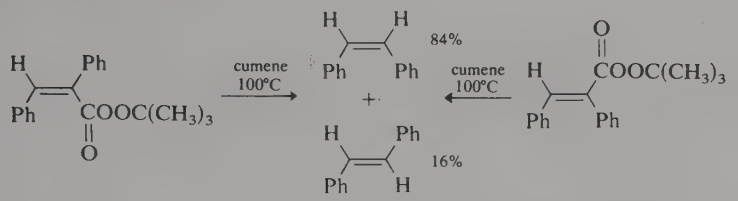


Subsequently, rate studies have shown significant rate retardations for reactions in which the norbornyl radical is generated in a rate-determining step.[30] Typically, such reactions proceed 500 to 1000 times slower than the corresponding reaction generating the *t*-butyl radical. But this is a much smaller rate retardation than the 10^{14} found in S_N1 solvolyses. Rate retardations are less for less strained bicyclic ring systems. The general conclusion drawn from these studies is that for radicals the energy associated with a nonplanar geometry is not nearly so large as with a carbonium ion intermediate.[31]

28. P. J. Krusic, T. A. Rettig, and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 995 (1972).
29. W. v. E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.* **74**, 3000 (1952).
30. A. Oberlinner and C. Rüchardt, *Tetrahedron Lett.*, 4685 (1969); L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.* **46**, 3099 (1968); D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.* **87**, 2194 (1965).
31. C. Rüchardt, *Angew. Chem. Int. Ed. Engl.* **9**, 830 (1970).

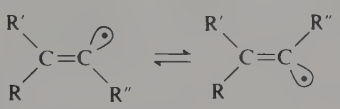
To summarize, structural studies of radicals and the stereochemistry of radical reactions both lead to the conclusion that alkyl radicals are not rigid pyramids. Instead, they are either planar or shallow pyramids, and barriers to inversion of the pyramidal structures are low. Radicals also seem to be able to tolerate small geometric distortions associated with strained rings without great increase in their energy.

There has also been study of the stereochemistry of vinyl free radicals.[32] Radicals formed at trigonal centers can rapidly undergo equilibration with the geometric isomer, giving rise to the same product mixture from isomeric *cis* and *trans* starting materials:



Ref. 33

In this case, there is good evidence from EPR spectra that the radical is not linear in its ground state, but is an easily inverted bent species.[34] The barrier is very low (~2 kcal/mol), so that the lifetime of the individual isomers is short (10^{-8}–10^{-10} sec):



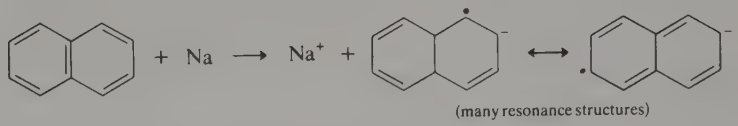
There is some evidence that when the radical carbon bears a substituent, such as methoxy or chloro, the rate of stereoisomeric equilibration decreases relative to hydrogen abstraction by the radical.[35] In this case, the product composition depends on the stereochemistry of the reactant.

12.1.6. Charged Radical Species

Unpaired electrons can be present in charged species as well as in the neutral systems that have been considered up to this point. There have been many studies of such radical cations and radical anions, and we will consider some representative examples in this section.

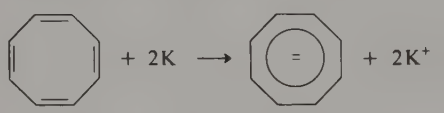
32. For general reviews of structure and reactivity of vinyl radicals, see W. G. Bentrude, *Annu. Rev. Phys. Chem.* **18**, 283 (1967); L. A. Singer, in *Selective Organic Transformations*, Vol. II, B. S. Thyagarajan (ed.), John Wiley, New York, 1972, p. 239; O. Simamura, *Top. Stereochem.* **4**, 1 (1969).
33. L. A. Singer and N. P. Kong, *J. Am. Chem. Soc.* **88**, 5213 (1966); J. A. Kampmeier and R. M. Fantazier, *J. Am. Chem. Soc.* **88**, 1959 (1966).
34. R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.* **39**, 2147 (1963).
35. M. S. Liu, S. Soloway, D. K. Wedegaertner, and J. A. Kampmeier, *J. Am. Chem. Soc.* **93**, 3809 (1971); L. A. Singer and N. P. Kong, *J. Am. Chem. Soc.* **89**, 5251 (1967).

Various aromatic and polyolefinic hydrocarbons undergo one-electron reduction by alkali metals.[36] Benzene and naphthalene are good examples. The spectrum of the benzene radical anion was shown in Fig. 12.2a (p. 631). Such reactions must be carried out in aprotic media, and ethers are the most commonly used solvents. The ease of formation of such radical anions increases as the number of fused rings



(many resonance structures)

increases. In the presence of a proton source, the radical anion is protonated, and further reduction occurs (the Birch reduction, Part B, Chapter 5). In general, when no proton source is present, it is relatively difficult to add a second electron, and the radical anion can remain unchanged for long periods. Among the polyolefinic compounds, cyclooctatetraene provides an interesting case to contrast with the usual preference for one-electron reduction. It is converted to a dianion (diamagnetic) by addition of two electrons.[37] It is easy to rationalize the ease with which the cyclooctatetraene radical anion readily accepts a second electron in terms of the aromaticity of the ten-π-electron system that results:



Radical cations can be derived from aromatic hydrocarbons or olefins by reaction with one-electron oxidants. Antimony pentachloride and cobaltic ion are among the oxidants that have been used.[38] Most radical cations have limited stability, but the sensitivity of EPR spectral parameters to structure have permitted structural characterization of radical cations despite their limited stability.

In addition to chemical oxidations and reductions, electrochemical processes are an important means of generation of charged-radical species. One-electron oxidation at the anode of an electrolysis cell generates radical cations, while one-electron reduction at the cathode generates radical anions.

Two classes of charged radicals derived from ketones have been well studied. *Ketyls* are radical anions formed by one-electron reduction of a carbonyl compound. The formation of the benzophenone radical anion by reduction with sodium metal

36. D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Am. Chem. Soc.* **78**, 116 (1956); T. R. Tuttle, Jr., and S. I. Weissman, *J. Am. Chem. Soc.* **80**, 5342 (1958).
37. T. J. Katz, *J. Am. Chem. Soc.* **82**, 3784 (1960).
38. I. C. Lewis and L. S. Singer, *J. Chem. Phys.* **43**, 2712 (1965); R. M. Dessau, *J. Am. Chem. Soc.* **92**, 6356 (1970).

is an example:

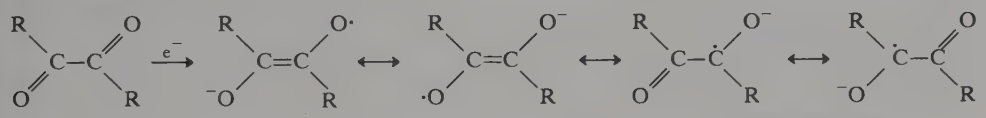
$$Ph_2C{=}O + Na \longrightarrow Ph_2\dot{C}{-}O^- \ Na^+$$

The radical anion is deep blue and is very reactive toward both oxygen and water, and must therefore be kept in an inert atmosphere. Many detailed studies on the structure and spectral properties of this and related systems have been carried out.[39] Both ion pairing and coupling to give a diamagnetic dianion can occur reversibly for the simple aromatic ketyls, and the positions of the equilibria are strongly solvent dependent:

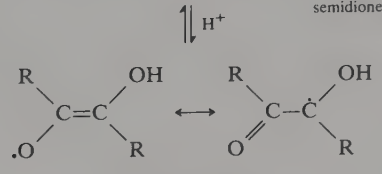
$$Na^+ + Ar_2\dot{C}{-}O^- \rightleftharpoons Ar_2\dot{C}{-}O^- \ Na^+ \rightleftharpoons Ar_2C(O^-Na^+)CAr_2$$

The diamagnetic dimer is involved as an intermediate in reductive dimerization of certain carbonyl compounds, a reaction that is discussed in Part B, Chapter 5.

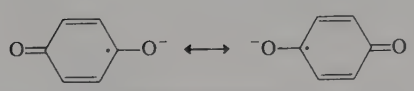
Reduction of α-dicarbonyl compounds gives radical anions known as *semidiones*.[40] Closely related are the one-electron reduction products of aromatic quinones, the *semiquinones*. Both the semidiones and semiquinones are capable of protonation to give neutral radicals.



semidione radical anion



neutral semidione radical

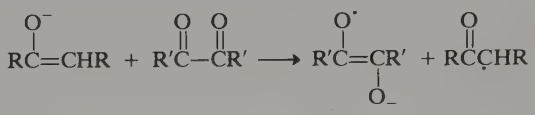


semiquinone radical anion

Several methods can be used to introduce an electron into the dicarbonyl compound. Metals such as zinc or inorganic reductants such as sodium dithionite generate the semidione. Electrolytic methods can also be used. A variety of

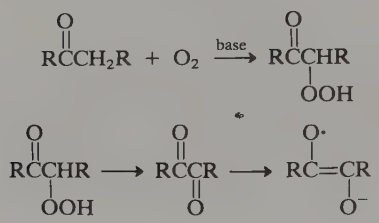
39. For a summary, see N. Hirota, in *Radical Ions*, E. T. Kaiser and L. Kevan (eds.), Interscience, New York, 1968, pp. 35–85.
40. G. A. Russell, in *Radical Ions*, E. T. Kaiser and L. Kevan (eds.), Interscience, New York, 1968, pp. 87–150.

electron transfer processes have also been shown to give the semidiones. Organic carbanions are also suitable reducing agents:



The radicals derived from the enolate are unstable and couple or undergo other modes of decomposition, so that only the stable semidione remains for study by EPR techniques. Because of the sensitivity of EPR methods, the amount of dione converted to semidione does not have to be high to permit structural information to be obtained.

Semidiones can also be generated oxidatively from monoketones in the presence of a base and small amounts of oxygen[41]:



The diketone is presumably generated oxidatively and then reduced to the semidione via reduction by carbanion present in the basic solution. Interpretation of EPR spectra can provide the spin density at the individual atoms, and this information gives some insight into the importance of the various resonance structures. Such interpretation of the spectra of the semidione from butane-2,3-dione indicates that each carbonyl oxygen has a spin density of 0.22 and each carbonyl carbon 0.23. The small amount of remaining spin density is associated with the hydrogen atoms.

12.2. Characteristics of Reaction Mechanisms Involving Radical Intermediates

12.2.1. Kinetic Characteristics of Chain Reactions

Certain aspects of free radical reactions are unique in comparison with other reaction types that have been considered to this point. The underlying difference is that many free radical reactions are chain reactions; that is, the reaction mechanism is such that many molecules are converted to product by a repetitive process initiated

41. G. A. Russell and E. T. Strom, *J. Am. Chem. Soc.* **86**, 744 (1964).

by the generation of a single reactive species. The following hypothetical mechanism illustrates a typical example:

	A–A	$\xrightarrow{k_i}$	2A·	initiation
repeated many times	A· + B–C	$\xrightarrow{k_{p1}}$	A–B + C·	propagation
	C· + A–A	$\xrightarrow{k_{p2}}$	A–C + A·	
	A· + B–C	$\xrightarrow{k_{p1}}$	A–B + C·	
	C· + A–A	$\xrightarrow{k_{p2}}$	A–C + A·	
	2A·	$\xrightarrow{k_{t1}}$	A–A	termination
	2C·	$\xrightarrow{k_{t2}}$	C–C	
	A· + C·	$\xrightarrow{k_{t3}}$	A–C	
overall reaction	A–A + B–C	$\longrightarrow$	A–B + A–C	

The step in which the reactive intermediate, in this case A·, is generated is called the *initiation step*. In the next four equations in the example, a sequence of two reactions is repeated; this is the *propagation phase*. Chain reactions are characterized by a *chain length*, which is the number of propagation steps that take place per initiation step. Finally, there are *termination steps*; these include any reaction that destroys one of the reactive intermediates necessary for the propagation of the chain. Clearly, the greater the frequency of termination steps, the lower the chain length will be.

The overall rate of a chain process is determined by the rates of the initiation, propagation, and termination reactions. Analysis of the kinetics of chain reactions normally depends on application of the steady state approximation to the radical intermediates. Such intermediates are highly reactive, and their concentrations are low and nearly constant through most of the course of the reaction:

$$\frac{d[\mathrm{A}\cdot]}{dt} = \frac{d[\mathrm{C}\cdot]}{dt} = 0$$

The result of the steady state condition is that the overall rate of initiation equals the rate of termination. The application of the steady state approximation and the resulting equality of the initiation and termination rates permits formulation of a rate law for the reaction mechanism above. The overall stoichiometry of a free radical chain reaction is independent of the initiating and termination steps.

$$\mathrm{A_2 + B\text{–}C \longrightarrow A\text{–}B + AC}$$

The overall rate of the reaction is:

$$\text{rate} = \frac{d[\mathrm{AB}]}{dt} = \frac{d[\mathrm{AC}]}{dt} = \frac{-d[\mathrm{A_2}]}{dt} = \frac{-d[\mathrm{BC}]}{dt}$$

Setting the rate of initiation equal to the rate of termination, assuming that k_{t2} is the dominant rate constant for termination:

$$k_i[\mathrm{A_2}] = 2k_{t2}[\mathrm{C}\cdot]^2$$

$$[\mathrm{C}\cdot] = \left(\frac{k_i}{2k_{t2}}\right)^{1/2}[\mathrm{A_2}]^{1/2}$$

In general, the rate constants for termination reactions involving coupling of two radicals are very large. Since the concentration of the reactive intermediates is very low, however, the overall rate of the termination reaction is low enough so that the propagation steps can compete. The rate of the overall reaction is that of either propagation step:

$$\text{rate} = k_{p2}[C\cdot][A_2]$$

Both must proceed at the same rate or the concentration of A· or C· would build up. By substituting for the concentration of the intermediate C·,

$$\text{rate} = k_{p2}\left(\frac{k_i}{2k_t}\right)^{1/2}[A_2]^{3/2} = k_{obs}[A_2]^{3/2}$$

The observed rate law is then three-halves order in the reagent A_2.

In most real systems, the situation is considerably complicated by the possibility that more than one termination reaction makes a contribution to the total termination rate. A more complete discussion of the effect of termination steps on the form of the rate law is given by Huyser.[42]

The overall rates of chain reactions can be greatly modified by changing the rate at which initiation or termination steps occur. The idea of initiation has been touched on in Section 12.1.4, where sources of free radicals were discussed. Many chain reactions of interest in organic chemistry depend on the presence of an *initiator*, which is a source of free radicals that provides the initial radical intermediate which starts the chain sequence. Peroxides are frequently used as initiators, since they give radicals by thermal decomposition at relatively low temperatures. An initiator serves the function of starting a chain process at a much lower temperature than is possible in a reaction mixture containing only reactants. Initiation by photochemical decomposition of a photosensitive molecule is also a common procedure. Conversely, chain reaction rates can be greatly retarded by *inhibitors*. A compound can act as an inhibitor if it is so highly reactive toward a radical involved in the chain process that it effectively traps the radical, thus causing termination of the chain. An inhibitor can completely stop a chain reaction if its reactivity is sufficiently high. The sensitivity of free radical chain reactions to both initiators and inhibitors can be used in mechanistic studies to distinguish radical chain reactions from polar or concerted processes.

Free radical chain inhibitors are of considerable economic importance. The term *antioxidant* is commonly applied to inhibitors that retard the free radical chain oxidations that can cause relatively rapid deterioration of many commercial products derived from organic molecules. Their function is particularly crucial in such organic materials as lubricating oils, which must remain chemically inert at relatively high

42. E. S. Huyser, *Free Radical Chain Reactions*, Wiley–Interscience, New York, 1970, pp. 39–54.

temperatures. The basic chain mechanism for autoxidation of hydrocarbons is:

$$\text{In}\cdot + \text{R–H} \longrightarrow \text{R}\cdot + \text{In–H}$$
$$\text{R}\cdot + \text{O}_2 \longrightarrow \text{ROO}\cdot$$
$$\text{ROO}\cdot + \text{R–H} \longrightarrow \text{ROOH} + \text{R}\cdot$$

The function of an antioxidant is to divert the peroxy radicals and thus prevent a chain process. Other antioxidants function by reacting with potential initiators, and thus retard oxidative degradation by preventing initiation of chains. Many sulfur and phosphorus compounds are believed to function in the latter way. The hydroperoxide products from autoxidation are potential chain initiators. This fact gives autoxidations the potential of being autocatalytic, since the more oxidation product is formed, the higher the initiator concentration. Divalent sulfur compounds and trivalent phosphorus compounds can reduce hydroperoxides, yielding stable products:

$$\text{ROOH} + \text{PR}'_3 \longrightarrow \text{ROH} + \text{O=PR}'_3$$

Such substances thus act as inhibitors by keeping the concentration of potential initiator low. Aromatic amines and phenols are also widely used as antioxidants. Generally, these types of substances are believed to function by undergoing hydrogen atom transfer with alkylperoxy radicals in preference to hydrocarbons. The resulting radicals are relatively stable and do not propagate a chain process, but instead dimerize or react in other ways to effect chain termination.

The sensitivity of free radical chain reactions to initiators and inhibitors can be used in mechanistic investigations. Strong variation in reaction rate on addition of relatively small amounts of compounds known to act as chain reaction inhibitors is evidence for a free radical chain mechanism. Such additives are often referred to as *free radical scavengers.* The types of compounds used as antioxidants can be used in such studies, but there are other substances that act as inhibitors. Molecular oxygen inhibits many free radical chain processes. The triplet oxygen molecule is extremely reactive toward many organic radicals:

$$\text{R}\cdot + \text{O}_2 \longrightarrow \text{R–O–O}\cdot$$

Stable free radicals, for example, galvinoxyl, (see Scheme 12.1, entry 5, for the structure of galvinoxyl) often act in the same way. Since they contain an unpaired electron, combination with a radical is very fast, and occurs in preference to the atom abstraction or addition steps that make up most radical-chain processes.

12.2.2. Structure–Reactivity Relationships

Structure–reactivity relationships can be probed by measurement of rates and equilibrium, as was discussed in Chapter 4. Direct kinetic measurements have been used relatively less often in the study of radical reactions than for heterolytic

reactions. Instead, *competition methods* have been widely used. The basis of the competition method lies in the rate expression for the reaction, and is just as valid a comparison of relative reactivity as individually measured rates, *provided the two competing processes are of the same kinetic order.* Suppose it is desired to compare the reactivity of two related compounds, B–X and B–Y, in a hypothetical sequence:

$$\text{A–A} \longrightarrow 2\text{A}\cdot$$

$$\text{A}\cdot + \text{B–X} \xrightarrow{k_X} \text{AB} + \text{X}\cdot$$

$$\text{X}\cdot + \text{A–A} \longrightarrow \text{A–X} + \text{A}\cdot$$

and

$$\text{A}\cdot + \text{B–Y} \xrightarrow{k_Y} \text{A–B} + \text{Y}\cdot$$

$$\text{Y}\cdot + \text{A–A} \longrightarrow \text{A–Y} + \text{A}\cdot$$

The data required are the relative magnitudes of k_X and k_Y. When both B–X and B–Y are present in the reaction system, they will be consumed at rates that are a function of their reactivity and their concentration:

$$\frac{-d[\text{B–X}]}{dt} = k_X[\text{A}\cdot][\text{B–X}]$$

$$\frac{-d[\text{B–Y}]}{dt} = k_Y[\text{A}\cdot][\text{B–Y}]$$

$$\frac{k_X}{k_Y} = \frac{d[\text{B–X}]/[\text{B–X}]}{d[\text{B–Y}]/[\text{B–Y}]}$$

Integration of this expression with the limits $[\text{B–X}] = [\text{B–X}]_{\text{initial}}$ to $[\text{B–X}]_t$ and $[\text{B–Y}]_{\text{initial}}$ to $[\text{B–Y}]_t$, where t is a point in time during the course of the reaction, gives

$$\frac{k_X}{k_Y} = \frac{\ln([\text{B–X}]_{in}/[\text{B–X}]_t)}{\ln([\text{B–Y}]_{in}/[\text{B–Y}]_t)}$$

This relationship permits the measurement of the ratio k_X/k_Y. The initial concentrations $[\text{B–X}]_{in}$ and $[\text{B–Y}]_{in}$ are known from the conditions of the experiment. The reaction can be stopped when some B–X and B–Y remain unreacted, or an excess of B–X and B–Y can be used, so that neither is completely consumed when the other reagent, A–A, has completely reacted. Analysis for [B–X] and [B–Y] then provides the information needed to calculate k_X/k_Y. Is it clear why the reactions being compared must be of the same order? If they were not, division of the two rate expressions would leave uncanceled concentration terms.

Another experiment that can be considered to be of the competition type involves the determination of the reactivity of different atoms in the same molecule. For example, gas phase chlorination of butane can lead to 1- or 2-chlorobutane. The relative reactivity (k_p/k_s) of the primary and secondary hydrogens is the sort of information that helps to characterize the details of the reaction process:

$$Cl_2 \longrightarrow 2\,Cl\cdot$$

$$Cl\cdot + CH_3CH_2CH_2CH_3 \xrightarrow{k_p} HCl + \cdot CH_2CH_2CH_2CH_3$$

$$Cl_2 + \cdot CH_2CH_2CH_2CH_3 \longrightarrow Cl\cdot + ClCH_2CH_2CH_2CH_2CH_3$$

$$Cl\cdot + CH_3CH_2CH_2CH_3 \xrightarrow{k_s} HCl + CH_3\dot{C}HCH_2CH_3$$

$$CH_3\dot{C}HCH_2CH_3 + Cl_2 \longrightarrow Cl\cdot + CH_3\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3$$

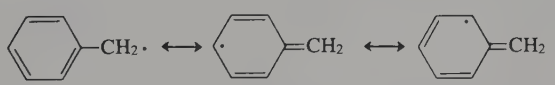
The value of k_p/k_s can be determined by measuring the ratio of the products 1-chlorobutane:2-chlorobutane at any point during the course of the reaction. A statistical correction is then made to take account of the fact that primary hydrogens outnumber secondary by 3 to 2:

$$\frac{k_p}{k_s} = \frac{2[\text{1-chlorobutane}]_t}{3[\text{2-chlorobutane}]_t}$$

Some general remarks about structure–reactivity relationships in radical reactions can be made at this point. Other examples of structural effects on reactivity will be discussed for specific reactions. Reactivity of C–H groups toward a radical that abstracts hydrogen atoms is usually pri < sec < tert. Vinyl and phenyl substituent groups increase the reactivity of hydrogen toward abstraction by radicals. This reactivity order reflects the bond dissociation energies of C–H bonds, which are in the order allyl < benzyl < tert < sec < pri.[43] The relative reactivity of primary, secondary, and tertiary positions in aliphatic hydrocarbons toward hydrogen abstraction by the methyl radical is 1:4.3:46.[44] The relative reactivity toward the *t*-butoxy radical is 1:10:44.[45] An allylic or benzylic hydrogen is more reactive by a factor of about 9 than a corresponding unactivated hydrogen toward methyl radical.[44] Data for other types of radicals have been obtained and tabulated.[43] In the gas phase, the bromine atom, for example, is very selective, with relative reactivities of 1:250:6300 for primary, secondary, and tertiary hydrogen having been measured.[46]

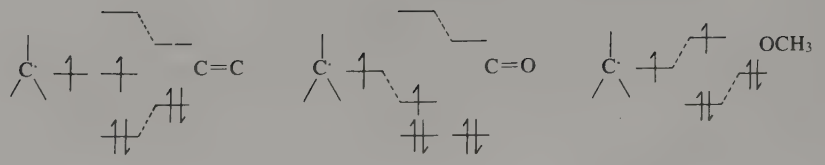
The stabilizing effects of vinyl groups (in allyl radicals) and phenyl groups (in benzyl radicals) are very familiar and can be satisfactorily rationalized in resonance terminology:

$$CH_2{=}CH{-}CH_2\cdot \leftrightarrow \cdot CH_2{-}CH{=}CH_2$$



The stabilizing role of other functional groups can also be explained in resonance

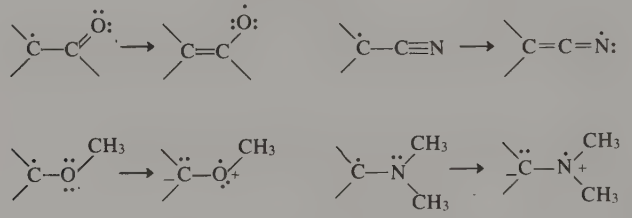
43. J. A. Kerr, *Chem. Rev.* **66**, 465 (1966).
44. W. A. Pryor, D. L. Fuller, and J. P. Stanley, *J. Am. Chem. Soc.* **94**, 1632 (1972).
45. C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.* **82**, 6108 (1960).
46. A. F. Trotman-Dickenson, *Adv. Free Radical Chem.* **1**, 1 (1965).



(a) vinyl (b) carbonyl (c) methoxy

Fig. 12.4. Qualitative MO description of interaction of a radical center with (a) vinyl, (b) carbonyl, and (c) methoxy substituents.

terms. Both electron-attracting groups such as carbonyl and cyano and electron-releasing groups such as methoxy and dimethylamino have a stabilizing effect on a radical center on an adjacent carbon. The resonance structures which depict these interactions indicate delocalization of the unpaired electron on to the adjacent substituents:



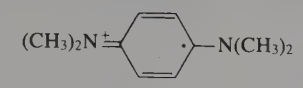
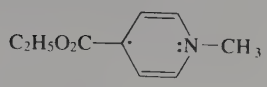
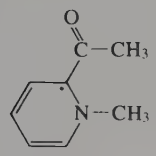
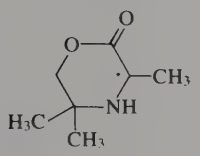
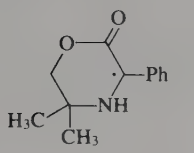
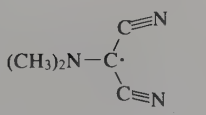
A description of the radical stabilizing effect of these substituent groups can also be presented in MO terms. In this case the question we ask is how will the unpaired electron in a p orbital on carbon interact with orbitals of an adjacent substituent such as a vinyl, carbonyl, or methoxy group? Figure 12.4 presents a qualitative description of the situation.

The basic tenet of PMO theory that the orbitals of closest energy will interact most strongly is employed in this analysis. In the case of an electron-accepting substituent such as a carbonyl group, the strongest interaction is with the LUMO and results in lowering of the energy of the orbital centered on the radical carbon. For an electron-releasing substituent there is a mutual interaction of the p orbital and one of the heteroatom lone-pair p-type orbitals. This interaction results in one orbital of lower energy and one of higher energy. Since the lower orbital is doubly occupied and the upper one only singly occupied, there is a net stabilization.

For the vinyl substituent we can analyze the stabilization in terms of simple Hückel MO theory. The interaction of a p orbital with an adjacent vinyl group creates the allyl radical. In Hückel calculations the resulting orbitals have energies of $\alpha + 1.4\beta$, α, and $\alpha - 1.4\beta$. Thus the interaction of the p orbital with both the π and π^* C=C orbitals leaves it unchanged but the π and π^* become ψ_1 and ψ_3 of an allyl radical. There is a net stabilization of 0.4β.

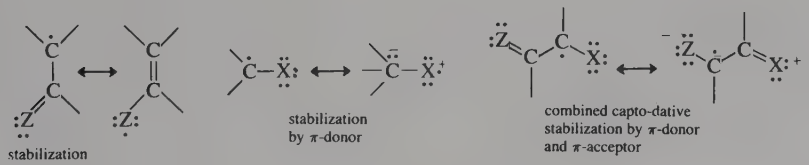
Radicals are particularly strongly stabilized when both an electron-attracting and an electron-releasing substituent are present on the radical carbon. This has

Scheme 12.3. Radicals with Capto-dative Stabilization

1[a]		Wurster's salts. Generated by one-electron oxidation of the diamine. Indefinitely stable.
2[b]		Generated by one-electron reduction of the pyridinium salt. Stable, distillable and only moderately reactive to oxygen.
3[c]		Stable and distillable. A small amount of dimer is present in equilibrium with the radical.
4[d]		Generated by spontaneous dissociation of the dimer. In equilibrium with dimer.
5[e]		Generated by spontaneous dissociation of the dimer. Stable for several days at room temperature. Oxidized by oxygen.
6[f]		Generated spontaneously from dimethylaminomalonitrile at room temperature. Observed to be persistent over many hours by EPR.

a. A. R. Forrester, J. M. Hay, and R. H. Thompson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, 1968, pp. 254–261.
b. J. Hermolin, M. Levin, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 4808 (1981).
c. J. Hermolin, M. Levin, Y. Ikegami, M. Sawayangai, and E. M. Kosower, *J. Am. Chem. Soc.* **103**, 4795 (1981).
d. T. H. Koch, J. A. Oleson, and J. DeNiro, *J. Am. Chem. Soc.* **97**, 7285 (1975).
e. J. M. Burns, D. L. Wharry, and T. H. Koch, *J. Am. Chem. Soc.* **103**, 849 (1981).
f. L. de Vries, *J. Am. Chem. Soc.* **100**, 926 (1978).

been called "*mero-stabilization*"[47] or "*capto-dative stabilization.*"[48] This type of stabilization results from mutual reinforcement of the two substituent effects. Scheme 12.3 gives some information on the stability of this type of radical.



47. R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. I*, 1422 (1974).
48. H. G. Viehe, R. Merenyi, L. Stella, and Z. Janousek, *Angew. Chem. Int. Ed. Engl.* **18**, 917 (1979).

Table 12.1. Bond-Dissociation Energies (kcal/mol)[a]

Bond	D.E.	Bond	D.E.
CH_3-H	104	$HOCH_2-H$	92
CH_3CH_2-H	98	$CH_3\overset{O}{\overset{\|}{C}}CH_2-H$	92
$(CH_3)_2CH-H$	94.5	$N\equiv CCH_2-H$	86
$(CH_3)_3C-H$	91	$CH_3\overset{O}{\overset{\|}{C}}O-\overset{O}{\overset{\|}{C}}CH_3$	30
$CH_2=CH-H$	104	$(CH_3)CO-OH$	44
	101	$F-F$	38
$PhCH_2-H$	85	$Cl-Cl$	58
$CH_2=CHCH_2-H$	85	$Br-Br$	46
F_3C-H	106	$I-I$	36
Cl_3C-H	96		
C_2H_5-F	106	$H-F$	136
C_2H_5-Cl	81	$H-Cl$	103
C_2H_5-Br	69	$H-Br$	87.5
C_2H_5-I	53	$H-I$	71

a. Data taken from J. A. Kerr, *Chem. Rev.* **66**, 465 (1966), and S. W. Benson, *J. Chem. Ed.* **42**, 502 (1965).

The radical stabilization provided by various functional groups results in reduced bond dissociation energies for bonds to the stabilized radical center. Some bond dissociation energy values are given in Table 12.1. The bond dissociation energies of the primary C–H bonds in acetonitrile (86 kcal/mol) and acetone (92 kcal/mol), for example, are weaker than a primary C–H bond in ethane (98 kcal/mol).

The stabilization of radical centers has been expressed in terms of the "radical reorganization energy." This is a quantity which can be determined by a systematic dissection of thermochemical data so that bond dissociation energies can be considered as the sum of an invariant bond energy and the "reorganization energy" of the product radical.[49] We do not wish to examine this system in detail here but the "reorganization energy" is a convenient measure of the stabilizing influence that certain functional groups have on carbon-centered radicals. Table 12.2 gives the reorganization energy from some radicals. These data reveal the familiar stabilization of allyl and benzyl radicals, which appear as negative reorganization energies. The trend of increasing stability of alkyl radicals in the order tertiary > secondary > primary > methyl is also apparent. The assignment of a significantly positive reorganization energy implies that the substituent will increase the bond energy of adjacent bonds. The phenyl and vinyl radicals are examples of groups which have positive reorganization energies.

49. R. T. Sanderson, *J. Org. Chem.*, **47**, 3835 (1982).

Table 12.2. Reorganization Energies in kcal/mol of Some Organic Free Radicals[a]

$PhCH_2\cdot$	−13.9	$(CH_3)_3C\cdot$	−1.7
$CH_2{=}CHCH_2\cdot$	−10.5	$(CH_3)_2CH\cdot$	+0.7
$CH_3\overset{\displaystyle O}{\overset{\|}{C}}\cdot$	−7.1	$CH_3CH_2\cdot$	+1.5
$H\overset{\displaystyle O}{\overset{\|}{C}}\cdot$	−5.8	$Ph\cdot$	+12.3
$HOCH_2\cdot$	−1.7	$CH_2{=}CH\cdot$	+10.0

a. As defined and calculated by R. T. Sanderson, *J. Org. Chem.* **47**, 3835 (1982).

Bond dissociation energies such as those in Table 12.1 are also useful for estimation of the energy balance in individual steps in free radical reaction sequences.

Example 12.1. Calculate the enthalpy for each step in the bromination of ethane by bromine atoms from molecular bromine. What is the overall enthalpy of the reaction?

Initiation	$Br{-}Br \longrightarrow 2\,Br\cdot$	$Br{-}Br$	+46 kcal/mol
propagation	$Br\cdot + CH_3{-}CH_3 \longrightarrow H{-}Br + \cdot CH_2{-}CH_3$	$H{-}Br$	−87
		$H{-}C$	+98
			+11
	$Br{-}Br + \cdot CH_2{-}CH_3 \longrightarrow BrCH_2{-}CH_3 + Br\cdot$	$Br{-}Br$	+46
		$Br{-}C$	−69
			−23
		total	−12 kcal/mol

The enthalpy of the reaction is given by the sum of the propagation steps and is −12 kcal/mol. Analysis of the energy changes associated with individual steps is useful in identifying endothermic steps. Since the activation enthalpy of any step cannot be less than its endothermicity, it follows that steps that are appreciably endothermic will have significant activation energies. Radical-chain processes depend on a series of rapid steps that maintain the reactive radicals at low concentration. Since termination reactions (combination of radicals) are usually very fast, the presence of an endothermic step in a chain sequence means that chains will be short, if a chain reaction can exist at all, because of competing recombination.

Enthalpy calculations, on the other hand, cannot give direct evidence about the activation energy of exothermic steps. Some progress appears to have been made toward calculation of activation energies for hydrogen-abstraction reactions. A method for calculation of activation energies for such reactions from available physical data that give agreement with experimental activation energies for a variety of reacting systems has been described.[50] The method estimates the energy of the linear three-atom array that represents the transition state for hydrogen abstraction by calculating the difference between the bonding and antibonding forces in this molecular arrangement. The data required for the calculation are bond-dissociation energies, atomic masses, bond lengths, and IR stretching frequencies of the reacting molecules.

Radical stability is reflected in a variety of ways in addition to the bond-dissociation energy of the corresponding C–H bond. It has already been indicated that radical structure and stability determines the temperature at which azo compounds undergo elimination of nitrogen (Section 12.1.4). Similar trends have been established in other radical-forming reactions. Rates of thermal decomposition of *t*-butyl peroxyesters, for example, vary over a wide range, depending on the structure of the carbonyl substituent.[51] This clearly indicates not only that the bonding changes involved in the rate-determining step are not completely localized in stretching the O–O bond, but also that radical character must be developing at the alkyl group by concerted cleavage of the alkyl–carbonyl bond:

$$R{-}\overset{\overset{O}{\|}}{C}{-}O{-}O{-}C(CH_3)_3 \longrightarrow R{\cdots}\overset{\overset{O}{\|}}{C}{\cdots}O{\cdots}OC(CH_3)_3 \longrightarrow R\cdot + CO_2 + \cdot OC(CH_3)_3$$

R	Relative rate at 60°C
CH_3	1
Ph	17
$PhCH_2$	290
$(CH_3)_3C$	1,700
Ph_2CH	19,300
$Ph(CH_3)_2C$	41,500
$PhCHCH{=}CH_2$	125,000

Free radical reactions written in the simplest way imply no separation of electrical charge. The case of toluene bromination can be used to illustrate this point:

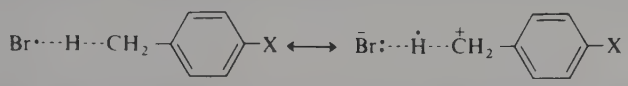
$$Br\cdot + H{-}CH_2Ph \longrightarrow Br{\cdots}H{\cdots}CH_2Ph \longrightarrow Br{-}H + \cdot CH_2Ph$$

$$PhCH_2\cdot + Br{-}Br \longrightarrow PhCH_2{\cdots}Br{\cdots}Br \longrightarrow PhCH_2Br + Br\cdot$$

50. For a full discussion, see A. Zavitsas, *J. Am. Chem. Soc.* **94**, 2779 (1972).
51. P. D. Bartlett and R. R. Hiatt, *J. Am. Chem. Soc.* **80**, 1398 (1958).

Nevertheless, many typical free radical processes respond to introduction of polar substituents just as do heterolytic processes that involve charge separation. Thus, analysis of toluene bromination using the Hammett equation gives a ρ value of -1.4, suggesting that the benzene ring experiences a substantial decrease of electron density in the transition state. Other radicals, for example the *tert*-butoxy radical, show a positive ρ for hydrogen abstraction reactions involving toluene.[52]

Why do free radical reactions involving neutral substrates and intermediates respond to substituent changes that modify electron density? One explanation has been based on the idea that there would be some polar character in the transition state because of the electronegativity differences of the reacting atoms[52]:



This idea receives general support from the fact that the most negative ρ values are found for more electronegative radicals such as Br·, Cl·, and Cl_3C·, There is, however, no simple correlation with a single property and this probably reflects the fact that the *selectivity* of the radicals is also different. Furthermore, in hydrogen abstraction reactions, where much of the quantitative work has been done, the C–H bond dissociation energy is also subject to a substituent effect.[53] Thus the extent of bond cleavage and formation at the transition state may be quite different for varying radicals. Successful interpretation of radical reactions therefore requires consideration of factors such as the electronegativity and polarizability of the radical, which govern its selectivity as well as the bond dissociation energy of the reacting C–H bond. The relative importance of these effects probably varies from system to system so that substituent effect trends in radical reactions appear to be less straightforward than for polar substituent effects which are dominated by the electron-releasing or electron-donating capacity of the substituent.[54]

12.3. Free-Radical Substitution Reactions

12.3.1. Halogenation

Free radical bromination of hydrocarbons is an important method of selective

52. R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.* **85**, 3142 (1963); J. Hradil and V. Chvalovsky, *Collect. Czech. Chem. Commun.* **33**, 2029 (1968); G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.* **77**, 4578 (1955); E. S. Huyser, *Free Radical Chain Reactions*, Wiley–Interscience, New York, 1970, Chap. 4; G. A. Russell in *Free Radicals*, J. Kochi (ed.), Vol. 1, Wiley, New York, 1973, Chap. 7.
53. A. A. Zavitsas and J. A. Pinto, *J. Am. Chem. Soc.* **94**, 7390 (1972).
54. W. H. Davis, Jr., and W. A. Pryor, *J. Am. Chem. Soc.* **99**, 6365 (1977); W. H. Davis, Jr., J. H. Gleaton, and W. A. Pryor, *J. Org. Chem.* **42**, 7 (1977); W. A. Pryor, G. Gojon and D. F. Church, *J. Org. Chem.* **43**, 793 (1978).

functionalization.[55] The process is a chain reaction involving the following steps:

initiation

$$Br\text{–}Br \longrightarrow 2\,Br\cdot$$

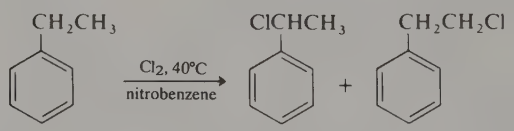
propagation

$$Br\cdot + R_3CH \longrightarrow R_3C\cdot + HBr$$

$$R_3C\cdot + Br_2 \longrightarrow R_3CBr + Br\cdot$$

The reaction is often initiated by photolysis of bromine. The hydrogen-abstraction step is rate limiting, and the product composition is governed by the selectivity of the hydrogen abstraction. The enthalpy requirements for abstraction of hydrogen from methane, ethane (primary), propane (secondary), and isobutane (tertiary), by bromine atoms are +16.5, +10.5, +7.0, and +3.5 kcal/mol, respectively.[56] These differences are reflected in the activation energies, and there is a substantial kinetic preference for hydrogen abstraction in the order tertiary > secondary > primary. Substituents that promote radical stability, such as phenyl, vinyl, or carbonyl groups, also lead to kinetic selectivity in radical brominations. Bromination at benzylic positions is a particularly efficient process, as illustrated by entries 2 and 4 in Scheme 12.4.

There are important differences in the reactions of the other halogens relative to bromination. In the case of chlorination, although the same chain mechanism described for bromination is operative, there is a key difference in the *greatly diminished selectivity of the chlorination*. Because of the greater energy of the chlorine atom relative to the bromine atom, abstractions of primary, secondary, and tertiary hydrogen are all exothermic, in contrast to bromination. As a result of this exothermicity, the stability of the product radical has less influence on the activation energy. With reference to the Hammond postulate, the transition state would be very reactant-like. As an example of the low selectivity, ethylbenzene is chlorinated at both the methyl and the methylene position, despite the much greater stability of the benzyl radical:



Ref. 57

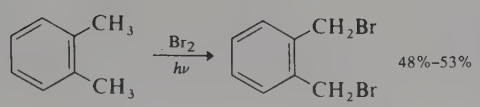
Radical chlorination reactions show a substantial polar effect. Positions substituted by electron-withdrawing groups are relatively unreactive toward chlorination, even though the substituents may be potentially capable of stabilizing the free radical

55. W. A. Thaler, *Meth. Free Radical Chem.* **2**, 121 (1969); A. Nechvatal, *Adv. Free Radicals*, **4**, 175 (1972).
56. E. S. Huyser, *Free Radical Chain Reactions*, Wiley–Interscience, New York, 1970, p. 91.
57. G. A. Russell, A. Ito, and D. G. Hendry, *J. Am. Chem. Soc.* **85**, 2976 (1963).

Scheme 12.4. Radical Halogenation

Molecular bromine

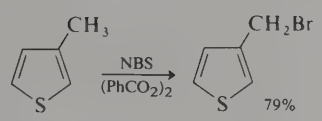
1[a] $(CH_3)_2CHCH_2CH_2CH_3 \xrightarrow[h\nu]{Br_2} (CH_3)_2\underset{\displaystyle Br}{\underset{|}{C}}CH_2CH_2CH_3$ 90%

2[b] 

48%–53%

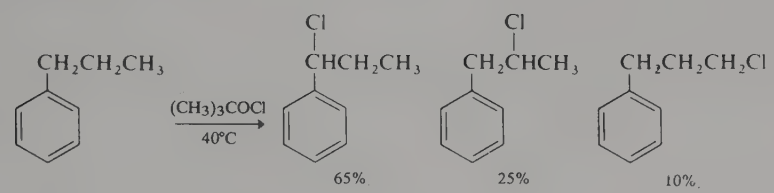
N-Bromosuccinimide

3[c] $CH_3(CH_2)_3CH{=}CHCH_3 \xrightarrow[(PhCO_2)_2]{NBS} CH_3(CH_2)_2\underset{\displaystyle Br}{\underset{|}{C}}HCH{=}CHCH_3$ 58%–64%

4[d] 

79%

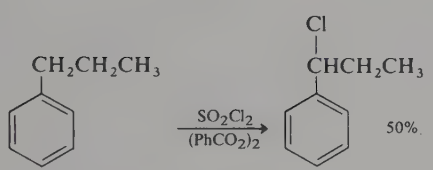
Other halogenating agents

5[e] 

65% 25% 10%

6[f] $CH_2{=}CHCH_2CH_3 + (CH_3)_3COCl \xrightarrow[-78°C]{h\nu} CH_3CH{=}CHCH_2Cl$ 74%

$+ CH_2{=}\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$ 26%

7[g] 

50%

a. G. A. Russell and H. C. Brown, *J. Am. Chem. Soc.* **77**, 4025 (1955).
b. E. F. M. Stephenson, *Org. Synth.* **IV**, 984 (1963).
c. F. L. Greenwood, M. D. Kellert, and J. Sedlak, *Org. Synth.* **IV**, 108 (1963).
d. E. Campaigne and B. F. Tullar, *Org. Synth.* **IV**, 921 (1963).
e. C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.* **82**, 6108 (1960).
f. C. Walling and W. Thaler, *J. Am. Chem. Soc.* **83**, 3877 (1961).
g. H. C. Brown and A. B. Ash, *J. Am. Chem. Soc.* **77**, 4019 (1955).

intermediate[58]:

$$CH_3CH_2CH_2CN + Cl_2 \longrightarrow \underset{\underset{Cl}{|}}{CH_3CHCH_2CN}\ (69\%) + ClCH_2CH_2CH_2CN\ (31\%)$$

The polar effect is attributed to the fact that the chlorine atom is a quite electrophilic species, and the relatively electron-deficient carbon atoms adjacent to electron-withdrawing groups are therefore avoided.

Functional groups such as carbonyl and ether groups also have strong directive effects on radical halogenations. Ethers tend to undergo chlorination α to the ether linkage, presumably because of the decreased bond energy of the α-C–H bond. Ester and carboxylic acid carbonyl groups tend to direct chlorination to the β and γ positions, presumably by the polar effect that causes attack at the α position by the electrophilic chlorine atom to be unfavorable. The contrasting behavior of electron-attracting and electron-releasing substituents can be understood in terms of the PMO diagram given in Fig. 12.4 (p. 650). The chlorine atom, being highly electronegative, will react preferentially with an electron-rich reaction site. The effect of an electron-attracting substituent is to decrease the electron density at the potential radical site, even though there is a net stabilization of the radical that is eventually formed. On the other hand, the electron-releasing substituent increases the electron density. Since the chlorine atom is highly reactive, the reaction would be expected to have a very early transition state, and the selectivity would then be governed by the electron density differences, rather than by the stability of the product radical.

Iodinations are inefficient reactions because the abstraction of hydrogen from C–H bonds by iodine radicals is highly endothermic, even for stable radicals. As a result, iodinations via chain reactions involving molecular iodine are not observed.

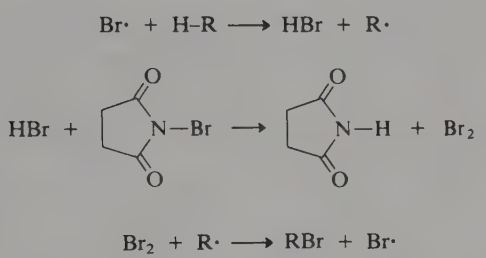
Fluorination presents problems of the other extreme. Both steps in the chain halogenation process are so exothermic that the reactions are violent if not performed under carefully controlled conditions. Furthermore, fluorine atoms are capable of cleaving carbon–carbon bonds:

$$F\cdot + CH_3CH_3 \longrightarrow CH_3F + CH_3\cdot$$

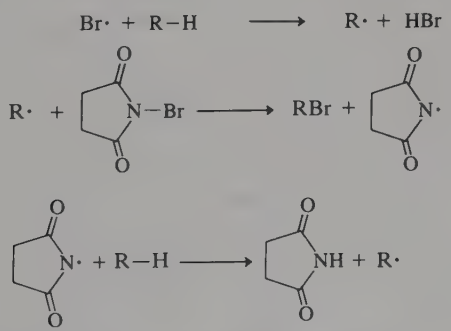
Saturated hydrocarbons such as neopentane, norbornane, and cyclooctane have been converted to the corresponding perfluoro derivatives in 10%–20% yield by reaction with fluorine gas diluted with helium at −78°C.[59] Because of the high reactivity of fluorine, it would be expected to be highly nonselective so that controlled monofluorination has not been developed as a laboratory synthetic method.

58. A. Bruylants, M. Tits, C. Dieu, and R. Gauthier, *Bull. Soc. Chim. Belg.* **61**, 266 (1952); A. Bruylants, M. Tits, and R. Danby, *Bull. Soc. Chim. Belg.* **58**, 210 (1949); M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.* **62**, 925 (1940).
59. N. J. Maraschin, B. D. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.* **97**, 513 (1975).

Halogenations of organic molecules can also be carried out with several other chemical reagents in addition to the molecular halogens. *N*-Bromosuccinimide (NBS) has been used quite extensively, especially for allylic and benzylic bromination. Mechanistic investigations have established that molecular bromine is the active halogenating agent under these conditions.[60] It is maintained at a low concentration through the course of the reaction by formation from NBS and hydrogen bromide. The fact that the bromine concentration is maintained at very low levels is important to the success of the allylic halogenation process. The failure of the double bond to undergo addition of bromine is the result of the reversibility of the bromine atom addition. In the absence of a sufficient concentration of bromine to complete the addition, the allylic halogenation is the dominant reaction:



N-Bromosuccinimide can also be used to brominate alkanes. For example, cyclopropane, cyclopentane, and cyclohexane give the corresponding bromides when irradiated with NBS in dichloromethane solution. Under these conditions the succinimidyl radical appears to be involved as the hydrogen-abstracting radical[61]:



The succinimidyl radical is less selective than the bromine atom so that bromination with NBS of unsymmetrical alkanes gives a mixture of isomeric alkyl bromides.

Another useful reagent for radical halogenation is *t*-butyl hypochlorite. The hydrogen-abstracting species in this case is the *t*-butoxy radical:

60. R. E. Pearson and J. C. Martin, *J. Am. Chem. Soc.* **85**, 354, 3142 (1963); G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Am. Chem. Soc.* **85**, 365 (1963); J. H. Incremona and J. C. Martin, *J. Am. Chem. Soc.* **92**, 627 (1970); J. C. Day, M. J. Lindstrom, and P. S. Skell, *J. Am. Chem. Soc.* **96**, 5616 (1974).
61. J. G. Traynham and Y.-S. Lee, *J. Am. Chem. Soc.* **96**, 3590 (1974).

$$(CH_3)_3CO\cdot + H\text{–}R \longrightarrow (CH_3)_3COH + R\cdot$$

$$R\cdot + (CH_3)_3COCl \longrightarrow (CH_3)_3CO\cdot + RCl$$

It is intermediate in selectivity between the chlorine atom and the bromine atom. The precise selectivity is solvent and temperature dependent, but in chlorobenzene as solvent, for example, a ratio of tert:sec:pri of 60:10:1 is typical.[62] A number of examples of radical-chain halogenation that illustrate the preparative use of these reactions are given in Scheme 12.4.

12.3.2. Oxidation

Free radical chain oxidation of organic molecules by molecular oxygen is often referred to as *autoxidation*. The general mechanism is outlined below:

initiation $\quad In\cdot + R\text{—}H \longrightarrow In\text{—}H + R\cdot$

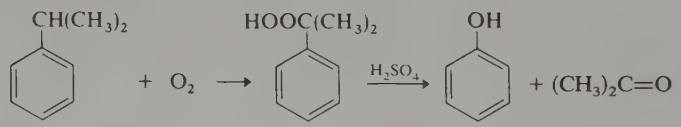
propagation $\quad R\cdot + O_2 \longrightarrow R\text{—}O\text{—}O\cdot$

$$R\text{—}O\text{—}O\cdot + R\text{—}H \longrightarrow R\text{—}O\text{—}O\text{—}H + R\cdot$$

The rate of reaction of oxygen with most radicals is very rapid because of the triplet character of molecular oxygen. The ease of the autoxidation is therefore largely governed by the ease of hydrogen abstraction in the second step of the propagation sequence. The alkylperoxy radicals that act as the abstracting species are fairly selective. Substrates that are relatively electron rich or that provide particularly stable radicals are the most easily oxidized. Benzylic, allylic, and tertiary positions are most susceptible to oxidation. This selectivity makes radical-chain oxidation a suitable preparative reaction in some cases.

The reactivity of various hydrocarbons toward oxygen under a standard set of conditions has been measured, and these measurements give some indication of the relative susceptibility of various structural units to autoxidation.[63] The relative rates of several compounds obtained in this study are shown in Table 12.3. The activating effect of alkyl, vinyl, and aryl substituent groups is apparent from these rate data.

The best preparative results from autoxidation are encountered when only one relatively reactive hydrogen is available for abstraction. The oxidation of isopropylbenzene (cumene), for example, is carried out efficiently on an industrial scale, with the ultimate products being acetone and phenol:



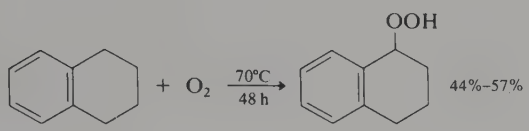
62. C. Walling and P. J. Wagner, *J. Am. Chem. Soc.* **86**, 3368 (1964).
63. G. A. Russell, *J. Am. Chem. Soc.* **78**, 1047 (1956).

Table 12.3. Relative Reactivities of Some Aromatic Hydrocarbons toward Oxygen[a]

$PhCH(CH_3)_2$	1.0	$PhCH_2CH_3$	0.18
$PhCH_2CH{=}CH_2$	0.8	$PhCH_3$	0.015
$(Ph)_2CH_2$	0.35		

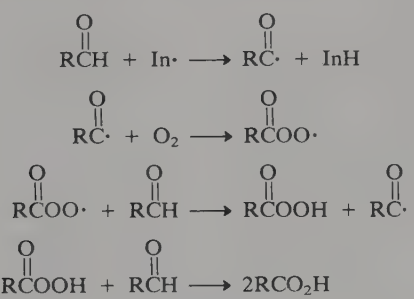
a. Data from Ref. 63.

A preparatively useful yield of the hydroperoxide of tetralin can be obtained by autoxidation:



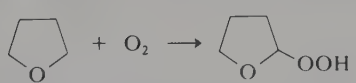
Ref. 64

Functional groups that stabilize radicals would be expected to increase susceptibility to autoxidation. This is illustrated by two cases that are relatively well studied. Aldehydes, in which abstraction of the aldehydic hydrogen is facile, are easily autoxidized. The autoxidation of aldehydes can lead to peroxycarboxylic acids, but usually carboxylic acids are isolated because the peroxyacid is capable of oxidizing unreacted aldehyde:



The final step involving oxidation of a mole of aldehyde by the peroxycarboxylic acid is not a radical reaction, but an example of the Baeyer–Villiger reaction, which will be discussed in Part B, Chapter 10.

Similarly, the α position in ethers is autoxidized quite readily to give hydroperoxides. Autoxidation of ethers to the α-hydroperoxy derivatives is not an important preparative reaction, but is the basis of a widely recognized laboratory hazard. The peroxides formed from commonly used ethers such as diethyl ether, tetrahydrofuran, diglyme, and diisopropyl ether are explosive. Appreciable amounts

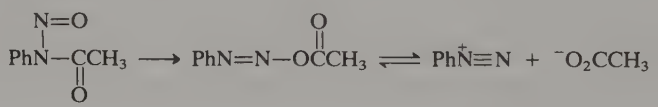


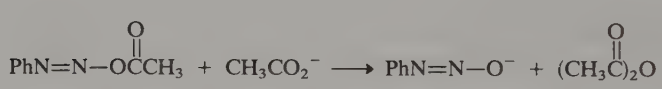
64. H. B. Knight and D. Swern, *Org. Synth.* **IV**, 895 (1963).

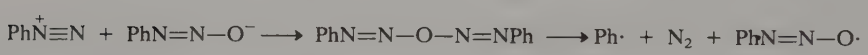
of such peroxides can build up in ether samples that have been exposed to the atmosphere. Since the hydroperoxides are less volatile than the ethers, they are concentrated by evaporation or distillation and may explode. For this reason, extended storage of ethers that have been exposed to oxygen is extremely hazardous.

12.3.3. Substitutions Involving Aryl Radicals

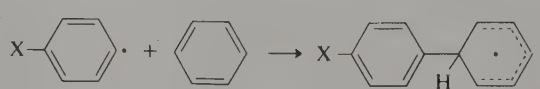
Substitution reactions involving aryl radicals have been quite important in synthesis. The reason, in part, is that the resistance of aryl halides and related compounds to nucleophilic substitution greatly restricts the utility of S_N2 processes for synthetic purposes. Radical substitution reactions can be carried out with any of the sources of aryl radicals mentioned in Section 12.1.4, but acylnitrosoanilines and aryl diazonium compounds have been most widely used in synthesis. The decomposition of acylnitrosoanilines is a relatively complex process. The principal points of evidence supporting the mechanism shown below have been briefly reviewed[65]:

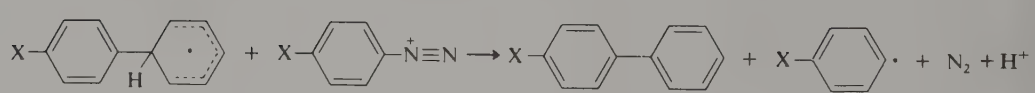






The radical-generating step is a special case of the decomposition of an azo compound. An important use for this reaction is in the synthesis of biphenyls, by reactions in which a second aromatic molecule is attacked by the aryl radical.[66] Under these conditions, hydrogen abstraction from the intermediate arylcyclohexadienyl radical becomes part of the chain mechanism, with the aryl diazonium ion oxidizing the radical intermediate to give the biphenyl. Aryl diazonium ions generated in the usual way by diazotization of aryl amines can also serve as sources of aryl radicals. Substituted biphenyls can be synthesized by base-catalyzed decomposition of the diazonium salt, usually in the presence of an excess of the aromatic substrate:





65. J. I. G. Cadogan, *Acc. Chem. Res.* **4**, 186 (1971).
66. D. H. Hey, *Adv. Free Radical*, **2**, 47 (1966).

Aryl groups can be introduced into alkenes by use of a related reaction. Copper salts are also involved in the reaction, undergoing reversible oxidation state changes and thereby catalyzing the overall reaction[67]:

$$ArN_2^+ + Cu(I) \longrightarrow Ar\cdot + Cu(II) + N_2$$

$$Ar\cdot + PhCH{=}CH_2 \longrightarrow PhCHCH_2Ar$$

$$PhCHCH_2Ar + Cu(II) \longrightarrow PhCHCH_2Ar + Cu(I)$$

$$PhCHCH_2Ar \xrightarrow{-H^+} PhCH{=}CHAr$$

$$PhCHCH_2Ar \xrightarrow{Cl^-} PhCHCH_2Ar \quad (Cl)$$

The final product is either the substituted alkene or the halide which results from capture of the intermediate cation by chloride ion.

Another convenient source of aryl radicals involves reaction of aromatic amines with an alkyl nitrite in organic solvent. The nitrosated aniline is the precursor of the radical:

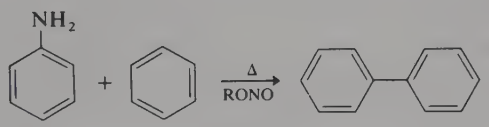
$$ArNH_2 + RONO \rightarrow ArNHN{=}O + ROH \rightarrow ArN{=}NOR + H_2O$$

$$ArN{=}NOR + H_2O \rightleftharpoons ArN{=}NOH + ROH$$

$$2\,ArN{=}NOH \rightleftharpoons ArN{=}NON{=}NAr + H_2O$$

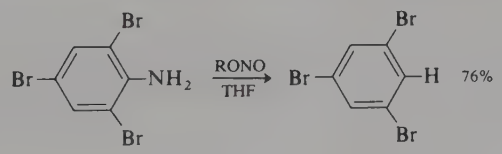
$$ArN{=}NON{=}NAr \rightarrow Ar\cdot + N_2 + ArN{=}NO\cdot$$

The radicals generated in this way have been used to synthesize biphenyls.

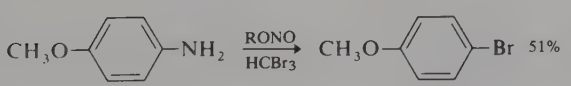


50% Ref. 68

Aryl radicals are also intermediates in reactions that replace the amino group by bromine or by hydrogen. In these reactions, bromine atoms and hydrogen atoms, respectively, are abstracted from suitable solvent molecules by the intermediate radical:



76% Ref. 69



51% Ref. 70

67. C. S. Rondestvedt, Jr., *Org. React.* **11**, 189 (1960); *Org. Reactions*, **24**, 225 (1976).
68. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
69. J. I. G. Cadogan and G. A. Molina, *J. Chem. Soc. Perkin Trans. I*, 541 (1973).
70. J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc. C*, 1249 (1966).

12.4. Free-Radical Addition Reactions

12.4.1. Addition of Hydrogen Halides

The anti-Markownikoff addition of hydrogen bromide to olefins was one of the earliest free-radical reactions to be put on a firm mechanistic basis. In the presence of a suitable initiator, such as peroxides, a radical-chain mechanism becomes competitive with the ionic mechanism for addition of hydrogen bromide:

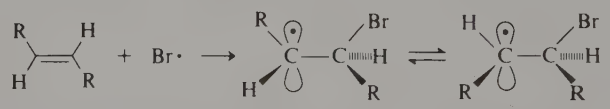
$$\text{In}\cdot + \text{HBr} \longrightarrow \text{Br}\cdot + \text{HIn}$$

$$\text{Br}\cdot + \text{RCH}{=}\text{CH}_2 \longrightarrow \text{R}\dot{\text{C}}\text{HCH}_2\text{Br}$$

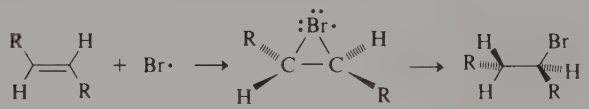
$$\text{R}\dot{\text{C}}\text{HCH}_2\text{Br} + \text{HBr} \longrightarrow \text{RCH}_2\text{CH}_2\text{Br} + \text{Br}\cdot$$

Since the bromine adds to the least-substituted carbon atom of the double bond, thus generating the more-substituted radical intermediate, the regiospecificity of radical-chain hydrobromination of olefins is opposite that of ionic addition. The early work on the mechanism of the reaction was undertaken to understand why Markownikoff's rule was violated under certain circumstances. Anti-Markownikoff additions were eventually traced to reaction conditions under which peroxides or light were causing initiation of the radical-chain process. The radical-chain addition of hydrogen bromide to alkenes is a synthetically useful reaction, as illustrated by entries 1, 2, and 3 in Scheme 12.5.

The stereochemistry of radical addition of hydrogen bromide to alkenes has been studied with both acylic and cyclic alkenes.[71] *Anti* addition is favored,[72,73] which is contrary to what would be expected if the sp^2 carbon in the intermediate radical were rapidly rotating with respect to the remainder of the molecule:



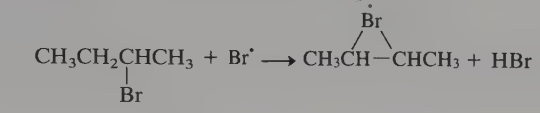
The stereospecificity can be explained in terms of a bridged structure similar to that involved in discussion of ionic bromination of olefins:

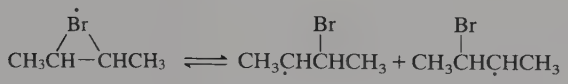


Further evidence for a bromine-bridged radical comes from radical substitution of optically active 2-bromobutane. Although the main product, as expected from

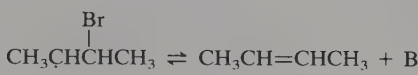
71. B. A. Bohm and P. I. Abell, *Chem. Rev.* **62**, 599 (1962).
72. P. S. Skell and P. K. Freeman, *J. Org. Chem.* **29**, 2524 (1964).
73. H. L. Goering and D. W. Larsen, *J. Am. Chem. Soc.* **81**, 5937 (1959).

substitution selectivity, is 2,2-dibromobutane, some 2,3-dibromobutane is formed. Both *meso*- and *d,l*-diastereomers are possible and the *d,l* material which is formed is found to be largely racemic. This can be accounted for by bromine bridging[74]:



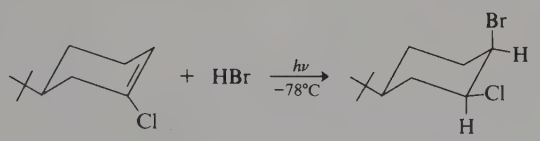


Other mechanisms must also operate, however, to account for the fact that 5%–10% of the optical activity at the initial chiral center is maintained. Isotopic labels also demonstrate that the 3-bromo-2-butyl radical undergoes reversible loss of bromine atom to give 2-butene at a rate which is competitive with the bromination reaction:



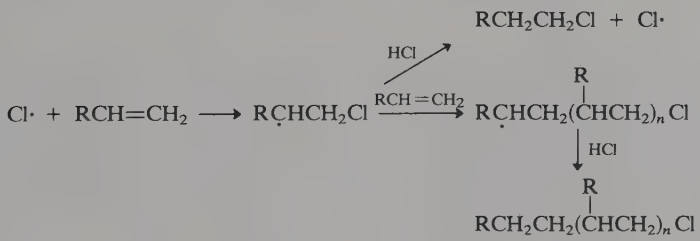
This process can account for some of the observed loss of optical activity by a mechanism which may not involve the bromine-bridged intermediate.[75]

trans-Diaxial addition is the preferred stereochemical mode in cyclohexene and its derivatives[76]:



This stereochemistry is also explained in terms of bromine-bridged radicals.

Product mixtures from radical chain addition of hydrogen chloride to alkenes are much more complicated than is the case for hydrogen bromide. The problem is that the rate of abstraction of hydrogen from HCl is not large relative to addition of the alkyl radical to the alkenes, and this results in the formation of short polymers called *telomers*:



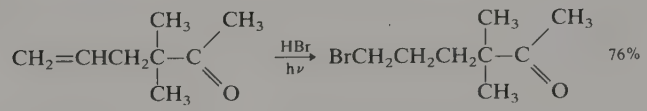
74. P. S. Skell, R. R. Pavlis, D. C. Lewis, and K. J. Shea, *J. Am. Chem. Soc.* **95**, 6735 (1973).
75. D. D. Tanner, E. V. Blackburn, Y. Kosugi, and T. C. S. Rao, *J. Am. Chem. Soc.* **99**, 2714 (1977).
76. H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.* **77**, 3465 (1955); N. A. LeBel, R. F. Czaja, and A. DeBoer, *J. Org. Chem.* **34**, 3112 (1969); P. D. Readio and P. S. Skell, *J. Org. Chem.* **31**, 753 (1966); H. L. Goering, P. I. Abell, and B. F. Aycock, *J. Am. Chem. Soc.* **74**, 3588 (1952).

Scheme 12.5. Free-Radical Chain

Hydrogen bromide

1[a] $CH_3CH{=}C(CH_3)_2 \xrightarrow{HBr} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH(CH_3)_2$ 55%

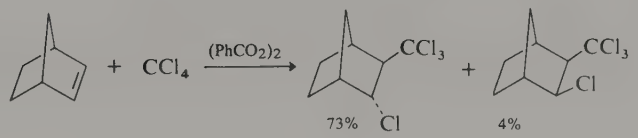
2[b] $CH_2{=}CHCO_2CH_3 \xrightarrow{HBr} BrCH_2CH_2CO_2CH_3$ 80%–84%

3[c]  76%

Addition of halomethanes

4[d] $CCl_4 + H_2C{=}CH(CH_2)_5CH_3 \xrightarrow{(PhCO_2)_2} Cl_3CCH_2\underset{\displaystyle Cl}{\underset{|}{C}}H(CH_2)_5CH_3$ 75%

5[e] $BrCCl_3 + CH_2{=}C(C_2H_5)_2 \xrightarrow{h\nu} Cl_3CCH_2\underset{\displaystyle Br}{\underset{|}{C}}(C_2H_5)_2$ 91%

6[f]  73% 4%

7[g] $CCl_4 + CH_2{=}CH\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)_2 \xrightarrow[80°C]{(PhCO_2)_2} Cl_3CCH_2\underset{\displaystyle Cl}{\underset{|}{C}}H\overset{\displaystyle OH}{\overset{|}{C}}(CH_3)_2$ 70%

a. W. J. Bailey and S. S. Hirsch, *J. Org. Chem.* **28**, 2894 (1963).
b. R. Mozingo and L. A. Patterson, *Org. Synth.* **III**, 576 (1955).
c. H. O. House, C.-Y. Chu, Chu, W. V. Phillips, T. S. B. Sayer, and C.-C. Yau, *J. Org. Chem.* **42**, 1709 (1977).
d. M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Am. Chem. Soc.* **69**, 1100 (1947).
e. M. S. Kharasch and M. Sage, *J. Org. Chem.* **14**, 537 (1949).
f. C. L. Osborn, T. V. Van Auken, and D. J. Trecker, *J. Am. Chem. Soc.* **90**, 5806 (1968).
g. P. D. Klemmensen, H. Kolind-Andersen, H. B. Madsen, and A. Svendsen, *J. Org. Chem.* **44**, 416 (1979).
h. M. S. Kharasch, W. H. Urry, and B. M. Kuderna, *J. Org. Chem.* **14**, 248 (1949).

Radical chain additions of hydrogen fluoride and hydrogen iodide to alkenes are not observed. In the case of hydrogen iodide, the addition of an iodine atom to an alkene is an endothermic process and is too slow to permit a chain reaction, even though the hydrogen-abstraction step would be favorable. In the case of hydrogen fluoride, it is the abstraction of hydrogen from hydrogen fluoride that is energetically prohibitive.

12.4.2. Addition of Halomethanes

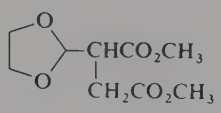
One of the more useful preparative free radical reactions is the addition of polyhalomethanes to alkenes. Many examples of addition of tetrabromomethane,

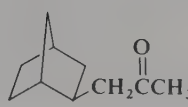
Addition of other carbon radicals

$$8^{h}\quad CH_3CH{=}O + CH_2{=}CH(CH_2)_5CH_3 \longrightarrow CH_3\overset{\overset{O}{\|}}{C}(CH_2)_7CH_3 \quad 64\%$$

$$9^{i}\quad CH_3(CH_2)_5CH{=}O + H_5C_2O_2CCH{=}CHCO_2C_2H_5 \longrightarrow CH_3(CH_2)_5\overset{\overset{O}{\|}}{C}\underset{\underset{CH_2CO_2C_2H_5}{|}}{C}HCO_2C_2H_5$$

$$10^{j}\quad CH_2{=}CHCH_2CH_2CO_2CH_3 + \overset{\overset{O}{\|}}{HCNH_2} \xrightarrow[\text{acetone}]{h\nu} \overset{\overset{O}{\|}}{H_2NC}(CH_2)_4CO_2CH_3 \quad 58\%$$

$$11^{k}\quad \text{  } + H_3CO_2CCH{=}CHCO_2CH_3 \xrightarrow[\text{acetone}]{h\nu} \text{  }$$

$$12^{l}\quad \text{  } + CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{h\nu} \text{  }$$

$$13^{m}\quad CH_2{=}CH(CH_2)_5CH_3 + CH_2(CO_2C_2H_5)_2 \xrightarrow{ROOR} CH_3(CH_2)_7CH(CO_2C_2H_5)_2 \quad (67\text{–}85\%)$$

$$14^{n}\quad CH_2{=}CH(CH_2)_5CH_3 + N{\equiv}CCH_2CO_2C_2H_5 \xrightarrow{CuO} C_2H_5O_2C\underset{\underset{C{\equiv}N}{|}}{C}H(CH_2)_7CH_3 \quad 75\%$$

Additions of thiols and thio acids

$$15^{o}\quad CH_3\overset{\overset{O}{\|}}{C}SH + C_6H_5CH{=}CHCH{=}O \longrightarrow CH_3\overset{\overset{O}{\|}}{C}S\underset{\underset{C_6H_5}{|}}{C}HCH_2CH{=}O \quad (90\%)$$

$$16^{p}\quad CH_3CH_2CH_2CH_2SH + CH_2{=}CH(CH_2)_4CH_3 \xrightarrow{(PhCO_2)_2} CH_3(CH_2)_3S(CH_2)_6CH_3 \quad 68\%$$

i. T. M. Patrick, Jr., and F. B. Erikson, *Org. Synth.* **IV**, 430 (1963).
j. D. Elad and J. Rokach, *J. Org. Chem.* **29**, 1855 (1964).
k. I. Rosenthal and D. Elad, *J. Org. Chem.* **33**, 805 (1968).
l. W. Reusch, *J. Org. Chem.* **27**, 1882 (1962).
m. J. C. Allen, J. I. G. Cadogan, B. W. Harris,, and D. H. Hey, *J. Chem. Soc.*, 4468 (1962).
n. A. Hajek and J. Malek, *Synthesis*, 454 (1977).
o. R. Brown, W. E. Jones, and A. R. Pinder, *J. Chem. Soc.*, 2123 (1951).
p. D. W. Grattan, J. M. Locke, and S. R. Wallis, *J. Chem. Soc. Perkin Trans I*, 2264 (1973).

carbon tetrachloride, and bromoform have been recorded.[77] These reactions are chain processes that depend on facile abstraction of halogen or hydrogen from the halomethane:

$$In\cdot + CBr_4 \longrightarrow InBr + \cdot CBr_3$$
$$\cdot CBr_3 + CH_2{=}CHR \longrightarrow Br_3CCH_2\dot{C}HR$$
$$Br_3CCH_2\dot{C}HR + CBr_4 \longrightarrow Br_3CCH_2\underset{\underset{Br}{|}}{C}HR + \cdot CBr_3$$

77. E. Sosnovsky, *Free Radical Reactions in Preparative Organic Chemistry*, Macmillan, New York, 1964, Chap. 2.

or

$$In\cdot + HCBr_3 \longrightarrow InH + \cdot CBr_3$$
$$\cdot CBr_3 + CH_2{=}CHR \longrightarrow Br_3CCH_2\dot{C}HR$$
$$Br_3CCH_2\dot{C}HR + HCBr_3 \longrightarrow Br_3CCH_2CH_2R + \cdot CBr_3$$

Bromotrichloromethane can also be used effectively in the addition reaction. Because of the preferential abstraction of bromine, a trichloromethyl unit is added to the less-substituted carbon atom.

$$BrCCl_3 + CH_2{=}CHR \xrightarrow[\Delta]{\text{peroxide}} Cl_3CCH_2\underset{\displaystyle Br}{\underset{|}{C}}HR$$

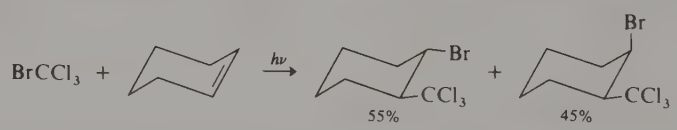
The efficiency of the halomethane addition process depends on the relative rate of atom abstraction versus that of addition to the alkene:

$$X_3CCH_2\dot{C}HR \xrightarrow{\text{atom abstraction}} X_3CCH_2\underset{\displaystyle X}{\underset{|}{C}}HR$$
$$X_3CCH_2\dot{C}HR \xrightarrow{\text{addition to } RCH{=}CH_2} X_3CCH_2\underset{\displaystyle R}{\underset{|}{C}}H\underset{\displaystyle R}{\underset{|}{C}}H_2\dot{C}H \longrightarrow \text{telomer}$$

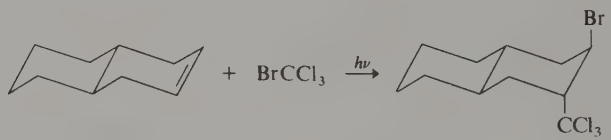
For a given alkene, the order of reactivity of the halomethanes is $CBr_4 > CBrCl_3 > CCl_4 > CH_2Cl_2 > CH_3Cl$. The efficiency of 1:1 addition for a given alkene depends on the ease with which it undergoes radical chain polymerization. Polymerization is usually most rapid for terminal alkenes bearing stabilizing substituents such as a phenyl or ester group. If addition is competitive with halogen abstraction, telomers are formed.

Specific examples of addition of polyhaloalkanes by free-radical chain processes are included in Scheme 12.5 (p. 666).

The addition of bromotrichloromethane to cyclohexene gives a mixture of the two possible stereoisomers[78]:



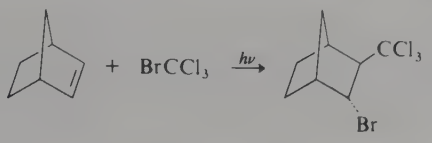
This is the expected result for a nonstereospecific reaction involving a cyclohexyl radical intermediate. With $\Delta^{2,3}$-octahydronaphthalene, the addition is exclusively *trans*-diaxial:



78. J. G. Traynham, A. G. Lane, and N. S. Bhacca, *J. Org. Chem.* **34**, 1302 (1969).

In the rigid *trans*-decalin system where conformational inversion is prevented, only the *trans*-diaxial product is formed. The initial attack would be expected to occur from the axial direction to maximize overlap with the π electrons. The subsequent attack on bromotrichloromethane must be stereoselective and probably occurs from the axial direction to avoid a *gauche* interaction with the trichloromethyl group.

Addition of bromotrichloromethane to norbornene is also *anti*:



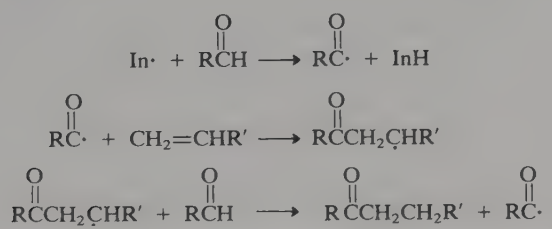
Ref. 78

This is the result of a strong steric factor working against *syn* addition. The trichloromethyl group will provide steric resistance to approach from the *exo* direction and thereby favor abstraction of bromine from the *endo* side of the intermediate radical.

12.4.3. Addition of Other Carbon Radicals

Although the case of polyhalomethyl radicals is the most general reaction studied to date, other functional groups provide sufficient stabilization of potential radical centers to permit successful chain reactions. Although none of these reactions has been widely applied in synthesis, some would seem to be efficient enough to merit consideration as synthetic processes.

Acyl radicals are formed by abstraction of the formyl hydrogen from aldehydes. Both the hydrogen abstraction and addition step are favorable, and a chain reaction can occur:



The reaction has been used preparatively on some occasions. Specific examples are included in Scheme 12.5 (p. 666).

Closely related is the chain addition of formamide to alkenes, a reaction that provides primary amides.[79] The initiating radicals are generated photolytically. Excited-state acetone abstracts a hydrogen atom from formamide, and the addition is a chain process:

79. D. Elad and J. Rokach, *J. Org. Chem.* **29**, 1855 (1964).

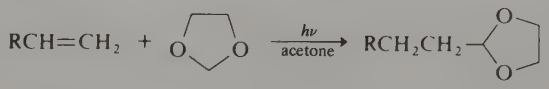
$$CH_3COCH_3 \xrightarrow{h\nu} CH_3COCH_3^*$$

$$CH_3COCH_3^* + HCONH_2 \longrightarrow \cdot CONH_2 + (CH_3)\dot{C}OH$$

$$\cdot CONH_2 + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2CONH_2$$

$$R\dot{C}HCH_2CONH_2 + HCONH_2 \longrightarrow RCH_2CH_2CONH_2 + \cdot CONH_2$$

1,3-Dioxolane, the cyclic ethylene glycol acetal of formaldehyde, is also alkylated by alkenes under free-radical conditions. Here, it is the CH_2 group between the two oxygen atoms that is the preferred site of hydrogen abstraction.



A variety of other monofunctional organic molecules add to olefins to give products of free radical alkylation. The cases in which the reaction has been demonstrated to occur include ketones,[80] cyclic ethers,[81] malonate esters and other similar active methylene compounds.[82] In these reactions, one of the two principal reagents is usually used in large excess. These additions always occur primarily α to the functional group, since this is the most easily abstracted hydrogen atom.

12.4.4. Addition of S–H Compounds

The addition of S–H compounds to alkenes by a radical-chain mechanism is a quite general and efficient reaction.[83] The chain mechanism is analogous to that for hydrogen bromide addition, and the energetics of both the hydrogen abstraction and addition steps are favorable. Thiols and thio acids are both suitable sulfur

$$In\cdot + R'SH \longrightarrow In{-}H + R'S\cdot$$

$$R'S\cdot + CH_2{=}CHR \longrightarrow R'SCH_2\dot{C}HR$$

$$R'SCH_2CHR + R'SH \longrightarrow R'SCH_2CH_2R + R'S\cdot$$

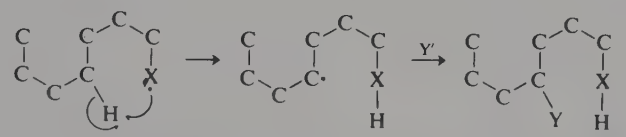
substrates for these addition reactions. Several cyclic alkenes have been studied in

80. W. Reusch, *J. Org. Chem.* **27**, 1882 (1962); M. S. Kharasch, J. Kuderna and W. Nudenberg, *J. Org. Chem.* **18**, 1225 (1953).
81. I. Rosenthal and D. Elad, *Tetrahedron* **23**, 3193 (1967); T. J. Wallace and R. J. Gritter, *J. Org. Chem.* **27**, 3067 (1962).
82. J. I. G. Cadogan, D. H. Hey, and J. T. Sharp, *J. Chem. Soc.*, 1743 (1966); H. Hajek and J. Malek, *Synthesis*, 454 (1977).
83. K. Griesbaum, *Angew. Chem. Int. Ed. Engl.* **9**, 273 (1970).

order to establish the stereochemistry of thiol addition.[84] Although the preferred product is ordinarily that resulting from *trans*-diaxial addition, the reactions are not so highly stereoselective as hydrogen bromide addition, and bridged radicals are probably not involved. Entries 15 and 16, Scheme 12.5 (p. 667) are examples of synthetic use of radical addition reactions of sulfur compounds.

12.5. Intramolecular Free-Radical Reactions

Both substitution and addition reactions can occur intramolecularly. Intramolecular substitution reactions that involve hydrogen abstraction have some important synthetic utility, since they permit functionalization of carbon atoms relatively remote from the initial reaction site. The preference for a six-membered cyclic transition state in the hydrogen-abstraction step[85] imparts considerable selectivity to these intramolecular hydrogen abstractions. An important example of this



type of reaction is the photolytically initiated decomposition of *N*-haloamines in acidic media, a reaction known as the *Hofmann–Loeffler reaction*.[86] The initial products are δ-haloamines, but these are usually converted to pyrrolidines by an intramolecular nucleophilic substitution:

$$RCH_2CH_2CH_2CH_2\overset{+}{N}(Cl)HCH_3 \xrightarrow{h\nu} RCH_2CH_2CH_2CH_2\overset{+}{N}HCH_3 + Cl\cdot$$

$$RCH_2CH_2CH_2CH_2\overset{+}{N}HCH_3 \longrightarrow RCHCH_2CH_2CH_2\overset{+}{N}H_2CH_3$$

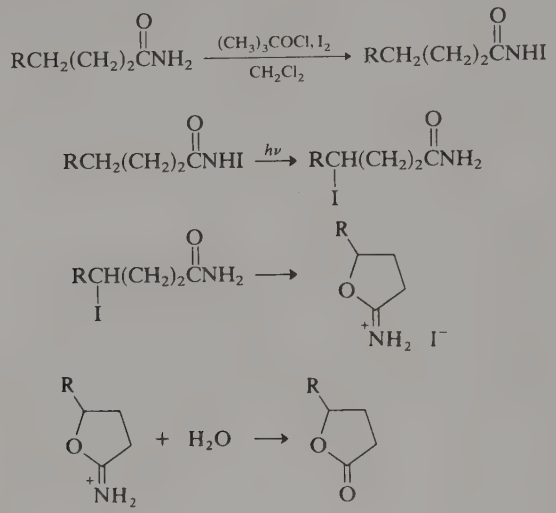
$$RCHCH_2CH_2CH_2\overset{+}{N}H_2CH_3 + RCH_2CH_2CH_2CH_2\overset{+}{N}(Cl)HCH_3 \longrightarrow$$

$$RCH(Cl)CH_2CH_2CH_2\overset{+}{N}H_2CH_3 + RCH_2CH_2CH_2CH_2\overset{+}{N}HCH_3$$

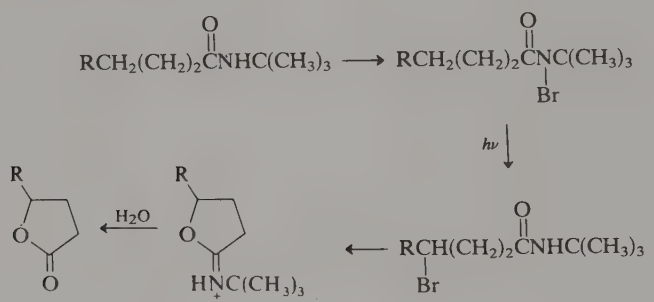
$$RCH(Cl)CH_2CH_2CH_2\overset{+}{N}H_2CH_3 \xrightarrow{NaOH} \text{N-methylpyrrolidine, 2-R}$$

84. N. A. LeBel, R. F. Czaja and A. DeBoer, *J. Org. Chem.* **34**, 3112 (1969); P. D. Readio and P. S. Skell, *J. Org. Chem.* **31**, 759 (1966); F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.* **30**, 3764 (1965); E. S. Huyser, H. Benson and H. J. Sinnige, *J. Org. Chem.* **32**, 622 (1967).
85. D. H. R. Barton and L. R. Morgan, Jr., *J. Chem. Soc.*, 622 (1962).
86. M. E. Wolff, *Chem. Rev.* **63**, 55 (1963).

Very closely related are two procedures that result in formation of γ-lactones. In one procedure, amides are converted to *N*-iodoamides by reaction with iodine and *t*-butyl hypochlorite. Photolysis of the *N*-iodoamides gives lactones via imino lactone intermediates[87]:



An alternative procedure is most efficient when *N*-*t*-butyl amides are employed as starting materials. The *N*-bromoamides are formed by halogenation with *t*-butyl hypobromite. Photolysis gives hydrobromide salts of iminolactones, which are easily hydrolyzed to lactones[88]:

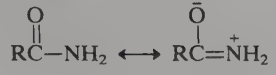


The remote halogenation is believed to proceed by a chain mechanism analogous to the Hofmann–Loeffler reaction in both the iodoamide and bromoamide reactions.

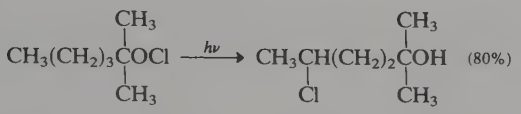
A significant point to be noted in connection with the final step in these reaction sequences is that the intramolecular nucleophilic attack by the amide group involves the oxygen, not the nitrogen, as the site of nucleophilic reactivity. This is a general

87. D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).
88. R. S. Neale, N. L. Marcus and R. G. Schepers, *J. Am. Chem. Soc.* **88**, 3051 (1966).

feature of the chemistry of amides, and is a result of the relatively high electron density at oxygen:

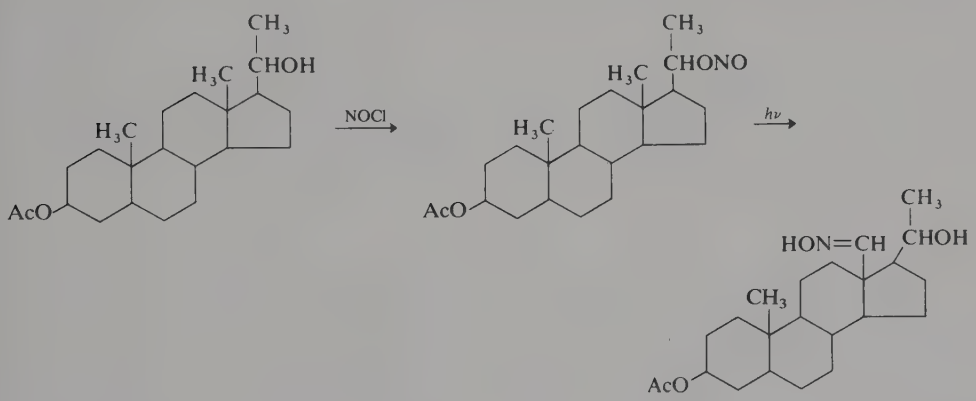


Intramolecular hydrogen abstraction by alkoxy radicals generated from hypochlorites has also been observed[89]:



There are often important competing processes in this reaction.[90]

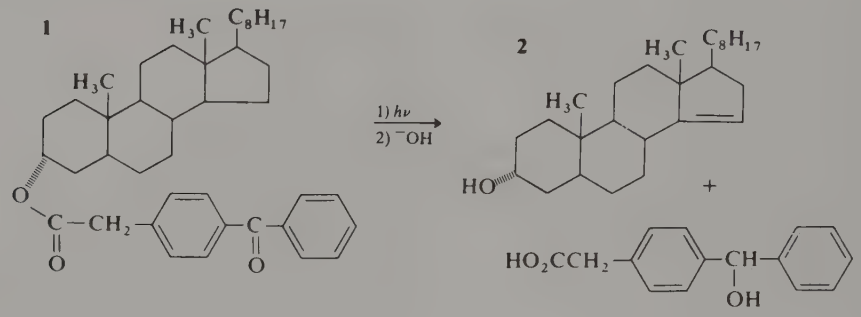
A procedure for intramolecular functionalization of alcohols has been developed by studies primarily carried out with steroid derivatives.[91] The alcohol is converted to a nitrite ester by reaction with nitrosyl chloride. Photolysis effects introduction of a nitroso function at an adjacent unsubstituted carbon atom. The nitrosoalkyl group is equivalent to an aldehyde or ketone group, since alkyl nitroso compounds rearrange to oximes. This reaction involves a hydrogen abstraction by photolytically generated alkoxy radicals, but is not believed to be a chain process, since the quantum yield is less than unity.[92] Labeling studies using nitrogen-15 have



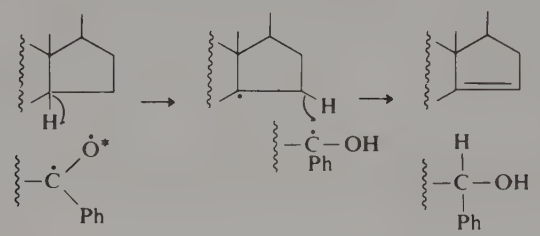
established that the NO group is transferred intermolecularly, rather than in a cage process.[93]

89. C. Walling and A. Padwa, *J. Am. Chem. Soc.* **83**, 2207 (1961).
90. F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith and P. M. Zanet, *J. Org. Chem.* **28**, 55 (1963).
91. R. H. Hesse, *Adv. Free Radical* **3**, 83 (1969); D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.* **83**, 4076 (1961).
92. P. Kabasakalian and E. R. Townley, *J. Am. Chem. Soc.* **84**, 2711 (1962).
93. M. Akhtar and M. M. Pechet, *J. Am. Chem. Soc.* **86**, 265 (1964).

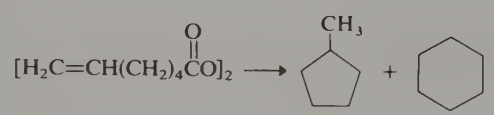
The selectivity observed in most intramolecular functionalizations depends on the preference for a six-membered transition state in the hydrogen atom abstraction step. Appropriate molecules can be constructed in which steric or conformational effects dictate a preference for selective abstraction of a hydrogen more remote from the reactive radical. A dramatic example of this involves functionalization of the D ring of a steroid by a functional group covalently attached to the A ring.[94] Irradiation of the ester **1**, followed by saponification, gives a 44% yield of the unsaturated steroid **2**.



The preferred conformation of the reactant is such that the aromatic rings are folded back over the steroid skeleton. The photoexcited ketone acts as a hydrogen-abstracting radical and introduces the unsaturation:

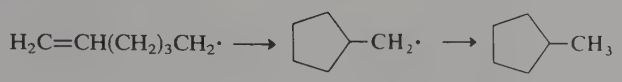


There are other examples of intramolecular reactions of free radicals that occur when a functional group, particularly a carbon–carbon double bond, is situated in a sterically favorable position. For example, methylcyclopentane is the major product in the thermal decomposition of 6-heptenoyl peroxide[95]:



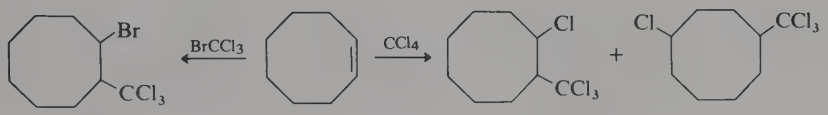
94. R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Am. Chem. Soc.* **95**, 3251 (1973).
95. R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Am. Chem. Soc.* **85**, 3483 (1963).

It arises as the result of cyclization of the intermediate 5-hexenyl radical, followed by hydrogen abstraction:

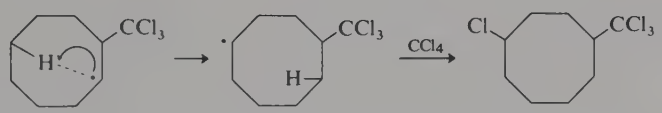


The preference for closure to the five- rather than six-membered ring is opposite to what would be predicted on the basis of product radical stability (pri < sec). The observed preference for the five-membered ring is based on a kinetic preference which is probably stereoelectronic in origin. The conformation corresponding to closure of the five-membered ring is more easily achieved than that leading to formation of the six-membered ring.[96] It is known that the cyclization is very rapid ($k \approx 10^5$ sec^{-1} at 25°C).[97]

With medium-sized cyclic compounds, transannular reactions have been observed. The reaction of cyclooctene with carbon tetrachloride and bromotrichloromethane is an interesting example. As shown in the equation below, bromotrichloromethane adds in a completely normal manner, but carbon tetrachloride gives some 4-chloro-1-trichloromethylcyclooctane as well as the expected product[98]:



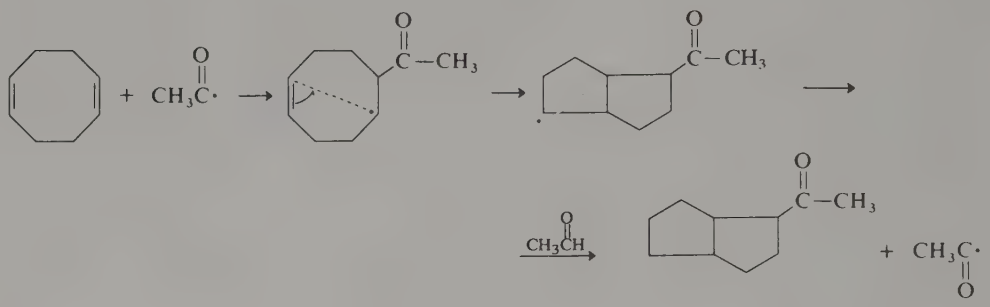
In the case of carbon tetrachloride, the radical intermediate is undergoing two competitive reactions; intramolecular hydrogen abstraction is competitive with abstraction of a chlorine atom from carbon tetrachloride:



No product derived from the transannular hydrogen abstraction is observed in the addition of bromotrichloromethane because bromine atom abstraction is sufficiently rapid to prevent effective competition by the hydrogen-abstraction process. Another example of transannular cyclization of unsaturated radicals is found in the

96. A. L. J. Beckwith and K. U. Ingold, in *Rearrangements in Ground and Excited States*, P. de Mayo (ed.), Academic Pres , New York, 1980, pp. 182–198.
97. D. Lal, D. Griller, S. Husband, and K. U. Ingold, *J. Am. Chem. Soc.*, **96**, 6355 (1974); C. Chatgilialoglu, K. U. Ingold, and J. C. Scaiano, *J. Am. Chem. Soc.* **103**, 7739 (1981).
98. J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.* **32**, 529 (1967); J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.* **87**, 5806 (1965); **89**, 3205 (1967).

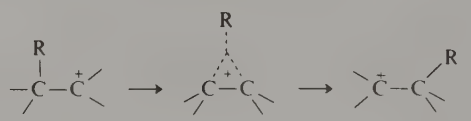
reaction of 1,4-cyclooctadiene with acetaldehyde in the presence of benzoyl peroxide, which gives a cyclized ketone by a process involving an intramolecular addition[99]:



12.6. Rearrangement and Fragmentation Reactions of Free Radicals

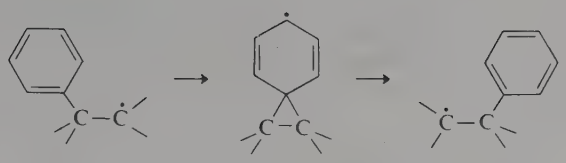
12.6.1. Rearrangement

Compared with rearrangement of cationic species, rearrangement of radical intermediates is quite rare. Furthermore, only a relatively small number of groups are known to migrate. The most common cases involve phenyl migrations, but other unsaturated groups such as vinyl and acyl substituents have been shown to migrate on occasion. There is a simple structural rationalization for the improbability of saturated-group migrations in free radicals. In cationic intermediates, migration occurs through a bridged intermediate or transition state that involves a three-center bond, using the two electrons from the migrating group:

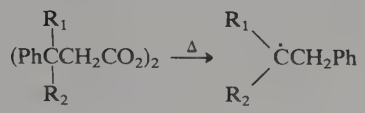


In a free radical, there is a third electron in the system. It cannot occupy the same orbital as the other two electrons. It is instead associated with an antibonding level, and therefore leads to a less favorable transition state for migration. The relatively more facile migration of unsaturated groups is associated with the ability of such groups to form bridged intermediates by an addition process. The unpaired electron can then be located in a more stable delocalized orbital:

99. R. Dowbenko, *J. Am. Chem. Soc.* **86**, 946 (1964).

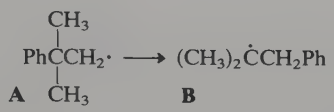


The extent of radical rearrangement increases when there is considerable steric crowding at the carbon atom from which migration occurs. This trend is illustrated by the results of thermal decomposition of a series of diacyl peroxides.[100] The amounts of product derived from rearrangement increase as R_1 and R_2 become larger:

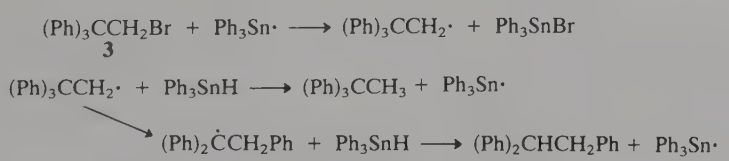


R_1	R_2	Rearrangement
CH_3	H	39%
Ph	H	63%
Ph	Ph	100%

Even in the most favorable cases, such as rearrangement of the primary radical **A** to the tertiary radical **B** by phenyl migration, a modest activation energy is required:

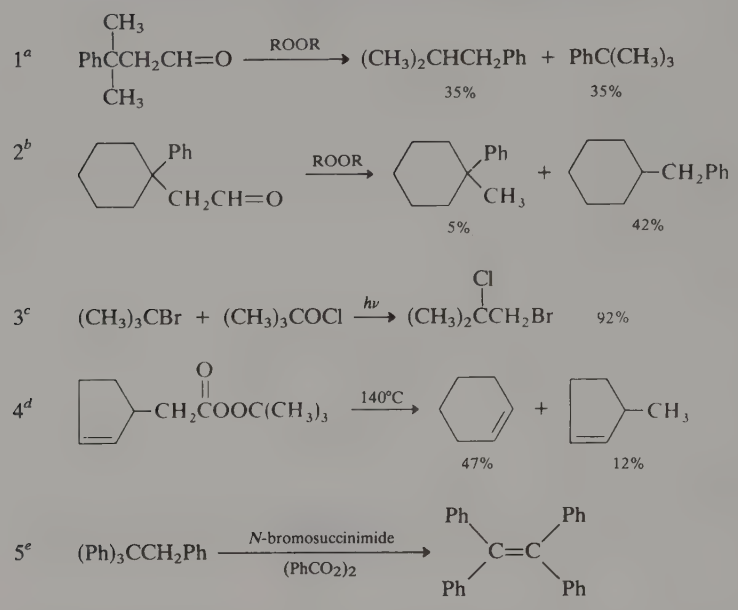


ESR studies have shown that below −60°C, the rearrangement does not occur, although it is commonly encountered in reactions carried out at higher temperatures.[101] Very rapid reactions can therefore occur at rates faster than the rearrangement. For example, dehalogenation of **3** with triphenyltin hydride (see Section 5.4 Part B, for a discussion of the mechanism of reduction of halides by Sn–H compounds) gives mainly unrearranged product when the triphenyltin hydride concentrations are high. The rate of abstraction of hydrogen from the Sn–H bond exceeds the rearrangement rate.[102] As the concentration of the triphenyltin hydride is lowered, the rate of the rearrangement becomes competitive with that of the hydrogen abstraction, and the rearranged reduction product is formed. Scheme 12.6 gives some typical free radical reactions in which products of rearranged radicals have been observed in significant amount.



100. W. Rickatson and T. S. Stevens, *J. Chem. Soc.*, 3960 (1963).
101. D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 7695 (1972).
102. L. Kaplan, *J. Am. Chem. Soc.* **88**, 4531 (1966).

Scheme 12.6. Free-Radical Rearrangements



a. S. Winstein and F. H. Seubold, Jr., *J. Am. Chem. Soc.* **69**, 2916 (1947).
b. J. W. Wilt and H. P. Hogan, *J. Org. Chem.* **24**, 441 (1959).
c. P. S. Skell, R. G. Allen, and N. D. Gilmour, *J. Am. Chem. Soc.* **83**, 504 (1961).
d. L. H. Slaugh, *J. Am. Chem. Soc.* **87**, 1522 (1965).
e. H. Meislich, J. Costanza, and J. Strelitz, *J. Org. Chem.* **33**, 3221 (1968).

12.6.2. Fragmentation

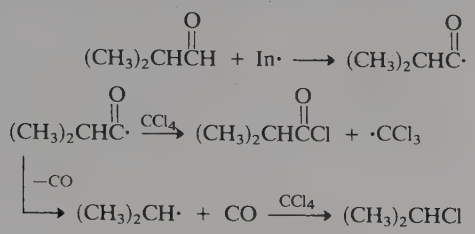
Earlier sections have already brought forward several examples of radical fragmentation reactions, although the terminology was not explicitly used. The most frequently encountered case in the previous sections of this chapter is the elimination of CO_2 from acyloxy radicals:

$$RCOOC(CH_3)_3 \longrightarrow RCO\cdot \longrightarrow R\cdot + CO_2$$

This fragmentation reaction occurs very readily. Acyl radicals also have a tendency to undergo fragmentation with elimination of carbon monoxide, but decarbonylation is a function of the stability of the radical formed by elimination of CO, and products derived from the acyl radical and its decarbonylation product are often formed competitively.[103] For example, when isobutyraldehyde reacts in carbon tetrachloride

103. (a) D. E. Applequist and L. Kaplan, *J. Am. Chem. Soc.* **87**, 2194 (1965);
(b) W. H. Urry, D. J. Trecker, and H. D. Hartzler, *J. Org. Chem.* **29**, 1663 (1964).

with initiation by *t*-butyl peroxide, both isopropyl chloride and isobutyryl chloride are formed:



Ref. 103a

Another common fragmentation reaction is the cleavage of an alkoxy radical to an alkyl radical and a carbonyl compound:

$$(CH_3)_3CO\cdot \longrightarrow CH_3\cdot + (CH_3)_2C{=}O$$

This fate of the *t*-butoxy radical is competitive with hydrogen abstraction in many solvents.[104]

The same fragmentation process is involved in the chain decomposition of alkyl hypochlorites[105]:

$$RCH_2OCl \longrightarrow RCH_2O\cdot + Cl\cdot$$
$$RCH_2O\cdot \longrightarrow R\cdot + CH_2{=}O$$
$$R\cdot + RCH_2OCl \longrightarrow RCl + RCH_2O\cdot$$

In this reaction, too, the stability of the alkyl radical being eliminated influences the ease of fragmentation. The order of ease of elimination based on results from the two studies cited above is *t*-butyl > isopropyl > benzyl > ethyl > chloromethyl > methyl ~ 1-bicyclo[2.2.1]heptyl. Radicals derived from ethers and acetals by hydrogen abstraction are also subject to fragmentation, with elimination of a ketone or ester, respectively.

$$R_2\dot{C}OR' \longrightarrow R_2C{=}O + R'\cdot$$
$$R\dot{C}(OR')_2 \longrightarrow R\overset{\overset{O}{\|}}{C}OR' + R'\cdot$$

These fragmentations are sufficiently slow that the initial radicals can react with olefins and other suitable radical substrates at rates competitive with fragmentation.

12.7. Electron Transfer Reactions Involving Transition Metal Ions

Most of the free-radical mechanisms discussed thus far have involved some combination of steps involving homolytic bond dissociation, atom abstraction, and

104. P. Gray and A. Williams, *Chem. Rev.* **59**, 239 (1959).
105. F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith and P. M. Zanet, *J. Org. Chem.* **28**, 55 (1963); C. Walling and A. Padwa, *J. Am. Chem. Soc.* **85**, 1593, 1597 (1963).

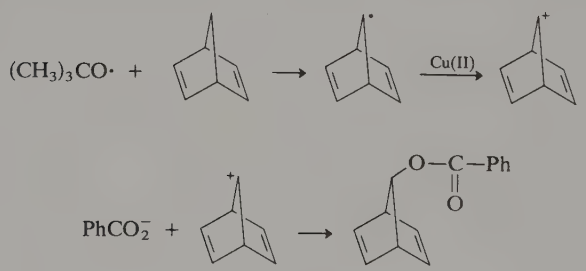
radical addition in the initiation and propagation phases of the reaction. In this section, we will discuss reactions that involve discrete electron transfer steps. Addition to or removal of one electron from a diamagnetic organic molecule generates a radical, and the importance of reactions that involve electron transfer is becoming increasingly recognized. The study of electron transfer processes has long been of importance in inorganic chemistry, and the involvement of metal ions in many organic reactions that involve electron transfer processes is common, because many transition metal ions have more than one relatively stable oxidation state. Transition metal ions can therefore often act as catalysts or reagents in processes involving electron transfer.

The decomposition of peresters has been shown to be strongly catalyzed by Cu(I), and the decomposition is believed to involve a one-electron redox process[106]:

$$\mathrm{RC(=O)OOR + Cu(I) \longrightarrow RC(=O)O^- + RO\cdot + Cu(II)}$$

An example of the synthetic application of this reaction is the introduction of a benzoate substituent into the 7-position of norbornadiene. Decomposition of *t*-butyl peroxybenzoate is effected by Cu(I). The *t*-butyl radical then abstracts hydrogen from norbornadiene. The Cu(I) is regenerated by oxidation of the resulting radical. The cation then captures benzoate ion, giving the product[107]:

$$\mathrm{PhCO_3C(CH_3)_3 + Cu(I) \longrightarrow PhCO_2^- + (CH_3)_3CO\cdot + Cu(II)}$$



The reactions of copper salts with diacyl peroxides have been investigated quite thoroughly, and the mechanistic studies indicate that both radicals and carbonium ions are involved. The radicals are oxidized to carbonium ions by Cu(II), and the final products can be recognized as having arisen from carbonium ions because characteristic patterns of substitution, elimination, and rearrangement can be discerned[108]:

106. M. S. Kharasch, G. Sosnovsky, and N. C. Yang, *J. Am. Chem. Soc.* **81**, 5819 (1959).
107. P. R. Story, *J. Org. Chem.* **26**, 287 (1960).
108. J. K. Kochi, *J. Am. Chem. Soc.* **85**, 1958 (1963); J. K. Kochi and A. Bemis, *J. Am. Chem. Soc.* **90**, 4038 (1968).

$$[(CH_3)_3CCH_2CO_2]_2 + Cu(I) \longrightarrow (CH_3)_3CCH_2CO_2^- + (CH_3)_3CCH_2\cdot + CO_2 + Cu(II)$$
$$(CH_3)_3CCH_2\cdot + Cu(II) \longrightarrow (CH_3)_3CCH_2^+ + Cu(I)$$

$$(CH_3)_3CCH_2^+ \xrightarrow{-H^+} H_5C_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2$$

$$(CH_3)_3CCH_2^+ \longrightarrow (CH_3)_2\overset{+}{C}CH_2CH_3 \longrightarrow (CH_3)_2C{=}CHCH_3$$
$$\downarrow$$
$$(CH_3)_2\overset{\displaystyle O_2CCH_3}{\overset{|}{C}}CH_2CH_3$$

When the radicals have β-hydrogens, alkenes are formed by a process in which carbonium ions are probably bypassed as intermediates. Instead, the oxidation and elimination of a proton probably occur in a single step:

$$R_2CHCH_2\cdot + Cu(II) \longrightarrow R_2C{=}CH_2 + Cu(I) + H^+$$

When halide ions or anions such as thiocyanate or azide are present, these anions are incorporated into the organic radical generated by decomposition of the peroxide. This anion transfer presumably occurs in the same step as the redox interaction with Cu(II), and such reactions have been called *ligand-transfer reactions*.[109] These reactions apparently do not involve free carbonium ions, because they

$$(RCO_2)_2 + Cu(I) \longrightarrow RCO_2^- + R\cdot + CO_2 + Cu(II)$$
$$R\cdot + Cu(II)X \longrightarrow RX + Cu(I)$$

proceed effectively in nucleophilic solvents that would successfully compete with halide or similar anions for free carbonium ions. Also, rearrangements are unusual, although they are observed with systems that are very prone to rearrange, such as the *p*-methoxyphenylethyl system.

A unified concept of these reactions is provided by the proposal that alkyl copper intermediates are involved in each of these reactions at the stage of the oxidation of the radical[110]:

$$R\cdot + Cu(II)X \longrightarrow RCuX$$
$$RCuX \longrightarrow H^+ + \text{olefin} + Cu(I)$$
$$RCuX \longrightarrow \text{carbonium ion} + Cu(I) \longrightarrow \text{products} + Cu(I)$$
$$RCuX \longrightarrow RX + Cu(I)$$

The organocopper intermediate has three possible fates, and the preferred path is determined by the structure of the group R and the identity of the copper ligand X. If

109. C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 856 (1972).
110. C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.* **94**, 843 (1972).

R is potentially a very stable carbonium ion, the intermediate breaks down to generate the carbonium ion, and the products are those to be expected from a carbonium ion. When X is halide or pseudohalide anions (^-CN, ^-SCN, N_3^-, etc.) the preferred pathway is to the alkyl halide or pseudohalide by ligand transfer. If the R group is not capable of sustaining formation of the carbonium ion and no easily transferred anion is present, the organocopper intermediate is converted primarily to alkene by elimination of a proton.

One-electron oxidation of carboxylate ions generates acyloxy radicals, which undergo the usual decarboxylation. This electron transfer can be effected by strong one-electron oxidants. Such reactions have been observed with Mn(III), Ag(II), Ce(IV), and Pb(IV).[111] The metal ion is also capable of oxidizing the radical intermediate, so the products are of the same type as those observed in reactions involving oxidation of radicals by Cu(II), although there are competing reactions. In terms of preparative usefulness, the oxidative decarboxylation by Pb(IV) in the presence of halide salts probably is of the most value.[112] For example, oxidation of valeric acid with lead tetraacetate in the presence of lithium chloride gives butyl chloride in 71% yield:

$$CH_3(CH_2)_3CO_2H \xrightarrow[LiCl]{Pb(OAc)_4} CH_3(CH_2)_3Cl + CO_2$$

A chain mechanism is proposed. The first step is oxidation of a carboxylate ion coordinated to Pb(IV) with formation of alkyl radical, carbon dioxide, and Pb(III). The alkyl radical then abstracts halogen from a Pb(IV) complex, generating a Pb(III) species that decomposes to Pb(II) with release of an alkyl radical, which can continue the chain process. The step involving abstraction of halide from a complex with a change in metal ion oxidation state is quite similar to the ligand-transfer reaction described earlier:

$$RCO_2{-}\overset{X}{\underset{|}{Pb(IV)}}{-} \longrightarrow R\cdot + \overset{X}{\underset{|}{Pb(III)}}{-} + CO_2$$

$$R\cdot + X{-}\underset{|}{Pb(IV)}{-} \longrightarrow R{-}X + \underset{|}{Pb(III)}{-}$$

$$\underset{|}{Pb(III)}{-} + RCO_2^- \longrightarrow R\cdot + CO_2 + Pb(II)$$

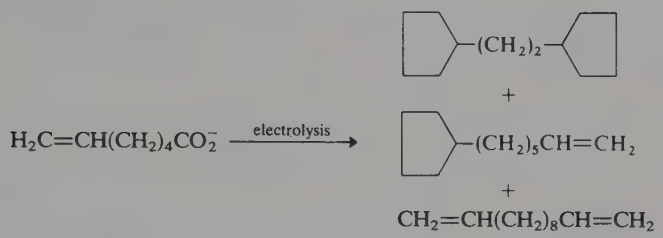
111. J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.* **92**, 2450 (1970); J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.* **92**, 1651 (1970); R. A. Sheldon and J. K. Kochi, *J. Am. Chem. Soc.* **90**, 6688 (1968); W. A. Mosher and C. L. Kehr, *J. Am. Chem. Soc.* **75**, 3172 (1953); J. K. Kochi, *J. Am. Chem. Soc.* **87**, 1811 (1965).
112. J. K. Kochi, *J. Org. Chem.* **30**, 3265 (1965); R. A. Sheldon and J. K. Kochi, *Org. React.* **19**, 279 (1972).

In the absence of halide salts, the principal products may be alkanes, alkenes, or acetate esters. In some cases, conditions can be established that allow any of these products to be formed in good yield.

A classic reaction involving electron transfer and decarboxylation of acyloxy radicals is the Kolbe electrolysis, in which an electron is abstracted from a carboxylate ion because of the oxidation potential (voltage) at the anode. The most important synthetic use of this reaction is to give products derived from coupling of

$$RCO_2^- \longrightarrow RCO_2\cdot + e^-$$
$$RCO_2\cdot \longrightarrow R\cdot + CO_2$$
$$2\,R\cdot \longrightarrow RR$$

the decarboxylated radicals. Other fates are open to radicals generated by electrolytic processes, however, and side products are usually found. For example, the hexenyl radical partially cyclizes before coupling[113]:



Carbonium ions can also be generated during the electrolysis, and they give rise to alcohols and alkenes.[114] The carbonium ions are presumably formed by a second oxidation of the radical at the electrode before it reacts or diffuses into the solution. For example, an investigation of the electrolysis of phenylacetic acid in methanol has led to the identification of benzyl methyl ether (30%), toluene (1%), benzaldehyde dimethylacetal (1%), methyl phenylacetate (6%), and benzyl alcohol (5%), as well as the coupling product bibenzyl (26%).[115]

12.8. $S_{RN}1$ Substitution Processes

Electron transfer processes are also involved in a family of reactions which are designated by the mechanistic description $S_{RN}1$. This refers to a nucleophilic substitution via a radical intermediate, involving a unimolecular decomposition of a radical anion of the substrate. There are two families of such reactions which have been

113. R. F. Garwood, C. J. Scott, and B. C. L. Weedon, *Chem. Commun.*, 14 (1965).
114. P. S. Skell and P. H. Reichenbacher, *J. Am. Chem. Soc.* **90**, 3436 (1968).
115. S.D. Ross and M. Finkelstein, *J. Org. Chem.* **34**, 2923 (1969).

developed to a stage of solid mechanistic understanding and also synthetic utility. The common mechanistic pattern involves electron transfer to the substrate, generating a radical anion which then expels the leaving group. This becomes a chain process if the radical generated by expulsion of the leaving group then reacts with the nucleophile to give a radical anion capable of sustaining a chain reaction:

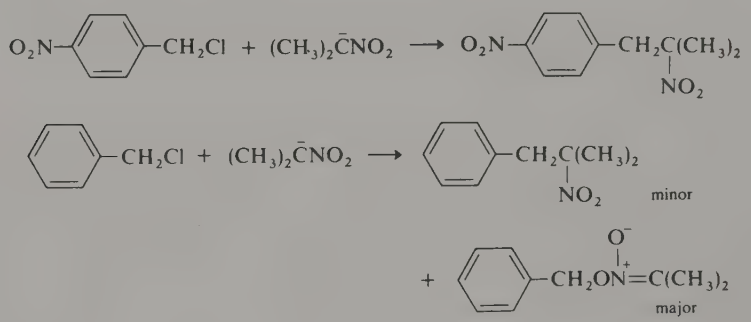
$$\text{Initiation:} \quad R{-}X + e^- \rightarrow RX^{\cdot -} \rightarrow R\cdot + X^-$$

$$\text{propagation:} \quad R\cdot + Nu^- \rightarrow R{-}Nu^{\cdot -}$$

$$R{-}Nu^{\cdot -} + R{-}X \rightarrow R{-}Nu + R{-}X^{\cdot -}$$

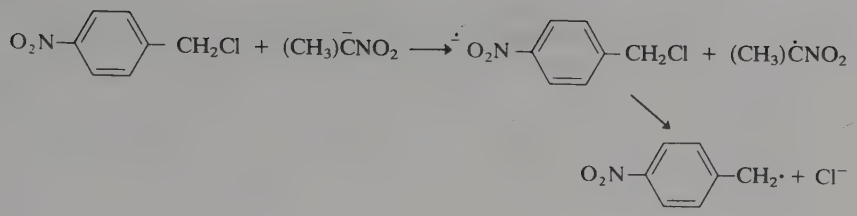
$$R{-}X^{\cdot -} \rightarrow R\cdot + X^-$$

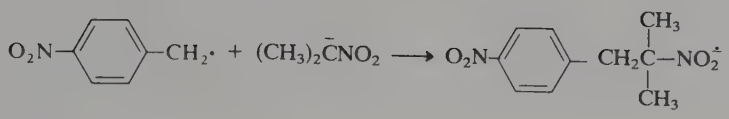
A mechanism of this type permits substitution of certain aromatic and aliphatic nitro compounds by a variety of nucleophiles. These reactions were discovered as the result of efforts to explain the mechanistic basis for high-yield carbon alkylation of the 2-nitropropane anion by *p*-nitrobenzyl chloride. The corresponding bromide and iodide and benzyl halides that do not contain a nitro substituent give mainly the unstable oxygen alkylation product with this ambident anion.[116] The mixture

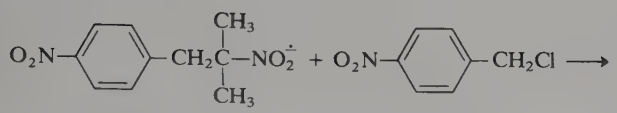


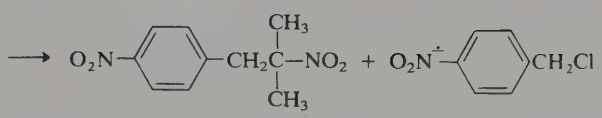
of carbon and oxygen alkylation is what would be expected for an S_N2 substitution process. The high preference for carbon alkylation suggests that a new mechanism operates with *p*-nitrobenzyl chloride, and this conclusion is further strengthened by the fact that the chloride is more reactive than would be predicted by application of the usual I > Br > Cl reactivity trend for leaving groups in S_N2 reactions. The involvement of a free radical process was indicated by EPR studies and by demonstrating that typical free radical inhibitors decrease the rate of the carbon alkylation process. The mechanism proposed is a free radical chain process initiated by electron transfer from the nitronate anion to the nitroaromatic compound.[117] This process is the principal reaction only for the chloride, because with the better leaving groups bromide and iodide, a direct S_N2 process is more rapid:

116. N. Kornblum, *Angew. Chem. Int. Ed. Engl.* **14**, 734 (1975); N. Kornblum in *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*, S. Patai (ed.), Interscience, New York, 1982, Chap. 10.
117. N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.* **88**, 5662 (1966); G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.* **88**, 5663 (1966).

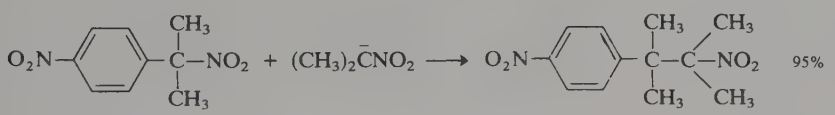








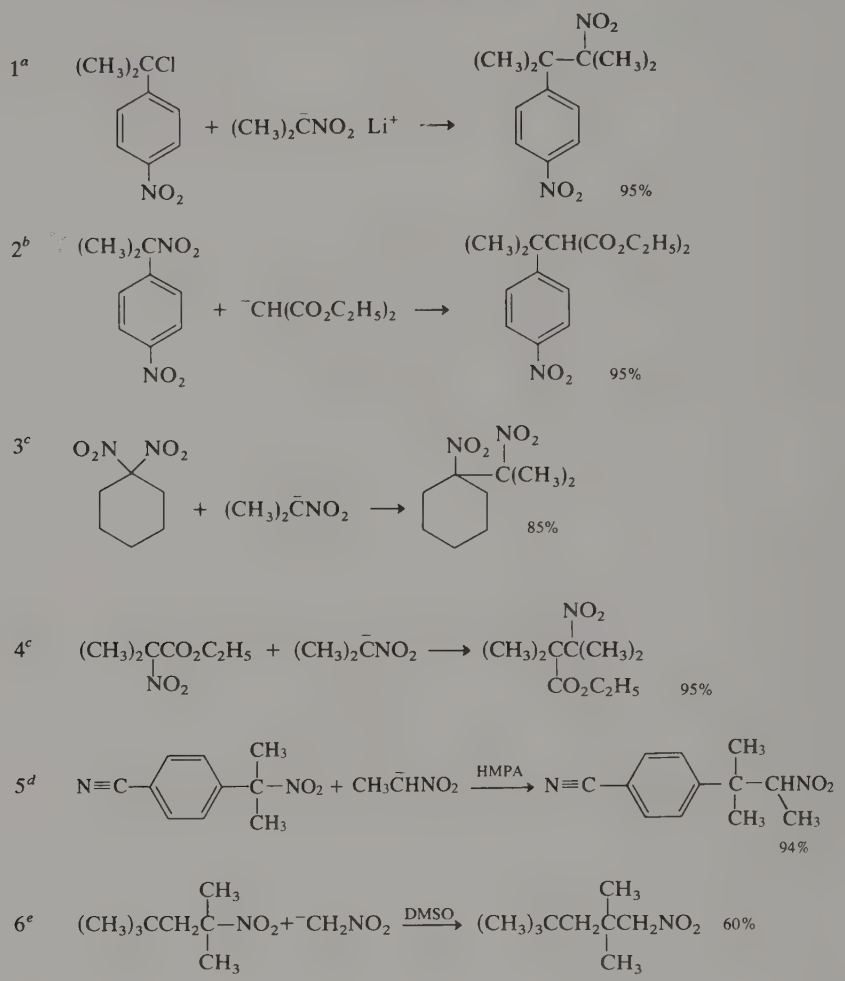
The synthetic value of the reaction has been developed from this basic mechanistic understanding, and the reaction has been shown to be capable of providing highly substituted carbon skeletons that would be inaccessible by normal S_N2 processes. For example, tertiary *p*-nitrocumyl halides can act as alkylating agents in high yield. The same mechanisms are considered to be operative in these related reactions. The nucleophile need not be a nitroalkane anion, but can be such anions as thiolate, phenolate, or carbanions such as those derived from malonate esters.[118] Furthermore, the leaving group need not be halide. Displacement of nitrite ion from α,*p*-dinitrocumene occurs with good efficiency[119]:



This reaction also can be made to proceed with tertiary benzyl nitro compounds lacking the *p*-nitro substituent. The nitro substituent at the benzyl position provides sufficient stabilization to permit the electron transfer to proceed, generating the radical anion. This species decomposes to a tertiary benzyl radical by loss of nitrite ion. Substituted nitrocumyl systems can alkylate nitronate anions in HMPA solution.[120] Entry 5 of Scheme 12.7 provides a specific example.

118. N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 725 (1967).
119. N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 5714 (1967).
120. N. Kornblum, S. C. Carlson, J. Widmer, M. J. Fifolt, B. N. Newton, and R. G. Smith, *J. Org. Chem.* **43**, 1394 (1978).

Scheme 12.7. Carbon Alkylation via Nitroalkane Radical Anions Generated by Electron Transfer

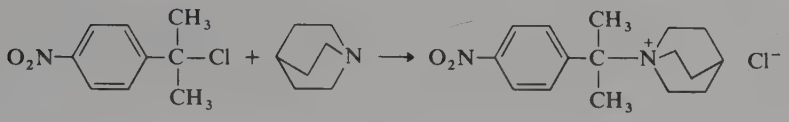


a. N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 725 (1967).
b. N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Am. Chem. Soc.* **89**, 5714 (1967).
c. N. Kornblum, S. D. Boyd, and F. W. Stuchal, *J. Am. Chem. Soc.* **92**, 5783 (1970).
d. N. Kornblum, S. C. Carlson, J. Widmer, M. Fifolt, B. N. Newton, and R. G. Smith, *J. Org. Chem.* **43**, 1394 (1978).
e. N. Kornblum and A. S. Erickson, *J. Org. Chem.* **46**, 1037 (1981).

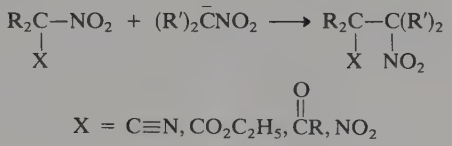
A similar mechanism has been proposed for the alkylation of amines by *p*-nitrocumyl chloride.[121] Clearly, the tertiary nature of the chloride would make any proposal of an S_N2 mechanism highly suspect. Furthermore, the nitro substituent is

121. N. Kornblum and F. W. Stuchal, *J. Am. Chem. Soc.* **92**, 1804 (1970).

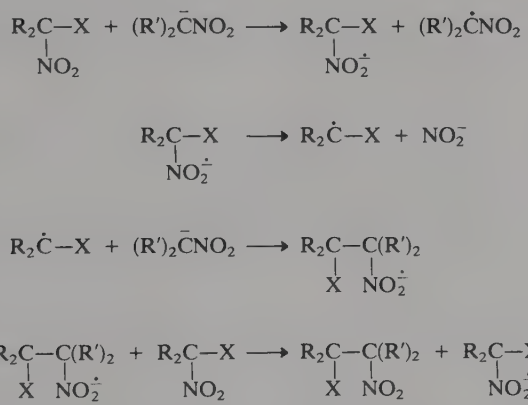
essential to the success of these reactions. Cumyl chloride itself undergoes elimination of HCl on reaction with amines:



A related process constitutes a method of carrying out alkylation reactions to give highly branched alkyl chains that cannot be obtained easily by S_N2 mechanisms. Compounds with one nitro group and one other electron-withdrawing group react with nitroalkane anions to give the product of substitution of the nitro group by the nitroalkane anion:



Experiments in which free radical scavengers are added indicate that a chain reaction is involved, because the reaction is greatly retarded in the presence of the scavengers. The mechanism shown below indicates that one of the steps in the chain is an electron transfer process and that none of the steps involves atom abstractions. The elimination of nitrite occurs as a unimolecular decomposition of a radical anion.[122]



This reaction can also be applied to tertiary nitroalkanes lacking any additional functional groups. The reactions with nitro compounds lacking additional anion-

122. N. Kornblum and S. D. Boyd, *J. Am. Chem. Soc.* **92**, 5784 (1970).

stabilizing functional groups are carried out in dimethyl sulfoxide solution[123]:

$$R_3CNO_2 + {}^-CH_2NO_2 \xrightarrow{DMSO} R_3CCH_2NO_2$$

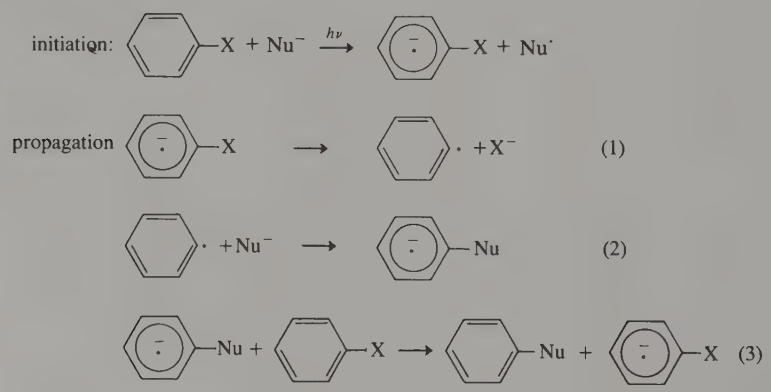
These reactions also appear to be chain reactions which proceed through the $S_{RN}1$ mechanism. Dimethyl sulfoxide is a particularly favorable solvent for this reaction, probably because its conjugate base acts as an efficient chain initiator by undergoing an electron transfer reaction with the substrate.

Although the nitro group plays a crucial role in most of these $S_{RN}1$ reactions, they have synthetic application beyond the area of nitro compounds. The nitromethyl groups can be converted to other functional groups including aldehyde and carboxyl.[124] Nitro groups at tertiary positions can be reductively removed by reaction with the methanethiol anion.[125] This reaction also appears to be of the electron transfer type, with the methanethiolate anion acting as the electron donor:

$$R_3C{-}NO_2 + CH_3S^- \rightarrow R_3C{-}NO_2^{\cdot -} + CH_3S\cdot$$
$$R_3C{-}NO_2^{\cdot -} \rightarrow R_3C\cdot + NO_2^-$$
$$R_3C\cdot + CH_3S^- \rightarrow R_3C{-}H + H_2\dot{C}S^-$$
$$H_2\dot{C}S^- + R_3C{-}NO_2 \rightarrow H_2C{=}S + R_3C{-}NO_2^{\cdot -}$$

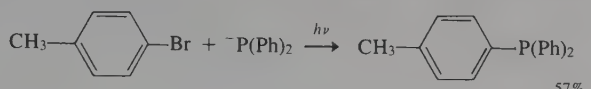
The unique feature of this group of reactions is the facility with which it can form carbon–carbon bonds between highly branched centers, as is illustrated by the examples given in Scheme 12.7.

The second general reaction which proceeds by an $S_{RN}1$ mechanistic pattern involves aryl halides. Aryl halides react with a variety of potential electron donors to give nucleophilic aromatic substitution by a chain mechanism of the $S_{RN}1$ class.[126] Many of the reactions are initiated photochemically and most have been conducted in liquid ammonia solutions.



123. N. Kornblum and A. S. Erickson, *J. Org. Chem.* **46**, 1037 (1981).
124. N. Kornblum, A. S. Erickson, W. J. Kelly, and B. Henggeler, *J. Org. Chem.* **47**, 4534 (1982).
125. K. Kornblum, S. C. Carlson, and R. G. Smith, *J. Am. Chem. Soc.* **101**, 647 (1979).
126. J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).

Scheme 12.8. Aromatic Substitution by the $S_{RN}1$ Mechanism

1[a] 

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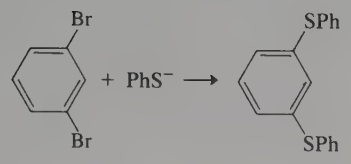
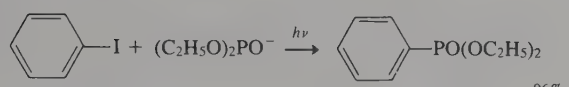
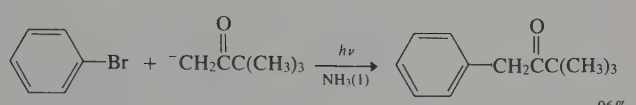
2[b] 

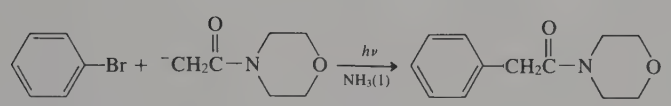
92%

3[c] 

96%

4[d] 

96%

5[e] 

56%

a. J. E. Swartz and J. F. Bunnett, *J. Org. Chem.* **44**, 340 (1979).
b. J. F. Bunnett, and X. Creary, *J. Org. Chem.* **39**, 3611 (1974).
c. J. F. Bunnett, and X. Creary, *J. Org. Chem.* **39**, 3612 (1974).
d. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.* **102**, 7765 (1980).
e. R. A. Rossi and R. A. Alonso, *J. Org. Chem.* **45**, 1239 (1980).

The reactions can also be initiated by a strong chemical reductant or electrochemically.[127] There are several lines of evidence which support the operation of a chain mechanism, one of the most general observations being that the reactions are stopped or greatly retarded by radical traps. The reaction is not particularly sensitive to the aromatic ring substituents that are present. Both electron-releasing groups such as methoxy and electron-attracting groups such as benzoyl can be present.[128,129] Groups which easily undergo one electron reduction, especially the nitro group, cause the reaction to fail. The nucleophile must be capable of acting as a one-electron donor and among the species which have been found to react by the $S_{RN}1$ mechanism are certain enolates, dialkyl phosphite anions, and substituted phosphide anions. Scheme 12.8 illustrates some typical reactions.

127. C. Amatore, J. Chaussard, J. Pinson, J.-M. Saveant, and A. Thiebault, *J. Am. Chem. Soc.* **101**, 6012 (1979).
128. J. F. Bunnett, and J. E. Sundberg, *Chem. Pharm. Bull.* **23**, 2620 (1975).
129. R. A. Rossi, R. H. deRossi, and A. F. Lopez, *J. Org. Chem.* **41**, 3371 (1976).

Kinetic studies have shown that the enolate and phosphorus nucleophiles all react at about the same rate. This suggests that the only step directly involving the nucleophile (step 2 of the propagation sequence) occurs at essentially the diffusion-controlled rate so that there is little selectivity among the individual nucleophiles.[130] The synthetic potential of the reaction lies in the fact that other substituents which activate the halide are not required, in contrast to aromatic nucleophilic substitution which proceeds by an addition–elimination mechanism.

General References

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W. A. Pryor, *Free Radicals*, McGraw-Hill, New York, 1966.
E. S. Huyser, *Free Radical Chain Reactions*, Wiley-Interscience, New York, 1970

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A. R. Forrester, J. M. Hay, and R. H. Thomson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, 1968.

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M. Bersohn and J. C. Baird, *An Introduction to Electron Paramagnetic Resonance*, W. A. Benjamin, New York, 1966.
L. Kevan, in *Methods in Free Radical Chemistry*, Vol. 1, E. Huyser (ed.), Marcel Dekker, New York, 1969, pp. 1–33.

CIDNP

A. G. Lawler and H. R. Ward, in *Determination of Organic Structures by Physical Methods*, Vol. 5, F. C. Nachod and J. J. Zuckerman (eds.), Academic Press, New York, 1973, Chap. 3.

Charged Radicals

E. T. Kaiser and L. Kevan (eds.), *Radical Ions*, Interscience, New York, 1968.

Autoxidation

G. Scott, *Atmospheric Oxidation and Antioxidants*, Elsevier, Amsterdam, 1965; L. Reich and S. S. Stivala, *Autoxidation of Hydrocarbons and Polyolefins*, Marcel Dekker, New York, 1969.

Free Radical Rearrangements

A. L. J. Beckwith and K. U. Ingold in *Rearrangements in Ground and Excited States*, P. deMayo (ed.), Academic Press, New York, 1980, Chap. 4.

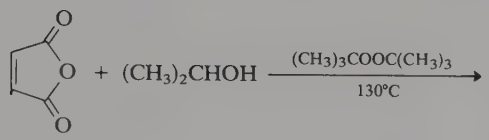
130. C. Galli and J. F. Bunnett, *J. Am. Chem. Soc.* **103**, 7140 (1981).

Problems

(*References for these problems will be found on page 709.*)

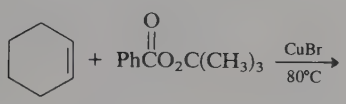
1. Predict the products of the following reactions.

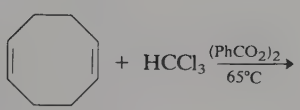
(a) 

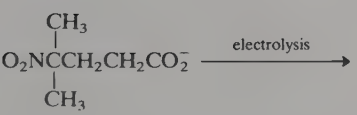
(b) 

(c) 

(d) 

(e) 

(f) 

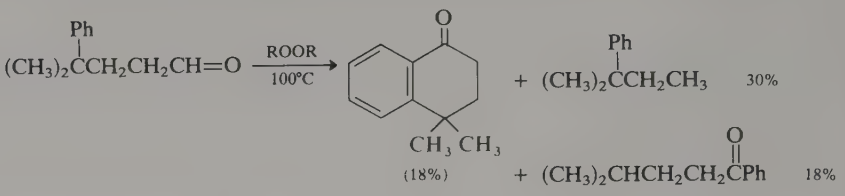
(g) 

2. Using Table III in Ref. 44 (p. 649), calculate the expected product composition from the gas phase photochemical chlorination and bromination of 3-methylpentane under conditions (excess hydrocarbon) in which only monohalogenation would occur.

3. A careful study of the photoinitiated addition of HBr to 1-hexene established the following facts: (1) The quantum yield is 400; (2) the products are 1-bromohexane, 2-bromohexane, and 3-bromohexane. The amounts of 2- and 3-bromohexane formed are always nearly identical, and increase from about 8% each at 4°C to about 22% at 63°C; (3) during the course of the reaction, small amounts of 2-hexene can be detected. Write a mechanism that could accommodate all these facts.

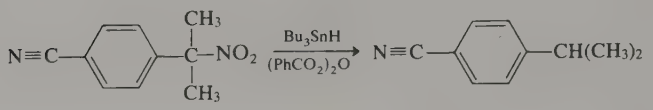
4. Write a mechanism which satisfactorily accounts for the following reactions.

(a)

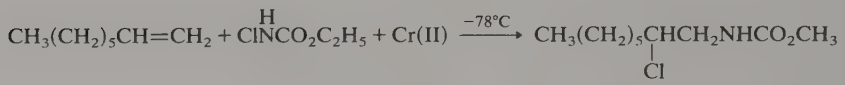


(b)

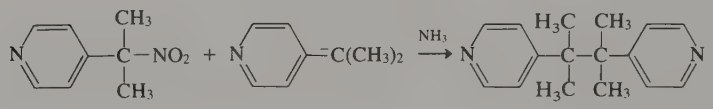
(c)



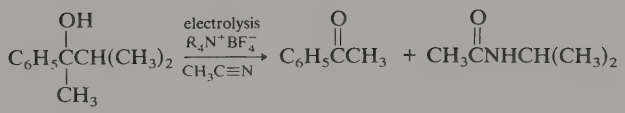
(d)



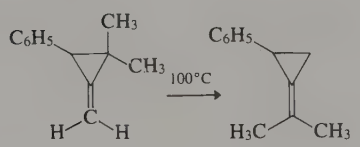
(e)



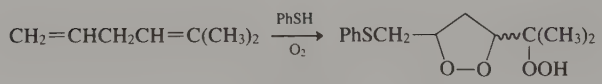
(f)



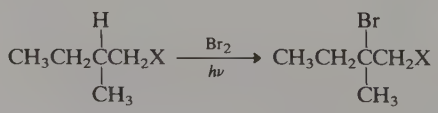
(g)



(h)



5. Photochemical bromination of **1**, $\alpha_D + 4.21°$, affords **2**, which is optically active, $\alpha_D - 3.23°$, but **3** under the same conditions gives **4**, which is optically inactive. Explain.



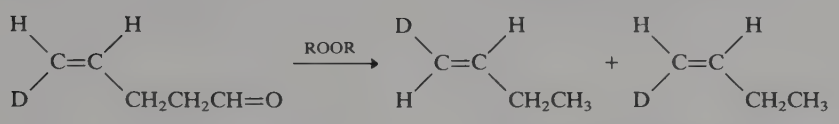
1: X = Br
3: X = F

2: X = Br
4: X = F

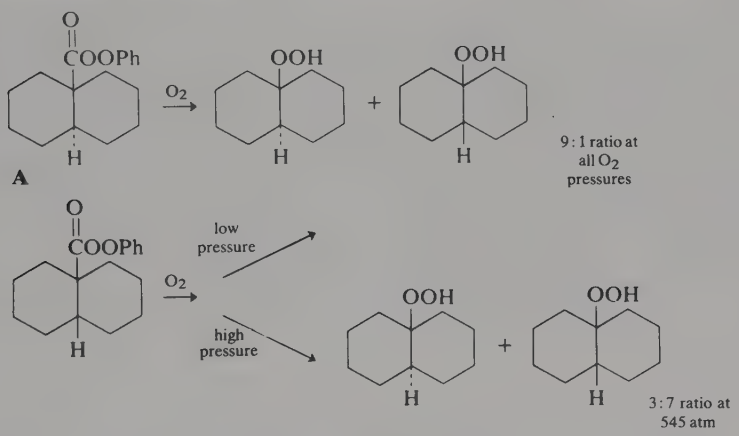
6. The decarbonylation of the two labeled pentenals shown below has been studied. Write a mechanism that could explain the distribution of deuterium label found in the two products.

$$CH_2{=}CHCH_2CD_2CH{=}O \xrightarrow{ROOR} CH_2{=}CHCD_2CH_3 + CH_2{=}CHCH_2CHD_2$$

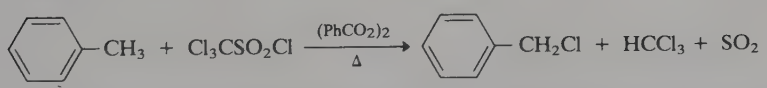
1 : 1 ratio in dilute solution, increasing to 1 : 1.5 in concentrated solution



7. Decomposition of the *trans*-decalyl perester **A** gives a 9 : 1 ratio of *trans* : *cis* hydroperoxide product at all oxygen pressures studied. The product ratio from the *cis* isomer is dependent on the oxygen pressure. At 1 atm O_2, it is 9 : 1 *trans* : *cis*, as with the *trans* substrate, but this ratio decreases and eventually inverts with increasing O_2 pressure. It is 7 : 3 *cis* : *trans* at 545 atm oxygen pressure. What deduction about the stereochemistry of the decalyl free radical can be made from these data?



8. (a) Trichloromethanesulfonyl chloride, Cl_3CSO_2Cl, can chlorinate hydrocarbons as described in the stoichiometric equation below. The reaction is a chain process. Write at least two possible sequences for chain propagation. Suggest some likely termination steps.



(b) Given the following additional information, choose between the chain propagation sequences you have postulated in part (a).

(1) In the reaction

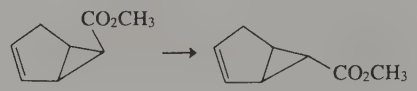
$$R{-}H + BrCCl_3 \xrightarrow{h\nu} RBr + HCCl_3$$

the reactivity of cyclohexane is about one-fifth that of toluene.

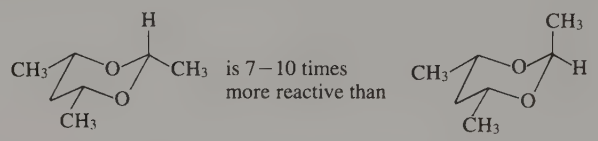
(2) In the chlorination by trichloromethylsulfonyl chloride, cyclohexane is about three times as reactive as toluene.

9. Provide an explanation for the following observations.

(a) The stereoisomerization shown below proceeds efficiently, with no other chemical change occurring at a comparable rate, when the compound is warmed with *N*-bromosuccinimide and a radical chain initiator.

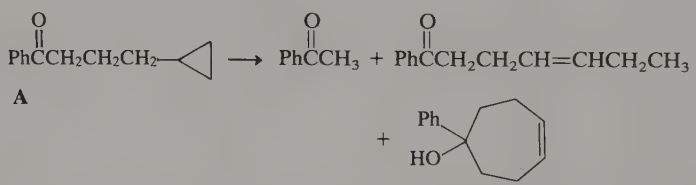


(b) There is a substantial difference in the reactivity of the two stereoisomeric compounds shown below toward abstraction of a hydrogen atom by the *tert*-butoxy radical.

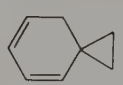


(c) Free radical chlorination of optically active 1-chloro-2-methylbutane yields six dichloro derivatives of which four are optically active and two are not. Identify the optically active and optically inactive products and provide an explanation for the origin of each product.

(d) Photolysis of the ketone **A** gives a mixture of the three products shown. Account for the formation of each product.



(e) Irradiation of a mixture of the hydrocarbon **B** and di-*tert*-butyl peroxide generates a free radical which can be identified as the 2-phenylethyl radical by its EPR spectrum. This is the only spectrum which can be observed, even when the photolysis is carried out at low temperature (−173°C)



B

(f) Among the products from heating 1,5-heptadiene with 1-iodoperfluoropropane in the presence of azo-*bis*-isobutyronitrile are two saturated 1:1 adducts. Both adducts gave the same olefin on dehydrohalogenation, and this olefin was shown by spectral means to contain a $CH_2{=}C$ unit. Give the structures of the two adducts and propose a mechanism for their formation.

10. A highly selective photochemical chlorination of esters, amides and alcohols can be effected in 70%–90% H_2SO_4 using *N*-chlorodialkylamines as chlorinating agents. Mechanistic studies indicate that a chain reaction is involved:

$$R_2\overset{+}{N}H \underset{Cl}{|} \xrightarrow{\text{initiation}} R_2\overset{+}{\dot{N}}H + Cl^-$$

$$R_2\overset{+}{\dot{N}}H + CH_3CH_2(CH_2)_nX \rightarrow R_2^+NH_2 + CH_3\dot{C}H(CH_2)_nX$$

$$CH_3\dot{C}H(CH_2)_nX + R_2\overset{+}{N}H \underset{Cl}{|} \rightarrow CH_3\underset{Cl}{\underset{|}{C}}H(CH_2)_nX + R_2\overset{+}{\dot{N}}H$$

where $X = CO_2CH_3$, CH_2OH, or $CONH_2$. A very interesting feature of the reaction is that the chlorine atom is introduced on the next to terminal carbon atom for reactant molecules with $n = 4$ or 6. In contrast, chlorination of these same compounds with chlorine in nonpolar solvents shows little position selectivity. Rationalize the observed selectivity.

11. Analyze the hyperfine coupling in the spectrum of the butadiene radical anion given in Fig. 12.P8. What is the spin density at each carbon atom according to the McConnell equation?

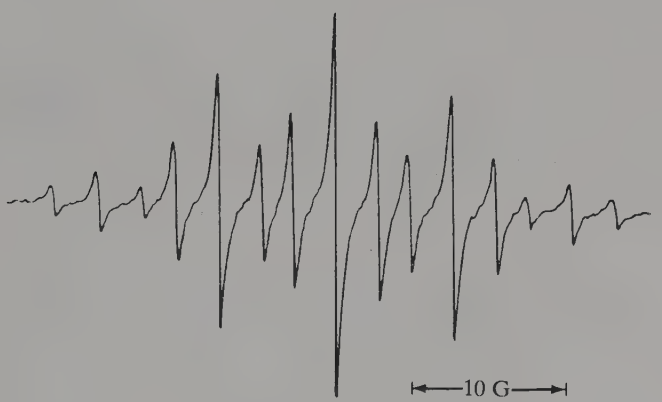
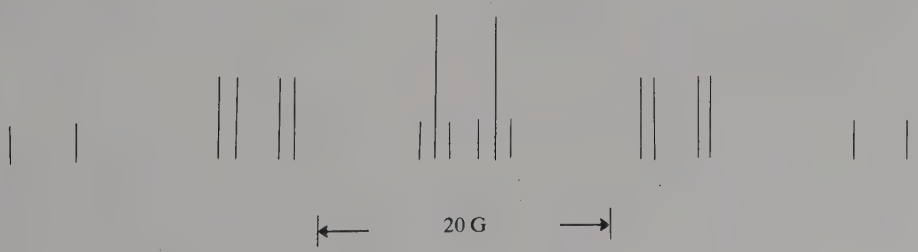
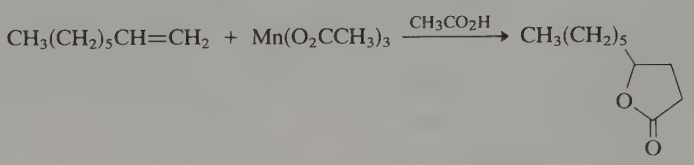


Fig. 12.P8. Spectrum of the butadiene radical anion. [From D. H. Levy and R. J. Myers, *J. Chem. Phys.* **41**, 1062 (1964).]

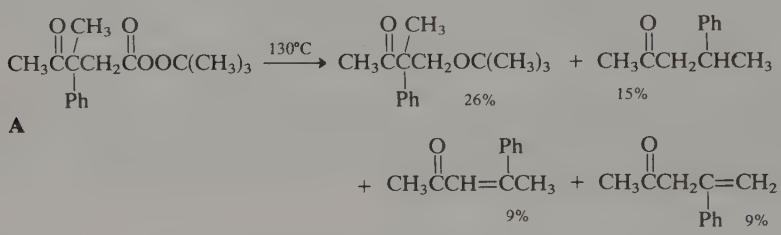
12. A representation of the ESR spectrum of allyl radical is presented below. Interpret the splitting pattern and determine the values of the hyperfine splitting constants.



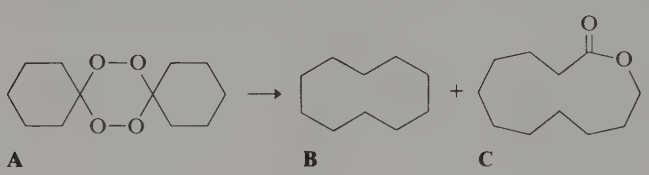
13. A very direct synthesis of certain lactones can be achieved by heating an alkene, a carboxylic acid, and the Mn(III) salt of the acid. Suggest a mechanism by which this reaction might proceed.



14. Indicate mechanisms that would account for each of the products observed in the thermal decomposition of compound **A**:

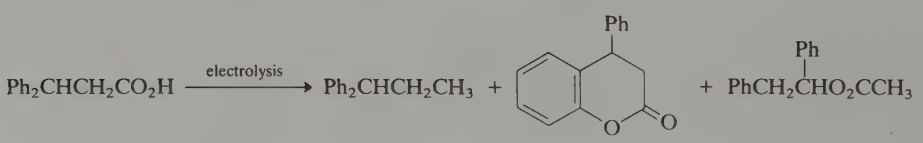


15. The *spiro* peroxide **A**, which is readily prepared from cyclohexanone and hydrogen peroxide, decomposes thermally to give substantial amounts of cyclodecane and 11-undecanolactone (**C**). Account for the efficient formation of these macrocyclic compounds.



16. Methylcyclopropane shows strikingly different reactivity toward chlorination and bromination under radical-chain conditions. With chlorine, cyclopropyl chloride (56%) is the major product, along with small amounts of 1,3-dichlorobutane (7%). Bromine gives a quantitative yield of 1,3-dibromobutane. Offer an explanation for the difference.

17. Electrolysis of 3,3-diphenylpropanoic acid in acetic acid–acetate solution gives the products shown below. Propose mechanisms for the formation of each of the major products.



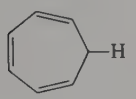
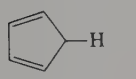
18. By measurements in an ion cyclotron resonance spectrometer the proton affinity (PA) of free radicals can be measured.

$$RH^+ \rightarrow R^\cdot + H^+, \qquad \Delta H_{298} = PA$$

These data can be combined with ionization potential data according to the scheme below to determine bond dissociation energies (BDE).

$RH^+ \rightarrow R^\cdot + H^+$	$\Delta H_{298} = PA$
$RH \rightarrow RH^+ + e^-$	$\Delta H_{298} = IP$
$e^- + H^+ \rightarrow H^\cdot$	$\Delta H_{298} = -313.6$ kcal/mol
$RH \rightarrow R^\cdot + H^\cdot$	$\Delta H_{298} = BDE$

Data for PA and IP are given for several hydrocarbons of interest.

	IP	PA
$PhCH_2-H$	203	198
	190	200
	198	199
	224	180
$CH_2=CHCH_2-H$	224	180
	232	187
$CH_2=CH-H$	242	183

According to these data which structural features provide stabilization of radical centers? Which appear to destabilize radical centers? Determine the level of agreement between these data and the "Radical reorganization energies" given in Table 12.2 if the standard C–H bond dissociation energy is taken to be 98.8 kcal/mol. (Compare the calculated and observed bond-dissociation energies for the benzyl, allyl, and vinyl systems.)

References for Problems

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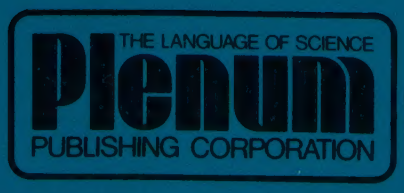

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