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ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

SECOND EDITION

Jerry March
Professor of Chemistry
Adelphi University

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ADVANCED
ORGANIC
CHEMISTRY
REACTIONS,
MECHANISMS, AND
STRUCTURE

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Preface

The vast growth in our knowledge of organic reactions, mechanisms, and structure since the completion of the first edition of this book has prompted this second edition. Every topic retained from the first edition has been brought up to date. Changes, ranging from minor to extensive, have been made on virtually every page of the first edition. Furthermore, a number of significant new topics have come to the fore in recent years, and these have also been included. Among the changes and additions are the following: (1) more than 100 new reactions including, among others, sigmatropic rearrangements, olefin metathesis, extrusion reactions, new 2 + 2 and other cycloadditions, many new reactions involving organoboranes, lithium dialkylcopper reagents, and metal carbonyl and other metallic coordination compounds, the Meyers and Story syntheses, the di-π-methane rearrangement, $AlCl_3$-catalyzed rearrangements, the synthetic use of organoselenium and arylthallium compounds, and a number of new oxidation and reduction reactions; (2) major advances in our understanding of many mechanisms, among them elimination, electrophilic addition to C=C bonds, both nucleophilic and electrophilic substitution at saturated carbon, amide hydrolysis, aromatic sulfonation, the Stevens and Wittig rearrangements, ozonolysis, and the addition of Grignard reagents to ketones; (3) other newly-included topics, including crown ethers, phase-transfer catalysts, memory effects, antiaromaticity, the syn-anti dichotomy, heterogeneous hydrogenation catalysts, correlation diagrams, Hückel and Möbius transition states, hard and soft acids and bases, CIDNP, photoelectron spectroscopy, enantiotopic and diastereotopic atoms, groups, and faces, introduction of functionality at remote positions, and $(CH)_n$ compounds.

Two chapters from the first edition have been dropped. One of these, on instrumental methods of structure determination, is no longer pertinent for an advanced organic chemistry course (though some of the material from this chapter has been used elsewhere in the book). This chapter has been replaced by a new one on photochemistry. In addition, the coverage of photochemical reactions and mechanisms in Part 2 of this book has been expanded. The other deleted chapter is the former appendix chapter on nomenclature, which was dropped with great reluctance, but the large size of the manuscript made its deletion necessary. Apart from these changes the structure of the second edition is essentially the same as that of the first.

The second edition, like the first, is intended to be a textbook for a course in advanced organic chemistry taken by students who have had the standard undergraduate organic and physical chemistry courses. I have attempted to give equal weight to the three fundamental aspects of the study of organic chemistry: reactions, mechanisms, and structure. A student who has completed a course based on this book should be able to approach the literature directly, with a sound knowledge of modern basic organic chemistry. I have treated lightly, or not at all, the major special areas of organic chemistry: terpenes, carbohydrates, proteins, polymerization and electrochemical reactions, steroids, and the like. It is my opinion that these topics are best approached after the first year of graduate study, when the fundamentals have been mastered, either in advanced courses, or directly, by consulting the many excellent books and review articles available on these subjects.

The organization is based on reaction types, so that the student can be shown that despite the large number of organic reactions, a relatively few principles suffice to explain nearly all of them. Accordingly, the reactions-mechanisms section of this book (Part 2) is divided into 10 chapters, each concerned with a different type of reaction. In the first part of each chapter the appropriate basic mechanisms are discussed along with considerations of reactivity and orientation, while the second part consists of numbered sections devoted to individual reactions, where the scope and the mechanism of each reaction are discussed. I have used numbered sections for the reactions, because I have found that students learn better when they are presented with clear outlines (for a further discussion of the arrangement of Part 2, see pp. 261–263). Since the methods for the preparation of individual classes of compounds, (e.g., ketones, nitriles, etc.) are not treated all in one place, an index has been provided (Appendix B) by use of which all methods for the preparation of a given type of compound will be found. For each reaction, a list of *Organic Synthesis* references is given. Thus for most reactions the student can consult actual examples in *Organic Syntheses.*

The structure of organic compounds is discussed in the first five chapters of Part 1. This section provides a necessary background for understanding mechanisms and is also important in its own right. The discussion begins with chemical bonding and ends with a chapter on stereochemistry. There follow two chapters on reaction mechanisms in general, one for ordinary reactions and the other for photochemical reactions. Part 1 concludes with two more chapters which give further background to the study of mechanisms.

In addition to reactions, mechanisms, and structure, the student should have some familiarity with the literature of organic chemistry. A chapter devoted to this topic has been placed in Appendix A, though many teachers may wish to cover this material at the beginning of the course.

In treating a subject as broad as the basic structures, reactions, and mechanisms of organic chemistry, it is obviously not possible to cover each topic in great depth. Nor would this be desirable even if possible. Nevertheless, students will often wish to pursue individual topics further. An effort has therefore been made to guide the reader to pertinent review articles and books published since about 1950. In this respect, this book is intended to be a guide to the secondary literature (since about 1950) of the field it covers. Furthermore, in a graduate course, students should be encouraged to consult primary sources. To this end I have included more than 6000 references to original papers.

Although basically designed for a one-year course on the graduate level, this book can also be used in advanced undergraduate courses as long as they are preceded by one-year courses in organic and physical chemistry. It can also be adapted, by the omission of a large part of its contents, to a one-semester course. Indeed, even for a one-year course, more is included than can be conveniently covered. Many individual sections can be easily omitted without disturbing continuity.

The reader will observe that this text contains much material which is included in first-year organic and physical chemistry courses, though in most cases it goes more deeply into each subject and, of course, provides references, which first-year texts do not. It has been my experience that students who have completed the first-year courses often have a hazy recollection of the material, and greatly profit from a re-presentation of the material if it is organized in a different way. It is hoped that the organization of the material on reactions and mechanisms will greatly aid the memory and the understanding. In any given course the teacher may want to omit some chapters because his students already have an adequate knowledge of the material, or because there are other graduate courses which cover the areas more thoroughly. Chapters 1, 4, and 7 especially may fall into one of these categories.

Although this is a textbook, it has been designed to have reference value also. Students who are preparing for qualifying examinations and practicing organic chemists will find that Part 2 contains a survey of what is known about the mechanism and scope of about 610 reactions, arranged in an orderly manner based on reaction type and on which bonds are broken and formed. Also valuable for reference purposes are the previously mentioned lists of reactions classified by type of compound prepared (Appendix B) and of all of the *Organic Syntheses* references to each reaction.

Once again, it is a pleasure to acknowledge the assistance of a number of chemists who have been kind enough to read portions of the manuscript and to send me their comments, which were exceedingly helpful. I wish to thank Professors J. F. Bunnett, A. W. Burgstahler, D. J. Cram, P. de Mayo, E. L. Eliel, R. W. Griffin, Jr., G. S. Hammond, M. Kreevoy, J. Landesberg, S. Moon, G. A. Olah, G. C. Pimentel, W. H. Saunders, Jr., C. G. Swain, R. W. Taft, Jr., W. S. Trahanovsky, N. J. Turro, C. Walling, and R. Wistar, each of whom read one or more chapters of either the first or second editions, and Professor B. B. Jarvis, who read the entire manuscript of the second edition. Special thanks are due to Professor C. A. Bunton, who read the entire manuscript of both the first and second editions. In addition, I wish to thank many of my colleagues at Adelphi University who have rendered assistance in various ways, among them F. Bettelheim, W. P. Gallagher, M. Hall, R. Halliday, J. Landesberg, S. Milstein, S. Moon, D. Purins, R. Rudman, A. J. Sisti, and S. Windwer. I am also grateful to those readers who wrote to tell me about errors they discovered in the first edition or to make other comments. Such letters are always welcome.

Jerry March

Bibliographical Note

In this book the practices used in citing references are slightly different from those prevailing elsewhere. The reader should note:

1 For review articles, both the first and last page numbers are given, so that the reader may form an idea of the length of the article. If reference is made to only a portion of the article, these page numbers are also given.
2 Author's initials are omitted in references. They will be found, however, in the author index.
3 When a journal is available both in Russian and in English, the page numbers of each article are, of course, different. The language of the journal title indicates whether the page number cited is to be found in the Russian or in the English version. For articles which have appeared in *Angewandte Chemie, International Edition in English*, both the English and German page numbers are given.
4 Certain hardbound serial publications (see p. 1156) are here cited as journals rather than as books.

PART ONE

This book contains 19 chapters. Chapters 10 through 19, which make up Part 2, are directly concerned with organic reactions and their mechanisms. Chapters 1 through 9 may be thought of as an introduction to Part 2. The first five chapters constitute a unit dealing with the structure of organic compounds. In this unit we shall discuss the kinds of bonding important in organic chemistry, the three-dimensional structure of organic molecules, and the structure of species in which the valence of carbon is less than 4. Chapters 6 to 9 are concerned with other topics which help to form a background to Part 2: acids and bases, photochemistry, the relationship between structure and reactivity, and a general discussion of mechanisms and of the means by which they are determined.

One

Localized Chemical Bonding

Localized chemical bonding, which is treated in this chapter, may be defined as bonding in which the electrons are shared by two and only two nuclei. In Chapter 2 we shall consider *delocalized bonding*, in which electrons are shared by more than two nuclei. But before we can intelligently discuss bonding at all, we must consider the electronic structure of atoms, in which the electrons surround only one nucleus.

Atomic Orbitals[1]

The fundamental principle upon which wave mechanics is based is that electrons behave as waves (e.g., they can be diffracted) and that consequently a wave equation can be written for them, in the same sense that light waves, sound waves, etc., can be described by wave equations. The equation which serves as a mathematical model for electrons is known as the *Schrödinger equation*, and for a one-electron system is

$$\frac{\partial^2\psi}{\partial x^2} + \frac{\partial^2\psi}{\partial y^2} + \frac{\partial^2\psi}{\partial z^2} + \frac{8\pi^2 m}{h^2}(E - V)\psi = 0 \qquad (1)$$

where m is the mass of the electron, E is its total energy, V is its potential energy, and h is Planck's constant. In physical terms, the function ψ expresses the square root of the probability of finding the electron at any position defined by the coordinates x, y, and z, where the origin is at the nucleus. For systems containing more than one electron the equation is similar but more complicated.

The solutions to the Schrödinger equation are themselves equations. Solutions exist only for certain values of E. These are called *eigenvalues*, and the solutions are called *eigenfunctions*. This is another way of saying that the energy possessed by electrons is quantized. For the hydrogen atom, which is spherically symmetrical, the natural coordinate system is the system of spherical polar coordinates (r, θ, and ϕ), and solutions to (1) for the hydrogen atom are generally expressed in these coordinates. The spherical coordinates are related to the rectangular coordinates as follows (see Figure 1):

$$x = r \sin\theta \cos\phi \qquad (2)$$

$$y = r \sin\theta \sin\phi \qquad (3)$$

$$z = r \cos\theta \qquad (4)$$

$$r = (x^2 + y^2 + z^2)^{1/2} \qquad (5)$$

---

[1] The treatment of atomic and molecular orbitals given here is necessarily simplified. For much fuller treatments of orbital theory as applied to organic chemistry, see Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill Book Company, New York, 1969; Liberles, "Introduction to Molecular-Orbital Theory," Holt, Rinehart, and Winston, New York, 1966; Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, 1961; Coulson, "Valence," 2d ed., Oxford University Press, New York, 1961; Coulson and Stewart, in Patai, "The Chemistry of Alkenes," pp. 1–147, Interscience Publishers, Inc., New York, 1964; and Higasi, Baba, and Rembaum, "Quantum Organic Chemistry," Interscience Publishers, Inc., New York, 1965.

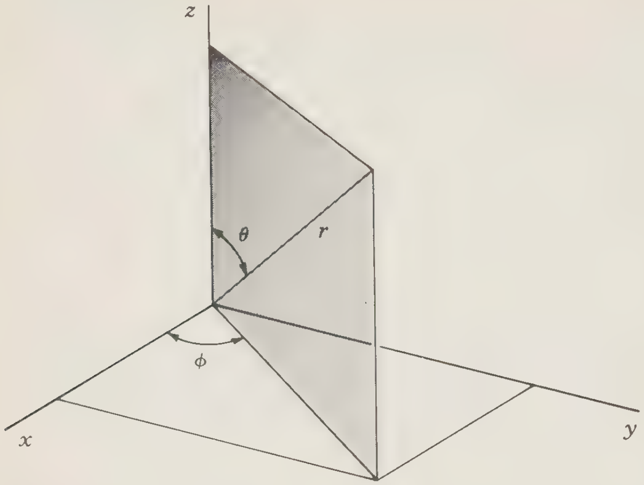


Figure 1 The spherical coordinates.

For a given point *P*, the coordinate r is the distance between the origin O and the point, while θ represents the angle between the line OP and the z axis and ϕ is the angle between the xz plane and the plane containing OP and the z axis.

For the hydrogen atom, the potential energy is

$$V = -\frac{Ze^2}{r} \tag{6}$$

where r is the distance between the nucleus and the electron, e the charge on the electron, and Z the nuclear charge (in this case, 1). The solution of the Schrödinger equation which corresponds to the lowest possible energy for the electron is

$$\psi = \frac{1}{\sqrt{\pi}}\left(\frac{Z}{a_0}\right)^{3/2} e^{-Zr/a_0} \tag{7}$$

where

$$a_0 = \frac{h^2}{4\pi^2 me^2} \tag{8}$$

The energy corresponding to this solution is

$$E = \frac{-2\pi^2 mZ^2e^4}{h^2} \tag{9}$$

which turns out to be -13.60 eV. The distance a_0, which is equal to 0.529Å, is called the *Bohr radius.*

Three of the higher solutions are

$$\psi = \frac{1}{\sqrt{32\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0}\cos\theta \tag{10}$$

$$\psi = \frac{1}{\sqrt{64\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0} \sin\theta \cos\phi \tag{11}$$

$$\psi = \frac{1}{\sqrt{64\pi}}\left(\frac{Z}{a_0}\right)^{5/2} re^{-Zr/2a_0} \sin\theta \sin\phi \tag{12}$$

Since the energies corresponding to these three eigenfunctions are equal, the energy levels are said to be *degenerate*. There are an infinite number of other solutions, each with its corresponding energy, but there are no solutions with an energy between those of any two successive solutions.

Since these eigenfunctions are equations, we can graph them. The graphs are three-dimensional pictures of the density of the electron. The graph corresponding to Eq. (7) shows that the electron density is distributed symmetrically about the nucleus. The density increases along a line beginning at the nucleus and proceeding in any direction until a maximum is reached, after which it rapidly drops off. This maximum is at $r = 0.529$ Å; i.e., it is at the Bohr radius. Although in theory there is still some density at an infinite distance from the nucleus, it is possible to draw a sphere with a radius of about 4 or 5 times that of the Bohr radius and enclose nearly all the electron density in it. Such a sphere is shown in Figure 2.

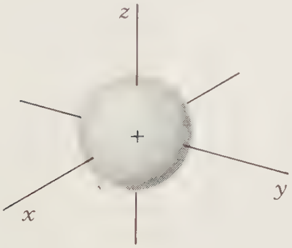
A wave function like that depicted in Figure 2 is called an *orbital* or an electron cloud. Some have spherical symmetry, like that in Figure 2. These are called s orbitals. The orbital corresponding to Eq. (10), shown in Figure 3, is called a p orbital. Unlike s orbitals, p orbitals are not spherically symmetrical but are directed along one of the axes. A p orbital consists of two lobes, separated by a *node*, which is a region in space where the probability of finding the electron is very small, almost zero.[2] In this case the node is the entire xy plane. In Figure 3 one lobe of the orbital is labeled + and the other −. These signs do not refer to positive or negative *charges*, since both lobes of an electron cloud must be negatively charged. They are the signs of the function ψ. When two parts of any orbital are separated by a node, ψ always has opposite signs on the two sides of the node. Other things being equal, the more nodes an orbital has, the higher its energy.

The orbitals corresponding to Eqs. (11) and (12) have the same shape as the one in Figure 3, but they are directed along the other axes. The three p orbitals are often called p_x, p_y, and p_z, to distinguish among them. There are also orbitals of higher energy, called d and f orbitals, but

---

[2] When wave-mechanical calculations are made according to the Schrödinger equation, the probability of finding the electron in a node is zero, but this treatment ignores relativistic considerations, and when such considerations are applied, Dirac has shown that nodes do have a very small electron density: Powell, *J. Chem. Educ.* **45**, 558 (1968).

Figure 2 The wave function for the lowest energy level (ground state) of the hydrogen atom.



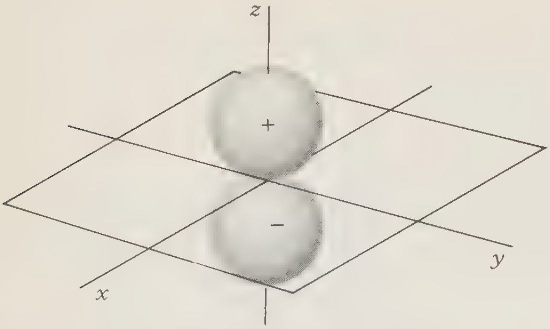


Figure 3 The orbital corresponding to Eq. (10).

we shall not consider their shapes here since they are less important to organic chemists than the *s* and *p* orbitals.[3]

The orbital shown in Figure 2 corresponds to the lowest possible energy for the electron of the hydrogen atom. It is called the 1*s* orbital. If we examine the eigenfunctions corresponding to the next energy value, we find four additional orbitals. One of these, called the 2*s* orbital, is spherical and contains a node (Figure 4). The others are the three *p* orbitals mentioned before, which are called 2*p* orbitals. Orbitals of higher energy are 3*s*, 3*p*, 3*d*, 4*s*, etc. In any given hydrogen atom, the electron at any instant is in only one of these orbitals. The others exist only as potential states. However, it is possible (and often happens) that an electron may pass from one orbital to another. When this occurs, the orbital previously occupied becomes a potential state and the new one is occupied. In order for an electron to go from a lower-energy orbital to a higher one, it must get energy from somewhere; and when it goes from a higher to a lower state, it must give up the necessary energy. Not all transitions are allowed; selection rules determine the ones which can occur. When the electron is in the 1*s* orbital, the hydrogen atom is said to be in the *ground state*. All levels above the ground state are called *electronically excited states.*

Unfortunately, the Schrödinger equation can be solved exactly only for one-electron atomic systems, such as the hydrogen atom or He^+. For all systems more complicated than this, approximations are required. For a number of simple cases, such as the hydrogen molecule and the helium atom, these approximate solutions are so accurate that for practical purposes they are as good as exact solutions.[4] Even for atoms much larger than helium, a good qualitative picture is at hand. By the use of the following principles, electronic structures can be determined for atoms up to about calcium:

1. In any atom the orbitals available for electron occupancy are similar in shape to those of the hydrogen atom, though the energies are different. The designations 1*s*, 2*s*, 2*p*, etc., are the same.

2. In the ground state of any atom the electrons occupy the lowest possible energy levels. If even one electron is in an orbital of energy higher than a vacant orbital, the atom is in an excited state.

---

[3] The shapes of many atomic and molecular orbitals can be found in Streitwieser and Owens, "Orbital and Electron Density Diagrams," The Macmillan Company, New York, 1973. For the shapes of all the molecular orbitals in 104 typical molecules, see Jorgensen and Salem, "The Organic Chemist's Book of Orbitals," Academic Press, Inc., New York, 1973.

[4] See, for example, Roothaan and Weiss, *Rev. Mod. Phys.* **32,** 194 (1960); Kolos and Roothaan, *Rev. Mod. Phys.* **32,** 219 (1960). For a review, see Clark and Stewart, *Q. Rev., Chem. Soc.* **24,** 95–118 (1970).

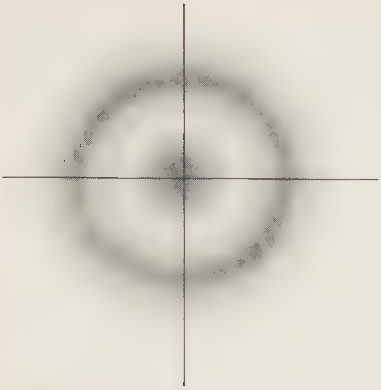


Figure 4 Cross section of a $2s$ orbital.

3. No more than two electrons may be present in an orbital, and they must have opposite spins.[5] This is the *Pauli exclusion principle*.

4. When a number of degenerate orbitals are available and there are not enough electrons to fill them all, then all the orbitals will be half-filled before any of them are filled. This is called *Hund's rule*. For example, the nitrogen atom has seven electrons. Four of these are accommodated in the two orbitals of lowest energy, the $1s$ and $2s$ orbitals. Above these are the three p orbitals, which can hold a maximum of six electrons. Hund's rule tells us that each of the three remaining electrons will go into a different $2p$ orbital; i.e., the configuration of the ground state of the nitrogen atom is $1s^2 2s^2 2p_x{}^1 2p_y{}^1 2p_z{}^1$ and not $1s^2 2s^2 2p_x{}^2 2p_y{}^1$. Hund's rule is valid because a situation in which two electrons have parallel spins is of lower energy than that in which the spins are opposite, owing to the greater mutual repulsion of electrons with opposite spins. In the case of a $2p_x{}^2 2p_y{}^1$ configuration, two of the electrons must have opposite spins (or they could not be in the same orbital), while for $2p_x{}^1 2p_y{}^1 2p_z{}^1$ all the spins may be and generally are parallel.

For atoms higher than hydrogen, the energy of the orbitals is in the order $1s < 2s < 2p < 3s < 3p < 4s$. From this, and the above rules, the electronic structures for the ground states of the first 20 atoms are

H	$1s^1$	**Na**	Ne core $3s^1$
He	$1s^2$	**Mg**	Ne core $3s^2$
Li	$1s^2 2s^1$	**Al**	Ne core $3s^2 3p_x{}^1$
Be	$1s^2 2s^2$	**Si**	Ne core $3s^2 3p_x{}^1 3p_y{}^1$
B	$1s^2 2s^2 2p_x{}^1$	**P**	Ne core $3s^2 3p_x{}^1 3p_y{}^1 3p_z{}^1$
C	$1s^2 2s^2 2p_x{}^1 2p_y{}^1$	**S**	Ne core $3s^2 3p_x{}^2 3p_y{}^1 3p_z{}^1$
N	$1s^2 2s^2 2p_x{}^1 2p_y{}^1 2p_z{}^1$	**Cl**	Ne core $3s^2 3p_x{}^2 3p_y{}^2 3p_z{}^1$
O	$1s^2 2s^2 2p_x{}^2 2p_y{}^1 2p_z{}^1$	**Ar**	Ne core $3s^2 3p_x{}^2 3p_y{}^2 3p_z{}^2$
F	$1s^2 2s^2 2p_x{}^2 2p_y{}^2 2p_z{}^1$	**K**	Ar core $4s^1$
Ne	$1s^2 2s^2 2p_x{}^2 2p_y{}^2 2p_z{}^2$	**Ca**	Ar core $4s^2$

It is the custom to designate the first occupied orbital of a set of p orbitals as the p_x orbital. Of course, this is purely arbitrary, since the three p orbitals differ only in direction. For example, it would be just as correct to show the electronic structure of boron as $1s^2 2s^2 2p_y{}^1$ or $1s^2 2s^2 2p_z{}^1$.

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[5] In this book we shall not define electron spin but merely state that it is a property of an electron for which two and only two possible states exist.

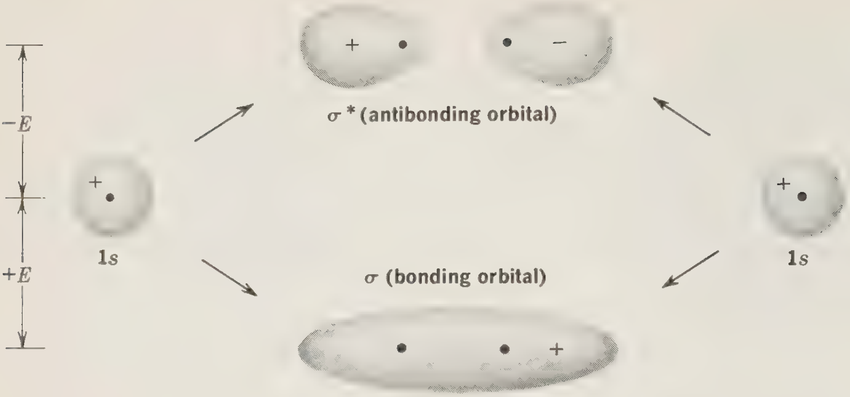

Figure 5 Overlap of two 1*s* orbitals gives rise to a σ and a σ^* orbital.

Covalent Bonding

If the Schrödinger equation could be exactly solved for molecules, we would have a complete picture which would show for each electron precisely the shape of the orbitals available to it (especially for the important ground state) and the energy for each orbital. Since exact solutions are not available, drastic approximations must be made. There are two chief general methods of approximation, called the *molecular-orbital* method and the *valence-bond* method.

In the molecular-orbital method bonding is considered to arise from the overlap of atomic orbitals. When any number of atomic orbitals overlap, they disappear and are replaced by the same number of new orbitals, called *molecular orbitals*. Molecular orbitals differ from atomic orbitals in that they are clouds which surround the nuclei of two or more atoms, rather than just one. In localized bonding the number of atomic orbitals which overlap is two (each containing one electron), so that two molecular orbitals are generated. One of these, called a *bonding orbital*, has a lower energy than the original atomic orbitals (otherwise a bond would not form), and the other, called an *antibonding orbital*, has a higher energy. Whereas the two original atomic orbitals each held one electron, both of these electrons may now go into the new molecular *bonding* orbital, since any orbital can hold two electrons. The antibonding orbital remains empty in the ground state. The greater the overlap, the stronger the bond, although total overlap is prevented by repulsion between the nuclei. Figure 5 shows the bonding and antibonding orbitals which arise by overlap of two 1*s* electrons.[3] Note that since the antibonding orbital has a node between the nuclei, there is practically no electron density in that area, so that this orbital cannot be expected to bond very well. Molecular orbitals formed by overlap of two atomic orbitals when the centers of electron density are on the axis common to the two nuclei are called σ orbitals, and the bonds so formed are called σ bonds. Corresponding antibonding orbitals are designated σ^*. Because total energy is conserved when molecular orbitals are formed from atomic orbitals, the total energy of the σ and σ^* orbitals must equal the total energy of the two atomic orbitals, so that the σ^* orbital is destabilized by the same amount of energy by which the σ orbital is stabilized (this is called the *bond energy D*, see p. 26). σ orbitals are formed not only by overlap of two *s* orbitals but also by overlap of any of the kinds of atomic orbital mentioned earlier (*s*, *p*, *d*, or *f*) whether they are the same or different, but the two lobes which overlap must have the same sign: a positive *s* orbital can form a bond only by overlapping with another positive *s* orbital or with a positive lobe of a *p*, *d*, or *f* orbital. Any σ orbital, no matter what kind of atomic orbitals it has arisen from, may be represented as approximately ellipsoidal in shape.

Orbitals are frequently designated by their symmetry properties. The σ orbital of hydrogen is often written Ψ_g. The g stands for *gerade*. A gerade orbital is one in which the sign of the orbital does not change when it is reflected through its center of symmetry. The σ^* orbital is *ungerade* (designated Ψ_u). An ungerade orbital changes sign when reflected through its center of symmetry.

In molecular-orbital calculations, a wave function is formulated which is a linear combination of the atomic orbitals which have overlapped (this method is often called the *linear combination of atomic orbitals*, or LCAO):

$$\Psi = c_\mathrm{A}\psi_\mathrm{A} + c_\mathrm{B}\psi_\mathrm{B} \tag{13}$$

The functions ψ_A and ψ_B are the functions for the atomic orbitals of atoms A and B, respectively, and c_A and c_B represent weighting factors.

In the valence-bond method, a wave equation is written for each of various possible electronic structures which a molecule may have (each of these is called a *canonical form*), and the total Ψ is obtained by summation of as many of these as seem plausible, each with its weighting factor:

$$\Psi = c_\mathrm{A}\psi_\mathrm{A} + c_\mathrm{B}\psi_\mathrm{B} + \cdots \tag{14}$$

This resembles Eq. (13), but here each ψ represents a wave equation for an imaginary canonical form and each c is the amount contributed to the total picture by that form. For example, a wave function can be written for each of the following canonical forms of the hydrogen molecule:[6]

$$\mathrm{H{-}H} \qquad {}^{\ominus}\overline{\mathrm{H}}\quad \mathrm{H}^{\oplus} \qquad {}^{\oplus}\mathrm{H}\quad \overline{\mathrm{H}}^{\ominus}$$

Values for c in each method are obtained by solving the equation for various values of each c and choosing the solution of lowest energy. In practice, both methods give similar solutions for molecules which contain only localized electrons, and these are in agreement with the Lewis structures long familiar to the organic chemist. Delocalized systems are considered in Chapter 2.

Multiple Valence

A univalent atom has only one orbital available for bonding. But atoms with a valence of 2 or more must form bonds by using at least two orbitals. From our previous discussion of atomic orbitals, we have seen that the oxygen atom has two half-filled orbitals, thus giving it a valence of

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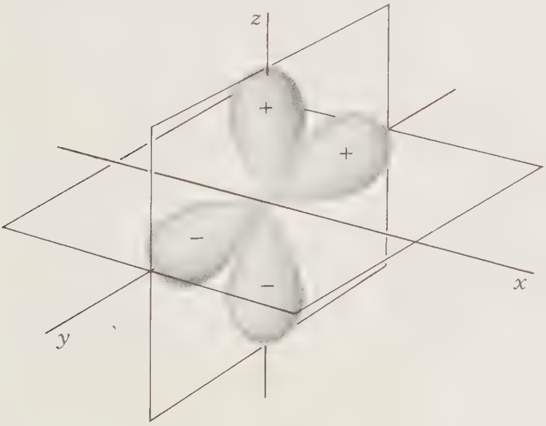
[6] In this book a pair of electrons, whether in a bond or unshared, is represented by a straight line.

Figure 6 The p orbitals of oxygen which are available for bonding.



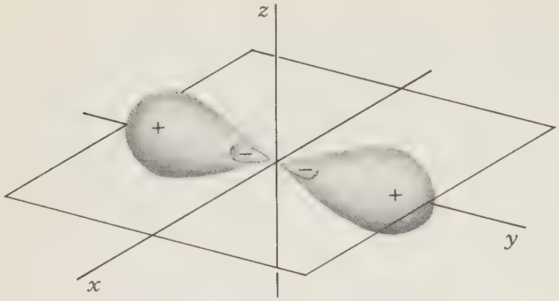


Figure 7 The two *sp* orbitals formed by mercury.

2. It forms single bonds by overlap of these with the orbitals of two other atoms. According to the principle of maximum overlap, the other two nuclei should form an angle of 90° with the oxygen nucleus, since the two available orbitals on oxygen are *p* orbitals, which are perpendicular (Figure 6). Similarly, we should expect that nitrogen, which has three mutually perpendicular *p* orbitals, would have bond angles of 90° when it forms three single bonds. However, these are not the observed bond angles. The bond angles are,[7] in water, 104°27′, and in ammonia, 106°46′. For alcohols and ethers the angles are even larger (see p. 25). A discussion of this will be deferred to p. 25, but it is important to note that covalent compounds do have definite bond angles. Although the atoms are continuously vibrating, the mean position is the same for each molecule of a given compound.

Hybridization

Consider the case of mercury. Its electronic structure is

$$\text{Xe core } 4f^{14}5d^{10}6s^2$$

Although it has no half-filled orbitals, it has a valence of 2 and forms two covalent bonds. We can explain this by imagining that one of the 6*s* electrons is promoted to a vacant 6*p* orbital to give the configuration

$$\text{Xe core } 4f^{14}5d^{10}6s^1 6p^1$$

In this state the atom has two half-filled orbitals, but they are not equivalent. If bonding were to occur by overlap of these orbitals with the orbitals of external atoms, the two bonds would not be equivalent and the bond formed from the 6*p* orbital would be more stable than the one formed from the 6*s* orbital, since a larger amount of overlap is possible with the former. A more stable situation is achieved when, in the course of bond formation, the 6*s* and 6*p* orbitals combine to form two new orbitals which *are* equivalent; these are shown in Figure 7.

Since these new orbitals are a mixture of the two original orbitals, they are called *hybrid orbitals*. Each is called an *sp* orbital, since a merger of an *s* and a *p* orbital was required to form it. The *sp* orbitals, each of which consists of a large lobe and a very small one, are atomic orbitals, although they can arise only in the bonding process and do not represent a possible structure for the free atom. A mercury atom forms its two bonds by overlapping each of the large lobes shown in Figure 7 with an orbital from an external atom. This external orbital may be any of the atomic orbitals previously considered (*s*, *p*, *d*, or *f*), or it may be another hybrid orbital, though of course

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[7] Bent, *Chem. Rev.* **61**, 275–311 (1961), p. 277.

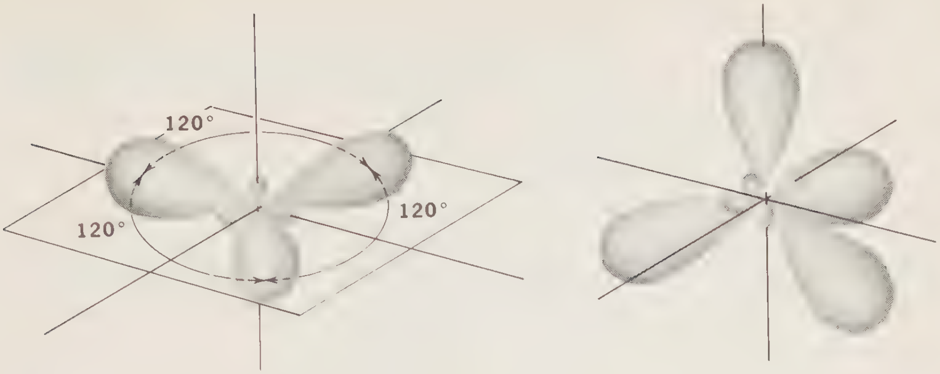


Figure 8 The three sp^2 and the four sp^3 orbitals.

only lobes of the same sign can overlap. In any of these cases the molecular orbital which arises is called a σ orbital since it fits our previous definition of a σ orbital (p. 8).

In general, because of mutual repulsion, equivalent orbitals lie as far away from each other as possible, and so the two *sp* orbitals form an angle of 180°. This means that $HgCl_2$, for example, should be a linear molecule (in contrast to H_2O), and it is. This kind of hybridization is called *digonal hybridization*. An *sp* hybrid orbital forms a stronger covalent bond than either an *s* or a *p* orbital because it extends out in space in the direction of the other atom's orbital farther than the *s* or the *p* and so permits greater overlap. Although it would require energy to promote a 6*s* electron to the 6*p* state, the extra bond energy more than makes up the difference.

Many other kinds of hybridization are possible, of which we shall discuss two. Consider boron, which has the electronic configuration

$$1s^2 2s^2 2p^1$$

yet has a valence of 3. Once again we may imagine promotion and hybridization:

$$1s^2 2s^2 2p^1 \longrightarrow 1s^2 2s^1 2p_x{}^1 2p_y{}^1 \longrightarrow 1s^2 (sp^2)^3$$

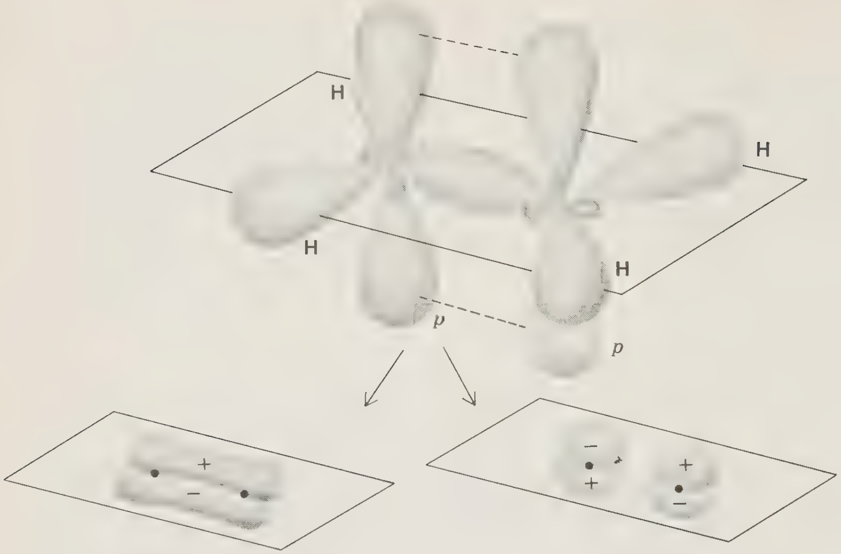
In this case there are three equivalent hybrid orbitals, each called sp^2 (*trigonal hybridization*). This method of designating hybrid orbitals is perhaps unfortunate since nonhybrid orbitals are designated by single letters, but it must be kept in mind that *each* of the three orbitals is called sp^2. These orbitals are shown in Figure 8. The three axes are all in one plane and point to the corners of an equilateral triangle. This is in accord with the known structure of BF_3, a planar molecule with angles of 120°.

The case of carbon (in forming four single bonds) may be represented as follows:

$$1s^2 2s^2 2p_x{}^1 2p_y{}^1 \longrightarrow 1s^2 2s^1 2p_x{}^1 2p_y{}^1 2p_z{}^1 \longrightarrow 1s^2 (sp^3)^4$$

Here there are four equivalent orbitals, each called sp^3, which point to the corners of a regular tetrahedron (Figure 8). The bond angles of methane would thus be expected to be 109°28′, which is the angle for a regular tetrahedron.

Although the hybrid orbitals discussed in this section satisfactorily account for most of the physical and chemical properties of the molecules involved, it is necessary to point out that the sp^3 orbitals, for example, stem from only one possible approximate solution of the Schrödinger equation. The *s* and the three *p* atomic orbitals can also be combined in many other equally valid ways. As we shall see on p. 15, the four C—H bonds of methane do not always behave as if they are equivalent.



π orbital (bonding)

π* orbital (antibonding)

Figure 9 Overlapping *p* orbitals form a π and a π* orbital. The σ orbitals are shown in the upper figure. They are still there in the diagrams below but have been removed from the picture for clarity.

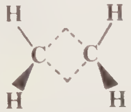
Multiple Bonds

If we consider the ethylene molecule in terms of the molecular-orbital concepts so far discussed, we have each carbon using sp^2 orbitals to form bonds with the three atoms to which it is connected. These sp^2 orbitals arise from hybridization of the $2s^1$, $2p_x{}^1$, and $2p_y{}^1$ electrons of the promoted state shown on p. 11. We may consider that any carbon atom which is bonded to only three different atoms uses sp^2 orbitals for this bonding. Each carbon of ethylene is thus bonded by three σ bonds: one to each hydrogen and one to the other carbon. Each carbon therefore has another electron in the $2p_z$ orbital, which, by the principle of maximum repulsion, is perpendicular to the plane of the sp^2 orbitals. The two parallel $2p_z$ orbitals can overlap sideways to generate two new orbitals, a bonding and an antibonding orbital (Figure 9). Of course, in the ground state both electrons go into the bonding orbital, and the antibonding orbital remains vacant. Molecular orbitals which are formed by overlap of atomic orbitals whose axes are parallel are called π orbitals if they are bonding and π* if they are antibonding.

In this picture of ethylene, the two orbitals which make up the double bond are not equivalent. The σ orbital is ellipsoidal and symmetrical about the C—C axis. The π orbital is in the shape of two ellipsoids, one above the plane and one below. The plane itself represents a node for the π orbital. In order for the *p* orbitals to maintain maximum overlap, they must be parallel. This means that free rotation is not possible about the double bond, since the two *p* orbitals would have to reduce their overlap to allow one H—C—H plane to rotate with respect to the other. The six atoms of a double bond are therefore in a plane with angles which should be about 120°. Double bonds are shorter than the corresponding single bonds because maximum stability is obtained when the *p* orbitals overlap as much as possible.

Figure 10 The σ electrons of acetylene

The lack of free rotation about double bonds can also be explained by the *bent-bond* picture,[8] in which the two bonds in the double bond of the ethylene molecule are equivalent. The centers of electron density are pointed *away* from the C—C axis:



That is, all four of the bonds of each carbon point to the corners of a tetrahedron. This is essentially the old picture of formation of a double bond by joining two tetrahedra together along one edge. Although there are some reasons to support this picture,[9] rather than the σ-π concept, in this book we shall use the latter because most of the recent literature is written in these terms. Similar pictures of both kinds can be drawn for double bonds between carbon and oxygen or nitrogen.

In triple-bond compounds, carbon is connected to only two other atoms and hence uses *sp* hybridization, which means that the four atoms involved are in a straight line (Figure 10).[10] Each carbon has two *p* orbitals remaining, with one electron in each. These orbitals are perpendicular to each other and to the C—C axis. They overlap in the manner shown in Figure 11 to form two π orbitals. A triple bond is thus composed of one σ and two π orbitals. (In the bent-bond

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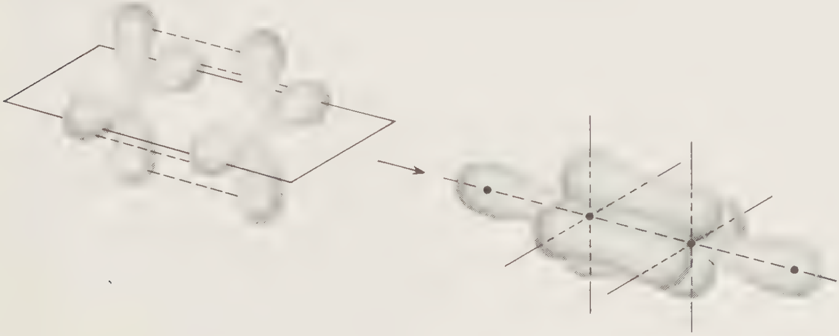
[8] Pauling, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 2-5, Butterworth Scientific Publications, London, 1959. Bent bonds are also called "banana bonds." See also Walters, *J. Chem. Educ.* **43**, 134 (1967).

[9] For example, the σ-π picture predicts an H—C—C angle of 120°, while this angle in the bent-bond picture would be 125°16′. Although the H—C—C angle in ethylene is about 121 to 122°, the corresponding angle is larger for other olefins: 124.8° for propylene, 124° for isobutylene, etc. (see Ref. 8). Also, charge-density calculations show that in ethylene the electrons associated with the C—C bond tend to accumulate above and below the molecular plane [Roux, Cornille, and Burnelle, *J. Chem. Phys.* **37**, 933 (1962)].

[10] For a review of triple bonds, see Dale, in Viehe, "Acetylenes," pp. 3–96, Marcel Dekker, Inc., New York, 1969.

Figure 11 Overlap of *p* orbitals in a triple bond. For clarity, the σ orbitals have been removed from the drawing on the left, though they are shown on the right.



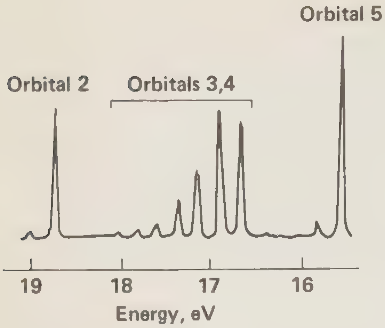


Figure 12 Photoelectron spectrum of N_2.[14]

picture, a triple bond is made up of two tetrahedra with a common face.) Triple bonds between carbon and nitrogen can be represented in a similar manner.

Double and triple bonds are important only for the first-row elements carbon, nitrogen, and oxygen. For second-row elements multiple bonds are rare and compounds containing them are unstable[10a] because the *p* orbitals necessary to form them are farther apart and hence overlap less. The only ones of any importance at all are C═S bonds, and C═S compounds are generally much less stable than the corresponding C═O compounds (however, see p. 39).

Photoelectron Spectroscopy

Although the four bonds of methane are equivalent according to most physical and chemical methods of detection (for example, neither the nmr nor the ir spectrum of methane contains peaks which can be attributed to different kinds of C—H bonds), there is one physical technique which shows that the eight valence electrons of methane can be differentiated. In this technique, called *photoelectron spectroscopy*,[11] a molecule or free atom is bombarded with vacuum ultraviolet radiation,[12] causing an electron to be ejected. The energy of the ejected electron can be measured, and the difference between the energy of the radiation used and that of the ejected electron is the *ionization potential* of that electron. A molecule which contains several electrons of differing energies can lose any one of them, as long as its ionization potential is less than the energy of the radiation used (a single molecule loses only one electron; loss of two electrons by any individual molecule almost never occurs). A photoelectron spectrum therefore consists of a series of bands, each of which corresponds to an orbital of a different energy. The spectrum gives a direct experimental picture of all of the orbitals present, in order of their energies, provided that radiation of sufficiently high energy is used.[13] Broad bands usually correspond to strongly bonding electrons

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[10a] For a review of double bonds between carbon and elements other than C, N, S, or O, see Jutzi, *Angew. Chem. Int. Ed. Engl.* **14**, 232–245 (1975) [*Angew. Chem.* **87**, 269–283].

[11] Only the briefest description of this subject is given here. For monographs, see Baker and Betteridge, "Photoelectron Spectroscopy," Pergamon Press, Elmsford, N.Y., 1972; and Turner, Baker, Baker, and Brundle, "High Resolution Molecular Photoelectron Spectroscopy," John Wiley & Sons, Inc., New York, 1970. For reviews, see Brundle and Robin, in Nachod and Zuckerman, "Determination of Organic Structures by Physical Methods," vol. 3, pp. 1 71, Academic Press, Inc., New York, 1971; Baker, Brundle, and Thompson, *Chem. Soc. Rev.* **1**, 355–380 (1972); Bock and Mollère, *J. Chem. Educ.* **51**, 506–514 (1974); Bock and Ramsey, *Angew. Chem. Int. Ed. Engl.* **12**, 734–752 (1973) [*Angew. Chem.* **85**, 773–792]; Turner, *Adv. Phys. Org. Chem.* **4**, 31–71 (1966); Baker, *Acc. Chem. Res.* **3**, 17–25 (1970); and Jonathan, *Essays Chem.* **3**, 17–25 (1970).

[12] Other kinds of radiation, of higher energy, can also be used.

[13] The correlation is not perfect, but the limitations do not seriously detract from the usefulness of the method.

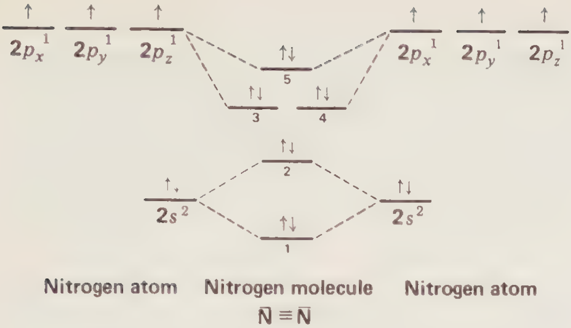

Figure 13 Electronic structure of N_2 (inner-shell electrons omitted).[14]

and narrow bands to weakly bonding or nonbonding electrons. A typical spectrum is that of N_2, shown in Figure 12.[14] The N_2 molecule has the electronic structure shown in Figure 13. The two 2*s* orbitals of the nitrogen atoms combine to give the two orbitals marked 1 (bonding) and 2 (antibonding), while the six 2*p* orbitals combine to give six orbitals, three of which (marked 3, 4, and 5) are bonding. The three antibonding orbitals (not indicated in Figure 13) are unoccupied. Electrons ejected from orbital 1 are not found in Figure 12 because the ionization potential of these electrons is greater than the energy of the light used (they can be seen when higher-energy light is used). The broad band in Figure 12 (the individual peaks within this band are caused by different vibrational levels; see Chapter 7) corresponds to the four electrons in the degenerate orbitals 3 and 4. The triple bond of N_2 is therefore composed of these two orbitals and of orbital 1. The bands corresponding to orbitals 2 and 5 are narrow; hence these orbitals contribute little to the bonding and may be regarded as the two unshared pairs of $\bar{N}\equiv\bar{N}$. Note that this result is contrary to that expected from a naïve consideration of orbital overlaps, where it would be expected that the two unshared pairs would be those of orbitals 1 and 2, which result from overlap of the filled 2*s* orbitals, and that the triple bond would be composed of orbitals 3, 4, and 5, resulting from overlap of the *p* orbitals. This example is one illustration of the value of photoelectron spectroscopy.

The photoelectron spectrum of methane[15] shows *two* bands,[16] at about 23 and 14 eV, and not the single band we would expect from the equivalency of the four C—H bonds. The reason is that ordinary sp^3 hybridization is not adequate to explain phenomena involving ionized molecules (such as the $CH_4{\cdot}^+$ radical ion, which is left behind when an electron is ejected from methane). For these phenomena it is necessary to use other combinations of atomic orbitals (see p. 11). The band at 23 eV comes from two electrons in a low energy level (called the a_1 level), which can be regarded as arising from a combination of the 2*s* orbital of carbon with an appropriate combination of hydrogen 1*s* orbitals. The band at 14 eV, which is more bonding than the other, comes from six electrons in a triply degenerate level (the (t_2 level) arising from a combination of the three 2*p* orbitals of carbon with other combinations of 1*s* hydrogen orbitals. As mentioned above, most physical and chemical processes cannot distinguish these levels, but photoelectron spectroscopy is one technique which can.

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[14] From Brundle and Robin, Ref. 11, p. 18.

[15] Brundle, Robin, and Basch, *J. Chem. Phys.* **53**, 2196 (1970); Baker, Betteridge, Kemp, and Kirby, *J. Mol. Struct.* **8**, 75 (1971); Potts and Price, *Proc. R. Soc.* (*London*), *Ser. A* **326**, 165 (1972).

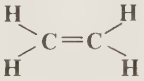
[16] A third band, at 290 eV, caused by the 1*s* electrons of carbon, can also be found if radiation of sufficiently high energy is used.

Electronic Structures of Molecules

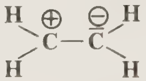
For each molecule, ion, or free radical which has only localized electrons, it is possible to draw an electronic formula, called a *Lewis structure*, which shows the location of these electrons. In practice only the valence electrons are shown. These may be found in covalent bonds connecting two atoms, or they may be unshared. It is important that the student be able to draw these structures correctly, since the position of electrons changes in the course of a reaction, and it is necessary to know which orbitals the electrons are in initially before one can follow where they are going. To this end, the following rules operate:

1. The total number of valence electrons in the molecule (or ion or free radical) must be the sum of all outer-shell electrons "contributed" to the molecule by each atom plus the negative charge or minus the positive charge, for the case of ions. Thus, for H_2SO_4, there are 2 (one for each hydrogen) + 6 (for the sulfur) + 24 (6 for each oxygen) = 32; while for SO_4^{2-}, the number is also 32, since each atom "contributes" 6, plus 2 for the negative charge.

2. Once the number of valence electrons has been ascertained, it is necessary to determine which of them are found in covalent bonds and which are unshared. Unshared electrons (either a single electron or a pair) form part of the outer shell of just one atom, but electrons in a covalent bond are part of the outer shell of both atoms of the bond. *First-row atoms* (B, C, N, O, F) *can have a maximum of eight valence electrons*, and usually have this number, although some cases are known where a first-row atom has only six or seven. Where there is a choice between a structure which has six or seven electrons around a first-row atom and one in which all such atoms have an octet, it is the latter which generally has the lower energy and which consequently exists. For example, ethylene is



and not



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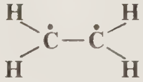

There are a few exceptions. In the case of the molecule O_2, the structure $|\dot{\underline{O}}-\dot{\underline{O}}|$ has a lower energy than $|\underline{O}=\underline{O}|$. Although first-row atoms are limited to 8 valence electrons, this is not so for second-row atoms, which can accommodate 10 or even 12 because they can use their empty d orbitals for this purpose.[17] For example, PCl_5 and SF_6 are stable compounds. In SF_6 one s and one p_x electron from the ground state $3s^2 3p_x^2 3p_y^1 3p_z^1$ are promoted to empty d orbitals, and the six orbitals hybridize to give six sp^3d^2 orbitals, which point to the corners of a regular octahedron.

3. It is customary to show the formal charge on each atom. For this purpose an atom is considered to "own" all unshared electrons but only *one-half of the electrons in covalent bonds.* The sum of electrons which thus "belong" to an atom is compared with the number "contributed" by the atom. An excess belonging to the atom results in a negative charge, and a deficiency results in a positive charge. The total of the formal charges on all atoms equals the charge on the whole molecule or ion. It should be noted that the counting procedure is not the same for determining formal charge as it is for determining the number of valence electrons. For both purposes an atom "owns" all unshared electrons, but for outer-shell purposes it "owns" both of the electrons of the covalent bond, while for formal-charge purposes, it "owns" only one-half of these electrons.

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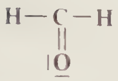
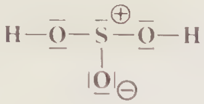
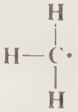
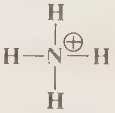
[17] For reviews concerning sulfur compounds with a valence shell larger than eight, see Cilento, *Chem. Rev.* **60,** 147-167 (1960), and Salmond, *Q. Rev., Chem. Soc.* **22,** 253-275 (1968).

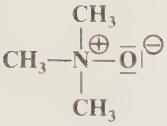
Examples of electronic structures are (as mentioned in footnote 6, in this book an electron pair, whether unshared or in a bond, is represented by a straight line):

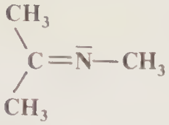


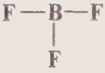


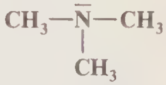




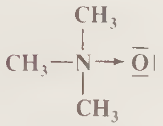








A coordinate-covalent bond, represented by an arrow, is one in which both electrons come from the same atom; i.e., the bond can be regarded as being formed by overlap of an orbital containing two electrons with an empty one. Thus trimethylamine oxide would be represented



For a coordinate-covalent bond the rule concerning formal charge is amended, so that both electrons count for the donor and neither for the recipient. Thus, as written here, the nitrogen and oxygen atoms of trimethylamine oxide bear no formal charges. However, it is apparent that the electronic picture is exactly the same as the picture of trimethylamine oxide given just above, and we have our choice of drawing an arrowhead or a charge separation. Some compounds, e.g., amine oxides, must be drawn one way or the other. It seems simpler to use charge separation, since this spares us from having to consider as a "different" method of bonding a way that is really the same as ordinary covalent bonding once the bond has formed.[18]

Electronegativity[19]

The electron cloud which bonds two atoms is not symmetrical (with respect to the plane which is the perpendicular bisector of the bond) except when the two atoms are the same and have the same substituents. The cloud is necessarily distorted toward one side of the bond or the other, depending on which atom (nucleus plus electrons) maintains the greater attraction for the cloud. This attraction is called *electronegativity*; it is greatest for atoms in the upper right corner of the periodic table and lowest for atoms in the lower left corner. Thus a bond between fluorine and chlorine will be distorted so that there is a higher probability of finding the electrons near the fluorine than near the chlorine. This gives the fluorine a partial negative charge and the chlorine a partial positive charge.

A number of attempts have been made to set up quantitative tables of electronegativity which indicate the direction and extent of electron-cloud distortion for a bond between any pair of

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[18] It has been suggested that the valence octet around atoms can better be understood as being made up of two quartets rather than four pairs. For this argument see Linnett, "The Electronic Structure of Molecules," John Wiley & Sons, Inc., New York, 1964.

[19] For reviews of this topic, see Batsanov, *Russ. Chem. Rev.* **37**, 332–351 (1968); Syrkin, *Russ. Chem. Rev.* **31**, 197–206 (1962); Pritchard and Skinner, *Chem. Rev.* **55**, 745–786 (1955); and Pauling, "The Nature of the Chemical Bond," 3d ed., Cornell University Press, Ithaca, N.Y., 1960.

TABLE 1 Electronegativities of some atoms[20]

F	4.0	S	2.5	B	2.0
O	3.5	C	2.5	Si	1.8
N	3.0	I	2.5	Mg	1.2
Cl	3.0	P	2.1	Na	0.9
Br	2.8	H	2.1	Cs	0.7

atoms. The most popular of these scales, devised by Pauling, is based on bond energies (see p. 26) of diatomic molecules. The reasoning here is that if in a molecule A—B the electron distribution were symmetrical, the bond energy would be the mean of the energies of A—A and B—B, since in these cases the cloud must be undistorted. If the actual bond energy of A—B is higher than this (and it usually is), it is the result of the partial charges, since the charges attract each other and make a stronger bond, which requires more energy to break. It is necessary to assign a value to one element arbitrarily (F = 4.0 is the one used); then the electronegativity of another is obtained from the difference between the actual energy of A—B and the mean of A—A and B—B (this difference is called Δ) by the formula

$$x_A - x_B = \sqrt{\frac{\Delta}{23.06}} \qquad (15)$$

where x_A and x_B are the electronegativities of the known and unknown atoms and 23.06 is an arbitrary constant. Part of the scale derived from this treatment is shown in Table 1.[20]

Other treatments have led to scales which are based on different principles, e.g., the sum of the ionization potential and the electron affinity,[21] or on the same principle with corrections.[22] In some of these treatments electronegativities can be calculated for different valence states, for different hybridizations (e.g., *sp* carbon atoms are more electronegative than sp^2, which are still more electronegative than sp^3)[23] and even differently for primary, secondary, and tertiary carbon atoms. Also, electronegativities can be calculated for groups rather than atoms (Table 2).[24]

Electronegativity information can be obtained from nmr spectra. In the absence of a magnetically anisotropic group[25] the chemical shift of a proton is approximately proportional to the electron density around it and hence to the electronegativity of the atom or group to which it is attached. The greater the electronegativity of the atom or group the lower the electron density around the proton and the further downfield the chemical shift. An example of the use of this correlation is found in the variation of chemical shift of the *ring* protons in the series toluene, ethylbenzene, isopropylbenzene, *t*-butylbenzene (there is a magnetically anisotropic group here, but its effect should be constant throughout the series). It is found that the electron density surrounding the ring protons decreases[26] in the order given.[27] However, this type of correlation

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[20] Taken from Pauling, Ref. 19, p. 93.

[21] Hinze and Jaffé, *J. Am. Chem. Soc.* **84**, 540 (1962); Iczkowski and Margrave, *J. Am. Chem. Soc.* **83**, 3547 (1961).

[22] Brown, *J. Am. Chem. Soc.* **83**, 36 (1961).

[23] Walsh, *Discuss. Faraday Soc.* **2**, 18 (1947).

[24] Hinze, Whitehead, and Jaffé, *J. Am. Chem. Soc.* **85**, 148 (1963). For a review of group electronegativities, see Wells, *Prog. Phys. Org. Chem.* **6**, 111–145 (1968).

[25] A magnetically anisotropic group is one which is not equally magnetized along all three axes. The most common such groups are benzene rings (see p. 42) and triple bonds.

[26] This order is opposite to that expected from the field effect (p. 20). It is an example of the Baker-Nathan order (p. 70).

[27] Moodie, Connor, and Stewart, *Can. J. Chem.* **38**, 626 (1960).

TABLE 2 Some group electronegativities[24]

CH_3	2.30	$CHCl_2$	2.63
CH_2Cl	2.47	CCl_3	2.79
CI_3	2.50	CF_3	3.29
CBr_3	2.57		

is by no means perfect, since all the measurements are being made in a powerful field, which itself may affect the electron-density distribution. Coupling constants between the two protons of a system $-\underset{|}{C}H-\underset{|}{C}H-X$ have also been found to depend on the electronegativity of X.[28] For carbons involved in π bonding, ^{13}C chemical shifts correlate with the π-electron density on the carbon.[29] For example, ^{13}C nmr spectra for a series of carbonyl compounds ($R^{13}COR'$) in a variety of solvents showed that the ^{13}C chemical shift was approximately proportional to the polarity of the $C{=}O$ bond.[30] It has also been found that ^{14}N chemical shifts of nonaromatic nitro compounds are dependent on the electronegativity of the rest of the molecule.[31]

When the difference in electronegativities is great, the orbital may be so far over to one side that it barely covers the other nucleus. This is an *ionic bond*, which is seen to arise naturally out of the previous discussion, leaving us with basically only one type of bond in organic molecules. Most bonds can be considered as intermediate between ionic and covalent. We may speak of percent ionic character of a bond, which indicates the extent of electron-cloud distortion. There is a continuous graduation from ionic to covalent bonds.

The *dipole moment* is a property of the molecule which results from charge separations like those discussed above. However, it is not possible to measure the dipole moment of an individual bond within a molecule; we can measure only the total moment of the molecule, which is the vectorial sum of the individual bond moments.[32] These individual moments are roughly the same from molecule to molecule, but this constancy is by no means universal. Thus, from the dipole moments of toluene and nitrobenzene (Figure 14) we should expect the moment of *p*-nitrotoluene to be about 4.36 D. The actual value 4.39 D is quite reasonable. However, the moment of *p*-cresol (1.57 D) is quite far from the predicted value of 1.11 D. In some cases, molecules may have substantial individual bond moments but no total moments at all because the individual moments are canceled out by the overall symmetry of the molecule. Some examples are CCl_4, *trans*-1, 2-dibromoethene, and *p*-dinitrobenzene.

Because of the small difference between the electronegativities of carbon and hydrogen, alkanes have very small dipole moments, so small that they are difficult to measure. For example, the dipole moment of isobutane is 0.132 D[33] and that of propane is 0.083 D[34]. Of course, methane

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[28] Williamson, *J. Am. Chem. Soc.* **85,** 516 (1963); Laszlo and Schleyer, *J. Am. Chem. Soc.* **85,** 2709 (1963); Niwa, *Bull. Chem. Soc. Jpn.* **40,** 2192 (1967). See also Williamson, Mosser, and Stedman, *J. Am. Chem. Soc.* **93,** 7208 (1971).

[29] Karplus and Pople, *J. Chem. Phys.* **38,** 2803 (1963); Tokuhiro and Fraenkel, *J. Am. Chem. Soc.* **91,** 5005 (1969).

[30] Maciel, *J. Chem. Phys.* **42,** 2746 (1965); Maciel and Natterstad, *J. Chem. Phys.* **42,** 2752 (1965).

[31] Witanowski, Urbánski, and Stefaniak, *J. Am. Chem. Soc.* **86,** 2569 (1964).

[32] For methods of determining dipole moments and discussions of their applications, see Exner, "Dipole Moments in Organic Chemistry," Georg Thieme Publishers, Stuttgart, 1975; Sutton, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 373–425, Academic Press, Inc., New York, 1955. For tables of dipole moments, see McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Company, San Francisco, 1963; and Landolt-Börnstein, "Zahlenwerte und Funktionen," I Band, 3 Teil, pp. 388–508, Springer-Verlag OHG, Berlin, 1951.

[33] Maryott and Birnbaum, *J. Chem. Phys.* **24,** 1022 (1956); Lide and Mann, *J. Chem. Phys.* **29,** 914 (1958).

[34] Lide, *J. Chem. Phys.* **33,** 1514 (1960).

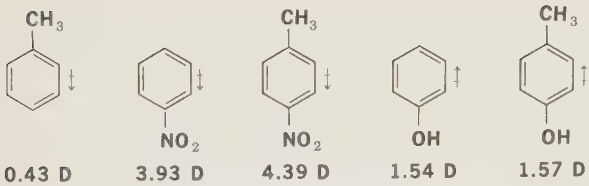
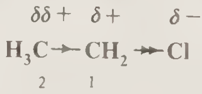


Figure 14 Some dipole moments, in debye units, measured in benzene. The arrow points to the negative part of the molecule.[35]

and ethane, because of their symmetry, have no dipole moments.[36] Few organic molecules have dipole moments greater than 7 D.

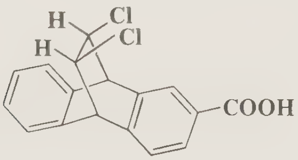
Inductive and Field Effects

The C—C bond in ethane is completely nonpolar because it connects two equivalent atoms. However, the C—C bond in chloroethane is polarized by the presence of the electronegative chlorine atom. This polarization is actually the sum of two effects. In the first of these, the C-1 atom, having been deprived of some of its electron density by the greater electronegativity



$$\overset{\delta\delta+}{\underset{2}{H_3C}}\rightarrow\overset{\delta+}{\underset{1}{CH_2}}\twoheadrightarrow\overset{\delta-}{Cl}$$

of Cl, is partially compensated by drawing the C—C electrons closer to itself, resulting in a polarization of this bond and a slightly positive charge on the C-2 atom. This polarization of one bond caused by the polarization of an adjacent bond is called the *inductive effect*. The effect is greatest for adjacent bonds but may also be felt farther away; thus the polarization of the C—C bond causes a (slight) polarization of the three methyl C—H bonds. The other effect operates directly through space or through solvent molecules, and is called the *field effect*.[37] It is often very difficult to separate the two kinds of effect, but it has been done in a number of cases, generally by taking advantage of the fact that the field effect depends on the geometry of the molecule but the inductive effect depends only on the nature of the bonds. For example, in isomers **1** and **2**[38] the inductive effect of the chlorine atoms on the position of the electrons



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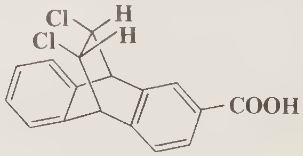

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[35] The values for toluene, nitrobenzene, and *p*-nitrotoluene are from McClellan, Ref. 32. The values for phenol and *p*-cresol were determined by Goode and Ibbitson, *J. Chem. Soc.* 4265 (1960).

[36] Actually, symmetrical tetrahedral molecules like methane do have extremely small dipole moments, caused by centrifugal distortion effects; these moments are so small that they can be ignored for all practical purposes. For CH_4 μ is about 5.4×10^{-6} D: Ozier, *Phys. Rev. Lett.* **27**, 1329 (1971); Rosenberg, Ozier, and Kudian, *J. Chem. Phys.* **57**, 568 (1972).

[37] Roberts and Moreland, *J. Am. Chem. Soc.* **75**, 2167 (1953).

[38] This example is from Grubbs, Fitzgerald, Phillips, and Petty, *Tetrahedron* **27**, 935 (1971).

TABLE 3 Field effects of various groups relative to hydrogen

The groups are listed approximately in order of decreasing strength for both $-I$ and $+I$ groups

$+I$	$-I$		
O^-	NR_3^+	COOH	OR
COO^-	SR_2^+	F	COR
CR_3	NH_3^+	Cl	SH
CHR_2	NO_2	Br	SR
CH_2R	SO_2R	I	OH
CH_3	CN	OAr	$C{\equiv}CR$
D	SO_2Ar	COOR	Ar
			$CH{=}CR_2$

in the COOH group (and hence on the acidity, see Chapter 8) should be the same since the same bonds intervene; but the field effect is different because the chlorines are closer in space to the COOH in **1** than they are in **2**. Thus a comparison of the acidity of **1** and **2** should reveal whether a field effect is truly operating. The evidence obtained from experiments of this kind is overwhelming that field effects are much more important than inductive effects.[39] In most cases the two types of effect are considered together, and in this book we shall not attempt to separate them but shall use the name *field effect* to refer to their combined action.

Functional groups can be classified as electron-withdrawing $(-I)$ or electron-donating $(+I)$ groups relative to hydrogen. This means, for example, that NO_2, a $-I$ group, will draw electrons to itself more than a hydrogen atom would if it occupied the same position in the molecule.

$$O_2N \twoheadleftarrow CH_2 \leftarrow Ph$$
$$H{-}CH_2{-}Ph$$

Thus, in α-nitrotoluene, the electrons in the N—C bond are farther away from the carbon atom than the electrons in the H—C bond of toluene. Similarly, the electrons of the C—Ph bond are farther away from the ring in α-nitrotoluene than they are in toluene. Field effects are always comparison effects. We compare the $-I$ or $+I$ effect of one group with another (usually hydrogen). It is commonly said that, compared with hydrogen, the NO_2 group is electron-withdrawing and the O^- group electron-donating or electron-releasing. However, there is no actual donation or withdrawal of electrons, though these terms are convenient to use; there is merely a difference in position of electrons due to the difference in electronegativity between H and NO_2 or between H and O^-.

Table 3 lists a number of the most common $-I$ and $+I$ groups.[40] It can be seen that compared with hydrogen, most groups are electron-withdrawing. The only electron-donating groups are groups with a formal negative charge (but not even all these), atoms of low electronegativity, such as Si, Mg, etc., and perhaps alkyl groups. Alkyl groups have usually been regarded as electron-donating, but in recent years many examples of behavior have been found which can be interpreted only by the conclusion that alkyl groups are electron-withdrawing compared with hydrogen.[41] In accord with this is the value of 2.30 for the group electronegativity of CH_3 (Table 2) compared with 2.1 for H (Table 1). We shall see that when an alkyl group is attached to an unsaturated or trivalent carbon (or other atom), its behavior is best explained by assuming it is $+I$ (see, for example, pp. 153, 161, 243, 463), but when it is connected to a saturated atom, the results are not as clear and alkyl groups seem to be $+I$ in some cases and $-I$ in others[42] (see also p. 244). Similarly, it is clear that the field-effect order of alkyl groups attached to unsaturated systems is tertiary > secondary > primary > CH_3, but this order is not always maintained when the groups are attached to saturated systems. Deuterium is electron-donating with respect to hydrogen.[43] Other things being equal, atoms with *sp* bonding generally have a greater electron-withdrawing power than those with sp^2 bonding, which in turn have more electron-withdrawing power than those with sp^3 bonding.[44] This accounts for the fact that aryl, vinyl, and ethynyl groups are $-I$. Field effects always decrease with increasing distance, and in most cases (except when a very powerful $+I$ or $-I$ group is involved) cause very little difference in a bond four bonds away or more.

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[39] For example see Dewar and Grisdale, *J. Am. Chem. Soc.* **84**, 3548 (1962); Dewar, Golden, and Harris, *J. Am. Chem. Soc.* **93**, 4187 (1971); Stock, *J. Chem. Educ.* **49**, 400 (1972); Baker, Parish, and Stock, *J. Am. Chem. Soc.* **89**, 5677 (1967); Golden and Stock, *J. Am. Chem. Soc.* **94**, 3080 (1972); Cole, Mayers, and Stock, *J. Am. Chem. Soc.* **96**, 4555 (1974); Modro and Ridd, *J. Chem. Soc. B* 528 (1968); Mossa, Ricci, and Ridd, *Chem. Commun.* 332 (1971); Ricci and Ridd, *J. Chem. Soc., Perkin Trans. 2* 1544 (1972); Danieli, Ricci, and Ridd, *J. Chem. Soc., Perkin Trans. 2* 2107 (1972); Liotta, Fisher, and Harris, *Chem. Commun.* 1312 (1971); Liotta, Fisher, Slighton, and Harris, *J. Am. Chem. Soc.* **94**, 2129 (1972); Liotta, Fisher, Greene, and Joyner, *J. Am. Chem. Soc.* **94**, 4891 (1972); Bowden and Parkin, *Can. J. Chem.* **46**, 3909 (1968); **47**, 177, 185 (1969); Wilcox and Leung, *J. Am. Chem. Soc.* **90**, 336 (1968); Butler, *J. Chem. Soc. B* 867 (1970); Adcock, Bettess, and Rizvi, *Aust. J. Chem.* **23**, 1921 (1970); Ricci, Danieli, Pirazzini, and Rossini, *Gazz. Chim. Ital.* **105**, 751 (1975).

[40] See also Ceppi, Eckhardt, and Grob, *Tetrahedron Lett.* 3627 (1973).

For discussions of field effects on acid and base strength and on reactivity, see Chapters 8 and 9, respectively.

Bond Distances[45]

The distances between atoms in a molecule are characteristic properties of the molecule and can give us information if we compare the same bond in different molecules. The chief methods of determining bond distances and angles are x-ray diffraction (only for solids), electron diffraction (only for gases), and spectroscopic methods.[46] The distance between the atoms of a bond is not constant, since the molecule is always vibrating; the measurements obtained are therefore average values, so that different methods give different results.[47] However, this must be taken into account only when fine distinctions are made.

Measurements vary in accuracy, but indications are that similar bonds have fairly constant lengths from one molecule to the next. The variation is generally less than 1%. Thus for a bond between two sp^3 carbons the following results have been found:

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[41] See Sebastian, *J. Chem. Educ.* **48,** 97 (1971).

[42] See for example, Schleyer and Woodworth, *J. Am. Chem. Soc.* **90,** 6528 (1968); Wahl and Peterson, *J. Am. Chem. Soc.* **92,** 7238 (1970).

[43] Streitwieser and Klein, *J. Am. Chem. Soc.* **85,** 2759 (1963).

[44] Bent, *Chem. Rev.* **61,** 275–311 (1961), p. 281.

[45] For reviews on this subject and on bond angles, see Ref. 44; Cottrell and Sutton, *Q. Rev., Chem. Soc.* **2,** 260–276 (1948); Costain and Stoicheff, *J. Chem. Phys.* **30,** 777 (1959); and papers in *Tetrahedron* **17,** 125–266 (1962). For tables of bond distances and angles, see Tables of Interatomic Distances and Configurations in Molecules and Ions, *Chem. Soc. Spec. Publ.* no. 11, (1958); Interatomic Distances Supplement, *Chem. Soc. Spec. Publ.* no. 18 (1965); Walsh, *Prog. Stereochem.* **1,** 1–35 (1954), pp. 10–23; Wheland, "Resonance in Organic Chemistry," pp. 165–167, John Wiley & Sons, Inc., New York, 1955; and Rogowski, *Fortschr. Chem. Forsch.* **4,** 1–50 (1963), pp. 22–31. For a review of molecular shapes and energies for many small organic molecules, radicals, and cations calculated by molecular-orbital methods, see Lathan, Curtiss, Hehre, Lisle, and Pople, *Prog. Phys. Org. Chem.* **11,** 175–261 (1974).

[46] For surveys of methods, see Walsh, Ref. 45, pp. 1–9; and Speakman, *Prog. Stereochem.* **2,** 1–38 (1958).

[47] Whiffen, *Chem. Br.* **7,** 57–61 (1971); Stals, *Rev. Pure Appl. Chem.* **20,** 1–22 (1970), pp. 2–5; Lide, *Tetrahedron* **17,** 125 (1962).

C—C bond in	Bond length, Å
Diamond	1.544[53]
C_2H_6	1.5324 ± 0.0011[48]
C_2H_5OH	1.55 ± 0.02[49]
C_2H_5Cl	1.5495 ± 0.0005[50]
C_3H_8	1.532 ± 0.003[54]
Cyclohexane	1.540 ± 0.015[49]
t-Butyl chloride	1.532[51]
n-Butane to *n*-heptane	1.531–1.534[52]
Isobutane	1.535 ± 0.001[55]

Bond distances for some important bond types are given in Table 4. As can be seen in this table, carbon bonds are shortened by increasing *s* character. This is most often explained by the fact that, as the percentage of *s* character in a hybrid orbital increases, the orbital becomes more like an *s* orbital and hence is held more tightly by the nucleus than an orbital with less *s* character. However, other explanations have also been offered (see p. 33), and the matter is not completely settled.

Indications are that a C—D bond is slightly shorter than a corresponding C—H bond. Thus, electron-diffraction measurements of C_2H_6 and C_2D_6 showed a C—H bond distance of 1.1122 ± 0.0012 Å and a C—D distance of 1.1071 ± 0.0012 Å.[48]

Bond Angles

It might be expected that the bond angles of sp^3 carbon would always be the tetrahedral angle 109°28′, but this is so only where the four groups are identical, as in methane, neopentane, or carbon tetrachloride. In most cases the angles deviate a little from the pure tetrahedral value. For

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[48] Bartell and Higginbotham, *J. Chem. Phys.* **42,** 851 (1965).

[49] Tables of Interatomic Distances, Ref. 45.

[50] Wagner and Dailey, *J. Chem. Phys.* **26,** 1588 (1957).

[51] Momany, Bonham, and Druelinger, *J. Am. Chem. Soc.* **85,** 3075 (1963); also see Lide and Jen, *J. Chem. Phys.* **38,** 1504 (1963).

[52] Bonham, Bartell, and Kohl, *J. Am. Chem. Soc.* **81,** 4765 (1959).

[53] Lonsdale, *Phil. Trans. R. Soc. London* **A240,** 219 (1947).

[54] Iijima, *Bull. Chem. Soc. Jpn.* **45,** 1291 (1972).

[55] Hilderbrandt and Wieser, *J. Mol. Struct.* **15,** 27 (1973).

[56] Somayajulu, *J. Chem. Phys.* **31,** 919 (1959). For a discussion of how sp^2-sp^2 distances vary with the structure of the molecule, see Kuchitsu, Fukuyama, and Morino, *J. Mol. Struct.* **1,** 463 (1968).

[57] Costain and Stoicheff, *J. Chem. Phys.* **30,** 777 (1959).

[58] Bartell, Roth, Hollowell, Kuchitsu, and Young, *J. Chem. Phys.* **42,** 2683 (1965).

[59] Blukis, Kasai, and Myers, *J. Chem. Phys.* **38,** 2753 (1963).

[60] Kwei and Curl, *J. Chem. Phys.* **32,** 1592 (1960).

[61] Higginbotham and Bartell, *J. Chem. Phys.* **42,** 1131 (1965).

[62] Levine, *J. Chem. Phys.* **38,** 2326 (1963).

[63] Abrahams, *Q. Rev., Chem. Soc.* **10,** 407–436 (1956).

[64] Tanimoto, Kuchitsu, and Morino, *Bull. Chem. Soc. Jpn.* **42,** 2519 (1969); Sugié, Fukuyama, and Kuchitsu, *J. Mol. Struct.* **14,** 333 (1972).

[65] Karakida, Fukuyama, and Kuchitsu, *Bull. Chem. Soc. Jpn.* **47,** 299 (1974).

[66] For reviews of C—halogen bonds, see Trotter, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 1, pp. 49–62, John Wiley & Sons, Inc., New York, 1973; and Mikhailov, *Russ. Chem. Rev.* **40,** 983–997 (1971).

[67] Lide, Ref. 47.

[68] Rajput and Chandra, *Bull. Chem. Soc. Jpn.* **39,** 1854 (1966).

TABLE 4 Bond distances

The values given are average lengths and do not necessarily apply exactly to the compounds mentioned

Bond type	Length, Å	Typical compounds
C—C[56]		
sp^3—sp^3	1.54	
sp^3—sp^2	1.50	Acetaldehyde, toluene, propene
sp^3—sp	1.46	Acetonitrile, propyne
sp^2—sp^2	1.48	Butadiene, glyoxal, biphenyl
sp^2—sp	1.43	Acrylonitrile, vinylacetylene
sp—sp	1.38	Cyanoacetylene, butadiyne
C=C[57]		
sp^2—sp^2	1.34	Ethylene
sp^2—sp	1.31	Ketene, allenes
sp—sp	1.28	Butatriene, carbon suboxide
C≡C[64]		
sp—sp	1.21	Acetylene
C—H[58]		
sp^3—**H**	1.11	Methane
sp^2—**H**	1.10	Benzene, ethylene
sp—**H**	1.08	**HCN**, acetylene
C—O		
sp^3—**O**	1.41[59]	Dimethyl ether, ethanol
sp^2—**O**	1.34[60]	Formic acid
C=O		
sp^2—**O**	1.20[60]	Formaldehyde, formic acid
sp—**O**	1.16[49]	CO_2
C—N		
sp^3—**N**	1.47[61]	Methylamine
sp^2—**N**	1.36[67]	Formamide
C=N[62]		
sp^2—**N**	1.28	Oximes, imines
C≡N[65]		
sp—**N**	1.16	**HCN**
C—S[63]		
sp^3—**S**	1.81	Methyl mercaptan
sp^2—**S**	1.75	Diphenyl sulfide
C=S[63]		
sp—**S**	1.56	CS_2

C—halogen[66]	**F**[67]	**Cl**[68]	**Br**[68]	**I**[68]
sp^3—halogen	1.38	1.78	1.94	2.14
sp^2—halogen	1.35	1.73	1.85	2.03
sp—halogen	1.27	1.63	1.79	1.99

TABLE 5 Oxygen, sulfur, and nitrogen bond angles in some compounds

Angle	Value	Compound	Ref.
H—O—H	104°27′	Water	7
C—O—H	107–109°	Methanol	49
C—O—C	111°43′	Dimethyl ether	59
C—O—C	124 ± 5°	Diphenyl ether	63
H—S—H	92.1°	H_2S	63
C—S—H	99.4°	Methyl mercaptan	63
C—S—C	109°	*p*-Tolyl sulfide	63
H—N—H	106°46′	Ammonia	7
H—N—H	106°	Methylamine	72
C—N—H	112°	Methylamine	72
C—N—C	108.7°	Trimethylamine	73

example, the C—C—Br angle in 2-bromopropane is 114.2°.[69] Similarly, slight variations are generally found from the ideal values of 120 and 180° for sp^2 and *sp* carbon, respectively.[9] These deviations occur because of slightly different hybridizations; i.e., a carbon bonded to four other atoms hybridizes one *s* and three *p* orbitals, but the four hybrid orbitals thus formed are generally not equivalent, nor does each contain exactly 25% *s* and 75% *p* character. Because the four atoms have (in the most general case) different electronegativities, each makes its own demand for electrons from the carbon atom. The carbon atom supplies more *p* character when it is bonded to more electronegative atoms, so that in chloromethane, for example, the bond to chlorine has somewhat more than 75% *p* character, which of course requires that the other three bonds have somewhat less, since there are only three *p* orbitals (and one *s*) to be divided among the four hybrid orbitals.[69a] The nmr coupling constant between ^{13}C and a hydrogen directly attached to it has been reported to be a linear function of the amount of *s* character of the orbitals of that carbon atom.[70] However, this relationship is not completely general, because other factors, e.g., the geometry of the molecule and electronegativity effects, also affect the coupling constants.[71] Of course, in strained molecules, the bond angles may be greatly distorted from the ideal values (see p. 140).

For oxygen and nitrogen, angles of 90° would be predicted from p^2 bonding. However, as we have seen (p. 10), the angles of water and ammonia are much larger than this, as are the angles of other oxygen and nitrogen compounds (Table 5); in fact they are much closer to the tetrahedral angle of 109°28′ than to 90°. These facts have led to the suggestion that in these compounds oxygen and nitrogen use sp^3 bonding; i.e., instead of forming bonds by the overlap of two (or three) *p* orbitals with 1*s* orbitals of the hydrogen atoms, they hybridize their 2*s* and 2*p* orbitals to form four sp^3 orbitals and then use only two (or three) of these for bonding with hydrogen, the others remaining occupied by unshared pairs (also called *lone pairs*). If this description is valid, and it is generally accepted by most chemists today, it becomes necessary to explain why the angles of these two compounds are in fact not 109°28′ but a few degrees smaller. One explanation which has been offered is that the unshared pair actually has a greater steric requirement than a pair in a bond, since there is no second nucleus to draw away some of the electron density and the bonds are thus crowded together. However, most evidence is that unshared pairs have smaller steric requirements than bonds[74] and the explanation most commonly accepted is that the hybridization is not pure sp^3. As we have seen above, an atom supplies more *p* character when it is bonded to more electronegative atoms. An unshared pair may be considered to be an "atom" of the lowest possible electronegativity, since there is no attracting power at all. Consequently, the unshared pairs have more *s* and the bonds more *p* character than pure sp^3 orbitals would have, making the bonds somewhat more like p^2 bonds and reducing the angle. As seen in Table 5, oxygen, nitrogen, and sulfur angles generally increase with decreasing electronegativity of the substituents. Note that the explanation given above cannot explain why some of these angles are *greater* than the tetrahedral angle.[75]

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[69] Schwendeman and Tobiason, *J. Chem. Phys.* **43,** 201 (1965).

[69a] This assumption has been challenged: see Pomerantz and Liebman, *Tetrahedron Lett.* 2385 (1975).

[70] See, for example, Muller and Pritchard, *J. Chem. Phys.* **31,** 768, 1471 (1959); Juan and Gutowsky, *J. Chem. Phys.* **37,** 2198 (1962); Foote, *Tetrahedron Lett.* 579 (1963); Olah and Comisarow, *J. Am. Chem. Soc.* **88,** 1818 (1966), and Douglas *J. Chem. Phys.* **45,** 3465 (1966).

[71] Muller and Rose, *J. Am. Chem. Soc.* **84,** 3975 (1962); Karabatsos and Orzech, *J. Am. Chem. Soc.* **87,** 560 (1965); Brown and Puckett, *J. Chem. Phys.* **44,** 2238 (1966); Considine, *J. Chem. Phys.* **42,** 1130 (1965); Huheey, *J. Chem. Phys.* **45,** 405 (1966); Grant and Litchman, *J. Am. Chem. Soc.* **87,** 3994 (1965); Yue, *Can. J. Chem.* **46,** 2675 (1968).

[72] Lide, *J. Chem. Phys.* **27,** 343 (1957).

[73] Lide and Mann, *J. Chem. Phys.* **28,** 572 (1958).

Bond Energies[76]

There are two kinds of bond energy. The energy necessary to cleave a bond to give the constituent radicals is called the *dissociation energy D*. For example, *D* for $H_2O \rightarrow HO + H$ is 118 kcal/mol. However, this is not taken as the energy of the O—H bond in water, since *D* for $H—O \rightarrow H + O$ is 100 kcal/mol. The average of these two values, 109 kcal/mol, is taken as the *bond energy E*. In diatomic molecules, of course, $D = E$.

D values may be easy or difficult to measure, but there is no question what they mean. With *E* values the matter is not so simple. For methane, the total energy of conversion from CH_4 to $C + 4H$ (at 0 K) is 393 kcal/mol.[77] Consequently, *E* for the C—H bond in methane is 98 kcal/mol at 0 K. The more usual practice, though, is not to measure the heat of atomization (i.e., the energy necessary to convert a compound to its atoms) directly but to calculate it from the heat of combustion. Such a calculation is shown in Figure 15.

Heats of combustion are very accurately known for hydrocarbons.[78] For methane the value is 212.8 kcal/mol (at 25°C), which leads to a heat of atomization of 398.0 kcal/mol (at 25°C), or a

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[74] See for example, Pumphrey and Robinson, *Chem. Ind.* (*London*) 1903 (1963); Allinger, Carpenter, and Karkowski, *Tetrahedron Lett.* 3345 (1964); Eliel and Knoeber, *J. Am. Chem. Soc.* **88**, 5347 (1966), **90**, 3444 (1968); Masamune, Takasugi, and Matsuki, *Bull. Chem. Soc. Jpn.* **41**, 2466 (1968); Buckley, Costain, and Parkin, *Chem. Commun.* 668 (1968); Jones, Katritzky, Richards, Wyatt, Bishop, and Sutton, *J. Chem. Soc. B* 127 (1970); Blackburne, Katritzky, and Takeuchi, *J. Am. Chem. Soc.* **96**, 682 (1974), *Acc. Chem. Res.* **8**, 300–306 (1975); Lambert, Bailey, and Michel, *J. Am. Chem. Soc.* **94**, 3812 (1972). For a discussion, see Riddell, *Q. Rev., Chem. Soc.* **21**, 364–378 (1967); pp. 366–372.

[75] For a discussion, see Bent, in Kharasch and Meyers, "The Chemistry of Organic Sulfur Compounds," vol. 2, pp. 1–34, Pergamon Press, New York, 1966.

[76] For reviews including methods of determination, see Kerr, *Chem. Rev.* **66**, 465–500 (1966); Szwarc, *Chem. Rev.* **47**, 75 173 (1950), *Q. Rev., Chem. Soc.* **5**, 22–43 (1951); Knox and Palmer, *Chem. Rev.* **61**, 247–255 (1961); Benson, *J. Chem. Educ.* **42**, 502–518 (1965); Cottrell, "The Strengths of Chemical Bonds," 2d ed., Academic Press Inc., New York, 1958; and Wiberg, in Nachod and Zuckerman, "Determination of Organic Structures by Physical Methods," vol. 3, pp. 207–245, Academic Press, Inc., New York, 1971.

[77] For the four steps, *D* values are 101 to 102, 88, 124, and 80 kcal/mol, respectively, though the middle values are much less reliable than the other two. Knox and Palmer, *Chem. Rev.* **61**, 247–255 (1961); Brewer and Kester, *J. Chem. Phys.* **40**, 812 (1964); Linevsky, *J. Chem. Phys.* **47**, 3485 (1967).

[78] For values of heats of combustion of large numbers of organic compounds, hydrocarbons and others, see Cox and Pilcher, "Thermochemistry of Organic and Organometallic Compounds," Academic Press, Inc., New York, 1970, and Domalski, *J. Phys. Chem. Ref. Data* **1**, 221-277 (1972). For large numbers of heats-of-formation values (from which heats of combustion are easily calculated) see Stull, Westrum, and Sinke, "The Chemical Thermodynamics of Organic Compounds," John Wiley & Sons, Inc., New York, 1969.

$$\begin{array}{lllr}
C_2H_{6\,(gas)} + 3\tfrac{1}{2}O_{2\,(gas)} & = 2CO_{2(gas)} & + 3H_2O_{(liq.)} & +372.9\ \text{kcal} \\
2CO_{2(gas)} & = 2C_{(graphite)} & + 2O_{2\,(gas)} & -188.2\ \text{kcal} \\
3H_2O_{(liq.)} & = 3H_{2\,(gas)} & + 1\tfrac{1}{2}O_{2(gas)} & -204.9\ \text{kcal} \\
3H_{2\,(gas)} & = 6H_{(gas)} & & -312.5\ \text{kcal} \\
2C_{(graphite)} & = 2C_{(gas)} & & -343.4\ \text{kcal} \\
\hline
C_2H_{6\,(gas)} & = 6H_{(gas)} & + 2C_{(gas)} & -676.1\ \text{kcal}
\end{array}$$

Figure 15 Calculation of the heat of atomization of ethane at 25°C.

value of E for the C—H bond of 99.5 kcal/mol at 25°C. This method is fine for molecules like methane in which all the bonds are equivalent, but for more complicated molecules assumptions must be made. Thus for ethane, the heat of atomization of 25°C is 676.1 kcal/mol (Figure 15), and we must decide how much of this energy is due to the C—C bond and how much to the six C—H bonds. Any assumption must be artificial, since there is no way of actually obtaining this information, and indeed the question has no real meaning. If we make the assumption that E for each of the C—H bonds is the same as E for the C—H bond in methane (99.5 kcal/mol), then $6 \times 99.5 = 597.0$, leaving 79.1 kcal/mol for the C—C bond. However, a similar calculation for propane gives a value of 80.3 for the C—C bond, and for isobutane, the value is 81.6. A consideration of heats of atomization of isomers also illustrates the difficulty. E values for the C—C bonds in pentane, isopentane, and neopentane, calculated from heats of atomization in the same way, are (at 25°C) 81.1, 81.8, and 82.4 kcal/mol, respectively, even though all of them have twelve C—H bonds and four C—C bonds.

These differences have been attributed to various factors caused by the introduction of new structural features. Thus isopentane has a tertiary carbon whose C—H bond does not have exactly the same amount of *s* character as the C—H bond in pentane, which for that matter contains secondary carbons not possessed by methane. It is known that D values, which *can* be measured, are not the same for primary, secondary, and tertiary C—H bonds (see Table 2 in Chapter 5). There is also the steric factor. Hence it is certainly not correct to use the value of 99.5 from methane as the E value for all C—H bonds. Several empirical equations have been devised which account for these factors; from these the total energy can be computed[79] if the proper set of parameters (one for each structural feature) is inserted. Of course these parameters are originally calculated from the known total energies of some molecules which contain the structural feature.

Table 6 gives E values for various bonds. The mean values given are those averaged over a large series of compounds. The other values are calculated for just one compound, using values for the other bonds from earlier values in the table. The literature contains charts which take account of hybridization (thus an sp^3 C—H bond does not have the same energy as an sp^2 C—H bond).[80]

Certain generalizations can be derived from the data in Table 6.

1. There is a correlation of bond strengths with bond distances. A comparison of Tables 4 and 6 shows that, in general, *shorter bonds are stronger bonds.* Since we have already seen that increasing *s* character shortens bonds (p. 23), it follows that bond strengths increase with increasing *s* character.

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[79] For reviews, see Cox and Pilcher, Ref. 78, pp. 531–597; and Skinner and Pilcher, *Q. Rev., Chem. Soc.* **17**, 264–288 (1963).

[80] Ref. 79; Cox, *Tetrahedron* **18**, 1337 (1962).

TABLE 6 Bond-energy *E* values for some important bond types

E values are arranged within each group in order of decreasing strength. The mean values are averaged over a large series of compounds. The calculated values are computed for just one compound using values for other bonds from earlier values in the table

Bond	Mean value[81] of *E* at 25°C, kcal/mol	Value calculated from	
O—H	110–111	110.6	H_2O
C—H	96–99	99.5	CH_4
N—H	93	93.4	NH_3
S—H	82	83	H_2S
C—F	. . .	116	CF_4
C—H	96–99	99.5	CH_4
C—O	85–91	76.8 84.2	CH_3OH C_2H_5OH
C—C	83–85	79.1	C_2H_6
C—Cl	79	78.3	CCl_4
C—N	69–75[82]	66.5	CH_3NH_2
C—Br	66	69 65	CBr_4 $CHBr_3$
C—S	66	64	C_2H_5SH
C—I	52	50.1	CH_3I
C≡C	199–200	194.4	C_2H_2
C=C	146–151	141.3	C_2H_4
C—C	83–85	79.1	C_2H_6
C≡N	204	206.1	HCN
C=O	173–81	164 192	HCHO CO_2
C=N	143[82]		
C=S	. . .	132	CS_2

2. Bonds become weaker as we move down the periodic table. Compare C—O and C—S or the four carbon-halogen bonds. This is a consequence of the first generalization, since bond distances must increase as we go down the periodic table because the number of inner electrons increases.

3. Double bonds are both shorter and stronger than the corresponding single bonds, but not twice as strong, because π overlap is less than σ overlap. The difference in energy between a single bond, say C—C, and the corresponding double bond is the amount of energy necessary to cause rotation around the double bond.

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[81] These values, except where noted, are from Lovering and Laidler, *Can. J. Chem.* **38,** 2367 (1960); and Levi and Balandin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 149 (1960).

[82] Bedford, Edmondson, and Mortimer, *J. Chem. Soc.* 2927 (1962).

Two

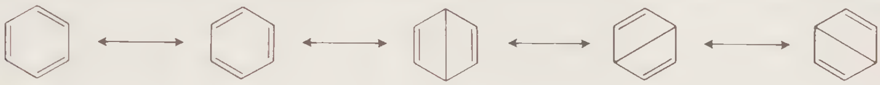
Delocalized Chemical Bonding

Although the bonding of many compounds can be adequately described by a single Lewis structure (page 16), this is not sufficient for many other compounds. These compounds contain one or more bonding orbitals which are not restricted to two atoms, but which are spread out over three or more. Such bonding is said to be *delocalized*.[1] In this chapter we shall see which types of compounds must be represented in this way.

The two chief general methods of approximately solving the wave equation, discussed in Chapter 1, are also used for compounds containing delocalized bonds.[2] In the valence-bond method several possible Lewis structures, called *canonical forms*, are drawn, and the molecule is taken to be a weighted average of them. Each ψ in Eq. (14), Chapter 1,

$$\Psi = c_A \psi_A + c_B \psi_B + \cdots$$

represents one of these structures. This representation of a real structure as a weighted average of two or more canonical forms is called *resonance*. For benzene the canonical forms are **1** and **2**.



1 **2** **3** **4** **5**

Double-headed arrows are used to indicate resonance. When the wave equation is solved, it is found that the energy value obtained by considering that **1** and **2** participate equally is lower than that for **1** or **2** alone, and if **3**, **4**, and **5** (called *Dewar structures*) are also considered, the value is lower still. According to this method, **1** and **2** each contribute 39% to the actual molecule, and the others 7.3% each.[3] The carbon-carbon bond order is 1.463 (not 1.5, which would be the case if only **1** and **2** contributed). In the valence-bond method the *bond order* of a particular bond is the sum of the weights of those canonical forms in which the bond is double plus 1 for the single bond which is present in all of them.[4] Thus, according to this picture, each C—C bond is not halfway between a single and a double bond but somewhat less. The energy of the actual molecule is obviously less than that of any one Lewis structure, since otherwise it would have one of those structures. The difference in energy between the actual molecule and the Lewis structure of lowest energy[5] is called the *resonance energy*.

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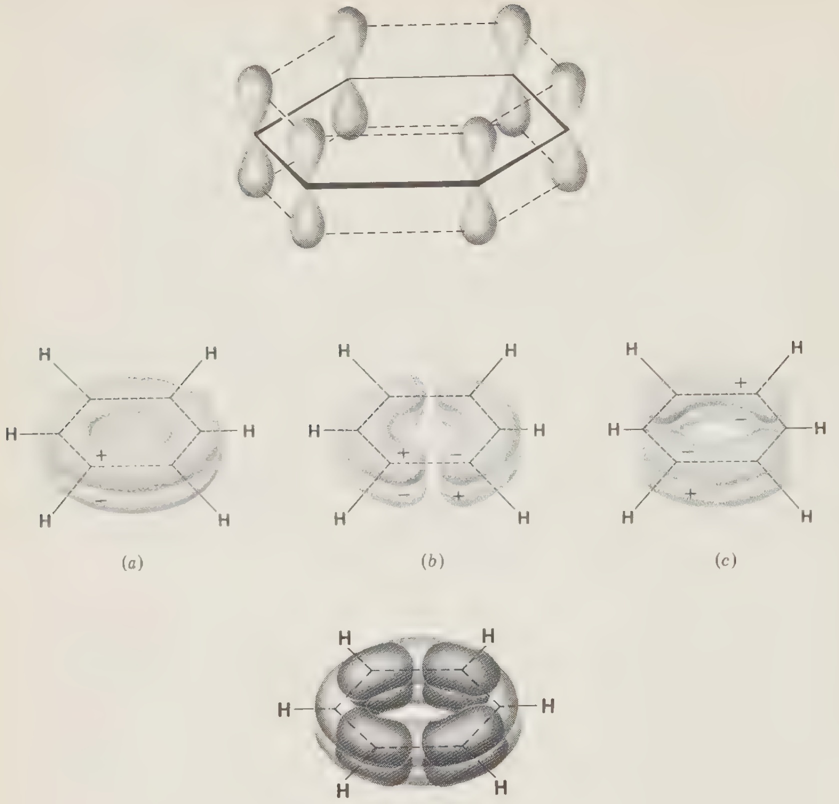
[1] For a definitive treatment of delocalization, see Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, Inc., New York, 1955.

[2] There are other methods. For a discussion of the free-electron method, see Streitwieser, "Molecular Orbital Theory for Organic Chemists," pp. 27–29, John Wiley & Sons, Inc., New York, 1961. For the nonpairing method, in which benzene is represented as having three electrons between adjacent carbons, see Hirst and Linnett, *J. Chem. Soc.* 1035 (1962); and Firestone, *J. Org. Chem.* **34**, 2621 (1969).

[3] Pullman and Pullman, *Prog. Org. Chem.* **4**, 31–71 (1958), p. 33.

[4] For a more precise method of calculating valence-bond bond orders, see Clarkson, Coulson, and Goodwin, *Tetrahedron* **19**, 2153 (1963). See also Herndon, *J. Am. Chem. Soc.* **96**, 7605 (1974).

[5] Of course, the Lewis structures are not real, and their energies can only be estimated.



(a) (b) (c)

Superposition of (a), (b), and (c).

(d)

Figure 1 The six *p* orbitals of benzene overlap to form three bonding orbitals, (*a*), (*b*), and (*c*). The three orbitals superimposed are shown in (*d*).

Qualitatively, the resonance picture is often used to describe the structure of molecules, but quantitative valence-bond calculations become much more difficult as the structures become more complicated (e.g., naphthalene, pyridine, etc.). Therefore the molecular-orbital method is much more often used for the solution of wave equations. If we look at benzene by this method (qualitatively), we see that each carbon atom, being connected to three other atoms, uses sp^2 orbitals to form σ bonds, so that all 12 atoms are in one plane. Each carbon has a *p* orbital (containing one electron) remaining, and each of these can overlap equally with the two adjacent *p* orbitals. This overlap of six orbitals (see Figure 1) produces six new orbitals, of which three (shown) are bonding. These three (called π orbitals) all occupy approximately the same space. One of the three is of lower energy than the other two, which are degenerate. They each have the plane of the ring as a node, and so are in two parts, one above and one below the plane. The two orbitals of higher energy (Figure 1*b* and *c*) also have another node. The six electrons which occupy this torus-shaped cloud are called the *aromatic sextet*. The carbon-carbon bond order for benzene, calculated by the molecular-orbital method, is 1.667.[6]

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[6] The molecular-orbital method of calculating bond order is more complicated than the valence-bond method. See Ref. 3, p. 36, and Clarkson, Coulson, and Goodwin, Ref. 4.

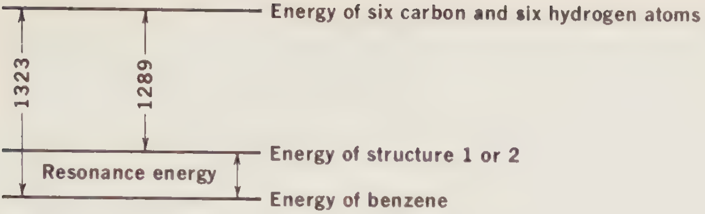

Energy of six carbon and six hydrogen atoms
1323
1289
Energy of structure 1 or 2
Resonance energy
Energy of benzene

Figure 2 Resonance energy in benzene (in kilocalories per mole).

For planar unsaturated and aromatic molecules, many molecular-orbital calculations have been made by treating the σ and π electrons separately. It is assumed that the σ orbitals can be treated as localized bonds and the calculations involve only the π electrons. The first such calculations were made by Hückel, and such calculations are often called *Hückel molecular-orbital* (HMO) *calculations.*[7] Because electron-electron repulsions are either neglected or averaged out in the HMO method, another approach, the *self-consistent field* (SCF), or *Hartree-Fock*, method, was devised.[8] Although these methods have given many useful results for planar unsaturated and aromatic molecules, they are often unsuccessful for other molecules, and it would obviously be better if all electrons, both σ and π, could be included in the calculations. The development of modern computers has now made this possible,[9] and many such calculations have now been made[10] using a number of methods, among them an extension of the Hückel method (EHMO)[11] and the application of the SCF method to all valence electrons.[12]

Although the valence-bond and molecular-orbital methods give slightly different results, both show that there is delocalization in benzene. For example, each predicts that the six carbon-carbon bonds should have equal lengths, which is true. Since each method is useful for certain purposes, we shall use one or the other, as appropriate.

Bond Distances and Energies in Compounds Containing Delocalized Bonds

If we add the energies of all the bonds in benzene, taking the values from a table like Table 6 in Chapter 1, the value for the heat of atomization turns out to be less than that actually found in benzene (Figure 2). The actual value is 1323 kcal/mol. If we use E values for a C=C double bond obtained from cyclohexene (148.8), for a C—C single bond from cyclohexane (81.8), and for C—H bonds from methane (99.5), we get a total of 1289 kcal/mol for structure **1** or **2**. The resonance energy by this calculation is therefore 34 kcal/mol. Of course, this is an arbitrary calculation since, in addition to the fact that we are calculating a heat of atomization for a nonexistent structure (**1**), we are forced to use E values, which themselves do not have a firm basis in reality. The resonance energy can never be measured, only estimated, since we can

[7] Streitwieser, Ref. 2; Liberles, "Introduction to Molecular-Orbital Theory," Holt, Rinehart, and Winston, Inc., New York, 1966.

[8] Roothaan, *Rev. Mod. Phys.* **23,** 69 (1951); Pariser and Parr, *J. Chem. Phys.* **21,** 466, 767 (1952); Pople, *Trans. Faraday Soc.* **49,** 1375 (1953), *J. Phys. Chem.* **61,** 6 (1975); Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill Book Company, New York, 1969; Dewar, in "Aromaticity," *Chem. Soc. Spec. Pub.* no. 21, pp. 177–215, 1967.

[9] For a discussion of the progress made in quantum chemistry calculations, see Hall, *Chem. Soc. Rev.* **2,** 21–28 (1973).

[10] For a review of molecular-orbital calculations on *saturated* organic compounds, see Herndon, *Prog. Phys. Org. Chem.* **9,** 99–177 (1972).

[11] Hoffmann, *J. Chem. Phys.* **39,** 1397 (1963).

[12] Dewar, "The Molecular Orbital Theory of Chemistry," Ref. 8; Jaffé, *Acc. Chem. Res.* **2,** 136–143 (1969); Kutzelnigg, Del Re, and Berthier, *Fortschr. Chem. Forsch.* **22,** 1–222 (1971).

measure the heat of atomization of the real molecule but can only make an intelligent guess at that of the Lewis structure of lowest energy. Another method frequently used for estimation of resonance energy involves measurements of heats of hydrogenation. Thus, the heat of hydrogenation of cyclohexene is 28.6 kcal/mol, so that we might expect a hypothetical **1** or **2** with three double bonds to have a heat of hydrogenation of about 85.8 kcal/mol. The real benzene has a heat of hydrogenation of 49.8 kcal/mol, giving a resonance energy by this calculation of 36 kcal/mol. The generally accepted value for the resonance energy of benzene is 36 kcal/mol, and by any calculation the real molecule is more stable than a hypothetical **1** or **2.**

The energies of the six benzene orbitals can be calculated from HMO theory in terms of two quantities, α and β. The quantity α is the amount of energy possessed by an isolated $2p$ orbital before overlap, while β (called the *resonance integral*) is an energy unit expressing the degree of stabilization resulting from π-orbital overlap. A negative value of β corresponds to stabilization, and the energies of the six orbitals are (lowest to highest): $\alpha + 2\beta$, $\alpha + \beta$, $\alpha + \beta$, $\alpha - \beta$, $\alpha - \beta$, and $\alpha - 2\beta$.[13] The total energy of the three occupied orbitals is $6\alpha + 8\beta$, since there are two electrons in each orbital. The energy of an ordinary double bond is $\alpha + \beta$, so that structure **1** or **2** would have an energy of $6\alpha + 6\beta$. The resonance energy of benzene is therefore 2β. Unfortunately, there is no convenient way to calculate the value of β from molecular-orbital theory, and it is often given (for benzene) as about 18 kcal/mol, this number being half of the resonance energy calculated from heats of combustion or hydrogenation.

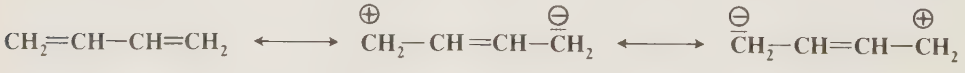
We might expect that bond distances in compounds exhibiting delocalization would lie between the values given in Table 4 in Chapter 1. For benzene this is certainly the case, since the carbon-carbon bond distance is 1.40 Å,[13a] which is between the 1.48 Å for an sp^2-sp^2 C—C single bond and the 1.34 Å of the sp^2-sp^2 C═C double bond.

Kinds of Molecules Which Have Delocalized Bonds

There are three main types of structure that exhibit delocalization:

1. *Double (or triple) bonds in conjugation.*[14] Benzene is, of course, an example, but the simplest is butadiene. In the molecular-orbital picture (Figure 3) the overlap of four orbitals gives two bonding orbitals, which contain the four electrons, and two vacant antibonding orbitals. It can be seen that each orbital has one more node than the one of next lower energy. The energies of the four orbitals are (lowest to highest): $\alpha + 1.618\beta$, $\alpha + 0.618\beta$, $\alpha - 0.618\beta$, and $\alpha - 1.618\beta$; hence the total energy of the two occupied orbitals is $4\alpha + 4.472\beta$. Since the energy of two isolated double bonds is $4\alpha + 4\beta$, the resonance energy by this calculation is 0.472β.

In the resonance picture, these structures are considered to contribute:



$$\mathrm{CH_2{=}CH{-}CH{=}CH_2} \longleftrightarrow \overset{\oplus}{\mathrm{C}}\mathrm{H_2{-}CH{=}CH{-}}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{H_2} \longleftrightarrow \overset{\ominus}{\bar{\mathrm{C}}}\mathrm{H_2{-}CH{=}CH{-}}\overset{\oplus}{\mathrm{C}}\mathrm{H_2}$$

6 7 8

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[13] For the method of calculating these results and similar results given in this chapter, see Higasi, Baba, and Rembaum, "Quantum Organic Chemistry," Interscience Publishers, Inc., New York, 1965; and Streitwieser, Ref. 2. For values of calculated orbital energies and bond orders for many conjugated molecules, see Coulson and Streitwieser, "Dictionary of π Electron Calculations," W. H. Freeman and Company, San Francisco, 1965.

[13a] Bastiansen, Fernholt, Seip, Kambara, and Kuchitsu, *J. Mol. Struct.* **18,** 163 (1973); Tamagawa, Iijima, and Kimura, *J. Mol. Struct.* **30,** 243 (1976).

[14] For reviews of conjugation in open-chain hydrocarbons, see Simmons, *Prog. Phys. Org. Chem.* **7,** 1–50 (1970); and Popov and Kogan, *Russ. Chem. Rev.* **37,** 119–141 (1968).

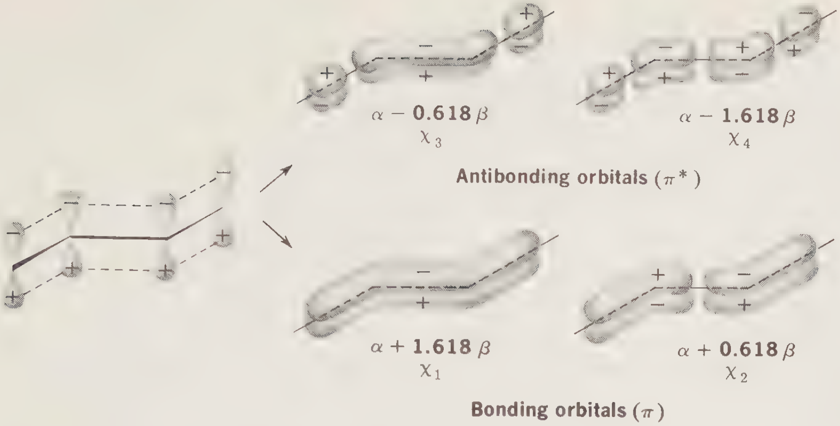

Figure 3 The four π orbitals of butadiene, formed by overlap of four *p* orbitals.

By either picture the bond order of the central bond should be higher than 1 and that of the other carbon-carbon bonds less than 2, although neither predicts that the three bonds have equal electron density. Molecular-orbital bond orders of 1.894 and 1.447 have been calculated.[15]

In recent years doubt has been cast on the reality of delocalization in butadiene and similar molecules. Thus, the bond lengths in butadiene are 1.34 Å for the double bonds and 1.48 Å for the single bond.[16] Since the typical single-bond distance of a bond which is not adjacent to an unsaturated group is 1.54 Å (p. 23), it has been argued that the shorter single bond in butadiene provides evidence for resonance. However, this shortening can also be explained as being caused by hybridization changes (see p. 23), and other explanations have also been offered.[17] Also, resonance energies for butadienes, calculated from heats of combustion or hydrogenation, are only about 4 kcal/mol, and these values may not be entirely attributable to resonance. Thus, a calculation from heats-of-atomization data gives a resonance energy of 4.6 kcal/mol for *cis*-1,3-pentadiene, and −0.2 kcal/mol for 1,4-pentadiene. These two compounds, each of which possesses two double bonds, two C—C single bonds, and eight C—H bonds, would seem to offer as similar comparison as we could make of a conjugated with a nonconjugated compound, but they are nevertheless not strictly comparable. The former has three sp^3 C—H and five sp^2 C—H bonds, while the latter has two and six, respectively. Also, the two single C—C bonds of the 1,4-diene are both sp^2-sp^3 bonds, while in the 1,3-diene, one is sp^2-sp^3, and the other is sp^2-sp^2. Therefore, it may be that some of the already small value of 4 kcal/mol is not resonance energy but arises from differing energies of bonds of different hybridization.[18]

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[15] Coulson, *Proc. R. Soc. London, Ser. A* **169,** 413 (1939).

[16] Marais, Sheppard, and Stoicheff, *Tetrahedron* **17,** 163 (1962).

[17] Bartell, *J. Am. Chem. Soc.* **81,** 3497 (1959), *J. Chem. Phys.* **32,** 827 (1960), *Tetrahedron* **17,** 177 (1962), *J. Chem. Educ.* **45,** 754–767 (1968); Wilson, *Tetrahedron* **17,** 191 (1962); Hughes, *Tetrahedron* **24,** 6423 (1968); Politzer and Harris, *Tetrahedron* **27,** 1567 (1971).

[18] For negative views on delocalization in butadiene and similar molecules, see Dewar and Gleicher, *J. Am. Chem. Soc.* **87,** 692 (1965); Dewar and Schmeising, *Tetrahedron* **5,** 166 (1959), **11,** 96 (1960); Dewar, *Tetrahedron* **19,** suppl. 2, 89 (1963); Brown, *Trans. Faraday Soc.* **55,** 694 (1959); Somayajulu, *J. Chem. Phys.* **31,** 919 (1959); Mikhailov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1284 (1960), *J. Gen. Chem. USSR* **36,** 379 (1966). For positive views, see Miyazaki, Shigetani, and Shinoda, *Bull. Chem. Soc. Jpn.* **44,** 1491 (1971); Miyazaki and Ohbayashi, *Bull. Chem. Soc. Jpn.* **42,** 2767 (1969); Miyazaki, *Tetrahedron Lett.* 1363 (1970); Berry, *J. Chem. Phys.* **30,** 936 (1962); and Kogan and Popov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1306 (1964). In general, the negative argument is that resonance involving excited structures, such as **7** and **8,** is unimportant. See rule 6 on p. 37. An excellent discussion of the controversy is found in Popov and Kogan, Ref. 14, pp. 119–124.

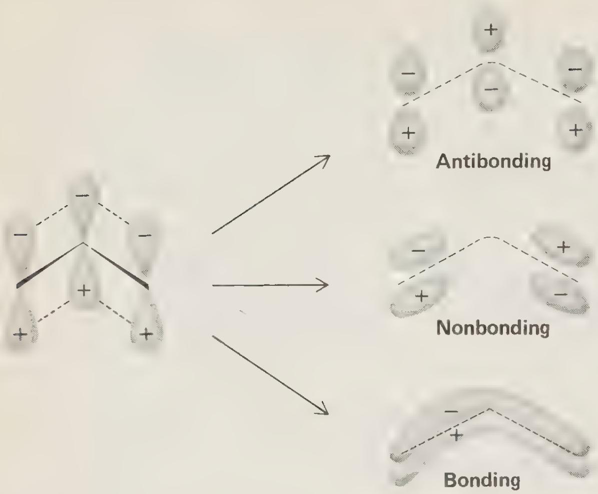

Figure 4 The three orbitals of an allylic system, formed by overlap of three *p* orbitals.

Although bond distances fail to show it and although the resonance energy is low, the fact that butadiene is planar[19] shows that there is some delocalization, even if not so much as previously thought.

Similar delocalization is found in other conjugated systems, e.g., C=C—C=O and C≡C—C=N, in longer systems, with three or more multiple bonds in conjunction, and where double or triple bonds are conjugated with aromatic rings.

2. *Double (or triple) bonds in conjugation with a p orbital on an adjacent atom.* Where a *p* orbital is on an atom adjacent to a double bond, there are three parallel *p* orbitals which overlap. As we have previously noted, it is a general rule that when *n* atomic orbitals overlap, *n* molecular orbitals are created, so that in this case overlap of a *p* orbital with an adjacent double bond gives rise to three new orbitals, shown in Figure 4. The middle orbital is a *nonbonding orbital* of zero bonding energy. The central carbon atom does not participate in the nonbonding orbital.

There are three cases: the original *p* orbital may have contained two, one, or no electrons. Since the original double bond contributes two electrons, the total number of electrons to be accommodated by the new orbitals is four, three, or two. A typical example of the first situation is vinyl chloride $\mathrm{CH_2{=}CH{-}Cl}$. In this case, although the *p* orbital of the chlorine atom is filled, it still overlaps with the double bond. The four electrons occupy the two molecular orbitals of lowest energies. This is our first example of resonance involving overlap between unfilled orbitals and a *filled* orbital. Canonical forms for vinyl chloride are

$$\mathrm{CH_2{=}CH{-}\overline{\underline{Cl}}|} \longleftrightarrow \mathrm{\overset{\ominus}{\overline{C}}H_2{-}CH{=}\overset{\oplus}{\underline{Cl}}|}$$

Any system containing an atom which has an unshared pair and which is directly attached to a multiple-bond atom can show this type of delocalization. Another example is the carbonate ion:

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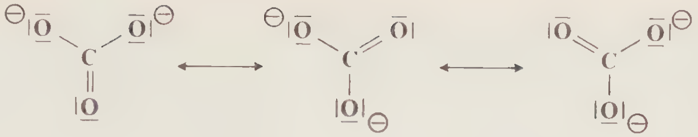
[19] See Ref. 16. See discussion of this in Bastiansen and Traetteberg, *Tetrahedron* **17**, 147 (1962); Fischer-Hjalmars, *Tetrahedron* **17**, 235 (1962), **19**, 1805 (1963); and Coulson, *Tetrahedron* **17**, 258 (1962).



The bonding in allylic carbanions, e.g., $CH_2{=}CH{-}\overline{C}H_2^{\ominus}$, is similar.

The other two cases, where the original p orbital contains only one or no electron, are generally found only in free radicals and cations, respectively. Allylic free radicals have one electron in the nonbonding orbital. In allylic cations this orbital is vacant, and only the bonding orbital is occupied. The orbital structures of the allylic carbanion, free radical, and cation differ from each other, therefore, only in that the nonbonding orbital is filled, half-filled, or empty. Since this is an orbital of zero bonding energy, it follows that the bonding π energies of the three species, relative to electrons in the $2p$ orbitals of free atoms, are the same. The electrons in the nonbonding orbital do not contribute to the bonding energy, positively or negatively.

By the resonance picture, the three species may be described as having double bonds in conjugation with, respectively, an unshared pair, an unpaired electron, and an empty orbital (see Chapter 5):

$$CH_2{=}CH{-}\overset{\ominus}{\overline{C}}H_2 \longleftrightarrow \overset{\ominus}{\overline{C}}H_2{-}CH{=}CH_2$$

$$CH_2{=}CH{-}\dot{C}H_2 \longleftrightarrow \dot{C}H_2{-}CH{=}CH_2$$

$$CH_2{=}CH{-}\overset{\oplus}{C}H_2 \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2$$

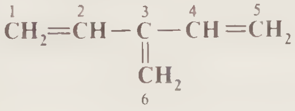
3. *Hyperconjugation.* The third type of delocalization, called *hyperconjugation*, is discussed on p. 69.

We shall find examples of delocalization which cannot be strictly classified as belonging to any of these types.

Cross Conjugation[20]

In a cross-conjugated compound, three groups are present, two of which are not conjugated with each other, though each is conjugated with the third. Some examples are

$$Ph{-}\underset{\underset{O}{\|}}{C}{-}Ph$$



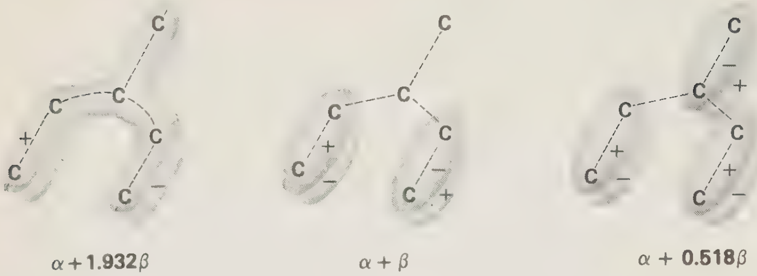
$$\overset{1}{C}H_2{=}\overset{2}{C}H{-}\underset{\underset{\underset{6}{CH_2}}{\|}}{\overset{3}{C}}{-}\overset{4}{C}H{=}\overset{5}{C}H_2$$

9

$CH_2{=}CH{-}O{-}CH{=}CH_2$

If we look at **9** by the molecular-orbital method, we find that overlap of six p orbitals gives six molecular orbitals, of which the three bonding orbitals are shown in Figure 5, along with their energies. Note that two of the carbon atoms do not participate in the $\alpha + \beta$ orbital. The total energy of the three occupied orbitals is $6\alpha + 6.900\beta$, so that the resonance energy is 0.900β.

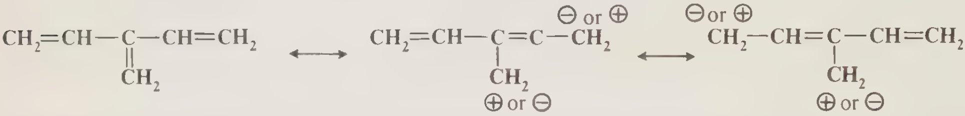
[20] For a discussion, see Phelan and Orchin, *J. Chem. Educ.* **45**, 633–637 (1968).



$\alpha + 1.932\beta$ $\alpha + \beta$ $\alpha + 0.518\beta$

Figure 5 The three bonding orbitals of 3-methylene-1,4-pentadiene (**9**).

Molecular-orbital bond orders are 1.930 for the C-1,C-2 bond, 1.859 for the C-3,C-6 bond, and 1.363 for the C-2,C-3 bond.[20] Comparing these values with those for butadiene (p. 33), we see that the C-1,C-2 bond contains more, and the C-3,C-6 bond less, double-bond character than the double bonds in butadiene. The resonance picture supports this conclusion, since each C-1,C-2 bond is double in three of the five canonical forms, while the C-3,C-6 bond is double in only one. In most cases it is easier to treat cross-conjugated molecules by the molecular-orbital method than by the valence-bond method.



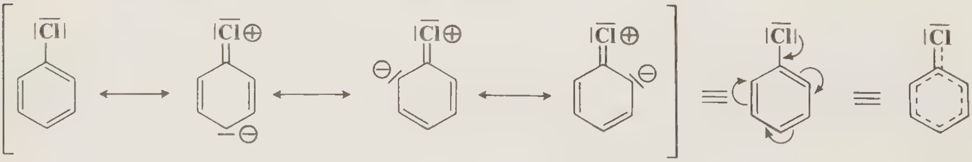
$$CH_2{=}CH{-}\underset{\overset{\|}{CH_2}}{C}{-}CH{=}CH_2 \longleftrightarrow CH_2{=}CH{-}\underset{\underset{\oplus \text{ or } \ominus}{\overset{|}{CH_2}}}{C}{=}\overset{\ominus \text{ or } \oplus}{C{-}CH_2} \longleftrightarrow \overset{\ominus \text{or} \oplus}{CH_2}{-}CH{=}\underset{\underset{\oplus \text{ or } \ominus}{\overset{|}{CH_2}}}{C}{-}CH{=}CH_2$$

The Rules of Resonance

We have seen that one way of expressing the actual structure of a molecule containing delocalized bonds is to draw several possible structures and to assume that the actual molecule is a hybrid of them. These canonical forms have no existence except in our imagination. The molecule does *not* rapidly shift between them. It is *not* the case that some molecules have one canonical form and some another. All the molecules of the substance have the same structure. That structure is always the same all the time and is a weighted average of all the canonical forms. In drawing canonical forms and in deriving the true structures from them, we are guided by certain rules, among them the following:

1. All the canonical forms must be bona fide Lewis structures (see p. 16). For instance, in none of them may carbon have five bonds.

2. The positions of the nuclei must be the same in all the structures. This means that all we are doing when we draw the various canonical forms is putting the *electrons* in in different ways. For this reason, shorthand ways of representing resonance are easy to devise:



10 11

The resonance interaction of chlorine with the benzene ring may be represented as shown in **10** or **11**, and either of these representations is often used to save space. However, we shall not use the curved-arrow method of **10** since in this book arrows will be used to express actual movement of electrons in reactions. We shall use representations like **11**, or else write out the canonical forms. The convention used in dashed-line formulas like **11** is that bonds which are present in all canonical forms are drawn as solid lines while bonds which are not present in all forms are drawn as dashed lines. In most resonance, σ bonds are not involved, and only the π or unshared electrons are put in in different ways. This means that if we write one canonical form for a molecule, we can then write the others by merely moving π and unshared electrons.

3. All atoms taking part in the resonance, i.e., covered by delocalized electrons, must lie in a plane, or nearly so (see p. 38). This, of course, does not apply to atoms which have the same bonding in all the canonical forms. The reason for planarity is maximum overlap of the p orbitals.

4. All canonical forms must have the same number of unpaired electrons. Thus $\dot{C}H_2-CH=CH-\dot{C}H_2$ is not a valid canonical form for butadiene.

5. The energy of the actual molecule is lower than that of any form, obviously. Therefore, delocalization is a stabilizing phenomenon. Many species which would not be expected to be stable solely on the basis of the Lewis structure of lowest energy turn out to be stable because of the resonance.

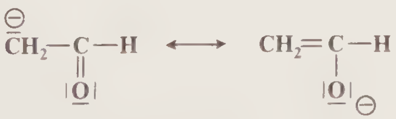
6. All canonical forms do not contribute equally to the true molecule. Each form contributes in proportion to its stability, the most stable form contributing most. Thus, for ethylene, the form $\overset{-}{C}H_2-\overset{+}{C}H_2$ has such a high energy compared with $CH_2=CH_2$ that it essentially does not contribute at all. We have seen the argument that such structures do not contribute even in such cases as butadiene.[18] Equivalent canonical forms, such as **1** and **2**, contribute equally. The greater the number of significant structures that can be written and the more nearly equal they are, the greater the resonance energy, other things being equal.

It is not always easy to decide relative stabilities of imaginary structures, and the chemist is often guided by intuition. However, the following rules may be helpful:

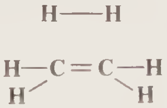
1. Structures with more covalent bonds are ordinarily more stable than those with fewer (compare **6** and **7**).

2. Stability is decreased by an increase in charge separation. Structures with formal charges are less stable than uncharged structures, and structures with more than two formal charges usually contribute very little. An especially unfavorable type of structure is one with two like charges on adjacent atoms. However, when a compound is dissolved in different solvents, ionic structures make a greater contribution in the more polar solvent.[21]

3. Structures which carry a negative charge on a more electronegative atom are more stable than those in which the charge is on a less electronegative atom. Thus, **13** is more stable than **12**. Similarly, positive charges are best carried on atoms of low electronegativity.



12 **13**



14

4. Structures with distorted bond angles or lengths are unstable, e.g., the structure **14** for ethane.

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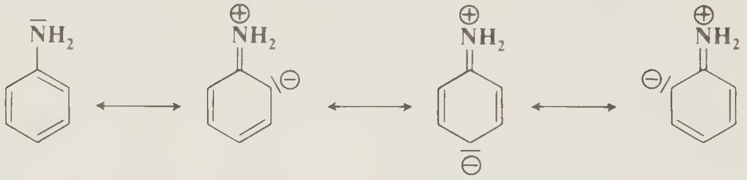
[21] Taft, Glick, Lewis, Fox, and Ehrenson, *J. Am. Chem. Soc.* **82**, 756 (1960).

The Resonance Effect

Resonance always results in a different distribution of electron density than would be the case if there were no resonance. For example, if **15** were the actual structure of aniline, the two unshared electrons of the nitrogen would reside entirely on that atom. Since the real structure is not **15** but a hybrid which includes contributions from the other canonical forms shown, the electron density of the unshared pair does not reside entirely on the nitrogen, but is spread over the ring. This decrease in electron density at one position (and corresponding increase elsewhere) is called the *resonance*, or *mesomeric*, *effect*. We loosely say that the NH_2 contributes or donates electrons to the ring by a resonance effect, although no actual contribution has taken place. The "effect" is caused by the fact that the electrons are in a different place from that we should expect if there were no resonance. In ammonia, where resonance is absent, the unshared pair *is* located on the nitrogen atom. As with the field effect (p. 20), we may think of a certain molecule (in this case ammonia) as a substrate and then see what happens to the electron density when we make a substitution. When one of the hydrogen atoms of the ammonia molecule is replaced by a benzene ring, the electrons are "withdrawn" by the resonance effect, just as when a methyl group replaces a hydrogen of benzene, electrons are "donated" by the field effect of the methyl. The idea of donation or withdrawal merely arises from the comparison of a compound with a closely related one or of a real compound with a canonical form.



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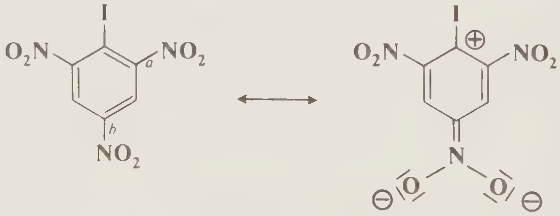
Steric Hindrance to Resonance

In rule 3 (p. 37), it was stated that all the atoms covered by delocalized electrons must lie in a plane, or nearly so. Many examples are known where resonance is reduced or prevented because the atoms are sterically forced out of planarity.

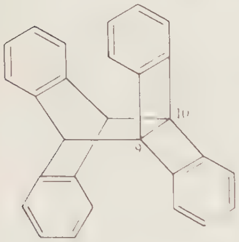
Bond lengths for the *o*- and *p*-nitro groups in picryl iodide are quite different.[22] Distance *a* is 1.45 Å, whereas *b* is 1.35 Å. The obvious explanation is that the oxygens of the *p*-nitro group are in the plane of the ring and thus in resonance with it, so that *b* has partial double-bond character, while the oxygens of the *o*-nitro groups are forced out of the plane by the large iodine atom.



[22] Wepster, *Prog. Stereochem.* **2**, 99–156 (1958), p. 125.

Another example is 2,3-di-*t*-butylbutadiene, which is a stable, *nonconjugated* diene.[23] The double bonds are not in the same plane but are forced out by the large *t*-butyl groups.

The Dewar-type structure for the central ring of the anthracene system in **16** is possible only because the 9,10 substituents prevent the system from being planar.[24] **16** is the actual structure of the molecule, and it is not in resonance with forms like **17**, though in anthracene itself, Dewar structures and structures like **17** both contribute. This is a consequence of rule 2 (p. 36). In order for a **17**-like structure to contribute to resonance in **16** the nuclei would have to be in the same positions in both forms.



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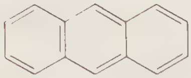

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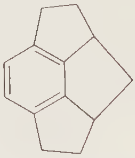

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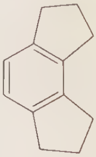

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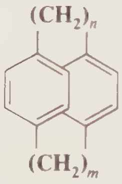
Even the benzene ring may be forced out of planarity.[25] Thus, **18** absorbs oxygen on standing and is easily hydrogenated, although **19** is almost completely unreactive.[26] Similarly, [*n.m*]paracyclophanes (**20**), where *n* and *m* are both 3 or less (the smallest yet prepared is [2.2]paracyclophane), have bent benzene rings and properties which depart significantly from those of ordinary benzene compounds.[27] Another molecule in which benzene rings are forced out of planarity is corannulene (**21**).[28]



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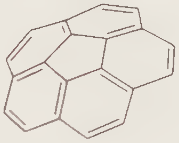

21

$p\pi$-$d\pi$ Bonding. Ylides

We have mentioned (p. 14) that, in general, atoms of the second row of the periodic table do not form stable double bonds because the parallel *p* orbitals are too far for a reasonable amount of overlap. However, there is another type of double bond which is particularly common for the second-row atoms sulfur and phosphorus. For example, such a double bond is found in the compound H_2SO_3, as written on the left. Like an ordinary double bond, this double bond contains one σ orbital,

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[23] Wynberg, DeGroot, and Davies, *Tetrahedron Lett.* 1083 (1963).

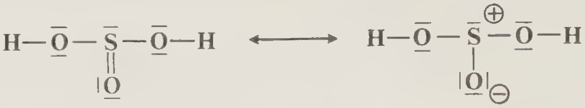
[24] Applequist and Searle, *J. Am. Chem. Soc.* **86,** 1389 (1964).

[25] For a review of planarity in aromatic systems, see Ferguson and Robertson, *Adv. Phys. Org. Chem.* **1,** 203–281 (1963).

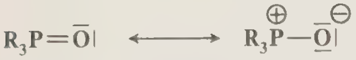
[26] Rapoport and Smolinsky, *J. Am. Chem. Soc.* **82,** 1171 (1960).

[27] For reviews, see Cram and Cram, *Acc. Chem. Res.* **4,** 204–213 (1971); and Vögtle and Neumann, *Top. Curr. Chem.* **48,** 67–129 (1974).

[28] Barth and Lawton, *J. Am. Chem. Soc.* **93,** 1730 (1971).

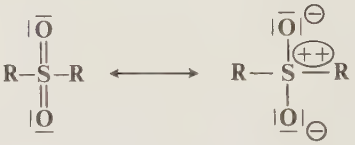


but the second orbital is not a π orbital formed by overlap of half-filled p orbitals; instead it is formed by overlap of a filled p orbital from the oxygen with an empty d orbital from the sulfur. It is called a *pπ-dπ orbital.* Note that we can represent this molecule by two canonical forms but that, despite the resonance, the bond is nevertheless localized. Some other examples of *pπ-dπ* bonding are

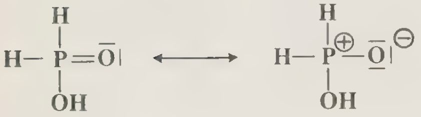


$R_3P{=}\overline{O}| \longleftrightarrow R_3\overset{\oplus}{P}-\overset{\ominus}{\underline{\overline{O}}}|$

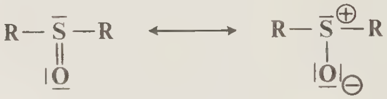
Phosphine oxides



Sulfones



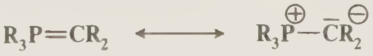
Hypophosphorous acid



Sulfoxides

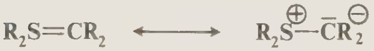
For some of these phosphorus compounds, nitrogen analogs are known, but they are less stable because the resonance is lacking. For example, amine oxides, analogs of phosphine oxides, can only be written $R_3\overset{\oplus}{N}-\overset{\ominus}{O}$. The *pπ-dπ* canonical form is impossible in this case, since nitrogen is limited to eight outer-shell electrons.

In all the examples given above the atom which donates the electron pair is oxygen, and indeed, oxygen is the most common such atom. But in another important class of compounds, called *ylides*, this atom is carbon.[29] There are three main types, phosphorus,[30] nitrogen,[31] and sulfur ylides,[32] although arsenic, selenium, etc., ylides are also known. Ylides may be defined as com-



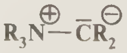
$R_3P{=}CR_2 \longleftrightarrow R_3\overset{\oplus}{P}-\overset{\ominus}{\overline{C}}R_2$

Phosphorus ylides



$R_2S{=}CR_2 \longleftrightarrow R_2\overset{\oplus}{S}-\overset{\ominus}{\overline{C}}R_2$

Sulfur ylides



$R_3\overset{\oplus}{N}-\overset{\ominus}{\overline{C}}R_2$

Nitrogen ylides

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[29] For a monograph, see Johnson, "Ylid Chemistry," Academic Press, Inc., New York, 1966. For reviews, see Hudson, *Chem. Br.* 7, 287–294 (1971); and Lowe, *Chem. Ind.* (*London*) 1070–1079 (1970).

[30] Although the phosphorus ylide shown has three R groups on the phosphorus atom, other phosphorus ylides are known where other atoms, e.g., oxygen, replace one or more of these R groups. When the three groups are all alkyl or aryl, the phosphorus ylide is also called a *phosphorane.*

[31] For a review of nitrogen ylides, see Musker, *Fortschr. Chem. Forsch.* **14**, 295–365 (1970).

[32] For a review of sulfur ylides, see König, *Fortschr. Chem. Forsch.* **9**, 487–533 (1968).

pounds in which an atom from group V or VI of the periodic table, bearing a positive charge, is connected to a carbon atom carrying an unshared pair of electrons. Because of $p\pi$-$d\pi$ bonding, two canonical forms can be written for phosphorus and sulfur ylides, but for nitrogen ylides there is only one. Once again, because of the resonance, phosphorus ylides are much more stable than nitrogen ylides (see also p. 865). In spite of their resonance, sulfur ylides also have a low stability.

In almost all compounds which have $p\pi$-$d\pi$ bonds, the central atom is connected to four atoms or to three atoms and an unshared pair, and the bonding is tetrahedral. The $p\pi$-$d\pi$ bond, therefore, does not change the geometry of the molecule, in contrast to the normal π bond, which changes an atom from tetrahedral to trigonal.

AROMATICITY

It was recognized in the nineteenth century that aromatic compounds[33] differed greatly from unsaturated aliphatic compounds,[34] but for many years chemists were hard pressed to arrive at a mutually satisfactory definition of aromatic character.[35] Qualitatively, there has never been real disagreement. Definitions have taken the form that aromatic compounds are characterized by a special stability and that they undergo substitution reactions more easily than addition reactions. The difficulty arises because these definitions are vague and not easy to apply in borderline cases.[36] In 1925 Armit and Robinson[37] recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the *aromatic sextet* (aromatic compounds are thus the arch examples of delocalized bonding), but it still was not easy to determine whether rings other than the benzene ring possessed such a loop. With the advent of magnetic techniques, most notably nmr, it is now possible to determine experimentally whether or not a compound has a closed ring of electrons; and aromaticity can now be defined as the *ability to sustain an induced ring current*. A compound which has this ability is called *diatropic*. Although this definition also has its flaws,[38] it is the one most commonly accepted today. There are several methods of determining whether a compound can sustain a ring current, but the most important one is based on nmr chemical shifts.[39] In order to understand this, it is necessary to remember that, as a general rule, the value of the chemical shift of a proton in an nmr spectrum depends upon the electron density of its bond: the greater the density of the electron cloud surrounding or partially surrounding a proton, the more upfield its chemical shift (a higher value of τ). However, this rule has several exceptions, one being for protons in the vicinity of an aromatic ring. When an external

[33] For books on aromaticity, see Badger, "Aromatic Character and Aromaticity," Cambridge University Press, London, 1969; Snyder, "Nonbenzenoid Aromatics," 2 vols., Academic Press, Inc., New York, 1969–1971; Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds," American Elsevier Publishing Company, New York, 1966; Ginsburg, "Non-Benzenoid Aromatic Compounds," Interscience Publishers, Inc., New York, 1959; Bergmann and Pullman, "Aromaticity, Pseudo-Aromaticity, and Anti-Aromaticity," Israel Academy of Sciences and Humanities, Jerusalem, 1971; and "Aromaticity," *Chem. Soc. Spec. Pub.* no. 21, 1967. For reviews, see Sondheimer, *Chimia* **28,** 163–172 (1974); Cresp and Sargent, *Essays Chem.* **4,** 91–114 (1972); Figeys, *Top. Carbocyclic Chem.* **1,** 269–359 (1969); Garratt and Sargent, *Adv. Org. Chem.* **6,** 1–108 (1969); Vol'pin, *Russ. Chem. Rev.* **29,** 129–160 (1960); Hafner, *Angew. Chem. Int. Ed. Engl.* **3,** 165–173 (1964) [*Angew. Chem.* **75,** 1041–1050 (1963)]; and Agranat, *MTP Int. Rev. Sci.: Org. Chem. Ser. One,* **3,** 139–178 (1973).

[34] For an account of the early history of aromaticity, see Snyder, in Snyder, Ref. 33, vol. 1, pp. 1–31.

[35] For a review of the criteria used to define aromatic character, see Jones, *Rev. Pure Appl. Chem.* **18,** 253–280 (1968). For a method of assigning aromaticity on the basis of Hückel theory, see Schaad and Hess, *J. Am. Chem. Soc.* **94,** 3068 (1972), *J. Chem. Educ.* **51,** 640 (1974).

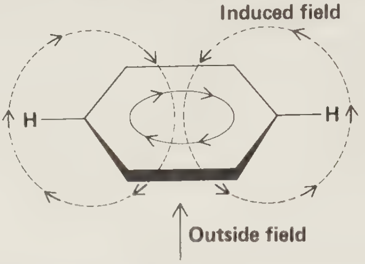
[36] It has been proposed that use of the word *aromatic* be discontinued altogether: see Lloyd and Marshall, *Angew. Chem. Int. Ed. Engl.* **11,** 404 (1972) [*Angew. Chem.* **84,** 477]; Labarre, in Bergmann and Pullman, Ref. 33, p. 55.

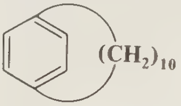
[37] Armit and Robinson, *J. Chem. Soc.* **127,** 1604 (1925).

[38] Jones, Ref. 35, pp. 266–274.

[39] For a review of nmr and other magnetic properties with respect to aromaticity, see Haddon, Haddon, and Jackman, *Fortschr. Chem. Forsch.* **16,** 103–220 (1971). For an example of a magnetic method other than nmr, see Dauben, Wilson, and Laity, in Snyder, Ref. 33, vol. 2, pp. 167–206.

magnetic field is imposed upon an aromatic ring (as in an nmr instrument), the closed loop of aromatic electrons circulates in a diamagnetic ring current, which sends out a field of its own. As can be seen in the diagram, this induced field curves around and in the area of the proton is parallel to the external field, so that the field "seen" by the aromatic protons is greater than it would have been in the absence of the diamagnetic ring current and the protons are moved downfield (to lower τ) compared with where they would be if electron density were the only factor. Thus ordinary olefinic hydrogens are found at approximately 3.5 to 5 τ, while the hydrogens of benzene rings are located at about 2 to 3 τ. However, if there were protons located above or within the ring, they would be subjected to a *decreased* field and should appear at higher τ values than normal CH_2 groups (normal τ for CH_2 is approximately 8 to 9). The nmr spectrum of [10]paracyclophane (**22**) showed that this was indeed the case[40] and that the CH_2 peaks were shifted to higher τ the closer they were to the middle of the chain.





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It follows, then, that aromaticity can be determined from an nmr spectrum. If the protons attached to the ring are shifted downfield from the normal olefinic region, we can conclude that the molecule is diatropic and hence aromatic. If, in addition, the compound has protons above or within the ring (we shall see an example of the latter on p. 61), then if the compound is diatropic, these will be shifted upfield. One drawback to this method is that it cannot be applied to compounds which have no protons in either category, e.g., the dianion of squaric acid (p. 67). Unfortunately, ^{13}C nmr is of no help here, since these spectra do not show ring currents.[40a]

It should be emphasized that the old and new definitions of aromaticity are not necessarily parallel. If a compound is diatropic (and is therefore aromatic under the new definition), it is more stable than the canonical form of lowest energy, but this does not mean that it will be in fact stable to air, light, or common reagents, since *this* stability is determined not by the resonance energy but by the difference in free energy between the actual molecule and the transition states for the reactions involved; and these differences may be quite small, even if the resonance energy is large.

The vast majority of aromatic compounds have a closed loop of six electrons in a ring (the aromatic sextet), and these compounds will be considered first.[41]

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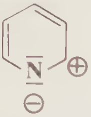
[40] Waugh and Fessenden, *J. Am. Chem. Soc.* **79,** 846 (1957). See also Shapiro, Gattuso, and Sullivan, *Tetrahedron Lett.* 223 (1971).

[40a] For a review of ^{13}C spectra of aromatic compounds, see Günther and Schmickler, *Pure Appl. Chem.* **44,** 807–828 (1975).

[41] Values of molecular-orbital energies for many aromatic systems, calculated by the HMO method, are given in Coulson and Streitwieser, Ref. 13. Values calculated by a variation of the SCF method are given by Dewar and Trinajstić, *Collect. Czech. Chem. Commun.* **35,** 3136, 3484 (1970).

Six-membered Rings

Not only is the benzene ring aromatic, but so are many heterocyclic analogs in which one or more hetero atoms replace carbon in the ring.[41a] When nitrogen is the hetero atom, little difference is made in the sextet and the unshared pair of the nitrogen does not participate in the aromaticity. Therefore, derivatives such as N-oxides or pyridinium ions are still aromatic. However, for nitrogen heterocycles there are more significant canonical forms (e.g., **23**) than for benzene. Where oxygen or sulfur is the hetero atom, it must be present in its ionic form (**24**) in order to possess the valence of 3 that participation in such a system demands. Thus, pyran (**25**) is not aromatic, but the pyrylium ion (**24**) is.[42]



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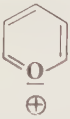

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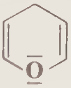

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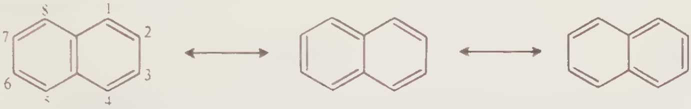
In systems of fused six-membered aromatic rings,[43] the principal canonical forms are usually not all equivalent. **26** has a central double bond and is thus different from the other two canonical forms of naphthalene, which are equivalent to each other:



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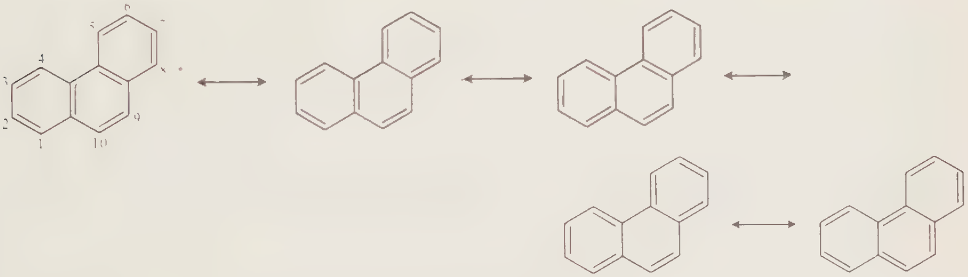
For naphthalene, these are the only forms that can be drawn without consideration of Dewar forms or those with charge separation.[44] If we assume that the three forms contribute equally, the 1,2 bond has more double-bond character than the 2,3 bond. Molecular orbital calculations show bond orders of 1.724 and 1.603, respectively (compare benzene, 1.667). In agreement with these predictions, the 1,2 and 2,3 bond distances are 1.36 and 1.415 Å, respectively,[45] and ozone preferentially attacks the 1,2 bond.[46] This nonequivalency of bonds, called *partial bond fixation*,[47] is found in nearly all fused aromatic systems. In phenanthrene, where the 9,10 bond is a single bond in only one of five forms, bond fixation becomes extreme, and this bond is readily attacked by many reagents:



[41a] For a review of aromaticity of heterocycles, see Cook, Katritzky, and Linda, *Adv. Heterocycl. Chem.* **17,** 255–356 (1974).

[42] For a review of pyrylium salts, see Balaban, Schroth, and Fischer, *Adv. Heterocycl. Chem.* **10,** 241–326 (1969).

[43] For a treatise, see Clar, "Polycyclic Hydrocarbons," 2 vols., Academic Press, Inc., New York, 1964.

[44] As the size of a given fused ring system increases, it becomes more difficult to draw all the canonical forms. For a discussion of methods for doing this, see Herndon, *J. Chem. Educ.* **51,** 10–15 (1974).

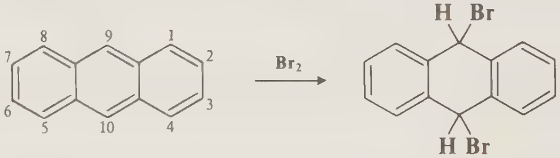
[45] Cruickshank, *Tetrahedron* **17,** 155 (1962).

[46] Kooyman, *Recl. Trav. Chim. Pays-Bas* **66,** 201 (1947).

[47] For reviews see Efros, *Russ. Chem. Rev.* **29,** 66–78 (1960); and Badger, *Q. Rev., Chem. Soc.* **5,** 147–170 (1951).

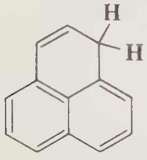
In general there is a good correlation between bond distances in fused aromatic compounds and bond orders, whether these are calculated by the valence-bond or molecular-orbital method. Another experimental quantity which correlates well with the bond order of a given bond in an aromatic system is the nmr coupling constant for coupling between the hydrogens on the two carbons of the bond.[48]

The resonance energies of fused systems increase as the number of principal canonical forms increases, as predicted by rule 6 (p. 37).[49] Thus, for benzene, naphthalene, anthracene, and phenanthrene, for which we can draw, respectively, two, three, four, and five principal canonical forms, the resonance energies are, respectively, 36, 61, 84, and 92 kcal/mol, calculated from heat-of-combustion data.[50] Note that when phenanthrene, which has a total resonance energy of 92 kcal/mol, loses the 9,10 bond by attack of a reagent such as ozone or bromine, two complete benzene rings remain, each with 36 kcal/mol of resonance energy, so that the molecule has lost only 20 kcal/mol, which is much less than the 36 kcal/mol which would be lost if benzene were similarly attacked. The fact that anthracene undergoes many reactions across the 9,10 positions can be explained in a similar manner. These reactions leave intact the outside aromatic rings, so that of the original resonance energy of 84 kcal/mol, 72 kcal/mol remains and only 12 kcal/mol is lost.



Anthracene

Not all fused systems can be fully aromatic. Thus for phenalene (**27**) there is no way double bonds can be distributed so that each carbon has one single and one double bond.[51] However, phenalene is acidic and reacts with potassium methoxide to give the corresponding anion (**28**), which is completely aromatic. So also are the corresponding free radical and cation, in which the resonance energies are the same (see p. 52).[52]



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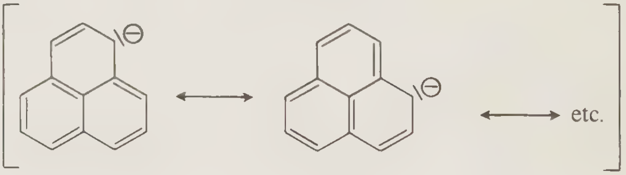

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In a fused system there are not six electrons for each ring. In naphthalene, if one ring is to have six, the other must only have four. One way to explain the greater reactivity of the ring system of naphthalene compared with benzene is to regard one of the naphthalene rings as aromatic and the other as a butadiene system.[53] This effect may become extreme, as in the case of triphenylene.[54] For this compound, there are eight canonical forms like **29**, in which none of the three bonds marked *a* is a double bond, and only one form (**30**) in which at least one of them is double. Thus the molecule behaves as if the 18 electrons were distributed so as to give each of the outer rings a sextet, while the middle ring is "empty." Since none of the outer rings need share any electrons with an adjacent ring, they are as stable as benzene; and triphenylene, unlike most fused aromatic hydrocarbons, does not dissolve in concentrated sulfuric acid and has a low reactivity.[55] This phenomenon, whereby in fused systems some rings give up part of their aromaticity to adjacent rings, is called *annellation* and can be demonstrated by uv spectra[43] as well as by reactivities.

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[48] Jonathan, Gordon, and Dailey, *J. Chem. Phys.* **36**, 2443 (1962); Cooper and Manatt, *J. Am. Chem. Soc.* **91**, 6325 (1969).

[49] See Herndon, *J. Am. Chem. Soc.* **95**, 2404 (1973); Herndon and Ellzey, *J. Am. Chem. Soc.* **96**, 6631 (1974).

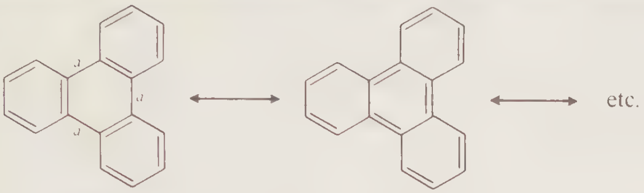
[50] Ref. 1, p. 98.

[51] For reviews, of phenalenes, see Murata, *Top. Nonbenzenoid Aromat. Chem.* **1**, 159–190 (1973); Reid, *Q. Rev., Chem. Soc.* **19**, 274–302 (1965).

[52] Pettit, *J. Am. Chem. Soc.* **82**, 1972 (1960).

[53] Meredith and Wright, *Can. J. Chem.* **38**, 1177 (1960).

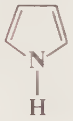
[54] For a review of triphenylenes, see Buess and Lawson, *Chem. Rev.* **60**, 313–330 (1960).



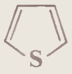
29 **30**

Five-membered Rings

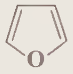
Five-membered rings containing two double bonds can also have an aromatic sextet if the fifth atom has an unshared pair of electrons. Such is the case in pyrrole, thiophene, and furan, though the latter has a lower degree of aromaticity than the other two.[56] Resonance energies for these compounds are, respectively, 21, 29, and 16 kcal/mol.[57] The filled orbital containing the unshared pair overlaps with the adjacent *p* orbitals to create five new orbitals, three of which are bonding and two antibonding. The three bonding orbitals contain the aromatic sextet. The aromaticity can also be shown by canonical forms; e.g., for pyrrole



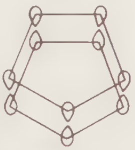
Pyrrole

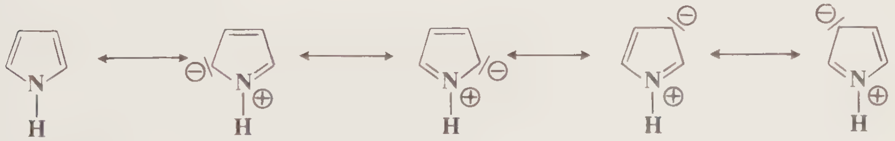


Thiophene



Furan





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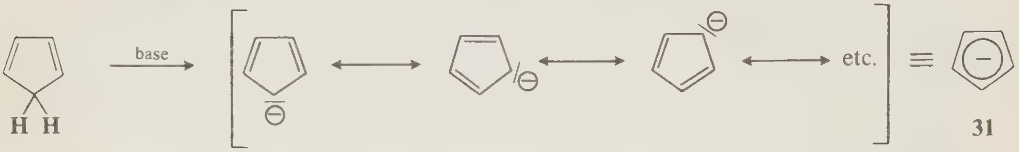
[55] Clar and Zander, *J. Chem. Soc.* 1861 (1958).

[56] The order of aromaticity in some of these compounds is benzene > thiophene > selenophene > tellurophene > furan: Fringuelli, Marino, Taticchi, and Grandolini, *J. Chem. Soc., Perkin Trans. 2* 332 (1974).

[57] Ref. 1, p. 99.

In contrast to the case of pyridine, the unshared pair in pyrrole is needed for the aromatic sextet. This is the reason pyrrole is so much weaker a base than pyridine.[58]

The fifth atom may be carbon if it has an unshared pair. Cyclopentadiene has unexpected acidic properties, since on loss of a proton, the resulting carbanion is greatly stabilized by resonance although it is quite reactive. The cyclopentadienide ion is usually represented as in **31**. Resonance in this ion is greater than in pyrrole, thiophene, and furan, since all five forms are equivalent. The calculated resonance energy for **31** is 42 kcal/mol.[59] That all five carbons are equivalent has been demonstrated by labeling the starting compound with ^{14}C and finding all positions equally labeled when cyclopentadiene was regenerated.[60] As expected for an aromatic system, the cyclopentadienide ion has been shown to be diatropic,[61] and aromatic substitutions on it have been successfully carried out.[62] Indene (**32**) and fluorene (**33**) are also acidic but less so than cyclopentadiene, since annellation causes the electrons to be less available to the five-membered ring.



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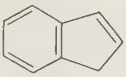

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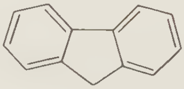

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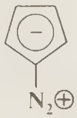
Cyclopentadienylides are a special type of cyclopentadienide (see ylides, p. 40) in which the five-membered ring is connected to a positively charged nitrogen atom. A number of these have been prepared, of which **34** and **35** are examples. **35** is further stabilized by the resonance shown. In these compounds, the cyclopentadiene ring has only four hydrogens, the nitrogen replacing the fifth. The electrons of the C—N bond may be regarded as having come from the nitrogen. Aromatic substitutions have been successfully carried out on **34**.[63]



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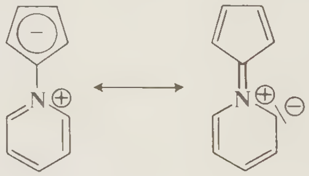

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Five-membered aromatic or aromatic-like rings are also found in other types of compounds: fulvenes and metallocenes. In *fulvenes*[64] (**36**) the exocyclic double bond is greatly polarized in

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[58] For a review of the physical properties of pyrroles, see Jones, *Adv. Heterocycl. Chem.* **11**, 383–472 (1970).

[59] Roberts, Streitwieser, and Regan, *J. Am. Chem. Soc.* **74**, 4579 (1952).

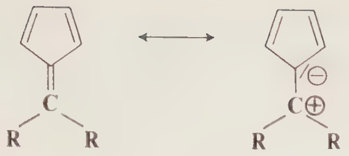
[60] Tkachuk and Lee, *Can. J. Chem.* **37**, 1644 (1959).

[61] Bradamante, Marchesini, and Pagani, *Tetrahedron Lett.* 4621 (1971).

[62] Webster, *J. Org. Chem.* **32**, 39 (1967); Rybinskaya and Korneva, *Russ. Chem. Rev.* **40**, 247–255 (1971).

[63] Cram and Partos, *J. Am. Chem. Soc.* **85**, 1273 (1963).

[64] For reviews, see Bergmann, *Chem. Rev.* **68**, 41–84 (1968); Yates, *Adv. Alicyclic Chem.* **2**, 59–184 (1968); and Hafner, Häfner, König, Kreuder, Ploss, Schulz, Sturm, and Vöpel, *Angew. Chem. Int. Ed. Engl.* **2**, 123 134 (1963) [*Angew. Chem.* **75**, 35–46].



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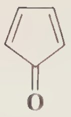

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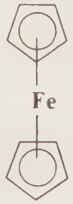
the direction of the ring. These compounds have dipole moments and react with $LiAlH_4$, which ordinarily does not reduce carbon-carbon double bonds but does so here because of the polarity. Also, cis-trans isomerism is not found in most fulvenes, since the exocyclic bond has a high degree of single-bond character. The ring attracts the electrons so as to have a sextet. Nevertheless, since fulvenes show no evidence of ring currents, the chemical shifts of the protons being found in the normal olefinic region,[65] they must therefore be regarded as nonaromatic compounds which show some aromatic properties. In cyclopentadienone (**37**) the oxygen, because of its electronegativity, attracts the electron pair away from the ring, and this compound is unknown, though some of its derivatives have been prepared.[66]

Metallocenes (also called *sandwich compounds*) are compounds in which two cyclopentadienylide rings form a sandwich around a metallic ion. The best known of these is ferrocene (**38**), although others have been prepared with Co, Ni, Cr, Ti, V, and many other metals.[67] Ferrocene is quite stable, subliming above 100 C and unchanged at 400 C. The two rings rotate freely, though the most stable position is a staggered one, in which the rings are not flush. Many aromatic substitutions have been carried out on metallocenes.[68] The compound **39**, prepared by Salzer and Werner, contains three cyclopentadienyl rings and two metal atoms.[69] Such compounds are called *triple-decker sandwiches.*[70]



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[65] Yates, Ref. 64, pp. 117–119. See also Hollenstein, Mooser, Neuenschwander, and Philipsborn, *Angew. Chem. Int. Ed. Engl.* **13,** 551 (1974) [*Angew. Chem.* **86,** 595].

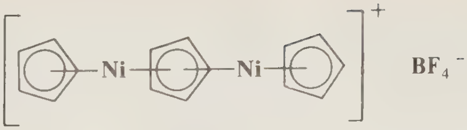
[66] For a review of cyclopentadienone derivatives and of attempts to prepare the parent compound, see Ogliaruso, Romanelli, and Becker, *Chem. Rev.* **65,** 261–367 (1965). See also Garbisch and Sprecher, *J. Am. Chem. Soc.* **91,** 6785 (1969).

[67] For a monograph on metallocenes, see Rosenblum, "Chemistry of the Iron Group Metallocenes," John Wiley & Sons, Inc., New York, 1965. For reviews, see Nesmeyanov and Kochetkova, *Russ. Chem. Rev.* **43,** 710–715 (1974); Shul'pin and Rybinskaya, *Russ. Chem. Rev.* **43,** 716–732 (1974); Perevalova and Nikitina, *Organomet. React.* **4,** 163–419 (1972); Bublitz and Rinehart, *Org. React.* **17,** 1–154 (1969); Leonova and Kochetkova, *Russ. Chem. Rev.* **42,** 278–292 (1973); Rausch, *Pure Appl. Chem.* **30,** 523–538 (1972); *Can. J. Chem.* **41,** 1289–1314 (1963); Fischer and Fritz, *Adv. Inorg. Chem. Radiochem.* **1,** 55–115 (1959); Wilkinson and Cotton, *Prog. Inorg. Chem.* **1,** 1–124 (1959); Pauson, *Q. Rev., Chem. Soc.* **9,** 391–414 (1955); Little, *Surv. Prog. Chem.* **1,** 133–210 (1963); Nesmeyanov, *Bull. Soc. Chim. Fr.* 1229–1239 (1965). For a bibliography of reviews on metallocenes, see Bruce, *Adv. Organomet. Chem.* **10,** 273–346 (1972), pp. 322–325.

[68] For a review on aromatic substitution on ferrocenes, see Plesske, *Angew. Chem. Int. Ed. Engl.* **1,** 312–327, 394–399 (1962) [*Angew. Chem.* **74,** 301–316, 347–352].

[69] Salzer and Werner, *Angew. Chem. Int. Ed. Engl.* **11,** 930 (1972) [*Angew. Chem.* **84,** 949]; Dubler, Textor, Oswald, and Salzer, *Angew. Chem. Int. Ed. Engl.* **13,** 135 (1974) [*Angew. Chem.* **86,** 125]; Court and Werner, *J. Organomet. Chem.* **65,** 245 (1974).

[70] Schumacher and Taubenest, *Helv. Chim. Acta* **47,** 1525 (1964).



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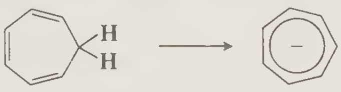
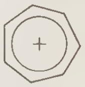
The bonding in ferrocene may be looked upon in simplified molecular-orbital terms as follows.[71] Each of the cyclopentadienide rings has five molecular orbitals: three filled bonding and two empty antibonding orbitals (p. 45). The outer shell of the Fe atom possesses nine atomic orbitals, i.e., one 4*s*, three 4*p*, and five 3*d* orbitals. The six filled orbitals of the two cyclopentadienide rings overlap with the *s*, three *p*, and two of the *d* orbitals of the Fe to form twelve new orbitals, six of which are bonding. These six orbitals make up two ring-to-metal triple bonds. In addition further bonding results from overlap of the empty antibonding orbitals of the rings with additional filled *d* orbitals of the iron. All told, there are eighteen electrons (ten of which may be considered to come from the rings and eight from iron in the zero oxidation state) in nine orbitals; six of these are strongly bonding and three weakly bonding or nonbonding.

Seven- and Eight-membered Rings[72]

Cycloheptatriene (**40**) is much less acidic than cyclopentadiene. This would be hard to explain without the aromatic-sextet theory, since, on the basis of resonance forms or a simple consideration of orbital overlaps, **41** should be as stable as the cyclopentadienyl anion (**31**). While **41** has been prepared in solution,[73] it is apparently less stable than **31** and far less stable than **42**, in which **40** has lost not a proton but a hydride ion. The six double-bond electrons of **42** overlap with the empty orbital on the seventh carbon, and there is a sextet of electrons covering seven carbon atoms. **42**, known as the *tropylium ion*, is quite stable. Tropylium bromide, which could be completely covalent if the electrons of the bromine were sufficiently attracted to the ring, is actually an ionic compound[74]



40 **41**



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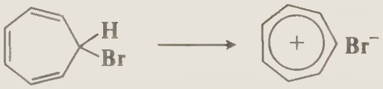

Just as with **31**, the equivalence of the carbons in **42** has been demonstrated by isotopic labeling.[75]

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[71] Rosenblum, Ref. 67, pp. 13–28; Coates, Green, and Wade, "Organometallic Compounds," 3d ed., vol. 2, pp. 97–104, Methuen & Co., Ltd., London, 1968.

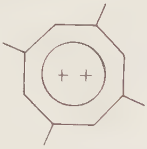
[72] For reviews, see Pietra, *Chem. Rev.* **73,** 293–364 (1973); Bertelli, *Top. Nonbenzenoid Aromat. Chem.* **1,** 29–46 (1973); Kolomnikova and Parnes, *Russ. Chem. Rev.* **36,** 735–753 (1967); Harmon, in Olah and Schleyer, "Carbonium Ions," vol. 4, pp. 1579–1641, John Wiley & Sons, Inc., New York, 1973; Nozoe and Murata, *MTP Int. Rev. Sci.: Org. Chem. Ser. One* **3,** 201–235 (1973); Doering and Krauch, *Angew. Chem.* **68,** 661–667 (1956); Cook and Loudon, *Q. Rev., Chem. Soc.* **5,** 99–130 (1951); Nozoe, *Prog. Org. Chem.* **5,** 132–163 (1961); Pauson, *Chem. Rev.* **55,** 9–136 (1955); and Doering, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 35–48, Butterworth Scientific Publications, London, 1959.

[73] Dauben and Rifi, *J. Am. Chem. Soc.* **85,** 3041 (1963); also see Breslow and Chang, *J. Am. Chem. Soc.* **87,** 2200 (1965).

[74] Doering and Knox, *J. Am. Chem. Soc.* **76,** 3203 (1954).

[75] Vol'pin, Kursanov, Shemyakin, Maimind, and Neiman, *J. Gen. Chem. USSR* **29,** 3667 (1959).

The tropylium ion has an aromatic sextet spread over seven carbon atoms. An analogous ion, with the sextet spread over eight carbon atoms, is 1,3,5,7-tetramethylcyclooctatetraene dianion (**43**).[75a] This ion, which is stable in solution at −50°C, is diatropic and approximately planar. **43** is not stable above about −30°C.



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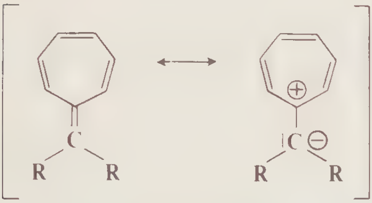
The search for aromaticity in seven-membered compounds has been extended to other types of systems, analogous to the five-membered ring compounds previously discussed. *Heptafulvenes* (**44**) would be expected to have the exocyclic double-bond electrons polarized *away* from the ring. The simplest heptafulvene (R = H) has been prepared[76] but is stable only at low temperatures or in dilute solutions. However, electron-withdrawing groups such as CN would stabilize the negative charge, and **45** is a more stable compound[77] with a very large dipole moment (7.49 D). In contrast to cyclopentadienone (**37**), cycloheptatrienone, called *tropone* (**46**), is predicted by the sextet theory to be stable, since the seven-membered ring *donates* electrons to the electronegative oxygen, while the five-membered ring requires them. In fact, in great contrast to cyclopentadienones, tropones are quite stable, and indeed tropolones (**47**) are found in nature.[78] However, analyses of dipole moments, nmr spectra, and x-ray diffraction measurements show that tropones, tropolones, and **45** display appreciable bond alternation[79] and these molecules, like fulvenes, must



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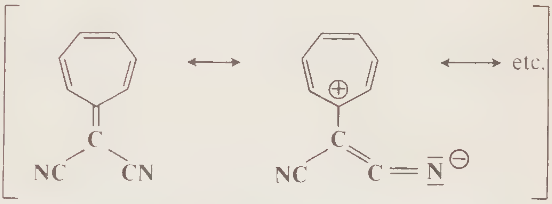

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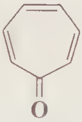

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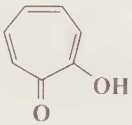

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[75a] Olah, Staral, and Paquette, *J. Am. Chem. Soc.* **98,** 1267 (1976). See also Olah and Liang, *J. Am. Chem. Soc.* **98,** 3033 (1976).

[76] Schenk, Kyburz, and Neuenschwander, *Helv. Chim. Acta* **58,** 1099 (1975); Doering and Wiley, *Tetrahedron* **11,** 183 (1960).

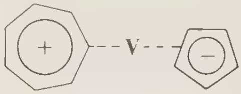
[77] Yamakawa, Watanabe, Mukai, Nozoe, and Kubo, *J. Am. Chem. Soc.* **82,** 5665 (1960); Nozoe, Mukai, Osaka, and Shishido, *Bull. Chem. Soc. Jpn.* **34,** 1384 (1961).

[78] For reviews of tropones and tropolones, see Nozoe, *Pure Appl. Chem.* **28,** 239–280 (1971); and Pauson, *Chem. Rev.* **55,** 9–136 (1955).

[79] Bertelli and Andrews, *J. Am. Chem. Soc.* **91,** 5280 (1969); Bertelli, Andrews, and Crews, *J. Am. Chem. Soc.* **91,** 5286 (1969); Schaefer and Reed, *J. Am. Chem. Soc.* **93,** 3902 (1971); Watkin and Hamor, *J. Chem. Soc. B* 2167 (1971); Barrow, Mills, and Filippini, *J. Chem. Soc., Chem. Commun.* 66 (1973).

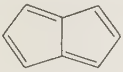
be regarded as nonaromatic, though with some aromatic character. Tropolones readily undergo aromatic substitution, emphasizing that the old and the new definitions of aromaticity are not always parallel.

Metallocenes containing tropylium ions have been prepared, e.g.,[80]



Other Systems Containing Aromatic Sextets

Simple resonance theory predicts that pentalene (**48**), azulene (**49**), and heptalene (**50**) should be aromatic, although no nonionic canonical form can have a double bond at the ring junction. Molecular-orbital calculations show that azulene should be stable but not the other two, and this



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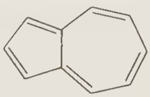

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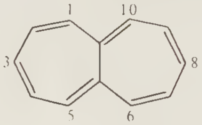

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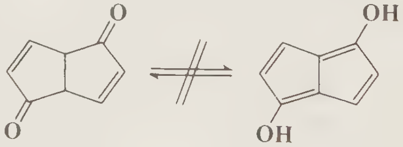
is borne out by experiment. Heptalene has been prepared[81] but reacts readily with oxygen, acids, and bromine, is easily hydrogenated, and polymerizes on standing. Analysis of its nmr spectrum shows that it is not planar.[82] The 3,8-dibromo and 3,8-dicarbomethoxy derivatives of **50** are stable in air at room temperature but are not diatropic.[83] Pentalene has not been prepared,[84] but the hexaphenyl derivative is known.[85] This compound is air-sensitive in solution. Pentalene and its methyl and dimethyl derivatives have been formed in solution, but they dimerize before they can be isolated.[86] Many other attempts to prepare these two systems have failed. One approach to hard-to-make aromatic systems involves preparation of ketones which can tautomerize to the desired phenolic systems. In such an attempt to produce a pentalene, **51** was prepared.[87] However, it did not tautomerize to the enol form (see p. 72):



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[80] King and Stone, *J. Am. Chem. Soc.* **81,** 5263 (1959).

[81] Dauben and Bertelli, *J. Am. Chem. Soc.* **83,** 4659 (1961); Vogel, Königshofen, Wassen, Müllen, and Oth, *Angew. Chem. Int. Ed. Engl.* **13,** 732 (1974) [*Angew. Chem.* **86,** 777].

[82] Bertelli, in Bergmann and Pullman, Ref. 33, p. 326.

[83] Vogel and Ippen, *Angew. Chem. Int. Ed. Engl.* **13,** 734 (1974) [*Angew. Chem.* **86,** 778]; Vogel and Hogrefe, *Angew. Chem. Int. Ed. Engl.* **13,** 735 (1974) [*Angew. Chem.* **86,** 779].

[84] Metal complexes of pentalene have been prepared: Knox and Stone, *Acc. Chem. Res.* **7,** 321–328 (1974).

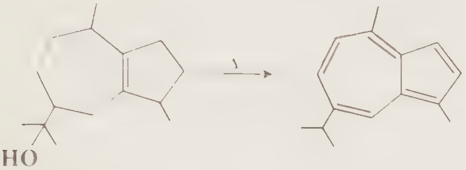
[85] LeGoff, *J. Am. Chem. Soc.* **84,** 3975 (1962). See also Hafner, Bangert, and Orfanos, *Angew. Chem. Int. Ed. Engl.* **6,** 451 (1967) [*Angew. Chem.* **79,** 414]; Hafner and Süss, *Angew. Chem. Int. Ed. Engl.* **12,** 575 (1973) [*Angew. Chem.* **85,** 626]; Hartke and Matusch, *Angew. Chem. Int. Ed. Engl.* **11,** 50 (1972) [*Angew. Chem.* **84,** 61].

[86] Bloch, Marty, and de Mayo, *J. Am. Chem. Soc.* **93,** 3071 (1971); *Bull. Soc. Chim. Fr.* 2031 (1972); Hafner, Dönges, Goedecke, and Kaiser, *Angew. Chem. Int. Ed. Engl.* **12,** 337 (1973) [*Angew. Chem.* **85,** 362].

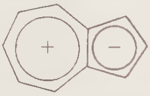
[87] Baker and McOmie, *Prog. Org. Chem.* **3,** 44–80 (1955), p. 69.

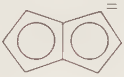
For pentalene, the only way each ring can have a sextet is for four electrons to be shared by the two rings, which is apparently not a stable situation. In heptalene, each ring can have six electrons, but then the two central carbons must belong to each sextet, and this is not a stable system either.

On the other hand, azulene can have six electrons in each ring if they share a pair (as in naphthalene). In sharp contrast to **48** and **50** azulene is quite stable, and many of its derivatives are known.[88] Many sesquiterpenes, found in nature, are easily converted to azulene derivatives, e.g., upon heating guaiol gives S-guaiazulene (see reaction **9-1**). Azulene readily undergoes aromatic substitution. Azulene may be regarded as a combination of **31** and **42** and, indeed, possesses a dipole moment of 0.8 D.[89] Interestingly, if two electrons are added to pentalene to give a dianion, each ring can have a sextet with one pair belonging to both. Such a dianion (**52**) has been prepared,[90] although pentalene itself has not been prepared. It can be concluded that an aromatic system of electrons will be spread over two rings only if 10 electrons (not 8 or 12) are available for aromaticity.



Guaiol S-Guaiazulene





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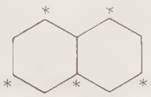
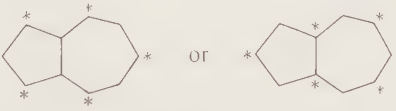
Alternant and Nonalternant Hydrocarbons[91]

Aromatic hydrocarbons can be divided into two types. In alternant hydrocarbons, the conjugated carbon atoms can be divided into two sets such that no two atoms of the same set are directly linked. For convenience one set may be starred. Naphthalene is an alternant and azulene a nonalternant hydrocarbon:





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[88] For reviews on azulene, see Reid, Chemical Society Symposia, *Chem. Soc. Spec. Publ.* no. 12, pp. 69–83 (1958); Hafner, *Angew. Chem.* **70,** 419–430 (1958); Gordon, *Chem. Rev.* **50,** 127–200 (1952).

[89] Tobler, Bauder, and Günthard, *J. Mol. Spectrosc.* **18,** 239 (1965).

[90] Katz, Rosenberger, and O'Hara, *J. Am. Chem. Soc.* **86,** 249 (1964).

[91] For discussions, see Dewar, *Prog. Org. Chem.* **2,** 1–28 (1953); and Longuet-Higgins, in "Theoretical Organic Chemistry. The Kekulé Symposium," pp. 9–19, Butterworth Scientific Publications, London, 1959.

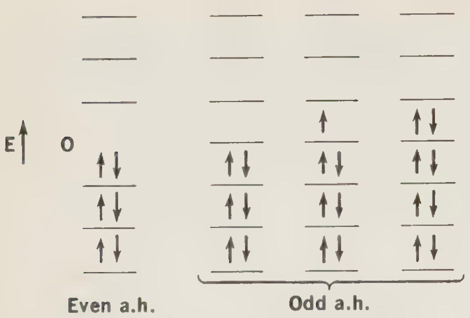
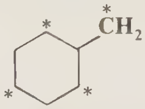


Figure 6 Energy levels in odd- and even-alternant hydrocarbons.[92] The arrows represent electrons. The orbitals are shown as having different energies, but some may be degenerate.

In alternant hydrocarbons, the bonding and antibonding orbitals occur in pairs; i.e., for every bonding orbital with an energy $-E$ there is an antibonding one with energy $+E$ (Figure 6). Even-alternant hydrocarbons are those with an even number of conjugated atoms, i.e., an equal number of starred and unstarred atoms. For these hydrocarbons all the bonding orbitals are filled and the π electrons are uniformly spread over the unsaturated atoms.

As with the allyl system, odd-alternant hydrocarbons (which must be carbonium ions, carbanions, or free radicals) in addition to equal and opposite bonding and antibonding orbitals also have a nonbonding orbital of zero energy. When an odd number of orbitals overlap, an odd number is created. Since orbitals of alternant hydrocarbons occur in $-E$ and $+E$ pairs, one orbital can have no partner and must therefore have zero bonding energy. For example, in the benzyl system the cation has an unoccupied nonbonding orbital, the free radical has one electron there, and the carbanion two (Figure 7). As with the allyl system, all three species have the same bonding energy. The charge distribution (or unpaired-electron distribution) over the entire molecule is also the same for the three species and can be calculated by a relatively simple process.[91]



For nonalternant hydrocarbons the energies of the bonding and antibonding orbitals are not equal and opposite, and charge distributions are not the same in cations, anions, and radicals. Calculations are much more difficult but have been carried out.[93]

Aromatic Systems with Electron Numbers Other than Six

Ever since the special stability of benzene was recognized, chemists have been thinking about homologous molecules and wondering whether this stability would also be associated with rings that are similar but of different sizes, such as cyclobutadiene (**53**), cyclooctatetraene (**54**), cyclo-

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[92] Taken from Dewar, Ref. 91, p. 8.

[93] Peters, *J. Chem. Soc.* 1023, 1028, 1039 (1958); Brown, Burden, and Williams, *Aust. J. Chem.* **21**, 1939 (1968). For reviews, see Zahradnik, in Snyder, Ref. 33, vol. 2, pp. 1–80; Zahradnik, *Angew. Chem. Int. Ed. Engl.* **4**, 1039–1050 (1965) [*Angew. Chem.* **77**, 1097–1109].

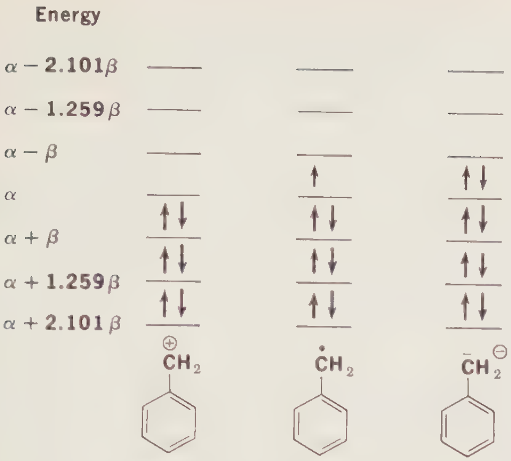
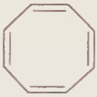


Figure 7 Energy levels for the benzyl cation, free radical, and carbanion. Since α is the energy of a *p* orbital (p. 32), the nonbonding orbital has no bonding energy.

decapentaene[94] (**55**), etc. The general name *annulene* is given to these compounds, with benzene being [6]annulene, and **53** to **55** being called, respectively, [4]-, [8]-, and [10]annulene. By a naïve consideration of resonance forms, these annulenes, and higher ones, should be as aromatic as

53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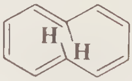

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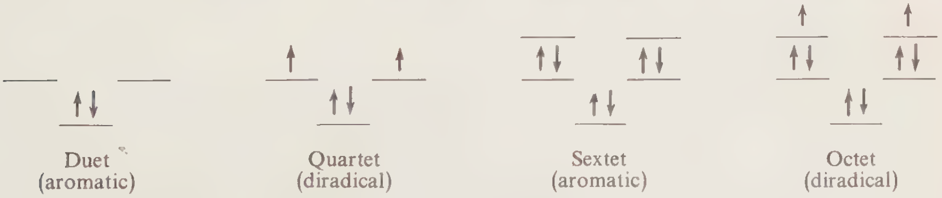
benzene. Yet they proved remarkably elusive. The benzene ring is ubiquitous, being found in thousands of natural products, in coal and petroleum, and being formed by strong treatment of many noncyclic compounds. None of the other annulene ring systems has ever been found in nature, and, except for cyclooctatetraene, their synthesis is not simple. Obviously, there is something special about the number six in a cyclic system of electrons.

Hückel's rule, based on molecular-orbital calculations, predicts that electron rings will constitute an aromatic system only if they contain a number of the form $4n + 2$, where n is any positive integer, including zero. Systems which contain $4n$ electrons are predicted to be nonaromatic. The rule predicts that rings of 2, 6, 10, 14, etc., electrons will be aromatic, while rings of 4, 8, 12, etc., will not be. This is actually a consequence of Hund's rule (p. 7). The first pair of electrons in an annulene goes into the π orbital of lowest energy. After that the bonding orbitals are degenerate, occurring in pairs of equal energy, so that when there is a total of four electrons,



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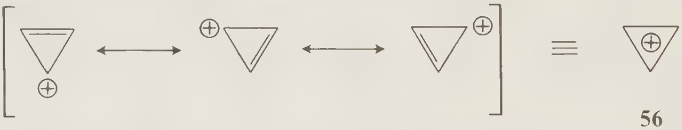
[94] The cyclodecapentaene shown here is the cis-trans-cis-cis-trans form. For other stereoisomers, see p. 60.

Hund's rule predicts that two will be in the lowest orbital but the other two will be unpaired, so that the system will exist as a diradical rather than as two pairs. The degeneracy can be removed if the molecule is distorted from maximum molecular symmetry to a structure of lesser symmetry. For example, if **53** assumes a rectangular rather than a square shape, one of the previously degenerate orbitals has a lower energy than the other and will be occupied by two electrons. In this case, of course, the double bonds are essentially separate, and the molecule still is not aromatic. Distortions of symmetry can also occur when one or more carbons are replaced by hetero atoms or in other ways.[95] Molecular-orbital calculations predict[96] that the aromaticity of $4n + 2$ systems decreases with increasing n, so that large systems will show alternation of single and double bonds and no aromaticity.[97] Calculations show that alternation should begin at $n = 6$, so that the largest aromatic ring should have 22 electrons.[98]

In the following sections systems with various numbers of electrons are discussed. In looking for aromaticity we shall be looking for these things: (1) the presence of a diamagnetic ring current; (2) equal or approximately equal bond distances, except when the symmetry of the system is disturbed by a hetero atom or in some other way; (3) planarity; (4) chemical stability; and (5) the ability to undergo aromatic substitution.

Systems of Two Electrons[99]

Obviously, there can be no ring of two carbon atoms, though a double bond may be regarded as a degenerate case. However, in analogy to the tropylium ion, a three-membered ring with a double bond and a positive charge on the third atom (the *cyclopropenyl cation*) would be a $4n + 2$ system and hence would be expected to show aromaticity. The unsubstituted **56** has been prepared,[100] as well as several derivatives, e.g., the trichloro, diphenyl, and dipropyl derivatives, and these are stable despite the angles of only 60°. In fact, the tripropylcyclopropenyl ion is one of the most stable carbonium ions known, being stable even in water solution.[101] The tri-*t*-butylcyclopropenyl cation is also very stable.[102] In addition, cyclopropenone (**57**) and several of its derivatives are stable compounds,[103] in accord with the corresponding stability of the tropones.[104]



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[95] For a discussion, see Hoffmann, *Chem. Commun.* 240 (1969).

[96] For reviews of molecular-orbital calculations of nonbenzenoid cyclic conjugated hydrocarbons, see Nakajima, *Pure Appl. Chem.* **28,** 219–238 (1971); *Fortschr. Chem. Forsch.* **32,** 1–42 (1972).

[97] Longuet-Higgins and Salem, *Proc. R. Soc. London, Ser. A* **251,** 172 (1959), **257,** 445 (1960).

[98] Dewar and Gleicher, *J. Am. Chem. Soc.* **87,** 685 (1965).

[99] For reviews, see Potts and Baum, *Chem. Rev.* **74,** 189–213 (1974); Yoshida, *Top. Curr. Chem.* **40,** 47–72 (1973); D'yakonov and Kostikov, *Russ. Chem. Rev.* **36,** 557–563 (1967); Closs, *Adv. Alicyclic Chem.* **1,** 53–127 (1966), pp. 102 126; and Krebs, *Angew. Chem. Int. Ed. Engl.* **4,** 10–22 (1965) [*Angew. Chem.* **77,** 10–22]. Also see Carter and Frampton, *Chem. Rev.* **64,** 497–525 (1964) for a review of cyclopropenes, which includes a large amount of material pertinent to this section.

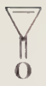
[100] Breslow, Groves, and Ryan, *J. Am. Chem. Soc.* **89,** 5048 (1967); Farnum, Mehta, and Silberman, *J. Am. Chem. Soc.* **89,** 5048 (1967); Breslow and Groves, *J. Am. Chem. Soc.* **92,** 984 (1970).

[101] Breslow, Höver, and Chang, *J. Am. Chem. Soc.* **84,** 3168 (1962).

[102] Ciabattoni and Nathan, *J. Am. Chem. Soc.* **90,** 4495 (1968).

[103] Breslow and Oda, *J. Am. Chem. Soc.* **94,** 4787 (1972); Breslow and Ryan, *J. Am. Chem. Soc.* **89,** 3073 (1967); Yoshida, Konishi, Tawara, and Ogoshi, *J. Am. Chem. Soc.* **95,** 3043 (1973); Breslow, Eicher, Krebs, Peterson, and Posner, *J. Am. Chem. Soc.* **87,** 1320 (1965); Breslow, Altman, Krebs, Mohacsi, Murata, Peterson, and Posner, *J. Am. Chem. Soc.* **87,** 1326 (1965); Kursanov, Vol'pin, and Koreshkov, *J. Gen. Chem. USSR* **30,** 2855 (1960); Breslow and Altman, *J. Am. Chem. Soc.* **88,** 504 (1966); Ref. 102.

[104] For a review of cyclopropenones, see Eicher and Weber, *Top. Curr. Chem.* **57,** 1–109 (1975); For discussions of cyclopropenone structure, see Schäfer, Schweig, Maier, Sayrac, and Crandall, *Tetrahedron Lett.* 1213 (1974); and Tobey, in Bergmann and Pullman, Ref. 33, pp. 351–362.



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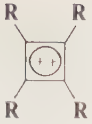
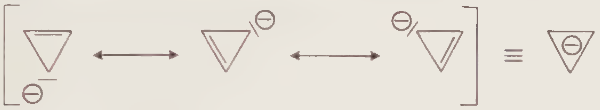


58

The ring system **56** is nonalternant, and the corresponding radical and anion (which do not have an aromatic duet) have electrons in antibonding orbitals, so that their energies are much higher. As with **31** and **42**, the equivalence of the three carbon atoms in the triphenylcyclopropenyl cation has been demonstrated by ^{14}C labeling experiments.[105] The interesting dications **58** (R = Me or Ph) have been prepared,[106] and they too should represent aromatic systems of two electrons.[107]

Systems of Four Electrons. Antiaromaticity

According to Hückel's rule, a closed loop of four electrons should not be aromatic. Many attempts have been made to prepare such systems: chiefly cyclobutadiene (**53**), cyclopropenyl anion (**59**), cyclopentadienyl cation (**60**),[107a] and their derivatives. The evidence to date is that not only are these systems not aromatic but actually *antiaromatic*. If they simply lacked aromaticity, we would expect them to be about as stable as similar nonaromatic compounds, but both theory and experiment show that they are in fact *much less stable*. For example, we may compare a conjugated **59** and an open-chain conjugated allyl carbanion.[108] By HMO theory, the latter is about 19 kcal mol more stable than a diradical conjugated **59.** Thus an allyl carbanion would be *destabilized* upon a hypothetical cyclization to **59,** though in $4n + 2$ systems, an open-chain conjugated system is *stabilized* by cyclizing to the aromatic system. We can therefore predict in the case of cyclopropenyl anion, not only that the canonical form **61** does not gain stability by conjugation but that it actually loses stability; i.e., *an unconjugated* **61** *is more stable than a conjugated* **59.**[109] The HMO theory is supported by experiment. Among other evidence, it has been shown that **62** (R = COPh) loses its proton in hydrogen-exchange reactions about 6000 times more slowly



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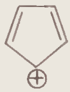

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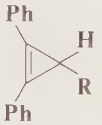

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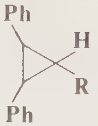

63

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[105] D'yakonov, Kostikov, and Molchanov, *J. Org. Chem. USSR* **5,** 171 (1969), **6,** 304 (1970).

[106] Freedman and Young, *J. Am. Chem. Soc.* **86,** 734 (1964); Olah, Bollinger, and White, *J. Am. Chem. Soc.* **91,** 3667 (1969); Olah and Mateescu, *J. Am. Chem. Soc.* **92,** 1430 (1970). See also Lambert and Holcomb, *J. Am. Chem. Soc.* **93,** 2994 (1971); and Seitz, Schmiedel, and Mann, *Synthesis* 578 (1974).

[107] See Pittman, Kress, and Kispert, *J. Org. Chem.* **39,** 378 (1974).

[107a] For a review of cyclopentadienyl cations, see Breslow, *Top. Nonbenzenoid Aromat. Chem.* **1,** 81–94 (1973).

[108] Breslow, *Chem. Br.* **4,** 100 (1968), *Angew. Chem. Int. Ed. Engl.* **7,** 565–570 (1968) [*Angew. Chem.* **80,** 573–578].

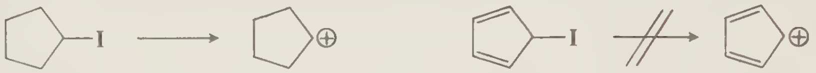
[109] For an example of molecular orbital calculations supporting this conclusion, see Clark, *Chem. Commun.* 637 (1969).

than **63** (R = COPh).[110] Where R = CN, the ratio is about 10,000.[111] This indicates that **62** are much more reluctant to form carbanions (which would have to be cyclopropenyl carbanions) than **63**, which form ordinary carbanions. Thus the carbanions of **62** are less stable than corresponding ordinary carbanions. There are also indications that **63** are not only weak acids kinetically but also thermodynamically:[112] the pK_a of 1,2,3-triphenylcyclopropene is extremely high.[113]

In compounds in which overlapping parallel *p* orbitals form a closed loop of $4n + 2$ electrons, the molecule is stabilized by resonance, and we have an aromatic ring. But the above evidence (and additional evidence cited below) indicates that when the closed loop contains $4n$ electrons, the molecule is destabilized by resonance. We define as *antiaromatic* any system in which cyclic electron delocalization raises the energy.[114]

Although derivatives of cyclopropenyl anion have been prepared as fleeting intermediates (as in the exchange reactions mentioned above), all attempts to prepare the ion or any of its derivatives as relatively stable species have so far met with failure.

In the case of **60**, the ion has been prepared and has been shown to be a diradical in the ground state,[115] as predicted by the discussion on p. 54.[116] Evidence that **60** is not only nonaromatic but also antiaromatic comes from studies on **64** and **66**.[117] When **64** is treated with silver perchlorate in propionic acid, the molecule is rapidly solvolyzed (a reaction in which the intermediate **65** is formed; see Chapter 5). Under the same conditions, **66** undergoes no solvolysis at all; i.e., **60** does not form. If **60** were merely nonaromatic, it should be about as stable as **65** (which of course has no resonance stabilization at all). The fact that it is so much more reluctant to form indicates that **60** is much less stable than **65**.



64 **65** **66** **60**

It is strong evidence for Hückel's rule that **59** and **60** are not aromatic while the cyclopropenyl cation (**56**) and the cyclopentadienyl anion (**31**) are, since simple resonance theory predicts no difference between **59** and **56** or between **60** and **31** (the same number of equivalent canonical forms can be drawn for **59** as for **56** and for **60** as for **31**).

The four-electron system which has received the most attention is cyclobutadiene (**53**). There is a long history of attempts to prepare this compound and its simple derivatives.[118] Though this goal has now been achieved, it is clear that simple cyclobutadienes are extremely unstable compounds which have very short lifetimes (they dimerize by a Diels-Alder reaction; see reaction 5-51) unless stabilized in matrixes (where the molecules are forced to remain apart from each other) at very low temperatures (generally below 35 K). The first successful preparation of **53** was that of Pettit and coworkers,[119] who treated a metallic complex of cyclobutadiene (see p. 59) with ceric ammonium nitrate at 0 C and condensed the resulting gas in a trap cooled with liquid nitrogen. The liquid thus obtained was assumed to be cyclobutadiene. When methyl propiolate was added to it, it gave small amounts of methyl benzoate, which would be expected to form in this manner (see reactions **5-51** and **8-32**):

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[110] Breslow, Brown, and Gajewski, *J. Am. Chem. Soc.* **89**, 4383 (1967).

[111] Breslow and Douek, *J. Am. Chem. Soc.* **90**, 2698 (1968).

[112] For the distinction between thermodynamic and kinetic acidity, see p. 161.

[113] Breslow and Chu, *J. Am. Chem. Soc.* **95**, 411 (1973).

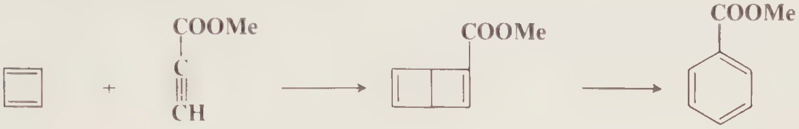
[114] For reviews, see Breslow, *Pure Appl. Chem.* **28**, 111–130 (1971), *Acc. Chem. Res.* **6**, 393–398 (1973), and Ref. 108.

[115] Saunders, Berger, Jaffe, McBride, O'Neill, Breslow, Hoffman, Perchonock, Wasserman, Hutton, and Kuck, *J. Am. Chem. Soc.* **95**, 3017 (1973).

[116] Derivatives of **60** show similar behavior: Breslow, Chang, and Yager, *J. Am. Chem. Soc.* **85**, 2033 (1963); Volz, *Tetrahedron Lett.* 1899 (1964); Breslow, Hill, and Wasserman, *J. Am. Chem. Soc.* **86**, 5349 (1964); Breslow, Chang, Hill, and Wasserman, *J. Am. Chem. Soc.* **89**, 1112 (1967).

[117] Breslow and Mazur, *J. Am. Chem. Soc.* **95**, 584 (1973); Breslow and Hoffman, *J. Am. Chem. Soc.* **94**, 2110 (1972). For further evidence, see Lossing and Traeger, *J. Am. Chem. Soc.* **97**, 1579 (1975).

[118] For a monograph, see Cava and Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, Inc., New York, 1967. For reviews, see Maier, *Angew. Chem. Int. Ed. Engl.* **13**, 425–438 (1974) [*Angew. Chem.* **86**, 491–505]; Criegee, *Angew. Chem. Int. Ed. Engl.* **1**, 519–527 (1962) [*Angew. Chem.* **74**, 703–712], *Bull. Soc. Chim. Fr.* 1–6 (1965); Vollhardt, *Top. Curr. Chem.* **59**, 113–136 (1975).

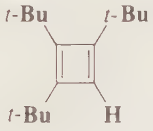


53

Since then **53** and some of its simple derivatives have been prepared a number of times using the low-temperature matrix technique.[120] Infrared studies of **53** under these conditions show that it has a square planar geometry.[121] Other evidence, though not yet conclusive, shows that the molecule seems to be a diene in the ground state[122] and not a diradical. However, it has been found[123] that *o*-diphenylcyclobutadiene (which was not isolated) behaves like a mixture of 1,2- and 1,4-diphenylcyclobutadiene, which is possible only if the ring is rectangular and not square planar. The extreme reactivity of simple cyclobutadienes is not caused merely by steric strain, since the strain should be no greater than that of simple cyclopropenes, which are known compounds. It is probably caused by antiaromaticity.[124]

There are some cyclobutadienes known that are stable at room temperature for varying periods of time. These fall into three classes.

1. *Cyclobutadienes which contain bulky substituents.* Examples are tri-*t*-butylcyclobutadiene (**67**)[125] and the dithia compound **68**.[126] These compounds are relatively stable because dimeriza-



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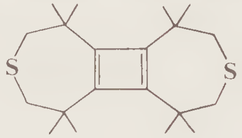

68

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[119] Watts, Fitzpatrick, and Pettit, *J. Am. Chem. Soc.* **87,** 3253 (1965), **88,** 623 (1966). See also Cookson and Jones, *J. Chem. Soc.* 1881 (1965), and Schmidt, *Angew. Chem. Int. Ed. Engl.* **12,** 777 (1973) [*Angew. Chem.* **85,** 820].

[120] Lin and Krantz, *J. Chem. Soc., Chem. Commun.* 1111 (1972); Chapman, McIntosh, and Pacansky, *J. Am. Chem. Soc.* **95,** 614 (1973); Chapman, De La Cruz, Roth, and Pacansky, *J. Am. Chem. Soc.* **95,** 1337 (1973); Maier, Fritschi, and Hoppe, *Angew. Chem. Int. Ed. Engl.* **9,** 529 (1970) [*Angew. Chem.* **82,** 551]; Maier and Schneider, *Angew, Chem. Int. Ed. Engl.* **10,** 809 (1971) [*Angew. Chem.* **83,** 885]; Maier, Mayer, Haacke, and Askani, *Angew. Chem. Int. Ed. Engl.* **12,** 1016 (1973) [*Angew. Chem.* **85,** 1057]; Maier and Bosslet, *Tetrahedron Lett.* 1025 (1972); Maier and Mende, *Tetrahedron Lett.* 3155 (1969); Maier and Hoppe, *Tetrahedron Lett.* 861 (1973). See also Masamune, Suda, Ona, and Leichter, *J. Chem. Soc., Chem. Commun.* 1268 (1972).

[121] Krantz, Lin, and Newton, *J. Am. Chem. Soc.* **95,** 2744 (1973); Chapman, McIntosh, and Pacansky, Ref. 120; Chapman, De La Cruz, Roth, and Pacansky, Ref. 120. See, however, Maier, Hartan, and Sayrac, *Angew. Chem. Int. Ed. Engl.* **15,** 226 (1976) [*Angew. Chem.* **88,** 252].

[122] See for example, Watts, Fitzpatrick, and Pettit, *J. Am. Chem. Soc.* **88,** 623 (1966); and Reeves, Henery, and Pettit, *J. Am. Chem. Soc.* **91,** 5888 (1969).

[123] Reeves, Devon, and Pettit, *J. Am. Chem. Soc.* **91,** 5890 (1969).

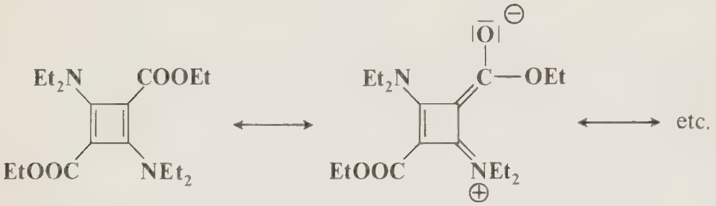
[124] For evidence, see Breslow, Murayama, Murahashi, and Grubbs, *J. Am. Chem. Soc.* **95,** 6688 (1973).

[125] Masamune, Nakamura, Suda, and Ona, *J. Am. Chem. Soc.* **95,** 8481 (1973); Maier and Alzérreca, *Angew. Chem. Int. Ed. Engl.* **12,** 1015 (1973) [*Angew. Chem.* **85,** 1056]. For a discussion, see Masamune, *Pure Appl. Chem.* **44,** 861-884 (1975).

[126] Kimling and Krebs, *Angew. Chem. Int. Ed. Engl.* **11,** 932 (1972) [*Angew. Chem.* **84,** 952].

tion is sterically hindered. Examination of the nmr spectrum of **67** showed that the ring proton ($\tau = 4.62$) was shifted *upfield*, compared with the position expected for a nonaromatic proton, e.g., cyclopentadiene. As we shall see on p. 65, this indicates that the compound is antiaromatic. A similar investigation cannot be made for **68** because it has no ring proton, but x-ray crystallography showed that the central ring is a rectangular diene (as shown) with single- and double-bond lengths of 1.600 and 1.344 Å, respectively.[127] The unusually long single-bond distance may be due to repulsion between the methyl groups. Photoelectron spectroscopy showed that **68** is not a diradical.[128]

2. *Cyclobutadienes bearing two electron-donating and two electron-withdrawing groups.* These are stable in the absence of water.[129] An example is **69.** The stability of these compounds is generally attributed to the resonance shown, a type of resonance stabilization called the *push-pull effect,*[130] though it has been concluded from a photoelectron spectroscopy study that second-order bond fixation is more important.[131] An x-ray crystallographic study of **69** has shown[132] the ring to be a distorted square, with bond lengths of 1.46 Å and angles of 87 and 93 . The azacyclobutane **70** is also stable,[133] for similar reasons.



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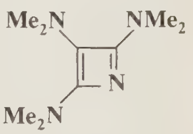

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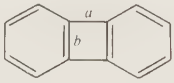
3. *Derivatives in which the cyclobutadiene system is fused to aromatic rings, the most important being biphenylene* (**71**).[134] However, annellation (p. 45) can result in an "empty" central ring



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[127] Irngartinger and Rodewald, *Angew. Chem. Int. Ed. Engl.* **13,** 740 (1974) [*Angew. Chem.* **86,** 783]. See also Delbaere, James, Nakamura, and Masamune, *J. Am. Chem. Soc.* **97,** 1973 (1975).

[128] Lauer, Müller, Schulte, Schweig, and Krebs, *Angew. Chem. Int. Ed. Engl.* **13,** 544 (1974) [*Angew. Chem.* **86,** 597]. See also Brown and Masamune, *Can. J. Chem.* **53,** 972 (1975); Lauer, Müller, Schulte, Schweig, Maier, and Alzérreca, *Angew. Chem. Int. Ed. Engl.* **14,** 172 (1975) [*Angew. Chem.* **87,** 194].

[129] Gompper, Seybold, *Angew. Chem. Int. Ed. Engl.* **7,** 824 (1968) [*Angew. Chem.* **80,** 804]; Neuenschwander and Niederhauser, *Chimia* **22,** 491 (1968); *Helv. Chim. Acta* **53,** 519 (1970); Gompper, Mensch, and Seybold, *Angew. Chem. Int. Ed. Engl.* **14,** 704 (1975) [*Angew. Chem.* **87,** 711]; Gompper, Kroner, Seybold, and Wagner, *Tetrahedron* **32,** 629 (1976).

[130] Manatt and Roberts, *J. Org. Chem.* **24,** 1336 (1959); Breslow, Kivelevich, Mitchell, Fabian, and Wendel, *J. Am. Chem. Soc.* **87,** 5132 (1965). For a discussion, see Gompper and Seybold, in Bergmann and Pullman, Ref. 33, pp. 215–226.

[131] Gompper, Holsboer, Schmidt, and Seybold, *J. Am. Chem. Soc.* **95,** 8479 (1973).

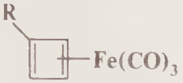
[132] Lindner and Gross, *Chem. Ber.* **107,** 598 (1974).

[133] Seybold, Jersak, and Gompper, *Angew. Chem. Int. Ed. Engl.* **12,** 847 (1973) [*Angew. Chem.* **85,** 918]; Wagner, *Angew. Chem. Int. Ed. Engl.* **12,** 848 (1973) [*Angew. Chem.* **85,** 920].

[134] For a review of biphenylenes, see Barton, in Snyder, Ref. 33, vol. 1, pp. 32–62. For a review of compounds in which only one aromatic ring is fused to a cyclobutadiene, see Cava, "Aromaticity," Ref. 33, pp. 163–176. See also Garratt, *Top. Nonbenzenoid Aromat. Chem.* **1,** 95–119 (1973), *Pure Appl. Chem.* **44,** 783–806 (1975); Vollhardt, Ref. 118.

here, and all the evidence is that this is the case. Thus the bond lengths[135] are *a*, 1.52 Å, and *b*, 1.43 Å.

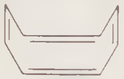
The unfused cyclobutadiene system is stable in complexes with metals[136] (see Chapter 3), but in these cases electron density is withdrawn from the ring by the metal and there is no aromatic quartet. In fact, these cyclobutadiene-metal complexes may be looked upon as systems containing an aromatic duet. The ring is square planar,[137] the compounds undergo aromatic substitution,[138] and nmr spectra of monosubstituted derivatives show that the C-2 and C-4 protons are equivalent.[138]



In summary, all the evidence to date indicates that **53**, **59**, and **60** and their simple derivatives are certainly not aromatic systems and very likely are antiaromatic.

Systems of Eight Electrons

Cyclooctatetraene[138a] (**54**) is not planar but tub-shaped.[139] Therefore it would be expected to be neither aromatic nor antiaromatic, since both these conditions require overlap of parallel *p* orbitals.



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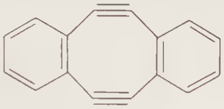

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The reason for the lack of planarity is that a regular octagon has angles of 135°, while sp^2 angles are most stable at 120°. To avoid the strain, the molecule assumes a nonplanar shape, in which orbital overlap is greatly diminished. Single- and double-bond distances in **54** are, respectively, 1.46 and 1.33 Å, which is just what is expected for a compound made up of four individual double bonds.[139] Also the reactivity is what would be expected for a linear polyene. However, the cyclooctadiendiyne **72** is a planar conjugated eight-electron system (the four extra triple-bond electrons do not participate), which nmr evidence shows to be antiaromatic.[140] There is evidence that part of the reason for lack of planarity in **54** itself is that a planar molecule would have to be antiaromatic.[141] Complexes of cyclooctatetraene with metals undergo typical aromatic substitution

[135] Fawcett and Trotter, *Acta Crystallogr.* **20,** 87 (1966); Yokozeki, Wilcox, and Bauer, *J. Am. Chem. Soc.* **96,** 1026 (1974).

[136] For example, see Criegee and Schröder, *Angew. Chem.* **71,** 70 (1959), *Justus Liebigs Ann. Chem.* **623,** 1 (1959); Blomquist and Maitlis, *J. Am. Chem. Soc.* **84,** 2329 (1962); Freedman, *J. Am. Chem. Soc.* **83,** 2194, 2195 (1961); Emerson, Watts, and Pettit, *J. Am. Chem. Soc.* **87,** 131 (1965). For reviews, see Pettit, *Pure Appl. Chem.* **17,** 253–272 (1968); Maitlis, *Adv. Organomet. Chem.* **4,** 95–143 (1966); Maitlis and Eberius, in Snyder, Ref. 33, vol. 2, pp. 359–409.

[137] Dodge and Schomaker, *Acta Crystallogr.* **18,** 614 (1965); *Nature* **186,** 798 (1960); Dunitz, Mez, Mills, and Shearer, *Helv. Chim. Acta* **45,** 647 (1962); Yannoni, Ceasar, and Dailey, *J. Am. Chem. Soc.* **89,** 2833 (1967).

[138] Fitzpatrick, Watts, Emerson, and Pettit, *J. Am. Chem. Soc.* **87,** 3255 (1965). For a discussion, see Pettit, *J. Organomet. Chem.* **100,** 205–217 (1975).

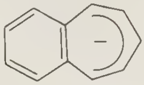
[138a] For a review of cyclooctatetraene chemistry, see Paquette, *Tetrahedron* **31,** 2855–2883 (1975).

[139] Bastiansen, Hedberg, and Hedberg, *J. Chem. Phys.* **27,** 1311 (1957).

[140] Wong, Garratt, and Sondheimer, *J. Am. Chem. Soc.* **96,** 5604 (1974); Destro, Pilati, and Simonetta, *J. Am. Chem. Soc.* **97,** 658 (1975).

[141] Figeys and Dralants, *Tetrahedron Lett.* 3901 (1971); Buchanan, *Tetrahedron Lett.* 665 (1972).

reactions[142] but are also nonplanar.[143] The cycloheptatrienyl anion (**41**) also has eight electrons but does not behave like an aromatic system.[72] The nmr spectrum of the benzocycloheptatrienyl anion (**73**) shows that, like **67** and **72**, this compound is antiaromatic.[144]



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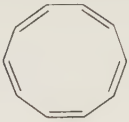

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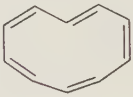

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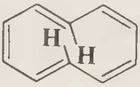
Systems of Ten Electrons[145]

There are three geometrically possible isomers of [10]annulene: the all-cis (**74**); the mono-trans (**75**); and the cis-trans-cis-cis-trans (**55**).[146] If Hückel's rule is to apply to these, they should be planar. But it is far from obvious that the molecules would adopt a planar shape, since in order to do so they must overcome considerable strain. For a regular decagon (**74**) the angles would have to be 144°, considerably larger than the 120° required for sp^2 angles. Some of this strain would also be present in **75**, but in **55** this kind of strain is eliminated, since all the angles are 120°. However, it was pointed out by Mislow[147] that the hydrogens in the 1 and 6 positions should interfere with each other and force the molecule out of planarity.



55

Compounds **74** and **75** have been prepared[148] as crystalline solids at −80°C. Nmr spectra show that all the hydrogens lie in the olefinic region and neither compound is aromatic. From ^{13}C and proton nmr spectra it has been deduced that neither is planar. Several derivatives of **74** and **75**, in which the ten-membered ring is fused to benzene rings, have also been prepared, and these likewise are nonaromatic and nonplanar.[149] However, that the angle strain is not insurmountable has been demonstrated by the preparation of several compounds which have large angles but are definitely planar 10-electron aromatic systems. Among these are the dianion **76**,

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[142] Johnson, Lewis, Parkins, and Randall, *Chem. Commun.* 595 (1969).

[143] Dickens and Lipscomb, *J. Chem. Phys.* **37**, 2084 (1962); Cotton, Davison, and Faller, *J. Am. Chem. Soc.* **88**, 4507 (1966).

[144] Staley and Orvedal, *J. Am. Chem. Soc.* **95**, 3382 (1973).

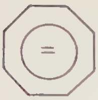
[145] For reviews, see Kemp-Jones and Masamune, *Top. Nonbenzenoid Aromat. Chem.* **1**, 121–157 (1973); Masamune and Darby, *Acc. Chem. Res.* **5**, 272–281 (1972); Burkoth and van Tamelen, in Snyder, Ref. 33, vol. 1, pp. 63–116; and Vogel, in "Aromaticity," Ref. 33, pp. 113–147.

[146] By the system given on p. 115, these compounds would be given the prefixes 0, 1, and 5, respectively.

[147] Mislow, *J. Chem. Phys.* **20**, 1489 (1952).

[148] Masamune, Hojo, Hojo, Bigam, and Rabenstein, *J. Am. Chem. Soc.* **93**, 4966 (1971). [10]Annulenes had previously been prepared, but it was not known which ones: van Tamelen and Burkoth, *J. Am. Chem. Soc.* **89**, 151 (1967); van Tamelen and Greeley, *Chem. Commun.* 601 (1971); van Tamelen, Burkoth, and Greeley, *J. Am. Chem. Soc.* **93**, 6120 (1971). See also Masamune and Seidner, *Chem. Commun.* 542 (1969); van Tamelen and Pappas, *J. Am. Chem. Soc.* **93**, 6111 (1971).

[149] Grohmann and Sondheimer, *J. Am. Chem. Soc.* **89**, 7119 (1967); Mitchell and Sondheimer, *J. Am. Chem. Soc.* **90**, 530 (1968).



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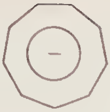

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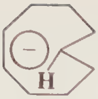

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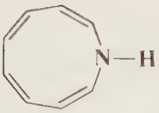

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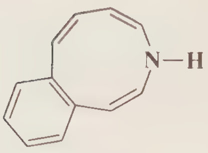
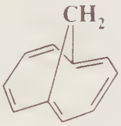


80

the anions **77** and **78**, and the azonine **79**.[150] **76**[151] has angles of about 135°, while **77**[152] and **79**[153] have angles of about 140°, which are not very far from 144°. The inner proton in **78**[154] (which is the mono-trans isomer of the all-cis **77**) is found far upfield in the nmr (13.5 τ). For **74** and **75**, the cost in strain energy to achieve planarity apparently outweighs the extra stability which would come from an aromatic ring. To emphasize the delicate balance between these factors, we add that the oxygen analog of **79** (oxonin) and the N-carbethoxy derivative of **79** are non-aromatic and nonplanar, while **79** itself is aromatic and planar.[155] Aromaticity in these cases seems to depend on the availability of the unshared pair. The azonine ring of the fused compound **80** is also nonaromatic.[156]

So far **55** has not been prepared, despite many attempts. However, there are various ways of avoiding the interference between the two inner protons. The approach which has been most successful involves bridging the 1 and 6 positions.[157] Thus, 1,6-methano[10]annulene (**81**)[158] and its oxygen and nitrogen analogs **82**[159] and **83**[160] have been prepared and are stable compounds which undergo aromatic substitution and are diatropic. For example, the perimeter protons of **81**



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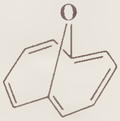

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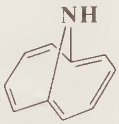

83

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[150] For reviews of **79** and other nine-membered rings containing four double bonds and a hetero atom (*heteronins*), see Anastassiou, *Acc. Chem. Res.* **5**, 281–288 (1972), *Top. Nonbenzenoid Aromat. Chem.* **1**, 1–27 (1973), *Pure Appl. Chem.* **44**, 691–749 (1975).

[151] Katz, *J. Am. Chem. Soc.* **82**, 3784, 3785 (1960); also see Katz, Yoshida, and Siew, *J. Am. Chem. Soc.* **87**, 4516 (1965); Noordik, van den Hark, Mooij, and Klaassen, *Acta Crystallogr. Sect. B* **30**, 833 (1974); Goldberg, Raymond, Harmon, and Templeton, *J. Am. Chem. Soc.* **96**, 1348 (1974).

[152] Katz and Garratt, *J. Am. Chem. Soc.* **86**, 5194 (1964); LaLancette and Benson, *J. Am. Chem. Soc.* **87**, 1941 (1965); Simmons, Chesnut, and LaLancette, *J. Am. Chem. Soc.* **87**, 982 (1965); Paquette, Ley, Meisinger, Russell, and Oku, *J. Am. Chem. Soc.* **96**, 5806 (1974); Radlick and Rosen, *J. Am. Chem. Soc.* **88**, 3461 (1966).

[153] Anastassiou and Gebrian, *Tetrahedron Lett.* 825 (1970).

[154] Boche, Martens, and Danzer, *Angew. Chem. Int. Ed. Engl.* **8**, 984 (1969) [*Angew. Chem.* **81**, 1003]. See also Anastassiou and Reichmanis, *Angew. Chem. Int. Ed. Engl.* **13**, 728 (1974) [*Angew. Chem.* **86**, 784]; Boche and Bieberbach, *Tetrahedron Lett.* 1021 (1976).

[155] Anastassiou and Cellura, *Chem. Commun.* 903 (1969); Anastassiou and Gebrian, *J. Am. Chem. Soc.* **91**, 4011 (1969); Anastassiou, Cellura, and Gebrian, *Chem. Commun.* 375 (1970); Anastassiou, Eachus, Cellura, and Gebrian, *Chem. Commun.* 1133 (1970); Anastassiou and Yamamoto, *J. Chem. Soc., Chem. Commun.* 286 (1972); Chiang, Paul, Anastassiou, and Eachus, *J. Am. Chem. Soc.* **96**, 1636 (1974).

[156] Anastassiou and Reichmanis, *Angew. Chem. Int. Ed. Engl.* **13**, 404 (1974) [*Angew. Chem.* **86**, 410]. See also Anastassiou and Reichmanis, *J. Chem. Soc., Chem. Commun.* 149 (1975).

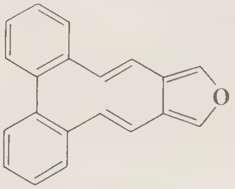
[157] For reviews of bridged [10]- and [14]annulenes, see Vogel, *Chimia* **22**, 21–32 (1968); and Vogel and Günther, *Angew. Chem. Int. Ed. Engl.* **6**, 385–401 (1967) [*Angew. Chem.* **79**, 429–446].

[158] Vogel and Roth, *Angew. Chem. Int. Ed. Engl.* **3**, 228 (1964) [*Angew. Chem.* **76**, 145]; Vogel and Böll, *Angew. Chem. Int. Ed. Engl.* **3**, 642 (1964) [*Angew. Chem.* **76**, 784]; Vogel, Böll, and Biskup, *Tetrahedron Lett.* 1569 (1966).

[159] Vogel, Biskup, Pretzer, and Böll, *Angew. Chem. Int. Ed. Engl.* **3**, 642 (1964) [*Angew. Chem.* **76**, 785], Sondheimer and Shani, *J. Am. Chem. Soc.* **84**, 3168 (1964); Shani and Sondheimer, *J. Am. Chem. Soc.* **89**, 6310 (1967); Bailey and Mason, *Chem. Commun.* 1039 (1967).

[160] Vogel, Pretzer, and Böll, *Tetrahedron Lett.* 3613 (1965). See also the first paper of Ref. 159.

are found at 2.7 to 3.1 τ, while the bridge protons are at 10.5 τ. The crystal structure of the 2-carboxylic acid derivative of **81** shows that the perimeter is nonplanar, but the bond distances are in the range 1.38 to 1.42 Å.[161] Although **55** itself has not been prepared, a fused derivative (**84**) has been made.[162] However, the molecule is not diatropic. Further emphasizing the correctness of Mislow's analysis is the fact that there are two stereoisomers of **84**: one has the two inner hydrogens on the same side of the ring and the other on opposite sides.

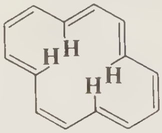


84

It has therefore been amply demonstrated that a closed loop of 10 electrons is an aromatic system, although some molecules which could conceivably have such a system are distorted too much from planarity to be aromatic.

Systems of More than Ten Electrons: $4n + 2$ Electrons[163]

Extrapolating from the discussion of [10]annulene, we expect larger $4n + 2$ systems to be aromatic (if planar) at least up to about [22]- or [26]annulene (p. 54). Mislow[147] predicted that [14]annulene (**85**) would possess the same type of interference as **55**, though in lesser degree, and this is borne out by experiment. **85** is aromatic (it is diatropic: inner protons at 10.0 τ, outer protons at 2.4 τ),[164] but it is completely destroyed by light and air in 1 day. X-ray analysis shows that although there are no alternating single and double bonds, the molecule is not planar.[165] However, a number



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[161] Dobler and Dunitz, *Helv. Chim. Acta* **48**, 1429 (1965).

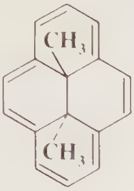
[162] Bindra, Elix, and Sargent, *Aust. J. Chem.* **22**, 1449 (1969). These workers also prepared another fused derivative which is also nonaromatic.

[163] For reviews of annulenes, with particular attention to their nmr spectra, see Sondheimer, *Acc. Chem. Res.* **5**, 81–91 (1972), *Pure Appl. Chem.* **28**, 331–353 (1971), *Proc. R. Soc. London. Ser. A* **297**, 173–204 (1967); Skrabal, *MTP Int. Rev. Sci.: Org. Chem. Ser. One*, **3**, 237–269 (1973); Sondheimer, Calder, Elix, Gaoni, Garratt, Grohmann, di Maio, Mayer, Sargent, and Wolovsky, in "Aromaticity," Ref. 33, pp. 75–107; and Haddon, Haddon, and Jackman, Ref. 39.

[164] Gaoni, Melera, Sondheimer, and Wolovsky, *Proc. Chem. Soc.* 397 (1964).

[165] Bregman, *Nature* **194**, 679 (1962); Chiang and Paul, *J. Am. Chem. Soc.* **94**, 4741 (1972). Another 14-electron system is the dianion of [12]annulene, which is also apparently aromatic though not planar: Oth and Schröder, *J. Chem. Soc. B* 904 (1971). See also Garratt, Rowland, and Sondheimer, *Tetrahedron* **27**, 3157 (1971); Oth, Müllen, Königshofen, Mann, Sakata, and Vogel, *Angew. Chem. Int. Ed. Engl.* **13**, 284 (1974) [*Angew. Chem.* **86**, 232]. For other 14-electron aromatic systems, see Anastassiou and Elliott, *J. Am. Chem. Soc.* **96**, 5257 (1974); Anastassiou, Elliott, and Reichmanis, *J. Am. Chem. Soc.* **96**, 7823 (1974); Wife and Sondheimer, *J. Am. Chem. Soc.* **97**, 640 (1975); Howes and Sondheimer, *J. Am. Chem. Soc.* **94**, 8261 (1972); Ogawa, Kubo, and Saikachi, *Tetrahedron Lett.* 4859 (1971); Oth, Smith, Prange, and Schröder, *Angew. Chem. Int. Ed. Engl.* **12**, 327 (1973) [*Angew. Chem.* **85**, 352]; and Oth, Müllen, Königshofen, Wassen, and Vogel, *Helv. Chim. Acta* **57**, 2387 (1974).

of stable bridged [14]annulenes have been prepared;[166] e.g., *trans*-15,16-dimethyldihydropyrene (**86**),[167] *syn*-1,6:8,13-bisoxido[14]annulene (**87**),[168] *syn*- and *anti*-1,6:8,13-bismethano[14]annulene (**88A** and **88B**),[169] and 1,6:8,13-propano[14]annulene (**89**).[170] The dihydropyrene **86** (and its



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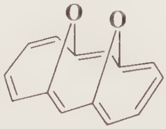

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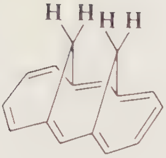

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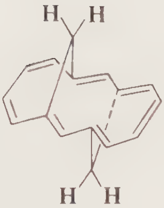

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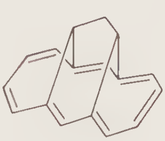


89

diethyl and dipropyl homologs) is undoubtedly aromatic: the π perimeter is approximately planar,[171] the bond distances are all 1.39 to 1.40 Å, and the molecule undergoes aromatic substitution[167] and is diatropic. The outer protons are found at 1.33 to 1.86 τ, while the CH_3 protons are at 14.25 τ. A comparison of the τ values of **85** and **86** would seem to indicate that the separation between inner and outer protons decreases with decreasing planarity, though the molecules are not quite comparable. **88A**, **87**, and **89** are also diatropic[172] (e.g., the bridge protons of **89** are found far upfield in the nmr spectrum[173]), although x-ray crystallography indicates that the π periphery in at least the latter two compounds is not quite planar.[174] **87** undergoes aromatic substitution.[168] However, **88B**, in which the geometry of the molecule greatly reduces overlap of the *p* orbitals at the bridgehead positions with adjacent *p* orbitals, is definitely not aromatic, as shown by nmr spectra[169] and x-ray crystallography, from which bond distances of 1.33 to 1.36 Å for the double bonds and 1.44 to 1.49 Å for the single bonds have been obtained.[175] In contrast, in **87** and **89**, all the bond distances are $\sim$1.38 to 1.40 Å.[174]

[166] For a review, see Vogel, *Pure Appl. Chem.* **28**, 355–377 (1971).

[167] Boekelheide and Phillips, *J. Am. Chem. Soc.* **89**, 1695 (1967); Phillips, Molyneux, Sturm, and Boekelheide, *J. Am. Chem. Soc.* **89**, 1704 (1967); Boekelheide and Miyasaka, *J. Am. Chem. Soc.* **89**, 1709 (1967). For reviews of dihydropyrenes see Boekelheide, *Top. Nonbenzoid Arom. Chem.* **1**, 47–79 (1973), *Pure Appl. Chem.* **44**, 807–828 (1975).

[168] Vogel, Biskup, Vogel, and Günther, *Angew. Chem. Int. Ed. Engl.* **5**, 734 (1966) [*Angew. Chem.* **78**, 755].

[169] Vogel, Haberland, and Günther, *Angew. Chem. Int. Ed. Engl.* **9**, 513 (1970) [*Angew. Chem.* **82**, 510]; Vogel, Sombroek, and Wagemann, *Angew. Chem. Int. Ed. Engl.* **14**, 564 (1975) [*Angew. Chem.* **87**, 591].

[170] Vogel, Vogel, Kübbeler, and Sturm, *Angew. Chem. Int. Ed. Engl.* **9**, 514 (1970) [*Angew. Chem.* **82**, 512].

[171] Hanson, *Acta Crystallogr.* **18**, 599 (1965), **23**, 476 (1967).

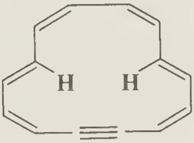
[172] As are several other similarly bridged [14]annulenes: see, for example, Vogel and Reel, *J. Am. Chem. Soc.* **94**, 4388 (1972); Batich, Heilbronner, and Vogel, *Helv. Chim. Acta* **57**, 2288 (1974); Flitsch and Peeters, *Chem. Ber.* **106**, 1731 (1973).

[173] Bremser, Roberts, and Vogel, *Tetrahedron Lett.* 4307 (1969); Alscher, Bremser, Cremer, Günther, Schmickler, Sturm, and Vogel, *Chem. Ber.* **108**, 640 (1975).

[174] Ganis and Dunitz, *Helv. Chim. Acta* **50**, 2369 (1967); Casalone, Gavezzotti, Mugnoli, and Simonetta, *Angew. Chem. Int. Ed. Engl.* **9**, 519 (1970) [*Angew. Chem.* **82**, 516].

[175] Gramaccioli, Mimun, Mugnoli, and Simonetta, *Chem. Commun.* 796 (1971).

Another way of eliminating the hydrogen interferences of [14]annulene is to introduce one or more triple bonds into the system, as in dehydro[14]annulene (**90**).[175a] All five known dehydro[14]annulenes are diatropic. **90** can be nitrated or sulfonated.[176] The extra electrons of the triple bond do not form part of the aromatic system but simply exist as a localized π bond.



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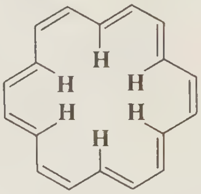


91

[18]Annulene (**91**) is diatropic:[177] the 12 outer protons are found at about $\tau = 1$ and the 6 inner protons at about $\tau = 13$. X-ray crystallography[178] shows that it is nearly planar, so that interference of the inner hydrogens is not important in annulenes this large. **91** is reasonably stable, being distillable at reduced pressures, and undergoes aromatic substitutions.[179] The C—C bond distances are not equal, but they do not alternate. There are 12 inner bonds of about 1.38 Å and 6 outer bonds of about 1.42 Å.[178] **91** has been estimated to have a resonance energy of about 37 kcal/mol, similar to that of benzene.[180] Most of the known dehydro[18]annulenes are also diatropic.[181] The dianions of open and bridged [16]annulenes are also 18-electron aromatic systems.[182]

[22]Annulene[183] and dehydro[22]annulene[184] are also diatropic. In the latter compound there are 13 outer protons at 1.55 to 3.75 τ and 7 inner protons at 6.55 to 9.30 τ. Some aromatic bridged [18]- and [22]annulenes are also known.[185] [26]Annulene has not yet been prepared, but while a tridehydro[26]annulene is not diatropic,[186] two monodehydro[26]annulenes are aromatic.[187]

[175a] For a review of dehydroannulenes, see Nakagawa, *Top. Nonbenzenoid Aromat. Chem.* **1**, 191–219 (1973).

[176] Gaoni and Sondheimer, *J. Am. Chem. Soc.* **86**, 521 (1964).

[177] Jackman, Sondheimer, Amiel, Ben-Efraim, Gaoni, Wolovsky, and Bothner-By, *J. Am. Chem. Soc.* **84**, 4307 (1962); Gilles, Oth, Sondheimer, and Woo, *J. Chem. Soc. B* 2177 (1971).

[178] Bregman, Hirshfeld, Rabinovich, and Schmidt, *Acta Crystallogr.* **19**, 227 (1965); Hirshfeld and Rabinovich, *Acta Crystallogr.* **19**, 235 (1965).

[179] Calder, Garratt, Longuet-Higgins, Sondheimer, and Wolovsky, *J. Chem. Soc. C* 1041 (1967); Woo and Sondheimer, *Tetrahedron* **26**, 3933 (1970).

[180] Oth, Bünzli, and de Julien de Zélicourt, *Helv. Chim. Acta* **57**, 2276 (1974).

[181] Okamura and Sondheimer, *J. Am. Chem. Soc.* **89**, 5991 (1967); Sondheimer, Ref. 163. For two that are not, see Endo, Sakata, and Misumi, *Bull. Chem. Soc. Jpn.* **44**, 2465 (1971).

[182] Oth, Anthoine, and Gilles, *Tetrahedron Lett.* 6265 (1968); Mitchell and Boekelheide, *Chem. Commun.* 1557 (1970); Oth, Baumann, Gilles, and Schröder, *J. Am. Chem. Soc.* **94**, 3498 (1972). See also Beeby and Sondheimer, *J. Am. Chem. Soc.* **94**, 2128 (1972); Griffiths and Sondheimer, *J. Am. Chem. Soc.* **91**, 7518 (1969); Brown and Sondheimer, *Angew. Chem. Int. Ed. Engl.* **13**, 337 (1974) [*Angew. Chem.* **86**, 346]; Cresp and Sargent, *J. Chem. Soc., Chem. Commun.* 101 (1974); Schröder, Plinke, Smith, and Oth, *Angew. Chem. Int. Ed. Engl.* **12**, 325 (1973) [*Angew. Chem.* **85**, 350].

[183] McQuilkin, Metcalf, and Sondheimer, *Chem. Commun.* 338 (1971).

[184] McQuilkin and Sondheimer, *J. Am. Chem. Soc.* **92**, 6341 (1970); Iyoda and Nakagawa, *J. Chem. Soc., Chem. Commun.* 1003 (1972). See also Iyoda, Miyazaki, and Nakagawa, *J. Chem. Soc., Chem. Commun.* 431 (1972).

[185] For examples, see Broadhurst, Grigg, and Johnson, *J. Chem. Soc., Perkin Trans. 1* 2111 (1972); Lawson, DuVernet, and Boekelheide, *J. Am. Chem. Soc.* **95**, 956 (1973). Many porphyrin molecules are 18-electron systems which are diatropic: Kowalsky and Cohn, *Annu. Rev. Biochem.* **33**, 481–518 (1964), pp. 499–502; Johnson, *Pure Appl. Chem.* **28**, 195–217 (1971); Bonnett, Gale, and Stephenson, *J. Chem. Soc. C* 1168 (1967). For a review of resonance energies of porphyrins, see George, *Chem. Rev.* **75**, 85–111 (1975).

[186] Leznoff and Sondheimer, *J. Am. Chem. Soc.* **89**, 4247 (1967).

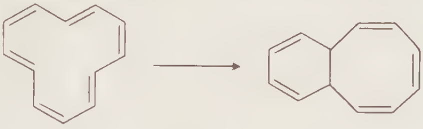
[187] Metcalf and Sondheimer, *J. Am. Chem. Soc.* **93**, 5271 (1971); Iyoda and Nakagawa, *Tetrahedron Lett.* 4253 (1972).

Furthermore, the dianion of 1,3,7,9,13,15,19,21-octadehydro[24]annulene[188] is another 26-electron system which is aromatic. A tetra-*t*-butyldidehydro[30]annulene has been reported to be diatropic,[189] but a number of other dehydro and bridged [30]annulenes have been prepared and show no ring currents.[190]

There is now no doubt that $4n + 2$ systems of up to 22 electrons are aromatic if they can be planar, although **84** and **88B**, among others, demonstrate that not all such systems are in fact planar enough for aromaticity. The cases of **85**, **87**, and **89** prove that absolute planarity is not required for aromaticity, but that aromaticity decreases with decreasing planarity. Beyond 22 electrons there is still doubt about where aromaticity ends. Dewar and Gleicher predicted that the largest aromatic system should have 22 electrons,[98] but the reports of aromaticity in at least three 26-electron compounds and a 30-electron compound indicate that the limit is greater than 22.

Systems of More than Ten Electrons: 4*n* Electrons[163]

As we have seen (p. 55), these systems are expected to be not only nonaromatic but actually antiaromatic. The chief criterion for antiaromaticity in annulenes is the presence of a *paramagnetic* ring current,[191] which causes protons on the outside of the ring to be shifted *upfield* while any inner protons are shifted *downfield*, in sharp contrast to a diamagnetic ring current, which causes shifts in the opposite directions. Compounds which sustain a paramagnetic ring current are called *paratropic*: we have already seen such behavior in certain four- and eight-electron systems. As with aromaticity, we should expect that antiaromaticity will be at a maximum when the molecule is planar and when bond distances are equal. The [12]annulene **92**[192] (this isomer is called [12]-21-annulene)[193] has been prepared. In solution this molecule undergoes rapid conformational mobility (as do many other annulenes),[194] so that above a certain temperature, in this case −150 C, all protons are magnetically equivalent. However, at −170°C the mobility is greatly slowed, and at this temperature the three inner protons are found at about 2 τ while the nine outer protons are at about 4 τ. **92** suffers from hydrogen interference and is certainly not planar. It is very unstable, and above −50°C rearranges to **93**. Several bridged and dehydro[12]-annulenes are known, e.g., 5-bromo-1,9-didehydro[12]annulene (**94**),[195] cycl[3.3.3]azine (**95**),[196] and 1,7-methano[12]annulene (**96**).[197] In these compounds not only is hydrogen interference



92 **93**

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[188] McQuilkin, Garratt, and Sondheimer, *J. Am. Chem. Soc.* **92**, 6682 (1970).

[189] Iyoda and Nakagawa, *Tetrahedron Lett.* 4743 (1973).

[190] Sondheimer and Gaoni, *J. Am. Chem. Soc.* **84**, 3520 (1962); Sondheimer and Wolovsky, *J. Am. Chem. Soc.* **84**, 260 (1962); Elix, *Aust. J. Chem.* **22**, 1951 (1969).

[191] Pople and Untch, *J. Am. Chem. Soc.* **88**, 4811 (1966); Longuet-Higgins, in "Aromaticity," Ref. 33, pp. 109–111.

[192] Oth, Röttele, and Schröder, *Tetrahedron Lett.* 61 (1970); Oth, Gilles, and Schröder, *Tetrahedron Lett.* 67 (1970).

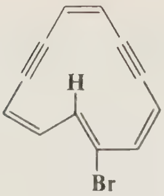
[193] The 21 is a prefix which indicates the stereochemistry. See p. 115 for an explanation.

[194] For a review of conformational mobility in annulenes, see Oth, *Pure Appl. Chem.* **25**, 573–622 (1971).

[195] Untch and Wysocki, *J. Am. Chem. Soc.* **89**, 6386 (1967).

[196] Farquhar and Leaver, *Chem. Commun.* 24 (1969). See also Paudler and Stephan, *J. Am. Chem. Soc.* **92**, 4468 (1970); Trost, Bright, Frihart, and Brittelli, *J. Am. Chem. Soc.* **93**, 737 (1971); Kinson and Trost, *J. Am. Chem. Soc.* **93**, 3823 (1971); Atwood, Hrncir, Wong, and Paudler, *J. Am. Chem. Soc.* **96**, 6132 (1974).

[197] Vogel, Königshofen, Müllen, and Oth, *Angew. Chem. Int. Ed. Engl.* **13**, 281 (1974) [*Angew. Chem.* **86**, 229]. See also Vogel, Mann, Sakata, Müllen, and Oth, *Angew. Chem. Int. Ed. Engl.* **13**, 283 (1974) [*Angew. Chem.* **86**, 231].



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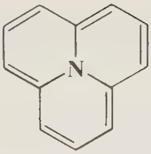

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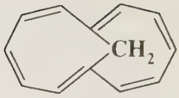
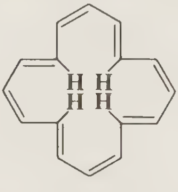


96

prevented but also conformational mobility. In **95** and **96** the bridge prevents conformational changes, while in **94** the bromine atom is too large to be found inside the ring. Nmr spectra show that all three compounds are paratropic, the inner proton of **94** being found at $-6.4\ \tau$.[198]

The results for [16]annulene are similar. The compound was synthesized in two different ways,[199] both of which gave [16]-85-annulene (**97**), which in solution is in equilibrium with [16]-91-annulene (see p. 115). Above $-50°C$ there is conformational mobility, resulting in the magnetic equivalence of all protons, but at $-130°C$ the compound is clearly paratropic: there are four protons at $-0.56\ \tau$ and twelve at $4.67\ \tau$. In the solid state, where the compound exists entirely as **97**, x-ray crystallography[200] showed that the molecules are nonplanar with almost complete bond alternation: the single bonds are 1.44 to 1.47 Å, and the double bonds 1.31 to 1.35 Å. A number of dehydro and bridged [16]annulenes have also been shown to be paratropic,[201] as have [20]annulene[202] and [24]annulene.[203]



97

As with aromaticity, antiaromaticity is predicted to end at about [24]annulene, but so far there is little evidence on this question, though a tetraaza[32]annulene and a bridged [36]annulene have been reported to be *atropic*,[204] i.e., neither diatropic nor paratropic.

The fact that many $4n$ systems are paratropic even though they may be nonplanar and have unequal bond distances indicates that if planarity were enforced, the ring currents might be even greater. That this is true is dramatically illustrated by the nmr spectrum of the dianion of **86** (and its diethyl and dipropyl homologs).[205] We may recall that in **86**, the outer protons were found

[198] For another paratropic 12-electron system, see Staley and Orvedal, *J. Am. Chem. Soc.* **95**, 3384 (1973).

[199] Schröder and Oth, *Tetrahedron Lett.* 4083 (1966); Sondheimer and Gaoni, *J. Am. Chem. Soc.* **83**, 4863 (1961); Oth and Gilles, *Tetrahedron Lett.* 6259 (1968); Calder, Gaoni, and Sondheimer, *J. Am. Chem. Soc.* **90**, 4946 (1968). For monosubstituted [16]annulenes, see Schröder, Kirsch, and Oth, *Chem. Ber.* **107**, 460 (1974).

[200] Johnson, Paul, and King, *J. Chem. Soc. B* 643 (1970).

[201] For example, see Calder, Garratt, and Sondheimer, *J. Am. Chem. Soc.* **90**, 4954 (1968); Murata, Nakazawa, and Okazaki, *Tetrahedron Lett.* 3269 (1970); Murata, Okazaki, and Nakazawa, *Angew. Chem. Int. Ed. Engl.* **10**, 576 (1971) [*Angew. Chem.* **83**, 623]; Ogawa, Kubo, and Tabushi, *Tetrahedron Lett.* 361 (1973); Nakatsuji, Morigaki, Akiyama, and Nakagawa, *Tetrahedron Lett.* 1233 (1975); and Elix, Ref. 190.

[202] Metcalf and Sondheimer, *J. Am. Chem. Soc.* **93**, 6675 (1971). See also Oth, Woo, and Sondheimer, *J. Am. Chem. Soc.* **95**, 7337 (1973); Beeby and Sondheimer, *Angew. Chem. Int. Ed. Engl.* **12**, 411 (1973) [*Angew. Chem.* **85**, 406]; Nakatsuji and Nakagawa, *Tetrahedron Lett.* 3927 (1975).

[203] Calder and Sondheimer, *Chem. Commun.* 904 (1966). See also Stöckel and Sondheimer, *J. Chem. Soc., Perkin Trans. 1* 355 (1972).

[204] Yamamoto and Sondheimer, *Tetrahedron* **30**, 4229 (1974); Elix, Ref. 190.

[205] Mitchell, Klopfenstein, and Boekelheide, *J. Am. Chem. Soc.* **91**, 4931 (1969).

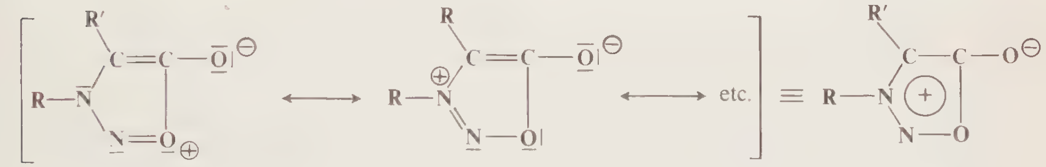
at 1.33 to 1.86 τ with the methyl protons at 14.25 τ. For the dianion, however, which is forced to have approximately the same planar geometry but now has 16 electrons, the outer protons are shifted to about 13 τ, while the methyl protons are found at about −11 τ, a shift of about 25 τ! We have already seen where the converse shift was made, when [16]annulenes which were antiaromatic were converted to 18-electron dianions which were aromatic.[182] In these cases, the changes in nmr chemical shifts were almost as dramatic.

We can therefore conclude that in 4*n* systems up to at least 24 electrons antiaromaticity will be at a maximum where the molecule is constrained to be planar (as in **59** or the dianion of **86**) but, where possible, the molecule will distort itself from planarity and avoid equal bond distances in order to reduce antiaromaticity. In some cases, such as cyclooctatraene, the distortion and bond alternation are great enough for antiaromaticity to be avoided completely, but in other cases, e.g., **92** or **97**, it is apparently not possible for the molecules to avoid at least some *p*-orbital overlap, and such molecules show paramagnetic ring currents and other evidence of antiaromaticity, though the degree of antiaromaticity is not as great as in such molecules as **59** or the dianion of **86**.

Other Aromatic Compounds

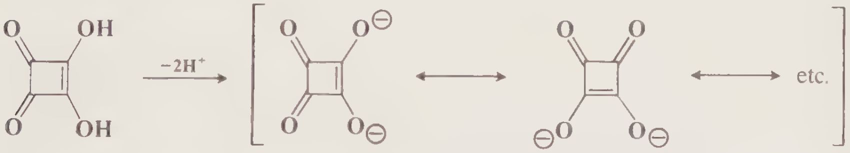
We shall briefly mention four other types of aromatic compounds.

1. *Mesoionic compounds*[206] cannot be satisfactorily represented by Lewis forms not involving charge separation. Nearly all known mesoionic compounds contain five-membered rings. The most common are the *sydnones* (**98**), stable aromatic compounds which undergo aromatic substitution when R′ is hydrogen.[207]



98

2. *The dianion of squaric acid*[208]



The stability of this system is illustrated by the fact that the pK_1 of squaric acid is about 1.5 and the pK_2 about 3.5,[209] which means that even the second proton is given up much more readily than the proton of acetic acid, for example. The analogous five- and six-membered ring compounds are also known.[210]

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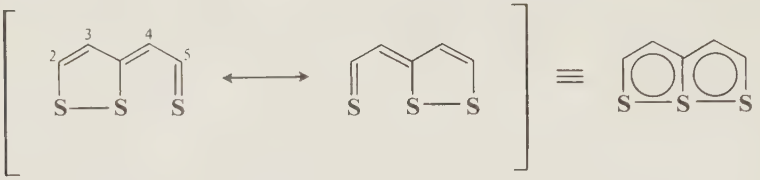
[206] For reviews, see Ohta and Kato, in Snyder, Ref. 33, vol. 1, pp. 117–248; Noël, *Bull. Soc. Chim. Fr.* 173–177 (1964); Stewart, *Chem. Rev.* **64,** 129–147 (1964); Baker and Ollis, *Q. Rev., Chem. Soc.* **11,** 15–29 (1957).

[207] For example, see Tien and Hunsberger, *J. Am. Chem. Soc.* **83,** 178 (1961); and Yashunskii, Vasil'eva, and Sheinker, *J. Gen. Chem. USSR* **29,** 2680 (1959).

[208] West and Powell, *J. Am. Chem. Soc.* **85,** 2577 (1963); Ito and West, *J. Am. Chem. Soc.* **85,** 2580 (1963).

[209] Ireland and Walton, *J. Phys. Chem.* **71,** 751 (1967); MacDonald, *J. Org. Chem.* **33,** 4559 (1968).

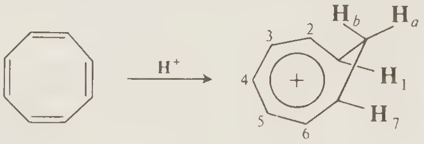
3. In *thiothiophthenes*[211] **99** (also called thiathiophthenes and 1,6,6*a*-S^{IV}-trithiapentalenes) each



99

canonical form has a pair of sulfur atoms with no bond at all. Nevertheless, in the parent compound and in the symmetrical 2,5-dimethyl derivative, the two sulfur-sulfur distances are equal, and the three sulfur atoms are in a straight line.[212] Furthermore, nmr chemical shifts indicate the presence of a diamagnetic ring current.[213] However, other symmetrical derivatives of **99** (e.g., the 2,5-diphenyl and 3,4-diphenyl compounds)[214] have been shown to have unequal S—S distances, and it has been argued that the system is not aromatic and that the two structures are better described as being in tautomeric equilibrium (p. 71) than as canonical forms.[215] If the system is aromatic, it is a naphthalene type of system with a total of ten π electrons.[216]

4. *Homoaromaticity.* When cyclooctatetraene is dissolved in concentrated H_2SO_4, a proton adds to one of the double bonds to form the homotropylium ion **100**.[217] In this species an



100

aromatic sextet is spread over seven carbons, as in the tropylium ion. The eighth carbon is an sp^3 carbon and so cannot take part in the aromaticity. Nmr spectra show the presence of a diatropic ring current: H_b is found at $\tau = 10.7$; H_a at 4.9 τ; H_1 and H_7 at 3.6 τ, and H_2 to H_6 at 1.5 τ. This ion is an example of a *homoaromatic* compound, which may be defined as a compound which contains one or more[218] sp^3-hybridized carbon atoms in an otherwise conjugated cycle.[219] In order for the orbitals to overlap most effectively so as to close a loop, the sp^3 atoms are forced to lie almost vertically above the plane of the aromatic atoms. In **100**, H_b is directly above the aromatic sextet and so is shifted far upfield in the nmr. Homoaromatic compounds of two and ten electrons are also known.

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[210] For reviews, see West and Niu, in Snyder, Ref. 33, vol. 1, pp. 311–345, and in Zabicky, "The Chemistry of the Carbonyl Group," vol. 2, pp. 241–275, John Wiley & Sons, Inc., New York, 1970; and Maahs and Hegenberg, *Angew. Chem. Int. Ed. Engl.* **5**, 888–893 (1966) [*Angew. Chem.* **78**, 927–931].

[211] For reviews, see Klingsberg, *Q. Rev., Chem. Soc.* **23**, 537–551 (1969); Salmond, *Q. Rev., Chem. Soc.* **22**, 253–275 (1968), pp. 272–275; Lozac'h, *Adv. Heterocycl. Chem.* **13**, 161–234 (1971); and Lozac'h, in Janssen, "Organosulfur Chemistry," pp. 179–201, Interscience Publishers, Inc., New York, 1967.

[212] Hansen and Hordvik, *Acta Chem. Scand.* **27**, 411 (1973); Shen and Hedberg, *J. Am. Chem. Soc.* **96**, 289 (1974); Bezzi, Mammi, and Garbuglio, *Nature* **182**, 247 (1958); Bezzi, Garbuglio, Mammi, and Traverso, *Gazz. Chim. Ital.* **88**, 1226 (1958); Leung and Nyburg, *Chem. Commun.* 137 (1969).

[213] Pfister-Guillouzo and Lozac'h, *Bull. Soc. Chim. Fr.* 3254 (1964); Dingwall, McKenzie, and Reid, *J. Chem. Soc. C* 2543 (1968).

[214] Johnson and Paul, *Chem. Commun.* 1014 (1969); Hordvik, *Acta Chem. Scand.* **25**, 1583 (1971); Johnson, Llaguno, and Paul, *J. Chem. Soc., Perkin Trans. 2* 234 (1976).

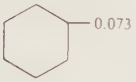
[215] Leaver and McKinnon, *Chem. Ind.* (*London*) 461 (1964); Gleiter, Schmidt, and Behringer, *Chem. Commun.* 525 (1971).

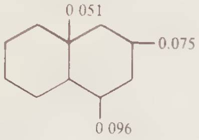
[216] Kroner and Proch, *Tetrahedron Lett.* 2537 (1972); Clark and Kilcast, *Tetrahedron* **27**, 4367 (1971).

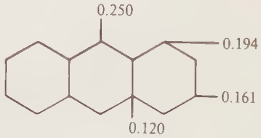
[217] Rosenberg, Mahler, and Pettit, *J. Am. Chem. Soc.* **84**, 2842 (1962); Keller and Pettit, *J. Am. Chem. Soc.* **88**, 604, 606 (1966); Winstein, Kaesz, Kreiter, and Friedrich, *J. Am. Chem. Soc.* **87**, 3267 (1965); Winstein, Kreiter, and Brauman, *J. Am. Chem. Soc.* **88**, 2047 (1966).

Free Valence

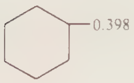
On p. 29 the concept of bond order was discussed. A closely related concept is that of free valence.[220] In the valence-bond method the free valence at a carbon is determined by adding the weights of all the structures in which a Dewar bond ends at that carbon. Free valences at various aromatic positions are shown:

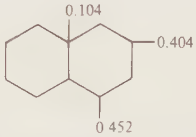


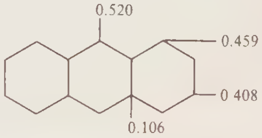




In the molecular-orbital method, free valence is defined as 1.732 minus the sum of the molecular-orbital bond orders to all carbons directly bound.[221] Molecular-orbital free valences for the same compounds are:







The absolute values of the two methods are not comparable, but the trends are similar in both. The free valence is supposed to be a measure of the ease of attack at a given position. Both methods are in accord with the fact that the 9 position of anthracene is the most reactive and that it is more reactive than any benzene carbon or any position of naphthalene. For free-valence values for other compounds, see Ref. 220.

HYPERCONJUGATION

All of the delocalization so far discussed involves π electrons. Another type, called *hyperconjugation*, involves σ electrons.[222] When a carbon attached to at least one hydrogen is attached to an unsaturated atom or one with an unshared orbital, canonical forms such as **101** can be drawn.

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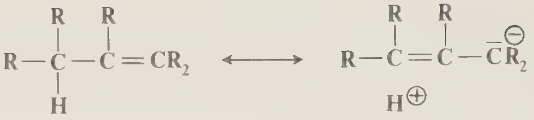
[218] If a compound contains two such atoms it is *bishomoaromatic*; if three, *trishomoaromatic*, etc. For examples of bishomotropylium ions, see Ahlberg, Harris, Roberts, Warner, Seidl, Sakai, Cook, Diaz, Dirlam, Hamberger, and Winstein, *J. Am. Chem. Soc.* **94**, 7063 (1972); Paquette, Broadhurst, Warner, Olah, and Liang, *J. Am. Chem. Soc.* **95**, 3386 (1973).

[219] For reviews, see Winstein, *Q. Rev., Chem. Soc.* **23**, 141–176 (1969); "Aromaticity," Ref. 33, pp. 5–45; and in Olah and Schleyer, "Carbonium Ions," John Wiley & Sons, Inc., vol. 3, 1972, the reviews by Story and Clark, 1007–1098, pp. 1073–1093; and Winstein, 965–1005. (The latter is a reprint of the *Q. Rev., Chem. Soc.* review mentioned above.)

[220] For reviews, see Greenwood and McWeeny, *Adv. Phys. Org. Chem.* **4**, 73–145 (1966); and Pullman and Pullman, *Prog. Org. Chem.* **4**, 31–71 (1958). For values of free valences for many compounds, see Coulson and Streitwieser, Ref. 13.

[221] 1.732 is chosen as the value for a "completely bonded" carbon. Anything less is the free part of the valence.

[222] For reviews, see Baker, "Hyperconjugation," Oxford University Press, Fair Lawn, N.J., 1952; Crawford, *Q. Rev., Chem. Soc.* **3**, 226–244 (1949); symposia in *Tetrahedron* **5**, 107–274 (1959), **17**, 125–289 (1962); and Dewar, "Hyperconjugation," The Ronald Press Company, New York, 1962.



$$\mathrm{R-\underset{H}{\overset{R}{C}}-\overset{R}{C}=CR_2 \longleftrightarrow R-\underset{H^{\oplus}}{\overset{R}{C}}=\overset{R}{C}-\overset{\ominus}{\underline{C}}R_2}$$

101

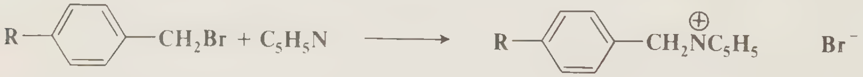
In such canonical forms there is no bond at all between the carbon and hydrogen, and this type of resonance is often called *no-bond resonance*. The hydrogen does not leave (because **101** does not exist but is only a canonical form which contributes to the actual structure of the molecule). The effect of **101** on the actual molecule is that the electrons in the C—H bond are closer to the carbon than they would be if **101** did not contribute at all.

Hyperconjugation in the above case may be regarded as an overlap of the σ orbital of the C—H bond and the π orbital of the C—C bond, analogous to the π-π-orbital overlap previously considered. As might be expected, those who reject the idea of resonance in butadiene (p. 33) believe it even less likely when it involves no-bond structures.

The concept of hyperconjugation arose from the discovery of apparently anomalous electron-release patterns for alkyl groups. By the field effect alone, the order of electron release for simple alkyl groups connected to an unsaturated system is *t*-butyl > isopropyl > ethyl > methyl, and this order is observed in many phenomena. Thus the dipole moments of the alkylbenzenes are, in the gas phase,[223]

Compound	Dipole moment, D
$PhCH_3$	0.37
PhC_2H_5	0.58
$PhCH(CH_3)_2$	0.65
$PhC(CH_3)_3$	0.70

However, Baker and Nathan observed that the rates of reaction with pyridine of *p*-substituted benzyl bromides (see p. 377) were about opposite that expected from inductive electron release.[224]

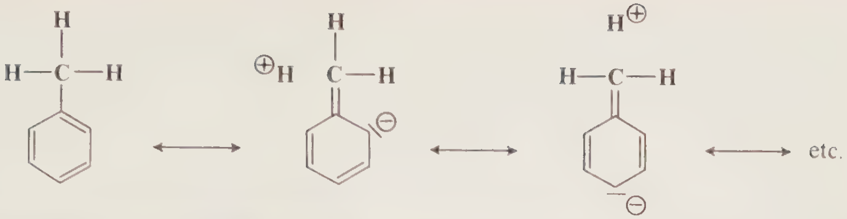


R	$k \times 10^4$ at 20°C
CH_3	2.02
C_2H_5	1.81
$CH(CH_3)_2$	1.63
$C(CH_3)_3$	1.65

This came to be called the *Baker-Nathan effect* and has since been found in many processes. Baker and Nathan explained it by considering that hyperconjugative forms contribute to the actual structure of toluene.

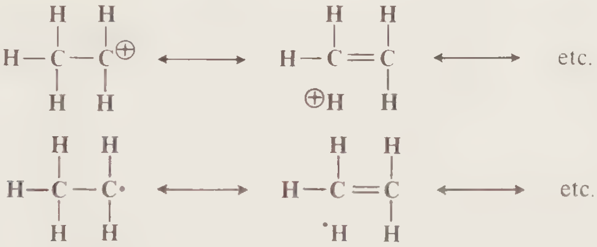
[223] Baker and Groves, *J. Chem. Soc.* 1144 (1939).

[224] Baker and Nathan, *J. Chem. Soc.* 1840, 1844 (1935).



For the other alkyl groups, hyperconjugation is diminished because the number of C—H bonds is diminished and in *t*-butyl there are none; hence, with respect to this effect, methyl is the strongest electron donor and *t*-butyl the weakest. The Baker-Nathan order may be considered to arise when the hyperconjugative resonance effect is greater than the field effect.

However, the fact that the Baker-Nathan order is observed in some processes and the inductive order in others has caused considerable controversy over the reality of hyperconjugation. Over the years, evidence from bond distances, bond energies, spectra, and reactivity has been brought forward to bolster the case for hyperconjugation, and all have been attacked as being otherwise caused.[225] Several other explanations have also been brought forward for the Baker-Nathan effect.[226] At present the evidence is against hyperconjugation in the ground states of neutral molecules.[227] However, for carbonium ions and free radicals[228] and for excited states of molecules,[229] there is evidence that hyperconjugation is important. In hyperconjugation in the ground state of neutral molecules, which Muller and Mulliken call *sacrificial hyperconjugation*,[230] the canonical forms involve not only no-bond resonance but also a charge separation not possessed by the main form. In free radicals and carbonium ions, the canonical forms display no more charge separation than the main form. Muller and Mulliken call this *isovalent hyperconjugation:*



Even here the main form contributes more to the hybrid than the others.

TAUTOMERISM

There remains one topic to be discussed in our survey of chemical bonding in organic compounds. For most compounds all the molecules have the same structure, whether or not this structure can be satisfactorily represented by a Lewis formula. But for many other compounds there is a

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[225] For attacks see Dewar and Schmeising, *Tetrahedron* **5**, 166 (1959); Dewar, Ref. 222; Bent, *Chem. Rev.* **61**, 275–311 (1961), p. 284; Schubert, Murphy, and Robins, *Tetrahedron* **17**, 199 (1962). For support of hyperconjugation, see Mulliken, *Tetrahedron* **6**, 68 (1959); Ballester and Riera, *Tetrahedron* **20**, 2217 (1964); and Kellogg and Simpson, *J. Am. Chem. Soc.* **87**, 4230 (1965).

[226] Schubert, Craven, Minton, and Murphy, *Tetrahedron* **5**, 194 (1959); Clement and Naghizadeh, *J. Am. Chem. Soc.* **81**, 3154 (1959); Brown, *J. Am. Chem. Soc.* **81**, 3229, 3232 (1959); Schubert and Minton, *J. Am. Chem. Soc.* **82**, 6188 (1960).

[227] See however, Schmidt and Schweig, *Angew. Chem. Int. Ed. Engl.* **12**, 307 (1973) [*Angew. Chem.* **85**, 299].

[228] Symons, *Tetrahedron* **18**, 333 (1962).

[229] Rao, Goldman, and Balasubramanian, *Can. J. Chem.* **38**, 2508 (1960).

[230] Muller and Mulliken, *J. Am. Chem. Soc.* **80**, 3489 (1958).

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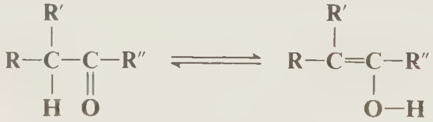
TABLE 1 The enol content of some carbonyl compounds[233]

Compound	Enol content, %
Acetone	1.5×10^{-4}
Acetaldehyde	No enol found[234]
CH_3COOEt	No enol found[234]
CH_3COEt	1.2×10^{-1}
CH_3COCH_2COOEt	8.0
$CH_3COCH_2COCH_3$	76.4
$PhCOCH_2COCH_3$	89.2
$EtOOCCH_2COOEt$	7.7×10^{-3}
$NCCH_2COOEt$	2.5×10^{-1}

mixture of two or more structurally distinct compounds which are in rapid equilibrium. When this phenomenon, called *tautomerism*,[231] exists, there is a rapid shift, back and forth, among the molecules. In nearly all cases, it is a proton which shifts from one atom of a molecule to another.

Keto-Enol Tautomerism[232]

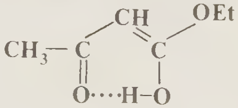
A very common form of tautomerism is that between a carbonyl compound containing an α hydrogen and its enol form:



$$\mathrm{R{-}\overset{\displaystyle R'}{\underset{\displaystyle H}{C}}{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}R''} \rightleftharpoons \mathrm{R{-}\overset{\displaystyle R'}{C}{=}\underset{\displaystyle O{-}H}{C}{-}R''}$$

Keto form Enol form

In simple cases (R″ = H, alkyl, OR, etc.) the equilibrium lies well over to the left. The reason can be seen by examining the table of bond energies on p. 28. The keto form differs from the enol form in possessing a C—H, a C—C, and a C═O bond where the enol has a C═C, a C—O, and an O—H bond. The approximate sum of the first three is 360 kcal/mol and of the second three is 345 kcal/mol. The keto form is therefore more stable by about 15 kcal/mol. When R contains a multiple bond which can be in conjugation with the enolic double bond, a larger amount of enol is present and it may even be the predominant form (Table 1). As Table 1 shows, esters have a much smaller enolic content than ketones. In molecules like acetoacetic ester, the enol is also stabilized by internal hydrogen bonding, which is unavailable to the keto form:



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[231] For reviews, see Kol'tsov and Kheifets, *Russ. Chem. Rev.* **40,** 773–788 (1971), **41,** 452-467 (1972); Forsén and Nilsson, in Zabicky, "The Chemistry of the Carbonyl Group," vol. 2, pp. 157–240, Interscience Publishers, Inc., New York, 1970; and Wheland, "Advanced Organic Chemistry," 3d ed., pp. 663–730, John Wiley & Sons, Inc., New York, 1960.

[232] The mechanism for conversion of one tautomer to another is discussed in Chapter 12 (reaction **2-3**).

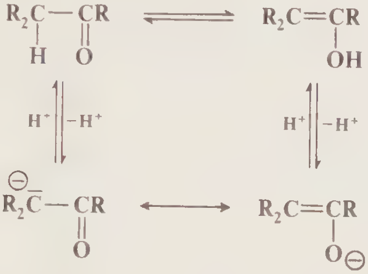
[233] Gero, *J. Org. Chem.* **19,** 469, 1960 (1954).

[234] Less than 1 part in 10 million.

Frequently, when the enol content is high, both forms can be isolated. The pure keto form of acetoacetic ester melts at −39°C, while the enol is a liquid even at −78°C. Each can be kept at room temperature for days if catalysts such as acids or bases are excluded.[235]

The extent of enolization is greatly affected by solvent, concentration, and temperature. Thus, acetoacetic ester has an enol content of 0.4% in water and 19.8% in toluene.[236] In this case, water reduces the enol concentration by hydrogen bonding with the carbonyl, making this group less available for internal hydrogen bonding.

When a strong base is present, both the enol and the keto form can lose a proton. The resulting anion (the *enolate ion*) is the same in both cases. Since **102** and **103** differ only in placement of electrons, *they* are not tautomers but canonical forms. The true structure of the enolate ion is a hybrid of **102** and **103**, though **103** contributes more, since in this form the negative charge is on the more electronegative atom.

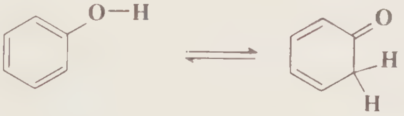


102 **103**

Other Proton-Shift Tautomerism

In all such cases, the anion resulting from removal of a proton from either tautomer is the same because of resonance. Some examples are:

1. Phenol-keto tautomerism:[237]



Phenol Cyclohexadienone

For most simple phenols this equilibrium lies well to the side of the phenol, since only on that side is there aromaticity. For phenol itself there is no evidence for the existence of the keto form. However, the keto form becomes important and may predominate: (1) where certain groups, such as a second OH group or an N=O group, are present;[238] (2) in systems of fused aromatic rings;[239] and (3) in heterocyclic systems. In many heterocyclic compounds in the liquid phase or in solution, the keto form is more stable[240] though in the vapor phase the positions of many of these equilibria are reversed.[241] For example, in the equilibrium between 4-pyridone (**104**) and 4-hydroxypyridine (**105**), **104** is the only form detectable in ethanolic solution, while **105** predominates in the vapor phase.[241]

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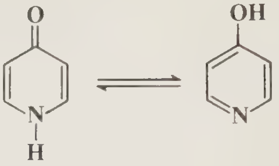
[235] For an example of particularly stable enol and keto forms, which could be kept in the solid state for more than a year without significant interconversion, see Schulenberg, *J. Am. Chem. Soc.* **90**, 7008 (1968).

[236] Meyer, *Justus Liebigs Ann. Chem.* **380**, 212 (1911).

[237] For reviews, see Ershov and Nikiforov, *Russ. Chem. Rev.* **35**, 817–833 (1966); Thomson, *Q. Rev., Chem. Soc.* **10**, 27–43 (1956); and Forsén and Nilsson, Ref. 231, pp. 168–198.

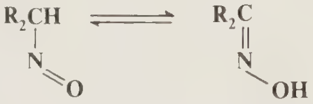
[238] Ershov and Nikiforov, Ref. 237.

[239] See for example, Majerski and Trinajstić, *Bull. Chem. Soc. Jpn.* **43**, 2648 (1970).



104 **105**

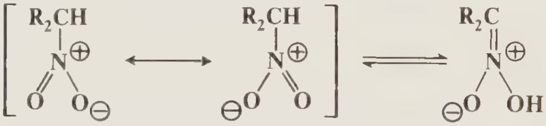
2. Nitroso-oxime tautomerism:



Nitroso Oxime

This equilibrium lies far over to the right, and as a rule nitroso compounds are stable only when there is no α-hydrogen.

3. Aliphatic nitro compounds are in equilibrium with aci forms.



Nitro form Aci form

The nitro form is much more stable than the aci form, in sharp contrast to the parallel case of nitroso-oxime tautomerism, undoubtedly because the nitro form has resonance not found in the nitroso case.

4. Imine-enamine tautomerism:

$$\underset{\text{Imine}}{R_2CH{-}CR{=}NR} \rightleftharpoons \underset{\text{Enamine}}{R_2C{=}CR{-}NHR}$$

Enamines are normally stable only when there is no hydrogen on the nitrogen ($R_2C{=}CR{-}NR_2$). Otherwise, the imine form predominates.[242]

Ring-chain tautomerism[243] (as in sugars) consists largely of cyclic analogs of the previous examples. There are many other highly specialized cases of proton-shift tautomerism.

Valence Tautomerism

This type of tautomerism is discussed on p. 1047.

[240] For reviews of tautomerism in heterocyclic compounds, see Katritzky, *Chimia* **24**, 134–146 (1970); Katritzky and Lagowski, *Adv. Heterocycl. Chem.* **1**, 311–437 (1963); **2**, 1–81 (1963).

[241] Beak, Fry, Lee, and Steele, *J. Am. Chem. Soc.* **98**, 171 (1976).

[242] For an example of the isolation of a primary enamine, see Shin, Masaki, and Ohta, *Bull. Chem. Soc. Jpn.* **44**, 1657 (1971).

[243] For reviews, see Valter, *Russ. Chem. Rev.* **42**, 464–476 (1973), **43**, 665–678 (1974); Escale and Verducci, *Bull. Soc. Chim. Fr.* 1203–1206 (1974); Jones, *Chem. Rev.* **63**, 461–487 (1963).

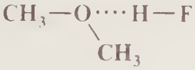
Three

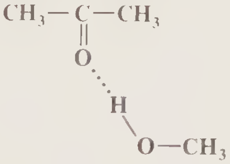
Bonding Weaker than Covalent

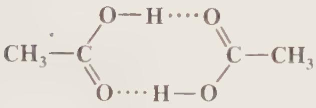
In the first two chapters we have discussed the structure of molecules each of which is an aggregate of atoms in a distinct three-dimensional arrangement held together by bonds whose energies are of the order of 50 to 100 kcal mol. There are also very weak attractive forces *between* molecules, on the order of a few tenths of a kilocalorie per mole. These forces, which are responsible for liquefaction of gases at sufficiently low temperatures, are caused by electrostatic attractions, such as those between dipole and dipole, induced dipole and induced dipole, etc. They are called *van der Waals forces*. The bonding to be discussed in this chapter has energies of the order of 2 to 10 kcal mol, intermediate between the two extremes, and produces clusters of molecules. We shall also discuss compounds in which portions of molecules are held together without any attractive forces at all.

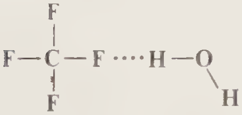
HYDROGEN BONDING

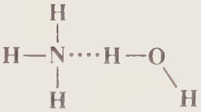
A *hydrogen bond* is a bond between a functional group A—H and an atom or group of atoms B in the same or a different molecule.[1] With exceptions to be noted later, hydrogen bonds are formed only when A is oxygen, nitrogen, or fluorine, and when B is oxygen, nitrogen, or fluorine. The oxygen may be singly or doubly bonded, and the nitrogen singly, doubly, or triply bonded. The bonds are usually represented by dotted lines, as shown in the following examples:











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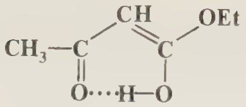
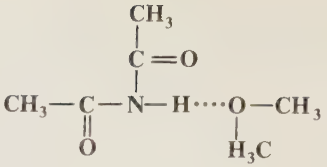
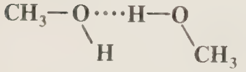
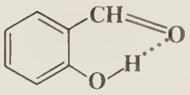
[1] For monographs, see Joesten and Schaad, "Hydrogen Bonding," Marcel Dekker, Inc., New York, 1974; Pimentel and McClellan, "The Hydrogen Bond," W. H. Freeman and Company, San Francisco, 1960. For reviews, see Pimentel and McClellan, *Annu. Rev. Phys. Chem.* **22,** 347–385 (1971); Kollman and Allen, *Chem. Rev.* **72,** 283–303 (1972); Huggins, *Angew. Chem. Int. Ed. Engl.* **10,** 147–151 (1971) [*Angew. Chem.* **83,** 163–168]; and Rochester, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, pp. 327–392, Interscience Publishers, Inc., New York, 1971; pp. 328–369. See also Hamilton and Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, Inc., New York, 1968.









Hydrogen bonds can exist in the solid and liquid phases and in solution. Even in the gas phase, compounds which form particularly strong hydrogen bonds may still be associated. Acetic acid, for example, exists in the gas phase as dimers, as shown above, except at very low pressures.[2] In solution and in the liquid phase, hydrogen bonds rapidly form and break. The mean lifetime of the $NH_3 \cdots\cdots H_2O$ bond is 2×10^{-12} sec.[3] Except for the $FH \cdots\cdots F^-$ bond, which has an energy of about 40 kcal/mol, the strongest hydrogen bonds are the $FH \cdots\cdots F$ bond and the bonds connecting one carboxylic acid with another. The energies of these bonds are in the range of 6 to 8 kcal/mol (for carboxylic acids, this refers to the energy of each bond). Other $OH \cdots\cdots O$ bonds and $NH \cdots\cdots N$ bonds have energies of 3 to 6 kcal/mol. To a first approximation, the strength of hydrogen bonds increases with increasing acidity of A—H and basicity of B,[4] but the parallel is far from exact.[5] A quantitative measure of the strengths of hydrogen bonds has been established. A parameter pK_{HB} has been devised, which measures the relative strengths with which an atom or group H—B forms hydrogen bonds with any suitable O—H reference acid[6] (in a similar way that pK_b is a measure of base strength).

The geometry of hydrogen bonds is difficult to determine, since hydrogen is not easy to detect in x-ray-diffraction measurements, but what little evidence there is is consistent with the hydrogen being on the straight line formed by A and B within about 15°,[7] except in some cases of intramolecular hydrogen bonding where the geometry forbids this.[8] It is significant that the vast majority of intramolecular hydrogen bonding occurs where *six-membered rings* (counting the hydrogen as one of the six) can be formed, in which linearity of the hydrogen bond is geometrically favorable, while five-membered rings, where linearity is usually not favored (though it is known), are much rarer. Except for the special case of $FH \cdots\cdots F^-$ bonds (see p. 78), the hydrogen is not equidistant between A and B. For example, in ice the O—H distance is 0.97 Å, while the $H \cdots\cdots O$ distance is 1.79 Å.[9]

Hydrogen bonding has been detected in many ways, including measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing, but the most important ways are by the effect of the hydrogen bond on ir[10] and other spectra. The ir frequencies of groups such as O—H or C=O are shifted when the group is hydrogen-bonded. Hydrogen bonding always moves the peak toward higher wavelengths, for both the A—H and the B groups, although the shift is greater for the former. For example, a free OH group absorbs at about 3600 to 3650 cm^{-1}, while a hydrogen-bonded OH group is found about 50 to 100 cm^{-1} lower, at 3500 to 3600 cm^{-1}.[11] In many cases there is partial hydrogen bonding, i.e., some OH groups are free and some are hydrogen-bonded. In such cases two peaks appear. Infrared spectroscopy can also distinguish between inter- and intramolecular hydrogen bonding, since intermolecular peaks are intensified by an increase in concentration while intramolecular peaks are unaffected. Other types of spectra which have been used for the detection of hydrogen bonding include Raman, electronic,[12] and nmr.[13] Since hydrogen bonding involves a rapid movement of protons from one atom to another, nmr records an average value. Hydrogen bonding can be detected because it usually produces a chemical shift to a lower field. Hydrogen bonding changes with temperature and concentration, and comparison of spectra taken under different conditions also serves to detect and measure it. As with infrared spectra, intramolecular hydrogen bonding can be distinguished from intermolecular by its constancy when the concentration is varied.

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[2] For a review of hydrogen bonding in carboxylic acids, see Allen and Caldin, *Q. Rev., Chem. Soc.* **7**, 255–278 (1953).

[3] Emerson, Grunwald, Kaplan, and Kromhout, *J. Am. Chem. Soc.* **82**, 6307 (1960).

[4] Gordon, *J. Org. Chem.* **26**, 738 (1961).

[5] See for example, Arnett and Mitchell, *J. Am. Chem. Soc.* **93**, 4052 (1971); Arnett, Mitchell, and Murty, *J. Am. Chem. Soc.* **96**, 3875 (1974).

[6] Taft, Gurka, Joris, Schleyer, and Rakshys, *J. Am. Chem. Soc.* **91**, 4801 (1969). See also Kamlet, Minesinger, and Gilligan, *J. Am. Chem. Soc.* **94**, 4744 (1972); Kamlet and Taft, *J. Am. Chem. Soc.* **98**, 377 (1976); Taft and Kamlet, *J. Am. Chem. Soc.* **98**, 2886 (1976).

[7] A statistical analysis of x-ray crystallographic data has shown that most hydrogen bonds in crystals are nonlinear by about 10 to 15°: Kroon, Kanters, van Duijneveldt–van de Rijdt, van Duijneveldt, and Vliegenthart, *J. Mol. Struct.* **24**, 109 (1975).

[8] For a review on the stereochemistry of hydrogen bonds, see Hunter, *Prog. Stereochem.* **1**, 223 249 (1954).

[9] Pimentel and McClellan, "The Hydrogen Bond," Ref. 1, p. 260.

Hydrogen bonds are important because of the effects they have on the properties of compounds, among them the following:

1. Intermolecular hydrogen bonding raises boiling points and frequently melting points.

2. If hydrogen bonding is possible between solute and solvent, this greatly increases solubility and often results in large or even infinite solubility where none would otherwise be expected. It is interesting to speculate what the effect on the human race would be if ethyl alcohol had the same solubility in water as ethane or ethyl chloride.

3. Hydrogen bonding causes lack of ideality in gas and solution laws.

4. As previously mentioned, hydrogen bonding changes the position of bands in all kinds of spectra.

5. Hydrogen bonding, especially the intramolecular variety, changes many chemical properties. For example, it is responsible for the large amount of enol present in certain tautomeric equilibria (see p. 72). Also, by influencing the conformation of molecules (see Chapter 4), it often plays a significant role in determining reaction rates.[14] Hydrogen bonding is also important in maintaining the three-dimensional structures of protein and nucleic acid molecules.

In addition to oxygen, nitrogen, and fluorine, mentioned earlier, there is evidence that weaker hydrogen bonding exists in other systems. Although many searches have been made for hydrogen bonding where A is carbon,[15] only three types of C—H bonds have been found which are acidic enough to form weak hydrogen bonds. These are found in terminal acetylenes, RC≡CH, chloroform and some other halogenated alkanes, and HCN. Weak hydrogen bonds are formed by compounds containing S—H bonds.[16] There has been much speculation regarding other possibilities for B. There is evidence that Cl can form weak hydrogen bonds[17] (e.g., *o*-chlorophenol is known to exhibit intramolecular hydrogen bonding[18]), but Br and I form very weak bonds if at all.[19] However, the *ions* Cl^-, Br^-, and I^- form hydrogen bonds which are much stronger than those of the covalently bonded atoms.[20] As we have already seen, the $FH \cdots\cdots F^-$ bond is especially strong. In this case the hydrogen is equidistant from the fluorines.[21] Similarly, a sulfur atom[16] can be the B component in weak hydrogen bonds,[22] but the SH^- ion forms much stronger bonds.[23] The $HS^- \cdots\cdots H_2S$ bond is particularly strong, with an energy of about 14 kcal/mol.[23] A system which seems to form rather strong hydrogen bonds is the isonitrile system $R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}}$.[24] There is evidence that double and triple bonds, aromatic rings,[25] and even cyclopropane rings[26] may be the B component of hydrogen bonds, but these bonds are very weak.

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[10] For reviews of the use of infrared spectra to detect hydrogen bonding, see Tichý, *Adv. Org. Chem.* **5,** 115–298 (1965); and Ratajczak and Orville-Thomas, *J. Mol. Struct.* **1,** 449 (1968).

[11] Tichý, Ref. 10, contains a lengthy table of free and intramolecularly hydrogen-bonded peaks.

[12] For a discussion of the effect of hydrogen bonding on electronic spectra, see Lees and Burawoy, *Tetrahedron* **19,** 419 (1963).

[13] For a review of the use of nmr to detect hydrogen bonding, see Davis and Deb, *Adv. Magn. Reson.* **4,** 201–270 (1970).

[14] For a review of the effect of intramolecular hydrogen bonding on reactivity, see Sadekov, Minkin, and Lutskii, *Russ. Chem. Rev.* **39,** 179–195 (1970).

[15] For a monograph on this subject, see Green, "Hydrogen Bonding by C—H Groups," John Wiley & Sons, New York, 1974.

[16] For reviews of hydrogen bonding in sulfur-containing compounds, see Zuika and Bankovskii, *Russ. Chem. Rev.* **42,** 22–36 (1973); Crampton, in Patai, "The Chemistry of the Thiol Group," pt. 1, pp. 379–396, John Wiley & Sons, Inc., New York, 1974.

Deuterium also forms hydrogen bonds; in some systems these seem to be stronger than the corresponding hydrogen bonds; in others, weaker.[27]

ADDITION COMPOUNDS

When reaction of two compounds results in a product which contains all the mass of the two compounds, the product is called an *addition compound*.[28] There are several kinds of addition compounds. Two of these do not fall within the scope of this chapter, since they do not contain bonds weaker than covalent bonds:

1. Regular covalent compounds, such as the product of reaction of ethylene and bromine.
2. Compounds formed by overlap of an orbital containing an unshared pair with an empty orbital, e.g., $H_3\overset{\oplus}{N}-\overset{\ominus}{B}F_3$ (see Lewis acids and bases, p. 236).

In other addition compounds the molecules of the starting materials remain more or less intact, and weak bonds hold two or more molecules together in a cluster. We can divide these compounds into four broad classes: electron donor-acceptor complexes; complexes formed by crown ethers and similar compounds; inclusion compounds; and catenanes.

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[17] For a review of hydrogen bonding to halogens, see Smith, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 1, pp. 265–300, John Wiley & Sons, Inc., New York, 1973.

[18] When halogen atoms form intramolecular hydrogen bonds, five-membered rings are favored rather than six: Mori, Nakamura, and Tsuzuki, *Bull. Chem. Soc. Jpn.* **40,** 2189 (1967).

[19] West, Powell, Whatley, Lee, and Schleyer, *J. Am. Chem. Soc.* **84,** 3221 (1962); Fujimoto, Takeoka, and Kozima, *Bull. Chem. Soc. Jpn.* **43,** 991 (1970); Azrak and Wilson, *J. Chem. Phys.* **52,** 5299 (1970).

[20] Allerhand and Schleyer, *J. Am. Chem. Soc.* **85,** 1233 (1963); McDaniel and Valleé, *Inorg. Chem.* **2,** 996 (1963); Fujiwara and Martin, *J. Am. Chem. Soc.* **96,** 7625 (1974).

[21] A few exceptions have been found, where the presence of an unsymmetrical cation causes the hydrogen to be closer to one fluorine than to the other: Williams and Schneemeyer, *J. Am. Chem. Soc.* **95,** 5780 (1973).

[22] Vogel and Drago, *J. Am. Chem. Soc.* **92,** 5347 (1970); Mukherjee, Palit, and De, *J. Phys. Chem.* **74,** 1389 (1970); Sherry and Purcell, *J. Am. Chem. Soc.* **94,** 1848 (1972).

[23] McDaniel and Evans, *Inorg. Chem.* **5,** 2180 (1966); Sabin, *J. Chem. Phys.* **54,** 4675 (1971).

[24] Ferstandig, *J. Am. Chem. Soc.* **84,** 3553 (1962); Allerhand and Schleyer, *J. Am. Chem. Soc.* **85,** 866 (1963).

[25] For example, see Yoshida and Ishibe, *Bull. Chem. Soc. Jpn.* **42,** 3254, 3259, 3263, (1969); Levy and Winstein, *J. Am. Chem. Soc.* **90,** 3574 (1968); Lutskii, Kul'chitskaya, and Obukhova, *J. Gen. Chem. USSR* **36,** 1573 (1966); West, *J. Am. Chem. Soc.* **81,** 1614 (1959); DePuy and Story, *Tetrahedron Lett.*, no. 6, 20 (1959); Basila, Saier, and Cousins, *J. Am. Chem. Soc.* **87,** 1665 (1965); McPhail and Sim, *Chem. Commun.* 124 (1965).

[26] Joris, Schleyer, and Gleiter, *J. Am. Chem. Soc.* **90,** 327 (1968); Yoshida, Ishibe, and Kusumoto, *J. Am. Chem. Soc.* **91,** 2279 (1969).

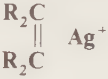
[27] Dahlgren and Long, *J. Am. Chem. Soc.* **82,** 1303 (1960); Creswell and Allred, *J. Am. Chem. Soc.* **84,** 3966 (1962); Singh and Rao, *Can. J. Chem.* **44,** 2611 (1966); Cummings and Wood, *J. Mol. Struct.* **23,** 103 (1974).

[28] For a general reference, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 136–183, John Wiley & Sons, Inc., New York, 1960.

Electron Donor-Acceptor (EDA) Complexes[29]

In *EDA complexes*,[30] there is always a donor molecule and an acceptor. The donor may donate an unshared pair (an *n* donor) or a pair of electrons in a π orbital of a double bond or aromatic system (a π donor). One test for the presence of an EDA complex is the electronic spectrum. These complexes generally exhibit a spectrum (called a *charge-transfer spectrum*) which is not the same as the sum of the spectra of the two individual molecules.[31] Because the first excited state of the complex is relatively close in energy to the ground state, there is usually a peak in the visible or near-uv region, and EDA complexes are often colored. Many EDA complexes are unstable and exist only in solutions in equilibrium with their components, but others are stable solids. In most EDA complexes the donor and acceptor molecules are present in an integral ratio, most often 1 : 1, but some complexes with nonintegral ratios are also known. There are several types of acceptor, and we shall classify complexes into three groups, depending on the nature of the acceptor.

1. *Complexes in which the acceptor is a metal ion and the donor an olefin or an aromatic ring* (*n* donors do not give EDA complexes with metal ions but form covalent bonds instead).[32] Many metal ions form complexes, which are often stable solids, with olefins, dienes (usually conjugated, but not always), and aromatic rings. The generally accepted picture of the bonding in these complexes,[33] first proposed by Dewar,[34] can be illustrated for the complex in which silver ion is bonded to an olefin. There are two bonds between the metal ion and the olefin. One of



$$\begin{array}{l} R_2C \\ \;\;\;\| \quad Ag^+ \\ R_2C \end{array}$$

these is a σ bond formed by overlap of the filled π orbital of the olefin with the empty 5*s* orbital of the silver ion, and the other is a π bond formed by overlap of a filled 4*d* orbital of the silver ion and an empty antibonding π^* orbital of the olefin. The bond is not from the silver ion to one atom but to the whole π center, and the net result is that some electron density is transferred from the olefin to the metal ion.[35]

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[29] For monographs, see Foster, "Organic Charge-Transfer Complexes," Academic Press, Inc., New York, 1969; Mulliken and Person, "Molecular Complexes," Interscience Publishers, Inc., New York, 1969; Rose, "Molecular Complexes," Pergamon Press, London, 1967; and Andrews and Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964. For reviews, see Banthorpe, *Chem. Rev.* **70,** 295–322 (1970); Andrews, *Chem. Rev.* **54,** 713–776 (1954); Kosower, *Prog. Phys. Org. Chem.* **3,** 81–163 (1965); Foster, *Chem. Br.* **12,** 18–23 (1976).

[30] These have often been called *charge-transfer complexes*, but this term implies that the bonding involves charge transfer, which is not always the case, so that the more neutral name EDA complex is preferable. See Ref. 44.

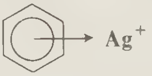
[31] For examples of EDA complexes that do not show charge-transfer spectra, see Dewar and Thompson, *Tetrahedron Suppl.* **7,** 97 (1966); Bentley and Dewar, *Tetrahedron Lett.* 5043 (1967).

[32] For monographs, see King, "Transition-Metal Organic Chemistry," Academic Press, Inc., New York, 1969; Green, "Organometallic Compounds," vol. 2, Methuen & Co., Ltd., London, 1968; and Briegleb, "Elektronen-Donator-Acceptor-Komplexe," Springer-Verlag, Göttingen, 1961. For general reviews, see Churchill and Mason, *Adv. Organomet. Chem.* **5,** 93–135 (1967) and Cais, in Patai, "The Chemistry of Alkenes," vol. 1, pp. 335–385, Interscience Publishers, Inc., New York, 1964. Among the many reviews limited to certain classes of complexes are: transition metals-olefins and acetylenes, Pettit and Barnes, *Fortschr. Chem. Forsch.* **28,** 85–139 (1972); Quinn and Tsai, *Adv. Inorg. Chem. Radiochem.* **12,** 217–373 (1969); Guy and Shaw, *Adv. Inorg. Chem. Radiochem.* **4,** 77–131 (1962); Bennett, *Chem. Rev.* **62,** 611–652 (1962); Pt- and Pd-olefins and acetylenes, Hartley, *Chem. Rev.* **69,** 799–844 (1969); silver ion–olefins and aromatics, Beverwijk, van der Kerk, Leusink, and Noltes, *Organomet. Chem. Rev., Sect. A,* **5,** 215–280 (1970); metals-substituted olefins, Jones, *Chem. Rev.* **68,** 785–806 (1968); transition metals–allylic compounds, Clarke, *J. Organomet. Chem.* **80,** 155–173 (1974); Lobach, Babitskii, and Kormer, *Russ. Chem. Rev.* **36,** 476–498 (1967); iron-dienes, Pettit, Emerson, and Mahler, *J. Chem. Educ.* **40,** 175 180 (1963); Pettit and Emerson, *Adv. Organomet. Chem.* **1,** 1–40 (1964); metals-di- and oligoolefins, Fischer and Werner, *Angew. Chem. Int. Ed. Engl.* **2,** 80–93 (1963); [*Angew. Chem.* **75,** 57–71]; metals–allylic compounds, Green and Nagy, *Adv. Organomet. Chem.* **2,** 325-363 (1964); and metals–seven- and eight-membered rings, Bennett, *Adv. Organomet. Chem.* **4,** 353–387 (1966). For a list of review articles on this subject, see Bruce, *Adv. Organomet. Chem.* **10,** 273–346 (1972), pp. 317 321.

[33] For reviews, see Hartley, *Chem. Rev.* **73,** 163–190 (1973); *Angew. Chem. Int. Ed. Engl.* **11,** 596-606 (1972) [*Angew. Chem.* **84,** 657–667].

[34] Dewar, *Bull. Soc. Chim. Fr.* **18,** C79 (1951).

Among the compounds which form complexes with silver and other metals are benzene[36] (represented as in **1**) and cyclooctatetraene. When the metal involved has a coordination number greater than 1, more than one donor molecule participates. In many cases, this extra electron density comes from CO groups, which in these complexes are called carbonyl groups. Thus, benzenechromium tricarbonyl (**2**) is a stable compound.[37] Three arrows are shown, since all three aromatic bonding orbitals contribute some electron density to the metal. Metallocenes (p. 47) may be considered a special case of this type of complex, though the bonding in metallocenes is much stronger.



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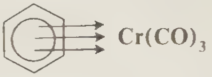

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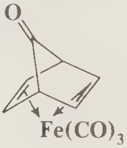
In a number of cases olefins which are too unstable for isolation have been isolated in the form of metal complexes. An example is norbornadienone, which was isolated in the form of its iron-tricarbonyl complex (**3**).[38] The free dienone spontaneously decomposes to carbon monoxide and benzene (reaction **7-38**).



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2. *Complexes in which the acceptor is an organic molecule.* Picric acid, 1,3,5-trinitrobenzene, 2,4,7-trinitrofluorene, and similar polynitro compounds are the most important of these.[39] Picric acid forms addition compounds with many aromatic hydrocarbons, aromatic amines, aliphatic amines, olefins, and other compounds. These addition compounds are usually solids with definite melting points and are often used as derivatives of the compounds in question. They are called picrates, though they are not salts of picric acid but addition compounds. Unfortunately, salts of picric acid are also called picrates. Not only picric acid but other aromatic nitro compounds and even some aliphatic nitro compounds form similar addition compounds. Similar complexes are formed between phenols and quinones (quinhydrones).[40] Olefins which contain electron-withdrawing substituents also act as acceptor molecules. A particularly strong one is tetracyanoethylene.[41]

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[35] For a discussion of how the nature of the metal ion affects the stability of the complex, see p. 238.

[36] For a monograph, see Zeiss, Wheatley, and Winkler, "Benzenoid-Metal Complexes," The Ronald Press Company, New York, 1966. For a review, see Fischer and Fritz, *Angew. Chem.* **73,** 353–363 (1961).

[37] Nicholls and Whiting, *J. Chem. Soc.* 551 (1959). For a review of arene–transition-metal complexes, see Silverthorn, *Adv. Organomet. Chem.* **13,** 47–137 (1975)

[38] Landesberg and Sieczkowski, *J. Am. Chem. Soc.* **93,** 972 (1971).

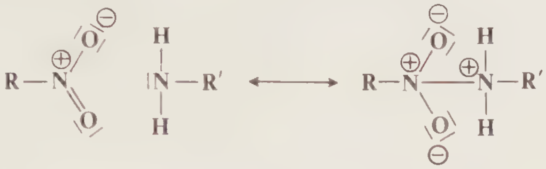
[39] For a review, see Parini, *Russ. Chem. Rev.* **31,** 408–417 (1962); also see Ref. 29.

[40] For a review of quinone complexes, see Foster and Foreman, in Patai, "The Chemistry of the Quinonoid Compounds," pt. 1, pp. 257–333, John Wiley & Sons, Inc., New York, 1974.

[41] For a review of complexes formed by tetracyanoethylene and other polycyano compounds, see Melby, in Rappoport, "The Chemistry of the Cyano Group," pp. 639–669, Interscience Publishers, Inc., New York, 1970.

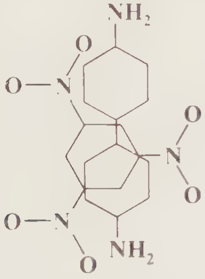
The bonding in these cases is more difficult to explain than in the previous case, and indeed no really satisfactory explanation is available.[42] The difficulty is that although the donor has a pair of electrons to contribute (both *n* donors and π donors are found here), the acceptor does not have a vacant orbital. Simple attraction of the dipole induced-dipole type accounts for some of the bonding[43] but is too weak to explain the bonding in all cases;[44] e.g., nitromethane, with about the same dipole moment as nitrobenzene, forms much weaker complexes. Some other type of bonding clearly must also be present in many EDA complexes. The exact nature of this bonding, called *charge-transfer bonding*, is not well understood, but it presumably involves some kind of donor-acceptor interaction.

One theory is that resonance of the type

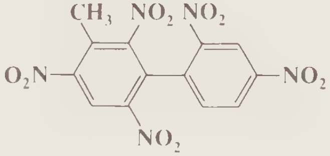


is responsible for attraction between nitro compounds and amines.[45] The amine (an *n* donor) thus contributes electrons to a partially filled orbital of the nitro group. Presumably, aromatic hydrocarbons and olefins behave similarly, though in these cases π electrons are donated. Another theory, a molecular-orbital one, suggests that electrons from one of the two original molecules can be transferred to higher vacant orbitals of the other.[46]

One difficulty with these explanations is that they predict that the functional groups should be close to each other, but this is not always so. Crystal structures, determined for a number of addition compounds, have shown that the molecules are stacked in parallel planes, consisting of alternate layers of donor and acceptor molecules.[47] The structure of the complex trinitrobenzene-benzidine is such that not only are the groups not close to each other, but even the rings do not



Trinitrobenzene-benzidine



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[42] For reviews, see Bent, *Chem. Rev.* **68,** 587–648 (1968); McGlynn, *Chem. Rev.* **58,** 1113–1156 (1958); Briegleb and Czekalla, *Angew. Chem.* **72,** 401–413 (1960); Cauquis and Basselier, *Ann. Chim. (Paris)* [13] **7,** 745–761 (1962); Murrell, *Q. Rev., Chem. Soc.* **15,** 191–206 (1961).

[43] See for example Le Fèvre, Radford, and Stiles, *J. Chem. Soc. B* 1297 (1968); and Ref. 31.

[44] Mulliken and Person, *J. Am. Chem. Soc.* **91,** 3409 (1969).

[45] Mulliken, *J. Am. Chem. Soc.* **74,** 811 (1952).

[46] Dewar and Lepley, *J. Am. Chem. Soc.* **83,** 4560 (1961); Dewar and Rogers, *J. Am. Chem. Soc.* **84,** 395 (1962).

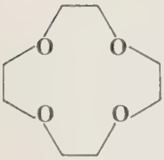
[47] For reviews of the crystal structures of complexes, see Herbstein, *Perspect. Struct. Chem.* **4,** 166–395 (1971); Prout and Wright, *Angew. Chem. Int. Ed. Engl.* **7,** 659–667 (1968) [*Angew. Chem.* **80,** 688–697].

overlap.[48] The ability to form a plane seems to be important. Thus **4**, in which the two rings cannot be coplanar, did not form a complex with anthracene.[49]

3. *Complexes in which the acceptor is* I_2, Br_2, *or even* Cl_2.[50] These molecules accept electrons from both *n* donors and π donors, presumably by expansion of the outer shell to hold 10 electrons. Such complexes are formed with amines, aromatic hydrocarbons, ketones, etc. This is the reason iodine is not its normal purple color in solvents such as acetone, ethanol, or benzene. IBr and ICl also form complexes, in which the iodine end of the molecule is the acceptor.[51] Even in these cases the bonding is not simple. The authors of a review article state[52] that despite the presumption about expansion of the octet, "a satisfactory theoretical interpretation of the observed geometry of the atomic arrangements associated with charge-transfer bonding [in these complexes] is still lacking." That there is charge transfer here seems certain, since the iodine-benzene complex has a dipole moment, though iodine and benzene are themselves nonpolar.[53] An important contribution to the bonding of the benzene-halogen complexes is quadrupole–induced dipole interaction (the benzene molecule is the quadrupole).[54]

Complexes Formed by Crown Ethers and Similar Compounds[55]

Crown ethers are large ring compounds containing several oxygen atoms, usually in a regular pattern. Examples are 12-crown-4 (**5**),[56] dicyclohexyl-18-crown-6 (**6**), and 15-crown-5 (**7**). These compounds have the property[57] of forming complexes with positive ions, generally metallic ions (though not usually ions of transition metals) or ammonium and substituted ammonium ions.



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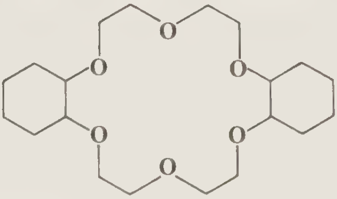

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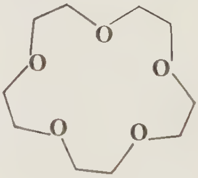

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In most cases the ions are held tightly in the center of the cavity. Each crown ether binds different ions, depending on the size of the cavity. For example, **5** binds Li^+ [58] but not K^+, while **6** binds K^+ but not Li^+ or Na^+.[59] Similarly, **6** binds Hg^{2+} but not Cd^{2+} or Zn^{2+}. The complexes can frequently be prepared as well-defined sharp-melting solids.

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[48] Wallwork, *J. Chem. Soc.* 494 (1961).

[49] Newman, in Newman (ed.), "Steric Effects in Organic Chemistry," p. 473, John Wiley & Sons, Inc., New York, 1956.

[50] For reviews, see Hassel and Rømming, *Q. Rev., Chem. Soc.* **16,** 1–18 (1962); Andrews and Keefer, *Adv. Inorg. Chem. Radiochem.* **3,** 91–131 (1961).

[51] Augdahl and Klaeboe, *Acta Chem. Scand.* **16,** 1647, 1655 (1962).

[52] Hassel and Rømming, Ref. 50.

[53] For a discussion see Ratajczak and Orville-Thomas, *J. Mol. Struct.* **14,** 149, 155 (1972); Ratajczak, Mielke, and Orville-Thomas, *J. Mol. Struct.* **14,** 165 (1972).

[54] Lippert, Hanna, and Trotter, *J. Am. Chem. Soc.* **91,** 4035 (1969); Hanna, *J. Am. Chem. Soc.* **90,** 285 (1968); Hanna and Williams, *J. Am. Chem. Soc.* **90,** 5358 (1968).

[55] For reviews, see Pedersen and Frensdorff, *Angew. Chem. Int. Ed. Engl.* **11,** 16–25 (1972) [*Angew. Chem.* **84,** 16–26]; Christensen, Eatough, and Izatt, *Chem. Rev.* **74,** 351–384 (1974); Cram and Cram, *Science* **183,** 803–809 (1974); Gokel and Durst, *Synthesis* 168–184 (1976).

[56] Cook, Caruso, Byrne, Bowers, Speck, and Liotta, *Tetrahedron Lett.* 4029 (1974).

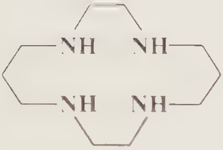
[57] Discovered by Pedersen, *J. Am. Chem. Soc.* **89,** 2495, 7017 (1967).

[58] Anet, Krane, Dale, Daasvatn, and Kristiansen, *Acta Chem. Scand.* **27,** 3395 (1973).

[59] Izatt, Nelson, Rytting, Haymore, and Christensen, *J. Am. Chem. Soc.* **93,** 1619 (1971).

Apart from their obvious utility in separating mixtures of cations, crown ethers can be very useful in organic synthesis; e.g., saponification of an ester by KOH (reaction **0-11**) is much faster in the presence of a crown ether, because the ether ties up the K^+, leaving the OH^- freer to attack the ester.[60] Also, many salts, e.g., NaCl, *t*-BuOK, or $KMnO_4$, can be made to dissolve in nonpolar solvents like benzene by the addition of a crown ether. Since many organic molecules are soluble only in nonpolar solvents, this means that organic molecules and appropriate salts can be brought together in one phase, where reactions between the molecule and the salt take place much more rapidly than they do in two-phase systems (for examples of the use of crown ethers in organic synthesis, see pp. 324, 367, 1095).

Macrocycles containing nitrogen or sulfur atoms, e.g., **8** and **9**[61], have similar properties, as do these containing more than one kind of hetero atom, e.g., **10**[62] and **11**[63].



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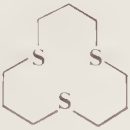

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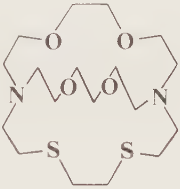

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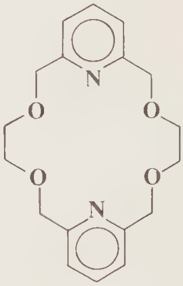

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The bonding in these complexes is the result of ion-dipole attractions between the hetero atoms and the positive ions.

Inclusion Compounds[64]

This type of addition compound is different from either the EDA complexes or the crown ether type of complexes previously discussed. One of the compounds, called the *host*, forms a crystal lattice in which there are spaces large enough for the second compound, called the *guest*, to fit. There is no bonding between the host and the guest except van der Waals forces. There are two main types, depending on the shape of the space. The spaces in *inclusion compounds* are in the shape of long tunnels or channels, while the other type, often called *clathrate*, or *cage*, *compounds* have spaces which are completely enclosed. In both types the guest molecule must fit into the space, and potential guests which are too large or too small will not go into the lattice, so that the addition compound will not form.

The most important host molecule among the inclusion compounds is urea. Ordinary crystalline urea is tetragonal, but when a guest is present, urea crystallizes in a hexagonal lattice, containing the guest in long channels.[65] The hexagonal type of lattice can form only when a guest molecule is present, showing that van der Waals forces between the host and the guest, while small, are essential to the stability of the structure. The diameter of the channel is about 5 Å,

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[60] Pedersen and Frensdorff, Ref. 55, p. 20.

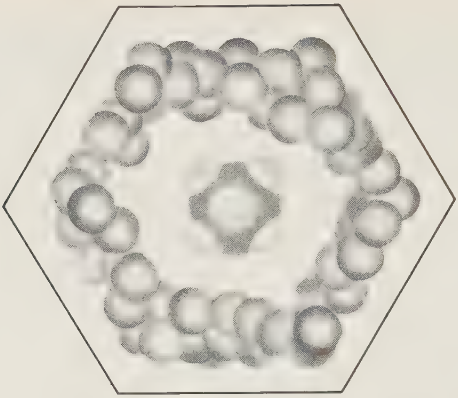
[61] Rosen and Busch, *Inorg. Chem.* **9**, 262 (1970).

[62] Dietrich, Lehn, and Sauvage, *Chem. Commun.* 1055 (1970).

[63] Newcomb, Gokel, and Cram. *J. Am. Chem. Soc.* **96**, 6810 (1974).

[64] For a review, see Cramer, *Rev. Pure Appl. Chem.* **5**, 143–164 (1955).

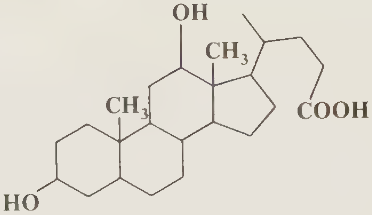
[65] This picture is taken from a paper by Montel, *Bull. Soc. Chim. Fr.* 1013 (1955).



and which molecules can be guests is dependent only on their shapes and sizes and not on any electronic or chemical effects. For example, octane and 1-bromooctane are suitable guests for urea, but 2-bromooctane, 2-methylheptane, and 2-methyloctane are not. Also both dibutyl maleate and dibutyl fumarate are guests; neither diethyl maleate or diethyl fumarate is a guest, but dipropyl fumarate is a guest and dipropyl maleate is not.[66] In these complexes, there is usually no integral molar ratio (though by chance there may be). For example, the octane-urea ratio is 1 : 6.73.[67]

The complexes are solids but are not useful as derivatives, since they melt, with decomposition of the complex, at the melting point of urea. They are useful, however, in separating isomers which would be quite difficult to separate otherwise.

Thiourea also forms inclusion compounds although with channels of larger diameter, so that *n*-alkanes cannot be guests but, for example, 2-bromooctane, cyclohexane, and chloroform readily fit. There are a number of other host compounds which form inclusion compounds, the most notable of which is deoxycholic acid:



Clathrate Compounds[68]

The most important host for this type of compound is hydroquinone. Three molecules, held together by hydrogen bonding, make a cage in which fits one molecule of guest. Typical guests are methanol (but not ethanol), SO_2, CO_2, and argon (but not neon). In contrast to the inclusion compounds, the crystal lattices here can exist partially empty. Another host is water. Usually six molecules of water form the cage, and many guest molecules, among them Cl_2 and methyl iodide, can fit. The water clathrates, which are solids, can normally be kept only at low temperatures; at room temperature they decompose.[69]

[66] Radell, Connolly, and Cosgrove, *J. Org. Chem.* **26,** 2960 (1961).

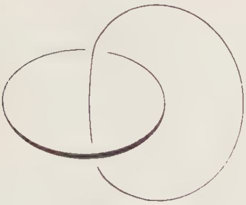
[67] Redlich, Gable, Dunlop, and Millar, *J. Am. Chem. Soc.* **72,** 4153 (1950).

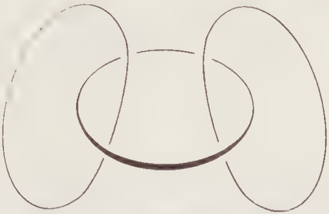
[68] For reviews, see Child, *Q. Rev., Chem. Soc.* **18,** 321-346 (1964), and Mandelcorn, *Chem. Rev.* **59,** 827 839 (1959).

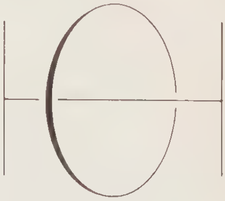
[69] For a review of water clathrates, see Byk and Fomina, *Russ. Chem. Rev.* **37,** 469-491 (1968).

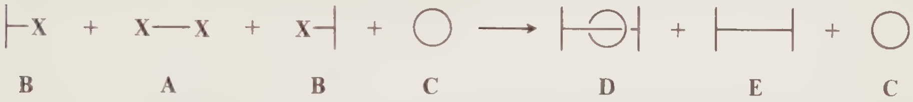
Catenanes and Rotaxanes[70]

These compounds contain two or more independent portions which are not bonded to each other by any valence forces but nevertheless must remain linked. *Catenanes* are made up of two or more rings held together as links in a chain, while in *rotaxanes* a linear portion is threaded through a ring and cannot get away because of bulky end groups. Catenanes and rotaxanes can be prepared by statistical methods or by directed syntheses. An example of a statistical synthesis of a rotaxane would be a reaction where a compound **A** is bonded at two positions to another compound **B** in the presence of a large ring **C**. In this case it is hoped that some **A** molecules would by chance be threaded through **C** before combining with the two **B** molecules, so that some rotaxane (**D**) would be formed along with the normal product **E**.[71] For examples of statistical syntheses of catenanes, see p. 1136. In a directed synthesis, the separate parts of the molecule are held together by other bonds, which are later cleaved. An example of a directed synthesis of a catenane is given on p. 1137.[72]


A [2]catenane


A [3]catenane


A rotaxane



Only a few syntheses of catenanes or rotaxanes have been reported by either the statistical or the directed approach,[73] though it is likely that additional examples will be forthcoming.

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[70] For a monograph, see Schill, "Catenanes, Rotaxanes, and Knots," Academic Press, Inc., New York, 1971. For a review, see Schill, in Chiurdoglu, "Conformational Analysis," pp. 229–239, Academic Press, Inc., 1971.

[71] A scheme of this type was carried out by Harrison and Harrison, *J. Am. Chem. Soc.* **89**, 5723 (1967). For a different kind of statistical synthesis of a rotaxane, see Harrison, *J. Chem. Soc., Chem. Commun.* 231 (1972), *J. Chem. Soc., Perkin Trans. 1* 301 (1974).

[72] For a directed synthesis of a rotaxane, see Schill and Zollenkopf, *Justus Liebigs Ann. Chem.* **721**, 53 (1969); Schill, Zürcher, and Vetter, *Chem. Ber.* **106**, 228 (1973).

[73] Ref. 70 has a complete discussion.

Four

Stereochemistry

In the previous chapters we have described what is known about electron distribution in organic molecules. In this chapter we shall discuss the three-dimensional structure of organic compounds.[1] The structure may be such that *stereoisomerism*[2] is possible. Stereoisomers are compounds made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. These three-dimensional structures are called *configurations*.

OPTICAL ACTIVITY AND CHIRALITY

A material which rotates the plane of polarized light is said to be *optically active*. If a pure compound is optically active, the molecule is nonsuperimposable on its mirror image. If a molecule is superimposable on its mirror image, the compound does not rotate the plane of polarized light; it is *optically inactive*. The property of nonsuperimposability of an object on its mirror image is called *chirality*. If a molecule is not superimposable on its mirror image, it is *chiral*. If it is superimposable on its mirror image, it is *achiral*. Although the relationship between optical activity and chirality is empirical, it is absolute. No exceptions are known, and many thousands of cases have been found in accord with it (however, see p. 89). The ultimate criterion, then, for optical activity is chirality (nonsuperimposability on the mirror image). This is both a necessary and a sufficient condition. This fact has been used as evidence for the structure determination of many compounds, and historically the tetrahedral nature of carbon was deduced from the hypothesis that the relationship might be true.

If a molecule is nonsuperimposable on its mirror image, the mirror image must be a different molecule (since superimposability is the same as identity), and in each case of optical activity of a pure compound there are two and only two isomers, called *enantiomers* (sometimes *enantiomorphs*), which differ in structure only in the left- and the right-handedness of their orientations (Figure 1). Enantiomers have identical physical and chemical properties except in two important respects:

1. They rotate the plane of polarized light in opposite directions, though in equal amounts. The isomer which rotates the plane to the left (counterclockwise) is called the *levo isomer* and is designated (−), while the one which rotates the plane to the right (clockwise) is called the *dextro isomer* and is designated (+).

2. They react at different rates with other chiral compounds. These rates may be so close together

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[1] For excellent lengthy treatments of this subject, see Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962, "Elements of Stereochemistry," John Wiley & Sons, Inc., New York, 1969; Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, 1965; Wheland, "Advanced Organic Chemistry," 3d ed., pp. 195–514, John Wiley & Sons, Inc., New York, 1960; and Shriner, Adams, and Marvel, in Gilman, "Advanced Organic Chemistry," vol. 1, 2d ed., pp. 214–488, John Wiley & Sons, Inc., New York, 1943. Although the last review is not recent, most of it remains quite valid and useful.

[2] The IUPAC 1974 Recommendations, Section E, Fundamental Stereochemistry, give definitions for most of the terms used in this chapter, as well as rules for naming the various kinds of stereoisomers. They can be found in *Pure Appl. Chem.* **45**, 13–30 (1976).

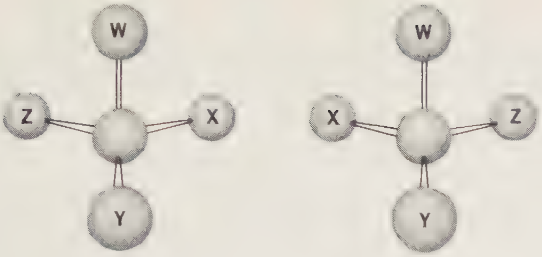

Figure 1 Enantiomers

as to make the distinction practically useless, or they may be so far apart that one enantiomer undergoes the reaction at a convenient rate while the other does not react at all. It is for this reason that many compounds are biologically active while their enantiomers are not. Enantiomers react at the same rate with achiral compounds.

In general it may be said that enantiomers have identical properties in a symmetric environment, but in an asymmetric environment their properties may differ. Besides the important differences previously noted, enantiomers may react at different rates with achiral molecules if there is an optically active *catalyst* present; they may have different solubilities in an optically active *solvent*; they may have different indexes of refraction or absorption spectra *when examined with circularly polarized light*, etc. In most cases these differences are too small to be useful and are often too small to be measured.

Although pure compounds are always optically active if they are composed of chiral molecules, mixtures of equal amounts of enantiomers are optically inactive, since the rotations cancel. Such mixtures are called *racemic mixtures*.[3] Their properties are not always the same as those of the individual enantiomers. Usually the properties in the gaseous or liquid state, or in solution, are the same, since such a mixture is nearly ideal, but properties involving the solid state, such as melting points and solubilities, are often different. Thus racemic tartaric acid has a melting point of 204–206°C and a solubility in water at 20°C of 206 g/liter; while for the (+) or the (−) enantiomer, the corresponding figures are 170°C and 1390. The separation of a racemic mixture into its two optically active components is called *resolution.*

Dependence of Rotation on Conditions of Measurement

The *amount* of rotation α is not a constant for a given enantiomer; it depends on the length of the sample vessel, the temperature, the solvent[4] and concentration (for solutions), the pressure (for gases), and the wavelength of light used. Of course, rotations determined for the same compound under the same conditions are identical. The length of the vessel and the concentration or pressure determine the number of molecules in the path of the beam, and α is linear with this. Therefore, a number is defined, called the *specific rotation* $[\alpha]$, which is,

$$[\alpha] = \begin{cases} \dfrac{\alpha}{lc} & \text{for solutions} \\[2ex] \dfrac{\alpha}{ld} & \text{for pure compounds} \end{cases}$$

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[3] Strictly speaking, the term *racemic mixture* applies only when the mixture of molecules is present as separate solid phases, but in this book we shall use this expression to refer to any equimolar mixture of enantiomeric molecules, liquid, solid, gaseous, or in solution.

[4] A good example is found in Kumata, Furukawa, and Fueno, *Bull. Chem. Soc. Jpn.* **43**, 3920 (1970).

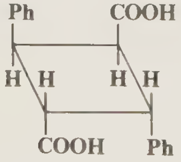
where α is the observed rotation, l is the cell length in decimeters, c is the concentration in grams per milliliter, and d is the density in the same units. The specific rotation is usually given along with the temperature and wavelength, in this manner: $[\alpha]^{25}_{546}$. These conditions must be duplicated for comparison of rotations, since there is no way to put them into a simple formula. The expression $[\alpha]_D$ means that the rotation was measured with sodium D light; i.e., $\lambda = 589$ nm. The molar rotation $[M]^t_\lambda$ is the specific rotation times the molecular weight, divided by 100.

It must be emphasized that although the value of α changes with conditions, the molecular structure is unchanged. This is true even when the changes in conditions are sufficient to change not only the amount of rotation but even the direction. Thus one of the enantiomers of aspartic acid, when dissolved in water, has $[\alpha]_D$ equal to $+4.36°$ at 20°C and $-1.86°$ at 90°C, though the molecular structure is unchanged. A consequence of cases like this is that there is a temperature at which there is *no* rotation (in this case 75°C). Of course, the other enantiomer exhibits opposite behavior. Other cases are known in which the direction of rotation is reversed by changes in wavelength (this is common; see the discussion of optical rotatory dispersion on p. 135), solvent, and even concentration.[5] In theory, there should be no change in $[\alpha]$ with concentration, since this is taken into account in the formula, but associations, dissociations, and solute-solvent interactions often cause nonlinear behavior. For example, $[\alpha]^{24}_D$ for (−)-2-ethyl-2-methylsuccinic acid in $CHCl_3$ is $-5.0°$ at $c = 16.5$, $-0.7°$ at $c = 10.6$, $+1.7°$ at $c = 8.5$, and $+18.9°$ at $c = 2.2$.[6]

It should be noted that any single reading of the polarimeter must be ambiguous. A reading of say, 38°, could also be 218°, or 398°, or any number of the form $38 \pm 180n$ degrees, where n is any integer. However, it is relatively simple to determine the true reading by measuring another sample of the substance at a different concentration or cell length. For example, if the correct reading is 38°, a solution of one-fifth the concentration will give a value of 7.6°. If the correct reading was 218°, the new reading will be 43.6°, etc.

What Kinds of Molecules Display Optical Activity?

Although the ultimate criterion is, of course, nonsuperimposability on the mirror image (chirality), other tests may be used, which are simpler to apply but not always accurate. One such test is the presence of a *plane of symmetry*. A plane of symmetry[7] (also called a *mirror plane*) is a plane passing through an object such that the part on one side of the plane is the exact reflection of the part on the other side (the plane acting as a mirror). *Compounds possessing such a plane are always optically inactive*, but there are a few cases known in which compounds lack a plane of symmetry and are nevertheless inactive. Such compounds possess a *center of symmetry*, such as in α-truxillic acid (**1**), or an *alternating axis of symmetry* as in **2**.[8] A center of symmetry[7] is a point within an



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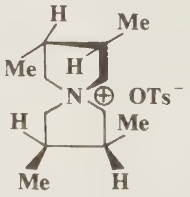

2

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[5] For examples, see Shriner, Adams, and Marvel, Ref. 1, pp. 291–301.

[6] Krow and Hill, *Chem. Commun.* 430 (1968).

[7] The definitions of plane, center, and alternating axis of symmetry are taken from Eliel, "Elements of Stereochemistry," Ref. 1, pp. 6, 7.

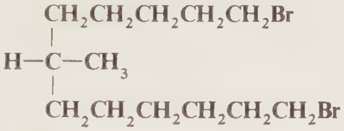
[8] McCasland and Proskow, *J. Am. Chem. Soc.* 77, 4688 (1955).

object such that a straight line drawn from any part or element of the object to the center and extended an equal distance on the other side encounters an equal part or element. An alternating axis of symmetry[7] of order n is an axis such that when an object containing such an axis is rotated by 360 n about the axis and then reflection is effected across a plane at right angles to the axis, a new object is obtained which is indistinguishable from the original one.

A molecule which contains just one *asymmetric carbon atom* (defined as a carbon atom connected to four different groups) is always chiral and hence optically active. As seen in Figure 1, such a molecule cannot have a plane of symmetry, whatever the identity of W, X, Y, and Z, so long as they are all different. However, the presence of an asymmetric carbon is neither a necessary nor a sufficient condition for optical activity, since optical activity may be present in molecules with no asymmetric atom and since some molecules with two or more asymmetric carbon atoms are superimposable on their mirror images and hence inactive. Examples of such compounds will be discussed subsequently.

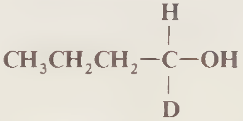
Optically active compounds may be classified into several categories.

1. *Compounds with an asymmetric carbon atom.* If there is only one such atom, the molecule must be optically active. This is so no matter how slight the differences are among the four groups. For example, optical activity is present in



$$\begin{array}{l} \quad\;\; CH_2CH_2CH_2CH_2CH_2Br \\ \quad\;\; | \\ H-C-CH_3 \\ \quad\;\; | \\ \quad\;\; CH_2CH_2CH_2CH_2CH_2CH_2Br \end{array}$$

Optical activity has been detected even in such cases[9] as 1-butanol-1-*d*, where one group is hydrogen and another deuterium:[10]



$$\begin{array}{c} \qquad\qquad\qquad H \\ \qquad\qquad\qquad | \\ CH_3CH_2CH_2-C-OH \\ \qquad\qquad\qquad | \\ \qquad\qquad\qquad D \end{array}$$

However, the amount of rotation is greatly dependent on the nature of the four groups, in general increasing with increasing differences in polarizabilities among the groups. Alkyl groups have very similar polarizabilities,[11] and the optical activity of 5-ethyl-5-propylundecane was too low to be measurable at any wavelength between 2800 and 5800 Å.[12]

2. *Compounds with other quadrivalent asymmetric atoms.*[13] Any molecule containing an atom which has four bonds pointing to the corners of a tetrahedron will be optically active if the four groups are different. Among atoms in this category are Si, Ge, N (in quaternary salts or N-oxides) and certain metals, such as Mn,[14] Cu, Be, and Zn, which form tetrahedral coordination compounds. In sulfones the sulfur bonds tetrahedrally, but since two of the groups are always oxygen, no optical activity can normally result. However, the preparation[15] of an optically active sulfone in which one oxygen is ^{16}O and the other ^{18}O illustrates the point that slight differences in groups are all that is necessary:

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[9] For reviews of compounds where chirality is due to the presence of deuterium or tritium, see Arigoni and Eliel, *Top. Stereochem.* **4**, 127–243 (1969); and Verbit, *Prog. Phys. Org. Chem.* **7**, 51-127 (1970).

[10] Streitwieser and Schaeffer, *J. Am. Chem. Soc.* **78**, 5597 (1956).

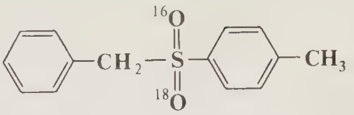
[11] For a discussion of optical activity in paraffins, see Brewster, *Tetrahedron* **30**, 1807 (1974).

[12] Wynberg, Hekkert, Houbiers, and Bosch, *J. Am. Chem. Soc.* **87**, 2635 (1965); Wynberg and Hulshof, *Tetrahedron* **30**, 1775 (1974).

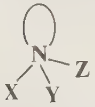
[13] For reviews of compounds with asymmetric atoms other than carbon, see Aylett, *Prog. Stereochem.* **4**, 213-271 (1969); Belloli, *J. Chem. Educ.* **46**, 640 (1969); and Sokolov and Reutov, *Russ. Chem. Rev.* **34**, 1-12 (1965).

[14] Brunner, *Angew. Chem. Int. Ed. Engl.* **10**, 249 (1971) [*Angew. Chem.* **83**, 274].

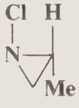
[15] Stirling, *J. Chem. Soc.* 5741 (1963); Sabol and Andersen, *J. Am. Chem. Soc.* **91**, 3603 (1969); Annunziata, Cinquini, and Colonna, *J. Chem. Soc., Perkin Trans. 1* 2057 (1972).



3. *Compounds with tervalent asymmetric atoms.* Atoms with pyramidal bonding[16] might be expected to give rise to optical activity if the atom is connected to three different groups, since the unshared pair of electrons is analogous to a fourth group, necessarily different from the others.



For example, a secondary or tertiary amine where X, Y, and Z are different would be expected to be chiral and thus resolvable. Many attempts have been made to resolve such compounds, but until recently all of them failed because of the *umbrella effect* (also called *pyramidal inversion*).[17] The umbrella effect is a rapid oscillation of the unshared pair from one side of the XYZ plane to the other, thus converting the molecule into its enantiomer. For ammonia there are 2 × 10^{11} inversions every second. The inversion is less rapid in substituted ammonias[18] (amines, amides, etc.). Two types of nitrogen atom invert particularly slowly, namely, a nitrogen atom in a three-membered ring and a nitrogen atom connected to another atom bearing an unshared pair. Even in such compounds, however, the umbrella effect has proved too rapid to permit isolation of separate isomers, and this goal was accomplished only when compounds were synthesized in which both features are combined: a nitrogen atom in a three-membered ring connected to an atom containing an unshared pair. For example, the two isomers of 1-chloro-2-methylaziridine (**3** and **4**) were separated, and do not interconvert at room temperature.[19] Similarly, it has been shown that aziridines in which the ring nitrogen atom is connected to a nitrogen or oxygen atom are also conformationally stable. For example, nmr spectra show that two of the ring protons of 1-aminoaziridine (**5**) are not equivalent to the other two,[20] which indicates that the amino group



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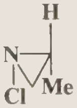

cis

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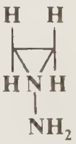

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[16] For a review of the stereochemistry of the Group V elements, see Mann, *Prog. Stereochem.* **2,** 196–227 (1958).

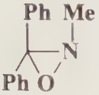
[17] For reviews of the mechanism of, and the effect of structure on, pyramidal inversion, see Lambert, *Top. Stereochem.* **6,** 19-105 (1971); Rauk, Allen, and Mislow, *Angew. Chem. Int. Ed. Engl.* **9,** 400–414 (1970) [*Angew. Chem.* **82,** 453–468]; Lehn, *Fortschr. Chem. Forsch.* **15,** 311–377 (1970); and Mislow, *Pure Appl. Chem.* **25,** 549–562 (1968).

[18] For example, see Andose, Lehn, Mislow, and Wagner, *J. Am. Chem. Soc.* **92,** 4050 (1970); Stackhouse, Baechler, and Mislow, *Tetrahedron Lett.* 3437, 3441 (1971).

[19] Brois, *J. Am. Chem. Soc.* **90,** 506, 508 (1968). See also Lehn and Wagner, *Chem. Commun.* 148 (1968); Felix and Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **7,** 224 (1968) [*Angew. Chem.* **80,** 197]; Kostyanovskii, Chervin, and Pan'shin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1354 (1968); Kostyanovskii, Samoilova, and Chervin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2705 (1968); *Tetrahedron Lett.* 719 (1969); Kostyanovskii, Markov, and Gella, *Tetrahedron Lett.* 1301 (1972). For a review, see Brois, *Trans. N.Y. Acad. Sci.* **31,** 931-951 (1969).

[20] Brois, *Tetrahedron Lett.* 5997 (1968). See also Atkinson, *Chem. Commun.* 676 (1968); Brois, *J. Am. Chem. Soc.* **92,** 1079 (1970); Ioffe and Koroleva, *Tetrahedron Lett.* 619 (1973).

stays on the same side of the ring as two of the hydrogens and does not interconvert at room temperature. In none of the above cases, however, was a compound prepared which was optically active solely because of an asymmetric ternary nitrogen atom. This has now been accomplished with the syntheses of several oxaziridines, e.g., **6**.[21] Both enantiomers of **6**, a compound which is chiral solely because of an asymmetric ternary nitrogen atom, have been prepared. Note that in this case too, the nitrogen is connected to an atom with an unshared pair. Conformational stability has also been demonstrated for diaziridines, e.g., **7**,[22] and for 1,2-oxazolidines, e.g., **8**,[23] even though in this case the ring is five-membered. However, note that the nitrogen atom here is connected to two oxygen atoms. The (+) isomer of **9** has been prepared.[24] It was completely racemized upon standing for 4 days at 0°C.



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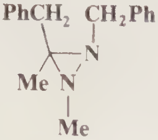

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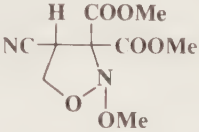

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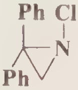
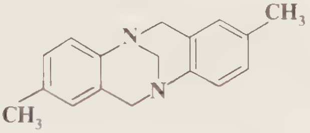


9

In molecules in which the nitrogen atom is at a bridgehead, pyramidal inversion is of course prevented, and such molecules, if chiral, can be resolved even without the presence of the two structural features noted above. For example, optically active **10** (Tröger's base) has been prepared.[25] Phosphorus inverts more slowly and arsenic still more slowly.[26] Optically active nonbridgehead phosphorus, arsenic, and antimony compounds have been resolved, e.g., **11**.[27] Sulfur exhibits pyramidal bonding in sulfoxides, sulfinic esters, sulfonium salts, and sulfites.[28] Examples of



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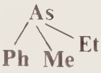

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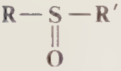
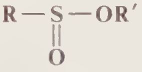
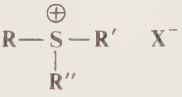


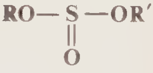
$R-\underset{O}{\underset{\|}{S}}-R'$



$R-\underset{O}{\underset{\|}{S}}-OR'$



$R-\overset{\oplus}{\underset{R''}{\underset{|}{S}}}-R' \quad X^-$



$RO-\underset{O}{\underset{\|}{S}}-OR'$

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[21] Boyd, *Tetrahedron Lett.* 4561 (1968); Boyd and Graham, *J. Chem. Soc. C* 2648 (1969); Boyd, Spratt, and Jerina, *J. Chem. Soc. C* 2650 (1969); Montanari, Moretti, and Torre, *Chem. Commun.* 1694 (1948), 1086 (1969). See also Mannschreck, Linss, and Seitz, *Justus Liebigs Ann. Chem.* **727**, 224 (1969); Bjørgo and Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1575 (1973); Betzecki and Mostowicz, *J. Chem. Soc., Chem. Commun.* 244 (1975).

[22] Mannschreck, Radeglia, Gründemann, and Ohme, *Chem. Ber.* **100**, 1778 (1967); Mannschreck and Seitz, *Angew. Chem. Int. Ed. Engl.* **8**, 212 (1969) [*Angew. Chem.* **81**, 224]; Kostyanovskii, Zakharov, Zaripova, and Rudtchenko, *Tetrahedron Lett.* 4207 (1974); Kostyanovskii, Polyakov, and Markov, *Bull. Acad. Sci. USSR., Div. Chem. Sci.* 1601 (1974).

[23] Müller and Eschenmoser, *Helv. Chim. Acta* **52**, 1823 (1969); Dobler, Dunitz, and Hawley, *Helv. Chim. Acta* **52**, 1831 (1969).

[24] Annunziata, Fornasier, and Montanari, *J. Chem. Soc., Chem. Commun.* 1133 (1972).

[25] Prelog and Wieland, *Helv. Chim. Acta* **27**, 1127 (1944).

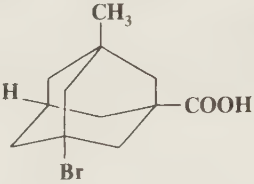
[26] For reviews, see Gallagher and Jenkins, *Top. Stereochem.* **3**, 1-96 (1968); Horner, *Pure Appl. Chem.* **9**, 225-244 (1964); and Kamaĭ and Usacheva, *Russ. Chem. Rev.* **35**, 601-613 (1966). The last review also covers arsenic compounds.

[27] Horner and Fuchs, *Tetrahedron Lett.* 203 (1962).

[28] Reid, Stein, and Fahrney, *J. Am. Chem. Soc.* **89**, 7125 (1967).

each of these have been resolved.[29] An interesting example is (+)-$Ph^{12}CH_2SO^{13}CH_2Ph$, a sulfoxide in which the two alkyl groups differ only in ^{12}C versus ^{13}C but which has $[\alpha]_{280} = +0.71°$.[30]

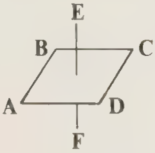
4 *Suitably substituted adamantanes.* Adamantanes bearing four different substituents at the bridgehead positions are chiral and optically active, and **12**, for example, has been resolved.[31]



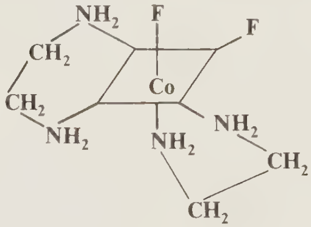
12

This type of molecule is a kind of expanded tetrahedron and has the same symmetry properties as any other tetrahedron.

5. *Compounds containing suitable substituted octahedral atoms.* Many metal ions, among them Cr(III), Pt(IV), and, most commonly, Co(III), form coordination compounds where six ligands surround the central atom. These ligands are usually found at the corners of an octahedron. If the ligands are sufficiently different, the compounds may be chiral. For example, if the six ligands are all different (as in **13**), the compound is theoretically resolvable, though no such example has yet been resolved.[32] However, many compounds with bidentate ligands, e.g., the *cis*-difluoro-bis(ethylenediamine)cobalt(III) ion (**14**), have been resolved.[33]



13



14

6. *Restricted rotation giving rise to perpendicular disymmetric planes.* Certain compounds which do not contain asymmetric atoms are nevertheless chiral because they contain a structure which can be schematically represented as in Figure 2. For these compounds we can draw two perpendicular planes neither of which can be bisected by a plane of symmetry. If either plane could be so bisected, the molecule would be superimposable on its mirror image, since such a plane would be a plane of symmetry. These points will be illustrated by examples.

Biphenyls containing four large groups in the ortho positions cannot freely rotate about the central bond because of steric hindrance.[34] In such compounds the two rings are in perpendicular

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[29] For discussion, see Shriner, Adams, and Marvel, Ref. 1, pp. 419–423.

[30] Andersen, Colonna, and Stirling, *J. Chem. Soc., Chem. Commun.* 645 (1973).

[31] Hamill and McKervey, *Chem. Commun.* 864 (1969); Applequist, Rivers, and Applequist, *J. Am. Chem. Soc.* **91**, 5705 (1969).

[32] Wilkins and Williams, in Lewis and Wilkins, "Modern Coordination Chemistry," pp. 174–228, Interscience Publishers, Inc., New York, 1960. This is a review article on the stereochemistry of coordination compounds.

[33] Matoush and Basolo, *J. Chem. Soc.* **78**, 3972 (1956).

[34] When the two rings of a biphenyl are connected by a bridge, rotation is of course impossible. For a review of such compounds, see Hall, *Prog. Stereochem.* **4**, 1-42 (1969).

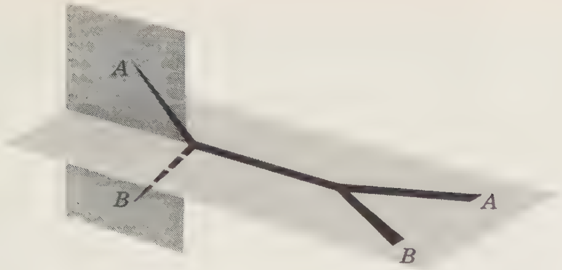
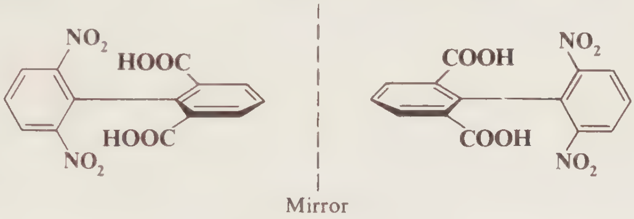


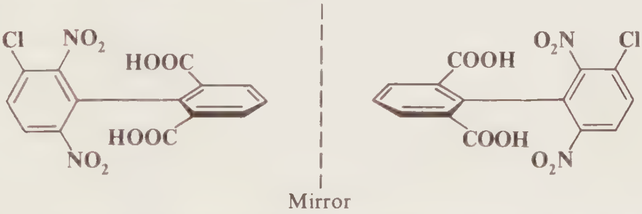
Figure 2 Perpendicular disymmetric planes.

planes. Three cases can be distinguished: both rings symmetric, one symmetric, neither symmetric. In the first case, e.g.,


NO₂
HOOC
HOOC
NO₂
COOH
COOH
NO₂
NO₂
Mirror

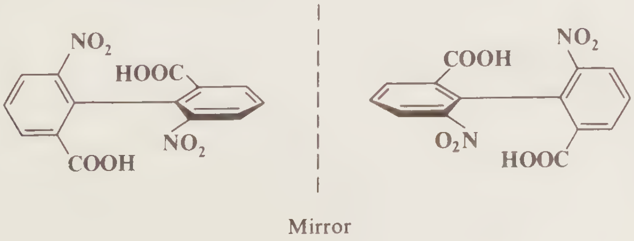
the molecule has two planes of symmetry. If a plane is drawn containing all atoms and groups in either ring, it is a *symmetrical* perpendicular bisector of the other ring. Such molecules are not chiral and, by the scheme in Figure 2, can be represented as $AA \cdots BB$.

In the second case only one ring is symmetric:


Cl
NO₂
HOOC
HOOC
NO₂
COOH
COOH
O₂N
Cl
O₂N
Mirror

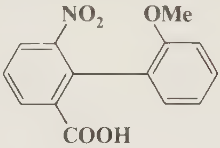
A plane drawn in the ring containing the nitro groups symmetrically bisects the other ring, but the plane of the ring containing the carboxyl groups is not a plane of symmetry. Nevertheless, one plane of symmetry is sufficient to make the compound achiral, and it is. The case can be symbolized as $AB \cdots CC$.

In the third case neither ring is symmetric:


NO₂
HOOC
NO₂
COOH
COOH
NO₂
O₂N
HOOC
Mirror

There is no plane of symmetry, and the molecule is chiral; many such compounds have been resolved. This corresponds to *AB* ··· *AB*. Of course *AB* ··· *CD* cases are also chiral. It is important to note that, if *either* ring is symmetrical, the molecule has a plane of symmetry and is achiral and that groups in the para position cannot cause lack of symmetry. Isomers which can be separated only because rotation about single bonds is prevented or greatly slowed are called *atropisomers.*

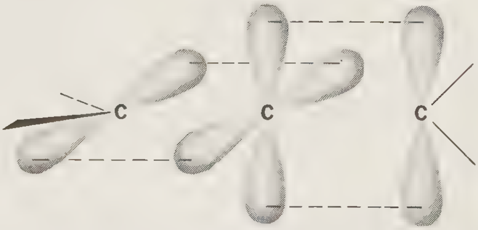
It is not always necessary for four large ortho groups to be present in order for rotation to be prevented. Compounds with three and even two groups, if large enough, can have hindered rotation and, if suitably substituted, can be resolved. An example is biphenyl-2,2′-bissulfonic acid.[35] In some cases, the groups may be large enough to slow rotation greatly but not prevent it completely. In such cases, optically active compounds can be prepared which slowly racemize on standing. Thus, **15** loses its optical activity with a half-life of 9.4 min in ethanol at 25°C.[36] Compounds with greater rotational stability can often be racemized if higher temperatures are used to supply the energy necessary to force the groups past each other.

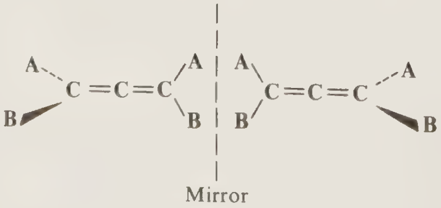


15

Many analogous cases are known, where optical activity arises from hindered rotation of other types of aromatic ring, e.g., binaphthyls, bipyrryls, etc.

In allenes the central carbon is *sp*-bonded. The remaining two *p* orbitals are perpendicular to each other, and each overlaps with the *p* orbital of one adjacent carbon atom, forcing the two remaining bonds of each carbon into perpendicular planes. Thus allenes fall into the category represented by Figure 2:





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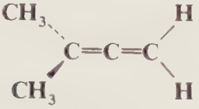
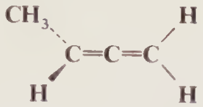
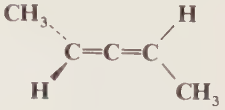
[35] Patterson and Adams, *J. Am. Chem. Soc.* **57**, 762 (1935).

[36] Stoughton and Adams, *J. Am. Chem. Soc.* **54**, 4426 (1932).

Like biphenyls, allenes are chiral only if both sides are dissymmetric.[37] Compounds corresponding to the three biphenyl cases are

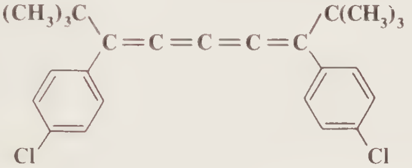

Inactive
AA ··· *BB*


Inactive
AB ··· *CC*


Active
AB ··· *AB*

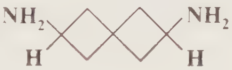
These cases are completely different from the cis-trans isomerism of compounds with one double bond (p. 113). In the latter cases the four groups are all in one plane, the isomers are not enantiomers, and neither is chiral, while in allenes the groups are in two perpendicular planes and the isomers are a pair of optically active enantiomers.

When three, five, or any *odd* number of cumulative double bonds exist, orbital overlap causes the four groups to occupy one plane, and cis-trans isomerism is observed. When four, six, or any *even* number of cumulative double bonds exist, the situation is analogous to that in the allenes, and optical activity is possible. **16** has been resolved.[38]



16

Among other types of compounds which contain the system illustrated in Figure 2 and which are similarly chiral if they are *AB* ··· *AB* substituted are spiranes, e.g., **17**, and compounds with exocyclic double bonds, e.g., **18**.



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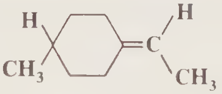

18

7. *Chirality due to a helical shape.* Several compounds have been prepared which are chiral because they have a shape which is actually helical and can therefore be left- or right-handed in orientation. The entire molecule is usually less than one full turn of the helix, but this does not alter the possibility of left- and right-handedness. An example is hexahelicene[39] (**19**), in which one side of the molecule must lie above the other because of crowding.[40] Another is *trans*-

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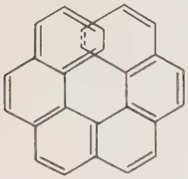
[37] For a review of chiral allenes, see Rossi and Diversi, *Synthesis* 25–36 (1973).

[38] Nakagawa, Shingū, and Naemura, *Tetrahedron Lett.* 802 (1961).

[39] Newman and Lednicer, *J. Am. Chem. Soc.* **78**, 4765 (1956). Optically active heptahelicene has also been prepared, as have higher helicenes: Flammang-Barbieux, Nasielski, and Martin, *Tetrahedron Lett.* 743 (1967); Martin, Flammang-Barbieux, Cosyn, and Gelbcke, *Tetrahedron Lett.* 3507 (1968); Martin, Morren, and Schurter, *Tetrahedron Lett.* 3683 (1969); Martin and Schurter, *Tetrahedron* **28**, 1749 (1972); Martin and Marchant, *Tetrahedron* **30**, 343 (1974); Martin and Baes, *Tetrahedron* **31**, 2135 (1975); Bernstein, Calvin, and Buchardt, *J. Am. Chem. Soc.* **94**, 494 (1972), **95**, 527 (1973). Even pentahelicene is crowded enough to be chiral: Goedicke and Stegemeyer, *Tetrahedron Lett.* 937 (1970); Bestmann and Röth, *Chem. Ber.* **107**, 2923 (1974).

[40] For a review of the helicenes, see Martin, *Angew. Chem. Int. Ed. Engl.* **13**, 649-660 (1974) [*Angew. Chem.* **86**, 727-738].

cyclooctene (**20**) (see p. 115), in which the carbon chain must lie above the plane of the double bond on one side and below it on the other.[41]



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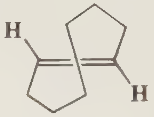

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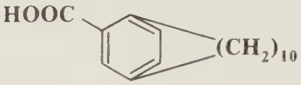
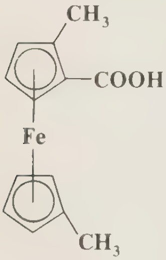
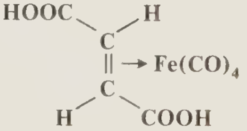


21

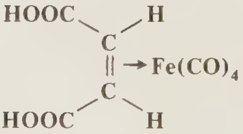
8. *Chirality caused by restricted rotation of other types.* Substituted paracyclophanes may be optically active, and **21**, for example, has been resolved.[42] In this case chirality results because the benzene ring cannot rotate in such a way that the carboxyl group goes through the alicyclic ring. Metallocenes substituted with at least two different groups on one ring are also chiral.[43] More than



22



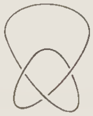
23



24

200 such compounds have been resolved, one example being **22.** Chirality is also found in other metallic complexes of suitable geometry.[44] For example, fumaric acid -iron tetracarbonyl (**23**) has been resolved.[45] The corresponding maleic acid compound (**24**) has a plane of symmetry and is not resolvable.

An interesting type of chirality has been proposed, though no example is yet known.[46] Rings containing 50 or more members should be able to exist as knots:



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[41] Cope, Ganellin, Johnson, Van Auken, and Winkler, *J. Am. Chem. Soc.* **85**, 3276 (1963). Also see Cope, Banholzer, Keller, Pawson, Whang, and Winkler, *J. Am. Chem. Soc.* **87**, 3644 (1965); Cope, Hecht, Johnson, Keller, and Winkler, *J. Am. Chem. Soc.* **88**, 761 (1966); and Levin and Hoffmann, *J. Am. Chem. Soc.* **94**, 3446 (1972).

[42] Blomquist, Stahl, Meinwald, and Smith, *J. Org. Chem.* **26**, 1687 (1961).

[43] For reviews on the stereochemistry of metallocenes, see Schlögl, *Top. Stereochem.* **1**, 39–91 (1967), *Pure Appl. Chem.* **23**, 413–432 (1970).

[44] For reviews of such complexes, see Paiaro, *Organomet. Chem. Rev., Sect. A* **6**, 319–335 (1970).

[45] Paiaro, Palumbo, Musco, and Panunzi, *Tetrahedron Lett.* 1067 (1965); also see Paiaro and Panunzi, *J. Am. Chem. Soc.* **86**, 5148 (1964).

[46] Frisch and Wasserman, *J. Am. Chem. Soc.* **83**, 3789 (1961).

Such a knot would be nonsuperimposable on its mirror image. Catenanes and rotaxanes (see p. 85) can also be chiral if suitably substituted.[47]

Creation of a Chiral Center

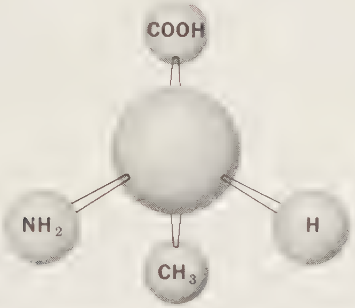
Any structural feature of a molecule which gives rise to optical activity may be called a chiral center. In many reactions a new chiral center is created, e.g.,

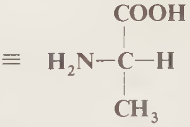
$$\mathrm{CH_3CH_2COOH + Br_2 \xrightarrow{P} CH_3CHBrCOOH}$$

If the reagents and reaction conditions are all symmetric, the product must be a racemic mixture. No optically active material can be created if all starting materials and conditions are optically inactive.[48] This statement also holds when one begins with a racemic mixture. Thus racemic 2-butanol, treated with HBr, must give racemic 2-bromobutane.

The Fischer Projection

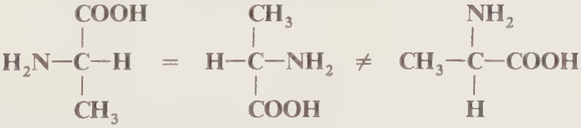
For a thorough understanding of stereochemistry it is useful to examine molecular models (like those depicted in Figure 1). However, when writing on paper or on the blackboard this is not feasible, and in 1891 Emil Fischer greatly served the interests of chemistry by inventing the Fischer projection, a method of representing tetrahedral carbons on paper. By this convention, the model is held so that the two bonds in front of the paper are horizontal and those behind the paper are vertical:





$$\equiv \begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H_2N{-}C{-}H} \\ | \\ \mathrm{CH_3} \end{array}$$

In order to obtain proper results from these formulas, it should be remembered that they are projections and must be treated differently from the models in testing for superimposability. Every plane is superimposable on its mirror image; hence with these formulas there must be added the restriction they they may not be taken out of the plane of the blackboard or paper. Also they may not be rotated 90°, though 180° rotation is permissible:



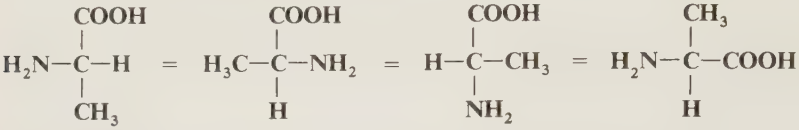
$$\begin{array}{c} \mathrm{COOH} \\ | \\ \mathrm{H_2N{-}C{-}H} \\ | \\ \mathrm{CH_3} \end{array} = \begin{array}{c} \mathrm{CH_3} \\ | \\ \mathrm{H{-}C{-}NH_2} \\ | \\ \mathrm{COOH} \end{array} \neq \begin{array}{c} \mathrm{NH_2} \\ | \\ \mathrm{CH_3{-}C{-}COOH} \\ | \\ \mathrm{H} \end{array}$$

---

[47] For a discussion of the stereochemistry of these compounds, see Schill, "Catenanes, Rotaxanes, and Knots," pp. 11–18, Academic Press, Inc., New York, 1971.

[48] There is one exception to this statement. In a very few cases racemic mixtures may crystallize from solution in such a way that all the (+) molecules go into one crystal and the (−) molecules into another. If one of the crystals crystallizes before the other, a rapid filtration results in optically active material. For a discussion, see Pincock and Wilson, *J. Chem. Educ.* **50**, 455 (1973).

It is also permissible to keep any one group fixed and to rotate the other three clockwise or counterclockwise (because this can be done with models):



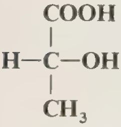
$$\begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ \mathrm{H_2N}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_3} & \end{array} = \begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ \mathrm{H_3C}- & \mathrm{C} & -\mathrm{NH_2} \\ & | & \\ & \mathrm{H} & \end{array} = \begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{CH_3} \\ & | & \\ & \mathrm{NH_2} & \end{array} = \begin{array}{rcl} & \mathrm{CH_3} & \\ & | & \\ \mathrm{H_2N}- & \mathrm{C} & -\mathrm{COOH} \\ & | & \\ & \mathrm{H} & \end{array}$$

However, the *interchange* of any two groups results in the conversion of an enantiomer into its mirror image (this applies to models as well as to the Fischer projections).

With these restrictions Fischer projections may be used instead of models to test whether a molecule containing asymmetric carbons is superimposable on its mirror image. However, there are no such conventions for molecules whose chirality arises from anything other than asymmetric atoms, and when such molecules are examined on paper, three-dimensional pictures must be used and there are no restrictions about the plane of the paper.

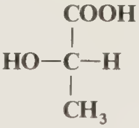
Absolute Configuration

Suppose we have two test tubes, one containing (−)-lactic acid, and the other the (+) enantiomer. One test tube contains **25** and the other **26**. How do we know which is which? Chemists in the early part of this century pondered this problem and decided that they could not know—for lactic acid or any other compound. Therefore Rosanoff proposed that one compound be chosen as a standard and a configuration be arbitrarily assigned to it. The compound chosen was glyceraldehyde because of its relationship to the sugars. The (+) isomer was assigned the configuration shown in **27**, and it was given the label D. The (−) isomer, designated to be **28**, was given the label L. Once a standard was chosen, other compounds could then be related to it. For example, (+)-glyceraldehyde, oxidized with mercuric oxide, gives (−)-glyceric acid:



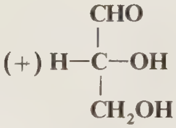
$$\begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

25



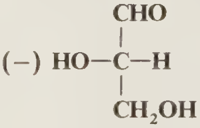
$$\begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

26



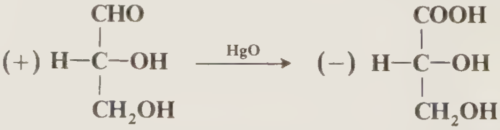
$$\begin{array}{rcl} & \mathrm{CHO} & \\ & | & \\ (+)\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

27



$$\begin{array}{rcl} & \mathrm{CHO} & \\ & | & \\ (-)\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

28



$$\begin{array}{rcl} & \mathrm{CHO} & \\ & | & \\ (+)\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array} \xrightarrow{\mathrm{HgO}} \begin{array}{rcl} & \mathrm{COOH} & \\ & | & \\ (-)\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{CH_2OH} & \end{array}$$

Since it is highly improbable that the configuration at the central carbon changed, it can be concluded that (−)-glyceric acid has the same configuration as (+)-glyceraldehyde, and therefore (−)-glyceric acid is also called D. This example emphasizes that molecules with the same configuration need not rotate the plane of polarized light in the same direction. This fact should not surprise us when we remember that the same compound can rotate the plane in opposite directions under different conditions.

Once the configuration of the glyceric acids was known (in relation to the glyceraldehydes), it was then possible to relate other compounds to either of these, and each time a new compound was related, others could be related to *it*. In this way many thousands of compounds have now been related, indirectly, to D- or L-glyceraldehyde, and it has been determined that **25**, which has the D configuration, is the isomer which rotates the plane of polarized light to the left. Even compounds without asymmetric atoms, such as biphenyls[49] and allenes,[50] have been placed in the D or L series.[51] When a compound has been placed in the D or L series, its *absolute configuration* is said to be known.

In 1951 it became possible to determine whether Rosanoff's guess had been right. Ordinary x-ray crystallography is powerless to distinguish between a D and an L isomer, but by use of a special technique, Bijvoet was able to examine sodium rubidium tartrate and found that Rosanoff had made the correct choice.[52] By this time the fact was interesting to know, but it would have made no difference to organic chemists if he had made the wrong choice, since this would not have affected the important thing, which is the relationship of one compound to another. It was perhaps historically fitting that the first true absolute configuration should have been determined on a salt of tartaric acid, since Pasteur made his great discoveries on another salt of this acid.

In spite of the former widespread use of D and L to denote absolute configuration, the method is not without faults. The designation of a particular enantiomer as D or L often depends on which compounds it is related to. Examples are known where an enantiomer can, by five or six steps, be related to a known D compound, and by five or six other steps, be related to the L enantiomer of the same compound. In a case of this sort, an arbitrary choice of D or L must be used. Because of this and other flaws, the DL system is seldom used today, except for certain groups of compounds such as carbohydrates and amino acids.

The system which has essentially replaced the DL system is the *Cahn-Ingold-Prelog* system, in which the four groups on an asymmetric carbon are ranked according to a set of sequence rules.[53] For our purposes we may confine ourselves to only a few of these rules, which are sufficient to deal with the vast majority of chiral compounds:

1. Substituents are listed in order of decreasing atomic number of the atom directly joined to the carbon.

2. Where two or more of the atoms connected to the asymmetric carbon are the same, the atomic number of the second atom determines the order. For example, in the molecule $Me_2CH—CHBr—CH_2OH$, the CH_2OH group takes precedence over the Me_2CH group because oxygen has a higher atomic number than carbon. Note that this is so even though there are two carbons in Me_2CH and only one oxygen in CH_2OH. If two or more atoms connected to the second atom are the same, the third atom determines the precedence, etc.

3. All atoms except hydrogen are formally given a valence of 4. Where the actual valence is less (as in nitrogen, oxygen, or a carbanion), phantom atoms are used to bring the valence up to four. These phantom atoms are assigned an atomic number of zero and necessarily rank lowest. Thus the ligand $—\overset{+}{N}HMe_2$ would rank higher than $—NMe_2$.

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[49] Newman, Rutkin, and Mislow, *J. Am. Chem. Soc.* **80**, 465 (1958).

[50] Eliel, *Tetrahedron Lett.* no. 8, 16 (1960); Jones, Loder, and Whiting, *Proc. Chem. Soc.* 180 (1960).

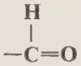
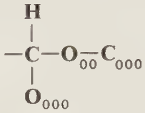
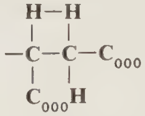
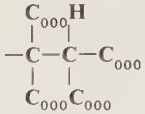
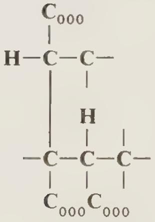
[51] The use of small *d* and *l* is now discouraged, since some authors used it for rotation, and some for configuration. However, a racemic mixture is still a *dl* mixture, since there is no ambiguity here.

[52] Bijvoet, Peerdeman, and van Bommel, *Nature* **168**, 271 (1951). For a list of organic structures whose absolute configurations have been determined by this method, see Allen and Rogers, *Chem. Commun.* 838 (1966), Allen, Neidle, and Rogers, *Chem. Commun.* 308 (1968), 452 (1969); Neidle, Rogers, and Allen, *J. Chem. Soc. C* 2340 (1970).

[53] For descriptions of the system and sets of sequence rules, see Ref. 2; Cahn, Ingold, and Prelog, *Angew. Chem. Int. Ed. Engl.* **5**, 385–415 (1966) [*Angew. Chem.* **78**, 413–447]; Cahn, *J. Chem. Educ.* **41**, 116 (1964); and Fernelius, Loening, and Adams, *J. Chem. Educ.* **51**, 735 (1974).

4. A tritium atom takes precedence over deuterium, which in turn takes precedence over ordinary hydrogen. Similarly, any higher isotope (such as ^{14}C) takes precedence over any lower one.

5. Double and triple bonds are counted as if they were split into two or three single bonds, respectively, as in these examples (note the treatment of the phenyl group):

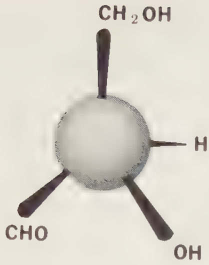
Group	Treated as if it were
 $-\overset{H}{\overset{\vert}{C}}=O$	
$-CH=CH_2$	
$-C\equiv CH$	
$-C_6H_5$	

The subscript $_0$ denotes a phantom atom. Note that in a C=C double bond, the two carbon atoms are *each* regarded as being connected to two carbon atoms and that one of the latter is counted as having three phantom substituents.

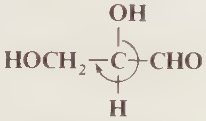
As an exercise, we shall compare the four groups shown above. The first atoms are connected, respectively, to (H, O, O), (H, C, C), (C, C, C), and (C, C, C). That is enough to establish that —CHO ranks first and $-CH=CH_2$ last, since even one oxygen outranks three carbons, and three carbons outrank two carbons and a hydrogen. To classify the remaining two groups we must proceed further along the chains. We note that $-C_6H_5$ has two of its (C, C, C) carbons connected to (C, C, H), while the third is $(_0, _0, _0)$ and is thus preferred to $-C\equiv CH$, which has only one (C, C, H) and two $(_0, _0, _0)$s.

By application of the above rules, some groups in descending order of precedence are COOH, COPh, COMe, CHO, $CH(OH)_2$, *o*-tolyl, *m*-tolyl, *p*-tolyl, phenyl, C≡CH, *t*-butyl, cyclohexyl, vinyl, isopropyl, benzyl, neopentyl, allyl, *n*-pentyl, ethyl, methyl, deuterium, hydrogen. Thus the four groups of glyceraldehyde are to be arranged in the sequence: OH, CHO, CH_2OH, H.

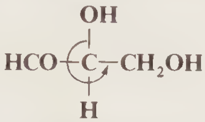
Once the order is determined, the molecule is held so that the lowest group in the sequence is pointed away from the viewer. Then if the other groups, in the order listed, are oriented clockwise, the molecule is designated *R*, and if counterclockwise, *S*. For glyceraldehyde, the (+) enantiomer is *R*:



Note that when a compound is written in the Fischer projection, the configuration can easily be determined without constructing the model. If the lowest-ranking group is at the bottom, the *R* configuration is present if the other three groups in descending order are clockwise, e.g.,

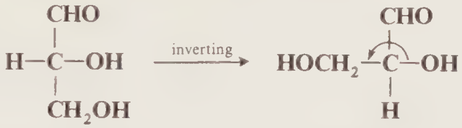


(*R*)-Glyceraldehyde



(*S*)-Glyceraldehyde

If the lowest ranking group is not at the bottom, one can simply interchange it with the bottom group, bearing in mind that in so doing, one is inverting the isomer:



(*S*)-Glyceraldehyde

Therefore the original compound was (*R*)-glyceraldehyde.

The Cahn-Ingold-Prelog system is unambiguous and easily applicable in most cases. Whether to call an enantiomer *R* or *S* does not depend on correlations, but of course the configuration must be known before the system can be applied, and this does depend on correlations. The Cahn-Ingold-Prelog system has also been extended to chiral compounds which do not contain asymmetric atoms.[54]

Methods of Determining Configuration[55]

In all the methods[56] it is necessary to relate the compound of unknown configuration to another whose configuration is known. The most important methods of doing this are:

1. Conversion of the unknown to, or formation of the unknown from, a compound of known configuration without disturbing the chiral center. See the glyceraldehyde glyceric acid example above (p. 98). Since the chiral center was not disturbed, the unknown obviously has the same configuration as the known. This does not necessarily mean that if the known is *R*, the unknown is also *R*. This will be so if the sequence is not disturbed but not otherwise. For example, when (*R*)-1-bromo-2-butanol is reduced to 2-butanol without disturbing the chiral center, the product

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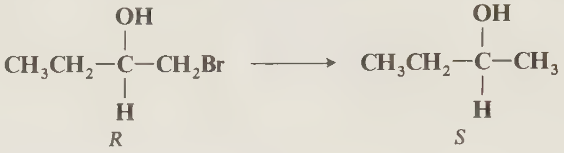
[54] For a discussion of these rules, as well as for a review of methods for establishing configurations of chiral compounds not containing asymmetric atoms, see Krow, *Top. Stereochem.* **5**, 31–68 (1970).

[55] For reviews, see Brewster, in Bentley and Kirby, "Elucidation of Organic Structures by Physical and Chemical Methods," 2d ed. (vol. 4 of Weissberger, "Techniques of Chemistry"), pt. 3, pp. 1–249, John Wiley & Sons, Inc., New York, 1972; Klyne and Scopes, *Prog. Stereochem.* **4**, 97–166 (1969); Schlenk, *Angew. Chem. Int. Ed. Engl.* **4**, 139–145 (1965) [*Angew. Chem.* **77**, 161–168]; and Mills and Klyne, *Prog. Stereochem.* **1**, 177–222 (1954). For a monograph on the determination of absolute configuration in coordination compounds, see Hawkins, "Absolute Configuration of Metal Complexes," John Wiley & Sons, Inc., New York, 1971.

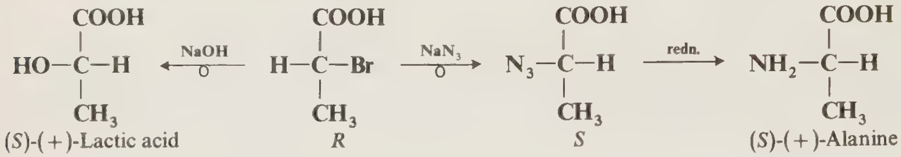
[56] Except the x-ray method of Bijvoet.



$$\underset{R}{CH_3CH_2-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-CH_2Br} \longrightarrow \underset{S}{CH_3CH_2-\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}-CH_3}$$

is the *S* isomer, even though the configuration is unchanged, because CH_3CH_2 ranks lower than $BrCH_2$ but higher than CH_3.

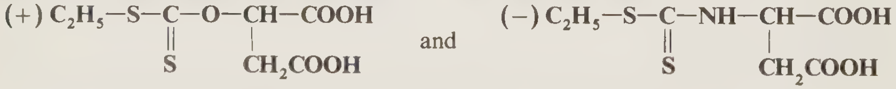
2. Conversion at the chiral center if the mechanism is known. Thus, the SN2 mechanism proceeds with inversion of configuration at an asymmetric carbon (see p. 267). It was by a series of such transformations that lactic acid was related to alanine (the symbol $\xrightarrow[o]{}$ is used to signify inversion of configuration):



$$\underset{(S)\text{-}(+)\text{-Lactic acid}}{HO-\overset{\displaystyle COOH}{\underset{\displaystyle CH_3}{C}}-H} \xleftarrow[o]{NaOH} \underset{R}{H-\overset{\displaystyle COOH}{\underset{\displaystyle CH_3}{C}}-Br} \xrightarrow[o]{NaN_3} \underset{S}{N_3-\overset{\displaystyle COOH}{\underset{\displaystyle CH_3}{C}}-H} \xrightarrow{redn.} \underset{(S)\text{-}(+)\text{-Alanine}}{NH_2-\overset{\displaystyle COOH}{\underset{\displaystyle CH_3}{C}}-H}$$

See also the discussion on pp. 267–268.

3. The method of quasi racemates.[57] It was mentioned (p. 87) that a solid racemic mixture often has a melting point which differs from that of the two enantiomers. In many such cases the molecules of the *R* isomer fit better into the lattice when they are next to molecules of *S* isomer, and there are fairly strong van der Waals forces between the *R* and *S* molecules. Such mixtures are known as *racemic compounds* and are recognizable by characteristic melting-point curves. In some cases it has been found that "racemic compounds" are formed between the *R* isomer of one compound and the *S* isomer of another compound which is similar to but not identical with the first. These *quasi racemates* are recognizable because their melting-point curves look like the curves of true racemic compounds. Mixtures are prepared of the unknown compound with known *R* and *S* forms of a similar compound. If the unknown is *R*, the mixture with the known *S* may be a quasi racemate but the mixture with the known *R* will not be. For example, two compounds which form a quasi racemate and hence have opposite configurations are



$$(+)\,C_2H_5-S-\underset{\displaystyle S}{\underset{\|}{C}}-O-\underset{\displaystyle CH_2COOH}{\underset{|}{CH}}-COOH \quad \text{and} \quad (-)\,C_2H_5-S-\underset{\displaystyle S}{\underset{\|}{C}}-NH-\underset{\displaystyle CH_2COOH}{\underset{|}{CH}}-COOH$$

4. Biochemical methods. In a series of similar compounds, such as amino acids or certain types of steroids, a given enzyme will usually attack only those molecules with one kind of configuration. If the enzyme attacks only the L form of eight amino acids, say, then attack on the unknown ninth amino acid will also be on the L form.

5. Optical comparison. It is sometimes possible to use the sign and extent of rotation to determine which isomer has which configuration. In a homologous series, the rotation usually changes gradually and in one direction. If the configurations of enough members of the series are known, the configurations of the missing ones can be determined by extrapolation. Also certain groups contribute more or less fixed amounts to the rotation of the parent molecule, especially when the parent is a rigid system such as a steroid.

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[57] For reviews, see Fredga, *Tetrahedron* **8**, 126–144 (1960), *Bull. Soc. Chim. Fr.* 173–182 (1973).

6. The special x-ray method of Bijvoet gives direct answers and has been used in a number of cases.[52]

Other methods have also been used, including optical rotatory dispersion (see p. 135) and asymmetric synthesis (see p. 107). It must be remembered that no method is completely foolproof, and false assignments are sometimes made.

The Cause of Optical Activity

The question may be asked: Just why does a chiral molecule rotate the plane of polarized light? Theoretically, the answer to this question is known and in a greatly simplified form may be explained as follows.[58]

Whenever any light hits any molecule in a transparent material, the light is slowed because of interaction with the molecule. This phenomenon on a gross scale is responsible for the refraction of light, and the decrease in velocity is proportional to the refractive index of the material. The extent of interaction depends on the polarizability of the molecule. Plane-polarized light may be regarded as being made up of two kinds of circularly polarized light. Circularly polarized light has the appearance (or would have, if one could see the wave) of a helix propagating around the axis of light motion, and one kind is a left-handed and the other a right-handed helix. As long as the plane-polarized light is passing through a symmetrical region, the two circularly polarized components travel at the same speed. However, a chiral molecule has polarizability which is different depending on whether it is approached from the left or the right. One circularly polarized component approaches the molecule, so to speak, from the left and sees a different polarizability (hence on a gross scale, a different refractive index) than the other and is slowed to a different extent. This would seem to mean that the left- and right-handed circularly polarized components travel at different velocities, since each has been slowed to a different extent. However, it is not possible for two components of the same light to be traveling at different velocities. What actually takes place, therefore, is that the faster component "pulls" the other toward it, resulting in rotation of the plane. These ideas can be expressed mathematically, and in principle it is possible to calculate the sign and amount of rotation for any molecule (this represents an additional way of determining absolute configuration). However, it is necessary to use wave equations, the limitations of which were discussed in Chapter 1. Hence, in practice, the sign and amount of rotation have been calculated for very few molecules, and the results have been wrong about as often as they have been right. Empirical methods for the prediction of the sign and amount of rotation based on bond refractions and on polarizabilities of groups in a molecule have been devised,[59] and these methods have given fairly good results in many cases.

In liquids and gases the molecules are randomly oriented. A molecule which is optically inactive because it has a plane of symmetry will very seldom be oriented so that the plane of the polarized light coincides with the plane of symmetry. When it is so oriented, that particular molecule does not rotate the plane but all others not oriented in that manner do rotate the plane, even though the molecules are achiral. There is no net rotation because, the molecules being present in large number and randomly oriented, there will always be another molecule later on in the path of the light which is oriented exactly opposite and will rotate the plane back again. Even though nearly all molecules are rotating the plane individually, the total rotation is zero. For chiral molecules, however (if there is no racemic mixture), no opposite orientation is present, and there is a net rotation.

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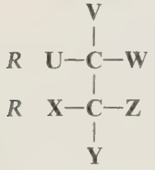
[58] For longer, nontheoretical discussions, see Eliel, "Stereochemistry of Carbon Compounds," Ref. 1, pp. 398 412; and Wheland, Ref. 1, pp. 204–211. For theoretical discussions, see Caldwell and Eyring, "The Theory of Optical Activity," John Wiley & Sons, Inc., New York, 1971; Kauzmann, "Quantum Chemistry," pp. 616 635, Academic Press, Inc., New York, 1957; Buckingham and Stiles, *Acc. Chem. Res.* **7**, 258 264 (1974); Mason, *Q. Rev., Chem. Soc.* **17**, 20 66 (1963); and Liehr, *J. Phys. Chem.* **68**, 665, 3629 (1964).

[59] Brewster, *Top. Stereochem.* **2**, 1–72 (1967), *J. Am. Chem. Soc.* **81**, 5475, 5483, 5493 (1959); Davis and Jensen, *J. Org. Chem.* **35**, 3410 (1970). See also Applequist, *J. Am. Chem. Soc.* **95**, 8255, 8258 (1973).

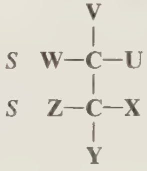
Molecules with More than One Chiral Center

When a molecule has two chiral centers, each center has its own configuration. Each center can be classified *R* or *S* by the Cahn-Ingold-Prelog method. There is a total of four isomers, since the first center may be *R* or *S* and so may the second. Since a molecule can have only one mirror image, only one of the other three can be the enantiomer of **29.** This is **30. 31** and **32** are a second pair of enantiomers, and the relationship of these to **29** and **30** is designated by the term *diastereomer*. Diastereomers may be defined as *stereoisomers which are not enantiomers*. **31** and **32,** being enantiomers, must have identical properties, except as noted on p. 86, and the same is true for **29** and **30.** However, the properties of **29** and **30** are not identical with those of **31** and **32.** They have different melting points, boiling points, solubilities, reactivity, and all other physical and chemical properties. The properties are usually *similar* but not *identical*. In particular, diastereomers have different specific rotations; indeed one diastereomer may be chiral and rotate the plane of polarized light while another may be achiral and not rotate at all (we shall see an example below).



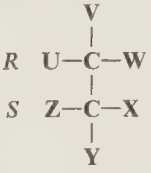
$$\begin{array}{rccc} & & \mathrm{V} & \\ & & | & \\ R & \mathrm{U}- & \mathrm{C} & -\mathrm{W} \\ & & | & \\ R & \mathrm{X}- & \mathrm{C} & -\mathrm{Z} \\ & & | & \\ & & \mathrm{Y} & \end{array}$$

29



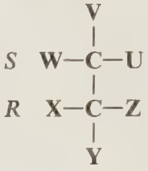
$$\begin{array}{rccc} & & \mathrm{V} & \\ & & | & \\ S & \mathrm{W}- & \mathrm{C} & -\mathrm{U} \\ & & | & \\ S & \mathrm{Z}- & \mathrm{C} & -\mathrm{X} \\ & & | & \\ & & \mathrm{Y} & \end{array}$$

30



$$\begin{array}{rccc} & & \mathrm{V} & \\ & & | & \\ R & \mathrm{U}- & \mathrm{C} & -\mathrm{W} \\ & & | & \\ S & \mathrm{Z}- & \mathrm{C} & -\mathrm{X} \\ & & | & \\ & & \mathrm{Y} & \end{array}$$

31

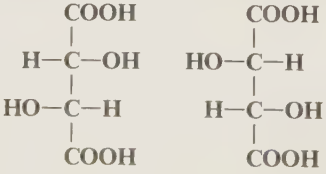


$$\begin{array}{rccc} & & \mathrm{V} & \\ & & | & \\ S & \mathrm{W}- & \mathrm{C} & -\mathrm{U} \\ & & | & \\ R & \mathrm{X}- & \mathrm{C} & -\mathrm{Z} \\ & & | & \\ & & \mathrm{Y} & \end{array}$$

32

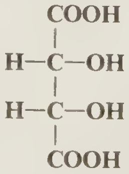
It is now possible to see why, as mentioned on p. 86, enantiomers react at different rates with other chiral molecules but at the same rate with achiral molecules. In the latter case, the activated complex formed from the *R* enantiomer and the other molecule is the mirror image of the activated complex formed from the *S* enantiomer and the other molecule. Since the two activated complexes are enantiomeric, their energies are the same and the rates of the reactions in which they are formed must be the same (see Chapter 6). However, when an *R* enantiomer reacts with a chiral molecule which has, say, the *R* configuration, the activated complex has two chiral centers, with configurations *R* and *R*, while the activated complex formed from the *S* enantiomer will have the configurations *S* and *R*. The two activated complexes are diastereomeric, do not have the same energies, and consequently are formed at different rates.

Although four is the usual (and the maximum possible) number of isomers when the compound has two chiral centers (chiral compounds without an asymmetric carbon, or with one asymmetric carbon and another type of chiral center also follow the rules described here), some compounds have fewer. When the three groups on one asymmetric atom are the same as those on the other, one of the isomers (called a *meso* form) has a plane of symmetry and hence is optically inactive, even though it has two asymmetric carbons. Tartaric acid is a typical case:



$$\begin{array}{ccc} & \mathrm{COOH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ & \mathrm{COOH} & \end{array} \qquad \begin{array}{ccc} & \mathrm{COOH} & \\ & | & \\ \mathrm{HO}- & \mathrm{C} & -\mathrm{H} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{COOH} & \end{array}$$

dl pair

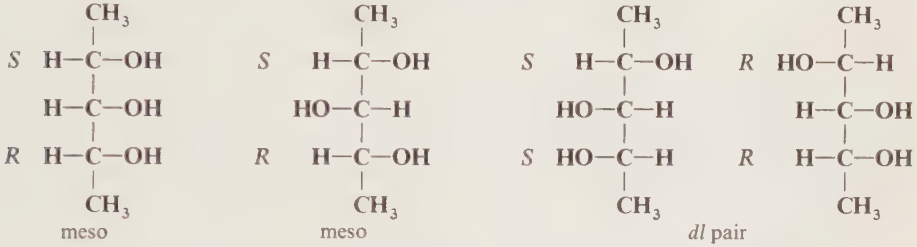


$$\begin{array}{ccc} & \mathrm{COOH} & \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ \mathrm{H}- & \mathrm{C} & -\mathrm{OH} \\ & | & \\ & \mathrm{COOH} & \end{array}$$

meso

There are only three isomers of tartaric acid: a pair of enantiomers and an inactive meso form.

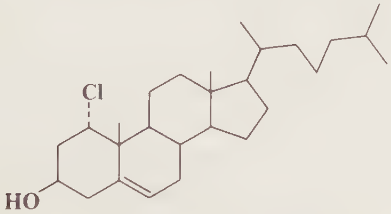
In most cases with more than two chiral centers, the number of isomers can be calculated from the formula 2^n, where n is the number of chiral centers, although in some cases the actual number is less than this, owing to meso forms. An interesting case is that of 2,3,4-pentanetriol (or any similar molecule). The middle carbon is not asymmetric when the 2- and 4-carbons are both *R* (or both *S*) but is asymmetric when one of them is *R* and the other *S*. Such a carbon is called a *pseudoasymmetric* carbon. In these cases there are four isomers: two meso forms and one *dl* pair:



The student should satisfy himself, remembering the rules governing use of the Fischer projections, that these isomers are different, that the meso forms are superimposable on their mirror images, and that there are no other stereoisomers. Two diastereomers which have a different configuration at only one chiral center are called *epimers*.

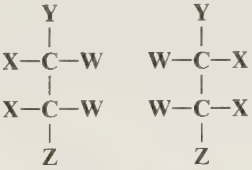
In compounds with two or more chiral centers, the absolute configuration must be separately determined for each center. The usual procedure is to determine the configuration at one center by the methods discussed on pp. 101–103 and then to relate the configuration at that center to the others in the molecule. One method for doing this is x-ray crystallography, which, as previously noted, cannot be used to determine the absolute configuration at any chiral center but which does give relative configurations of all of the chiral centers in a molecule and hence the absolute configurations of all once the first is independently determined. Other physical and chemical methods have also been used for this purpose (see, for example, pp. 116, 135).

The problem arises how to name the different stereoisomers of a compound when there are more than two.[2] Enantiomers are virtually always called by the same name, being distinguished by *R* and *S*, or D and L, or (+) and (−). In the early days of organic chemistry, it was customary to give each pair of enantiomers a different name, or at least a different prefix (such as *epi-*, *peri-*, etc.). Thus the aldohexoses are called glucose, mannose, idose, etc., though they are all 2,3,4,5,6-pentahydroxyhexanal. This practice was partially due to lack of knowledge of which isomers had which configurations. In recent years it has been customary to describe *each chiral position* separately, as either *R* or *S* or, in special fields, using other symbols. Thus, in the case of steroids, groups above the "plane" of the ring system are designated β, and those below it α. Solid lines are used to depict β groups, and dashed lines for α groups. An example is



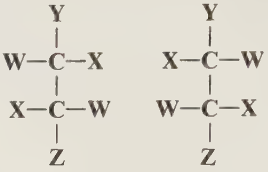
1α-Chloro-5-cholesten-3β-ol

For many open-chain compounds prefixes are used which are derived from the names of the corresponding sugars and which describe the whole system rather than each chiral center separately. Two such prefixes in common use are *erythro-* and *threo-*, which are applied to systems containing two asymmetric carbons when two of the groups are the same and the third is different.



$$\begin{array}{c}Y\\|\\X-C-W\\|\\X-C-W\\|\\Z\end{array}\qquad\begin{array}{c}Y\\|\\W-C-X\\|\\W-C-X\\|\\Z\end{array}$$

erythro *dl* pair



$$\begin{array}{c}Y\\|\\W-C-X\\|\\X-C-W\\|\\Z\end{array}\qquad\begin{array}{c}Y\\|\\X-C-W\\|\\W-C-X\\|\\Z\end{array}$$

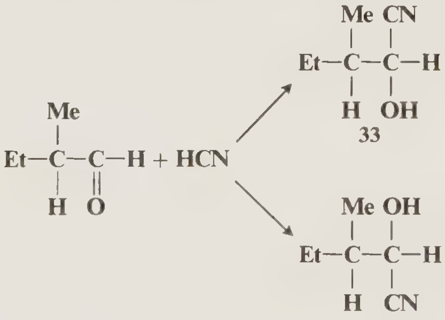
threo *dl* pair

The erythro pair has the identical groups on the same side when drawn in the Fischer convention, and if Y were changed to Z, it would be meso. The threo pair has them on opposite sides, and if Y were changed to Z, it would still be a *dl* pair.

Asymmetric Synthesis[60]

As mentioned before, optically active materials cannot be created from inactive starting materials and conditions; hence true asymmetric synthesis is impossible, except in the manner previously noted.[48] However, when a new chiral center is created, the two possible configurations need not be formed in equal amounts if anything is present which is not symmetric. Such syntheses, usually called *asymmetric syntheses*, may be discussed under four headings.

1. *Active substrate*. If a new chiral center is created in a molecule which is already optically active, the two diastereomers are not (except fortuitously) formed in equal amounts. The reason is that the direction of attack by the reagent is determined by the groups already there. For certain additions to the carbon-oxygen double bond of ketones containing an asymmetric α-carbon, *Cram's rule* predicts which diastereomer will predominate.[61] If the molecule is observed along



$$\begin{array}{c}Me\\|\\Et-C-C-H\\|\quad\|\\H\quad O\end{array} + HCN \longrightarrow \begin{array}{c}Me\;\;CN\\|\quad|\\Et-C-C-H\\|\quad|\\H\;\;\;OH\end{array}\;(33) \quad\text{or}\quad \begin{array}{c}Me\;\;OH\\|\quad|\\Et-C-C-H\\|\quad|\\H\;\;\;CN\end{array}\;(34)$$

33

34

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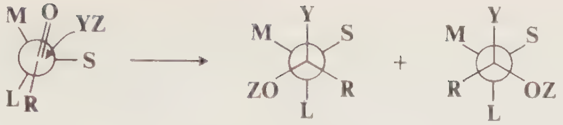
[60] For an excellent treatise on this subject, see Morrison and Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1971. For reviews, see Scott and Valentine, *Science* **184**, 943–952 (1974); ApSimon, in Bentley and Kirby, Ref. 55, pp. 251–408; Boyd and McKervey, *Q. Rev., Chem. Soc.* **22**, 95–122 (1968); Goldberg, *Sel. Org. Transform.* **1**, 363–394; Klabunovskii and Levitina, *Russ. Chem. Rev.* **39**, 1035–1049 (1970); Inch, *Synthesis* 466–473 (1970); Mathieu and Weill-Raynal, *Bull. Soc. Chim. Fr.* 1211–1244 (1968); Amariglio, Amariglio, and Duval, *Ann. Chim. (Paris)* [14] **3**, 5–25 (1968); Pracejus, *Fortschr. Chem. Forsch.* **8**, 493–553 (1967); and Velluz, Valls, and Mathieu, *Angew. Chem. Int. Ed. Engl.* **6**, 778–789 (1967) [*Angew. Chem.* **79**, 774–785].

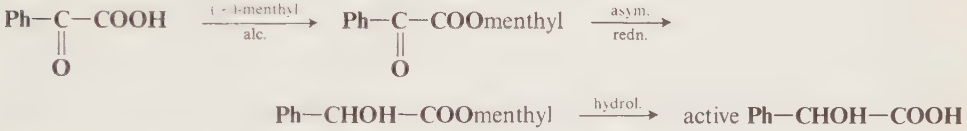
[61] Cram and Elhafez, *J. Am. Chem. Soc.* **74**, 5828 (1952); Cram and Kopecky, *J. Am. Chem. Soc.* **81**, 2748 (1959); Leitereg and Cram, *J. Am. Chem. Soc.* **90**, 4019 (1968). For reviews, see Ref. 3 in Chapter 16. For discussions, see Eliel, "Stereochemistry of Carbon Compounds," Ref. 1, pp. 68–74; and Salem, *J. Am. Chem. Soc.* **95**, 94–101 (1973).



35 Major product Minor product

its axis, it may be represented as in **35** (see p. 124), where S, M, and L stand for small, medium, and large, respectively. The oxygen of the carbonyl orients itself so as to be between the small- and the medium-sized groups. The rule is that the incoming group preferentially attacks on the side of the plane containing the small group. By this rule, it can be predicted that **34** will be formed in larger amount than **33**.

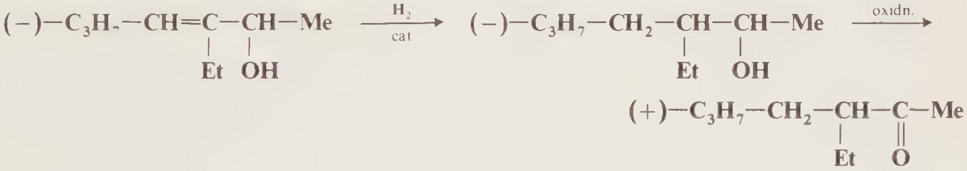
Many reactions of this type are known, in some of which the extent of favoritism approaches 100%. The farther away the reaction site is from the chiral center, the less influence the latter has and the more equal the amounts of diastereomers formed. In some cases the product may easily be cleaved at a point between the old chiral center and the new one. It is not surprising that in a case such as



$$\mathrm{Ph-\underset{\underset{O}{\|}}{C}-COOH} \xrightarrow[\text{alc.}]{(-)\text{-menthyl}} \mathrm{Ph-\underset{\underset{O}{\|}}{C}-COOmenthyl} \xrightarrow[\text{redn.}]{\text{asym.}}$$

$$\mathrm{Ph-CHOH-COOmenthyl} \xrightarrow{\text{hydrol.}} \text{active } \mathrm{Ph-CHOH-COOH}$$

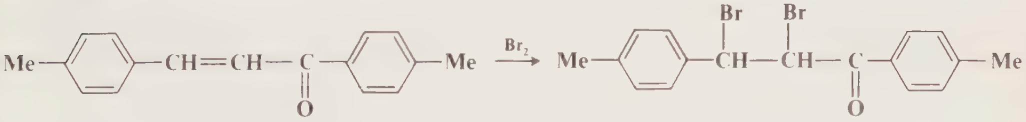
an investigator may feel that he has actually carried out an asymmetric synthesis. Another set of reactions which seems at first glance uncanny also involves the use of one chiral center to create another with subsequent destruction of the first, though in this case without cleavage.[62]



$$(-)\mathrm{-C_3H_7-CH{=}\underset{\underset{Et}{|}}{C}-\underset{\underset{OH}{|}}{CH}-Me} \xrightarrow[\text{cat}]{H_2} (-)\mathrm{-C_3H_7-CH_2-\underset{\underset{Et}{|}}{CH}-\underset{\underset{OH}{|}}{CH}-Me} \xrightarrow{\text{oxidn.}}$$

$$(+)\mathrm{-C_3H_7-CH_2-\underset{\underset{Et}{|}}{CH}-\underset{\underset{O}{\|}}{C}-Me}$$

A special case of this type of asymmetric synthesis was reported by Penzien and Schmidt.[63] The molecules of 4,4′-dimethylchalcone (**36**) are of course achiral, but the crystals are chiral; and when only one of the enantiomeric forms of the crystal (in the solid state) was treated with bromine, optically active **37**, of about 6% optical purity, was obtained.



36 **37**

2. *Active reagent*. A pair of enantiomers can be separated by an active reagent which reacts with one of them faster than it does with the other (this is also a method of resolution). If the absolute configuration of the reagent is known, the configuration of the enantiomers can often be

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[62] Arcus and Smyth, *J. Chem. Soc.* 34 (1955).

[63] Penzien and Schmidt, *Angew. Chem. Int. Ed. Engl.* **8**, 608 (1969) [*Angew. Chem.* **81**, 628]. See also Elgavi, Green, and Schmidt, *J. Am. Chem. Soc.* **95**, 2058 (1973).

determined by a knowledge of the mechanism and by seeing which diastereomer is preferentially formed.[64] Creation of a new asymmetric center in an inactive molecule can also be accomplished with an active reagent, though it is rare for 100% selectivity to be observed. An example[65] is reduction of isopropyl phenyl ketone with the Grignard reagent from (+)-1-chloro-2-phenylbutane to obtain isopropylphenylcarbinol which contains 91% of the (+) and 9% of the (−) isomer. (For another example, see p. 720.)

3. *Active catalyst or solvent.* A number of such examples are present in the literature, the most important of which involve reduction of ketones and substituted alkenes to optically active (though not optically pure) secondary alcohols and substituted alkanes by treatment with hydrogen and a chiral homogeneous hydrogenation catalyst (reactions **6-27** and **5-12**). In some instances, the ratio of enantiomers prepared in this way has reached as high as 80 : 20.[66] Other examples of the use of a chiral catalyst or solvent are the conversion of benzaldehyde to optically active mandelonitrile by treatment with HCN in the presence of an enzyme[67] and the preparation of optically active alcohols by the treatment of Grignard reagents with aldehydes in optically active ether solvents.[68]

4. *Reactions in the presence of circularly polarized light.*[69] If the light used to initiate a photochemical reaction (Chapter 7) of achiral reagents is circularly polarized, then in theory, a chiral product richer in one enantiomer might be obtained. A number of such experiments have been run, and the results have been disappointing. In certain instances, the use of left and right circularly polarized light *has* given products with opposite rotations[70] (showing that the principle is valid), but up to now the extent of favoritism has always been less than 1%. In a similar procedure, optically active products were obtained when reactions were run under the simultaneous influence of electric and magnetic fields,[70a] but here too, only a small degree of favoritism has been achieved.

Methods of Resolution[71]

A pair of enantiomers can be separated in several ways, of which conversion to diastereomers and separation of these by fractional crystallization is by far the most often used. In this method, and in some of the others, both isomers can be recovered, but in some methods it is necessary to destroy one.

1. *Conversion to diastereomers.* If the racemic mixture to be resolved contains a carboxyl group (and no strongly basic group), it is possible to form a salt with an optically active base. Since the base used is, say, the *S* form, there will be a mixture of two salts produced having the configurations *SS* and *RS*:

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[64] See for example, Horeau, *Tetrahedron Lett.* 506 (1961); Weidmann and Horeau, *Bull. Soc. Chim. Fr.* 117 (1967); Marquet and Horeau, *Bull. Soc. Chim. Fr.* 124 (1967); Brockmann and Risch, *Angew. Chem. Int. Ed. Engl.* **13,** 664 (1974) [*Angew. Chem.* **86,** 707].

[65] Birtwistle, Lee, Morrison, Sanderson, and Mosher, *J. Org. Chem.* **29,** 37 (1964). For reviews of asymmetric reduction, see Morrison, *Surv. Prog. Chem.* **3,** 147 182 (1966); Yamada and Koga, *Sel. Org. Transform.* **1,** 1–33 (1970); and Ref. 215 in Chapter 15.

[66] See for example Morrison, Burnett, Aguiar, Morrow, and Phillips, *J. Am. Chem. Soc.* **93,** 1301 (1971).

[67] Wheland, Ref. 1, p. 323.

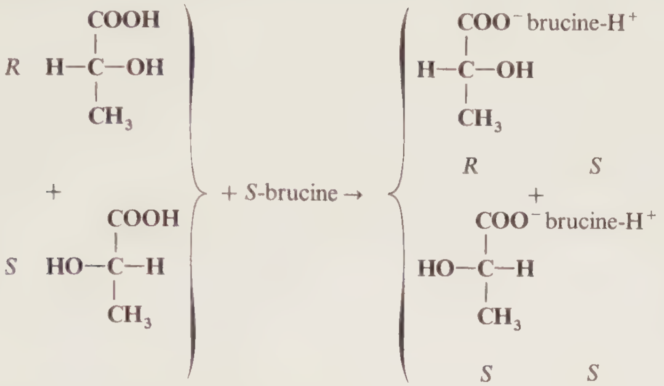
[68] See for example Blomberg and Coops, *Recl. Trav. Chim. Pays-Bas* **83,** 1083 (1964); Inch, Lewis, Sainsbury, and Sellers, *Tetrahedron Lett.* 3657 (1969).

[69] For reviews, see Buchardt, *Angew. Chem. Int. Ed. Engl.* **13,** 179–185 (1974) [*Angew. Chem.* **86,** 222]; and Ulbricht, *Q. Rev., Chem. Soc.* **13,** 48–60 (1959).

[70] Moradpour, Nicoud, Balavoine, Kagan, and Tsoucaris, *J. Am. Chem. Soc.* **93,** 2353 (1971); Kagan, Moradpour, Nicoud, Balavoine, Martin, and Cosyn, *Tetrahedron Lett.* 2479 (1971); Bernstein, Calvin, and Buchardt, *J. Am. Chem. Soc.* **94,** 494 (1972), **95,** 527 (1973), *Tetrahedron Lett.* 2195 (1972).

[70a] Gerike, *Naturwissenschaften* **62,** 38 (1975).

[71] For reviews, see Wilen, *Top. Stereochem.* **6,** 107–176 (1971); Boyle, *Q. Rev., Chem. Soc.* **25,** 323–341 (1971); Buss and Vermeulen, *Ind. Eng. Chem.* **60** (8), 12–28 (August 1968).



Although the acids are enantiomers, the salts are diastereomers and have different properties. The property most often utilized is differential solubility. The mixture of diastereomeric salts is allowed to crystallize from a suitable solvent. Since the solubilities are different, the initial crystals formed will be richer in one diastereomer. Filtration at this point will already have achieved a partial resolution. Unfortunately, the difference in solubilities is rarely if ever great enough to effect total separation with one crystallization. Usually fractional crystallizations must be used, and the process is long and tedious. Nevertheless, it is the best general method known. Fortunately, naturally occurring optically active bases (mostly alkaloids) are readily available. Among the most commonly used are brucine, ephedrine, strychnine, and morphine. Once the two diastereomers have been separated, it is easy to convert the salts back to the free acids, and the recovered base can be used again.

Most resolution is done on carboxylic acids, and often, when a molecule does not contain a carboxyl group, it is converted to a carboxylic acid before resolution is attempted. However, the principle of conversion to diastereomers is not confined to carboxylic acids, and other groups[72] may serve as handles to be coupled to an optically active reagent.[73] Racemic bases can be converted to diastereomeric salts with active acids. Alcohols[74] can be converted to diastereomeric esters, aldehydes to diastereomeric hydrazones, etc. Even hydrocarbons can be converted to diastereomeric inclusion compounds with optically active deoxycholic acid (see p. 84) or even with urea. Urea is not chiral, but the cage structure is.[75] Chiral crown ethers (p. 82) have been used to separate mixtures of ènantiomeric alkyl and arylammonium ions, by the formation of diastereomeric complexes.[76] In this case, separation is often simplified by fact that one diastereomer may form much more rapidly than the other. *trans*-Cyclooctene (**20**) was resolved by conversion to a platinum complex containing an optically active amine.[77]

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[72] For summaries of methods used to resolve particular types of compounds, see Boyle, Ref. 71; and Eliel, "Stereochemistry of Carbon Compounds," Ref. 1, pp. 49–63.

[73] For an extensive list of reagents which have been used for this purpose and of compounds resolved, see Wilen, "Tables of Resolving Agents and Optical Resolutions," University of Notre Dame Press, Notre Dame, Ind., 1972.

[74] For a review of resolution of alcohols, see Klyashchitskii and Shvets, *Russ. Chem. Rev.* **41,** 592–602 (1972).

[75] See Schlenk, *Justus Liebigs Ann. Chem.* 1145, 1156, 1179, 1195 (1973).

[76] Kyba, Koga, Sousa, Siegel, and Cram, *J. Am. Chem. Soc.* **95,** 2692 (1973); Helgeson, Koga, Timko, and Cram, *J. Am. Chem. Soc.* **95,** 3021 (1973); Helgeson, Timko, Moreau, Peacock, Mayer, and Cram, *J. Am. Chem. Soc.* **96,** 6762 (1974); Sousa, Hoffman, Kaplan, and Cram, *J. Am Chem. Soc.* **96,** 7100 (1974); Newcomb, Helgeson, and Cram, *J. Am. Chem. Soc.* **96,** 7367 (1974); Gokel, Timko, and Cram, *J. Chem. Soc., Chem. Commun.* 394, 444 (1975). For a review, see Cram and Cram, *Science* **183,** 803–809 (1974).

[77] Ref. 41. For a review, see Tsuji, *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 220–227.

Although fractional crystallization is by far the most common method for the separation of diastereomers, its tediousness and the fact that it is limited to solids have prompted a search for other methods. Fractional distillation has given only limited separation, but gas chromatography[78] and preparative liquid chromatography[79] have proved more useful and may in time supplant fractional crystallization.

2. *Differential absorption.* When a racemic mixture is placed on a chromatographic column, if the column consists of chiral substances, then in principle the enantiomers should move down the column at different rates and should be separable without having to be converted into diastereomers. This has been successfully accomplished with paper, column, and gas chromatography.[80] For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch,[81] and racemic cysteine has been resolved by paper chromatography.[82] The cellulose in the paper is, of course, chiral. Gil-Av and others have achieved separations with gas chromatography by the use of columns packed with chiral absorbents.[83] In a variation of this method, an achiral absorbent was used, but the racemic mixture was mixed with an appropriate optically active compound before injection.[83a]

3. *Biochemical processes.* The chiral compound which reacts at different rates with the two enantiomers may be present in a living organism. For instance, a certain bacterium may digest one enantiomer and not the other. This method is limited, since it is necessary to find the proper organism and since one of the enantiomers is destroyed in the process. However, when the proper organism is found, the method leads to a high extent of resolution since biological processes are usually very stereoselective.

4. *Mechanical separation.* This is the method by which Pasteur proved that racemic acid was actually a mixture of (+)- and (−)-tartaric acids.[84] In the case of racemic sodium ammonium tartrate the enantiomers crystallize separately, all the (+) molecules going into one crystal and all the (−) into another. Since the crystals too are nonsuperimposable, their appearance is not identical, and a trained crystallographer can separate them with tweezers.[85] However, this is seldom a practical method, since few compounds are known which crystallize in this manner. Even sodium ammonium tartrate does so only when it is crystallized below 27°C. A more useful variation of the method, though still not very common, is the seeding of a racemic solution with something which will cause only one enantiomer to crystallize.[86] An interesting example of the mechanical separation technique was reported in the isolation of heptahelicene (p. 95). One enantiomer of this compound, which incidentally has the extremely high rotation of $[\alpha]_D^{20} = +6200$, spontaneously crystallizes from benzene.[87]

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[78] See, for example, Casanova and Corey, *Chem. Ind.* (*London*) 1664 (1961); Gil-Av and Nurok, *Proc. Chem. Soc.* 146 (1962); Gault and Felkin, *Bull. Soc. Chim. Fr.* 742 (1965); Gil-Av, Charles, and Fischer, *J. Chromatog.* **17,** 408 (1965); Vitt, Saporovskaya, Gudkova, and Belikov, *Tetrahedron Lett.* 2575 (1965); Westley, Halpern, and Karger, *Anal. Chem.* **40,** 2046 (1968); Pereira and Halpern, *Aust. J. Chem.* **25,** 667 (1972). For a review, see Karger, *Anal. Chem.* **39** (8), 24A–50A (July 1967).

[79] For example, see Pirkle and Hoekstra, *J. Org. Chem.* **39,** 3904 (1974).

[80] For reviews, see Rogozhin and Davankov, *Russ. Chem. Rev.* **37,** 565–575 (1968); and Karger, Ref. 78.

[81] Ohara, Fujita, and Kwan, *Bull. Chem. Soc. Jpn.* **35,** 2049 (1962); Ohara, Ohta, and Kwan, *Bull. Chem. Soc. Jpn.* **37,** 76 (1964). See also Blaschke and Donow, *Chem. Ber.* **108,** 2792 (1975).

[82] de Ligny, Nieboer, de Vijlder, and van Willigen, *Recl. Trav. Chim. Pays-Bas* **82,** 213 (1963).

[83] Gil-Av, Feibush, and Charles-Sigler, *Tetrahedron Lett.* 1009 (1966); Gil-Av and Feibush, *Tetrahedron Lett.* 3345 (1967); Feibush and Gil-Av, *Tetrahedron* **26,** 1361 (1970); Feibush, Gil-Av, and Tamari, *J. Chem. Soc., Perkin Trans. 2* 1197 (1972); Rubinstein, Feibush, and Gil-Av, *J. Chem. Soc., Perkin Trans. 2* 2094 (1973); Bayer, Gil-Av, König, Nakaparksin, Oró, and Parr, *J. Am. Chem. Soc.* **92,** 1738 (1970); Blaschke, *Angew. Chem. Int. Ed. Engl.* **10,** 520 (1971) [*Angew. Chem.* **83,** 547].

[83a] Maestas and Morrow, *Tetrahedron Lett.* 1047 (1976).

[84] Besides discovering this method of resolution, Pasteur also discovered the method of conversion to diastereomers and separation by fractional crystallization and the method of biochemical separation.

[85] This is a case of optically active materials arising from inactive materials. However, it may be argued that an optically active investigator is required to use the tweezers. Perhaps a hypothetical human being constructed entirely of inactive molecules would be unable to tell the difference between left- and right-handed crystals.

[86] For a review of the seeding method, see Secor, *Chem. Rev.* **63,** 297 (1963).

5. *Differential reactivity.* Since enantiomers react with chiral compounds at different rates, it is sometimes possible to effect a partial separation by stopping the reaction before completion.[88] This method is very similar to the asymmetric syntheses discussed on p. 107. The most important application of this method[89] is the resolution of racemic alkenes by treatment with optically active diisopinocampheylborane, since alkenes do not easily lend themselves to conversion to diastereomers if no other functional groups are present. Circularly polarized light has been used to destroy selectively one enantiomer in the presence of the other. Racemic camphor was converted to a 60 : 40 mixture of enantiomers in this way,[90] but the disadvantage of this method is that the extent of favoritism increases as the extent of the reaction increases and it was necessary to destroy 99% of the starting material in order to get the 60 : 40 mixture, making the method virtually useless as a synthetic tool. However, the fact that it can be done at all is evidence that the original generation of optical activity on earth (before the origin of life) might possibly have occurred in this way.

Optical Purity[91]

Suppose we have just attempted to resolve a racemic mixture by one of the methods described in the previous section. How do we know that the two enantiomers we have obtained are pure? For example, how do we know that the (+) isomer is not contaminated by, say, 20% of the (−) isomer, and vice versa? If we knew the value of $[\alpha]$ for the pure material ($[\alpha]_{\max}$), we could easily determine the purity of our sample by measuring its rotation. For example, if $[\alpha]_{\max}$ is $+80°$ and our (+) enantiomer contains 20% of the (−) isomer, $[\alpha]$ for our sample will be $+48°$.[92] We define *optical purity* as

$$\text{Percent optical purity} = \frac{[\alpha]_{\text{obs}}}{[\alpha]_{\max}} \times 100$$

Assuming that there is a linear relationship between $[\alpha]$ and concentration, which is true for most cases, the optical purity is equal to the percent excess of one enantiomer over the other:

$$\text{Optical purity} = \text{percent excess} = \frac{[R]-[S]}{[R]+[S]} \times 100 = \%R - \%S$$

But how do we determine the value of $[\alpha]_{\max}$? It is plain that we have two related problems here; namely, what are the optical purities of our two samples, and what is the value of $[\alpha]_{\max}$, and that if we solve one, the other is also solved. Several methods for solving these problems are known.

One of these methods involves the use of nmr.[93] Suppose we have a nonracemic mixture of two enantiomers and wish to know the proportions. We convert the mixture into a mixture of diastereomers with an optically pure reagent and look at the nmr spectrum of the resulting mixture, e.g.,

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[87] Martin et al., Ref. 39. See also Wynberg and Groen, *J. Am. Chem. Soc.* **90,** 5339 (1968).

[88] For example, see Meurling, *Chem. Scr.* **6,** 92 (1974); Meurling and Bergson, *Chem. Scr.* **6,** 104 (1974).

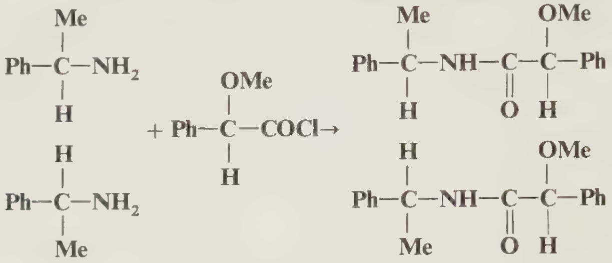
[89] Brown, Ayyangar, and Zweifel, *J. Am. Chem. Soc.* **86,** 397 (1964).

[90] Balavoine, Moradpour, and Kagan, *J. Am. Chem. Soc.* **96,** 5152 (1974).

[91] For a review, see Raban and Mislow, *Top. Stereochem.* **2,** 199–230 (1967).

[92] If a sample contains 80% (+) and 20% (−) isomer, the (−) isomer cancels an equal amount of (+) isomer and the mixture behaves as if 60% of it were (+) and the other 40% inactive. Therefore the rotation is 60% of 80°, or 48°. This type of calculation, however, is not valid for cases in which $[\alpha]$ is dependent on concentration (p. 88); see Horeau, *Tetrahedron Lett.* 3121 (1969).

[93] Raban and Mislow, *Tetrahedron Lett.* 4249 (1965), 3961 (1966); Gerlach, *Helv. Chim. Acta* **49,** 2481 (1966); Dale and Mosher, *J. Am. Chem. Soc.* **90,** 3732 (1968); Jacobus, Raban, and Mislow, *J. Org. Chem.* **33,** 1142 (1968); Dale, Dull, and Mosher, *J. Org. Chem.* **34,** 2543 (1969); Jacobus and Jones, *J. Am. Chem. Soc.* **92,** 4583 (1970); Baxter and Richards, *Tetrahedron Lett.* 3357 (1972); Jacobus and Raban, *J. Chem. Educ.* **46,** 351 (1969). See also Ref. 91.



$$\begin{array}{ccc}
\mathrm{Ph{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle Me}{|}}{C}}{-}NH_2} & & \mathrm{Ph{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle Me}{|}}{C}}{-}NH{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle OMe}{|}}{C}}{-}Ph} \\
 & \mathrm{+\ Ph{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle OMe}{|}}{C}}{-}COCl} \rightarrow & \\
\mathrm{Ph{-}\underset{\underset{\displaystyle Me}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}NH_2} & & \mathrm{Ph{-}\underset{\underset{\displaystyle Me}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}NH{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle OMe}{|}}{C}}{-}Ph}
\end{array}$$

If we examined the nmr spectrum of the starting mixture, we would find only one peak (split into a doublet by the C—H) for the Me protons, since enantiomers give identical nmr spectra.[94] But the two amides are not enantiomers, and each Me will give its own doublet. From the intensity of the two peaks, the relative proportions of the two diastereomers (and hence of the original enantiomers) can be determined. Alternatively, the unsplit OMe peaks could have been used. This method was satisfactorily used to determine the optical purity of a sample of 1-phenylethylamine (the case shown above),[95] and in other cases as well, but it is obvious that sometimes corresponding groups in diastereomeric molecules will give nmr signals which are too close together for resolution. In such cases one may resort to the use of a different optically pure reagent.

A closely related method does not require conversion of enantiomers to diastereomers but relies on the fact that (in principle, at least) enantiomers have different nmr spectra *in a chiral solvent*. In some cases the peaks are separated enough to permit the proportions of enantiomers to be determined from their intensities.[96] Another variation, which gives better results in many cases, is to use an achiral solvent but with the addition of a *chiral lanthanide shift reagent* such as tris[3-trifluoroacetyl-*d*-nopinonato]europium(III) or tris[3-trifluoroacetyl-*d*-camphorato]europium-(III).[97] Lanthanide shift reagents have the property of spreading nmr peaks of compounds with which they can form coordination compounds, e.g., alcohols, carbonyl compounds, amines, etc. Chiral lanthanide shift reagents shift the peaks of the two enantiomers of many such compounds to different extents.

Another method, involving gas chromatography,[98] is similar in principle to the nmr method. A mixture of enantiomers whose purity is to be determined is converted by means of an optically pure reagent into a mixture of two diastereomers. These diastereomers are then separated by gas chromatography (p. 110) and the ratios determined from the peak heights. Once again the ratio of diastereomers is the same as that of the original enantiomers. High-pressure liquid chromatography has been used in a similar manner.[99]

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[94] Though enantiomers give identical nmr spectra, the spectrum of a single enantiomer may be different from that of the racemic mixture, even in solution. See Williams, Pitcher, Bommer, Gutzwiller, and Uskoković, *J. Am. Chem. Soc.* **91,** 1871 (1969).

[95] Ref. 91, pp. 216–218.

[96] Pirkle, *J. Am. Chem. Soc.* **88,** 1837 (1966); Burlingame and Pirkle, *J. Am. Chem. Soc.* **88,** 4294 (1966); Pirkle and Burlingame, *Tetrahedron Lett.* 4039 (1967); Pirkle and Beare, *J. Am. Chem. Soc.* **89,** 5485 (1967), **90,** 6250 (1968), **91,** 5150 (1969), *Tetrahedron Lett.* 2579 (1968); Pirkle, Burlingame, and Beare, *Tetrahedron Lett.* 5849 (1968); Pirkle, Beare, and Muntz, *J. Am. Chem. Soc.* **91,** 4575 (1969); Anet, Sweeting, Whitney, and Cram, *Tetrahedron Lett.* 2617 (1968); Moretti, Taddei, Torre, and Spassky, *J. Chem. Soc., Chem. Commun.* 25 (1973).

[97] Whitesides and Lewis, *J. Am. Chem. Soc.* **92,** 6979 (1970), **93,** 5914 (1971); Fraser, Petit and Saunders, *Chem. Commun.* 1450 (1971); Fraser, Petit, and Miskow, *J. Am. Chem. Soc.* **94,** 3253 (1972); Goering, Eikenberry and Koermer, *J. Am. Chem. Soc.* **93,** 5913 (1971); Goering, Eikenberry, Koermer, and Lattimer, *J. Am. Chem. Soc.* **96,** 1493 (1974); Dongala, Solladié-Cavallo, and Solladié, *Tetrahedron Lett.* 4233 (1972); McCreary, Lewis, Wernick, and Whitesides, *J. Am. Chem. Soc.* **96,** 1038 (1974); Yamamoto, Hayashi, and Kumada, *Bull. Chem. Soc. Jpn.* **47,** 1555 (1974).

[98] Charles, Fischer, and Gil-Av, *Isr. J. Chem.* **1,** 234 (1963); Halpern and Westley, *Chem. Commun.* 246 (1965); Vitt, Saporovskaya, Gudkova, and Belikov, *Tetrahedron Lett.* 2575 (1965); Guetté and Horeau, *Tetrahedron Lett.* 3049 (1965); Westley and Halpern, *J. Org. Chem.* **33,** 3978 (1968).

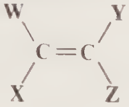
Other methods involve isotopic dilution,[100] kinetic resolution,[101] circular polarization of luminescence,[102] and calorimetry.[103]

CIS-TRANS ISOMERISM

Compounds in which rotation is restricted may exhibit cis-trans isomerism.[104] These compounds do not rotate the plane of polarized light (unless they also happen to be chiral), and the properties of the isomers are not identical. The two most important types are isomerism resulting from double bonds and that resulting from rings.

Cis-Trans Isomerism Resulting from Double Bonds

It has been mentioned (p. 12) that the two carbon atoms of a $C{=}C$ double bond and the four atoms directly attached to them are all in the same plane and that rotation around the double bond is prevented. This means that in the case of a molecule $WXC{=}CYZ$, isomerism exists when $W \neq X$ and $Y \neq Z$. There are two and only two isomers (**38** and **39**), each superimposable on its mirror image unless one of the groups happens to carry a chiral center. Note that **38** and **39** are diastereomers, by the definition given on p. 104. There are two ways to name such isomers. In the older method, one isomer is called *cis* and the other *trans*. When $W = Y$, **38** is the cis and **39** the trans isomer. Unfortunately, there is no easy way to apply this method when the four groups are different. The newer method, which can be applied to all cases, is based on the Cahn-Ingold-Prelog system (p. 99). The two groups at each carbon are ranked by the sequence rules. Then that isomer which has the two higher-ranking groups on the same side of the double bond is called *Z* (for the German word *zusammen* meaning *together*); the other is *E* (for *entgegen* meaning *opposite*).[105] A few examples are shown. Note that the *Z* isomer is not necessarily the one that would be called cis under the older system (e.g., **40, 41**). Like cis and trans, *E* and *Z* are used as prefixes; e.g., **41** is called (*Z*)-1-bromo-1,2-dichloroethene.



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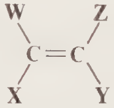

39

This type of isomerism is also possible with other double bonds, such as $C{=}N$,[106] $N{=}N$, or even $C{=}S$,[107] although in these cases only two or three groups are connected to the double-

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[99] Eberhardt, Glotzmann, Lehner, and Schlögl, *Tetrahedron Lett.* 4365 (1974).

[100] Berson and Ben-Efraim, *J. Am. Chem. Soc.* **81,** 4083 (1959).

[101] Horeau, *J. Am. Chem. Soc.* **86,** 3171 (1964); *Bull. Soc. Chim. Fr.* 2673 (1964); Horeau, Guetté, and Weidmann, *Bull. Soc. Chim. Fr.* 3513 (1966).

[102] Kokke, *J. Am. Chem. Soc.* **96,** 2627 (1974).

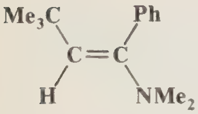
[103] Fouquey and Jacques, *Bull. Soc. Chim. Fr.* 165 (1966), *Tetrahedron* **23,** 4009 (1967); Fouquey and Leclerq, *Tetrahedron* **26,** 5637 (1970).

[104] Cis-trans isomerism was formerly called *geometrical isomerism.* For a review, see Crombie, *Q. Rev., Chem. Soc.* **6,** 101-140 (1952).

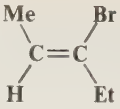
[105] For a complete description of the system, see Ref. 2.

[106] For reviews of isomerizations about C=N bonds, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Interscience Publishers, Inc., New York, 1970, see the articles by McCarty, 363-464 (pp. 364-408), and Wettermark, 565-596 (pp. 574-582).

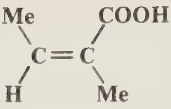
[107] King and Durst, *Can. J. Chem.* **44,** 819 (1966).



E

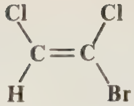


Z



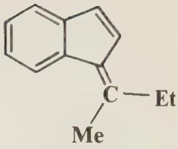
Z

40



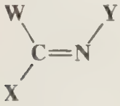
E

41

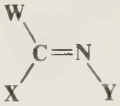


E

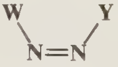
bond atoms. In the case of imines, oximes, and other C=N compounds, if W = Y, **42** is usually called syn and **43** anti, though cis, trans, *E*, and *Z* are sometimes used here too. In azo compounds there is no ambiguity, and **44** is always cis, syn, or *Z* regardless of the nature of W and Y.



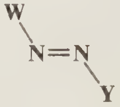
42



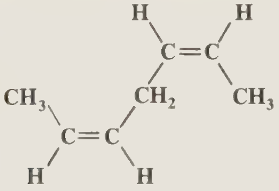
43



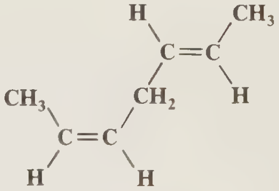
44



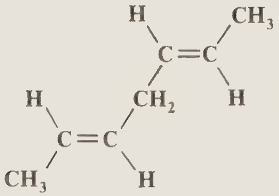
If there is more than one double bond in a molecule and if, for each, W ≠ Y and Y ≠ Z, the number of isomers in the most general case is 2^n, although this number may be decreased if some of the substituents are the same, as in



cis-cis or
Z, *Z*

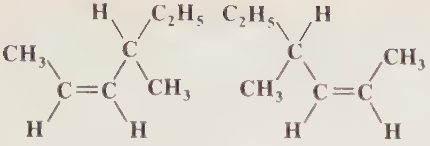


cis-trans or
Z, *E*

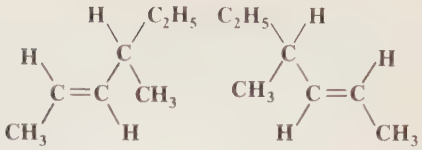


trans-trans or
E, *E*

Of course, allenes do not show cis-trans isomerism at all (see p. 94). When a molecule contains a double bond and an asymmetric carbon, there are four isomers, a cis pair of enantiomers and a trans pair:

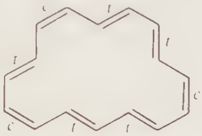


Z or cis *dl* pair



E or trans *dl* pair

An interesting system has been devised for designating the stereochemistry of annulenes, which are troublesome to name by the ordinary cis-trans or *Z*, *E* systems because there are so many double bonds (see Chapter 2). In this system,[108] a cis double bond is given the number 0 and a trans double bond the number 1. The geometry of each double bond is then cited in sequence around the ring, forming a binary number, e.g.,

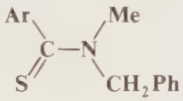


c t c t t c t t
0 1 0 1 1 0 1 1

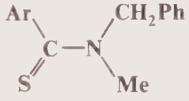
This binary number, 01011011, is $2^6 + 2^4 + 2^3 + 2^1 + 2^0 = 91$, so the compound is [16]-91-annulene. Since different binary numbers will result from starting at different double bonds, a rule is needed for deciding where to begin the sequence. The rule is to begin at whichever position will give the lowest binary number.

Double bonds in small rings are so constrained that they must be cis. From cyclopropene (a known system) to cycloheptene, double bonds in a ring cannot be trans. However, the cyclooctene ring is large enough to permit trans double bonds to exist (see **20**), and for rings larger than 10- or 11-membered, trans isomers are more stable.[109]

In a few cases, single-bond rotation is so slowed that cis and trans isomers can be isolated even where no double bond exists. One example is N-methyl-N-benzylthiomesitylide (**A** and **B**),[110]



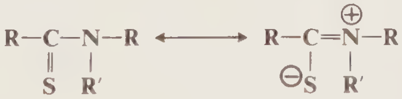
A



B

Ar = mesityl

the isomers of which are stable in the crystalline state but interconvert with a half-life of about 25 hr in $CDCl_3$ at 50°C. This type of isomerism is rare; it is found chiefly in certain amides and thioamides, because resonance gives the single bond some double-bond character and slows rotation. (For other examples of restricted rotation about single bonds, see p. 149.)



$$\underset{\displaystyle S}{\overset{\|}{\mathrm{R{-}C}}}{-}\underset{\displaystyle R'}{\overset{|}{\mathrm{N}}}{-}\mathrm{R} \longleftrightarrow \mathrm{R}{-}\underset{\displaystyle ^{\ominus}S}{\overset{|}{\mathrm{C}}}{=}\underset{\displaystyle R'}{\overset{\oplus}{\mathrm{N}}}{-}\mathrm{R}$$

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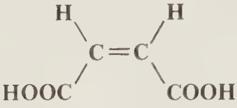
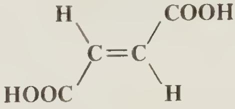
[108] Oth, *Pure Appl. Chem.* **25,** 573–622 (1971), p. 576. For a similar system, see Feldman, *J. Org. Chem.* **24,** 1556 (1959).

[109] Cope, Moore, and Moore, *J. Am. Chem. Soc.* **81,** 3153 (1959).

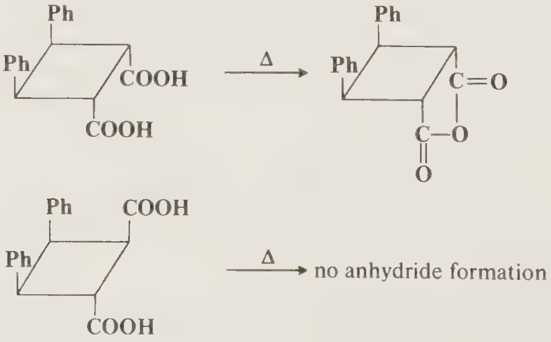
[110] Mannschreck, *Angew. Chem. Int. Ed. Engl.* **4,** 985 (1965) [*Angew. Chem.* **77,** 1032]. See also Mannschreck, *Tetrahedron Lett.* 1341 (1965); Toldy and Radics, *Tetrahedron Lett.* 4753 (1966); Walter and Schaumann, *Chem. Ber.* **104,** 3361 (1971).

TABLE 1 Some properties of maleic and fumaric acids

Property	 Maleic acid	 Fumaric acid
Melting point, °C	130	286
Solubility in water at 25°C, g/liter	788	7
K_1 (at 25°C)	1.5×10^{-2}	1×10^{-3}
K_2 (at 25°C)	2.6×10^{-7}	3×10^{-5}

Since they are diastereomers, cis-trans isomers always differ in properties; the differences may range from very slight to considerable. The properties of maleic acid are so different from those of fumaric acid (Table 1) that it is not surprising they have different names. Since they generally have more symmetry than cis isomers, trans isomers usually have higher melting points and lower solubilities in inert solvents. The cis isomer usually has a higher heat of combustion, which indicates a lower thermochemical stability. For this reason, cis compounds can often be transformed into the trans isomers by heating, which at a high enough temperature supplies enough energy to cause rotation about the double bond. Since this is a process leading to thermodynamic equilibrium, trans compounds can seldom be converted to the cis isomers in this manner.[111] Other noticeably different properties are densities, acid strengths, boiling points, and various types of spectra, but the differences are too involved to be discussed here. It should be emphasized that the principles discussed in this paragraph are no more than general rules and that many exceptions are known. One important class of exceptions is the ten 1,2-dihaloethenes, for each of which (except the diiodo compound) the cis isomer is more stable than the trans.

There are many ways of telling which of a pair of isomers is cis and which is trans. The most dependable are x-ray and electron diffraction, though these methods have not often been used for this purpose. Other physical methods include ir, uv, and nmr spectra, the measurement of dipole moments (a trans isomer of the type WYC=CWY has no dipole moment, while the cis isomer usually has one), and a comparison of melting points, solubilities, etc., according to the rules mentioned in the preceding paragraph. The most foolproof *chemical* method is that of closing or opening a ring. Thus, if two groups capable of combining are cis-oriented, they often can be treated so as to close a ring, but not if the orientation is trans; e.g.,



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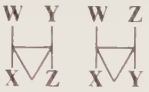
[111] For a review of cis-trans isomerization see Wyman, *Chem. Rev.* **55**, 625–657 (1955).

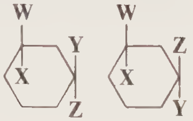
Note that if the absolute configuration at one of the COOH positions is known, this experiment establishes the configuration at the other position. Similarly, if only one isomer can be prepared by a ring opening, it is the cis isomer. For example, only maleic and not fumaric acid can be prepared by oxidation of benzene (reaction **9-11**). Other chemical methods of distinguishing cis from trans isomers involve correlation with known compounds and reaction by routes of known mechanism.

Cis-Trans Isomerism of Monocyclic Compounds

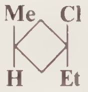
Although rings of four carbons and larger are not generally planar (see p. 132), they will be treated as such in this section, since the correct number of isomers can be determined when this is done[111a] and the principles are easier to visualize (see p. 130).

The presence of a ring, like that of a double bond, prevents rotation, and cis and trans isomers are possible whenever there are two carbons on a ring each of which is substituted by two different groups. The two carbons need not be adjacent. Examples are



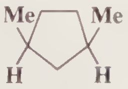


As with double bonds, W may equal Y and X may equal Z, but W may not equal X and Y may not equal Z if cis and trans isomers are to be possible. There is an important difference from the double-bond case: the substituted carbons are asymmetric. This means that there are not *only* two isomers. In the most general case, where W ≠ X ≠ Y ≠ Z, there are four isomers, since neither the cis nor the trans isomer is superimposable on its mirror image. This is true regardless of ring size or which carbons are involved, except that in rings of even-numbered size when the asymmetric carbons are opposite each other, no chirality is present, e.g., in **45.** Note that a plane of symmetry exists in such compounds. When W = Y and X = Z, the cis isomer is always superimposable on its mirror image and hence is a meso compound, while the trans isomer consists of a *dl* pair, except in the case noted above,

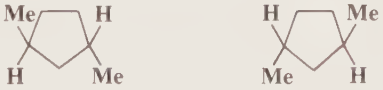


meso

45



cis meso



trans *dl* pair

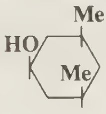
Again, the cis isomer has a plane of symmetry while the trans does not.

Rings with more than two differently substituted carbons can be dealt with on similar principles. In some cases it is not easy to tell by inspection just how many isomers there are. The best method for the student is to count the number n of differently substituted carbons (these will normally be asymmetric, but not always, e.g., in **45**) and then draw 2^n structures, crossing out those which can be superimposed on others (usually the easiest method is to look for a plane of symmetry). By this means it can be determined that for 1,2,3-cyclohexanetriol there are two meso compounds and a *dl* pair; and for 1,2,3,4,5,6-hexachlorocyclohexane there are seven meso compounds and a *dl* pair. The drawing of these structures is left as an exercise for the student.

[111a] For a discussion of why this is so, see Leonard, Hammond, and Simmons, *J. Am. Chem. Soc.* **97**, 5052 (1975).

Similar principles apply to heterocyclic rings as long as there are carbons (or other ring atoms) containing two different groups.

Cyclic stereoisomers containing only two differently substituted carbons are named either cis or trans, as previously indicated. The *Z*, *E* system is not used for cyclic compounds. However, if one tries to name ring compounds with more than two differently substituted atoms using only the prefixes cis and trans, one soon runs into difficulties, and yet until recently this was the way they were most commonly named. For example, **46** could unambiguously be given the prefix cis, cis, but **47** might be trans, trans or, perhaps with equal justice, cis, trans. For chiral compounds, a way out of this dilemma is to use the *R*, *S* system to label each asymmetric carbon, but this could hardly be applied to cases like **46** and **47,** where C-1 is not asymmetric. A solution to this problem is the following system, in which the configuration of each group is given with respect to a reference group, which is chosen as the group attached to the lowest-numbered ring member bearing a substituent giving rise to cis-trans isomerism. The reference group is indicated by the symbol *r*. Thus, **46** is *c*-3,*c*-5-dimethylcyclohexan-*r*-1-ol; **47** is *t*-3,*t*-5-dimethylcyclohexan-*r*-1-ol; and **48** is *c*-3,*t*-5-dimethylcyclohexan-*r*-1-ol. The last example demonstrates the rule that when there are two otherwise equivalent ways of going around the ring, one chooses the path that gives cis attachment to the first substituent after the reference. Another example is *r*-2,*c*-4-dimethyl-*t*-6-ethyl-1,3-dioxane (**49**). This system is clear and unambiguous.



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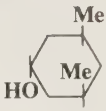

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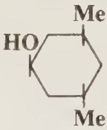

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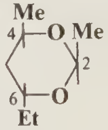

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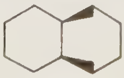
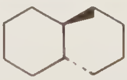
Cis-Trans Isomerism of Fused-Ring Systems

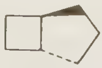
Where the rings are fused through adjacent atoms, there is no new principle. The fusion may be cis or trans, as illustrated by *cis*- and *trans*-decalin. However, when the rings are small enough, the trans configuration is impossible and the junction must be cis. The smallest trans junction which has been prepared when one ring is four-membered is a four-five junction: *trans*-bicyclo-[3.2.0]heptane (**50**) is known.[112] For the bicyclo[2.2.0] system (a four-four fusion) only cis com-



cis-Decalin



trans-Decalin



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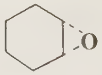

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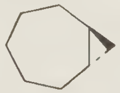

52

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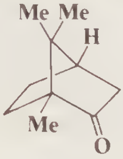
[112] Meinwald, Tufariello, and Hurst, *J. Org. Chem.* **29,** 2914 (1964).

pounds have been made. Trans junctions are also unknown when one ring is three-membered and the other six-membered or smaller; e.g., only *cis*-cyclohexene oxide (**51**) is known, though *trans*-bicyclo[5.1.0]octane (**52**) and some of its derivatives have been prepared.[113]

Rings which are fused through nonadjacent atoms are called *bridged*. In bridged-ring systems there may be fewer than 2^n isomers because of the structure of the system. For example, there are only two isomers of camphor (**53**) (a *dl* pair) although it has two asymmetric carbons. In both isomers the methyl and hydrogen are cis. The trans pair of enantiomers is impossible in this case, since the bridge *must* be cis. When one of the bridges contains a substituent, the question arises as to how to name the isomers involved. When the two bridges which do *not* contain the substituent are of unequal length, the rule generally followed is that the prefix *endo-* is used when the substituent is closer to the longer of the two unsubstituted bridges; the prefix *exo-* is used when the substituent is closer to the shorter bridge; e.g.,



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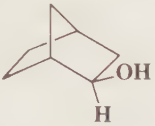
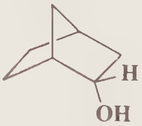
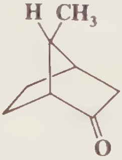


exo-2-Norborneol

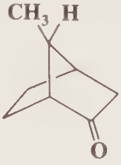


endo-2-Norborneol

When the two bridges not containing the substituent are of equal length, this convention cannot be applied, but in some cases a decision can still be made; e.g., if one of the two bridges contains a functional group, the endo isomer is the one in which the substituent is closer to the functional group:



endo-7-Methyl-2-norcamphor



exo-7-Methyl-2-norcamphor

Out-In Isomerism

Another type of stereoisomerism, called *out-in isomerism*, is found in salts of tricyclic diamines with nitrogen at the bridgeheads. In cases where k, l, and $m > 6$, the N—H bonds can be inside the molecular cavity or outside, giving rise to three isomers, as shown. Simmons and Park[114] have

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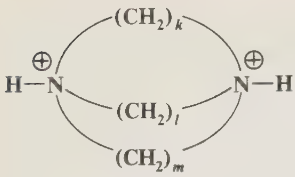
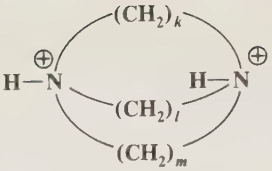
[113] Gassman, Williams, and Seter, *J. Am. Chem. Soc.* **90,** 6893 (1968); Kirmse and Hase, *Angew. Chem. Int. Ed. Engl.* **7,** 891 (1968) [*Angew. Chem.* **80,** 914]; Wiberg and de Meijere, *Tetrahedron Lett.* 519 (1969); Ashe, *Tetrahedron Lett.* 523 (1969).

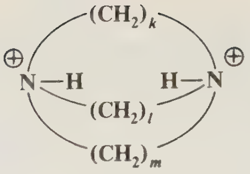
[114] Simmons and Park, *J. Am. Chem. Soc.* **90,** 2428 (1968); Park and Simmons, *J. Am. Chem. Soc.* **90,** 2429, 2431 (1968); Simmons, Park, Uyeda, and Habibi, *Trans. N.Y. Acad. Sci.* **32,** 521 (1970). See also Dietrich, Lehn, and Sauvage, *Tetrahedron Lett.* 2885, 2889 (1969), *Tetrahedron* **29,** 1647 (1973); Lehn, Sauvage, and Dietrich, *J. Am. Chem. Soc.* **92,** 2916 (1970); Dietrich, Lehn, Sauvage, and Blanzat, *Tetrahedron* **29,** 1629 (1973); Cheney and Lehn, *J. Chem. Soc., Chem. Commun.* 487 (1972).



out-out isomer



out-in isomer

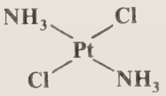


in-in isomer

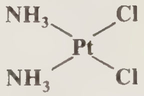
isolated several such isomers, with k, l, and m varying from 6 to 10. In the 9,9,9 compound, the cavity of the in-in isomer is large enough to encapsulate a chloride ion which is hydrogen-bonded to the two N—H groups (see also p. 82). Out-in and in-in isomers have also been prepared in analogous all-carbon tricyclic systems.[115]

Inorganic Cis-Trans Isomerism[116]

There are several types of cis-trans isomerism in inorganic compounds; we shall mention only two. In coordination compounds whose geometry is square planar, cis and trans isomerism may exist, as in

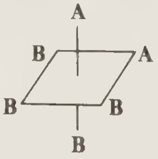


trans

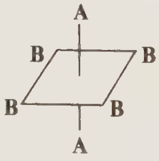


cis

In octahedral coordination compounds of the type MA_2B_4, cis-trans isomerism also exists.[117] Similarly, there are 2 isomers of MA_3B_3; 5 of $MA_2B_2C_2$, and 15 of MABCDEF. As an exercise, the student may wish to verify these numbers.



cis



trans

Enantiotopic and Diastereotopic Atoms, Groups, and Faces[118]

Many molecules contain atoms or groups which appear to be equivalent but which a close inspection will show to be actually different. We can test to see whether two atoms are equivalent by replacing each of them in turn with some other atom or group. If the new molecules which are created by this process are identical, the original atoms are equivalent; otherwise not. We can distinguish three cases.

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[115] Park and Simmons, *J. Am. Chem. Soc.* **94,** 7184 (1972); Gassman and Thummel, *J. Am. Chem. Soc.* **94,** 7183 (1972); Gassman, Korn, and Thummel, *J. Am. Chem. Soc.* **96,** 6948 (1974).

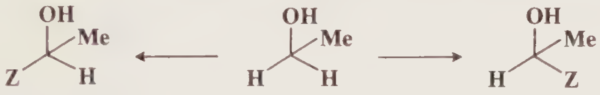
[116] For a review, see Gillespie and Nyholm, *Q. Rev., Chem. Soc.* **11,** 339–380 (1957).

[117] For a discussion of isomerism in octahedral and other coordination compounds, see Hawkins, Ref. 55, pp. 2–15.

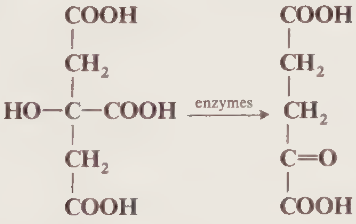
[118] These terms were coined by Mislow. For a lengthy discussion of this subject, see Mislow and Raban, *Top. Stereochem.* **1,** 1–38 (1967). See also Ault, *J. Chem. Educ.* **51,** 729 (1974); Kaloustian and Kaloustian, *J. Chem. Educ.* **52,** 56 (1975); Jennings, *Chem. Rev.* **75,** 307–322 (1975).

1. In the case of malonic acid $CH_2(COOH)_2$, propane CH_2Me_2, or any other molecule of the form CH_2Y_2,[119] if we replace either of the CH_2 hydrogens by a group Z, the identical compound results. The two hydrogens are thus equivalent. Equivalent atoms and groups need not, of course, be located on the same carbon atom. For example, all the chlorine atoms of hexachlorobenzene are equivalent, as are the two bromine atoms of 1,3-dibromopropane.

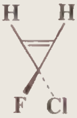
2. In the case of ethanol CH_2MeOH, if we replace one of the CH_2 hydrogens by a group Z, we get one enantiomer of the compound ZCHMeOH (**54**), while replacement of the other hydrogen gives the *other* enantiomer (**55**). Since the two compounds which result upon replacement of H by Z (**54** and **55**) are not identical but enantiomeric, the hydrogens are *not* equivalent. We define as *enantiotopic* two atoms or groups which upon replacement with a third group give enantiomers. In any symmetric environment the two hydrogens behave as equivalent, but in a dissymmetric environment they may behave differently. For example, in a reaction with a chiral reagent they may be attacked at different rates. This has its most important consequences in enzymatic reactions[120] since enzymes are capable of much greater discrimination than ordinary chiral reagents. An example is the biological conversion of citric acid (**56**) to α-oxoglutaric acid (**57**).



54 **55**



56 **57**



58

The two CH_2COOH groups are enantiotopic, and labeling experiments have shown that only one of these is converted to the COCOOH group.[121] Note that the X atoms or groups of any molecule of the form CX_2WY are always enantiotopic, though enantiotopic atoms and groups may also be found in other molecules, e.g., the hydrogen atoms in 3-fluoro-3-chlorocyclopropene (**58**). In this case, substitution of an H by a group Z makes the C-3 atom asymmetric, and substitution at C-1 gives the opposite enantiomer from substitution at C-2.

The term *prochiral*[122] is used for a compound or group which has two enantiotopic atoms or groups, e.g., CX_2WY. That atom or group X which would lead to an *R* compound if preferred to the other is called *pro-R*. The other is *pro-S*; e.g.,

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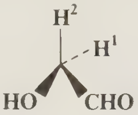
[119] In the case where Y is itself a chiral group this statement is only true when the two Y groups have the same configuration.

[120] For a nonenzymatic example, see Job and Bruice, *J. Am. Chem. Soc.* **96**, 809 (1974).

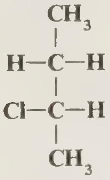
[121] The experiments were carried out by Evans and Slotin, *J. Biol. Chem.* **141**, 439 (1941) and Wood, Werkman, Hemingway, and Nier, *J. Biol. Chem.* **142**, 31 (1942). The correct interpretation was given by Ogston, *Nature* **162**, 963 (1948). For discussion, see Hirschmann, in Florkin and Stotz, "Comprehensive Biochemistry," vol. 12, pp. 236–260, Elsevier Publishing Company, Amsterdam, 1964; Cornforth, *Tetrahedron* **30**, 1515 (1974); and Vennesland, *Top. Curr. Chem.* **48**, 39–65 (1974).

[122] Hanson, *J. Am. Chem. Soc.* **88**, 2731 (1966); Hirschmann and Hanson, *Tetrahedron* **30**, 3649 (1974).



H^2 = pro-*S*
H^1 = pro-*R*

3. Where two atoms or groups in a molecule are in such positions that replacing each of them in turn by a group Z gives rise to diastereomers, the atoms or groups are called *diastereotopic*. Some examples are the CH_2 groups of 2-chlorobutane (**59**) and chlorocyclopropane (**60**) and the two olefinic hydrogens of **61**. Note that in **60** one hydrogen from the CH_2 group is cis to the Cl while the other is trans, so that they are obviously different. Diastereotopic atoms and groups are different in any environment, symmetric or asymmetric. These hydrogens react at different rates with achiral reagents, but an even more important consequence is that in nmr spectra, diastereotopic hydrogens theoretically give different peaks and split each other. This is in sharp contrast to equivalent or enantiotopic hydrogens, which are indistinguishable in the nmr, except when chiral solvents are used, in which case enantiotopic (but not equivalent) protons give different peaks.[123] The term *isochronous* is used for hydrogens which are indistinguishable in the nmr.[124] In practice, the nmr signals from diastereotopic protons are often found to be indistinguishable, but this is merely because they are very close together. Theoretically they are distinct, and they have been resolved in many cases. When they appear together, it is sometimes possible to resolve them by the use of lanthanide shift reagents[125] (p. 112) or by changing the solvent or concentration. Note that X atoms or groups in CX_2WY are diastereotopic if either W or Y is chiral.



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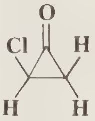

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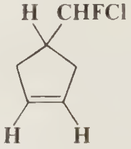

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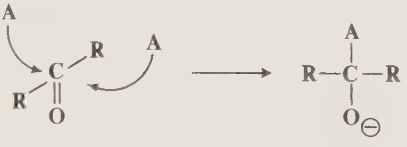
Just as there are enantiotopic and diastereotopic atoms and groups, so we may distinguish *enantiotopic and diastereotopic faces* in trigonal molecules. Again we have three cases: (1) In formaldehyde or acetone (**62**) attack by an achiral reagent A from either face of the molecule gives



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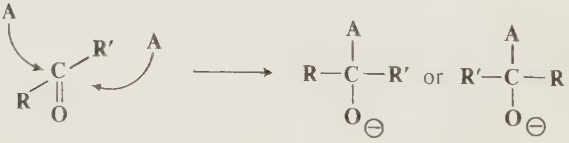
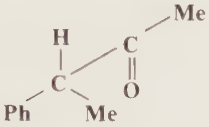


63

rise to the same transition state and product, and the two faces are thus equivalent. (2) In butanone or acetaldehyde (**63**) attack by an achiral A at one face gives a transition state and product which are the enantiomers of those arising from attack at the other face. Such faces are enantiotopic. As we have already seen (p. 97), a racemic mixture must result in this situation. However, attack at an enantiotopic face by a chiral reagent gives diastereomers, which are not formed in equal amounts. (3) In a case like **64**, the two faces are obviously not equivalent and are called diastereotopic. Enantiotopic and diastereotopic faces can be named by an extension of the Cahn-Ingold-Prelog system.[122] If the three groups as arranged by the sequence rules have the order X > Y > Z, that face in which the groups in this sequence are clockwise (as in **65**) is the *re* face (from Latin *rectus*) whereas **66** shows the *si* face (from Latin *sinister*).



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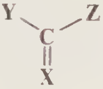

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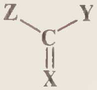

66

The word *stereoheterotopic* has been suggested[126] as a term which would include both enantiotopic and diastereotopic atoms, groups, and faces. Equivalent atoms, groups, and faces would then be *homotopic*.

Stereospecific and Stereoselective Syntheses

Any reaction in which only one of a set of stereoisomers is formed exclusively or predominantly is called a *stereoselective* synthesis.[127] The same term is used when a mixture of two or more stereoisomers is exclusively or predominantly formed at the expense of other stereoisomers. In a *stereospecific* reaction, a given isomer leads to one product while another stereoisomer leads to the opposite product. All stereospecific reactions are necessarily stereoselective, but the converse is not true. These terms are best illustrated by examples. Thus, if maleic acid treated with bromine gives the *dl* pair of 2,3-dibromosuccinic acid while fumaric acid gives the meso isomer (this is the case), the reaction is stereospecific as well as stereoselective because two opposite isomers give two opposite isomers:

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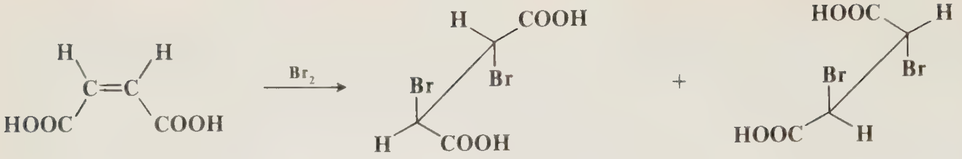
[123] Pirkle, *J. Am. Chem. Soc.* **88**, 1837 (1966); Burlingame and Pirkle, *J. Am. Chem. Soc.* **88**, 4294 (1966); Pirkle and Burlingame, *Tetrahedron Lett.* 4039 (1967).

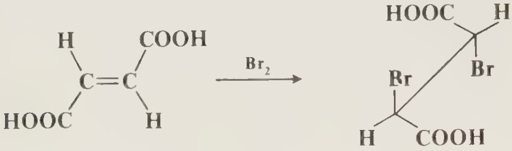
[124] For a review of isochronous and nonisochronous nuclei in the nmr, see van Gorkom and Hall, *Q. Rev., Chem. Soc.* **22**, 14–29 (1968).

[125] For example, see Schiemenz and Rast, *Tetrahedron Lett.* 4685 (1971).

[126] Eliel, *J. Chem. Educ.* **48**, 163 (1971).

[127] For a further discussion of these terms and of stereoselective reactions in general, see Eliel, "Stereochemistry of Carbon Compounds," Ref. 1, pp. 434–446.





However, if both maleic and fumaric acid gave the *dl* pair or a mixture in which the *dl* pair predominated, the reaction would be stereoselective but not stereospecific. If more or less equal amounts of *dl* and meso forms were produced in each case, the reaction would be nonstereoselective. A consequence of these definitions is that if a reaction is carried out on a compound which has no stereoisomers, it cannot be stereospecific, but at most stereoselective. For example, addition of bromine to methylacetylene could (and does) result in preferential formation of *trans*-1,2-dibromopropene, but this can be only a stereoselective and not a stereospecific reaction. Unfortunately, the term stereospecific is sometimes used in the literature where stereoselective is meant.

CONFORMATIONAL ANALYSIS

If two different three-dimensional arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called *conformations*; if not, *configurations*.[128] Configurations represent *isomers* which can be separated, as previously discussed in this chapter. Conformations represent *conformers*, which are rapidly interconvertible and thus nonseparable. The term "conformational isomer" (unfortunately, sometimes, just "isomer") is often used instead of "conformer."

Conformation in Open-Chain Systems

In an open-chain system there are an infinite number of conformations possible, each of which has a certain energy associated with it. For ethane there are two extremes, a conformation of highest and one of lowest potential energy, depicted in **67** and **68** and, by another type of diagram, in **69** and **70**. In the latter type of diagram, called the *Newman projection formula*, the observer is looking at the C—C bond head on. The three lines emanating from the center of the circle represent the valences of the front carbon, with respect to the observer.

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[128] For treatises on conformational analysis, see Eliel, Allinger, Angyal, and Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, 1965; Hanack, "Conformation Theory," Academic Press, Inc., New York, 1965; and Chiurdoglu, "Conformational Analysis," Academic Press, Inc., New York, 1971. For reviews, see Eliel, *J. Chem. Educ.* **52**, 762–767 (1975); Bastiansen, Seip, and Boggs, *Perspect. Struct. Chem.* **4**, 60–165 (1971); Golding, *MTP Int. Rev. Sci.: Org. Chem.. Ser. One*, **5**, 45–85 (1973); Lau, *Angew. Chem.* **73**, 423–432 (1961); Barton and Cookson, *Q. Rev., Chem. Soc.* **10**, 44–82 (1956); and Dauben and Pitzer, in Newman, "Steric Effects in Organic Chemistry," pp. 1–60, John Wiley & Sons, Inc., New York, 1956.

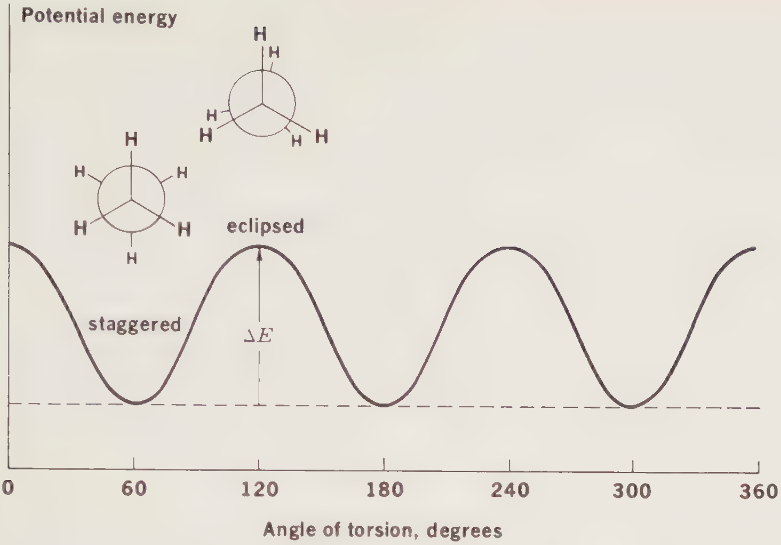
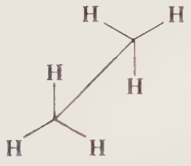
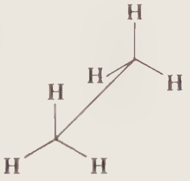


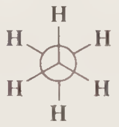
Figure 3 Conformational energy diagram for ethane.



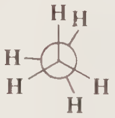
67
Staggered



68
Eclipsed

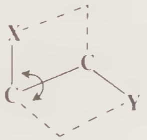


69
Staggered



70
Eclipsed

The staggered conformation (**67** or **69**) is the conformation of lowest potential energy for ethane. As the bond rotates, the energy gradually increases until the eclipsed conformation (**68** or **70**) is reached, when the energy is at a maximum. Further rotation decreases the energy again. Figure 3 illustrates this. The *angle of torsion*, which is a dihedral angle, is the angle between the XCC and the CCY planes, as shown:



For ethane the difference in energy is about 2.9 kcal/mol.[129] This difference is called the *energy barrier*, since in free rotation about a single bond there must be enough rotational energy present to cross the barrier every time two hydrogen atoms are opposite each other. The cause of such barriers is not yet understood.[130] At ordinary temperatures enough rotational energy is present for the ethane molecule to be rapidly rotating, though it still spends most of its time at or near the energy minimum. Groups larger than hydrogen cause larger barriers, and when the barriers are large enough, as in the case of suitably substituted biphenyls (p. 92), rotation at room temperature is completely prevented and we speak of configurations and not conformations. Even for compounds with small barriers, cooling to low temperatures may remove enough rotational energy for what would otherwise be conformational isomers to become configurational isomers.

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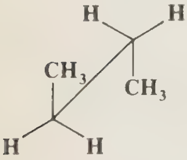
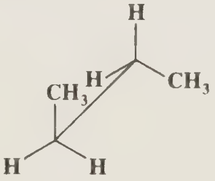
[129] Lide, *J. Chem. Phys.* **29**, 1426 (1958); Weiss and Leroi, *J. Chem. Phys.* **48**, 962 (1968).

A slightly more complicated case than ethane is that of a 1,2-disubstituted ethane (YCH_2-CH_2Y or YCH_2-CH_2X), such as *n*-butane, for which there are four extremes: a fully staggered conformation, called *anti* or *antiperiplanar* (**71**); another staggered conformation, called *gauche* or *synclinal* (**73**); and two types of eclipsed conformations, called *synperiplanar* (**74**) and *anticlinal* (**72**). An energy diagram for this system is given in Figure 4. Although there is constant rotation about the central bond, it is possible to estimate what percentage of the molecules are in each conformation at a given time. For example, for 1,2-dichloroethane in CCl_4 solution at 25°C about 70% of the molecules are in the anti and about 30% in the gauche conformation.[131] The corresponding figures for 1,2-dibromoethane are 89% anti and 11% gauche. The eclipsed conformations are unpopulated and serve only as pathways from one staggered conformation to another. Solids normally consist of a single conformer.



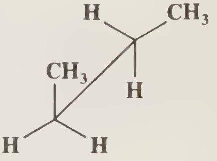
anti or
antiperiplanar

71



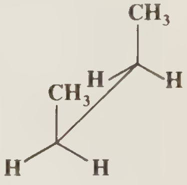
anticlinal

72



gauche or
synclinal

73



synperiplanar

74

It may be observed that the gauche conformation of butane (**73**) or of any other similar molecule is chiral. The lack of optical activity in such compounds arises from the fact that **73** and its mirror image are always present in equal amounts and interconvert too rapidly for separation.

For butane and for most other molecules of the forms YCH_2-CH_2Y and YCH_2-CH_2X, the anti conformer is the most stable, but exceptions are known. One group of exceptions consists of molecules containing small electronegative atoms, especially fluorine and oxygen. Thus 2-fluoroethanol,[132] 1,2-difluoroethane,[133] and 2-fluoroethyl trichloroacetate[134] ($FCH_2CH_2OCOCCl_3$) exist almost entirely in the gauche form, and compounds such as 2-chloroethanol and 2-bromoethanol[132] also prefer the gauche form. There is as yet no generally accepted explanation

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[130] For a review of methods of measuring barriers, of attempts to explain barriers, and of values of barriers, see Lowe, *Prog. Phys. Org. Chem.* **6**, 1-80 (1968). For other reviews of this subject, see Oosterhoff, *Pure Appl. Chem.* **25**, 563-571 (1971); Wyn-Jones and Pethrick, *Top. Stereochem.* **5**, 205-274 (1970); Pethrick and Wyn-Jones, *Q. Rev., Chem. Soc.* **23**, 301-324 (1969); Brier, *J. Mol. Struct.* **6**, 23-36 (1970); Lowe, *Science* **179**, 527-533 (1973); Millen, *Prog. Stereochem.* **3**, 138-168 (1962); and Wilson, *Adv. Chem. Phys.* **2**, 367-393 (1959).

[131] Aroney, Izsak, and Le Fèvre, *J. Chem. Soc.* 1407 (1962); Le Fèvre and Orr, *Aust. J. Chem.* **17**, 1098 (1964).

[132] Wyn-Jones and Orville-Thomas, *J. Mol. Struct.* **1**, 79 (1967); Buckley, Giguère, and Yamamoto, *Can. J. Chem.* **46**, 2917 (1968); Hagen and Hedberg, *J. Am. Chem. Soc.* **95**, 8263 (1973).

[133] Klaboe and Nielsen, *J. Chem. Phys.* **33**, 1764 (1960); Abraham and Kemp, *J. Chem. Soc. B* 1240 (1971); Bulthuis, van den Berg, and MacLean, *J. Mol. Struct.* **16**, 11 (1973); van Schaick, Geise, Mijlhoff, and Renes, *J. Mol. Struct.* **16**, 23 (1973).

[134] Abraham and Monasterios, *Org. Magn. Reson.* **5**, 305 (1973).

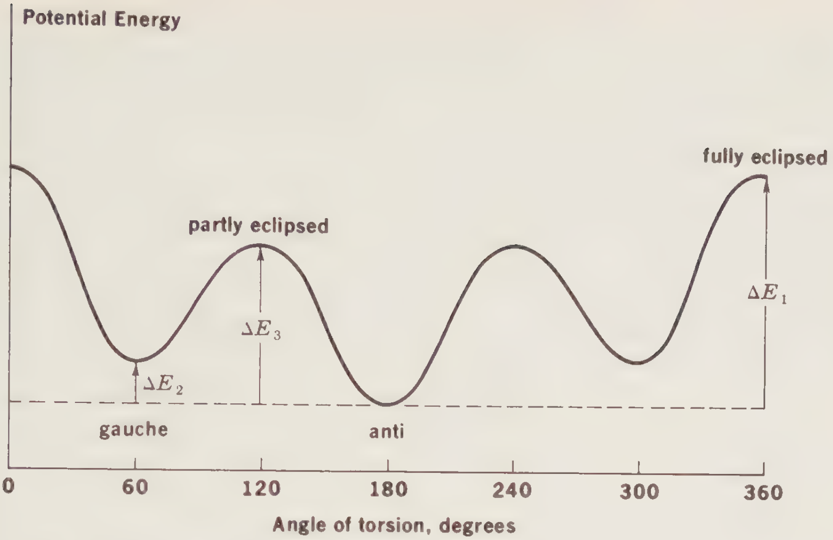
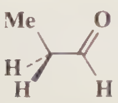


Figure 4 Conformational energy for $YCH_2—CH_2Y$ or $YCH_2—CH_2X$. For *n*-butane, $\Delta E_1 = 4$ to 6, $\Delta E_2 = 0.8$, and $\Delta E_3 = 3.4$ kcal/mol.

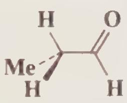
for this behavior.[135] It had been believed that the favorable gauche conformation of 2-fluoroethanol was the result of intramolecular hydrogen bonding, but this explanation of course will not do for molecules like 2-fluoroethyl trichloroacetate and it has in fact been ruled out for 2-fluoroethanol as well.[136] Other exceptions are known, where small electronegative atoms are absent. For example, 1,1,2,2-tetrachloroethane and 1,1,2,2-tetrabromoethane both prefer the gauche conformation.[137]

All the conformations so far discussed have involved rotation about sp^3-sp^3 bonds. Many studies have also been made of compounds with sp^3-sp^2 bonds.[138] For example, propionaldehyde (or any similar molecule) has four extreme conformations, two of which are called *eclipsing* and



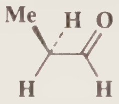
eclipsing

75

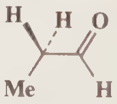


eclipsing

76



bisecting



bisecting

the other two *bisecting*. For propionaldehyde the eclipsing conformations have lower energy than the other two, with **75** favored over **76** by about 900 cal/mol.[139] As we have already pointed

[135] It has been proposed that the preference for the gauche conformation in these molecules is an example of a more general phenomenon, known as the *gauche effect*, i.e., a tendency to adopt that structure which has the maximum number of gauche interactions between adjacent electron pairs or polar bonds. This effect is ascribed to nuclear-electron attractive forces between the groups or unshared pairs: Wolfe, Rauk, Tel, and Csizmadia, *J. Chem. Soc. B* 136 (1971); Wolfe, *Acc. Chem. Res.* **5**, 102-111 (1972). See also Phillips and Wray, *J. Chem. Soc., Chem. Commun.* 90 (1973); Radom, Hehre, and Pople, *J. Am. Chem. Soc.* **94**, 2371 (1972); and Zefirov, *J. Org. Chem. USSR* **10**, 1147 (1974).

[136] Griffith and Roberts, *Tetrahedron Lett.* 3499 (1974).

[137] Kagarise, *J. Chem. Phys.* **24**, 300 (1956).

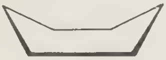
[138] For reviews, see Karabatsos and Fenoglio, *Top. Stereochem.* **5**, 167-203 (1970); and (for esters) Jones and Owen, *J. Mol. Struct.* **18**, 1-32 (1973).

[139] Butcher and Wilson, *J. Chem. Phys.* **40**, 1671 (1964); Allinger and Hickey, *J. Mol. Struct.* **17**, 233 (1973).

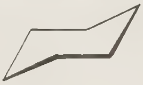
out (p. 115), for a few of these compounds, rotation is slow enough to permit cis-trans isomerism, though for simple compounds rotation is rapid. For example, acetaldehyde has a lower rotational barrier (about 1 kcal/mol) than ethane.[140]

Conformation in Six-membered Rings[141]

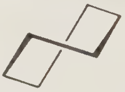
If the six carbons of cyclohexane were to lie in a plane, the bond angles would have to be 120° since these are the angles of a regular hexagon. Since the normal tetrahedral angle is about 109.5°, there would be strain. The existence of cyclopropane proves that molecules may contain a good deal more strain than this. However, cyclopropane *must* be planar (there is no other conformation possible), whereas for cyclohexane there are two extreme conformations in which all the angles are tetrahedral.[142] These are called the *boat* and the *chair* conformations, and in each the ring is said to be *puckered*. The chair conformation is a rigid structure, but the boat form is flexible[143] and can easily pass over to a somewhat more stable form known as the *twist* conformation, also called the *skew boat* form. The twist form is about 1.5 kcal/mol more stable than the boat because it has less eclipsing interaction (see p. 145).[144] The chair form is more stable than the twist form by about 5 kcal/mol.[145] In the vast majority of compounds containing a cyclohexane ring, the molecules exist almost entirely in the chair form. Yet it is known that the boat or twist form exists transiently. An inspection of the chair form shows that six of its bonds are directed differently from the other six:



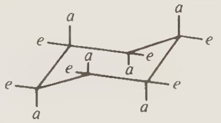
Boat



Chair



Twist



On each carbon one bond is directed up or down, and the other, more or less in the "plane" of the ring. The up or down bonds are called *axial* and the others *equatorial*. The axial bonds point alternately up and down. If a molecule were frozen into a chair form, there would be isomerism in monosubstituted cyclohexanes. For example, there would be an equatorial methylcyclohexane and an axial isomer. However, it has never been possible to isolate isomers of this type at room temperature. This proves the transient existence of the boat or twist form, since in order for the two types of methylcyclohexane to be nonseparable, there must be rapid interconversion of one chair form to another (in which all axial bonds become equatorial and vice versa) and this is possible only through a boat or twist conformation. Conversion of one chair form to another requires an activation energy of about 10 kcal/mol[146] and is very rapid at room temperature.[147] However, by working at low temperatures, Jensen and Bushweller have been able to obtain the pure equatorial conformers of chlorocyclohexane and trideuteriomethoxycyclohexane, as solids and in solution.[148] Equatorial chlorocyclohexane has a half-life of 22 years in solution at −160°C.

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[140] Davidson and Allen, *J. Chem. Phys.* **54,** 2828 (1971).

[141] For reviews, see Jensen and Bushweller, *Adv. Alicyclic Chem.* **3,** 139–194 (1971); Robinson and Theobald, *Q. Rev., Chem. Soc.* **21,** 314–330 (1967); Klyne, *Prog. Stereochem.* **1,** 36–89 (1954); Hassel, *Q. Rev., Chem. Soc.* **7,** 221–230 (1953); Orloff, *Chem. Rev.* **54,** 348–447 (1954); Eliel, *Angew. Chem. Int. Ed. Engl.* **4,** 761–774 (1965) [*Angew. Chem.* **77,** 784–797].

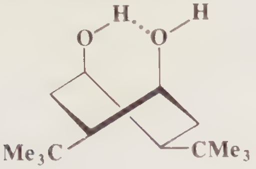
[142] The C—C—C angles in cyclohexane are actually 111.5° [Davis and Hassel, *Acta Chem. Scand.* **17,** 1181 (1963); Geise, Buys, and Mijlhoff, *J. Mol. Struct.* **9,** 447 (1971); Bastiansen, Fernholt, Seip, Kambara, and Kuchitsu, *J. Mol. Struct.* **18,** 163 (1973)], but this is within the normal tetrahedral range (see p. 23).

[143] See Dunitz, *J. Chem. Educ.* **47,** 488 (1970).

[144] For reviews of nonchair forms, see Kellie and Riddell, *Top. Stereochem.* **8,** 225–269 (1974); and Balasubramanian, *Chem. Rev.* **62,** 591 (1962).

[145] Margrave, Frisch, Bautista, Clarke, and Johnson, *J. Am. Chem. Soc.* **85,** 546 (1963); Squillacote, Sheridan, Chapman, and Anet, *J. Am. Chem. Soc.* **97,** 3244 (1975).

In some molecules the twist conformation is actually preferred.[149] An example is **77**, in which hydrogen bonding stabilizes the otherwise high-energy form. Of course in certain bicyclic compounds the six-membered ring is forced to maintain a boat or twist conformation, as in norbornane (**78**) or twistane (**79**).



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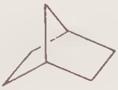

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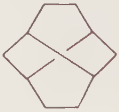

79

In monosubstituted cyclohexanes, the substituent normally prefers the equatorial position because in the axial position there is interaction between the substituent and the axial hydrogens in the 3 and 5 positions, but the extent of this preference depends greatly on the nature of the group. Alkyl groups have a greater preference than polar groups, and for alkyl groups the preference increases with size. For polar groups, size seems to be unimportant. Both the large HgBr[150] and HgCl[151] groups and the small F group have been reported to have little or no conformational preference (the HgCl group actually shows a slight preference for the axial position). Table 2 gives approximate values of the free energy required for various groups to go from the equatorial position to the axial,[152] though it must be kept in mind that these values vary somewhat with physical state, temperature, and solvent.[153]

In disubstituted compounds, the rule for nonpolar groups is that the conformation will be such that as many groups as possible adopt the equatorial position. How far it is possible depends on the configuration. In a *cis*-1,2-disubstituted cyclohexane, one substituent must be axial and the other equatorial. In a *trans*-1,2 compound both may be equatorial or both axial. This is also true for 1,4-disubstituted cyclohexanes, but for 1,3 compounds, the reverse holds: the trans isomer must have the *ae* conformation, and the cis isomer may be *aa* or *ee*. For alkyl groups, the diequatorial conformation predominates over the diaxial, but for other groups this is not necessarily so. For example, both *trans*-1,4-dibromocyclohexane and the corresponding dichloro compound have the *ee* and *aa* conformations about equally populated,[154] and most *trans*-1,2-

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[146] Jensen, Noyce, Sederholm, and Berlin, *J. Am. Chem. Soc.* **84**, 386 (1962); Anet, Ahmad, and Hall, *Proc. Chem. Soc.* 145 (1964); Bovey, Hood, Anderson, and Kornegay, *J. Chem. Phys.* **41**, 2041 (1964); Anet and Bourn, *J. Am. Chem. Soc.* **89**, 760 (1967). See also Strauss, *J. Chem. Educ.* **48**, 221 (1971).

[147] For a review of chair-chair interconversions, see Anderson, *Top. Curr. Chem.* **45**, 139–167 (1974).

[148] Jensen and Bushweller, *J. Am. Chem. Soc.* **88**, 4279 (1966); **91**, 3223 (1969).

[149] Stolow, *J. Am. Chem. Soc.* **83**, 2592 (1961), **86**, 2170 (1964); Stolow, McDonagh, and Bonaventura, *J. Am. Chem. Soc.* **86**, 2165 (1964).

[150] Jensen and Gale, *J. Am. Chem. Soc.* **81**, 6337 (1959).

[151] Anet, Krane, Kitching, Dodderel, and Praeger, *Tetrahedron Lett.* 3255 (1974).

[152] Except where otherwise indicated, these values are from Jensen and Bushweller, Ref. 141. See also Ref. 155.

[153] See, for example, Ford and Allinger, *J. Org. Chem.* **35**, 3178 (1970). For a critical review of methods used to obtain these values, see Jensen and Bushweller, Ref. 141.

[154] Atkinson and Hassel, *Acta Chem. Scand.* **13**, 1737 (1959); Abraham and Rossetti, *Tetrahedron Lett.* 4965 (1972).

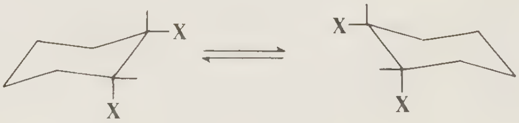
TABLE 2 Free-energy differences between equatorial and axial substituents on a cyclohexane ring[152]

Group	Approximate $-\Delta G°$, kcal/mol	Group	Approximate $-\Delta G°$, kcal/mol
HgCl[151]	−0.25	**NO_2**	1.1
HgBr	0	**COOEt**	1.1–1.2
CN	0.15–0.25	**SH**	1.2
F	0.25	**COOMe**	1.27–1.31
C≡CH	0.41	**COOH**	1.36–1.46
I	0.46	**NH_2**[156]	1.4
Br	0.48–0.62	**CH_3**[154a]	1.74
OTs	0.515	**C_2H_5**	~1.75
Cl	0.52	**iso-Pr**	~2.15
OAc	0.71	**C_6H_{11}**[157]	2.15
OMe[155]	0.75	**C_6H_5**[157]	3.0
OH	0.92–0.97	***t*-Bu**	>4

dihalocyclohexanes exist predominantly in the *aa* conformation.[158] Note that in the latter case the two halogen atoms are anti in the *aa* conformation but gauche in the *ee* conformation.

Since compounds with alkyl equatorial substituents are generally more stable, *trans*-1,2 compounds, which can adopt the *ee* conformation, are thermodynamically more stable than their *cis*-1,2 isomers, which must exist in the *ae* conformation. For the 1,2-dimethylcyclohexanes, the difference in stability is about 2 kcal/mol. Similarly, *trans*-1,4 and *cis*-1,3 compounds are more stable than their stereoisomers.

Incidentally, we can now see, in one case, why the correct number of stereoisomers could be predicted by assuming planar rings even though they are not planar (p. 117). In the case of both a *cis*-1,2-XX-disubstituted and a *cis*-1,2-XY-disubstituted cyclohexane, the molecule is nonsuperimposable on its mirror image; neither has a plane of symmetry. However, in the former case (**80**) conversion of one chair form to the other (which of course happens rapidly) turns the molecule into its mirror image, while in the latter case



80

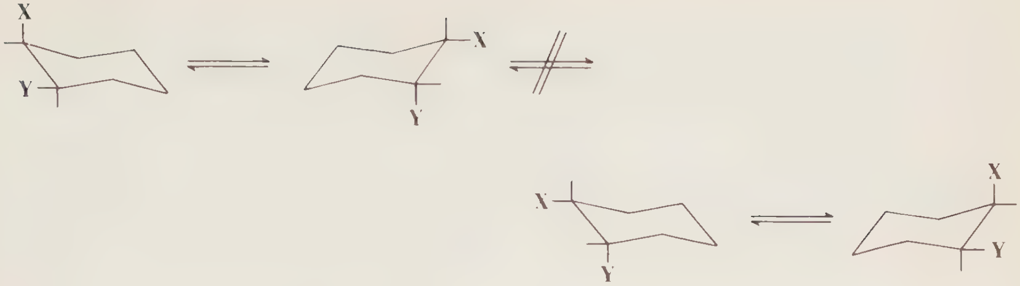
[154a] Booth and Everett, *J. Chem. Soc., Chem. Commun.* 278 (1976).

[155] Schneider and Hoppen, *Tetrahedron Lett.* 579 (1974).

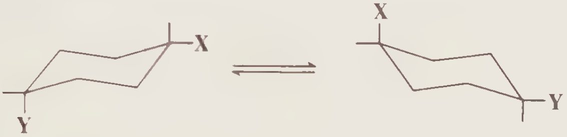
[156] Booth, *J. Chem. Soc., Chem. Commun.* 945 (1973).

[157] Hirsch, *Top. Stereochem.* **1**, 199–222 (1967).

[158] Hageman and Havinga, *Recl. Trav. Chim. Pays-Bas* **88**, 97 (1969); Klaeboe, *Acta Chem. Scand.* **25**, 695 (1971); and references cited in these papers.



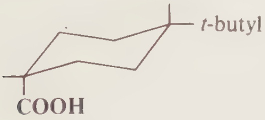
rapid interconversion does not give the mirror image but merely the conformer in which the original axial and equatorial substituents exchange places. Thus the optical inactivity of **80** is not due to a plane of symmetry but to a rapid interconversion of the molecule and its mirror image. A similar situation obtains for *cis*-1,3 compounds. However, for *cis*-1,4 isomers (both XX and XY) optical inactivity arises from a plane of symmetry in both conformations:



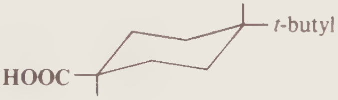
Symmetric Symmetric

All *trans*-1,2- and *trans*-1,3-disubstituted cyclohexanes are chiral (whether XX or XY), while *trans*-1,4 compounds (both XX and XY) are achiral, since all conformations have a plane of symmetry.

The conformation of a group can be frozen into a desired position by putting into the ring a large alkyl group (most often *t*-butyl), which must adopt the equatorial position.[159] For example, it was desired to compare the acidity of the carboxyl group in the axial and in the equatorial position. For this purpose the *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acids were synthesized. The geometry is such that in the cis compound the equatorial *t*-butyl group forces the carboxyl group to be axial, while in the trans compound it must be equatorial:



cis; *ae*



trans; *ee*

The equatorial COOH has the greater acidity.[160]

The principles involved in the conformational analysis of six-membered rings containing one or two trigonal atoms, e.g., cyclohexanone and cyclohexene, are similar.[161]

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[159] This idea was suggested by Winstein and Holness, *J. Am. Chem. Soc.* **77**, 5562 (1955).

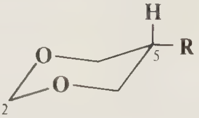
[160] Stolow, *J. Am. Chem. Soc.* **81**, 5806 (1959).

[161] For a review, see Johnson, *Chem. Rev.* **68**, 375–413 (1968). See also Refs. 128, 141.

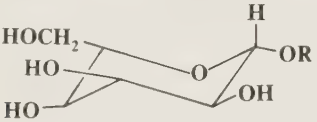
Conformation in Six-membered Rings Containing Hetero Atoms[162]

In six-membered rings containing hetero atoms, the basic principles are the same; i.e., there are chair, twist, and boat forms, axial and equatorial groups, etc., but in certain compounds a number of new factors enter the picture. We shall deal with only two of these.[163]

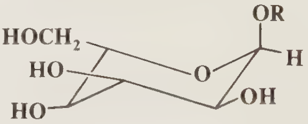
1. In 5-alkyl-substituted 1,3-dioxanes, the 5-substituent has a much smaller preference for the equatorial position than in cyclohexane derivatives;[164] the values of $-\Delta G^\circ$ are much lower. This indicates that the lone pairs on the oxygens have a smaller steric requirement than the C—H bonds in the corresponding cyclohexane derivatives. Similar behavior is found in the 1,3-dithianes.[165] With certain nonalkyl substituents (e.g., F, NO_2, SOMe, $NMe_3{}^+$) the axial position is actually preferred.[165a]



2. An alkyl group located on a carbon α to a hetero atom prefers the equatorial position, which is of course the normally expected behavior, but a *polar* group in such a location prefers the *axial* position. An example of this phenomenon, known as the *anomeric effect*,[166] is the greater stability of α-glucosides over β-glucosides. The reason for the anomeric effect is not completely understood, though several explanations have been offered.[167]



A β-glucoside



An α-glucoside

Conformation in Other Rings

Three-membered rings must be planar, but they seem to be the only saturated rings which generally are. Cyclobutane[168] is not planar but exists as in **81**, with an angle between the planes

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[162] For reviews, see Eliel, *Angew. Chem. Int. Ed. Engl.* **11**, 739–750 (1972) [*Angew. Chem.* **84**, 779–791], *Pure Appl. Chem.* **25**, 509–525 (1971), *Acc. Chem. Res.* **3**, 1–8 (1970); Lambert, *Acc. Chem. Res.* **4**, 87–94 (1971); Romers, Altona, Buys, and Havinga, *Top. Stereochem.* **4**, 39–97 (1969); and Riddell, *Q. Rev., Chem. Soc.* **21**, 364–378 (1967).

[163] These factors are discussed by Eliel, Ref. 162.

[164] Riddell and Robinson, *Tetrahedron* **23**, 3417 (1967); Eliel and Knoeber, *J. Am. Chem. Soc.* **90**, 3444 (1968); see also Abraham, Banks, Eliel, Hofer, and Kaloustian, *J. Am. Chem. Soc.* **94**, 1913 (1972); Eliel and Evans, *J. Am. Chem. Soc.* **94**, 8587 (1972); Eliel and Hofer, *J. Am. Chem. Soc.* **95**, 8041 (1973); Eliel and Alcudia, *J. Am. Chem. Soc.* **96**, 1939 (1974).

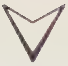
[165] Hutchins and Eliel, *J. Am. Chem. Soc.* **91**, 2703 (1969).

[165a] Kaloustian, Dennis, Mager, Evans, Alcudia, and Eliel, *J. Am. Chem. Soc.* **98**, 956 (1976).

[166] For reviews, see Zefirov and Shekhtman, *Russ. Chem. Rev.* **40**, 315–329 (1971); Lemieux, *Pure Appl. Chem.* **27**, 527–547 (1971); Angyal, *Angew. Chem. Int. Ed. Engl.* **8**, 157–166 (1969) [*Angew. Chem.* **81**, 172–182]; Martin, *Ann. Chim. (Paris)* [14] **6**, 205–218 (1971); and Stoddart, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **7**, 1–30, pp. 7–13 (1973).

[167] See for example, Ponec and Chvalovský, *Collect. Czech. Chem. Commun.* **39**, 2613 (1974); Zhdanov, Minyaev, and Minkin, *J. Mol. Struct.* **16**, 357 (1973), *Doklad. Chem.* **211**, 563 (1973); David, Eisenstein, Hehre, Salem, and Hoffmann, *J. Am. Chem. Soc.* **95**, 3806 (1973); Hutchins, Kopp, and Eliel, *J. Am. Chem. Soc.* **90**, 7174 (1968); Wolfe, Rauk, Tel, and Csizmadia, Ref. 135; and Ref. 166.

[168] For reviews of the stereochemistry of four-membered rings, see Moriarty, *Top. Stereochem.* **8**, 271–421 (1974); Cotton and Frenz, *Tetrahedron* **30**, 1587–1594 (1974).



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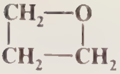
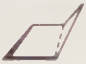
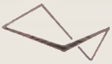


82

of about 35°.[169] The deviation from planarity is presumably caused by eclipsing in the planar form (see p. 145). Oxetane (**82**), in which eclipsing is less, is planar.[170] Cyclopentane might be expected to be planar, since the angles of a regular pentagon are 108°, but it is not so, also because of eclipsing effects.[171] There are two puckered conformations, the *envelope* and the *half-chair*. There is little energy difference between these two forms, and many five-membered ring systems have conformations somewhere in between them.[172] Although in the envelope conformation one carbon is shown above the others, ring motions cause each of the carbons in rapid succession to assume this position. The puckering rotates around the ring in what may be called a *pseudorotation*.[173] In substituted cyclopentanes, and in five-membered rings in which at least one atom does not contain two substituents (such as tetrahydrofuran, cyclopentanone, etc.), one conformer may be more stable than the others. The barrier to planarity in cyclopentane has been reported to be 5.2 kcal/mol.[174]



Envelope



Half-chair

Rings larger than six-membered are always puckered[175] unless they contain a large number of sp^2 atoms (see the section on strain in medium rings, p. 145).

Methods for Determining Conformations[176]

X-ray- and electron-diffraction techniques, which are capable of measuring bond distances and angles, obviously can give conformations too. X-ray diffraction, which can be used only on solids, has been more successful in this respect, because all the molecules in a crystal have the same

[169] Dows and Rich, *J. Chem. Phys.* **47**, 333 (1967); Stone and Mills, *Mol. Phys.* **18**, 631 (1970); Miller and Capwell, *Spectrochim. Acta, Part A* **27**, 947 (1971); Miller, Capwell, Lord, and Rea, *Spectrochim. Acta, Part A* **28**, 603 (1972). However, some cyclobutane derivatives are planar, at least in the solid state: for example, see Margulis and Fischer, *J. Am. Chem. Soc.* **89**, 223 (1967); Adman and Margulis, *J. Am. Chem. Soc.* **90**, 4517 (1968); Margulis, *Chem. Commun.* 215 (1969), *J. Am. Chem. Soc.* **93**, 2193 (1971).

[170] Chan, Zinn, Fernandez, and Gwinn, *J. Chem. Phys.* **33**, 1643 (1960).

[171] For discussions of the conformational analysis of five-membered rings, see Altona, in Chiurdoglu, Ref. 128, pp. 1–13; and Lambert, Papay, Khan, Kappauf, and Magyar, *J. Am. Chem. Soc.* **96**, 6112 (1974).

[172] Willy, Binsch, and Eliel, *J. Am. Chem. Soc.* **92**, 5394 (1970); Lipnick, *J. Mol. Struct.* **21**, 423 (1974).

[173] Kilpatrick, Pitzer, and Spitzer, *J. Am. Chem. Soc.* **69**, 2438 (1947); Pitzer and Donath, *J. Am. Chem. Soc.* **81**, 3213 (1959); Durig and Wertz, *J. Chem. Phys.* **49**, 2118 (1968); Lipnick, *J. Mol. Struct.* **21**, 411 (1974).

[174] Carreira, Jiang, Person, and Willis, *J. Chem. Phys.* **56**, 1440 (1972).

[175] For reviews of conformations in larger rings, see Casanova and Waegell, *Bull. Soc. Chim. Fr.* 911–921 (1975); Anet, *Top. Curr. Chem.* **45**, 169–220 (1974); Dunitz, *Pure Appl. Chem.* **25**, 495–508 (1971), *Perspect. Struct. Chem.* **2**, 1–70 (1968); Baird, *MTP Int. Rev. Sci.: Org. Chem.. Ser. One*, **5**, 205–238 (1973); Tochtermann, *Fortchr. Chem. Forsch.* **15**, 378–444 (1970); Dale, *Angew. Chem. Int. Ed. Engl.* **5**, 1000–1021 (1966) [*Angew. Chem.* **78**, 1070–1093]; Dunitz and Prelog, *Angew. Chem.* **72**, 896–902 (1960); Prelog, *Pure Appl. Chem.* **6**, 545–560 (1963); and Sicher, *Prog. Stereochem.* **3**, 202–264 (1962). Also see the monographs by Hanack and by Eliel, Allinger, Angyal, and Morrison, Ref. 128.

[176] For reviews, see Lau, *Angew. Chem.* **73**, 423–432 (1961); Klyne, *Prog. Stereochem.* **1**, 36–89 (1954); and Eliel, Allinger, Angyal, and Morrison, Ref. 128, pp. 129–188.

conformation. However, this very virtue is also a drawback, because the conformation of the solid is not necessarily the same as that of the molecules in other phases. Dipole moments can often be used to determine conformations. For example, 1,2-dibromoethane should have no dipole moment in the anti conformation but should have a moment in the gauche conformation. Since the compound has a dipole moment of 0.93 D, it must exist at least partially in the gauche form. A consideration of dipole moments and polarizabilities led to the conclusion that 89% of the molecules are in the anti and 11% in the gauche conformations.[131] Conformations have also been determined from ir, Raman, uv, nmr, and microwave[177] spectra. For example, each conformer has its own ir spectrum, and the peak positions are often different. For example, the C—F bond in equatorial fluorocyclohexane absorbs at 1062 cm^{-1}, while the axial C—F bond absorbs at 1129 cm^{-1}.[178] Many relationships of this kind are known, and it is often possible to tell which conformation a molecule has and, for mixtures, what percentage is in each conformation. Because of the relationship between configuration and conformation in cyclic compounds (see p. 129), configuration can frequently be determined too.

As for nmr,[179] if a molecule can exist in several conformations which rapidly interconvert, then any proton in the molecule assumes all possible positions in a very short time and the nmr spectrum represents an average. This is the case in most open-chain compounds. Even in cyclohexanes the chair-chair interconversion is so rapid that the nmr spectrum shows only one peak. However, in cases where interconversion of conformers is slowed or prevented (either by cooling the compound or by the inherent structure of the molecule) the hydrogens of each conformer appear separately (in cases where only one is stable only that one appears). An example is the cooling of cyclohexane to −110°C, at which temperature two peaks appear. Only the chair form is present, and one peak is due to the equatorial and the other to the axial hydrogens.[180]

When axial and equatorial protons do appear at different positions, they can often be told apart, since axial protons usually absorb at a slightly higher field than equatorials.[181] However, care must be taken, since this is not always the case.[182] When the peaks due to axial and equatorial protons have been identified, the proportions of the conformers can be established by measuring the area under the peaks.[183] Another aid to conformational determination is the fact that the nmr coupling constant J is higher for coupling between two adjacent axial hydrogens than for two equatorials or for an axial and an equatorial.[184] In fact J_{anti} is usually greater than J_{gauche} in most cases. ^{13}C nmr has also been used to obtain conformational information.[185]

Energy barriers and rates of conversion from one conformer to another can be obtained from the shape of nmr peaks and the way they split with decreasing temperature[186] (see also p. 202).

Another important method for determining conformation when the absolute configuration is

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[177] For a review with respect to microwave spectra, see Wilson, *Chem. Soc. Rev.* **1,** 293–318 (1972).

[178] Larnaudie, *C. R. Acad. Sci.* **235,** 154 (1952).

[179] For a review of the use of nmr to study conformation, see Anet and Anet, in Nachod and Zuckerman, "Determination of Organic Structures by Physical Methods," vol. 3, pp. 343–420, Academic Press, Inc., New York, 1971.

[180] For reviews of the use of nmr to study conformational mobility in cyclic systems, see Anderson, *Q. Rev., Chem. Soc.* **19,** 426–439 (1965); and Franklin and Feltkamp, *Angew. Chem. Int. Ed. Engl.* **4,** 774–783 (1965) [*Angew. Chem.* **77,** 798–807].

[181] Eliel, *Chem. Ind.* (*London*) 568 (1959); Lemieux, Kullnig, Bernstein, and Schneider, *J. Am. Chem. Soc.* **80,** 6098 (1958); Eliel and Martin, *J. Am. Chem. Soc.* **90,** 682 (1968).

[182] Williamson and Johnson, *J. Am. Chem. Soc.* **83,** 4623 (1961); Wellman and Bordwell, *Tetrahedron Lett.* 1703 (1963); Nickon, Castle, Harada, Berkoff, and Williams, *J. Am. Chem. Soc.* **85,** 2185 (1963).

[183] Berlin and Jensen, *Chem. Ind.* (*London*) 998 (1960); Jensen, Bushweller, and Beck, *J. Am. Chem. Soc.* **91,** 344 (1969).

[184] Trager, Vincenzi, and Huitric, *J. Org. Chem.* **27,** 3006 (1962).

[185] Buchanan, Ross, and Stothers, *J. Am. Chem. Soc.* **88,** 4301 (1966); Jones, Eliel, Grant, Knoeber, and Bailey, *J. Am. Chem. Soc.* **93,** 4772 (1971); Brouwer and Stothers, *Can. J. Chem.* **50,** 601 (1972).

[186] For reviews, see Johnson, *Adv. Magn. Reson.* **1,** 33–102 (1965); Kessler, *Angew. Chem. Int. Ed. Engl.* **9,** 219–235 (1970) [*Angew. Chem.* **82,** 237–253]; Ivanova and Kugatova-Shemyakina, *Russ. Chem. Rev.* **39,** 510–528 (1970).

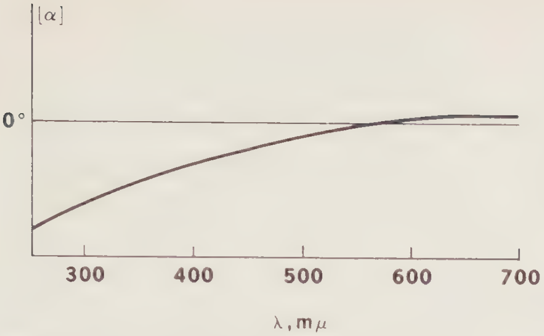

Figure 5 A plain curve

known depends on measuring the *optical rotatory dispersion* (ord).[187] It has been mentioned that when a chiral compound rotates the plane of polarized light, the amount of rotation depends on the wavelength of the polarized light. In ord, rotations are measured over a range of wavelengths rather than at a single wavelength, usually covering the uv as well as the visible region. Instruments which do this and plot the rotation as a continuous function of the wavelength are commercially available. Some compounds give what is called a *plain curve* (Figure 5), while others illustrate the *Cotton effect* (Figure 6). In a *positive* Cotton effect, as the wavelength decreases, the rotation takes a fairly sharp increase, reaches a peak, and then precipitously sinks to a trough, after which it rises again. The descending line always crosses the zero axis at a wavelength at which the compound absorbs light, though not all such wavelengths show the Cotton effect. A *negative* Cotton effect is the reverse: as the wavelength decreases, there is first a drop and then a sharp rise. Obviously, if any compound shows a positive Cotton effect, its enantiomer must show a negative one.

Plain curves are much less useful than curves which show a Cotton effect, but sometimes a comparison of the plain curves of two similar compounds can show the absolute configuration of one if the configuration of the other is known. Another use for plain curves is in the detection of optical activity when a measurement at the usual wavelength (589 nm corresponding to the D line of Na) does not indicate activity. In some cases the rotation at 589 nm is so low that it is undetectable, but it is usually greater in the uv region.

Curves which exhibit Cotton effects have been much more useful, yielding information on structure, configuration, and conformation, though the relationships are largely empirical. The basic method is one of comparison of the peaks of unknown with those of known compounds. Most of the early studies were performed on cyclic ketones. The keto group absorbs in the ultraviolet at about 280 to 290 nm, and this absorption generally gives rise to a Cotton effect. Cyclic compounds are more rigid than acyclic ones and thus more amenable to conformational study.

An illustration of the type of correlations made possible by a comparison of Cotton-effect curves

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[187] For monographs, see Crabbé, "ORD and CD in Chemistry and Biochemistry," Academic Press, Inc., New York, 1972, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, 1965; Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Sadtler Research Laboratories, Philadelphia, 1967; and Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Company, New York, 1960. For reviews, see Barrett, in Bentley and Kirby, Ref. 55, pt. 1, pp. 515–610, 1972; Jones, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **1**, 85–121 (1973); Snatzke, *Angew. Chem. Int. Ed. Engl.* **7**, 14–25 (1968) [*Angew. Chem.* **80**, 15–26]; Crabbé in Nachod and Zuckerman, Ref. 179, vol. 3, pp. 133–205; Crabbé and Klyne, *Tetrahedron* **23**, 3449 (1967); Crabbé, *Top. Stereochem.* **1**, 93–198 (1967); Eyring, Liu, and Caldwell, *Chem. Rev.* **68**, 525–540 (1968); Yufit and Kucherov, *Russ. Chem. Rev.* **31**, 235–244 (1962); Djerassi, *Pure Appl. Chem.* **2**, 475–504 (1961); and Klyne, *Adv. Org. Chem.* **1**, 239–348 (1960).

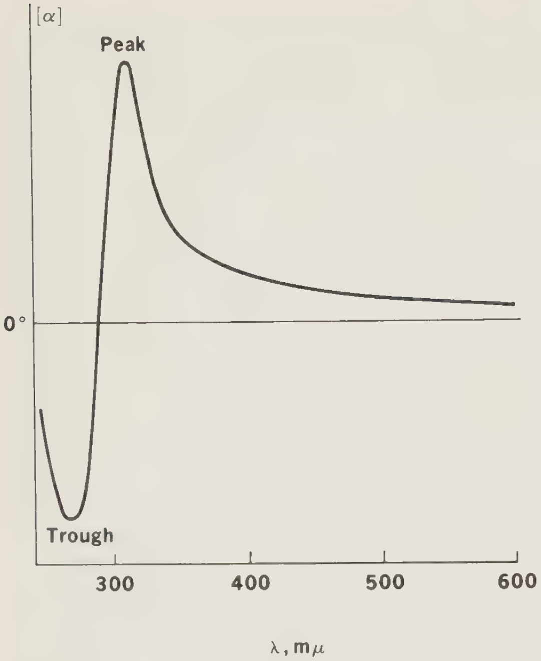
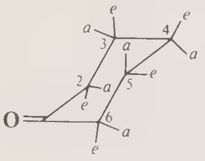


Figure 6 An ord curve showing a positive Cotton effect.

can be obtained by a consideration of the *octant rule*.[188] According to this rule, a carbonyl compound is cut into octants by three perpendicular planes which meet at the carbonyl carbon (Figure 7). For a six-membered ring (**83**) one plane is the plane which includes C-1, C-2, C-6, and the carbonyl oxygen. In the diagram this plane lies below C-3, C-4, and C-5. The second plane is perpendicular to the first, includes C-1, C-4, and the oxygen, and bisects the ring. In the diagram, C-2 and C-3 lie behind this plane and C-5 and C-6 in front of it. The third plane includes C-1 and is perpendicular to the other two. In **83** only the oxygen lies to the left of the third plane; all other atoms lie to the right. The three planes cut the molecule into eight sections, four of which, in this case, are unoccupied by atoms. The octant rule can then be stated for the four octants which are occupied in **83.** Substituents which are *in the planes* (unmarked in **84**) have little or no effect on the ord curve; substituents in the lower right and upper left octants (marked *) make a positive contribution to the Cotton-effect curve; and substituents in the upper right and lower left octants



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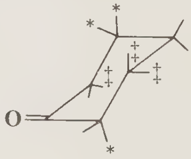

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[188] Moffitt, Woodward, Moscowitz, Klyne, and Djerassi, *J. Am. Chem. Soc.* **83,** 4013 (1961); Djerassi and Klyne, *J. Chem. Soc.* 4929 (1962). For a discussion, see Murphy, *J. Chem. Educ.* **52,** 774–776 (1975).

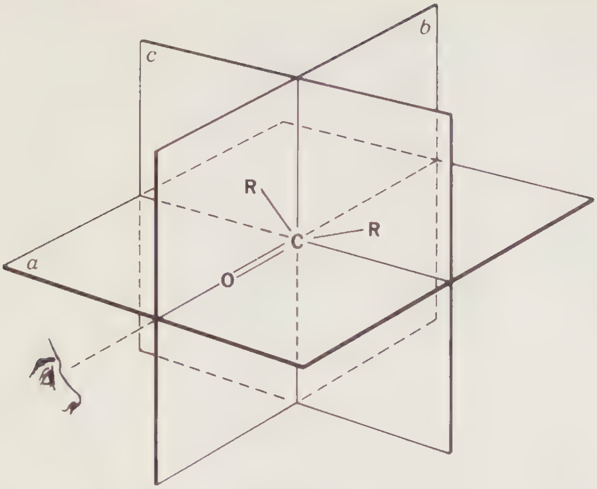
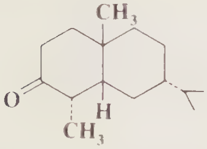


Figure 7 The three perpendicular planes of the octant rule.

(marked ‡) make a negative contribution. For the other four octants (these are occupied in some compounds with fused ring systems) the contributions are reversed.[189]

An example of the use of ord to establish conformation can be seen for the *cis*-tetrahydrocyperones, the absolute configurations of which are known and are shown in **85** and **86.** The



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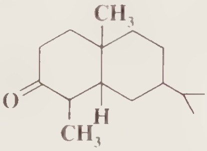

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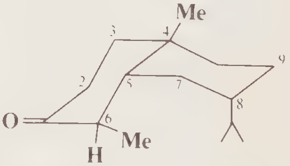

87

question in each case is: Is the isopropyl group axial or equatorial? If **85** has an axial isopropyl group, it has the configuration shown in **87.** If we number the ketone ring as in **83,** we see that the C-4 methyl group makes no contribution but that the isopropyl group projects into the lower right octant and thus makes a positive contribution, as does the C-6 methyl. A look at the model (Figure 8*a*) shows that the positive contributions outweigh the negative, and **87** should show a positive, though weak, Cotton effect. Similarly, a photograph of the conformation which would result if the isopropyl group in **85** were equatorial (Figure 8*b*) shows that this conformer should exhibit a strong positive Cotton effect. The actual ord curve for **85** showed a strong positive Cotton effect, indicating that **85** has the conformation shown in Figure 8*b*, with an equatorial isopropyl group. Similarly, **86** exhibited a weak negative Cotton effect,[190] showing that in this isomer too the isopropyl group is equatorial (Figure 8*c*). If the isopropyl group had been axial, the Cotton effect would have been strongly positive (Figure 8*d*).

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[189] Kirk, Klyne, and Mose, *Tetrahedron Lett.* 1315 (1972); Lightner and Jackman, *J. Chem. Soc., Chem. Commun.* 344 (1974); Lightner and Chang, *J. Am. Chem. Soc.* **96,** 3015 (1974).

[190] Djerassi, "Optical Rotatory Dispersion," Ref. 187, p. 186.

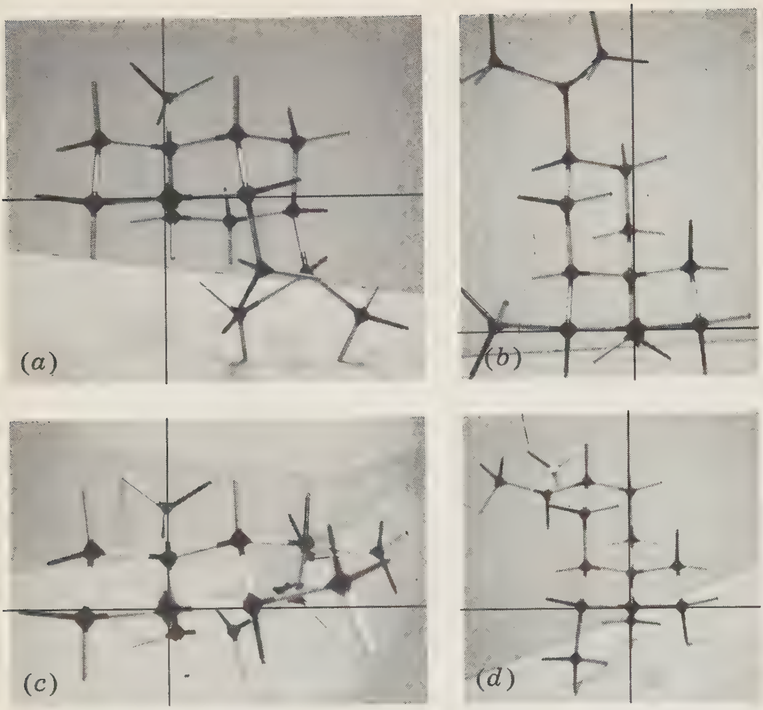


Figure 8 Photographs of models of the *cis*-tetrahydrocyperones: (*a*) **85** in the conformation in which the isopropyl group is axial; (*b*) **85** in the conformation in which the isopropyl group is equatorial; (*c*) **86** in the conformation in which the isopropyl group is equatorial; (*d*) **86** in the conformation in which the isopropyl group is axial.

Rules similar to the carbonyl group octant rule have been established for other chromophores, e.g., lactones,[191] azides,[192] carbon-carbon double bonds,[193] and allenes.[194] In many cases, compounds may be made amenable to ord study by conversion of a group which does not absorb in the visible to one that does (if this change does not affect the stereochemistry). For example, the OH group can be converted to the ONO group. In some cases, e.g., chiral biphenyls, where the chromophore itself is chiral, the Cotton effect is created almost entirely by the chromophore alone, so that almost regardless of what other groups are present, the sign of the Cotton effect will show the absolute configuration of the chiral center.[195]

If the conformation is known, ord can be used to establish configuration. This is done by comparison of the ord curve of the compound of unknown configuration with that of a substance of known configuration, provided that the two compounds contain the same light-absorbing group

[191] Jennings, Klyne, and Scopes, *J. Chem. Soc.* 7211, 7229 (1965).

[192] Djerassi, Moskowitz, Ponsold, and Steiner, *J. Am. Chem. Soc.* **89,** 347 (1967).

[193] Scott and Wrixon, *Tetrahedron* **26,** 3695 (1970), **28,** 933 (1972), *Chem. Commun.* 1182 (1969); Andersen, Costin, Syrdal, and Svedberg, *J. Am. Chem. Soc.* **95,** 2049 (1973); see also Yogev, Sagiv, and Mazur, *J. Chem. Soc., Chem. Commun.* 411 (1972).

[194] Crabbé, Velarde, Anderson, Clark, Moore, Drake, and Mason, *Chem. Commun.* 1261 (1971).

[195] Mislow, Glass, O'Brien, Rutkin, Steinberg, Weiss, and Djerassi, *J. Am. Chem. Soc.* **84,** 1455 (1962); Bunnenberg, Djerassi, Mislow, and Moscowitz, *J. Am. Chem. Soc.* **84,** 2823 (1962); Mislow, Bunnenberg, Records, Wellman, and Djerassi, *J. Am. Chem. Soc.* **85,** 1342 (1963).

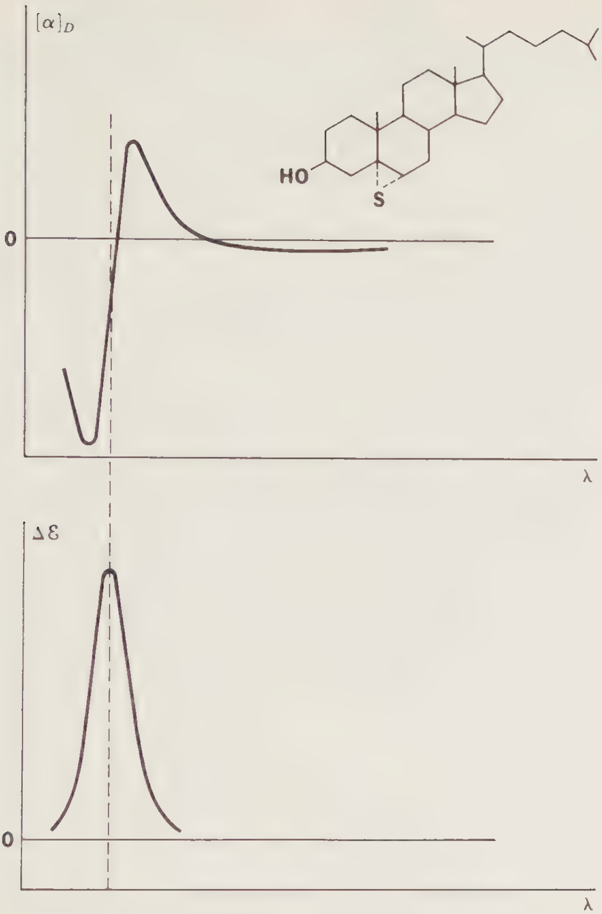
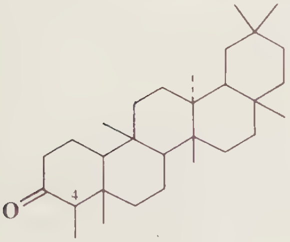


Figure 9 An ord curve (*top*) and a cd curve (*bottom*) for 3β-hydroxycholestan-5α,6α-episulfide.[198]

in the same environment. For example, a comparison of the ord curve of friedelin (**88**) with those of the known compounds **89** and **90** (which differ only in configuration at C-18) shows that **88** and **90** have almost identical curves while that of **89** is much shallower. Although the configuration at C-4 of friedelin was already known, ord provided confirmatory evidence.[196]



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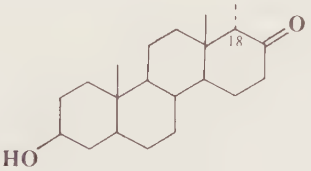

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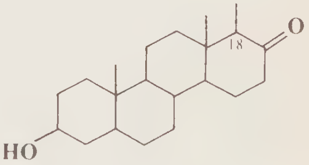

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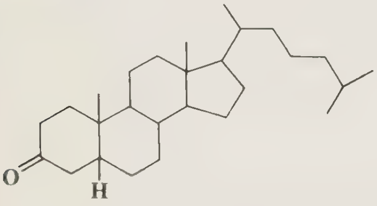
[196] Djerassi, Riniker, and Riniker, *J. Am. Chem. Soc.* **78**, 6362 (1956).

A technique closely related to ord is *circular dichroism* (cd).[197] In this method the molecular extinction coefficients (p. 209) of a compound are measured with both left and right circularly polarized light, and the difference between these values (called $\Delta\varepsilon$) is plotted against the wavelength of the light used. Instruments are available which automatically plot $\Delta\varepsilon$ against λ in the visible and ultraviolet regions of the spectrum. As with ord, information is obtained chiefly in regions where the molecule absorbs light. Circular-dichroism curves are typically bell-shaped, with a maximum or a minimum at the absorption peak. In Figure 9 an ord curve and a cd curve for the same compound are compared.[198] As illustrated in Figure 9, a positive Cotton effect is associated with a positive $\Delta\varepsilon$. Of course, the enantiomer of the compound illustrated in Figure 9 would have a negative Cotton effect and a negative $\Delta\varepsilon$. As with ord, interpretation of cd curves is largely empirical, and information is obtained by comparison of curves of known and unknown compounds. The octant rule also applies to cd, and it is used to determine conformations and configurations, in ways similar to those described for ord.

In many cases either ord or cd can be used with equal success to solve the same types of structural and configurational problems. However, cd has the advantage that the curves are generally simpler and easier to interpret. This is largely due to the fact that each absorption peak in a molecule gives rise to a cd peak which is relatively uninfluenced by other parts of the molecule, while an ord peak in a given absorption region is often complicated by background effects from other regions, so that the result is an overlapping of effects. On the other hand, this very complexity often becomes an advantage for ord, since a more complicated curve often yields more information. For example, the cd curves for 3-coprostanone (**91**), 1-cholestanone (**92**), and 7-cholestanone (**93**) are similar because each is a saturated ketone, but the ord curves are different because of contributions from the rest of the molecule. The two methods are therefore complementary.



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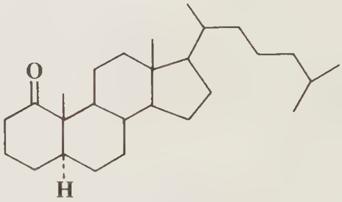

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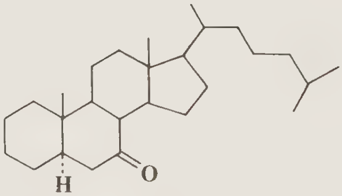

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STRAIN

Steric strain exists in a molecule when bonds are forced to make angles which are abnormal. This results in a higher energy than would be the case in the absence of angle distortions. There are, in general, two kinds of structural features which result in sterically caused abnormal bond angles. One of these is found in small-ring compounds, where the angles must be less than those resulting from normal orbital overlap. Such strain is called *small-angle strain.* The other arises where nonbonded atoms are forced into close proximity by the geometry of the molecule. These are called *nonbonded interactions.*

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[197] For a monograph, see Velluz, Legrand, and Grosjean, "Optical Circular Dichroism," Academic Press, Inc., New York, 1965. For reviews, see Schellman, *Chem. Rev.* **75**, 323-331 (1975); Velluz and Legrand, *Bull. Soc. Chim. Fr.* 1785–1795 (1970). See also Ref. 187.

[198] From Djerassi, *Proc. Chem. Soc.* 315 (1964).

Strain in Small Rings[199]

Three-membered rings have a great deal of angle strain, since 60° angles represent a large departure from the tetrahedral angles. In sharp contrast to other ethers, ethylene oxide is quite reactive, the ring being opened by many reagents (see p. 326). Ring opening, of course, relieves the strain. Cyclopropane,[200] which is even more strained than ethylene oxide, is also cleaved more easily than would be expected for an alkane. Thus, pyrolysis at 450 to 500°C converts it to propene, bromination gives 1,3-dibromopropane,[201] and it can be hydrogenated to propane (though at high pressure).[202] Other three-membered rings are similarly reactive.[203]

There is much evidence, chiefly derived from nmr coupling constants, that the bonding in cyclopropanes is not the same as in compounds which lack small-angle strain.[204] For a normal carbon atom, one *s* and three *p* orbitals are hybridized to give four approximately equivalent sp^3 orbitals (see p. 25), each containing about 25% *s* character. But for a cyclopropane carbon atom, the four hybrid orbitals are far from equivalent. The two orbitals directed to the outside bonds have more *s* character than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less, because the more *p*-like they are the more they resemble ordinary *p* orbitals, whose preferred bond angle is 90° rather than 109.5°. Since the small-angle strain in cyclopropanes is the difference between the preferred angle and the real angle of 60°, this additional *p* character relieves some of the strain. The external orbitals have about 33% *s* character, so that they are approximately sp^2 orbitals, while the internal orbitals have about 17% *s* character, so that they may be called approximately sp^5 orbitals.[205] Each of the three carbon-carbon bonds of cyclopropane is therefore formed by overlap of two sp^5 orbitals. Molecular-orbital calculations show that such bonds are not completely σ in character. In normal C—C bonds, sp^3 orbitals overlap in such a way that the straight line connecting the nuclei becomes an axis about which the electron density is symmetrical. But in cyclopropane, the electron density is directed *away from* the ring. Figure 10 shows the direction of orbital overlap.[206] For cyclopropane, the angle (marked θ) is 21°. Cyclobutane exhibits the same phenomenon but to a lesser extent, θ being 7°.[206] These bonds, called *bent* or *banana bonds* (see also p. 13), are intermediate in character between σ and π, so that cyclopropanes behave in some respects like double-bond compounds.[207] For one thing, there is much evidence, chiefly from uv spectra,[208] that a cyclopropane ring is conjugated with an adjacent double bond and that this conjugation is greatest for the conformation shown in *a* in

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[199] For a review, see Vogel, *Angew. Chem.* **72,** 4–25 (1960).

[200] For a review on cyclopropanes, see Lukina, *Russ. Chem. Rev.* **31,** 419 (1962).

[201] Ogg and Priest, *J. Am. Chem. Soc.* **60,** 217 (1938).

[202] Shortridge, Craig, Greenlee, Derfer, and Boord, *J. Am. Chem. Soc.* **70,** 946 (1948).

[203] For a review of the pyrolysis of three- and four-membered rings, see Frey, *Adv. Phys. Org. Chem.* **4,** 147–193 (1966).

[204] For discussions of bonding in cyclopropanes, see Bernett, *J. Chem. Educ.* **44,** 17–24 (1967); and Ref. 207.

[205] Randić and Maksić, *Theor. Chim. Acta* **3,** 59 (1965); Foote, *Tetrahedron Lett.* 579 (1963); Weigert and Roberts, *J. Am. Chem. Soc.* **89,** 5962 (1967).

[206] Coulson and Goodwin, *J. Chem. Soc.* 2851 (1962), 3161 (1963); Peters, *Tetrahedron* **19,** 1539 (1963); Hoffmann and Davidson, *J. Am. Chem. Soc.* **93,** 5699 (1971).

[207] For a review, see Charton, in Zabicky, "The Chemistry of Alkenes," vol. 2, pp. 511–610, Interscience Publishers, Inc., New York, 1970.

[208] See for example, Cromwell and Hudson, *J. Am. Chem. Soc.* **75,** 872 (1953); Kosower and Ito, *Proc. Chem. Soc.* 25 (1962); Dauben and Berezin, *J. Am. Chem. Soc.* **89,** 3449 (1967); Jorgenson and Leung, *J. Am. Chem. Soc.* **90,** 3769 (1968); Heathcock and Poulter, *J. Am. Chem. Soc.* **90,** 3766 (1968); Bischof, Gleiter, Heilbronner, Hornung, and Schröder, *Helv. Chim. Acta* **53,** 1645 (1970).

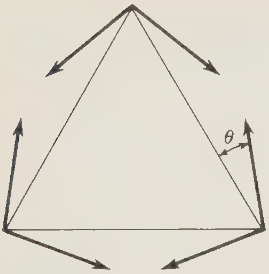
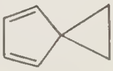


Figure 10 Orbital overlap in cyclopropane. The arrows point toward the center of electron density.

Figure 11 and least or absent for the conformation shown in *b*, since overlap of the double-bond π orbital with two of the *p*-like orbitals of the cyclopropane ring is greatest in conformation *a*. However, the conjugation between a cyclopropane ring and a double bond is less than that between two double bonds.[209] In **94**, the conjugation is enough to impart some aromatic character to the five-membered ring.[210] For other examples of the similarities in behavior of a cyclopropane ring and a double bond, see p. 691.



94

Four-membered rings also exhibit angle strain,[211] but much less, and are less easily opened. Cyclobutane is more resistant than cyclopropane to bromination, and though it can be hydrogenated to butane, more strenuous conditions are required. Nevertheless, pyrolysis at 420°C gives two molecules of ethylene. As mentioned earlier (p. 132), cyclobutane is not planar.

In recent years quite a few highly strained compounds containing fused small rings have been prepared,[212] showing that organic molecules can exhibit much more strain than simple cyclopropanes or cyclobutanes. Table 3 shows some of these compounds. Perhaps the most interesting are

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[209] Staley, *J. Am. Chem. Soc.* **89,** 1532 (1967); Pews and Ojha, *J. Am. Chem. Soc.* **91,** 5769 (1969).

[210] Clark and Fiato, *J. Am. Chem. Soc.* **92,** 4736 (1970).

[211] For a review, see Wilson and Goldhamer, *J. Chem. Educ.* **40,** 504–517 (1963).

[212] For a review discussing the properties of many of these compounds, see Seebach, *Angew. Chem. Int. Ed. Engl.* **4,** 121–131 (1965) [*Angew. Chem.* **77,** 119–129]. For a review of bicyclo[*n.m.*0]alkanes, see Wiberg, *Adv. Alicyclic Chem.* **2,** 185–254 (1968).

Figure 11 Conformations of α-cyclopropylalkenes. Conformation *a* leads to maximum conjugation and conformation *b* to minimum conjugation.

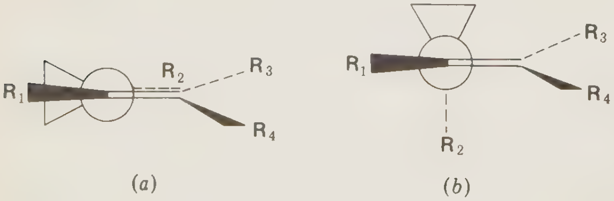
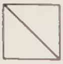
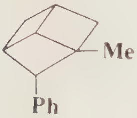
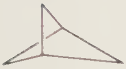
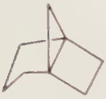
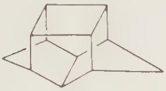
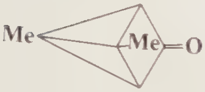
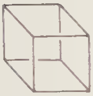
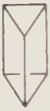
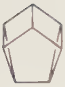
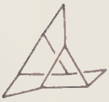
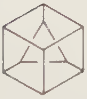
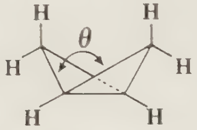


TABLE 3 Some recently prepared strained small-ring systems

Structural formula of compound prepared	Systematic name of ring system	Common name if any	Ref.
	Bicyclo[1.1.0]butane	Bicyclobutane	213
	Tricyclo[3.1.1.0^{3,6}]heptane		214
	Bicyclo[1.1.1]pentane		215
	Tricyclo[3.2.1.0^{1,5}]octane	A 3,2,1-propellane	216
	Hexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]-dodecane	The birdcage hydrocarbon	217
	Tricyclo[2.1.0.0^{2,5}]pentane		218
	Pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane	Cubane	219
	Tetracyclo[2.2.0.0^{2,6}.0^{3,5}]hexane	Prismane	220
	Pentacyclo[3.3.0.0^{2,4}.0^{3,7}.0^{6,8}]octane	Cuneane	221
	Tetracyclo[3.3.1.0^{2,8}.0^{4,6}]nonane	Triasterane	222
	Hexacyclo[4.4.0.0^{2,4}.0^{3,9}.0^{5,8}.0^{7,10}]decane		223

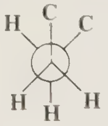
cubane and prismane, since preparation of these ring systems had been the object of much endeavor. Prismane has the structure which Ladenburg proposed as a possible structure for benzene. The bicyclobutane molecule is bent, with the angle θ between the planes equal to



126 ± 3°.[224] The rehybridization effect, described above for cyclopropane, is even more extreme in this molecule, and calculations have shown that the central bond is essentially formed by overlap of two p orbitals, with little or no s character.[225]

Strain in Medium Rings[226]

In rings larger than four-membered, there is no small-angle strain, but there are three other kinds of strain. First let us examine the chair form of cyclohexane, which does not exhibit any of the three kinds of strain. Each carbon-carbon bond in the chair form can be represented as in **95**; i.e., each bond is in the gauche conformation. In five-membered rings and in rings containing from 7 to 13 carbons any conformation in which all the bonds are as in **95** contains transannular interac-



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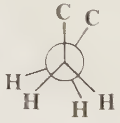

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[213] Lemal, Menger, and Clark, *J. Am. Chem. Soc.* **85**, 2529 (1963); Wiberg and Lampman, *Tetrahedron Lett.* 2173 (1963). For reviews of preparations and reactions of this system, see Wiberg, Lampman, Ciula, O'Connor, Schertler, and Lavanish, *Tetrahedron* **21**, 2749–2769 (1965); Wiberg, *Rec. Chem. Prog.* **26**, 143–154 (1965); and Wiberg, Ref. 212.

[214] Meinwald and Mioduski, *Tetrahedron Lett.* 4137 (1974). See also Harless and Monti, *J. Am. Chem. Soc.* **96**, 4714 (1974); Perrin and Hsia, *Tetrahedron Lett.* 751 (1975).

[215] Wiberg, Connor, and Lampman, *Tetrahedron Lett.* 531 (1964); Wiberg and Connor, *J. Am. Chem. Soc.* **88**, 4437 (1966); Meinwald, Szkrybalo, and Dimmel, *Tetrahedron Lett.* 731 (1967); Chiang and Bauer, *J. Am. Chem. Soc.* **92**, 1614 (1970); Almenningen, Andersen, and Nyhus, *Acta Chem. Scand.* **25**, 1217 (1971). For a review of [*n*.1.1] systems, see Meinwald and Meinwald, *Adv. Alicyclic Chem.* **1**, 1–51 (1966).

[216] Wiberg and Burgmaier, *Tetrahedron Lett.* 317 (1969), *J. Am. Chem. Soc.* **94**, 7396 (1972); Wiberg, Lupton, and Burgmaier, *J. Am. Chem. Soc.* **91**, 3372 (1969); Gassman, Topp, and Keller, *Tetrahedron Lett.* 1093 (1969); Wiberg, Burgmaier, Shen, La Placa, Hamilton, and Newton, *J. Am. Chem. Soc.* **94**, 7402 (1972).

[217] de Vries and Winstein, *J. Am. Chem. Soc.* **82**, 5363 (1960).

[218] Doering and Pomerantz, *Tetrahedron Lett.* 961 (1964). Also see Masamune, *J. Am. Chem. Soc.* **86**, 735 (1964).

[219] Eaton and Cole, *J. Am. Chem. Soc.* **86**, 3157 (1964), Barborak, Watts, and Pettit, *J. Am. Chem. Soc.* **88**, 1328 (1966).

[220] Katz and Acton, *J. Am. Chem. Soc.* **95**, 2738 (1973). See also Viehe, Merényi, Oth, Senders, and Valange, *Angew. Chem. Int. Ed. Engl.* **3**, 755 (1964) [*Angew. Chem.* **76**, 923]; Lemal and Lokensgard, *J. Am. Chem. Soc.* **88**, 5934 (1966), Wilzbach and Kaplan, *J. Am. Chem. Soc.* **87**, 4004 (1965); and Criegee and Askani, *Angew. Chem. Int. Ed. Engl.* **5**, 519 (1966) [*Angew. Chem.* **78**, 494].

[221] Cassar, Eaton, and Halpern, *J. Am. Chem. Soc.* **92**, 6366 (1970).

[222] Musso and Biethan, *Chem. Ber.* **100**, 119 (1967).

[223] Allred and Beck, *J. Am. Chem. Soc.* **95**, 2393 (1973).

[224] Haller and Srinivasan, *J. Chem. Phys.* **41**, 2745 (1964).

[225] Schulman and Fisanick, *J. Am. Chem. Soc.* **92**, 6653 (1970).

[226] For reviews, see Gol'dfarb and Belen'kii, *Russ. Chem. Rev.* **29**, 214–235 (1960); Raphael, *Proc. Chem. Soc.* 97 105 (1962), and Sicher, *Prog. Stereochem.* **3**, 202–264 (1962).

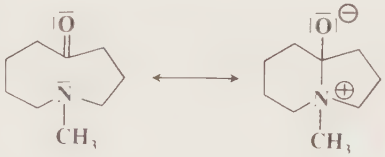
TABLE 4 Heats of combustion in the gas phase for cycloalkanes, per CH_2 group[229]

Size of ring	$-\Delta H_c(g)$, kcal mol	Size of ring	$-\Delta H_c(g)$, kcal/mol
3	166.3	10	158.6
4	163.9	11	158.4
5	158.7	12	157.8
6	157.4	13	157.7
7	158.3	14	157.4
8	158.6	15	157.5
9	158.8	16	157.5

tions, i.e., interactions between the substituents on C-1 and C-3, or C-1 and C-4, etc. These interactions occur because the internal space is not large enough for all the quasi-axial hydrogen atoms to fit without coming into conflict. The molecule can adopt other conformations in which this *transannular strain* is reduced, but then some of the carbon-carbon bonds must adopt eclipsed (**96**) or partially eclipsed conformations. The strain resulting from eclipsed conformations is called *Pitzer strain*. For saturated rings from 3- to 13-membered (except for the chair form of cyclohexane) there is no escape from at least one of these two types of strain. In practice each ring adopts conformations which minimize both sorts of strain as much as possible. For cyclopentane, as we have seen (p. 133), this means that the molecule is not planar. In rings larger than 9-membered, Pitzer strain seems to disappear, but transannular strain is still present.[227] For 9- and 10-membered rings, some of the transannular and Pitzer strain may be relieved by the adoption of a third type of strain, *large-angle strain*. Thus, C—C—C angles of 115 to 120° have been found in x-ray diffraction of cyclononylamine hydrobromide and 1,6-diaminocyclodecane dihydrochloride.[228]

The amount of strain in cycloalkanes can be seen in Table 4,[229] which lists heats of combustion per CH_2 group. As can be seen, cycloalkanes larger than 13-membered are as strain-free as cyclohexane.

Transannular interactions may exist across rings from 8- to 11-membered and even larger.[230] Spectral and dipole measurements on **97** show that the carbonyl group is affected by the nitrogen.[231] **98** is probably another canonical form. It is significant that when this base accepts a proton,



97 **98**

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[227] Huber-Buser and Dunitz, *Helv. Chim. Acta* **43**, 760 (1960).

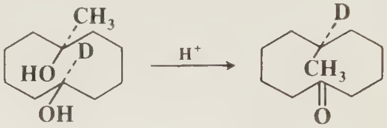
[228] Bryan and Dunitz, *Helv. Chim. Acta* **43**, 1 (1960); Dunitz and Venkatesan, *Helv. Chim. Acta* **44**, 2033 (1961).

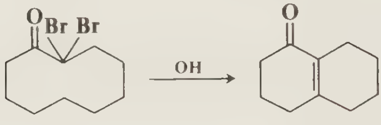
[229] Gol'dfarb and Belen'kii, Ref. 226, p. 218.

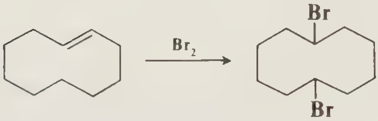
[230] For a review, see Cope, Martin, and McKervey, *Q. Rev., Chem. Soc.* **20**, 119–152 (1966).

[231] Leonard, Fox, and Ōki, *J. Am. Chem. Soc.* **76**, 5708 (1954); Leonard, Morrow, and Rogers, *J. Am. Chem. Soc.* **79**, 5476 (1957); Leonard, *Rec. Chem. Prog.* **17**, 243 (1956).

it goes to the oxygen rather than to the nitrogen. Many examples of transannular reactions are known. A few are given below.[232]







In summary, we can divide saturated rings into four groups, of which the first and third are more strained than the other two.

1. *Small rings* (3- and 4-membered). Small-angle strain predominates.
2. *Common rings* (5-, 6-, and 7-membered). Largely unstrained. The strain that is present is mostly Pitzer strain.
3. *Medium rings* (8- to 11-membered). Considerable strain; Pitzer, transannular, and large-angle strain.
4. *Large rings* (12-membered and larger). Little or no strain.

Unsaturated Rings[233]

Double bonds can exist in rings of any size. As we would expect, the most highly strained are the 3-membered rings. Small-angle strain, which is so important in cyclopropane, is even greater in cyclopropene because the ideal angle is greater. In cyclopropane, the bond angle is forced to be 60°, about 50° smaller than the tetrahedral angle; but in cyclopropene, the angle, also about 60°, is now about 60° smaller than the ideal angle of 120°. Thus, the angle in cyclopropene is about 10° more strained than in cyclopropane. However, this additional strain is offset by a decrease in strain arising from another factor. Cyclopropene, lacking two hydrogens, has none of the eclipsing strain present in cyclopropane. Cyclopropene has been prepared[234] and is stable at liquid-nitrogen temperatures, though on warming even to −80°C it rapidly polymerizes. Many other cyclopropenes are stable at room temperature and above.[235] The highly strained benzocyclopropene[236] (**99**), in which the cyclopropene ring is fused to a benzene ring, has been prepared[237] and is

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[232] References are, in the order shown, Prelog and Küng, *Helv. Chim. Acta* **39**, 1394 (1956); Schenker and Prelog, *Helv. Chim. Acta* **36**, 896 (1953); Sicher, Závada, and Svoboda, *Collect. Czech. Chem. Commun.* **27**, 1927 (1962).

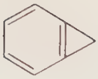
[233] For a review of strained double bonds, see Zefirov and Sokolov, *Russ. Chem. Rev.* **36**, 87–100 (1967).

[234] Dem'yanov and Doyarenko, *Bull. Acad. Sci. Russ.* **16**, 297 (1922), *Ber.* **56**, 2200 (1923); Schlatter, *J. Am. Chem. Soc.* **63**, 1733 (1941); Wiberg and Bartley, *J. Am. Chem. Soc.* **82**, 6375 (1960); Stigliani, Laurie, and Li, *J. Chem. Phys.* **62**, 1890 (1975).

[235] For reviews of cyclopropenes, see Closs, *Adv. Alicyclic Chem.* **1**, 53–127 (1966); and Carter and Frampton, *Chem. Rev.* **64**, 497–525 (1964).

[236] For a review of benzocyclopropenes, see Halton, *Chem. Rev.* **73**, 113–126 (1973).

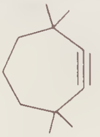
[237] Vogel, Grimme, and Korte, *Tetrahedron Lett.* 3625 (1965). Also see Anet and Anet, *J. Am. Chem. Soc.* **86**, 526 (1964).



99

stable for weeks at room temperature, though it decomposes on distillation at atmospheric pressure. As in cyclopropanes, the orbitals of cyclopropenes are not directed along the straight line connecting the nuclei, and rehybridization often causes the strained double bond to behave like a triple bond.[233]

As previously mentioned, double bonds in relatively small rings must be cis. A stable trans double bond first appears in an 8-membered ring, and above about 11 members, the trans isomer is more stable than the cis.[109] The smallest unstrained cyclic triple bond is found in cyclononyne.[238] Cyclooctyne has been isolated,[239] but its heat of hydrogenation shows that it is considerably strained. There have been a few compounds isolated with triple bonds in 7-membered rings. 3,3,7,7,-Tetramethylcycloheptyne (**100**) dimerizes within an hour at room temperature,[240] but 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne (**101**) is indefinitely stable even at 140°C.[241] Cycloheptyne itself has not been isolated, though its transient existence has been shown.[242] Transient triple bonds have also been demonstrated in 6-, 5-, and even 4-membered rings.[243] Although cycloheptyne and cyclohexyne have not been isolated, Pt(0) complexes of these compounds have been prepared and are stable.[244] The smallest cyclic allene so far isolated is 1,2-cyclonanadiene,[245] but cyclic allenes are in general less strained than their acetylenic isomers.[246] The transient existence of 1,2-cyclooctadiene, 1,2-cycloheptadiene, and 1,2-cyclohexadiene has been demonstrated,[247] and the first two have been isolated in platinum complexes.[248]



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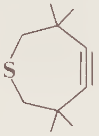

101

In bridged bicyclic compounds double bonds at the bridgehead are impossible in small systems. This is the basis of *Bredt's rule*,[249] which states that in a case like **102** elimination always leads

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[238] For reviews of triple bonds in rings, see Krebs, in Viehe, "Acetylenes," pp. 987–1062, Marcel Dekker, Inc., New York, 1969; Wittig, *Angew. Chem. Int. Ed. Engl.* **1**, 415–419 (1962) [*Angew. Chem.* **74**, 479–483]; Kolinskii, *Russ. Chem. Rev.* **30**, 309–327 (1961).

[239] Blomquist and Liu, *J. Am. Chem. Soc.* **75**, 2153 (1953).

[240] Krebs and Kimling, *Angew. Chem. Int. Ed. Engl.* **10**, 509 (1971) [*Angew. Chem.* **83**, 540]; Schmidt, Schweig, and Krebs, *Tetrahedron Lett.* 1471 (1974).

[241] Krebs and Kimling, *Tetrahedron Lett.* 761 (1970).

[242] Wittig and Meske-Schüller, *Justus Liebigs Ann. Chem.* **711**, 65 (1968); Krebs and Kimling, *Angew. Chem. Int. Ed. Engl.* **10**, 509 (1971) [*Angew. Chem.* **83**, 540]; Bottini, Frost, Anderson, and Dev, *Tetrahedron* **29**, 1975 (1973).

[243] See, for example, Wittig and Mayer, *Chem. Ber.* **96**, 329, 342 (1963); Wittig and Wilson, *Chem. Ber.* **98**, 451 (1965); Wittig, Weinlich, and Wilson, *Chem. Ber.* **98**, 458 (1965); Wittig and Weinlich, *Chem. Ber.* **98**, 471 (1965).

[244] Bennett, Robertson, Whimp, and Yoshida, *J. Am. Chem. Soc.* **93**, 3797 (1971).

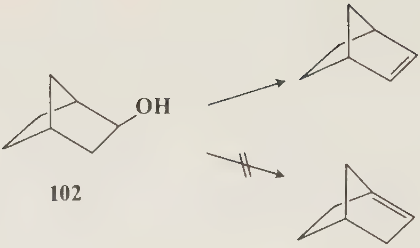
[245] Moore and Bertelson, *J. Org. Chem.* **27**, 4182 (1962); Moore and Bach, *J. Am. Chem. Soc.* **94**, 3148 (1972).

[246] Moore and Ward, *J. Am. Chem. Soc.* **85**, 86 (1963).

[247] Marquis and Gardner, *Tetrahedron Lett.* 2793 (1966); Wittig, Dorsch, and Meske-Schüller, *Justus Liebigs Ann. Chem.* **711**, 55 (1968); Wittig and Meske-Schüller, *Justus Liebigs Ann. Chem.* **711**, 76 (1968); Wittig and Fritze, *Justus Liebigs Ann. Chem.* **711**, 82 (1968); Oda, Itō, and Kitahara, *Tetrahedron Lett.* 2587 (1975).

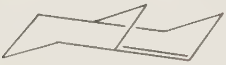
[248] Visser and Ramakers, *J. Chem. Soc., Chem. Commun.* 178 (1972).

[249] For reviews, see Buchanan, *Chem. Soc. Rev.* **3**, 41–63 (1974); and Köbrich, *Angew. Chem. Int. Ed. Engl.* **12**, 464 473 (1973) [*Angew. Chem.* **85**, 494 503]. For a review of methods for the preparation of bridgehead olefins, see Keese, *Angew. Chem. Int. Ed. Engl.* **14**, 528–538 (1975) [*Angew. Chem.* **87**, 568–578].



102

away from the bridgehead. This rule no longer applies when the rings are large enough. In determining whether a bicyclic system is large enough to accommodate a bridgehead double bond, we can use the *S* number,[250] which is defined as the sum of the number of atoms in the bridges of a bicyclic system. Thus the [2.2.1] system shown above has an *S* number of 5. The smallest *S* number for which stable compounds have been prepared with double bonds at a bridgehead is 7, and several of these are known, e.g., bicyclo[3.3.1]non-1-ene[251] (**103**) and bicyclo[4.2.1]non-1(8)-ene[252] (**104**). However, the *S* number is not the only factor. The size of the ring in which the double bond is located is also important. Both **103** and **104** may be looked upon as derivatives of *trans*-cyclooctene, and **103** has been shown to have a strain energy of the same order of magnitude as that of *trans*-cyclooctene.[253] Bicyclo[3.2.2]non-1-ene (**105**) also has an *S* number of 7, but in this case the double bond is in a 7-membered ring, so that it is a derivative of *trans*-cycloheptene, which is as yet unknown. **105** has been prepared but (despite its *S* number of 7) dimerized before it could be isolated.[254] No bridgehead double bond has yet been demonstrated in a stable bicyclic compound with *S* smaller than 7 (all such compounds would have to contain *trans*-cycloalkenes of 7 members or less), though a few of them have been shown to have transient existence.[255]



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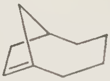

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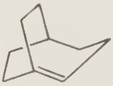

105

Strain Due to Unavoidable Crowding[256]

In some molecules, large groups are so close to each other than they cannot fit into the available space in such a way that normal bond angles are maintained. It has proved possible to prepare compounds with a high degree of this type of strain. For example, success has been achieved in synthesizing benzene rings containing ortho *t*-butyl groups. The 1,2,3-tri-*t*-butyl compounds **106**[257] (see p. 796) and **107**[258] have been prepared, as well as the 1,2-di-*t*-butyl compounds **108** and **109**.[259] So far no 1,2,3,4-tetra-*t*-butylbenzene is known, though a compound has been prepared

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[250] Fawcett, *Chem. Rev.* **47**, 219–274 (1950).

[251] Marshall and Faubl, *J. Am. Chem. Soc.* **89**, 5965 (1967), **92**, 948 (1970); Wiseman, *J. Am. Chem. Soc.* **89**, 5966 (1967); Wiseman and Pletcher, *J. Am. Chem. Soc.* **92**, 956 (1970); Becker, *Chimia* **28**, 726 (1974); Kim and White, *J. Am. Chem. Soc.* **97**, 451 (1975).

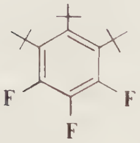
[252] Wiseman, Chan, and Ahola, *J. Am. Chem. Soc.* **91**, 2812 (1969); Carruthers and Qureshi, *Chem. Commun.* 832 (1969); Becker, *Tetrahedron Lett.* 2207 (1975).

[253] Lesko and Turner, *J. Am. Chem. Soc.* **90**, 6888 (1968).

[254] Wiseman and Chong, *J. Am. Chem. Soc.* **91**, 7775 (1969).

[255] For example, see Keese and Krebs, *Angew. Chem. Int. Ed. Engl.* **10**, 262 (1971) [*Angew. Chem.* **83**, 254]; Chong and Wiseman, *J. Am. Chem. Soc.* **94**, 8627 (1972); Grootveld, Blomberg, and Bickelhaupt, *J. Chem. Soc., Chem. Commun.* 542 (1973); Dauben and Robbins, *Tetrahedron Lett.* 151 (1975).

[256] For a review of steric hindrance in hydrocarbons, see Voronenkov and Osokin, *Russ. Chem. Rev.* **41**, 616–629 (1972).



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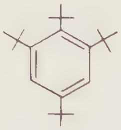

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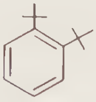

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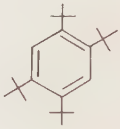
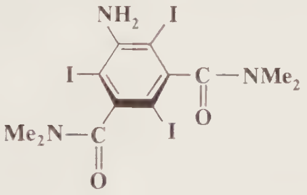


109

in which a benzene ring has four ferrocenyl groups in the 1, 2, 3, and 4 positions.[260] That the ortho di-*t*-butyl molecules are strained is demonstrated by uv and ir spectra, which showed that in 1,2,4-tri-*t*-butylbenzene the ring is not planar, and by a comparison of the heats of reaction of this compound and its 1,3,5 isomer, which show that the 1,2,4 compound possesses about 22 kcal mol more strain energy than its isomer.[261] Even smaller groups may sterically interfere in ortho positions. The van der Waals radius for chlorine is 1.80 Å, which means that two chlorine atoms whose centers are 3.60 Å apart or more should not interfere with each other. However, the distance between the centers of the chlorine atoms in 1,2-dichlorobenzene is 3.10 Å, so that there is crowding in this molecule.[262] There is even more crowding in ortho dibromobenzenes and diiodobenzenes. In hexaisopropylbenzene, prepared by Arnett and Bollinger, the six isopropyl groups are so crowded that they cannot rotate but are lined up around the benzene ring, all pointed in the same direction.[263] In another similar instance, it has proved possible to prepare cis and trans isomers of 5-amino-2,4,6-triiodo-N,N,N′,N′-tetramethylisophthalamide because there is no room for the CONMe$_2$ groups to rotate, caught as they are between two bulky iodine atoms.[264] The trans isomer is chiral and has been resolved, while the cis isomer is a meso form. Another example of cis-trans isomerism resulting from restricted rotation about single bonds[265] is found in 1,8-di-*o*-tolylnapthalene.[266]



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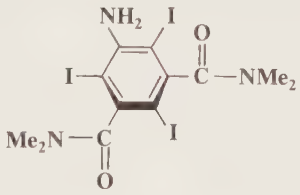

trans

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[257] Viehe, Merényi, Oth, and Valange, *Angew. Chem. Int. Ed. Engl.* **3,** 746 (1964) [*Angew. Chem.* **76,** 890].

[258] Arnett and Bollinger, *Tetrahedron Lett.* 3803 (1964).

[259] Hoogzand and Hübel, *Angew. Chem.* **73,** 680 (1961), *Tetrahedron Lett.* 637 (1961).

[260] Rosenblum, Brawn, and King, *Tetrahedron Lett.* 4421 (1967).

[261] Arnett, Sanda, Bollinger, and Barber, *J. Am. Chem. Soc.* **89,** 5389 (1967); Krüerke, Hoogzand, and Hübel, *Chem. Ber.* **94,** 2817 (1961); Dale, *Chem. Ber.* **94,** 2821 (1961).

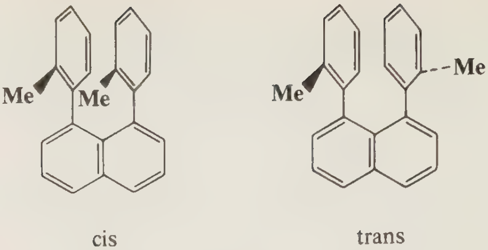
[262] Struchkov and Solenova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 93 (1960).

[263] Arnett and Bollinger, *J. Am. Chem. Soc.* **86,** 4730 (1964).

[264] Ackerman, Laidlaw, and Snyder, *Tetrahedron Lett.* 3879 (1969); Ackerman and Laidlaw, *Tetrahedron Lett.* 4487 (1969).

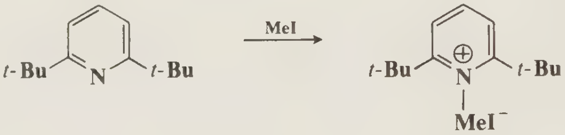
[265] For a review of restricted rotation about sp^3-sp^3 and sp^3-sp^2 single bonds, see Ōki, *Angew. Chem. Int. Ed. Engl.* **15,** 87–93 (1976) [*Angew. Chem.* **88,** 67–74].

[266] Clough and Roberts, *J. Am. Chem. Soc.* **98,** 1018 (1976).



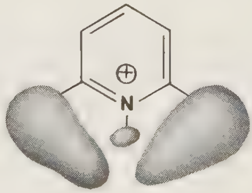
There are many other cases of intramolecular crowding resulting in distortion of bond angles. We have already mentioned hexahelicene (**19**, p. 96). The compounds tri-*t*-butylamine and tetra-*t*-butylmethane are as yet unknown. In the latter, there is no way for the strain to be relieved, and it is questionable whether this compound can ever be made. In tri-*t*-butylamine the crowding can be eased somewhat if the three bulky groups assume a planar instead of the normal pyramidal configuration. In tri-*t*-butylcarbinol, coplanarity of the three *t*-butyl groups is prevented by the presence of the OH group, and yet this compound has been prepared.[267] Tri-*t*-butylamine should have less steric strain than tri-*t*-butylcarbinol, and it should be possible to prepare it.

An interesting example of steric hindrance was reported by Okamoto and Shimagawa.[268] The compound 2,6-di-*t*-butylpyridine reacted with methyl iodide under high pressure to give the corresponding quaternary salt (**110**):



110

110 was remarkably stable, subliming under reduced pressure at 250°C without decomposition. In contrast, the corresponding 2,6-dimethyl salt was completely dissociated into 2,6-dimethylpyridine and methyl iodide under these conditions. It is likely that the inert character of **110** is caused by a structure in which the methyl group is essentially imprisoned between the two bulky *t*-butyl groups:



It is not easy to put the methyl group into its "prison" (the reaction does not succeed at ordinary pressures), and once it is there, it is not easy to get it out.

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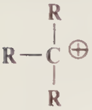
[267] Bartlett and Lefferts, *J. Am. Chem. Soc.* **77**, 2804 (1955); Bartlett and Tidwell, *J. Am. Chem. Soc.* **90**, 4421 (1968).

[268] Okamoto and Shimagawa, *Tetrahedron Lett.* 317 (1966); Okamoto, *J. Am. Chem. Soc.* **90**, 5639 (1968); Okamoto and Lee, *J. Am. Chem. Soc.* **97**, 4015 (1975).

Five

Carbonium Ions, Carbanions, Free Radicals, Carbenes, and Nitrenes

There are four known types of organic species in which a carbon atom has a valence of only 2 or 3.[1] These are usually very short-lived, and most are present (at least in solution) only as intermediates which are quickly converted to more stable molecules. However, some are more stable than others, and fairly stable examples have been prepared of three of the four types. The four types of species are *carbonium ions*[2] (**1**), *free radicals* (**2**), *carbanions* (**3**), and *carbenes* (**4**). Of the four, only carbanions have a complete octet around the carbon. There are many other organic ions and radicals with charges and unpaired electrons on atoms other than carbon, but of these we shall discuss only *nitrenes* (**5**), which are the nitrogen analogs of carbenes (see p. 184). We shall discuss each of the five types in a separate section, which in each case includes brief summaries of the ways in which the species form and react. These summaries are short and schematic. The generation and fate of the five types are more fully treated in appropriate places in Part 2 of this book.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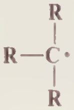
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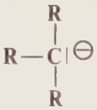
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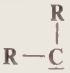
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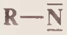
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5

CARBONIUM IONS[3]

Stability and Structure

Carbonium ions are intermediates in several kinds of reaction, and the more stable ones have been prepared in solution and in a few cases even as solid salts. In solution the carbonium ion may be free (this is more likely in polar solvents, in which it is solvated) or may exist as an ion pair,[4] which means that it is closely associated with a negative ion, called a *counterion*. Ion pairs are more likely in nonpolar solvents.

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[1] For general references, see Isaacs, "Reactive Intermediates in Organic Chemistry," John Wiley & Sons, Inc., New York, 1974; and McManus, "Organic Reactive Intermediates," Academic Press, Inc., New York, 1973.

[2] It was suggested as long ago as 1902 [Gomberg, *Ber.* **35**, 2397 (1902)] that "carbonium ion" is an inappropriate name for these species, since "-onium" usually refers to a covalency higher than that of the neutral atom. Recently the name *carbocation* has been proposed for all ions with a positive charge on a carbon atom. Tricoordinated ions (such as **1**) would be called *carbenium ions* and tetra- and pentacoordinated ions (such as CH_5^+) would be *carbonium ions*, both types being subclasses of carbocations [Olah, *Chem. Technol.* **1**, 566 (1971), *J. Am. Chem. Soc.* **94**, 808 (1972)]. However, the name "carbonium ion" has been used for many years to represent **1**, and we shall continue to use it in this book.

[3] For a treatise, see Olah and Schleyer, "Carbonium Ions," 5 vols., John Wiley & Sons, Inc., New York, 1968–. For a monograph, see Bethell and Gold, "Carbonium Ions," Academic Press, Inc., New York, 1967. For reviews, see Isaacs, Ref. 1, pp 92–199; McManus and Pittman, in McManus, Ref. 1, pp. 193–335; Olah, *Angew. Chem. Int. Ed. Engl.* **12**, 173–212 (1973) [*Angew. Chem.* **85**, 183–225] (this review has been reprinted as Olah, "Carbocations and Electrophilic Reactions," John Wiley & Sons, Inc., New York, 1974); Buss, Schleyer, and Allen, *Top. Stereochem.* **7**, 253–293 (1973); Olah and Pittman, *Adv. Phys. Org. Chem.* **4**, 305–347 (1966); Deno, *Prog. Phys. Org. Chem.* **2**, 129–193 (1964), *Chem. Eng. News* **42** (40), 88 (Oct. 5, 1964).

Evidence for the existence of carbonium ions is obtained from nmr and other spectra,[5] freezing-point lowering, chemical reactions, and conductivity.[6] The latter method detects only free carbonium ions and not ion pairs.

Among simple alkyl carbonium ions[7] the order of stability is tertiary > secondary > primary. Many examples are known of rearrangements of primary or secondary systems to tertiary. Since simple alkyl carbonium ions are not stable in ordinary strong-acid solutions, e.g., H_2SO_4, the study of these species was greatly facilitated by the discovery that many of them could be kept indefinitely in stable solutions in mixtures of fluorosulfonic acid and antimony pentafluoride. Such mixtures, usually dissolved in SO_2 or SO_2ClF, are among the strongest acidic solutions known and are often called *super acids*. The original experiments involved the addition of alkyl fluorides to SbF_5.[8] Subsequently it was found that the same cations could also be generated from alcohols

$$\mathbf{RF + SbF_5 \longrightarrow R^+ \quad SbF_6^-}$$

by solution in super acid–SO_2 at −60°C[9] and from alkenes by the addition of a proton from super acid or HF–SbF_5 in SO_2 or SO_2ClF at low temperatures.[10] Even alkanes give carbonium ions in super acid by loss of H^-. For example,[11] isobutane gives the *t*-butyl cation[12]

$$\mathbf{Me_3CH \xrightarrow{FSO_3H-SbF_5} Me_3C^+ \quad SbF_5FSO_3^- + H_2}$$

No matter how they are generated, study of the simple alkyl cations has provided dramatic evidence for the stability order. Both propyl fluorides gave isopropyl cation; all four butyl fluorides[13] gave *t*-butyl cation, and all seven of the pentyl fluorides which were tried gave *t*-pentyl cation. *n*-Butane, in super acid, gave only *t*-butyl cation, formed by rearrangement of the initially produced *n*-butyl cation. To date no primary cation has survived long enough for detection. Neither methyl nor ethyl fluoride gave the corresponding cations when treated with SbF_5. At low temperatures, methyl fluoride gave only an SbF_5–FMe complex,[14] while ethyl fluoride rapidly formed *t*-butyl and *t*-hexyl cations by addition of the initially formed ethyl cation to ethylene molecules also formed.[15] At room temperature, methyl fluoride also gave *t*-butyl cation.[16] In accord with the stability order, hydride ion is abstracted from alkanes by super acid most readily from tertiary and least readily from primary positions.

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[4] For a treatise, see Szwarc, "Ions and Ion Pairs in Organic Reactions," 2 vols., John Wiley & Sons, Inc., New York, 1972–1974.

[5] For reviews, see Cheradame and Mavel, *Ann. Chim. (Paris)* [14] **1**, 449–460 (1966), **2**, 91–102 (1967); and, in Olah and Schleyer, Ref. 3, vol. 1, the reviews by Olah, Pittman, and Symons, pp. 153–222, Evans, pp. 223–235, and Fraenkel and Farnum, pp. 237–255.

[6] For reviews, in Olah and Schleyer, Ref. 3, vol. 1, see Gillespie and Robinson, pp. 111–134, and Lichtin, pp. 135–151.

[7] For reviews, see Olah and Olah, in Olah and Schleyer, Ref. 3, vol. 2, pp. 715–782; and Olah, *Chem. Eng. News*. **45** (14), 77–88 (Mar. 27, 1967).

[8] Olah, Baker, Evans, Tolgyesi, McIntyre, and Bastien, *J. Am. Chem. Soc.* **86**, 1360 (1964); Brouwer and Mackor, *Proc. Chem. Soc.* 147 (1964); Kramer, *J. Am. Chem. Soc.* **91**, 4819 (1969).

[9] Olah, Comisarow, Cupas, and Pittman, *J. Am. Chem. Soc.* **87**, 2997 (1965); Olah, Sommer, and Namanworth, *J. Am. Chem. Soc.* **89**, 3576 (1967).

[10] Olah and Halpern, *J. Org. Chem.* **36**, 2354 (1971).

[11] Olah and Lukas, *J. Am. Chem. Soc.* **89**, 2227, 4739 (1967).

[12] We adopt the nomenclature of Deno (Ref. 3). "*t*-Butyl carbonium ion" is ambiguous, since it could mean either Me_3C^+ or $Me_3CCH_2^+$.

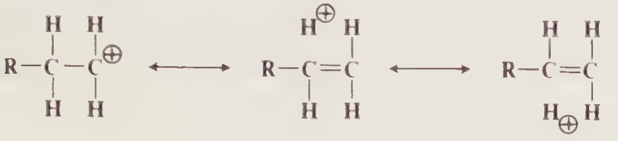
[13] The *sec*-butyl cation has been prepared by slow addition of *sec*-butyl chloride to SbF_5–SO_2ClF solution at −110 C [Saunders, Hagen, and Rosenfeld, *J. Am. Chem. Soc.* **90**, 6882 (1968)] and by allowing molecular beams of the reagents to impinge on a very cold surface [Saunders, Cox, and Ohlmstead, *J. Am. Chem. Soc.* **95**, 3018 (1973)].

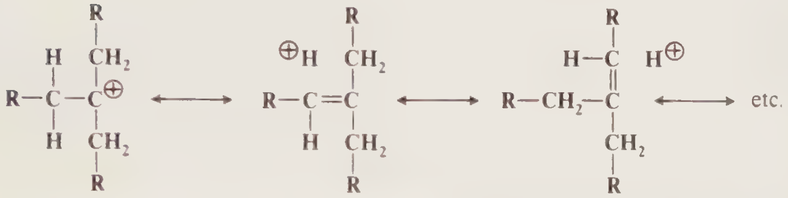
[14] Olah, DeMember, and Schlosberg, *J. Am. Chem. Soc.* **91**, 2112 (1969); Bacon and Gillespie, *J. Am. Chem. Soc.* **93**, 6914 (1971).

[15] Olah and Olah, Ref. 7, p. 722.

[16] Olah, DeMember, and Schlosberg, Ref. 14.

The stability order can be explained by hyperconjugation and by the field effect. If we compare a primary carbonium ion with a tertiary, it is seen that many more canonical forms are possible for the latter:



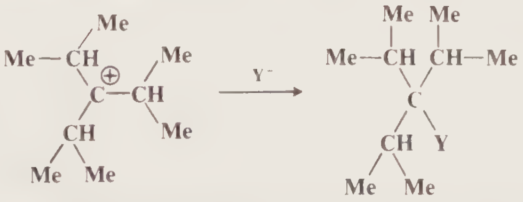


In the examples shown the primary ion has only two hyperconjugative forms while the tertiary has six. According to rule 6 (p. 37), the more equivalent forms, the more resonance stability. Muller and Mulliken have calculated resonance (hyperconjugation) energies for aliphatic carbonium ions:[17]

$CH_3CH_2^{\oplus}$	36 kcal/mol
$(CH_3)_2CH^{\oplus}$	66 kcal/mol
$(CH_3)_3C^{\oplus}$	84 kcal/mol

The field effect explanation is that the electron-donating effect of alkyl groups increases the electron density at the charge-bearing carbon, reducing the net charge on the carbon and in effect spreading the charge over the α-carbons. It is a general rule that the more concentrated any charge is, the less stable the species bearing it will be.

Another factor responsible for the greater stability of tertiary carbonium ions is B strain (see p. 249), although this becomes important only when large groups are present on the central carbon. For example, the bond angles at the central carbon of the triisopropylmethyl cation are 120°, but if a fourth group came in, the three isopropyl groups would have to crowd in together to allow the central carbon to attain the tetrahedral angle, causing the compression from nonbonded interactions known as B strain.



The most stable of all simple alkyl carbonium ions is the *t*-butyl cation. Even the relatively stable *t*-pentyl and *t*-hexyl cations fragment at higher temperatures to produce the *t*-butyl cation, as do all other alkyl cations with four or more carbons so far studied.[18] Methane,[19] ethane, and propane, treated with super acid, also yield *t*-butyl cations as the main product (see reaction **2-16**). Even paraffin wax and polyethylene gave *t*-butyl cation. Solid salts of *t*-butyl and *t*-pentyl cations, e.g., $Me_3C^+SbF_6^-$, have been prepared from super-acid solutions and are stable below −20°C.[20]

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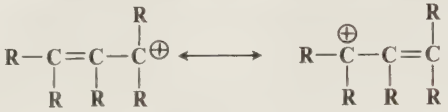
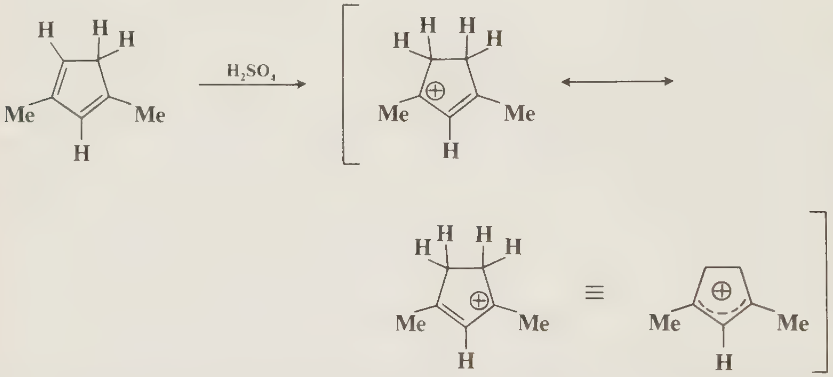
[17] Muller and Mulliken, *J. Am. Chem. Soc.* **80**, 3489 (1958).

Where the positive carbon is in conjugation with a double bond the stability is greater because of increased delocalization due to resonance and because the positive charge is spread over two atoms instead of being concentrated on one (see the molecular-orbital picture of this species on p. 34). Each of the two atoms has a charge of about $\frac{1}{2}$ (the charge is exactly $\frac{1}{2}$ if all of the R groups are the same). Stable allylic-type cations[21] have been prepared by the solution of conjugated dienes in concentrated sulfuric acid, e.g.,[22]



$$\mathrm{R{-}\underset{R}{C}{=}\underset{R}{C}{-}\underset{R}{\overset{R}{C}}{}^{\oplus}} \longleftrightarrow \mathrm{R{-}\underset{R}{\overset{\oplus}{C}}{-}\underset{R}{C}{=}\underset{R}{\overset{R}{C}}}$$



The nmr spectrum of this ion demonstrates that the two canonical forms indeed contribute equally. There are only three peaks, one due to the six methyl hydrogens, one to the four methylene hydrogens, and one to the single C—H hydrogen, and the area ratios are 6 : 4 : 1, as expected.[22] Both cyclic and acyclic allylic cations have been produced in this way. Stable allylic cations have also been obtained by the reaction between alkyl halides, alcohols, or olefins (by hydride extraction) and SbF_5 in SO_2 or SO_2ClF.[23] Divinylmethyl cations[24] are more stable than the simple allylic type, and some of these have been prepared in concentrated sulfuric acid.[25] However, many open-chain examples cyclize to the more stable cyclic allylic type.[24] Open-chain trivinylmethyl

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[18] Ref. 11; Olah and Olah, Ref. 7, pp. 750–764.

[19] Olah, Klopman, and Schlosberg, *J. Am. Chem. Soc.* **91**, 3261 (1969). See also Hogeveen and Gaasbeek, *Recl. Trav. Chim. Pays-Bas* **87**, 319 (1968).

[20] Olah, Svoboda, and Ku, *Synthesis* 492 (1973); Ref. 11.

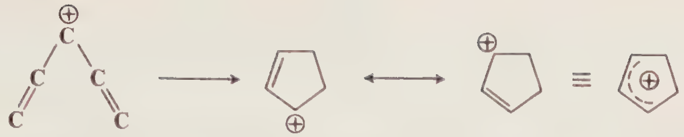
[21] For reviews, see Deno, in Olah and Schleyer, Ref. 3, vol. 2, pp. 783–806; and Richey, in Zabicky, "The Chemistry of Alkenes," vol. 2, pp. 39–114, Interscience Publishers, Inc., New York, 1970.

[22] Deno, Richey, Hodge, and Wisotsky, *J. Am. Chem. Soc.* **84**, 1498 (1962); Deno, Richey, Friedman, Hodge, Houser, and Pittman, *J. Am. Chem. Soc.* **85**, 2991 (1963).

[23] Olah and Comisarow, *J. Am. Chem. Soc.* **86**, 5682 (1964); Olah, Clifford, Halpern, and Johanson, *J. Am. Chem. Soc.* **93**, 4219 (1971); Olah, Liang, and Mo, *J. Am. Chem. Soc.* **94**, 3544 (1972); Saunders and Berger, *J. Am. Chem. Soc.* **94**, 4049 (1972); Olah and Liang, *J. Am. Chem. Soc.* **94**, 6434 (1972); Olah and Spear, *J. Am. Chem. Soc.* **97**, 1539 (1975).

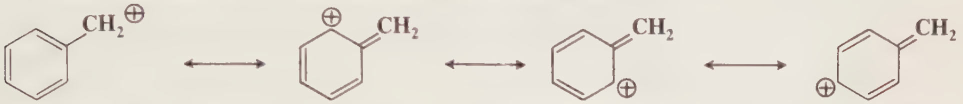
[24] For a review of divinylmethyl and trivinylmethyl cations, see Sorensen, in Olah and Schleyer, Ref. 3, vol. 2, pp. 807–835.

[25] Deno and Pittman, *J. Am. Chem. Soc.* **86**, 1871 (1964).



cations are stable at low temperatures (−55°C) in fluorosulfonic acid but cyclize at room temperature in this solvent or in H_2SO_4.[26] Propargyl cations ($RC{\equiv}CCR_2^+$) have also been prepared.[27]

Similar canonical forms can be drawn for benzylic cations,[28] e.g.,

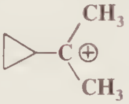


A number of benzylic cations have been obtained in solution as the SbF_6^- salts.[29] Diphenylmethyl and triphenylmethyl cations are still more stable. Triphenylchloromethane ionizes in polar solvents which do not, like water, react with the ion. In SO_2, the equilibrium

$$Ph_3CCl \rightleftharpoons Ph_3C^+ + Cl^-$$

has been known for many years. Both triphenylmethyl and diphenylmethyl cations have been isolated as solid salts.[30] Arylmethyl cations are further stabilized if they have electron-donating substituents in ortho or para positions.[31]

Cyclopropylmethyl cations[32] are even more stable than the benzyl type. **8** has been prepared by solution of the corresponding alcohol in 96% sulfuric acid,[33] and **6**, **7** and similar ions by solution of the alcohols in FSO_3H–SO_2–SbF_5.[34] This special stability, which increases with each additional cyclopropyl group, is a result of conjugation between the bent orbitals of the cyclopropyl rings (p. 141) and the vacant *p* orbital of the carbonium-ion carbon. Nmr and other studies have shown that the vacant *p* orbital lies parallel to the C-2,C-3 bond of the cyclopropane ring and not perpendicular to it.[35] In this respect the geometry is similar to that of a cyclopropane



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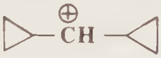

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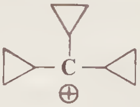

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[26] Sorensen, *Can. J. Chem.* **43**, 2744 (1965).

[27] Pittman and Olah, *J. Am. Chem. Soc.* **87**, 5632 (1965); Olah, Spear, Westerman, and Denis, *J. Am. Chem. Soc.* **96**, 5855 (1974).

[28] For a review of benzylic, diarylmethyl, and triarylmethyl cations, see Freedman, in Olah and Schleyer, Ref. 3, vol. 4, pp. 1501–1578.

[29] Bollinger, Comisarow, Cupas, and Olah, *J. Am. Chem. Soc.* **89**, 5687 (1967); Olah, Porter, Jeuell, and White, *J. Am. Chem. Soc.* **94**, 2044 (1972).

[30] Volz, *Angew. Chem. Int. Ed. Engl.* **2**, 622 (1963) [*Angew. Chem.* **75**, 921]; Volz and Schnell, *Angew. Chem. Int. Ed. Engl.* **4**, 873 (1965) [*Angew. Chem.* **77**, 864].

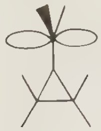
[31] Goldacre and Phillips, *J. Chem. Soc.* 1724 (1949); Deno and Schriesheim, *J. Am. Chem. Soc.* **77**, 3051 (1955).

[32] For reviews, see in Olah and Schleyer, Ref. 3, vol. 3: Richey, pp. 1201–1294, and Wiberg, Hess, and Ashe, pp. 1295–1345.

[33] Deno, Richey, Liu, Hodge, Houser, and Wisotsky, *J. Am. Chem. Soc.* **84**, 2016 (1962).

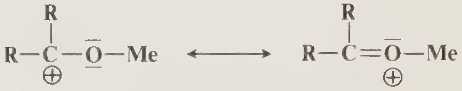
[34] Pittman and Olah, *J. Am. Chem. Soc.* **87**, 2998 (1965); Deno, Liu, Turner, Lincoln, and Fruit, *J. Am. Chem. Soc.* **87**, 3000 (1965).

[35] For example, see Ree and Martin, *J. Am. Chem. Soc.* **92**, 1660 (1970); Kabakoff and Namanworth, *J. Am. Chem. Soc.* **92**, 3234 (1970); Buss, Gleiter, and Schleyer, *J. Am. Chem. Soc.* **93**, 3927 (1971); Poulter and Spillner, *J. Am. Chem. Soc.* **96**, 7591 (1974); and Ref. 33.



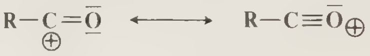
ring conjugated with a double bond (p. 142). Stable cations have also been obtained (at −50°C) where the central carbon is conjugated with both a cyclopropyl group and a double bond.[36] Cyclopropylmethyl cations are further discussed on pp. 298–300. The stabilizing effect just discussed is unique to cyclopropyl groups. Cyclobutyl and larger cyclic groups are about as effective at stabilizing a carbonium ion as ordinary alkyl groups.[37]

Another structural feature which increases carbonium-ion stability is the presence, adjacent to the cationic center, of a hetero atom bearing an unshared pair, e.g., oxygen, nitrogen,[38] or halogen.[39] Such ions are stabilized by resonance:



$$\mathrm{R-\underset{\oplus}{\overset{R}{C}}-\overline{\underline{O}}-Me \longleftrightarrow R-\overset{R}{C}=\underset{\oplus}{\overline{O}}-Me}$$

The methoxymethyl cation can be obtained as a stable solid, $\mathrm{MeOCH_2^+}$ $\mathrm{SbF_6^-}$.[40] Simple acyl cations, $\mathrm{RCO^+}$, have been prepared[41] in solution and in the solid state.[42] The 2,4,6-trimethylbenzoyl and 2,3,4,5,6-pentamethylbenzoyl cations are especially stable (for steric reasons) and are easily formed in 96% H_2SO_4.[43] These ions are stabilized by a canonical form containing a triple bond (**10**), though the positive charge is principally located on the carbon,[44] so that **9** contributes more than **10**.



$$\mathrm{R-\underset{\oplus}{C}=\overline{\underline{O}} \longleftrightarrow R-C\equiv\overline{O}^{\oplus}}$$

9 **10**

The stabilities of most other stable carbonium ions may also be attributed to resonance. Among these are the tropylium, cyclopropenium, and other aromatic cations discussed in Chapter 2. Where resonance stability is completely lacking, as in the phenyl or vinyl cations, the ion is usually very short-lived. Neither vinyl[45] nor phenyl cation has as yet been prepared as a stable species in solution.[46] Vinyl cations are probably more stable than the corresponding primary alkyl cations but less stable than the corresponding secondary alkyl cations.[47]

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[36] Sorensen and Rajeswari, *J. Am. Chem. Soc.* **93,** 4222 (1971).

[37] Sorensen, Miller, and Ranganayakulu, *Aust. J. Chem.* **26,** 311 (1973).

[38] For a review of such ions where nitrogen is the hetero atom, see Scott and Butler, in Olah and Schleyer, Ref. 3, vol. 4, pp. 1643–1696.

[39] For examples of stable solutions of such ions, see Kabuss, *Angew. Chem. Int. Ed. Engl.* **5,** 675 (1966) [*Angew. Chem.* **78,** 714]; Dimroth and Heinrich, *Angew. Chem. Int. Ed. Engl.* **5,** 676 (1966) [*Angew. Chem.* **78,** 715]; Hart and Tomalia, *Tetrahedron Lett.* 3383 (1966); Tomalia and Hart, *Tetrahedron Lett.* 3389 (1966); Ramsey and Taft, *J. Am. Chem. Soc.* **88,** 3058 (1966); Olah and Bollinger, *J. Am. Chem. Soc.* **89,** 2993 (1967); Olah and Comisarow, *J. Am. Chem. Soc.* **91,** 2955 (1969); Olah, Mo, and Halpern, *J. Am. Chem. Soc.* **94,** 3551 (1972); Olah, Liang, and Mo, *J. Org. Chem.* **39,** 2394 (1974); Borch, *J. Am. Chem. Soc.* **90,** 5303 (1968); Dusseau, Schaafsma, Steinberg, and de Boer, *Tetrahedron Lett.* 467 (1969); Rabinovitz and Bruck, *Tetrahedron Lett.* 245 (1971). For a review of such ions where fluorine is the hetero atom, see Olah and Mo, *Adv. Fluorine Chem.* **7,** 69–112 (1973).

[40] Olah and Svoboda, *Synthesis* 52 (1973).

[41] For a review of the preparation of acyl cations from acyl halides and Lewis acids, see Lindner, *Agnew. Chem. Int. Ed. Engl.* **9,** 114–123 (1970) [*Angew. Chem.* **82,** 143-153].

[42] Olah, Kuhn, Tolgyesi, and Baker, *J. Am. Chem. Soc.* **84,** 2733 (1962); Olah, Tolgyesi, Kuhn, Moffatt, Bastien, and Baker, *J. Am. Chem. Soc.* **85,** 1328 (1963); Deno, Pittman, and Wisotsky, *J. Am. Chem. Soc.* **86,** 4370 (1964); Olah, Dunne, Mo, and Szilagyi, *J. Am. Chem. Soc.* **94,** 4200 (1972); Olah and Svoboda, *Synthesis* 306 (1972); Olah and White, *J. Am. Chem. Soc.* **89,** 4752, 7072 (1967); Olah and Comisarow, *J. Am. Chem. Soc.* **88,** 3313 (1966).

[43] Hammett and Deyrup, *J. Am. Chem. Soc.* **55,** 1900 (1933); Newman and Deno, *J. Am. Chem. Soc.* **73,** 3651 (1951).

[44] Boer, *J. Am. Chem. Soc.* **90,** 6706 (1968); Le Carpentier and Weiss, *Acta Crystallogr., Sect. B* 1430 (1972). See also Mateescu, Riemenschneider, Svoboda, and Olah, *J. Am. Chem. Soc.* **94,** 7191 (1972); Olah and Westerman, *J. Am. Chem. Soc.* **95,** 3706 (1973).

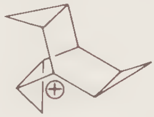
$$\mathrm{RCH_2^{\oplus}} \;<\; \mathrm{R\overset{\oplus}{C}{=}CH_2} \;<\; \mathrm{R\overset{\oplus}{C}H{-}CH_3}$$

Various quantitative methods have been developed to express the relative stabilities of carbonium ions.[48] One of the most common of these, though useful only for relatively stable cations which are formed by ionization of alcohols in acidic solutions, is based on the equation[49]

$$H_{\mathrm{R}} = \mathrm{p}K_{\mathrm{R}^+} - \log \frac{C_{\mathrm{R}^+}}{C_{\mathrm{ROH}}}$$

$\mathrm{p}K_{\mathrm{R}^+}$ is the pK for the reaction $\mathrm{R^+ + 2H_2O \rightleftharpoons ROH + H_3O^+}$ and is a measure of the stability of the carbonium ion. H_{R} (formerly called C_0 and J_0) is an easily obtainable measurement of the acidity of a solvent (see p. 234) and approaches pH at low concentrations of acid. In order to obtain $\mathrm{p}K_{\mathrm{R}^+}$ for a carbonium ion R^+, one dissolves the alcohol ROH in an acidic solution of known H_{R}. Then the concentrations of R^+ and ROH are obtained, generally from electronic spectra, and $\mathrm{p}K_{\mathrm{R}}$ can easily be calculated. Another quantitative method is based on nmr measurements.[50]

Since the central carbon of carbonium ions has only three bonds, and no other valence electrons, the bonds are sp^2 and should be planar.[51] Raman, ir, and nmr spectroscopic data on simple alkyl cations show this to be so.[52] Other evidence is that carbonium ions are difficult or impossible to form at bridgeheads,[53] where they cannot be planar (see p. 272). However, the adamantyl cation has been prepared, as the $\mathrm{SF_6^-}$ salt.[54] This represents an unusual type of bridgehead carbonium ion, and it may be planar or near-planar even though the positive charge is at a bridgehead. Another bridgehead carbonium ion which has been prepared in super-acid solution at -78°C is the 1-trishomobarrelyl cation (**11**).[55] In this case the instability



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[45] Solutions of aryl-substituted vinyl cations have been reported to be stable for at least a short time at low temperatures. Nmr spectra have been obtained: Abram and Watts, *J. Chem. Soc., Chem. Commun.* 857 (1974); Siehl, Carnahan, Eckes, and Hanack, *Angew. Chem. Int. Ed. Engl.* **13,** 675 (1974) [*Angew. Chem.* **86,** 677]; Masamune, Sakai, and Morio, *Can. J. Chem.* **53,** 784 (1975).

[46] For reviews of aryl and vinyl cations, see Richey and Richey, in Olah and Schleyer, Ref. 3, vol. 2, pp. 899–957; Richey, Ref. 21, pp. 42–49; Modena and Tonellato, *Adv. Phys. Org. Chem.* **9,** 185–280 (1971); and Stang, *Prog. Phys. Org. Chem.* **10,** 205–325 (1973).

[47] Richey, Ref. 21, p. 44.

[48] For a review, see Bethell and Gold, Ref. 3, pp. 59–87.

[49] Deno, Jaruzelski, and Schriesheim, *J. Am. Chem. Soc.* **77,** 3044 (1955); Deno and Schriesheim, *J. Am. Chem. Soc.* **77,** 3051 (1955); Deno, Berkheimer, Evans, and Peterson, *J. Am. Chem. Soc.* **81,** 2344 (1959).

[50] Young, Sandel, and Freedman, *J. Am. Chem. Soc.* **88,** 4532 (1966); McKinley, Rakshys, Young, and Freedman, *J. Am. Chem. Soc.* **93,** 4715 (1971).

[51] For discussions of the stereochemistry of carbonium ions, see Henderson, *Chem. Soc. Rev.* **2,** 397–413 (1973); Buss, Schleyer, and Allen, Ref. 3; Schleyer, in Chiurdoglu, "Conformational Analysis," pp. 241–249, Academic Press, Inc., New York, 1971; Hehre, *Acc. Chem. Res.* **8,** 369–376 (1975); and Ref. 28, pp. 1561–1574.

[52] Olah, DeMember, Commeyras, and Bribes, *J. Am. Chem. Soc.* **93,** 459 (1971); Olah et al., Ref. 8.

[53] For a review of bridgehead carbonium ions, see Fort, in Olah and Schleyer, Ref. 3, vol. 4, pp. 1783–1835.

[54] Schleyer, Fort, Watts, Comisarow, and Olah, *J. Am. Chem. Soc.* **86,** 4195 (1964).

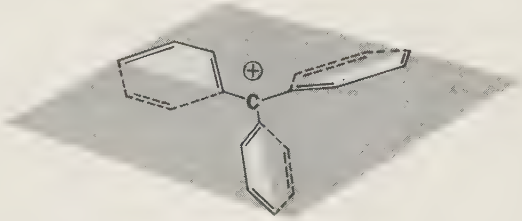
[55] deMeijere and Schallner, *Angew. Chem. Int. Ed. Engl.* **12,** 399 (1973) [*Angew. Chem.* **85,** 400].

TABLE 1 ^{13}C Chemical-shift values, in parts per million from $^{13}CS_2$, for some carbonium ions in $SO_2ClF-SbF_5$, $SO_2-FSO_3H-SbF_5$, or SO_2-SbF_5[57]

Ion	Chemical shift	Temp., °C	Ion	Chemical shift	Temp., °C
Et_2MeC^+	−139.4	−20	$C(OH)_3^+$	+28.0	−50
Me_2EtC^+	−139.2	−60	$PhMe_2C^+$	−61.1	−60
Me_3C^+	−135.4	−20	$PhMeCH^+$	−40[58]	
Me_2CH^+	−125.0	−20	Ph_2CH^+	−5.6	−60
Me_2COH^+	−55.7	−50	Ph_3C^+	−18.1	−60
$MeC(OH)_2^+$	−1.6	−30	Me_2(cyclopropyl)C^+	−86.8	−60
$HC(OH)_2^+$	+17.0	−30			

of the bridgehead position is balanced by the extra stability gained from the conjugation with the three cyclopropyl groups.

Triarylmethyl cations are propeller-shaped, though the central carbon and the three ring carbons connected to it are in a plane.[55a]



The three benzene rings cannot be all in the same plane because of steric hindrance, though increased resonance energy would be gained if they could.

An important tool for the investigation of carbonium-ion structure is measurement of the ^{13}C nmr chemical shift of the carbon atom bearing the positive charge.[56] This shift approximately correlates with electron density on the carbon (p. 19). ^{13}C chemical shifts for a number of ions are given in Table 1.[57] As shown in the table, the substitution of an ethyl for a methyl or of a methyl for a hydrogen causes a downfield shift, indicating that the central carbon becomes somewhat more positive. On the other hand, the presence of hydroxy or phenyl groups decreases the positive character of the central carbon. The ^{13}C chemical shifts are not always in exact order of carbonium-ion stabilities as determined in other ways. Thus the chemical shift shows that the triphenylmethyl cation has a more positive central carbon than diphenylmethyl cation, though the former is more stable. Also, the 2-cyclopropylpropyl and 2-phenylpropyl cations have shifts of −86.8 and −61.1, respectively, though we have seen that according to other criteria a cyclopropyl group is better than a phenyl group at stabilizing a carbonium ion.[59] The reasons for this discrepancy are not fully understood.[56, 59]

[55a] Sharp and Sheppard, *J. Chem. Soc.* 674 (1957); Gomes de Mesquita, MacGillavry, and Eriks, *Acta Crystallogr.* **18**, 437 (1965); Schuster, Colter, and Kurland, *J. Am. Chem. Soc.* **90**, 4679 (1968).

[56] For a review, see Farnum, *Adv. Phys. Org. Chem.* **11**, 123–175 (1975).

[57] Olah and White, *J. Am. Chem. Soc.* **90**, 1884 (1968), **91**, 5801 (1969).

[58] Olah, Porter, and Kelly, *J. Am. Chem. Soc.* **93**, 464 (1971).

[59] For discussions, see Brown and Peters, *J. Am. Chem. Soc.* **95**, 2400 (1973); Olah, Westerman, and Nishimura, *J. Am. Chem. Soc.* **96**, 3548 (1974); and Wolf, Harch, Taft, and Hehre, *J. Am. Chem. Soc.* **97**, 2902 (1975). See also Larsen and Bouis, *J. Am. Chem. Soc.* **97**, 4418 (1975); Volz, Shin, and Streicher, *Tetrahedron Lett.* 1297 (1975).

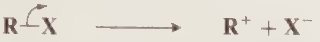
Nonclassical Carbonium Ions

These are discussed at pp. 284–302.

The Generation and Fate of Carbonium Ions

Carbonium ions, stable or unstable, are usually generated in one of two general ways:

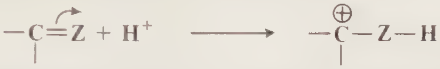
1. A direct ionization, in which a group attached to a carbon atom leaves with its pair of electrons (see Chapters 10, 13, 17, 18):



$$R{-}X \longrightarrow R^+ + X^-$$

(may be reversible)

2. A proton or other positive species adds to one atom of an unsaturated system, leaving the adjacent carbon atom with a positive charge (see Chapters 11, 15, 16):

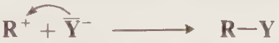


$$-\underset{|}{C}{=}Z + H^+ \longrightarrow -\overset{\oplus}{\underset{|}{C}}{-}Z{-}H$$

Formed by either process, carbonium ions are most often short-lived transient species and react further without being isolated. There are several ways in which a carbonium ion may react, some of them giving stable products and others leading to different carbonium ions, which themselves must react further to give stable products.

The two chief pathways by which carbonium ions react to give stable products are the reverse of the two pathways just described.

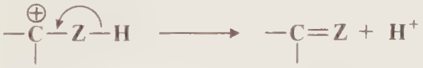
1. The carbonium ion may combine with a species possessing an electron pair (a Lewis acid-base reaction, see Chapter 8):



$$R^+ + Y^- \longrightarrow R{-}Y$$

This species may be H$^-$, OH$^-$, halide ion, or any other negative ion; or it may be a neutral species with a pair to donate, in which case, of course, the immediate product must bear a positive charge (see Chapters 10, 13, 15, 16).

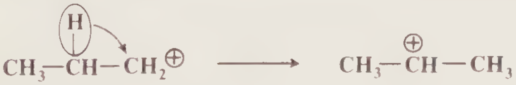
2. The carbonium ion may lose a proton (or much less often, another positive ion) from the adjacent atom (see Chapters 11, 17):



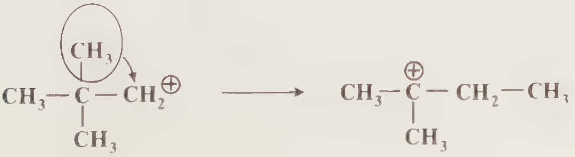
$$-\overset{\oplus}{\underset{|}{C}}{-}Z{-}H \longrightarrow -\underset{|}{C}{=}Z + H^+$$

Two pathways which lead to other carbonium ions are:

3. *Rearrangement.* An alkyl or aryl group or a hydrogen (sometimes another group) migrates with its electron pair to the positive center, leaving another positive charge behind (see Chapter 18):

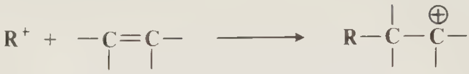


$$CH_3{-}\overset{H}{\overset{|}{C}}H{-}CH_2^{\oplus} \longrightarrow CH_3{-}\overset{\oplus}{C}H{-}CH_3$$



$$CH_3{-}\overset{CH_3}{\overset{|}{\underset{\underset{CH_3}{|}}{C}}}{-}CH_2^{\oplus} \longrightarrow CH_3{-}\overset{\oplus}{\underset{\underset{CH_3}{|}}{C}}{-}CH_2{-}CH_3$$

4. *Addition.* A carbonium ion may add to a double bond, generating a positive charge at a new position (see Chapters 11, 15):



$$R^+ + -\underset{|}{C}=\underset{|}{C}- \longrightarrow R-\overset{|}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}-$$

12

Whether formed by pathway 3 or 4, the new carbonium ion normally reacts further in an effort to stabilize itself, usually by pathway 1 or 2. However, **12** may add to another olefin molecule, and this product may add to still another, etc. This is one of the mechanisms for vinyl polymerization.

CARBANIONS

Stability and Structure[60]

There are many compounds known with a bond between carbon and a metal. Many carbon-metal bonds, e.g., carbon-mercury bonds, are undoubtedly covalent, but in bonds between carbon and the more active metals the electrons are closer to the carbon. Whether the position of the electrons in a given bond is close enough to the carbon to justify calling the bond ionic and the carbon moiety a carbanion depends on the metal, on the structure of the carbon moiety, and on the solvent and in many cases is a matter of speculation. In this section we shall discuss carbanions with little reference to the metal. In the next section we shall deal with the structures of organometallic compounds.

By definition, every carbanion possesses an unshared pair of electrons and is therefore a base. When it accepts a proton, it is converted into its conjugate acid (see Chapter 8). The stability of the carbanion is directly related to the strength of the conjugate acid. The weaker the acid, the greater the base strength and the lower the stability of the carbanion.[61] By stability here we mean stability toward a proton donor: the lower the stability, the more eager the carbanion is to accept a proton from any available source and hence to end its existence as a carbanion. Thus the determination of the order of stability of a series of carbanions is equivalent to a determination of the order of strengths of the conjugate acids, and one can obtain information about relative carbanion stability from a table of acid strengths like Table 1 in Chapter 8.

Unfortunately, it is not easy to measure acid strengths of very weak acids like the conjugate acids of simple unsubstituted carbanions. There is little doubt that these carbanions are very unstable in solution, and in contrast to the situation with carbonium ions, efforts to prepare solutions in which carbanions such as ethyl or isopropyl exist in a relatively free state have not yet been successful. Nevertheless, there have been several approaches to the problem. Applequist and O'Brien[62] studied the position of equilibrium for the reaction

$$\mathrm{RLi + R'I \rightleftharpoons RI + R'Li}$$

in ether and in ether-pentane. The reasoning in these experiments was that the R group which forms the more stable carbanion would be more likely to be bonded to lithium than to iodide.

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[60] For a monograph, see Cram, "Fundamentals of Carbanion Chemistry," Academic Press, Inc., New York, 1965. For reviews, see Isaacs, Ref. 1, pp. 234–293; Kaiser and Slocum, in McManus, Ref. 1, pp. 337–422; Ebel, *Fortchr. Chem. Forsch.* **12**, 387–439 (1969); Cram, *Surv. Prog. Chem.* **4**, 45–68 (1968), *Pure Appl. Chem.* **7**, 155–172 (1963); Reutov and Beletskaya, "Reaction Mechanisms of Organometallic Compounds," pp. 1-64, North-Holland Publishing Co., Amsterdam, 1968; and Streitwieser and Hammons, *Prog. Phys. Org. Chem.* **3**, 41–80 (1965).

[61] For a review of hydrocarbon acidity, see Fischer and Rewicki, *Prog. Org. Chem.* **7**, 116–161 (1968).

[62] Applequist and O'Brien, *J. Am. Chem. Soc.* **85**, 743 (1963).

Carbanion stability was found to be in this order: vinyl > phenyl > cyclopropyl > ethyl > *n*-propyl > isobutyl > neopentyl > cyclobutyl > cyclopentyl. In a somewhat similar approach, Dessy and coworkers[63] treated a number of alkylmagnesium compounds with a number of alkylmercury compounds in tetrahydrofuran, setting up the equilibrium

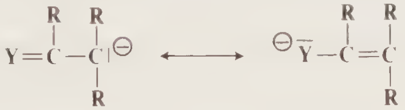
$$R_2Mg + R'_2Hg \rightleftharpoons R_2Hg + R'_2Mg$$

where the group of greater carbanion stability is linked to magnesium. The carbanion stability determined in this way was in the order phenyl > vinyl > cyclopropyl > methyl > ethyl > isopropyl. The two stability orders are in fairly good agreement, and they show that stability of simple carbanions decreases in the order methyl > primary > secondary. It was not possible by the experiments of Dessy and coworkers to determine the position of *t*-butyl, but there seems little doubt that it is still less stable. We can interpret this stability order solely as a consequence of the field effect since resonance is absent. The electron-donating alkyl groups of isopropyl result in a greater negative charge density at the central carbon atom (compared with methyl), thus decreasing its stability. The results of Applequist and O'Brien show that β branching also decreases carbanion stability. Cyclopropyl occupies an apparently anomalous position, but this is probably due to the large amount of *s* character in the carbanionic carbon (see p. 163).

A different approach to the problem of hydrocarbon acidity and hence carbanion stability was that of Shatenshtein and coworkers, who treated hydrocarbons with deuterated potassium amide and measured the rates of hydrogen exchange.[64] The experiments did not measure *thermodynamic* acidity, since rates were measured and not positions of equilibria. They measured *kinetic* acidity, i.e., which compounds gave up protons most rapidly (see p. 194 for the distinction between thermodynamic and kinetic control of product). Measurements of rates of hydrogen exchange enable one to compare acidities of a series of acids against a given base even where the positions of the equilibria cannot be measured because they lie too far to the side of the starting materials, i.e., where the acids are too weak to be converted to their conjugate bases in measurable amounts. Although the correlation between thermodynamic and kinetic acidity is far from perfect,[64a] the results of the rate measurements, too, indicated that the order of carbanion stability is methyl > primary > secondary > tertiary.[64]

Many carbanions are far more stable than the simple kind mentioned above. The increased stability is due to certain structural features:

1. *Conjugation of the unshared pair with an unsaturated bond:*



$$Y{=}\overset{R}{C}{-}\underset{R}{\overset{R}{C}}{}^{\ominus} \longleftrightarrow {}^{\ominus}\bar{Y}{-}\overset{R}{C}{=}\underset{R}{\overset{R}{C}}$$

In cases where a double or triple bond is located α to the carbanionic carbon, the ion is stabilized by resonance in which the unshared pair overlaps with the π electrons of the double bond. This factor is responsible for the stability of the allylic[65] and benzylic[66] types of carbanions:

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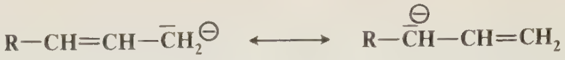
[63] Dessy, Kitching, Psarras, Salinger, Chen, and Chivers, *J. Am. Chem. Soc.* **88**, 460 (1966).

[64] For reviews, see Jones, *Surv. Prog. Chem.* **6**, 83–112 (1973); Shatenshtein and Shapiro, *Russ. Chem. Rev.* **37**, 845–854 (1968); and Shatenshtein, *Adv. Phys. Org. Chem.* **1**, 153–201 (1963).

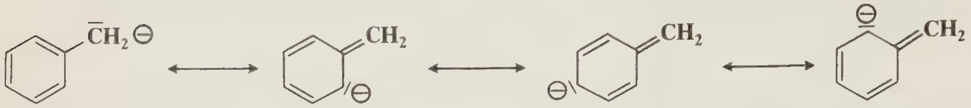
[64a] For example, see Bordwell, Matthews, and Vanier, *J. Am. Chem. Soc.* **97**, 442 (1975).

[65] For a review of allylic anions, see Richey, Ref. 21, pp. 67–77.

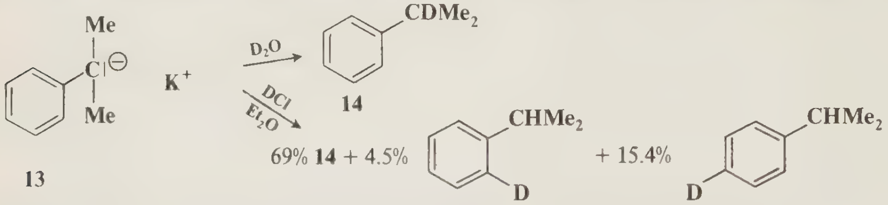
[66] Although benzylic carbanions are more stable than the simple alkyl type, they have so far not proved stable enough for isolation. The benzyl carbanion has been formed and studied in submicrosecond times: Bockrath and Dorfman, *J. Am. Chem. Soc.* **96**, 5708 (1974).



$$R{-}CH{=}CH{-}\bar{C}H_2^{\ominus} \longleftrightarrow R{-}\overset{\ominus}{\bar{C}}H{-}CH{=}CH_2$$

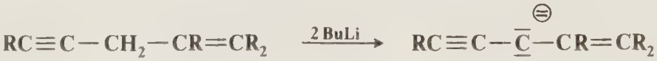


There is direct evidence for resonance in benzylic systems. When **13** was treated with D_2O, only **14** was obtained, but with DCl in ether, about 20% of the product contained deuterium in the ring.[67] Under these conditions, cumene itself did not exchange with deuterium. Diphenylmethyl and triphenylmethyl anions are still more stable and can be kept in solution indefinitely if water is rigidly excluded. Even more stable yet are completely chlorinated triphenylmethyl anions. The salt tetraethylammonium perchlorotriphenylmethide is so stable that it can be obtained in the solid form and does not react with water or ethanol, though it does take a proton from dilute HCl.[68] When a CH_2 group is α to both a double and a triple bond, it can lose two protons to a strong base to give the dicarbanion **15**, where both negative charges are formally on the same carbon.[69]



13

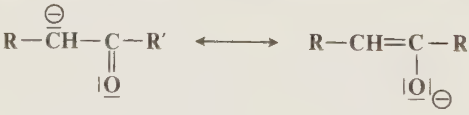
14



$$RC{\equiv}C{-}CH_2{-}CR{=}CR_2 \xrightarrow{2\,BuLi} RC{\equiv}C{-}\overset{\ominus}{\underline{\bar{C}}}{-}CR{=}CR_2$$

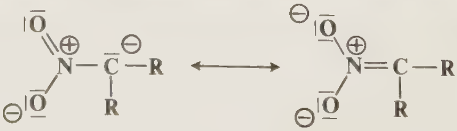
15

Where the carbanionic carbon is conjugated with a carbon-oxygen or carbon-nitrogen multiple bond (Y = O or N), stability of the ion is greater than that of unchlorinated triarylmethyl anions, since these electronegative atoms are better capable than carbon of bearing a negative charge. However, it is questionable whether ions of this type should be called carbanions at all, since in the case of enolate ions, for example, **17** contributes more to the hybrid than **16**, although



16 17

such ions more often react at the carbon than at the oxygen. Enolate ions can also be kept in stable solutions. A nitro group is particularly effective in stabilizing a negative charge on an



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[67] Russell, *J. Am. Chem. Soc.* **81**, 2017 (1959).

[68] Ballester and de la Fuente, *Tetrahedron Lett.* 4509 (1970).

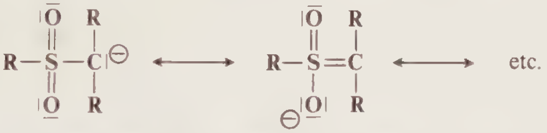
[69] Klein and Brenner, *J. Am. Chem. Soc.* **91**, 3094 (1969).

adjacent carbon, and the anions of simple nitro alkanes can exist in water. Thus pK_a for nitromethane is 10.2, which means that at a pH of 10.2 an aqueous solution of nitromethane contains equal amounts of nitromethane and its conjugate base, and at higher pH values there is even more of the carbanion. Dinitromethane is even more acidic ($pK = 3.6$).

In contrast to the stability of cyclopropylmethyl cations (p. 155), the cyclopropyl group exerts only a weak stabilizing effect on an adjacent carbanionic carbon.[70]

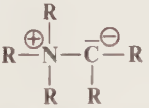
2. *Carbanions increase in stability with an increase in the amount of s character at the carbanionic carbon.* Thus the order of stability is $RC{\equiv}C^- > R_2C{=}CH^- \approx Ar^- > R_3C{-}CH_2^-$. Acetylene, where the carbon is *sp*-hybridized with 50% *s* character, is much more acidic than ethylene[71] (sp^2, 33% *s*), which in turn is more acidic than ethane, with 25% *s* character. Increased *s* character means that the electrons are closer to the nucleus and hence of lower energy. As previously mentioned, cyclopropyl carbanions are more stable than methyl, owing to the larger amount of *s* character as a result of strain (see p. 141).

3. *Stabilization by sulfur or phosphorus.* Attachment to the carbanionic carbon of a sulfur or phosphorus atom causes an increase in carbanion stability, although the reasons for this are in dispute. One theory is that there is overlap of the unshared pair with an empty *d* orbital[72] ($p\pi$-$d\pi$ bonding, see p. 39). For example, a carbanion containing the SO_2R group would be written



Evidence that this type of conjugation is important in stabilizing such ions comes from a study of H-D exchange rates of Me_4N^+, Me_4P^+, and Me_3S^+.[73] Me_4P^+ exchanged 2.4×10^6 times faster than Me_4N^+. There is no normal conjugation in these ions, and the electron-withdrawing field effect of positive nitrogen is greater than that of positive phosphorus, so that the only factor which could be causing the increased acidity is the presence of unoccupied low-lying *d* orbitals of the phosphorus. An even greater rate ratio ($2.0 \times 10^7 : 1$) was found for Me_3S^+ compared with Me_4N^+. However, there is evidence against *d*-orbital overlap in these cases, and the stabilizing effects have been attributed to other causes.[74]

4. *Field effects.* Most of the groups which stabilize carbanions by resonance effects (either the kind discussed in paragraph 1 above or the kind discussed in paragraph 3) have electron-withdrawing field effects and thereby stabilize the carbanion further by spreading the negative charge, though it is difficult to separate the field effect from the resonance effect. However, in a nitrogen ylide (see p. 40), where a positive nitrogen is adjacent to the carbanionic carbon, only the field effect is operating:



$$R_3\overset{\oplus}{N}-\overset{\ominus}{C}R_3$$

Ylides are more stable than the corresponding simple carbanions.

5. Certain carbanions are stable because they are aromatic (see the cyclopentadienyl anion p. 46, and other aromatic anions in Chapter 2).

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[70] Perkins and Ward, *Chem. Commun.* 1134 (1971).

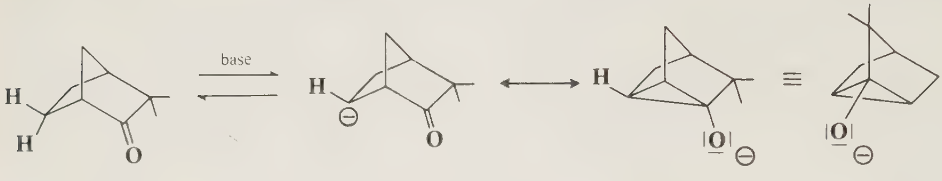
[71] For a review of vinyl anions, see Richey, Ref. 21, pp. 49–56.

[72] For a review of α-sulfinyl carbanions, see Durst and Viau, *Intra-Sci. Chem. Rep.* **7** (3), 63–74 (1973).

[73] Doering and Hoffmann, *J. Am. Chem. Soc.* **77**, 521 (1955).

[74] Bernardi, Csizmadia, Mangini, Schlegel, Whangbo, and Wolfe, *J. Am. Chem. Soc.* **97**, 2209 (1975).

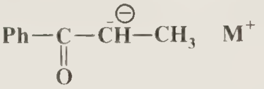
6. *Stabilization by a nonadjacent π bond.*[75] In contrast to the situation with carbonium ions (see pp. 284–302), there have only been a few reports of a carbanion stabilized by interaction with a nonadjacent π bond. One that may be mentioned is **20**, formed when optically active camphenilone (**18**) was treated with a strong base (potassium *t*-butoxide).[76] That **20** was truly formed was shown by the following facts: (1) A proton was abstracted; ordinary CH_2 groups are not acidic enough for this base; (2) recovered **18** was racemized: **20** is symmetrical and can be attacked equally well from either side; (3) when the experiment was performed in deuterated solvent, the rate of deuterium uptake was equal to the rate of racemization; and (4) recovered **18** contained up to three atoms of deuterium per molecule, though if **19** were the only ion, no more than two could be taken up.



18 **19** **20**

Overall, functional groups in the α position stabilize carbanions in the following order: $NO_2 > RCO > SO_2 > COOR > CN \approx CONH_2 > Hal > H > R$.

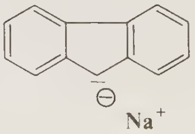
It is unlikely that free carbanions exist in solution. Like carbonium ions, they are usually in ion pairs[4] or else solvated.[77] Among experiments which demonstrated this was the treatment of **21** with ethyl iodide, where M was lithium, sodium, or potassium. The half-lives of the reaction



$$Ph{-}\underset{\underset{O}{\|}}{C}{-}\overset{\ominus}{C}H{-}CH_3 \quad M^+$$

21

were[78] for Li, 31×10^{-6}; Na, 0.39×10^{-6}; and K, 0.0045×10^{-6}, demonstrating that the species involved were not identical. Hogen-Esch and Smid have shown that sodium fluorenide



exists in tetrahydrofuran at room temperature as an intimate ion pair, but at 80°C as a solvent-separated ion pair; i.e., molecules of solvent are between the two ions.[79] This was shown by a study of the change in the visible and uv spectrum of the solution on going from 25 to −80°C: a peak at 355 nm disappears, while new peaks appear at 373 and 521 nm. The species are therefore different, but neither is the free carbanion since neither solution showed appreciable conductivity. Where ion pairs are unimportant, carbanions are solvated. Cram[60] has demonstrated solvation of carbanions in many solvents.

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[75] For a discussion, see Richey, Ref. 21, pp. 101–106.

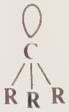
[76] Nickon and Lambert, *J. Am. Chem. Soc.* **88**, 1905 (1966). Also see Brown and Occolowitz, *Chem. Commun.* 376 (1965); Brown, *Chem. Commun.* 638 (1967); Winstein, Ogliaruso, Sakai, and Nicholson, *J. Am. Chem. Soc.* **89**, 3656 (1967); Grutzner and Winstein, *J. Am. Chem. Soc.* **90**, 6562 (1968); Staley and Reichard, *J. Am. Chem. Soc.* **91**, 3998 (1969); Nickon, Lambert, and Oliver, *J. Am. Chem. Soc.* **88**, 2787 (1966); Nickon, Lambert, Williams, and Werstiuk, *J. Am. Chem. Soc.* **88**, 3354 (1966); Hunter, Johnson, Stothers, Nickon, Lambert, and Covey, *J. Am. Chem. Soc.* **94**, 8582 (1972); Miller, *J. Am. Chem. Soc.* **91**, 751 (1969); Werstiuk, *Can. J. Chem.* **53**, 2211 (1975).

[77] For reviews, see Murdoch and Streitwieser, *Intra-Sci. Chem. Rep.* 7(3), 45–62 (1973); and Smid, *Intra-Sci. Chem. Rep.* 7(3), 75–84 (1973).

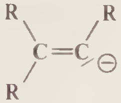
[78] Zook and Gumby, *J. Am. Chem. Soc.* **82**, 1386 (1960).

[79] Hogen-Esch and Smid, *J. Am. Chem. Soc.* **88**, 307, 318 (1966); **91**, 4580 (1969). See also Streitwieser, Chang, Hollyhead, and Murdoch, *J. Am. Chem. Soc.* **94**, 5288 (1972).

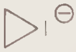
The structure of simple unsubstituted carbanions is not known with certainty since they have not been isolated, but it seems likely that the central carbon is sp^3-hybridized, with the unshared pair occupying one apex of the tetrahedron. Carbanions would thus have pyramidal structures, similar to those of amines:



If this structure is correct, and if the three R groups are different, the carbanion should be asymmetric (see Chapter 4) and reactions in which it is an intermediate should give retention of configuration. Attempts have been made to demonstrate this but without success.[80] A possible explanation is that the umbrella effect exists here, as in amines, so that the unshared pair and the central carbon rapidly oscillate from one side of the plane to the other. There is, though, other evidence for the sp^3 nature of the central carbon and for its tetrahedral structure. Carbons at bridgeheads, though extremely reluctant to undergo reactions in which they must be converted to carbonium ions, undergo with ease reactions in which they must be carbanions, and stable bridgehead carbanions are known.[81] Also, reactions at vinyl carbons proceed with retention,[82] indicating that the intermediate **22** has sp^2 hybridization and not the sp hybridization which



22



23

would be expected in the analogous carbonium ion. There is evidence that a cyclopropyl anion (**23**) can also hold its configuration.[83]

Carbanions in which the negative charge is stabilized by resonance involving overlap of the unshared-pair orbital with the π electrons of a multiple bond are essentially planar, as would be expected by the necessity for planarity in resonance, though unsymmetrical solvation or ion-pairing effects may cause the structure to deviate somewhat from true planarity.[84] Cram and coworkers have shown that where asymmetric carbanions possessing this type of resonance are generated, retention, inversion, or racemization can result depending on the solvent (see p. 526).

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[80] Retention of configuration has never been observed with simple carbanions. Cram has obtained retention with carbanions stabilized by resonance. However, these carbanions are known to be planar or nearly planar, and retention was caused by asymmetric solvation of the planar carbanions (see p. 526).

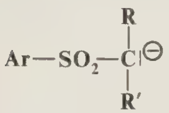
[81] For other evidence that carbanions are pyramidal, see Streitwieser and Young, *J. Am. Chem. Soc.* **91**, 529 (1969).

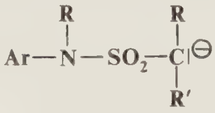
[82] Curtin and Harris, *J. Am. Chem. Soc.* **73**, 2716, 4519 (1951); Braude and Coles, *J. Chem. Soc.* 2078 (1951); Nesmeyanov and Borisov, *Tetrahedron* **1**, 158 (1957). Also see Miller and Lee, *J. Am. Chem. Soc.* **81**, 6313 (1959); and Hunter and Cram, *J. Am. Chem. Soc.* **86**, 5478 (1964); Walborsky and Turner, *J. Am. Chem. Soc.* **94**, 2273 (1972); Arnett and Walborsky, *J. Org. Chem.* **37**, 3678 (1972).

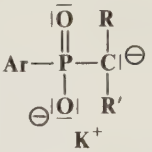
[83] Walborsky and Motes, *J. Am. Chem. Soc.* **92**, 2445 (1970); Motes and Walborsky, *J. Am. Chem. Soc.* **92**, 3697 (1970); and references cited in these papers.

[84] See the discussion in Cram, "Fundamentals of Carbanion Chemistry," pp. 85–105, Academic Press, Inc., New York, 1965.

This result is explained by unsymmetrical solvation of planar or near-planar carbanions. However, some carbanions which are stabilized by *d*-orbital overlap, e.g.,


$\text{Ar}-\text{SO}_2-\overset{\text{R}}{\underset{\text{R}'}{\text{C}}}|^{\ominus}$


$\text{Ar}-\overset{\text{R}}{\text{N}}-\text{SO}_2-\overset{\text{R}}{\underset{\text{R}'}{\text{C}}}|^{\ominus}$


$\text{Ar}-\overset{|\overline{\text{O}}}{\underset{^{\ominus}|\underline{\text{O}}|}{\text{P}}}-\overset{\text{R}}{\underset{\text{R}'}{\text{C}}}|^{\ominus}\quad \text{K}^+$

are inherently asymmetric, since retention of configuration is observed where they are generated, even in solvents which cause racemization or inversion with other carbanions.[85] There has been a controversy over whether this inherent asymmetry is the result of a pyramidal structure which does not invert or of a structure which is planar at the carbanionic carbon but is asymmetric because rotation about the C—S bond is hindered. The question is not yet settled.[86]

The Structure of Organometallic Compounds[87]

Whether the carbon-metal bond is ionic or polar-covalent is determined chiefly by the electronegativity of the metal and the structure of the organic part of the molecule. Ionic bonds become more likely as the negative charge on the metal-bearing carbon is decreased by resonance or field effects. Thus the sodium salt of acetoacetic ester has a more ionic carbon-sodium bond than methylsodium does.

Most organometallic bonds are polar-covalent. Only the alkali metals have electronegativities low enough to form ionic bonds with carbon, and even here the behavior of lithium alkyls is more covalent than ionic. The simple alkyls and aryls of sodium, potassium,[88] rubidium, and cesium are nonvolatile solids insoluble in benzene or other organic solvents, while alkyllithiums are soluble, though they too are generally nonvolatile solids. Alkyllithiums do not exist as monomeric species in hydrocarbon solvents or ether.[89] In benzene and cyclohexane, freezing-point-depression studies have shown that alkyllithiums are normally hexameric unless steric interactions favor tetrameric aggregates.[90] Where steric hindrance is great enough, as in menthyllithium, dimeric aggregates are found in hydrocarbon solvents.[91] In such cases the alkyllithium is much more reactive than ordinary alkyllithiums. Boiling-point-elevation studies have been performed in ether solutions, where alkyllithiums exist in two- to fivefold aggregates.[92] The structure of alkyllithium tetramers in ether has been shown by evidence obtained from ^{13}C–^{7}Li nmr coupling to be tetrahedral, with the four lithium atoms at the corners of a tetrahedron and one alkyl group directly over the center of each face of the tetrahedron.[93] Even in the gas phase[94] and in the solid state,[95] alkyllithiums exist as aggregates. X-ray crystallography has shown that methyllithium has the same tetrahedral structure in the solid state as in ether solution.[95]

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[85] Cram, Nielsen, and Rickborn, *J. Am. Chem. Soc.* **82,** 6415 (1960); Cram, Scott, and Nielsen, *J. Am. Chem. Soc.* **83,** 3696 (1961); Cram and Wingrove, *J. Am. Chem. Soc.* **84,** 1496 (1962); Corey and Kaiser, *J. Am. Chem. Soc.* **83,** 490 (1961); Goering, Towns, and Dittmer, *J. Org. Chem.* **27,** 736 (1962); Corey and Lowry, *Tetrahedron Lett.* 803 (1965); Bordwell, Phillips, and Williams, *J. Am. Chem. Soc.* **90,** 426 (1968). For a discussion, see Ref. 84, pp. 105-113.

[86] See Rauk, Wolfe, and Csizmadia, *Can. J. Chem.* **47,** 113 (1969); Fraser and Schuber, *Chem. Commun.* 1474 (1969); Brown, Cook, Hutchinson, and Katritzky, *Tetrahedron* **27,** 593 (1971); Paquette, Freeman, and Wyvratt, *J. Am. Chem. Soc.* **93,** 3216 (1971); and Henderson, Ref. 51.

[87] For reviews, see Coates, Green, and Wade, "Organometallic Compounds," 3d ed., vol. 1, Methuen & Co., Ltd., London, 1967; Schlosser, *Angew. Chem. Int. Ed. Engl.* **3,** 287–306 (1964), pp. 287–291 [*Angew. Chem.* **76,** 124–143].

[88] X-ray crystallography of potassium methyl shows a completely ionic crystal lattice: Weiss and Sauermann, *Angew. Chem. Int. Ed. Engl.* **7,** 133 (1968); [*Angew. Chem.* **80,** 123].

[89] For reviews of the structure of alkyllithium compounds, see Wakefield, "The Chemistry of Organolithium Compounds," pp. 3–18, Pergamon Press, New York, 1974; Brown, *Pure Appl. Chem.* **23,** 447–462 (1970), *Adv. Organomet. Chem.* **3,** 365–395 (1965); Kovrizhnykh and Shatenshtein, *Russ. Chem. Rev.* **38,** 840 (1969); McKeever, Ref. 4, vol. 1, pp. 263–287.

[90] Lewis and Brown, *J. Am. Chem. Soc.* **92,** 4664 (1970); Brown and Rogers, *J. Am. Chem. Soc.* **79,** 1859 (1957); Weiner, Vogel, and West, *Inorg. Chem.* **1,** 654 (1962).

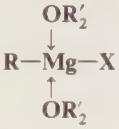
[91] Glaze and Freeman, *J. Am. Chem. Sec.* **91,** 7198 (1969).

[92] Wittig, Meyer, and Lange, *Justus Liebigs Ann. Chem.* **571,** 167 (1951).

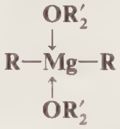
It is fairly certain that the C—Mg bond in Grignard reagents is covalent and not ionic. Thus, organolithiums, organomagnesiums, and Grignard reagents have virtually identical nmr spectra when the alkyl group is the same.[96] The actual structure of Grignard reagents in solution has been a matter of much controversy over the years.[97] In 1929 it was discovered[98] that the addition of dioxane to an ethereal Grignard solution precipitates all the magnesium halide and leaves a solution of R_2Mg in ether; i.e., there can be no RMgX in the solution since there is no halide. The following equilibrium, now called the *Schlenk equilibrium*, was proposed as the composition of the Grignard solution:

$$\mathrm{2RMgX} \rightleftharpoons \mathrm{R_2Mg + MgX_2} \rightleftharpoons \underset{\mathbf{24}}{\mathrm{R_2Mg{\cdot}MgX_2}}$$

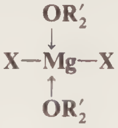
in which **24** is a complex of some type. Much work in recent years has demonstrated that the Schlenk equilibrium actually exists and that the position of the equilibrium is dependent on the identity of R, X, the solvent, the concentration, and the temperature.[99] It has been known for many years that the magnesium in a Grignard solution, no matter whether it is RMgX, R_2Mg, or MgX_2, can coordinate with two molecules of ether in addition to the two covalent bonds:



$$\mathrm{R}-\underset{\underset{\mathrm{OR'_2}}{\uparrow}}{\overset{\overset{\mathrm{OR'_2}}{\downarrow}}{\mathrm{Mg}}}-\mathrm{X}$$

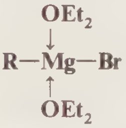


$$\mathrm{R}-\underset{\underset{\mathrm{OR'_2}}{\uparrow}}{\overset{\overset{\mathrm{OR'_2}}{\downarrow}}{\mathrm{Mg}}}-\mathrm{R}$$



$$\mathrm{X}-\underset{\underset{\mathrm{OR'_2}}{\uparrow}}{\overset{\overset{\mathrm{OR'_2}}{\downarrow}}{\mathrm{Mg}}}-\mathrm{X}$$

Rundle and coworkers performed x-ray-diffraction studies on solid phenylmagnesium bromide dietherate and on ethylmagnesium bromide dietherate, which they obtained by cooling ordinary ethereal Grignard solutions until the solids crystallized.[100] They found that the structures were monomeric:



$$\mathrm{R}-\underset{\underset{\mathrm{OEt_2}}{\uparrow}}{\overset{\overset{\mathrm{OEt_2}}{\downarrow}}{\mathrm{Mg}}}-\mathrm{Br} \qquad \mathrm{R} = \text{ethyl, phenyl}$$

A similar result was found by Schröder for phenylmagnesium bromide crystallized from a Grignard solution prepared in tetrahydrofuran.[101] These solids still contained ether or tetrahydrofuran. When ordinary ethereal Grignard solutions prepared from methyl bromide, methyl chloride, ethyl bromide, and ethyl chloride were evaporated at about 100°C under vacuum, so that the solid remaining contained no ether, x-ray diffraction showed *no* RMgX but a mixture of R_2Mg and MgX_2.[102] These results indicate that in the presence of ether $RMgX \cdot 2Et_2O$ is the preferred structure, while the loss of ether drives the Schlenk equilibrium to $R_2Mg + MgX_2$. However, conclusions drawn from a study of the solid materials do not necessarily apply to the structures in solution.

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[93] McKeever, Waack, Doran, and Baker, *J. Am. Chem. Soc.* **90**, 3244 (1968), **91**, 1057 (1969).

[94] Berkowitz, Bafus, and Brown, *J. Phys. Chem.* **65**, 1380 (1961); Brown, Dickerhoof, and Bafus, *J. Am. Chem. Soc.* **84**, 1371 (1962).

[95] Dietrich, *Acta Crystallogr.* **16**, 681 (1963); Weiss and Lucken, *J. Organomet. Chem.* **2**, 197 (1964).

[96] Fraenkel, Adams, and Williams, *Tetrahedron Lett.* 767 (1963).

[97] For reviews, see Ashby, *Bull. Soc. Chim. Fr.* 2133–2142 (1972), *Q. Rev., Chem. Soc.* **21**, 259–285 (1967); Wakefield, *Organomet. Chim. Rev.* **1**, 131–156 (1966); Bell, *Educ. Chem.* 143–145 (1973); Salinger, *Surv. Prog. Chem.* **1**, 301–324 (1963).

[98] Schlenk and Schlenk, *Ber.* **62B**, 920 (1929).

[99] See Parris and Ashby, *J. Am. Chem. Soc.* **93**, 1206 (1971); Salinger and Mosher, *J. Am. Chem. Soc.* **86**, 1782 (1964); Kirrmann, Hamelin, and Hayes, *Bull. Soc. Chim. Fr.* 1395 (1963).

[100] Guggenberger and Rundle, *J. Am. Chem. Soc.* **90**, 5375 (1968); Stuckey and Rundle, *J. Am. Chem. Soc.* **86**, 4825 (1964).

[101] Schröder, *Chem. Ber.* **102**, 2035 (1969).

Boiling-point-elevation and freezing-point-depression measurements have demonstrated that in tetrahydrofuran at all concentrations and in ether at low concentrations (up to about 0.1 *M*) Grignard reagents prepared from alkyl bromides and iodides are monomeric; i.e., there are few or no molecules with two magnesium atoms.[103] Thus, part of the Schlenk equilibrium is operating

$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

but not the other part; i.e, **24** is not present in measurable amounts. That the equilibrium between RMgX and R_2Mg lies far over to the left for "ethylmagnesium bromide" in ether was shown by Smith and Becker, who mixed 0.1 *M* ethereal solutions of Et_2Mg and $MgBr_2$ and found that a reaction occurred with a heat evolution of 3.6 kcal/mol of Et_2Mg, and that the product was *monomeric* (by boiling-point-elevation measurements).[104] When either solution was added little by little to the other, there was a linear output of heat until almost a 1 : 1 molar ratio was reached. Addition of an excess of either reagent gave no further heat output. In tetrahydrofuran also, mixing of solutions of R_2Mg and MgX_2 gave RMgX, though in this case heat was absorbed on mixing because tetrahydrofuran coordinates more strongly with $MgBr_2$ than it does with EtMgBr.[105] These results show that at least under some conditions *the Grignard reagent is largely RMgX* (coordinated with solvent) but that the equilibrium can be driven to R_2Mg by evaporation of all the ether or by addition of dioxane.

For some aryl Grignard reagents it has proved possible to distinguish separate nmr chemical shifts for ArMgX and Ar_2Mg.[106] From the area under the peaks the concentrations of the two species can be calculated and from them, equilibrium constants for the Schlenk equilibrium. These data show[106] that the position of the equilibrium depends very markedly on the aryl group and the solvent but that conventional aryl Grignard reagents in ether are largely ArMgX, while in tetrahydrofuran the predominance of ArMgX is less, and with some aryl groups there is actually more Ar_2Mg present. Separate nmr chemical shifts have also been found for alkyl RMgBr and R_2Mg in hexamethylphosphoric triamide (HMPT)[107] and in ether at low temperatures.[108] When Grignard reagents from alkyl bromides or chlorides are prepared in triethylamine the predominant species is RMgX.[109] Thus the most important factor determining the position of the Schlenk equilibrium is the solvent. For primary alkyl groups the equilibrium constant for the reaction as written above is lowest in Et_3N, higher in ether, and still higher in tetrahydrofuran.[110]

However, Grignard reagents prepared from alkyl bromides or iodides in ether at higher concentrations (0.5 to 1 *M*) contain dimers, trimers, and higher polymers, and those prepared from alkyl chlorides in ether at all concentrations are dimeric,[111] so that **24** is in solution, probably in equilibrium with RMgX and R_2Mg; i.e., the complete Schlenk equilibrium seems to be present. The structure of **24** is probably **25**,[112] though some **26** might also be present. X-ray analysis of

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[102] Weiss, *Chem. Ber.* **98,** 2805 (1965).

[103] Ashby and Becker, *J. Am. Chem. Soc.* **85,** 118 (1963); Ashby and Smith, *J. Am. Chem. Soc.* **86,** 4363 (1964); Vreugdenhil and Blomberg, *Recl. Trav. Chim. Pays-Bas* **82,** 453, 461 (1963).

[104] Smith and Becker, *Tetrahedron* **22,** 3027 (1966).

[105] Smith and Becker, *Tetrahedron* **23,** 4215 (1967).

[106] Evans and Khan, *J. Chem. Soc. A* 1643 (1967); Evans and Fazakerley, *Chem. Commun.* 974 (1968).

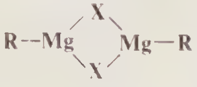
[107] Ducom, *Bull. Chem. Soc. Fr.* 3518, 3523, 3529 (1971).

[108] Ashby, Parris, and Walker, *Chem. Commun.* 1464 (1969); Parris and Ashby, Ref. 99.

[109] Ashby and Walker, *J. Org. Chem.* **33,** 3821 (1968).

[110] Parris and Ashby, Ref. 99.

[111] Ashby and Smith, Ref. 103.



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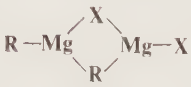

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solid EtMgBr coordinated with diisopropyl ether or with triethylamine showed **25** to be the species present.[113] Also, solutions of alkylmagnesium fluorides in ether or tetrahydrofuran are entirely dimeric, because of the unusual stability of the Mg—F—Mg bridgeheads.[114]

The Grignard reagent prepared from 1-chloro-3,3-dimethylpentane in ether undergoes rapid inversion of configuration at the magnesium-containing carbon (demonstrated by nmr; this compound is not chiral).[115] The mechanism of this inversion is not completely known.

It might be mentioned that matters are much simpler for organometallic compounds with less polar bonds. Thus Et_2Hg and EtHgCl are both definite compounds, the former a liquid and the latter a solid.

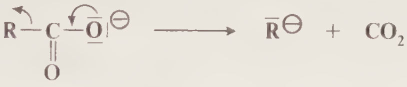
The Generation and Fate of Carbanions

The two principal ways in which carbanions are generated are parallel with the ways of generating carbonium ions.

1. A group attached to a carbon leaves without its electron pair:

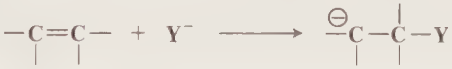
$$R—H \longrightarrow \overline{R}^{\ominus} + H^+$$

The leaving group is most often a proton. This is a simple acid-base reaction, and a base is required to remove the proton. However, other leaving groups are known (see Chapter 12):



$$R—\underset{\underset{O}{\|}}{C}—\overline{\underline{O}}|^{\ominus} \longrightarrow \overline{R}^{\ominus} + CO_2$$

2. A negative ion adds to a carbon-carbon double or triple bond (see Chapter 15):



$$—\underset{|}{C}=\underset{|}{C}— + Y^- \longrightarrow \overset{\ominus}{—}\underset{|}{C}—\overset{|}{\underset{|}{C}}—Y$$

The addition of a negative ion to a carbon-oxygen double bond does not give a carbanion, since the negative charge resides on the oxygen.

The most common reaction of carbanions is combination with a positive species, usually a proton, or with another species which has an empty orbital in its outer shell (a Lewis acid-base reaction):

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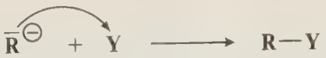
[112] Walker and Ashby, *J. Am. Chem. Soc.* **91**, 3845 (1969).

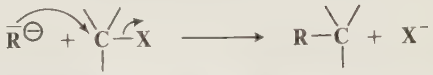
[113] Toney and Stuckey, *Chem. Commun.* 1168 (1967); Spek, Voorbergen, Schat, Blomberg, and Bickelhaupt, *J. Organomet. Chem.* **77**, 147 (1974).

[114] Ashby and Yu, *J. Organomet. Chem.* **29**, 339 (1971).

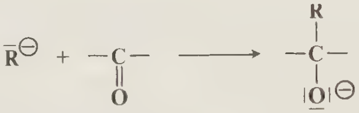
[115] Whitesides, Witanowski, and Roberts, *J. Am. Chem. Soc.* **87**, 2854 (1965); Whitesides and Roberts, *J. Am. Chem. Soc.* **87**, 4878 (1965). Also see Witanowski and Roberts, *J. Am. Chem. Soc.* **88**, 737 (1966); Fraenkel and Dix, *J. Am. Chem. Soc.* **88**, 979 (1966); Fraenkel, Dix, and Carlson, *Tetrahedron Lett.* 579 (1968); Fraenkel, Cottrell, and Dix, *J. Am. Chem. Soc.* **93**, 1704 (1971); Pechhold, Adams, and Fraenkel, *J. Org. Chem.* **36**, 1368 (1971); Maercker and Geuss, *Angew. Chem. Int. Ed. Engl.* **10**, 270 (1971) [*Angew. Chem.* **83**, 288].



Carbanions may also form a bond with a carbon which already has four bonds, by pushing out one of the four groups (SN2 reaction, see Chapter 10):



Like carbonium ions, carbanions may also react in ways in which they are converted to species which are still not neutral molecules. They may add to double bonds (usually C=O double bonds; see Chapters 10 and 16),



$$\bar{R}^{\ominus} + -\underset{\underset{O}{\|}}{C}- \longrightarrow -\overset{\overset{R}{|}}{\underset{\underset{|\underline{O}|^{\ominus}}{|}}{C}}-$$

or rearrange, though this is rare (see Chapter 18),

$$Ph_3C\bar{C}H_2^{\ominus} \longrightarrow Ph_2\overset{\ominus}{\bar{C}}CH_2Ph$$

or be oxidized to free radicals.

Organometallic compounds which are not ionic but polar-covalent behave very much as if they were ionic and give similar reactions.

FREE RADICALS

Stability and Structure[116]

A free radical may be defined as a species which contains one or more unpaired electrons. Note that this definition includes certain stable inorganic molecules such as NO and NO_2, as well as many individual atoms, such as Na and Cl. Associated with the spin of an electron is a magnetic moment, which can be expressed by a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$. According to the Pauli principle, any two electrons occupying the same orbital must have opposite spins, so that the total magnetic moment is zero for any species in which all the electrons are paired. In free radicals, however, one or more electrons are unpaired, so that there is a net magnetic moment and the species is paramagnetic. Free radicals can therefore be detected by magnetic-susceptibility measurements, but for this technique a relatively high concentration of free radicals is required. A much more important technique is *electron spin resonance* (esr), also called *electron paramagnetic resonance* (epr).[117] The principle of esr is similar to that of nmr, except that electron spin is involved rather than nuclear spin. Like protons, electrons have two possible spin states when placed within a strong magnetic field; and as in nmr, a strong external field is applied, and electrons are caused to flip from the lower state to the higher by the application of the appropriate radio-frequency signal. Inasmuch as two electrons paired in one orbital must have opposite spins which cancel, an esr spectrum arises only from species which have one or more unpaired electrons, i.e., free radicals.

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[116] For monographs, see Nonhebel and Walton, "Free-Radical Chemistry," Cambridge University Press, London, 1974; Kochi, "Free Radicals," John Wiley & Sons, Inc., New York, 1973; Hay, "Reactive Free Radicals," Academic Press, Inc., New York, 1974; and Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1966. For reviews, see Griller and Ingold, *Acc. Chem. Res.* **9**, 13–19 (1976); Huyser, in McManus, Ref. 1, pp. 1–59; Isaacs, Ref. 1, pp. 294–374; and Beckwith, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **10**, 1–47 (1973).

[117] For monographs, see Wertz and Bolton, "Electron Spin Resonance," McGraw-Hill Book Company, New York, 1972; Assenheim, "Introduction to Electron Spin Resonance," Plenum Press, New York, 1967; and Bersohn and Baird, "An Introduction to Electron Paramagnetic Resonance," W. A. Benjamin, Inc., New York, 1966. For reviews, see Russell, in Nachod and Zuckerman, "Determination of Organic Structures by Physical Methods," vol. 3, pp. 293–341, Academic Press, Inc., New York, 1971; Rassat, *Pure Appl. Chem.* **25**, 623–634 (1971); Kevan, *Methods Free-Radical Chem.* **1**, 1–33 (1969); Geske, *Prog. Phys. Org. Chem.* **4**, 125–211 (1967); Norman and Gilbert, *Adv. Phys. Org. Chem.* **5**, 53 119 (1967); Schneider, Möbius, and Plato, *Angew. Chem. Int. Ed. Engl.* **4**, 856–867 (1965) [*Angew. Chem.* **77**, 888–900]; Carrington, *Q. Rev., Chem. Soc.* **17**, 67–99 (1963); Symons, *Adv. Phys. Org. Chem.* **1**, 284–363 (1963). For a review on the application of esr to photochemistry, see Wan, *Adv. Photochem.* **9**, 1–145 (1974).

Since only free radicals give an esr spectrum, the method can be used to detect the presence of free radicals, and determine their concentration. The method is very sensitive (much more sensitive than nmr), and concentrations as low as 10^{-7} *M* can be detected. Furthermore, information concerning the electron distribution (and hence the structure) of free radicals can be obtained from the splitting pattern of the esr spectrum (esr peaks are split by nearby protons).[118] Fortunately (for the existence of most free radicals is very short), it is not necessary for a radical to have a long lifetime in order for an esr spectrum to be obtained. Esr spectra have been observed for radicals with lifetimes considerably less than 1 sec.[119] Because there is an equal probability that a given unpaired electron will have a quantum number of $+\frac{1}{2}$ or $-\frac{1}{2}$, free radicals cause two lines to appear on an electronic spectrum, and are often referred to as *doublets*.

As with carbonium ions and carbanions, simple alkyl radicals are very reactive. In solution their lifetimes are extremely short, but they can be kept for relatively long periods frozen within the crystal lattices of other molecules,[120] and many esr and other spectral[121] measurements have been made on radicals trapped in this manner. Even under these conditions the methyl radical decomposes with a half-life of 10 to 15 min in a methanol lattice at 77 K.[122]

Another magnetic technique for the detection of free radicals uses an ordinary nmr instrument. It was discovered[123] that if an nmr spectrum is taken during the course of a reaction, certain signals may be enhanced, either in a positive or negative direction; others may be reduced. When this type of behavior, called *chemically induced dynamic nuclear polarization*[124] (CIDNP), is found in the product of a reaction, it means that *at least a portion of that product was formed via the intermediacy of a free radical*. For example, the question was raised whether free radicals were intermediates in the exchange reaction between ethyl iodide and ethyllithium (reaction **2-38**)

$$\mathbf{EtI + EtLi \rightleftharpoons EtLi + EtI}$$

Curve *a* in Figure 1[125] shows an nmr spectrum taken during the course of the reaction. Curve *b* is a reference spectrum of ethyl iodide (CH_3 protons at $\tau = 8.15$; CH_2 protons at $\tau = 6.8$). Note that in curve *a* some of the ethyl iodide signals are enhanced; others go below the base line (*negative enhancement*; also called *emission*). Thus the ethyl iodide formed in the exchange shows CIDNP and hence was formed via a free-radical intermediate. CIDNP results when protons in a reacting molecule become dynamically coupled to an unpaired electron while traversing the path

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[118] For a review of the use of esr spectra to determine structures, see Kochi, *Adv. Free-Radical Chem.* **5**, 189–317 (1975). For esr spectra of a large number of free radicals, see Bielski and Gebicki, "Atlas of Electron Spin Resonance Spectra," Academic Press, Inc., New York, 1967.

[119] For example, see Kochi and Krusic, *J. Am. Chem. Soc.* **91**, 3940 (1969).

[120] For a review, see Mile, *Angew. Chem. Int. Ed. Engl.* **7**, 507–519 (1968) [*Angew. Chem.* **80**, 519–531].

[121] For a review of infrared spectra of radicals trapped in matrices, see Andrews, *Annu. Rev. Phys. Chem.* **22**, 109–132 (1971).

[122] Sullivan and Koski, *J. Am. Chem. Soc.* **85**, 384 (1963).

[123] Ward and Lawler, *J. Am. Chem. Soc.* **89**, 5518 (1967); Lawler, *J. Am. Chem. Soc.* **89**, 5519 (1967); Ward, Lawler, and Cooper, *J. Am. Chem. Soc.* **91**, 746 (1969); Bargon, Fischer, and Johnsen, *Z. Naturforsch., Teil A* **22**, 1551 (1967); Bargon and Fischer, *Z. Naturforsch., Teil A* **22**, 1556 (1967); Lepley, *J. Am. Chem. Soc.* **90**, 2710 (1968), **91**, 749 (1969); Lepley and Landau, *J. Am. Chem. Soc.* **91**, 748 (1969).

[124] For a monograph on CIDNP, see Lepley and Closs, "Chemically Induced Magnetic Polarization," John Wiley & Sons, Inc., New York, 1973. For reviews, see Lawler and Ward, in Nachod and Zimmerman, "Determination of Organic Structures by Physical Methods," vol. 5, pp. 99–150, Academic Press, Inc., New York, 1973; Ward, *Acc. Chem. Res.* **5**, 18–24 (1972); Lawler, *Acc. Chem. Res.* **5**, 25–32 (1972); Kaptein, *Adv. Free-Radical Chem.* **5**, 319–380 (1975); Bethell and Brinkman, *Adv. Phys. Org. Chem.* **10**, 53–128 (1973).

[125] Ward, Lawler, and Cooper, Ref. 123.

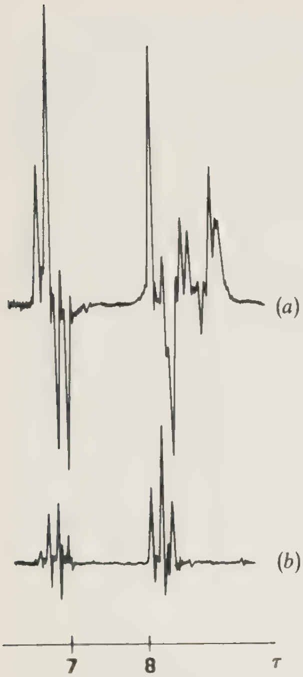

Figure 1[125] (*a*) Nmr spectrum taken during reaction between EtI and EtLi in benzene (the region between 6.5 and 7.5 τ was scanned with an amplitude twice that of the remainder of the spectrum). The signals at 8.4 to 9.0 τ are due to butane, some of which is also formed in the reaction. (*b*) Reference spectrum of EtI.

from reactants to products.[126] Although the presence of CIDNP always means that a free radical is involved, its absence does not prove that a free-radical intermediate is necessarily absent, since reactions involving free-radical intermediates can also take place without observable CIDNP. Also, the presence of CIDNP does not prove that *all* of a product was formed via a free-radical intermediate, only that some of it was.

Simple alkyl radicals have also been detected in the gas phase, and indeed this was the first proof of their existence. In a typical experiment tetramethyllead vapor in a stream of inert gas was passed through a glass tube which was heated at one spot. At that spot a lead mirror was deposited, and ethane was found in the condensate. When another organometallic compound, say, trimethylbismuth, was passed through the tube, which was heated at a spot ahead of the lead deposit, a new deposit (of bismuth) appeared at the freshly heated spot and the old mirror disappeared, though neither the carrier gas nor the ethane product could remove the mirror. Although at this point trimethylbismuth was being passed through the tube, tetramethyllead was found in the condensate. The rate of disappearance of the mirror increased with increased distance between the original deposit and the new position of heating. All this and other evidence may be taken as proof of the existence of alkyl radicals,[127] which stabilized themselves by dimerization unless a metallic surface was available for reaction to give an organometallic compound.

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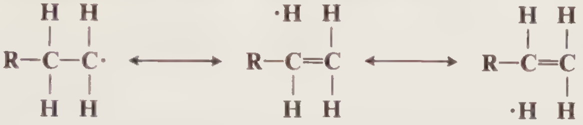
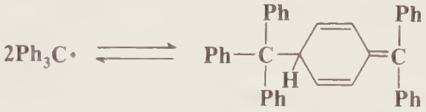
[126] Information about the nature of the free radicals involved can also be derived from CIDNP spectra: see Kaptein, *Chem. Commun.* 732 (1971).

As with carbonium ions, the stability order of free radicals is tertiary > secondary > primary, explainable by hyperconjugation, analogous to that in carbonium ions (p. 153):

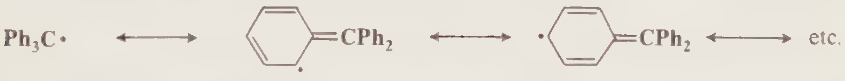


With resonance possibilities, the stability of free radicals increases, and some may be kept indefinitely.[128] Benzylic and allylic radicals for which canonical forms can be drawn similar to those shown for the corresponding cations (pp. 154, 155) and anions (pp. 161, 162) are more stable than simple alkyl radicals but still have only a transient existence. However, the triphenylmethyl and similar radicals[129] are stable enough to exist in solution at room temperature, though in equilibrium with a dimeric form. The concentration of triphenylmethyl radical in benzene solution



27

is about 2% at room temperature. For many years it had been assumed that $Ph_3C\cdot$, the first stable free radical known,[130] dimerized to hexaphenylethane ($Ph_3C{-}CPh_3$), but uv and nmr investigation has shown that the true structure is **27**.[131] Although triphenylmethyl-type radicals are stabilized by resonance:



it is steric hindrance to dimerization and not resonance that is the major cause of their stability. This fact was demonstrated by the preparation of the radicals **28** and **29**.[132] These radicals are electronically very similar, but **28**, being planar, has much less steric hindrance to dimerization than $Ph_3C\cdot$, while **29**, with six groups in ortho positions, has much more. On the other hand, the planarity of **28** means that it has a maximum amount of resonance stabilization, while **29** must

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[127] Paneth and Hofeditz, *Ber.* **62,** 1335 (1929).

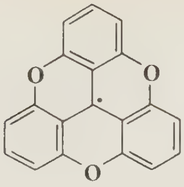
[128] For a monograph on stable free radicals, including those in which the unpaired electron is not on a carbon atom, see Forrester, Hay, and Thomson, "Organic Chemistry of Stable Free Radicals," Academic Press, Inc., New York, 1968.

[129] For a review, see Sholle and Rozantsev, *Russ. Chem. Rev.* **42,** 1011–1020 (1973).

[130] Gomberg, *J. Am. Chem. Soc.* **22,** 757 (1900), *Ber.* **33,** 3150 (1900).

[131] Lankamp, Nauta, and MacLean, *Tetrahedron Lett.* 249 (1968); Staab, Brettschneider, and Brunner, *Chem. Ber.* **103,** 1101 (1970); Volz, Lotsch, and Schnell, *Tetrahedron* **26,** 5343 (1970); McBride, *Tetrahedron* **30,** 2009 (1974). See also Guthrie and Weisman, *Chem. Commun.* 1316 (1969); Takeuchi, Nagai, and Tokura, *Bull. Chem. Soc. Jpn.* **44,** 753 (1971).

[132] Sabacky, Johnson, Smith, Gutowsky, and Martin, *J. Am. Chem. Soc.* **89,** 2054 (1967).



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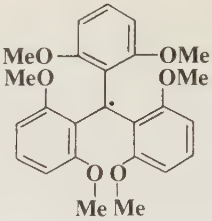

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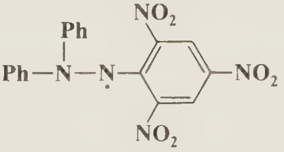
have much less, since its degree of planarity should be even less than $Ph_3C\cdot$, which itself is propeller-shaped and not planar. Thus if resonance is the chief cause of the stability of $Ph_3C\cdot$, **29** should dimerize and **28** should not, but if steric hindrance is the major cause, the reverse should happen. In the event, it was found[132] that **29** gave no evidence of dimerization, even in the solid state, while **28** existed primarily in the dimeric form, which is dissociated to only a small extent in solution,[133] indicating that steric hindrance to dimerization is the major cause for the stability of triarylmethyl free radicals.

Completely chlorinated triarylmethyl free radicals are more stable than the unsubstituted kind, probably for steric reasons, and many are quite inert in solution and in the solid state.[134] Certain radicals with the unpaired electron not on a carbon are also very stable. Diphenylpicrylhydrazyl (**30**) is a solid which can be kept for years, and **31** is so stable that reactions can be performed on it without affecting the unpaired electron.[135]



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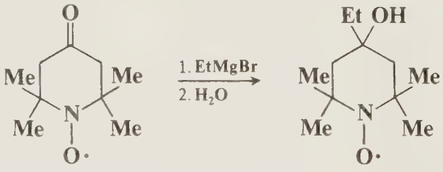

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Dissociation energies (D values) of R—H bonds provide a measure of the relative stability of free radicals R. Table 2 lists such values.[136] The higher the D value, the less stable the radical.

There are two possible structures for simple alkyl radicals. They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding

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[133] Müller, Moosmayer, Rieker, and Scheffler, *Tetrahedron Lett.* 3877 (1967).

[134] Ballester, *Pure Appl. Chem.* **15**, 123 (1967); Ballester, Riera, Castañer, Badía, and Monsó, *J. Am. Chem. Soc.* **93**, 2215 (1971); Ballester, Castañer, and Pujadas, *Tetrahedron Lett.* 1699 (1971).

[135] Neiman, Rozantsev, and Mamedova, *Nature*, **200**, 256 (1963). For a review of such radicals, see Rozantsev and Sholle, *Synthesis* 190–202, 401–414 (1971).

[136] These values are from Kerr, *Chem. Rev.* **66**, 465–500 (1966), except for the value for $CH_2{=}CHCH_2\cdot$, which is from Golden, Gac, and Benson, *J. Am. Chem. Soc.* **91**, 2136 (1969). See also Egger and Cocks, *Helv. Chim. Acta* **56**, 1516, 1537 (1973).

TABLE 2 D_{298} values (see p. 26) for some R—H bonds[136]
Free-radical stability is in the reverse order

R	D, kcal/mol	R	D, kcal/mol	R	D, kcal/mol
$CF_3\cdot$	106	$Me_3CCH_2\cdot$	99.3	Cyclohexyl	94
$CH_3\cdot$	104.0	$C_2H_5\cdot$	98.0	$Me_3C\cdot$	91.0
$C_6H_5\cdot$	104	$CH_3CH_2CH_2\cdot$	98	$CH_2{=}CHCH_2\cdot$	88.4
$CH_2{=}CH\cdot$	104	$CCl_3\cdot$	95.7	$HCO\cdot$	88
Cyclopropyl	101	$Me_2CH\cdot$	94.5	$C_6H_5CH_2\cdot$	85

might be sp^3, which would make the structure pyramidal and place the odd electron in an sp^3 orbital. Esr spectra of $CH_3\cdot$ and other simple alkyl radicals indicate that these radicals have planar structures.[137] This is in accord with the known loss of optical activity when a free radical is generated at an asymmetric carbon.[138] Kinetic evidence obtained from iodine exchange reactions also indicates that simple alkyl radicals are planar.[139] In addition, electronic spectra of the CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase have definitely established that under these conditions the radicals are planar or near-planar,[140] and infrared spectra of $CH_3\cdot$ trapped in solid argon led to a similar conclusion.[141]

Evidence from studies on bridgehead compounds shows that though a planar configuration is more stable, pyramidal structures are not impossible. In contrast to the situation with carbonium ions, free radicals have often been generated at bridgeheads, although studies have shown that bridgehead free radicals are less rapidly formed than the corresponding open-chain radicals.[142] In sum, the available evidence indicates that though simple alkyl free radicals prefer a planar or near-planar shape, the energy difference between a planar and a pyramidal free radical is not great. However, free radicals in which the carbon is connected to atoms of high electronegativity, e.g., $CF_3\cdot$,[143] prefer a pyramidal shape;[144] increasing the electronegativity increases the deviation from planarity.[145]

Free radicals with resonance are definitely planar, though triphenylmethyl-type radicals are propeller-shaped,[146] like the analogous carbonium ions (p. 158).

A number of diradicals are known,[147] either stable or as intermediates. When the unpaired electrons of a diradical are widely separated, e.g., as in $\cdot CH_2CH_2CH_2CH_2\cdot$, the species behaves spectrally like two doublets, but when they are close enough for interaction or can interact through an unsaturated system (as in trimethylenemethane, **32**), they can have total spin numbers of $+1$, 0, or -1, since each electron could be either $+\frac{1}{2}$ or $-\frac{1}{2}$. Spectroscopically they are called *triplets*,[148]

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[137] Cole, Pritchard, Davidson, and McConnell, *Mol. Phys.* **1,** 406 (1958); Fessenden and Schuler, *J. Chem. Phys.* **39,** 2147 (1963); Symons, *Nature* **222,** 1123 (1969), *Tetrahedron Lett.* 207 (1973).

[138] There are a few exceptions. See p. 624.

[139] Benson, Golden, and Egger, *J. Chem. Phys.* **42,** 4265 (1965), **43,** 4189 (1965). However, see Applequist, *J. Chem. Phys.* **43,** 4189 (1965), and Noyes, Applequist, Benson, Golden, and Skell, *J. Chem. Phys.* **46,** 1221 (1967).

[140] Herzberg and Shoosmith, *Can. J. Phys.* **34,** 523 (1956); Herzberg, *Proc. R. Soc. London, Ser. A* **262,** 291 (1961).

[141] Andrews and Pimentel, *J. Chem. Phys.* **47,** 3637 (1967); Milligan and Jacox, *J. Chem. Phys.* **47,** 5146 (1967). See also Tan, Winer, and Pimentel, *J. Chem. Phys.* **57,** 4028 (1972).

[142] Lorand, Chodroff, and Wallace, *J. Am. Chem. Soc.* **90,** 5266 (1968); Fort and Franklin, *J. Am. Chem. Soc.* **90,** 5267 (1968); Humphrey, Hodgson, and Pincock, *Can. J. Chem.* **46,** 3099 (1968); Oberlinner and Rüchardt, *Tetrahedron Lett.* 4685 (1969); Danen, Tipton, and Saunders, *J. Am. Chem. Soc.* **93,** 5186 (1971).

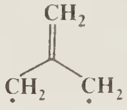
[143] Fessenden and Schuler, *J. Chem. Phys.* **43,** 2704 (1965); Rogers and Kispert, *J. Chem. Phys.* **46,** 3193 (1967).

[144] Pauling, *J. Chem. Phys.* **51,** 2767 (1969).

[145] For example, 1,1-dichloroalkyl radicals are closer to planarity than the corresponding 1,1-difluoro radicals, though still not planar: Chen, Tang, Montgomery, and Kochi, *J. Am. Chem. Soc.* **96,** 2201 (1974). For a discussion, see Krusic and Bingham, *J. Am. Chem. Soc.* **98,** 230 (1976).

[146] Adrian, *J. Chem. Phys.* **28,** 608 (1958); Andersen, *Acta Chem. Scand.* **19,** 629 (1965).

[147] For reviews, see Salem and Rowland, *Angew. Chem. Int. Ed. Engl.* **11,** 92–111 (1972) [*Angew. Chem.* **84,** 86–106]; Salem, *Pure Appl. Chem.* **33,** 317–328 (1973); Jones, *J. Chem. Educ.* **51,** 175–181 (1974); Morozova and Dyatkina, *Russ. Chem. Rev.* **37,** 376–391 (1968).



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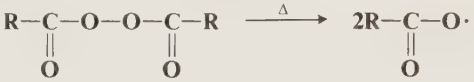
since each of the three possibilities is represented among the molecules and gives rise to its own spectral peak. In triplet *molecules* the two unpaired electrons have the same spin. Radicals with both unpaired electrons on the same carbon are discussed under carbenes (p. 178).

The Generation and Fate of Free Radicals[149]

Free radicals are formed from molecules by breaking a bond so that each fragment keeps one electron.[150] The energy necessary to break the bond is supplied in one of two ways.

1. *Thermal cleavage*. Subjection of any organic molecule to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with D values of 20 to 40 kcal/mol, cleavage can be caused in the liquid phase. Two common examples are cleavage of acyl peroxides and of azo compounds:

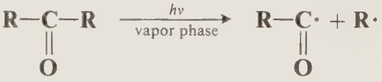


$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R} \xrightarrow{\Delta} 2\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O\cdot}$$

$$\mathrm{R{-}N{=}N{-}R} \xrightarrow{\Delta} 2\mathrm{R\cdot} + \mathrm{N_2}$$

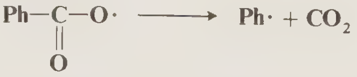
2. *Photochemical cleavage* (see p. 214). The energy of light of 600 to 300 nm is 48 to 96 kcal/mol, which is of the order of magnitude of covalent-bond energies. Typical examples are photochemical cleavage of chlorine and of ketones:

$$\mathrm{Cl_2} \xrightarrow{h\nu} 2\mathrm{Cl\cdot}$$



$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R} \xrightarrow[\text{vapor phase}]{h\nu} \mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}\cdot} + \mathrm{R\cdot}$$

Free radicals are also formed from other free radicals, either by the reaction between a radical and a molecule (which *must* give another radical, since the total number of electrons is odd) or by cleavage of a radical to give another radical, e.g.,



$$\mathrm{Ph{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O\cdot} \longrightarrow \mathrm{Ph\cdot} + \mathrm{CO_2}$$

Free radicals may also be formed by oxidation or reduction, including electrolytic methods.

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[148] For discussions of the triplet state, see Wagner and Hammond, *Adv. Photochem.* **5**, 21-156 (1968); and Turro, *J. Chem. Educ.* **46**, 2-6 (1969).

[149] For a review on formation of free radicals, see Walling, "Free Radicals in Solution," pp. 467-563, John Wiley & Sons, Inc., New York, 1957.

[150] It is also possible for free radicals to be formed by collision of two nonradical species. For a review, see Harmony, *Methods Free-Radical Chem.* **5**, 101-176 (1974).

Reactions of free radicals either give stable products (termination reactions) or lead to other radicals, which themselves must usually react further (propagation reactions). The most common termination reactions are simple combinations of similar or different radicals:

$$\mathrm{R\cdot + R'\cdot \longrightarrow R{-}R'}$$

Another termination process is disproportionation:[151]

$$\mathrm{2CH_3{-}CH_2\cdot \longrightarrow CH_3{-}CH_3 + CH_2{=}CH_2}$$

There are four principal propagation reactions, of which the first two are most common:

1. *Abstraction of another atom or group, usually a hydrogen atom* (see Chapter 14):

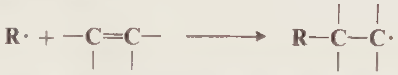
$$\mathrm{R\cdot + R'{-}H \longrightarrow R{-}H + R'\cdot}$$

The hydrogen may also be abstracted from a position which would give the same radical, e.g.,

$$\mathrm{CH_3{-}CH_2{-}CH_2\cdot + CH_3{-}CH_2{-}CH_3 \longrightarrow CH_3{-}CH_2{-}CH_3 + CH_3{-}CH_2{-}CH_2\cdot}$$

This of course leads to no net structural change.[152]

2. *Addition to a multiple bond* (Chapter 15):

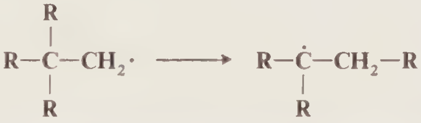


$$\mathrm{R\cdot + {-}\underset{|}{C}{=}\underset{|}{C}{-} \longrightarrow R{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}\cdot}$$

The radical formed here may add to another double bond, etc. This is one of the chief mechanisms for vinyl polymerization.

3. *Decomposition.* This can be illustrated by the decomposition of the benzoxy radical (p. 176).

4. *Rearrangement:*



$$\mathrm{R{-}\overset{R}{\underset{R}{C}}{-}CH_2\cdot \longrightarrow R{-}\underset{R}{\dot{C}}{-}CH_2{-}R}$$

This is less common than rearrangement of carbonium ions, but it does occur (though not when R = alkyl or hydrogen; see Chapter 18).

In addition to these reactions, free radicals may be oxidized to carbonium ions or reduced to carbanions.

Radical Ions[153]

Several types of radical ions are known with the unpaired electron, or the charge, or both on atoms other than carbon. Important examples are semiquinones (**33**) and ketyls (**34**). Only a few radical ions are known where both the unpaired electron and the charge reside on carbon atoms. One

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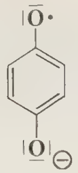
[151] For a review of the competition between disproportion and combination reactions, see Gibian and Corley, *Chem. Rev.* **73**, 441-464 (1973).

[152] For a review of this type of process, see Petukhov, *Russ. Chem. Rev.* **30**, 626-634 (1961).

[153] For a monograph, see Kaiser and Kevan, "Radical Ions," Interscience Publishers, New York, 1968. For reviews, see Russell and Norris, in McManus, Ref. 1, pp. 423-448; Evans and Emes, *MTP Int. Rev. Sci.: Org. Chem. Ser. One*, **10**, 293-319 (1973); Holy and Marcum, *Angew. Chem. Int. Ed. Engl.* **10**, 115-124 (1971) [*Angew. Chem.* **83**, 132-142]; Bilevich and Okhlobystin, *Russ. Chem. Rev.* **37**, 954-968 (1968); Szwarc, *Prog. Phys. Org. Chem.* **6**, 323-438 (1968); McClelland, *Chem. Rev.* **64**, 301-315 (1964).



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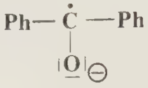

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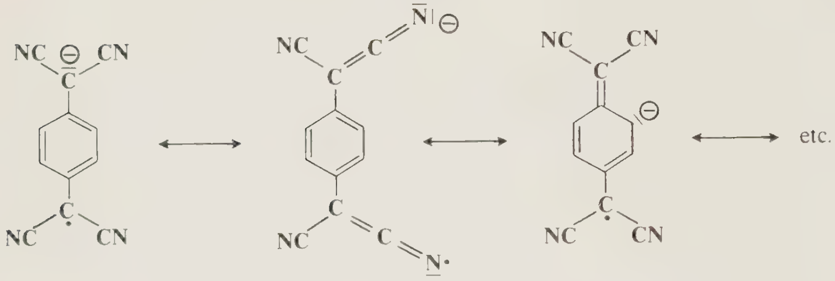

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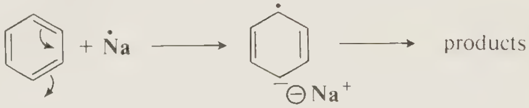
stable example is **35**.[154] Reactions in which alkali metals are reducing agents often involve radical ion intermediates, e.g., reaction **5-13**:



Several types of radical cations are also known.

CARBENES

Stability and Structure[155]

Carbenes are highly reactive species, practically all having lifetimes considerably under 1 sec. Carbenes have been isolated only by entrapment in matrices at low temperatures (77 K or less).[156] The parent species CH_2 is usually called *methylene*, although derivatives are more often named by the carbene nomenclature. Thus CCl_2 is generally known as dichlorocarbene, though it can also be called dichloromethylene.

The two nonbonded electrons of a carbene may be either paired or unpaired. If they are paired, the species is spectrally a *singlet*, while, as we have seen (p. 176), two unpaired electrons appear as a *triplet*. An ingenious method of distinguishing between the two possibilities was developed by Skell,[157] based on the common reaction of addition of carbenes to double bonds to form cyclopropane derivatives (reaction **5-53**). If the singlet species adds to *cis*-2-butene, the resulting

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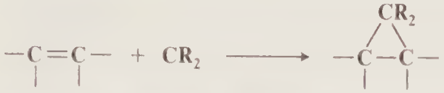
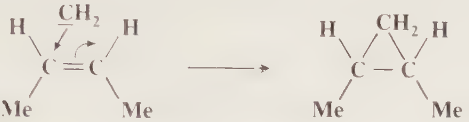
[154] Melby, Harder, Hertler, Mahler, Benson, and Mochel, *J. Am. Chem. Soc.* **84**, 3374 (1962).

[155] For monographs, see Jones and Moss, "Carbenes," 2 vols., John Wiley & Sons, Inc., New York, 1973–1975; Kirmse, "Carbene Chemistry," 2d ed., Academic Press, Inc., New York, 1971; Rees and Gilchrist, "Carbenes, Nitrenes, and Arynes," Nelson, London, 1969; and Hine, "Divalent Carbon," The Ronald Press Company, New York, 1964. For reviews, see Isaacs, Ref. 1, pp. 375–407; Bethell, *Adv. Phys. Org. Chem.* **7**, 153–209 (1969); Bethell, in McManus, Ref. 1, pp. 61–126; Closs, *Top. Stereochem.* **3**, 193–235 (1968); Herold and Gaspar, *Fortschr. Chem. Forsch.* **5**, 89–146 (1966); Rozantsev, Fainzil'berg, and Novikov, *Russ. Chem. Rev.* **34**, 69–88 (1965); Schreck, *J. Chem. Educ.* **42**, 260 (1965); Kirmse, *Prog. Org. Chem.* **6**, 164–213 (1964); and Chinoporos, *Chem. Rev.* **63**, 235–255 (1963).

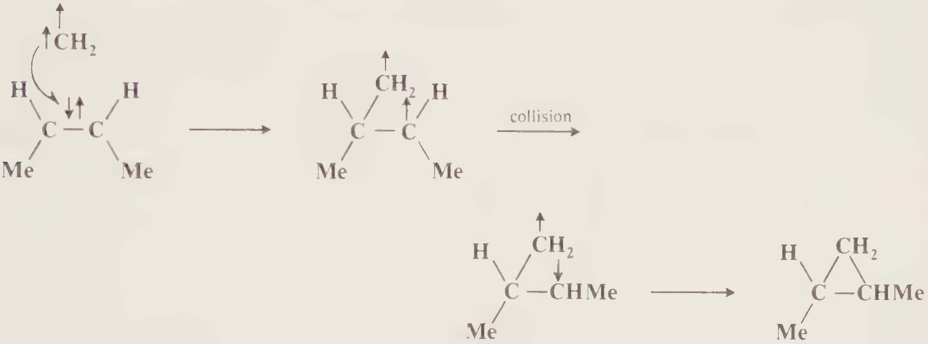
[156] For example, see Murray, Trozzolo, Wasserman, and Yager, *J. Am. Chem. Soc.* **84**, 3213 (1962); Brandon, Closs, and Hutchison, *J. Chem. Phys.* **37**, 1878 (1962); Milligan, Mann, Jacox, and Mitsch, *J. Chem. Phys.* **41**, 1199 (1964); Trozzolo and Gibbons, *J. Am. Chem. Soc.* **89**, 239 (1967); Trozzolo, *Acc. Chem. Res.* **1**, 329–335 (1968); and Nefedov, Maltsev, and Mikaelyan, *Tetrahedron Lett.* 4125 (1971).



cyclopropane should be the cis isomer since the movements of the two pairs of electrons should occur either simultaneously or with one succeeding another rapidly. However, if the attack is by



a triplet species, the two unpaired electrons cannot *both* go into a new covalent bond, since by Hund's rule they have parallel spins. So one of the unpaired electrons will form a bond with the electron from the double bond which has the opposite spin, leaving two unpaired electrons which



cannot form a bond at once but must wait until, by some collision process, one of the electrons can reverse its spin. During this time, there is free rotation, and a mixture of *cis*- and *trans*-1,2-dimethylcyclopropanes should result.[158]

The results of this type of experiment show that CH_2 itself is usually formed as a singlet species, which can decay to the triplet state, which consequently has a lower energy (molecular-orbital calculations show that the difference in energy between singlet and triplet CH_2 is about 11 kcal mol[159]). However, it is possible to prepare triplet CH_2 directly, by a photosensitized decomposition of diazomethane.[160] CH_2 is so reactive that it generally reacts as the singlet before it has a chance to decay to the triplet state. As to other carbenes, some react as triplets, some as singlets, and others as singlets or triplets, depending on how they are generated. For gaseous reactions it is possible to increase the amount of carbene which reacts as the triplet by generating the carbene in the presence of an inert gas, since collisions with these molecules cause singlet carbenes to decay to the triplet state.[161]

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[157] Skell and Woodworth, *J. Am. Chem. Soc.* **78,** 4496 (1956).

[158] These conclusions are generally accepted though the reasoning given here may be oversimplified. For discussions, see Closs, Ref. 155, pp. 203–210; Bethell, *Adv. Phys. Org. Chem.*, Ref. 155, pp. 194 200; and Hoffmann, *J. Am. Chem. Soc.* **90,** 1475 (1968).

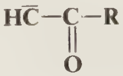
[159] Bender, Schaefer, Franceschetti, and Allen, *J. Am. Chem. Soc.* **94,** 6888 (1972); Hay, Hunt, and Goddard, *Chem. Phys. Lett.* **13,** 30 (1972); Dewar, Haddon, and Weiner, *J. Am. Chem. Soc.* **96,** 253 (1974). See also Frey, *J. Chem. Soc., Chem. Commun.* 1024 (1972); Frey and Kennedy, *J. Chem. Soc., Chem. Commun.* 233 (1975).

[160] Kopecky, Hammond, and Leermakers, *J. Am. Chem. Soc.* **83,** 2397 (1961), **84,** 1015 (1962); Duncan and Cvetanović, *J. Am. Chem. Soc.* **84,** 3593 (1962).

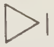
There is a limitation to the use of stereospecificity of addition as a diagnostic test for singlet or triplet carbenes. When carbenes are generated by photolytic methods, they are often in a highly excited singlet state. When they add to the double bond, the addition is stereospecific; but the cyclopropane formed carries excess energy; i.e., it is in an excited state. It has been shown that under certain conditions (low pressures in the gas phase) the excited cyclopropane may undergo cis-trans isomerization *after* it is formed, so that triplet carbene may seem to be involved although in reality the singlet was present.[162]

The most common carbenes are CH_2 and CCl_2,[163] but many others have been reported, e.g.,[164]

$\cdot\dot{C}Ph_2$ $\qquad$ $R_2C{=}C{=}\overline{C}$

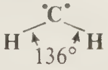


$H\overline{C}-\underset{\underset{O}{\|}}{C}-R$

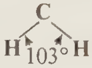


Studies of the infrared spectrum of CCl_2 trapped at low temperatures in solid argon indicate that the ground state for this species is the singlet.[165] A dicarbene, $\overline{C}{=}C{=}\overline{C}$, is the major constituent of carbon vapor.[166]

The geometrical structure of triplet methylene can be investigated by esr measurements, since triplet species are diradicals. Such measurements made on triplet CH_2 trapped in matrices at very low temperatures (4 K) show that triplet CH_2 is a bent molecule, with an angle of about 136°.[167] Epr measurements cannot be made on singlet species, but from electronic spectra of CH_2 formed in flash photolysis of diazomethane it was concluded that singlet CH_2 is also bent, with an angle of about 103°.[168] It had previously been thought that electronic spectra showed



Triplet
methylene



Singlet
methylene

triplet CH_2 to be linear, but a reinterpretation of the spectra indicates that they are compatible with a bent structure.[169] Theoretical treatments also predict that triplet CH_2 should have an angle of about 136°.[170] Singlet CCl_2[165] and CBr_2[171] are also bent, with angles of about 100 and 114°, respectively. It had long been known that triplet aryl carbenes are bent. In one particularly convincing experiment, two conformations each of 1- and 2-naphthylcarbene were detected by esr.[172] If the Ar—C—H bond were linear, only one conformation could exist.

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[161] See Frey, *J. Am. Chem. Soc.* **82,** 5947 (1960); Braun, Bass, and Pilling, *J. Chem. Phys.* **52,** 5131 (1970).

[162] Rabinovitch, Tschuikow-Roux, and Schlag, *J. Am. Chem. Soc.* **81,** 1081 (1959); Frey, *Proc. R. Soc. London, Ser. A* **251,** 575 (1959).

[163] For reviews concerning CH_2, see Bell, *Prog. Phys. Org. Chem.* **2,** 1–61 (1964), and DeMore and Benson, *Adv. Photochem.* **2,** 219–261 (1964). For reviews of halocarbenes, see Margrave, Sharp, and Wilson, *Fort. Chem. Forsch.* **26,** 1–35 (1972), pp. 3–13, and Parham and Schweizer, *Org. React.* **13,** 55–90 (1963).

[164] For a review of carbalkoxycarbenes, see Marchand and Brockway, *Chem. Rev.* **74,** 431–469 (1974).

[165] Andrews, *J. Chem. Phys.* **48,** 979 (1968).

[166] Skell and Wescott, *J. Am. Chem. Soc.* **85,** 1023 (1963).

[167] Wasserman, Kuck, Hutton, and Yager, *J. Am. Chem. Soc.* **92,** 7491 (1970); Wasserman, Yager, and Kuck, *Chem. Phys. Lett.* **7,** 409 (1970); Wasserman, Kuck, Hutton, Anderson, and Yager, *J. Chem. Phys.* **54,** 4120 (1971); Bernheim, Bernard, Wang, Wood, and Skell, *J. Chem. Phys.* **53,** 1280 (1970), **54,** 3223 (1971).

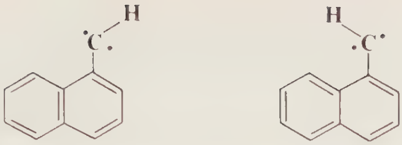
[168] Herzberg and Shoosmith, *Nature* **183,** 1801 (1959); Herzberg, *Proc. R. Soc. London, Ser. A* **262,** 291 (1961); Herzberg and Johns, *Proc. R. Soc. London, Ser. A* **295,** 107 (1967).

[169] Herzberg and Johns, *J. Chem. Phys.* **54,** 2276 (1971).

[170] Harrison and Allen, *J. Am. Chem. Soc.* **91,** 807 (1969); Harrison, *J. Am. Chem. Soc.* **93,** 4112 (1971), *Acc. Chem. Res.* **7,** 378 384 (1974); Bender and Schaefer, *J. Am. Chem. Soc.* **92,** 4984 (1970).

[171] Ivey, Schulze, Leggett, and Kohl, *J. Chem. Phys.* **60,** 3174 (1974).

[172] Trozzolo, Wasserman, and Yager, *J. Am. Chem. Soc.* **87,** 129 (1965). Also see Wasserman, Trozzolo, Yager, and Murray, *J. Chem. Phys.* **40,** 2408 (1964).



The intermediate **36** has been proposed in the photolysis of diethyl mercurybisdiazoacetate. This intermediate, which would be a *carbyne*, was trapped by reaction with cyclohexene.[173]

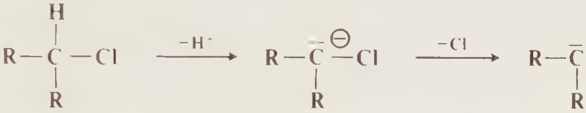
$$\mathrm{Hg(N_2CCOOEt)_2} \xrightarrow{h\nu} 2\cdot\bar{\mathrm{C}}\mathrm{-COOEt} + \mathrm{Hg} + 2\mathrm{N_2}$$

36

The Generation and Fate of Carbenes[174]

Carbenes are chiefly formed in two ways, though other pathways are also known.

1. In α elimination a carbon loses a group without its electron pair, usually a proton, and then a group with its pair, usually a halide ion:[175]

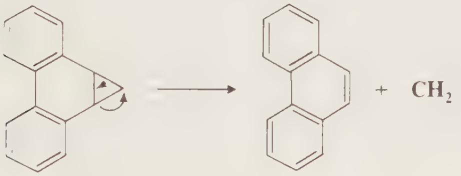


$$\mathrm{R{-}\underset{R}{\overset{H}{C}}{-}Cl} \xrightarrow{-\mathrm{H}^+} \mathrm{R{-}\underset{R}{\overset{\ominus}{\bar{C}}}{-}Cl} \xrightarrow{-\mathrm{Cl}^-} \mathrm{R{-}\underset{R}{\bar{C}}}$$

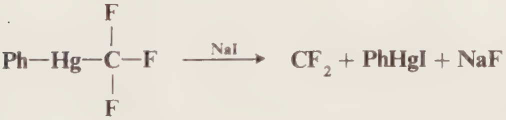
The most common example of this is formation of dichlorocarbene by treatment of chloroform with a base (see reaction **0-3**), but many other examples are known, a few of which are

$$\mathrm{CCl_3{-}COO^-} \xrightarrow{\Delta} \mathrm{CCl_2} + \mathrm{CO_2} + \mathrm{Cl^-} \qquad \text{Ref. 176}$$

$$\mathrm{Ph{-}\underset{Li}{CH}{-}OPh} \longrightarrow \mathrm{PhCH} + \mathrm{PhOLi} \qquad \text{Ref. 177}$$



+ CH_2 Ref. 178



$$\mathrm{Ph{-}Hg{-}\underset{F}{\overset{F}{C}}{-}F} \xrightarrow{\mathrm{NaI}} \mathrm{CF_2} + \mathrm{PhHgI} + \mathrm{NaF} \qquad \text{Ref. 179}$$

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[173] DoMinh, Gunning, and Strausz, *J. Am. Chem. Soc.* **89**, 6785 (1967); Strausz, DoMinh, and Font, *J. Am. Chem. Soc.* **90**, 1930 (1968); Strausz, Kennepohl, Garneau, DoMinh, Kim, Valenty, and Skell, *J. Am. Chem. Soc.* **96**, 5723 (1974). A solid tantalum carbyne complex has been prepared: Guggenberger and Schrock, *J. Am. Chem. Soc.* **97**, 2935 (1975).

[174] For reviews, see Jones, *Acc. Chem. Res.* **7**, 415–421 (1974); Kirmse, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 373–415, Elsevier, New York, 1973; and Ref. 155.

[175] For a review of formation of carbenes in this manner, see Kirmse, *Angew. Chem. Int. Ed. Engl.* **4**, 1–10 (1965) [*Angew. Chem.* **77**, 1–10].

[176] Wagner, *Proc. Chem. Soc.* 229 (1959).

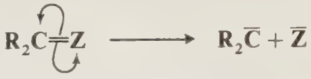
[177] Schöllkopf and Eistert, *Justus Liebigs Ann. Chem.* **664**, 76 (1963).

[178] Richardson, Durrett, Martin, Putnam, Slaymaker, and Dvoretzky, *J. Am. Chem. Soc.* **87**, 2763 (1965). For reviews of this type of reaction, see Hoffmann, *Angew. Chem. Int. Ed. Engl.* **10**, 529–537 (1971) [*Angew. Chem.* **83**, 595–603]; Griffin, *Angew. Chem. Int. Ed. Engl.* **10**, 537–547 (1971) [*Angew. Chem.* **83**, 604–613].

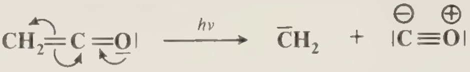
[179] Seyferth, Hopper, and Darragh, *J. Am. Chem. Soc.* **91**, 6536 (1969); Seyferth, *Acc. Chem. Res.* **5**, 65–74 (1972).

Though in most cases of α elimination the positive group is lost first, it is also possible for the negative group to be lost first[180] and for the two to be lost simultaneously.

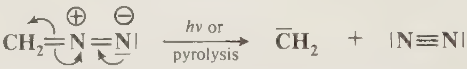
2. Disintegration of compounds containing certain types of double bonds.



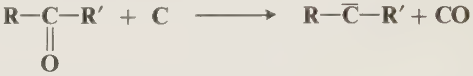
The two most important ways of forming CH_2 are examples: the photolysis of ketene



and the isoelectronic decomposition of diazomethane

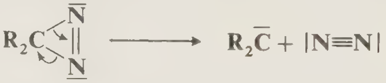


Another example is the treatment of aldehydes and ketones with carbon atoms under high vacuum at −196°C, in a reaction known as deoxygenation:[181]



$$R{-}\underset{\underset{O}{\|}}{C}{-}R' + C \longrightarrow R{-}\overline{C}{-}R' + CO$$

Diazirines (isomeric with diazoalkanes) also give carbenes:[182]

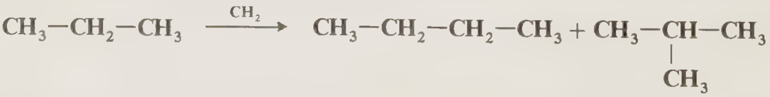


Because carbenes are so reactive, it is often difficult to prove that they are actually present in a given reaction. In many instances where a carbene is *apparently* produced by an α elimination or by disintegration of a double-bond compound there is evidence that no free carbene is actually involved. The neutral term *carbenoid* is used where it is known that a free carbene is not present or in cases where there is doubt. α-Halo organometallic compounds R_2CXM are often called carbenoids because they readily give α-elimination reactions (for example, see p. 568).

The reactions of carbenes are more varied than those of the species previously discussed in this chapter.

1. Additions to carbon-carbon double bonds have already been mentioned. Carbenes also add to aromatic systems, but the immediate products rearrange, usually with ring enlargement (see reaction **5-53**). Additions of carbenes to other double bonds, such as C=N (reactions **6-65** to **6-67**), and to triple bonds have also been reported.

2. An unusual reaction of carbenes is that of insertion into C—H bonds (reaction **2-18**). Thus CH_2 reacts with methane to give ethane and with propane to give *n*-butane and isobutane. This



$$CH_3{-}CH_2{-}CH_3 \xrightarrow{CH_2} CH_3{-}CH_2{-}CH_2{-}CH_3 + CH_3{-}\underset{\underset{CH_3}{|}}{CH}{-}CH_3$$

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[180] For example, see Olofson, Walinsky, Marino, and Jernow, *J. Am. Chem. Soc.* **90,** 6554 (1968).

[181] Skell and Plonka, *J. Am. Chem. Soc.* **92,** 836, 2160 (1970); Plonka and Skell, *Tetrahedron Lett.* 4557 (1970).

[182] Frey and Stevens, *Proc. Chem. Soc.* 79 (1962); Schmitz, Habisch, and Stark, *Angew. Chem. Int. Ed. Engl.* **2,** 548 (1963) [*Angew. Chem.* **75,** 723]; for a review, see Frey, *Adv. Photochem.* **4,** 225–256 (1966).

reaction is virtually useless for synthetic purposes but illustrates the extreme reactivity of carbene. Treatment in the liquid phase of an alkane such as pentane with carbene formed from the photolysis of diazomethane gives the three possible products in statistical ratios[183] demonstrating that carbene is displaying no selectivity. It is a general principle that the lower the selectivity, the higher the reactivity. Singlet CH_2 generated by photolysis of diazomethane is probably the most reactive organic species known, but triplet CH_2 is somewhat less reactive, and other carbenes are still less reactive. The following series of carbenes of decreasing reactivity has been proposed on the basis of discrimination between insertion and addition reactions: $CH_2 > HCCOOR > PhCH > BrCH \approx ClCH$.[184] Dihalocarbenes generally do not give insertion reactions at all. Insertion of carbenes into other bonds has also been demonstrated, though not insertion into C—C bonds.[185]

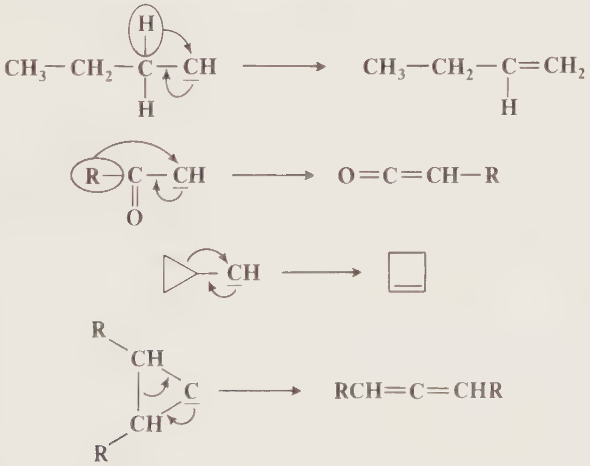
3. It would seem that dimerization should be an important reaction of carbenes

$$R_2\bar{C} + R_2\bar{C} \longrightarrow R_2C{=}CR_2$$

but it is not, because the reactivity is so great that the carbene species do not have time to find each other and because the dimer generally has so much energy that it dissociates again. Apparent dimerizations have been observed, but it is likely that the products in many reported instances of "dimerization" do not arise from an actual dimerization of two carbenes but from attack by a carbene on a molecule of carbene precurser, e.g.,

$$R_2\bar{C} + R_2CN_2 \longrightarrow R_2C{=}CR_2 + N_2$$

4. Alkylcarbenes can undergo rearrangement, with migration of alkyl or hydrogen. Indeed these rearrangements are generally so rapid that additions to multiple bonds and insertion reactions, which are so common for CH_2, are seldom encountered with alkyl or dialkyl carbenes. Unlike rearrangement of the species previously encountered in this chapter, most rearrangements of carbenes directly give stable molecules. Some examples are[186]



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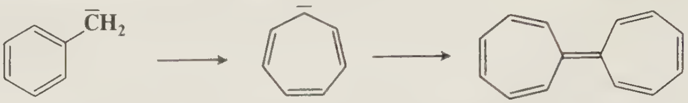
[183] Doering, Buttery, Laughlin, and Chaudhuri, *J. Am. Chem. Soc.* **78**, 3224 (1956); Richardson, Simmons, and Dvoretzky, *J. Am. Chem. Soc.* **83**, 1934 (1961); Halberstadt and McNesby, *J. Am. Chem. Soc.* **89**, 3417 (1967).

[184] Closs and Coyle, *J. Am. Chem. Soc.* **87**, 4270 (1965).

[185] For example, see Doering, Knox, and Jones, *J. Org. Chem.* **24**, 136 (1959); Franzen, *Justus Liebigs Ann. Chem.* **627**, 22 (1959); Bradley and Ledwith, *J. Chem. Soc.* 1495 (1961); Frey and Voisey, *Chem. Commun.* 454 (1966); Seyferth, Damrauer, Mui, and Jula, *J. Am. Chem. Soc.* **90**, 2944 (1968).

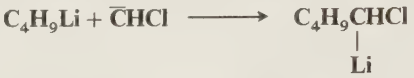
[186] Kirmse and Doering, *Tetrahedron* **11**, 266 (1960); Friedman and Berger, *J. Am. Chem. Soc.* **83**, 492, 500 (1961); Friedman and Shechter, *J. Am. Chem. Soc.* **82**, 1002 (1960); Moore and Ward, *J. Org. Chem.* **27**, 4179 (1962).

The rearrangement of acylcarbenes to ketenes is called the Wolff rearrangement (reaction **8-9**).[187] A few rearrangements in which carbenes rearrange to other carbenes are also known.[188] These are mostly rearrangements of arylcarbenes to ring-expanded aromatic carbenes, e.g.,



Of course, the new carbene must stabilize itself in one of the ways we have mentioned; in the above example it dimerized.

Carbenes may react with a Lewis base such as a carbanion[189] or even butyllithium:[190]



$$\mathrm{C_4H_9Li + \overline{C}HCl \longrightarrow \underset{\displaystyle Li}{C_4H_9\underset{|}{C}HCl}}$$

Carbenes, both triplet (which would be expected because they are free radicals) and singlet,[191] can abstract hydrogen or other atoms to give free radicals:

$$\mathrm{CH_2 + CH_3CH_3 \longrightarrow CH_3\cdot + CH_3CH_2\cdot}$$

A number of other possible carbene reactions are known but are less important.

NITRENES

Nitrenes,[192] R—N, are the nitrogen analogs of carbenes, and most of what we have said about carbenes also applies to them. Nitrenes are too reactive for isolation under ordinary conditions. Alkyl nitrenes have been isolated by trapping in matrices at 4 K,[193] while aryl nitrenes, which are less reactive, can be trapped at 77 K.[194] The ground state of NH, and probably of most

$$\underset{\text{Singlet}}{\mathrm{R{-}\overline{\underline{N}}}} \qquad \underset{\text{Triplet}}{\mathrm{R{-}\overline{\underset{\bullet}{N}}\cdot}}$$

nitrenes, is a triplet, though nitrenes can be generated in both triplet and singlet states. In additions of EtOOC—N to C=C double bonds two species are involved, one of which adds stereospecifically and the other not. By analogy with Skell's proposal involving carbenes (p. 179) these are taken to be the singlet and triplet species, respectively.[195]

The two principal means of generating nitrenes are analogous to those used to form carbenes.

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[187] For a review of carbene rearrangements, see Kirmse, "Carbene Chemistry," Ref. 155, pp. 457–496.

[188] Vander Stouw, Kraska, and Shechter, *J. Am. Chem. Soc.* **94,** 1655 (1972); Jones, Joines, Meyers, Mitsuhashi, Krajca, Waali, Davis, and Turner, *J. Am. Chem. Soc.* **95,** 826 (1973); Coburn and Jones, *J. Am. Chem. Soc.* **96,** 5218 (1974); Wentrup, *Tetrahedron* **30,** 1301 (1974).

[189] Krapcho, Huyffer, and Starer, *J. Org. Chem.* **27,** 3096 (1962).

[190] Closs, *J. Am. Chem. Soc.* **84,** 809 (1962).

[191] Roth, *J. Am. Chem. Soc.* **93,** 1527, 4935 (1971).

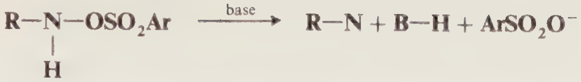
[192] For a monograph, see Lwowski, "Nitrenes," Interscience Publishers, Inc., New York, 1970. For reviews, see Abramovitch, in McManus, Ref. 1, pp. 127–192; Hünig, *Helv. Chim. Acta* **54,** 1721–1747 (1971); Belloli, *J. Chem. Educ.* **48,** 422–426 (1971); Lwowski, *Angew. Chem. Int. Ed. Engl.* **6,** 897–906 (1967) [*Angew. Chem.* **79,** 922–931]; Abramovitch and Davis, *Chem. Rev.* **64,** 149–185 (1964); Horner and Christmann, *Angew. Chem. Int. Ed. Engl.* **2,** 599–608 (1963) [*Angew. Chem.* **75,** 707–716]; Abramovitch and Sutherland, *Fortsch. Chem. Forsch.* **16,** 1–33 (1970) (sulfonyl nitrenes); and Ioffe and Kuznetsov, *Russ. Chem. Rev.* **41,** 131–146 (1972) (N-nitrenes).

[193] Wasserman, Smolinsky, and Yager, *J. Am. Chem. Soc.* **86,** 3166 (1964).

[194] Smolinsky, Wasserman, and Yager, *J. Am. Chem. Soc.* **84,** 3220 (1962).

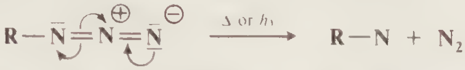
[195] McConaghy and Lwowski, *J. Am. Chem. Soc.* **89,** 2357, 4450 (1967); Mishra, Rice, and Lwowski, *J. Org. Chem.* **33,** 481 (1968).

1. *α Elimination.* An example is



$$\underset{\displaystyle H}{R-\underset{|}{N}-OSO_2Ar} \xrightarrow{\text{base}} R-N + B-H + ArSO_2O^-$$

2. *Disintegration of certain double-bond compounds.* The most common method of forming nitrenes is photolytic or thermal decomposition of azides[196]

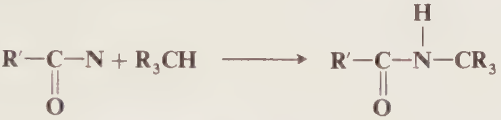


$$R-\bar{N}=\overset{\oplus}{N}=\underline{\overset{\ominus}{N}} \xrightarrow{\Delta \text{ or } h\nu} R-N + N_2$$

The unsubstituted nitrene NH has been generated by photolysis of or electric discharge through NH_3, N_2H_4, or HN_3.

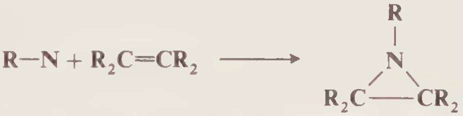
The reactions of nitrenes are also similar to those of carbenes. As in that case, many reactions in which nitrene intermediates are suspected probably do not involve free nitrenes. It is often very difficult to obtain proof in any given case that a free nitrene is or is not an intermediate.

1. *Insertion* (see reaction **2-11**). Nitrenes, especially acyl nitrenes and sulfonyl nitrenes, can insert into C—H and certain other bonds, e.g.,



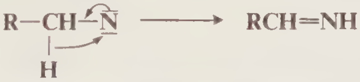
$$R'-\underset{\underset{\displaystyle O}{\|}}{C}-N + R_3CH \longrightarrow R'-\underset{\underset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{N}-CR_3$$

2. *Addition to* C=C *bonds* (see reaction **5-45**)



This reaction is most common for acyl nitrenes. There is no compelling evidence that aryl nitrenes can add to double bonds.[197] Though aziridines have been obtained in many such cases, they may have been formed by pathways not involving free nitrenes.[198]

3. *Rearrangements.* Alkyl nitrenes do not generally give either of the two preceding reactions because rearrangement is more rapid, e.g.,



$$R-\underset{\underset{\displaystyle H}{|}}{CH}-\underline{N} \longrightarrow RCH=NH$$

Such rearrangements are so rapid that it is usually difficult to exclude the possibility that a free nitrene was never present at all, i.e., that migration takes place at the same time that the nitrene is formed[199] (see p. 1003).

4. *Abstraction,* e.g.,

$$R-N + R-H \longrightarrow R-\dot{\underline{N}}-H + R\cdot$$

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[196] For a review, see L'Abbé, *Chem. Rev.* **69**, 345-363 (1969).

[197] Smith, in Lwowski, "Nitrenes," Ref. 192, p. 112. See, however, Abramovitch and Challand, *J. Chem. Soc., Chem. Commun.* 1160 (1972).

[198] For example, through triazoline intermediates (see reaction **5-45**).

[199] For example, see Moriarty and Reardon, *Tetrahedron* **26**, 1379 (1970); Abramovitch and Kyba, *J. Am. Chem. Soc.* **93**, 1537 (1971).

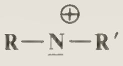
5. *Dimerization.* One of the principal reactions of NH is dimerization to diimide N_2H_2. Azobenzenes are often obtained in reactions where aryl nitrenes are implicated:

$$2\text{Ar—N} \longrightarrow \text{Ar—N=N—Ar}$$

It would thus seem that dimerization is more important for nitrenes than it is for carbenes, but again it has not been proved that free nitrenes are actually involved.

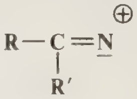
6. *Disproportionation.* NH can disproportionate to give the thermodynamically stable nitrogen and hydrogen: $2NH \rightarrow N_2 + H_2$.

At least two types of *nitrenium ions,* the nitrogen analogs of carbonium ions, can exist as intermediates, though much less work has been done in this area than on carbonium ions. In one type (**37**) the nitrogen is bonded to two atoms and in the other (**38**) to only one.[200] When



$$R-\overset{\oplus}{\underline{N}}-R'$$

37



$$R-\underset{R'}{\underset{|}{C}}=\overset{\oplus}{\underline{N}}$$

38

R = H in **37**, the species is a protonated nitrene. Like carbenes and nitrenes, nitrenium ions can exist in singlet or triplet states.[201]

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[200] For a review of **37**, see Gassman, *Acc. Chem. Res.* **3**, 26–33 (1970). For a review of **38**, see Lansbury, in Lwowski, "Nitrenes," Ref. 192, pp. 405 419.

[201] Gassman and Cryberg, *J. Am. Chem. Soc.* **91**, 5176 (1969).

Six

Mechanisms and Methods of Determining Them

A mechanism is the actual process by means of which a reaction takes place—which bonds are broken, in what order, how many steps are involved, the relative rate of each step, etc. In order to state a mechanism completely, we should have to specify the positions of all atoms, including those in solvent molecules, and the energy of the system, at every point in the process. A proposed mechanism must fit all the facts available. It is always subject to change as new facts are discovered. The usual course is that the gross features of a mechanism are the first to be known and then increasing attention is paid to finer details. The tendency is always to probe more deeply, to get more detailed descriptions.

Although for most reactions gross mechanisms can be written today with a good degree of assurance, no mechanism is known completely. There is much about the fine details which is still puzzling, and for some reactions even the gross mechanism is still not clear. Many facts are not yet understood. The problems involved are very difficult because there are so many variables. Many examples are known where reactions proceed by different mechanisms under different conditions. In many cases there are several proposed mechanisms each of which completely explains all the data.

Types of Mechanism

In any reaction bonds are broken and/or bonds are formed. We can divide all mechanisms into three basic types, depending on how the bonds break.

1. If a bond breaks in such a way that both electrons remain with one fragment, the mechanism is called *polar* or *heterolytic*. Polar reactions do not necessarily involve ionic intermediates, though they often do. The important thing is that the electrons are never unpaired. For most reactions it is convenient to call one reactant the *attacking reagent* and the other the *substrate*. In this book we shall always designate as the substrate that molecule which supplies carbon to the new bond. When carbon-carbon bonds are formed, it is necessary to be arbitrary about which is the substrate and which the attacking reagent. In polar reactions the reagent generally brings a pair of electrons to the substrate or takes a pair of electrons from it. A reagent which brings an electron pair is called a *nucleophile*, and the reaction is called *nucleophilic*. A reagent which takes an electron pair is called an *electrophile* and the reaction is *electrophilic*. In a reaction in which the substrate molecule becomes cleaved, part of it (the part not containing the carbon) is usually called the *leaving group*. A leaving group which carries away an electron pair is called *nucleofugal*. If it comes away without the electron pair, it is called *electrofugal*.

2. If a bond breaks in such a way that each fragment gets one electron, free radicals are formed and such reactions are said to take place by *free-radical mechanisms*.

3. It would seem that all bonds must break in one of the two ways previously noted. But there is a third type of mechanism in which electrons (usually six, but sometimes four or some other number) move in a closed ring. There are no intermediates, ions or free radicals, and it is impossible to say whether the electrons are paired or unpaired. Reactions with this type of mechanism are called *pericyclic*.[1]

Examples of all three types of mechanism will be given in the next section.

Types of Reaction

The number and range of organic reactions is so great as to seem bewildering, but actually almost all of them can be fitted into just six categories. In the description of the six types, which follows, the immediate products are shown, though in many cases they then react with something else. All the species are shown without charges, since differently charged reactants may undergo analogous changes. The descriptions given here are purely formal and are for the purpose of classification and comparison. All are discussed in detail in Part 2 of this book.

1. *Substitutions.* If polar, these can be classified as nucleophilic or electrophilic depending on which reactant is designated as the substrate and which as the attacking reagent (very often Y must first be formed by a previous bond cleavage).

a. Nucleophilic substitution (Chapters 10, 13)

$$A\wr{-}X + \bar{Y} \longrightarrow A{-}Y + \bar{X}$$

b. Electrophilic substitution (Chapters 11, 12)

$$A{-}\wr X + Y \longrightarrow A{-}Y + X$$

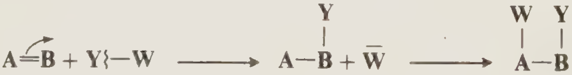
c. Free-radical substitution (Chapter 14)

$$A{-}X + Y\cdot \longrightarrow A{-}Y + X\cdot$$

In free-radical substitution, Y• is usually produced in situ by a free-radical cleavage, and X• goes on to react further.

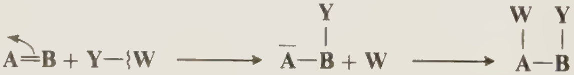
2. *Additions to double or triple bonds* (Chapters 15, 16). These reactions may take place by all three of the mechanistic possibilities.

a. Electrophilic addition (polar)



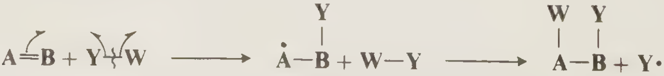
$$A{=}B + Y\wr{-}W \longrightarrow A{-}\overset{\overset{\textstyle Y}{|}}{B} + \bar{W} \longrightarrow \overset{\overset{\textstyle W}{|}}{A}{-}\overset{\overset{\textstyle Y}{|}}{B}$$

b. Nucleophilic addition (polar)



$$A{=}B + Y{-}\wr W \longrightarrow \bar{A}{-}\overset{\overset{\textstyle Y}{|}}{B} + W \longrightarrow \overset{\overset{\textstyle W}{|}}{A}{-}\overset{\overset{\textstyle Y}{|}}{B}$$

c. Free-radical addition



$$A{=}B + Y\wr W \longrightarrow \dot{A}{-}\overset{\overset{\textstyle Y}{|}}{B} + W{-}Y \longrightarrow \overset{\overset{\textstyle W}{|}}{A}{-}\overset{\overset{\textstyle Y}{|}}{B} + Y\cdot$$

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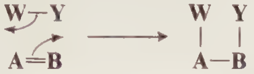
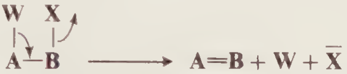
[1] For a classification of pericyclic reactions, see Hendrickson, *Angew. Chem. Int. Ed. Engl.* **13**, 47–76 (1974) [*Angew. Chem.* **86**, 71–100].

d. Simultaneous addition (pericyclic)

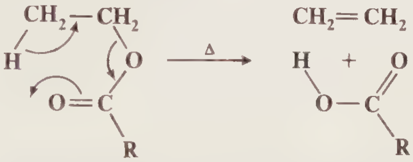


The examples show Y and W as coming from the same molecule, but very often (except in simultaneous addition) they come from different molecules. Also, the examples show the Y—W bond cleaving at the same time that Y is bonding to B, but often (again except for simultaneous addition) this cleavage takes place earlier.

3. *β-elimination* (Chapter 17).



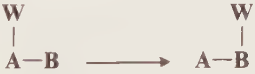
These reactions may take place by polar or pericyclic mechanisms, an example of the latter being (reaction **7-3**)



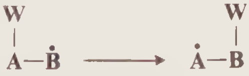
Free-radical β-eliminations are extremely rare. In polar eliminations W and X may or may not leave simultaneously, and they may or may not combine.

4. *Rearrangement* (Chapter 18). Many rearrangements involve migration of an atom or group from one atom to another. There are three types, depending on how many electrons the migrating atom or group carries with it.

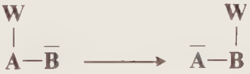
a. Migration with electron pair (nucleophilic)



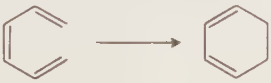
b. Migration with one electron (free-radical)



c. Migration without electrons (electrophilic; rare)



The illustrations show 1,2 rearrangements, in which the migrating group moves to the adjacent atom. These are the most common, although longer rearrangements are also possible. There are also some rearrangements which do not involve simple migration at all (see Chapter 18). Some of the latter involve pericyclic mechanisms. An example (reaction **8-32**) is



5. *Oxidation and reduction* (Chapter 19). Many oxidation and reduction reactions fall naturally into one of the four types mentioned above, but many others do not. For a description of oxidation-reduction mechanistic types, see p. 1075.

6. Combinations of the above.

Note that arrows are used to show movement of *electrons*. An arrow always follows motion of electrons and never of a nucleus or anything else, it being understood that the rest of the molecule follows behind the electrons. Ordinary arrows (double-headed) follow electron pairs, while single-headed arrows follow unpaired electrons. Double-headed arrows are also used in pericyclic reactions for convenience, although in these reactions we do not really know how or in which direction the electrons are moving.

Thermodynamic Requirements for Reaction

In order for a reaction to take place spontaneously, the free energy of the products must be lower than the free energy of the reactants; i.e., ΔG must be negative. Reactions may go the other way, of course, but only if free energy is added. Like water on the surface of the earth, which only flows downhill and never uphill (though it can be carried or pumped uphill), molecules seek the lowest possible potential energy. Free energy is made up of two components, enthalpy H and entropy S. These quantities are related by the equation

$$\Delta G = \Delta H - T\Delta S$$

The enthalpy change in a reaction is essentially the difference in bond energies (including resonance, strain, and solvation energies) between the reactants and the products. The enthalpy change can be calculated by totaling the bond energies of all the bonds broken, subtracting from this the total of the bond energies of all the bonds formed, and adding any changes in resonance, strain, or solvation energies. Entropy changes are quite different, and refer to the disorder or randomness of the system. The less order in a system, the greater the entropy. The preferred conditions in nature are *low* enthalpy and *high* entropy, and in reacting systems, enthalpy spontaneously decreases while entropy spontaneously increases.

For many reactions entropy effects are negligible, and the enthalpy alone determines whether the reaction can take place spontaneously. However, in certain types of reaction entropy is important and can dominate enthalpy. We shall discuss several examples.

1. In general, liquids have lower entropies than gases, since the molecules of gas have much more freedom and randomness. Solids, of course, have still lower entropies. Any reaction in which the reactants are all liquids and one or more of the products is a gas is therefore thermodynamically favored by the increased entropy: the equilibrium constant for that reaction will be higher than it would otherwise be. Similarly, the entropy of a gaseous substance is higher than that of the same substance dissolved in a solvent.

2. In a reaction in which the number of product molecules is equal to the number of reactant molecules, e.g., $A + B \rightarrow C + D$, entropy effects are usually small, but if the number of molecules is increased, e.g., $A \rightarrow B + C$, there will be a large gain in entropy because more arrangements in space are possible when more molecules are present. Reactions in which a molecule is cleaved into two or more parts are therefore thermodynamically favored by the entropy factor. Conversely, reactions in which the number of product molecules is less than the number of reactant molecules show entropy decreases, and in such cases there must be a sizable decrease in enthalpy to overcome the unfavorable entropy change.

3. Although reactions in which molecules are cleaved into two or more pieces have favorable entropy effects, many potential cleavages do not take place because of large increases in enthalpy.

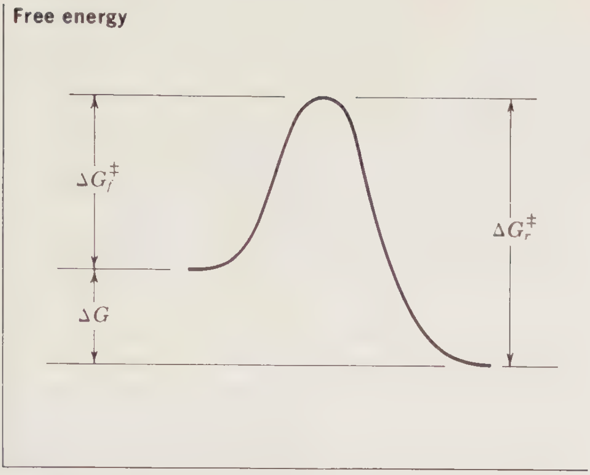


Figure 1 Free-energy profile of a reaction without an intermediate where the products have a lower free energy than the reactants

An example is cleavage of ethane into two methyl radicals. In this case a bond of about 79 kcal mol is broken, and no new bond is formed to compensate for this enthalpy increase. However, ethane can be cleaved at very high temperatures, which illustrates the principle that *entropy becomes more important as the temperature increases*, as is obvious from the equation $\Delta G = \Delta H - T\Delta S$. The enthalpy term is independent of temperature, while the entropy term is directly proportional to the absolute temperature. In a qualitative way, we can see that molecules have more freedom at higher temperatures.

4. An open-chain molecule has more entropy than a similar cyclic molecule because there are more conformations (compare hexane and cyclohexane). Ring opening therefore means a gain in entropy and ring closing a loss.

Kinetic Requirements for Reaction

Just because a reaction has a negative ΔG does not necessarily mean that it will take place in a reasonable period of time. A negative ΔG is a *necessary* but not a *sufficient* condition for a reaction to occur spontaneously. For example, the reaction between H_2 and O_2 to give H_2O has a negative ΔG, but mixtures of H_2 and O_2 can be kept at room temperature for many centuries without reacting to any significant extent. In order for a reaction to take place, *free energy of activation* $\Delta G^{\ddagger}$ must be added.[2] This situation is illustrated in Figure 1,[3] which is an energy profile[4] for a one-step reaction without an intermediate. In this type of diagram the horizontal axis signifies the progression of the reaction. $\Delta G_f^{\ddagger}$ is the free energy of activation for the forward reaction. If the reaction shown in Figure 1 is reversible, $\Delta G_r^{\ddagger}$ must be greater than $\Delta G_f^{\ddagger}$, since it is the sum of ΔG and $\Delta G_f^{\ddagger}$.

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[2] For mixtures of H_2 and O_2 this can be done by striking a match.

[3] Strictly speaking, this is an energy profile for a reaction of the type $XY + Z \rightarrow X + YZ$. However, it may be applied, in a rough way, to other reactions.

[4] For a fuller discussion, see Frost and Pearson, "Kinetics and Mechanism," 2d ed., pp. 77–102, John Wiley & Sons, Inc., New York, 1961.

When a reaction between two or more molecules has progressed to the point corresponding to the top of the curve, the term *transition state* is applied to the positions of the nuclei and electrons. The transition state possesses a definite geometry and charge distribution. The system at this point is called an *activated complex*.

In the *transition-state theory* the starting materials and the activated complex are taken to be in equilibrium, the equilibrium constant being designated $K^{\ddagger}$. According to the theory, all activated complexes go on to product at the same rate (which, though at first sight surprising, is not unreasonable, when we consider that they are all "falling downhill") so that the rate constant (see p. 199) of the reaction depends only on the position of the equilibrium between the starting materials and the activated complex, i.e., on the value of $K^{\ddagger}$. $\Delta G^{\ddagger}$ is related to $K^{\ddagger}$ by

$$\Delta G^{\ddagger} = -2.3RT \log K^{\ddagger}$$

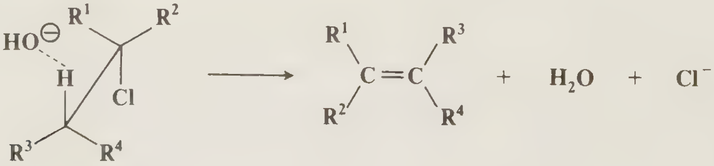
so that a higher value of $\Delta G^{\ddagger}$ indicates a smaller rate constant. The rate of a reaction almost always increases with increasing temperature because the additional energy thus supplied helps the molecules to overcome the activation energy barrier. Some reactions have no free energy of activation at all, meaning that $K^{\ddagger}$ is essentially infinite and that virtually all collisions lead to reaction. Such processes are said to be *diffusion-controlled.*

Like ΔG, $\Delta G^{\ddagger}$ is made up of enthalpy and entropy components

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\,\Delta S^{\ddagger}$$

$\Delta H^{\ddagger}$, the *enthalpy of activation*, is the difference in bond energies, including strain, resonance, and solvation energies, between the starting compounds and the *transition state*. In many reactions old bonds have been broken or partially broken by the time the transition state is reached, and the energy necessary for this is $\Delta H^{\ddagger}$. It is true that additional energy will be supplied by the formation of new bonds, but if this occurs after the transition state, it can affect only ΔH and not $\Delta H^{\ddagger}$.

Entropy of activation $\Delta S^{\ddagger}$, which is the difference in entropy between the starting compounds and the transition state, becomes important when two reacting molecules must approach each other in a specific orientation in order for the reaction to take place. For example, the reaction between a simple noncyclic alkyl chloride and hydroxide ion to give an alkene (reaction **7-13**) takes place



only if, in the transition state, the reactants are oriented as shown. Not only must the OH^- be near the hydrogen, but the hydrogen must be oriented anti to the chlorine atom.[5] When the two reacting molecules collide, if the OH^- should be near the chlorine atom or near R^1 or R^2, no reaction can take place. In order for a reaction to occur, the molecules must surrender the freedom they normally have to assume many possible arrangements in space and adopt only that one which leads to reaction. Thus, a considerable loss in entropy is involved; i.e., $\Delta S^{\ddagger}$ is negative.

Entropy of activation is also responsible for the difficulty in closing rings larger than six-membered. Consider a ring-closing reaction in which the two groups which must interact are

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[5] As we shall see in Chapter 17, with some molecules elimination is also possible if the hydrogen is oriented syn, instead of anti, to the chlorine atom. Of course, this orientation also requires a considerable loss of entropy.

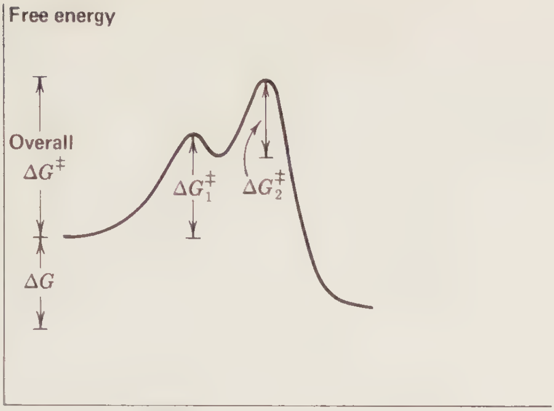

Figure 2 Free-energy profile for a reaction with an intermediate. ΔG_1‡ and ΔG_2‡ are the free energy of activation for the first and second stages, respectively.

situated on the ends of a ten-carbon chain. In order for reaction to take place, the groups must encounter each other. But a ten-carbon chain has many conformations, and in only a few of these are the ends of the chain near each other. Thus, forming the transition state requires a great loss of entropy.[6] This factor is also present, though less so, in closing rings of six members or less (except three-membered rings), but with rings of this size the entropy loss is less than that of bringing two individual molecules together. For example, a reaction between an OH group and a COOH group in the same molecule to form a lactone with a five- or six-membered ring takes place much faster than the same reaction between a molecule containing an OH group and another containing a COOH group. Though $\Delta H^{\ddagger}$ is about the same, $\Delta S^{\ddagger}$ is much less for the cyclic case. However, if the ring to be closed has three or four members, small-angle strain is introduced and the favorable $\Delta S^{\ddagger}$ may not be sufficient to overcome the unfavorable $\Delta H^{\ddagger}$ change.

Reactions in which the transition state has more disorder than the starting compounds, e.g., the pyrolytic conversion of cyclopropane to propene, have positive $\Delta S^{\ddagger}$ values and are thus favored by the entropy effect.

Reactions with intermediates are two-step (or more) processes. In these reactions there is an energy "well." There are two transition states, each with an energy higher than the intermediate (Figure 2). The deeper the well, the more stable the intermediate. In Figure 2 the second peak is higher than the first. The opposite situation is shown in Figure 3. Note that in reactions in which the second peak is higher than the first, the overall $\Delta G^{\ddagger}$ is less than the sum of the $\Delta G^{\ddagger}$ values for the two steps. Minima in free-energy-profile diagrams correspond to real species which have a finite though very short existence. These may be the carbonium ions, carbanions, free radicals, etc., discussed in Chapter 5, or they may be molecules in which all the atoms have their normal valences. In either case, under the reaction conditions they do not live long (because $\Delta G_2^{\ddagger}$ is small) but rapidly go on to products. Maxima in these curves, however, do not correspond to actual species but only to transition states in which bond breaking and/or bond making have partially taken place. Transition states have only a transient existence with an essentially zero lifetime.

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[6] Reaction rates can be greatly enhanced by restricting the conformational possibilities of the substrate to those which are in favorable positions for reaction. For examples, see Milstien and Cohen, *J. Am. Chem. Soc.* **94**, 9158 (1972); Borchardt and Cohen, *J. Am. Chem. Soc.* **94**, 9166, 9175 (1972), **95**, 8308, 8313, 8319 (1973); Karle and Karle, *J. Am. Chem. Soc.* **94**, 9182 (1972).

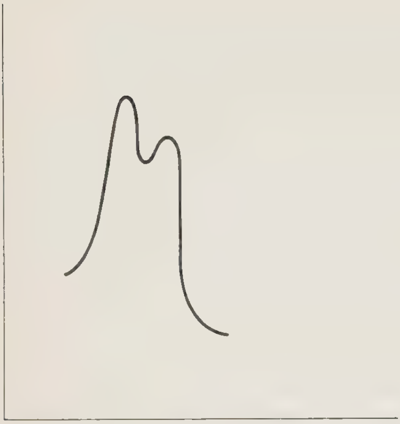

Figure 3 Free-energy profile for a reaction with an intermediate in which the first peak is higher than the second.

Kinetic and Thermodynamic Control

There are many cases in which a compound under a given set of reaction conditions may undergo competing reactions to give different products:

$$A \begin{array}{l} \nearrow B \\ \searrow C \end{array}$$

Figure 4 shows a free-energy profile for a reaction in which B is thermodynamically more stable than C (lower ΔG), but C is formed faster (lower $\Delta G^{\ddagger}$). If neither reaction is reversible, C will be formed in larger amount because it is formed faster. The product is said to be *kinetically controlled*. However, if the reactions are reversible, this will not necessarily be the case. If such a process is stopped well before the equilibrium has been established, the reaction will be kinetically controlled since more of the faster-formed product will be present. However, if the reaction is permitted to approach equilibrium, the predominant or even exclusive product will be B. Under these conditions the C which is first formed reverts to A, while the more stable B does so much less. Here we say the product is *thermodynamically controlled*. Of course, Figure 4 does not describe all reactions in which a compound A can give two different products. In many cases the more stable product is also the one which is formed faster. In such cases the product of kinetic control is also the product of thermodynamic control.

The Hammond Postulate

Since transition states have essentially zero lifetimes, it is impossible to observe them directly and information about their geometries must be obtained from inference. In some cases our inferences can be very strong. For example, in the SN2 reaction (p. 266) between CH_3I and I^- (a reaction in which the product is identical to the starting compound) the transition state should be perfectly symmetrical. In most cases, however, we cannot reach such easy conclusions, and we are greatly aided by the *Hammond postulate*,[7] which states that for any single reaction step, *the geometry of the*

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[7] Hammond, *J. Am. Chem. Soc.* **77**, 334 (1955). For a discussion, see Fărcasiu, *J. Chem. Educ.* **52**, 76–79 (1975).

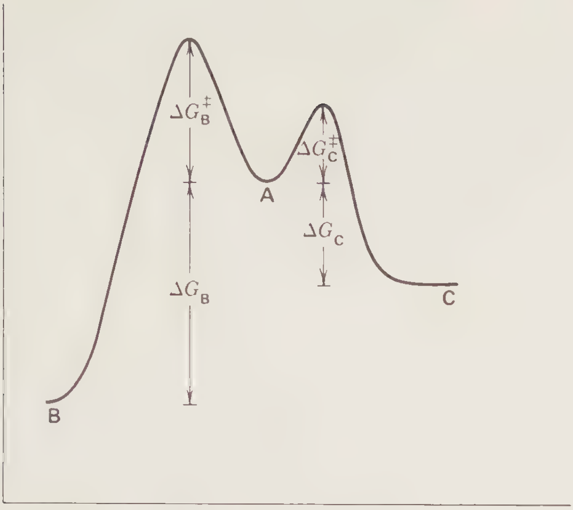
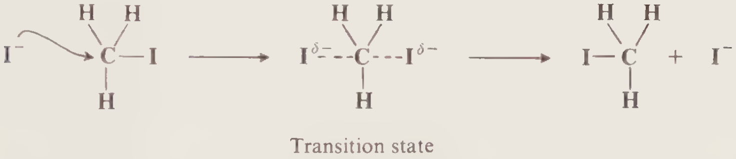


Figure 4 Free-energy profile illustrating kinetic versus thermodynamic control of product. The starting compound (**A**) can react to give either **B** or **C**



transition state for that step resembles the side to which it is closer in free energy. Thus, for an exothermic reaction like that shown in Figure 1, the transition state resembles the reactants more than the products, though not much more, because there is a substantial $\Delta G^{\ddagger}$ on both sides. The postulate is most useful in reactions with intermediates. In the reaction illustrated in Figure 2, the first transition state lies much closer in energy to the intermediate than it does to the reactants, and we can predict that the geometry of the transition state resembles that of the intermediate more than it does that of the reactants. Likewise, the second transition state also has a free energy much closer to that of the intermediate than to the products, so that both transition states resemble the intermediate more than they do the products or reactants. This is generally the case in reactions which involve very reactive intermediates. Since we usually know more about the structure of intermediates than of transition states, we often use our knowledge of intermediates to draw conclusions about the transition states (for examples, see pp. 316, 688).

Microscopic Reversibility

In the course of a reaction the nuclei and electrons assume positions which at each point correspond to the lowest free energies possible. If the reaction is reversible, these positions must be the same in the reverse process, too. This means that the forward and reverse reactions (run under the same conditions) must proceed by the same mechanism. This is called the *principle of microscopic reversibility*. For example, if in a reaction A → B there is an intermediate C, then C must also be an intermediate in the reaction B → A. This is a useful principle since it enables us to know the mechanism of reactions in which the equilibrium lies far over to one side. Reversible photochemical reactions are an exception, since a molecule which has been excited photochemically does not have to lose its energy in the same way (Chapter 7).

METHODS OF DETERMINING MECHANISMS

There are a number of commonly used methods for determining mechanisms.[8] In most cases one method is not sufficient, and the problem is generally approached from several directions.

Identification of Products

Obviously any mechanism proposed for a reaction must account for all the products obtained and for their relative proportions, including products formed by side reactions. Incorrect mechanisms for the von Richter reaction (**3-26**) were accepted for many years because it was not realized that nitrogen was a major product. A proposed mechanism cannot be correct if it fails to predict the products in approximately their correct proportions. Any mechanism for the reaction

$$CH_4 + Cl_2 \xrightarrow{h\nu} CH_3Cl$$

which fails to account for the formation of a small amount of ethane cannot be correct (see reaction **4-1**).

Determination of the Presence of an Intermediate

In many reactions, intermediates are postulated. There are several ways, none of them foolproof, for attempting to learn whether or not an intermediate is present and, if so, the structure of the intermediate.

1. *Isolation of an intermediate.* It is sometimes possible to isolate an intermediate from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. For example, in the reaction

$$RCONH_2 + NaOBr \longrightarrow RNH_2$$

the intermediate RCONHBr has been isolated (see reaction **8-17**). If it can then be shown that the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than the starting compound, this constitutes strong evidence that the reaction involves that intermediate, though it is not conclusive, since the compound may arise by an alternate path and by coincidence give the same product.

2. *Detection of an intermediate.* In many cases an intermediate cannot be isolated but can be detected by ir, nmr, or other spectra. The detection by Raman spectra of NO_2^+ was regarded as strong evidence that this is an intermediate in the nitration of benzene (see reaction **1-2**). Free-radical and triplet intermediates can often be detected by esr[9] and by CIDNP (see Chapter 5).

3. *Trapping of an intermediate.* In some cases, the suspected intermediate is known to be one which reacts in a given way with a certain compound. The intermediate can then be detected by running the reaction in the presence of that compound. For example, benzynes (p. 588) react with dienes in the Diels-Alder reaction (reaction **5-51**). In any reaction where a benzyne is a suspected

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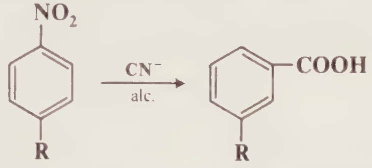
[8] For a treatise on this subject, see Lewis and Hammes, "Investigation of Rates and Mechanisms of Reactions," 3d ed. (vol. 6 of Weissberger, "Techniques of Chemistry"), 2 pts., John Wiley & Sons, Inc., New York, 1974.

[9] For a review of esr spectra of triplets, see Thomson, *Q. Rev., Chem. Soc.* **22**, 45–74 (1968).

intermediate, the addition of a diene and the detection of the Diels-Alder adduct indicate that the benzyne was probably present.

4. *Addition of a suspected intermediate.* If a certain intermediate is suspected, and if it can be obtained by other means, then under the same reaction conditions it should give the same products. This kind of experiment can provide conclusive negative evidence: if the same products are not obtained, the suspected compound is not an intermediate. However, if the correct products are obtained, this is not conclusive since they may arise by coincidence. The von Richter reaction (**3-26**) provides us with a good example here too. For many years it had been assumed that an aryl cyanide was an intermediate, since cyanides are easily hydrolyzed to carboxylic acids (reaction **6-5**). In fact, in 1954, *p*-chlorobenzonitrile was shown to give *p*-chlorobenzoic acid under the normal von Richter conditions.[10] However, when the experiment was repeated with 1-cyanonaphthalene, no 1-naphthoic acid was obtained, although 2-nitronaphthalene gave 13% 1-naphthoic acid under the same conditions.[11] This proved that 2-nitronaphthalene must have been converted to 1-naphthoic acid by a route which did not involve 1-cyanonaphthalene. It also showed that even the conclusion that *p*-chlorobenzonitrile was an intermediate in the conversion of *m*-nitrochlorobenzene to *p*-chlorobenzoic acid must now be suspected, since it is not likely that the mechanism would substantially change in going from the naphthalene to the benzene system.



The Study of Catalysis[12]

Much information about the mechanism of a reaction can be obtained from a knowledge of which substances catalyze the reaction, which inhibit it, and which do neither. Of course, just as a mechanism must be compatible with the products, so must it be compatible with its catalysts. In general, catalysts perform their actions by providing an alternate pathway for the reaction in which $\Delta G^{\ddagger}$ is less than it would be without the catalyst. Catalysts do not change ΔG.

Isotopic Labeling[13]

Much useful information has been obtained by using molecules which have been isotopically labeled and tracing the path of the reaction in that way. For example, in the reaction

$$\mathrm{RCOO^- + BrCN \longrightarrow RCN}$$

does the CN group in the product come from the CN in the BrCN? The use of ^{14}C supplied the answer, since $\mathrm{R^{14}CO_2^-}$ gave *radioactive* RCN.[14] This surprising result saved a lot of labor, since it ruled out a mechanism involving the replacement of $\mathrm{CO_2}$ by CN (see reaction **6-63**).

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[10] Bunnett, Rauhut, Knutson, and Bussell, *J. Am. Chem. Soc.* **76,** 5755 (1954).

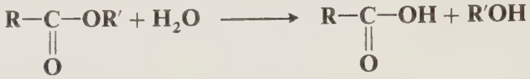
[11] Bunnett and Rauhut, *J. Org. Chem.* **21,** 944 (1956).

[12] For treatises, see Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Company, New York, 1969, and Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," John Wiley & Sons, Inc., New York, 1971.

[13] For reviews see Collins, *Adv. Phys. Org. Chem.* **2,** 3–91 (1964); Arnstein and Bentley, *Q. Rev., Chem. Soc.* **4,** 172–194 (1950); Raeen, in Ref. 8, pt. 1, pp. 257–284.

[14] Douglas, Eccles, and Almond, *Can. J. Chem.* **31,** 1127 (1953); Douglas and Burditt, *Can. J. Chem.* **36,** 1256 (1958).

Other radioactive isotopes are also frequently used as tracers, but even stable isotopes may be used. An example is the hydrolysis of esters.



$$R-\underset{\underset{O}{\|}}{C}-OR' + H_2O \longrightarrow R-\underset{\underset{O}{\|}}{C}-OH + R'OH$$

Which bond of the ester is broken, the acyl—O or the alkyl—O bond? The answer is found by the use of $H_2{}^{18}O$. If the acyl—O bond breaks, the labeled oxygen will appear in the acid; otherwise it will be in the alcohol (see reaction **0-11**). Although neither compound is radioactive, the one which contains ^{18}O can be determined by submitting both to mass spectrometry. In a similar way, deuterium can be used as a label for hydrogen. In this case it is not necessary to use mass spectrometry, since ir and nmr spectra can be used to determine when deuterium has been substituted for hydrogen.

In the labeling technique, it is not generally necessary to use completely labeled compounds. Partially labeled material is usually sufficient. There are some reactions, *exchange reactions*, which cannot be studied by any method which does not involve labeling, e.g.,[15] the iodide exchange reaction on p. 195.

Stereochemical Evidence[16]

If the products of a reaction are capable of existing in more than one stereoisomeric form, which form is obtained may give information about the mechanism. For example, (+)-malic acid was discovered by Walden[17] to give (−)-chlorosuccinic acid when treated with PCl_5 and the (+) enantiomer when treated with $SOCl_2$, showing that the mechanisms of these apparently similar conversions could not be the same (see pp. 267, 302). Much useful information has been obtained about nucleophilic substitution, elimination, rearrangement, and addition reactions from this type of experiment. The isomers involved need not be enantiomers. Thus, the fact that *cis*-2-butene treated with $KMnO_4$ gives *meso*-2,3-butanediol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side (see reaction **5-39**).

Kinetic Evidence[18]

The rate of a homogeneous reaction[19] is the rate of disappearance of a reactant or of appearance of a product. The rate nearly always changes with time, since it is usually proportional to concentration and the concentration of reactants decreases with time. However, the rate is not always proportional to the concentration of all reactants. In some cases a change in the concentration of a reactant produces no change at all in the rate, while in other cases the rate may be proportional to the concentration of a substance (a catalyst) which does not even appear in the stoichiometric equation. A study of which reactants affect the rate often tells a good deal about the mechanism.

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[15] For a review, see Gold and Satchell, *Q. Rev., Chem. Soc.* **9,** 51–72 (1955).

[16] For lengthy treatments of the relationship between stereochemistry and mechanism, see Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, New York, 1962; Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, 1956; Stevens, Billups, and Jacobson, in Ref. 8, pt. 1, pp. 285-366.

[17] Walden, *Ber.* **29,** 136 (1896), **30,** 3149 (1897), **32,** 1833 (1899).

[18] For the use of kinetics in determining mechanisms, see Hammett, "Physical Organic Chemistry," 2d ed., pp. 53–100, McGraw-Hill Book Company, New York, 1970; Gardiner, "Rates and Mechanisms of Chemical Reactions," W. A. Benjamin, Inc., New York, 1969; Leffler and Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley & Sons, Inc., New York, 1963; Jencks, Ref. 12, pp. 555–614; and Refs. 4 and 8.

[19] A homogeneous reaction occurs in one phase. Heterogeneous kinetics have been studied much less.

If the rate is proportional to the change in concentration of only one reactant (A), the rate law (the rate of change of concentration of A with time *t*) is

$$\text{Rate} = \frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}]$$

where *k* is the *rate constant* for the reaction. There is a minus sign because the concentration of A decreases with time. A reaction which follows such a rate law is called a *first-order reaction*. The units of *k* for a first-order reaction are $\sec^{-1}$. The rate of a *second-order reaction* is proportional to the concentration of two reactants, or to the square of the concentration of one:

$$\frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}][\mathrm{B}] \qquad \text{or} \qquad \frac{-d[\mathrm{A}]}{dt} = k[\mathrm{A}]^2$$

For a second-order reaction the units are liters mol^{-1} $\sec^{-1}$ or some other units expressing the reciprocal of concentration or pressure per unit time interval.

Similar expressions can be written for third-order reactions. A reaction whose rate is proportional to [A] and to [B] is said to be first order in A and in B, second order overall. A reaction rate may be measured in terms of any reactant or product, but the rates so determined are not necessarily the same. For example, if the stoichiometry of a reaction is

$$\mathbf{2A + B \longrightarrow C + D}$$

then, on a molar basis, A must disappear twice as fast as B, so that $-d[\mathrm{A}]/dt$ and $-d[\mathrm{B}]/dt$ are not equal but the former is twice as large as the latter.

The rate law of a reaction is an experimentally determined fact. From this fact we attempt to learn the *molecularity*, which may be defined as the number of molecules which come together to form the activated complex. It is obvious that if we know how many (and which) molecules take part in the activated complex, we know a good deal about the mechanism. The experimentally determined rate order is not necessarily the same as the molecularity. Any reaction, no matter how many steps are involved, has only one rate law, but each step of the mechanism has its own molecularity. For reactions which take place in one step (reactions without an intermediate) the order is the same as the molecularity. A first-order one-step reaction is always unimolecular; a one-step reaction which is second order in A always involves two molecules of A; if it is first order in A and in B, then a molecule of A reacts with one of B, etc. For reactions which take place in more than one step, the order *for each step* is the same as the molecularity *for that step*. This fact enables us to predict the rate law for any proposed mechanism, although the calculations may at times get lengthy.[20] If any one step of a mechanism is considerably slower than all the others (this is usually the case), the rate of the overall reaction is essentially the same as that of the slow step, which is consequently called the *rate-determining* step.

For reactions which take place in two or more steps, we can distinguish between two broad cases:

1. The first step is slower than any subsequent step and is consequently rate-determining. In such cases, the rate law simply includes the reactants which participate in the slow step. For example, if the reaction

$$\mathbf{A + 2B \longrightarrow C}$$

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[20] For a discussion of how order is related to molecularity in many complex situations, see Szabó, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 2, pp. 1–80, Elsevier Publishing Company, New York, 1969.

has the mechanism

$$\mathbf{A} + \mathbf{B} \xrightarrow{\text{slow}} \mathbf{I}$$

$$\mathbf{I} + \mathbf{B} \xrightarrow{\text{fast}} \mathbf{C}$$

where I is an intermediate, the reaction is second order, with the rate law

$$\text{Rate} = \frac{-d[\mathbf{A}]}{dt} = k[\mathbf{A}][\mathbf{B}]$$

2. When the first step is not rate-determining, determination of the rate law is usually much more complicated. For example, consider the mechanism

Step 1 $$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{I}$$

Step 2 $$\mathbf{I} + \mathbf{B} \xrightarrow{k_2} \mathbf{C}$$

where the first step is a rapid attainment of equilibrium, followed by a slow reaction to give C. The rate of disappearance of A is

$$\frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}]$$

Both terms must be included because A is being formed by the reverse reaction as well as being used up by the forward reaction. This equation is of very little help as it stands since we cannot measure the concentration of the intermediate. However, the combined rate law for the formation and disappearance of I is

$$\frac{d[\mathbf{I}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] - k_{-1}[\mathbf{I}] - k_2[\mathbf{I}][\mathbf{B}]$$

At first glance we seem to be no better off with this equation, but we may make the assumption that *the concentration of* I *does not change with time*, since it is an intermediate which is used up (going either to A + B or to C) as fast as it is formed. This assumption, called the assumption of the *steady state*, enables us to set $d[\mathrm{I}]/dt$ equal to zero and hence to solve for [I] in terms of the measurable quantities [A] and [B]:

$$[\mathbf{I}] = \frac{k_1[\mathbf{A}][\mathbf{B}]}{k_2[\mathbf{B}] + k_{-1}}$$

We now insert this value for [I] into the original rate expression to obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}]^2}{k_2[\mathbf{B}] + k_{-1}}$$

Note that this rate law is valid whatever the values of k_1, k_{-1}, and k_2. However, our original hypothesis was that the first step was faster than the second, or that

$$k_1[\mathbf{A}][\mathbf{B}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Since the first step is an equilibrium

$$k_1[\mathbf{A}][\mathbf{B}] = k_{-1}[\mathbf{I}]$$

we have

$$k_{-1}[\mathbf{I}] \gg k_2[\mathbf{I}][\mathbf{B}]$$

Canceling [I], we get

$$k_{-1} \gg k_2[\mathbf{B}]$$

We may thus neglect $k_2[\mathrm{B}]$ in comparison with k_{-1} and obtain

$$\frac{-d[\mathbf{A}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathbf{A}][\mathbf{B}]^2$$

The overall rate is thus third order: first order in A and second order in B. Incidentally, if the first step is rate-determining (as was the case in the preceding paragraph), then

$$k_2[\mathbf{B}] \gg k_{-1} \qquad \text{and} \qquad \frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{A}][\mathbf{B}]$$

which is the same rate law we deduced from the rule that where the first step is rate-determining, the rate law includes the reactants which participate in that step.

It is possible for a reaction to involve A and B in the rate-determining step although only [A] appears in the rate law. This occurs when a large excess of B is present, say 100 times the molar quantity of A. In this case the complete reaction of A uses up only 1 mol of B, leaving 99 mol. It is not easy to measure the change in concentration of B with time in such a case, and it is seldom attempted, especially when B is also the solvent. Since [B] is, for practical purposes, unchanging with time in such a case, the reaction appears to be first order in A though actually both A and B are involved in the rate-determining step. This is often referred to as a *pseudo-first-order* reaction. Pseudo-order reactions may also come about when one reactant is a catalyst whose concentration does not change with time because it is replenished as fast as it is used up and when a reaction is conducted in a medium which keeps the concentration of a reactant constant, e.g., in a buffer solution where H^+ or OH^- is a reactant.

What is actually being measured is the change in concentration of a product or a reactant with time. Many methods have been used to make such measurements. The choice of a method depends on its convenience and on its applicability to the reaction being studied. Among the most common methods are:[21]

1. *Periodic spectral readings.* In many cases the reaction can be carried out in the cell while it is in the instrument. Then all that is necessary is that the instrument be periodically read. Among the methods used are ir and uv spectroscopy, nmr, and esr.
2. *Quenching and analyzing.* A series of reactions may be set up and each stopped in some way (perhaps by suddenly lowering the temperature or adding an inhibitor) after a different amount of time has elapsed. The materials are then analyzed, by spectral readings, titrations, gas chromatography, polarimetry (if optically active), or any other method.
3. *Removal of aliquots at intervals.* Each aliquot is then analyzed as in method 2.
4. *Dilatometry.* The change in total volume of a solution may be measured.
5. Measurement of changes in total pressure, for gas-phase reactions.[22]
6. *Calorimetric methods.* The output or absorption of heat may be measured at time intervals.

Special methods exist for very fast reactions.[23]

In any case what is usually obtained is a graph showing how a concentration varies with time. This must be interpreted[24] to obtain a rate law and a value of k. If a reaction obeys simple first- or second-order kinetics, the interpretation is generally not difficult. For example, if the concentration at the start is A_0, the first-order rate law

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[21] For a discussion, see Batt, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 1, pp. 1–111, Elsevier Publishing Company, New York, 1969.

[22] For a review of the kinetics of reactions in solution at high pressures, see le Noble, *Prog. Phys. Org. Chem.* **5**, 207–330 (1967).

[23] For discussions, see Hague, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 1, pp. 112–179, Elsevier Publishing Company, New York, 1969; and Ref. 8, pt. 2.

[24] For discussions, much fuller than that given here, of methods for interpreting kinetic data, see Margerison, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 1, pp. 343–421, Elsevier Publishing Company, New York, 1969; Ref. 4, pp. 8–55; and Bunnett, in Ref. 8, pt. 1, pp. 367–488.

$$\frac{-d[A]}{dt} = k[A] \qquad \text{or} \qquad \frac{-d[A]}{[A]} = k\,dt$$

can be integrated between the limits $t = 0$ and $t = t$ to give

$$-\ln\frac{[A]}{A_0} = kt \qquad \text{or} \qquad \ln[A] = -kt + \ln A_0$$

Therefore, if a plot of ln [A] against t is linear, the reaction is first order and k can be obtained from the slope. For first-order reactions it is customary to express the rate not only by the rate constant k but also by the *half-life*, which is the time required for half of any given quantity of a reactant to be used up. Since the half-life $t_{1/2}$ is the time required for [A] to reach $A_0/2$, we may say that

$$\ln\frac{A_0}{2} = -kt_{1/2} + \ln A_0$$

so that

$$t_{1/2} = \frac{\ln \dfrac{A_0}{A_0/2}}{k} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

For the general case of a reaction first order in A and first order in B, second order overall, integration is complicated, but it can be simplified if equimolar amounts of A and B are used, so that $A_0 = B_0$. In this case

$$\frac{-d[A]}{dt} = k[A][B]$$

is equivalent to

$$\frac{-d[A]}{dt} = k[A]^2 \qquad \text{or} \qquad \frac{-d[A]}{[A]^2} = k\,dt$$

Integrating as before gives

$$\frac{1}{[A]} - \frac{1}{A_0} = kt$$

Thus, under equimolar conditions, if a plot of $1/[A]$ against t is linear, the reaction is second order, with a slope of k. It is obvious that the same will hold true for a reaction second order in A.[25]

Although many reaction-rate studies do give linear plots, which can therefore be easily interpreted, the results in many other studies are not so simple. In some cases a reaction may be first order at low concentrations but second order at higher concentrations. In other cases fractional orders are obtained, and even negative orders. The interpretation of complex kinetics often requires much skill and effort. Even where the kinetics are relatively simple, there is often a problem in interpreting the data because of the difficulty of obtaining precise enough measurements.[26]

Nmr spectra can be used to obtain kinetic information in a completely different manner from that mentioned on p. 201. This method, which involves the study of nmr line shapes, depends on the fact that nmr spectra have an inherent time factor: if a proton changes its environment less rapidly than about 10^3 times per second, an nmr spectrum shows a separate peak for each position the proton assumes. For example, if the rate of rotation around the C—N bond of N,N-dimethylacetamide is slower than 10^3 rotations per second, the two N-methyl groups each

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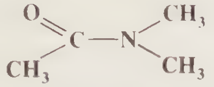
[25] We have given the integrated equations for simple first- and second-order kinetics. For integrated equations for a large number of kinetic types, see Margerison, Ref. 24, p. 361.

[26] See Hammett, Ref. 18, pp. 62–70.



have separate chemical shifts since they are not equivalent, one being cis to the oxygen and the other trans. However, if the environmental change takes place more rapidly than about 10^3 times per second, only one line is found, at a chemical shift which is the weighted average of the two individual positions. In many cases, two or more lines are found at low temperatures, but as the temperature is increased, the lines coalesce because the interconversion rate increases with temperature and passes the 10^3 per second mark. From studies of the way line shapes change with temperature it is often possible to calculate rates of reactions and of conformational changes.[27] The method is not limited to changes in proton line shapes but can also be used for other atoms which give nmr spectra and for esr spectra.

Several types of mechanistic information can be obtained from kinetic studies.

1. From the order of a reaction, information can be obtained about which molecules and how many take part in the rate-determining step. Such knowledge is very useful and often essential in elucidating a mechanism. Erroneous ideas about the mechanism of the benzidine rearrangement (reaction **8-44**) were accepted for many years, until it was discovered that the reaction was usually second order in H^+ (third order overall), indicating that *two* protons were required in the rate-determining step. For any mechanism which can be proposed for a given reaction, a corresponding rate law can be calculated by the methods discussed on pp. 199–201. If the experimentally obtained rate law fails to agree with this, the proposed mechanism is wrong. However, it is often difficult to relate the order of a reaction to the mechanism, especially when the order is fractional or negative. In addition, it is frequently the case that two or more proposed mechanisms for a reaction are kinetically indistinguishable; i.e., they predict the same rate law.

2. Probably the most useful data obtained kinetically are the rate constants themselves. They are important since they may tell us the effect on the rate of a reaction of changes in the structure of the reactants (see Chapter 9), the solvent, the ionic strength, the addition of catalysts, etc.

3. If the rate is measured at several temperatures, in most cases a plot of $\ln k$ against $1/T$ (T stands for absolute temperature) is nearly linear, with a negative slope, and fits the equation

$$\ln k = \frac{-E_a}{RT} + \ln A$$

where R is the gas constant and A a constant called the *frequency factor*. This permits calculation of E_a, which is the Arrhenius activation energy of the reaction. From this can be obtained $\Delta H^{\ddagger}$ by

$$E_a = \Delta H^{\ddagger} + RT$$

It is also possible to use these data to calculate $\Delta S^{\ddagger}$ by the formula[27a]

$$\frac{\Delta S^{\ddagger}}{4.576} = \log k - 10.753 - \log T + \frac{E_a}{4.576T}$$

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[27] For reviews, see Binsch, *Top. Stereochem.* **3,** 97–192 (1968); and Johnson, *Adv. Magn. Reson.* **1,** 33–102 (1965). See also Allerhand, Gutowsky, Jonas, and Meinzer, *J. Am. Chem. Soc.* **88,** 3185 (1966).

[27a] For a derivation of this equation, see Bunnett, in Ref. 8, pt. 1, p. 404.

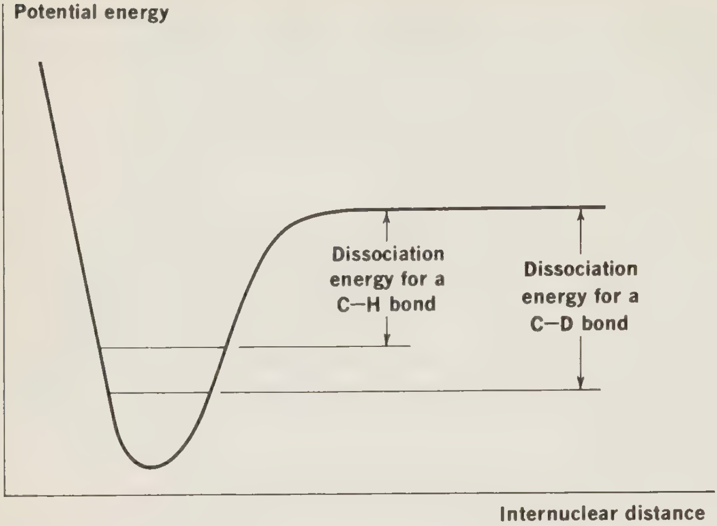
Potential energy
Dissociation energy for a C—H bond
Dissociation energy for a C—D bond
Internuclear distance

Figure 5 A C—D bond has a lower zero-point energy than does a corresponding C—H bond; thus the dissociation energy is higher.

Isotope Effects

When a hydrogen in a reactant molecule is replaced by deuterium, there is often a change in the rate. Such changes are known as *deuterium isotope effects*[28] and are expressed by the ratio k_H/k_D. The ground-state vibrational energy (called the zero-point vibrational energy) of a bond depends on the mass of the atoms and is lower when the reduced mass is higher.[29] Therefore, D—C, D—O, D—N bonds, etc., have lower energies in the ground state than the corresponding H—C, H—O, H—N bonds, etc. Complete dissociation of a deuterium bond therefore requires more energy than that for a corresponding hydrogen bond in the same environment (Figure 5). If an H—C, H—O, or H—N bond is not broken at all in a reaction or is broken in a non-rate-determining step, substitution of deuterium for hydrogen causes no change in the rate (see below for an exception to this statement), but if the bond is broken in the rate-determining step, the rate must be lowered by the substitution.

This provides a valuable diagnostic tool for determination of mechanism. For example, in the bromination of acetone (reaction **2-4**)

$$CH_3COCH_3 + Br_2 \longrightarrow CH_3COCH_2Br$$

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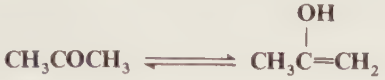
[28] For a monograph, see Melander, "Isotope Effects on Reaction Rates," The Ronald Press Company, New York, 1960. For reviews, see Saunders, in Ref. 8, pt. 1, pp. 211–255; Wolfsberg, *Annu. Rev. Phys. Chem.* **20**, 449–478 (1969); Bigeleisen, Lee, and Mandel, *Annu. Rev. Phys. Chem.* **24**, 407–440 (1973); Saunders, *Surv. Prog. Chem.* **3**, 109–146 (1966); Simon and Palm, *Angew. Chem. Int. Ed. Engl.* **5**, 920–933 (1966) [*Angew. Chem.* **78**, 993–1007]; Bell, "The Proton in Chemistry," 2d ed., pp. 226–296, Cornell University Press, Ithaca, N.Y., 1973, *Chem. Soc. Rev.* **3**, 513–544 (1974); Westheimer, *Chem. Rev.* **61**, 265–273 (1961); Wiberg, *Chem. Rev.* **55**, 713–743 (1955); Jencks, Ref. 12, pp. 243–281; and Thornton, "Solvolysis Mechanisms," pp. 194–229, The Ronald Press Company, New York, 1964.

[29] The reduced mass μ of two atoms connected by a covalent bond is

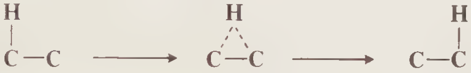
$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$

the fact that the rate is independent of the bromine concentration led to the postulate that the rate-determining step was tautomerization of the acetone:



$$CH_3COCH_3 \rightleftharpoons CH_3\overset{\displaystyle OH}{\overset{|}{C}}{=}CH_2$$

In turn, the rate-determining step of the tautomerization involves cleavage of a C—H bond (see reaction **2-3**). Thus there should be a substantial isotope effect if deuterated acetone is brominated. In fact, k_H/k_D was found to be about 7.[30] Deuterium isotope effects usually range from 1 (no isotope effect at all) to about 9 or 10, though in a few cases larger[31] or smaller values have been reported. Values of k_H/k_D which are smaller than 1 are called *inverse isotope effects.* Isotope effects are greatest when, in the transition state, the hydrogen is symmetrically bonded to the atoms between which it is being transferred.[32] Also, calculations show that isotope effects are at a maximum when the hydrogen in the transition state is on the straight line connecting the two atoms between which the hydrogen is being transferred and that for sufficiently nonlinear configurations they decrease to $k_H/k_D = 1$ to 2.[33] Of course, in open systems there is no reason for the transition state to be nonlinear, but this is not the case in many intramolecular mechanisms; e.g., in a 1,2 migration of a hydrogen



Transition
state

The substitution of tritium for hydrogen gives isotope effects which are numerically larger.[34] Isotope effects have also been observed with other elements, but they are much smaller, about 1.02 to 1.10. For example, $k_{^{12}C}/k_{^{13}C}$ for

$$Ph{*}CH_2Br + CH_3O^- \xrightarrow{CH_3OH} Ph{*}CH_2OCH_3$$

is 1.053.[35] Although they are small, heavy-atom isotope effects can be measured quite accurately and are often very useful.

Deuterium isotope effects have been found even where it is certain that the C—H bond does not break at all in the reaction. Such effects are called *secondary isotope effects,*[36] the term *primary isotope effect* being reserved for the type discussed previously. Secondary isotope effects can be divided, for convenience, into α and β effects, although it is possible that they have the same cause. In a β secondary isotope effect, substitution of deuterium for hydrogen β to the position of bond breaking slows the reaction. An example is solvolysis of isopropyl bromide:

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[30] Reitz and Kopp, *Z. Phys. Chem., Abt. A* **184,** 429 (1939).

[31] For an example of a reaction with a deuterium isotope effect of 24.2, see Lewis and Funderburk, *J. Am. Chem. Soc.* **89,** 2322 (1967). The high isotope effect in this case has been ascribed to *tunneling* of the proton: because it is so small a hydrogen atom can sometimes get through a thin potential barrier without going over the top, i.e., without obtaining the usually necessary activation energy. A deuterium, with a larger mass, is less able to do this. The phenomenon of tunneling is a consequence of the uncertainty principle and is important only for electrons and hydrogen atoms. k_H/k_T for the same reaction is 79: Lewis and Robinson, *J. Am. Chem. Soc.* **90,** 4337 (1968).

[32] Kwart and Latimore, *J. Am. Chem. Soc.* **93,** 3770 (1971); Pryor and Kneipp, *J. Am. Chem. Soc.* **93,** 5584 (1971); Bell and Cox, *J. Chem. Soc. B* 783 (1971); and references cited in these papers.

[33] More O'Ferrall, *J. Chem. Soc. B* 785 (1970), and references cited therein.

[34] Swain, Stivers, Reuwer, and Schaad, *J. Am. Chem. Soc.* **80,** 5885 (1958). For a review of tritium isotope effects, see Yakushin, *Russ. Chem. Rev.* **31,** 123–131 (1962).

[35] Stothers and Bourns, *Can. J. Chem.* **40,** 2007 (1962).

[36] For reviews see Laszlo and Welvart, *Bull. Soc. Chim. Fr.* 2412–2438 (1966); Halevi, *Prog. Phys. Org. Chem.* **1,** 109–221 (1963); and Shiner, Mahler, Baker, and Hiatt, *Ann. N.Y. Acad. Sci.* **84,** 583–595 (1960).

$$(CH_3)_2CHBr + H_2O \xrightarrow{k_H} (CH_3)_2CHOH$$

$$(CD_3)_2CHBr + H_2O \xrightarrow{k_D} (CD_3)_2CHOH$$

where k_H/k_D was found to be 1.34.[37] The cause of β isotope effects has been a matter of much controversy, but they are most likely due to hyperconjugation effects in the transition state. The effects are greatest when the transition state has considerable carbonium-ion character.[38] Although the C—H bond in question is not broken in the transition state, the carbonium ion is stabilized by hyperconjugation involving this bond. Because of hyperconjugation, the difference in vibrational energy between the C—H bond and the C—D bond in the transition state is less than it is in the ground state, so that the reaction is slowed by substitution of deuterium for hydrogen.

Support for hyperconjugation as the major cause of β isotope effects is the fact that the effect is greatest when D is trans to the leaving group[39] (because of the requirement that all atoms in a resonance system be coplanar, planarity of the D—C—C—X system would most greatly increase the hyperconjugation), and the fact that secondary isotope effects can be transmitted through unsaturated systems.[40] There is evidence that at least some β isotope effects are steric in origin[41] (e.g., a CD_3 group has a smaller steric requirement than a CH_3 group), and a field-effect explanation has also been suggested (CD_3 is apparently a better electron donor than CH_3[42]), but hyperconjugation is the most probable cause in most instances.[43] Part of the difficulty in attempting to explain these effects is their small size, ranging only as high as about 1.5. Another complicating factor is that they may change with temperature. In one case[44] k_H/k_D was 1.00 ± 0.01 at 0°C, 0.90 ± 0.01 at 25°C, and 1.15 ± 0.09 at 65°C. Whatever the cause, there seems to be a good correlation between β secondary isotope effects and carbonium character in the transition state, and they are thus a useful tool for probing mechanisms.

The other type of secondary isotope effect results from a replacement of hydrogen by deuterium at the carbon containing the leaving group. These (called α *secondary isotope effects*) are varied, values so far reported ranging from 0.87 to 1.26.[45] These effects are also correlated with carbonium-ion character. Nucleophilic substitutions which do not proceed through carbonium-ion intermediates (SN2 reactions) have α isotope effects near unity.[46] Those which do involve carbonium ions (SN1 reactions) have higher α isotope effects, which depend on the nature of the leaving group.[47] The accepted explanation for α isotope effects is that one of the bending C—H vibrations is affected by the substitution of D for H more or less strongly in the transition state than in the ground state.[48] Depending on the nature of the transition state, this may increase or decrease the rate of the reaction. γ secondary isotope effects have also been reported.[49]

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[37] Leffek, Llewellyn, and Robertson, *Can. J. Chem.* **38**, 2171 (1960).

[38] Bender and Feng, *J. Am. Chem. Soc.* **82**, 6318 (1960); Jones and Bender, *J. Am. Chem. Soc.* **82**, 6322 (1960).

[39] Shiner, Murr, and Heinemann, *J. Am. Chem. Soc.* **85**, 2413 (1963); Shiner and Humphrey, *J. Am. Chem. Soc.* **85**, 2416 (1963); Shiner and Jewett, *J. Am. Chem. Soc.* **86**, 945 (1964).

[40] Shiner and Kriz, *J. Am. Chem. Soc.* **86**, 2643 (1964). See also Shiner, Buddenbaum, Murr, and Lamaty, *J. Am. Chem. Soc.* **90**, 418 (1968).

[41] Bartell, *J. Am. Chem. Soc.* **83**, 3567 (1961); Brown and McDonald, *J. Am. Chem. Soc.* **88**, 2514 (1966); Brown, Azzaro, Koelling, and McDonald, *J. Am. Chem. Soc.* **88**, 2520 (1966); Kaplan and Thornton, *J. Am. Chem. Soc.* **89**, 6644 (1967); Carter and Dahlgren, *Acta Chem. Scand.* **24**, 633 (1970); Leffek and Matheson, *Can. J. Chem.* **49**, 439 (1971); Sherrod and Boekelheide, *J. Am. Chem. Soc.* **94**, 5513 (1972).

[42] Halevi, Nussim, and Ron, *J. Chem. Soc.* 866 (1963); Halevi and Nussim, *J. Chem. Soc.* 876 (1963).

[43] Karabatsos, Sonnichsen, Papaioannou, Scheppele, and Shone, *J. Am. Chem. Soc.* **89**, 463 (1967); Kresge and Preto, *J. Am. Chem. Soc.* **89**, 5510 (1967); Jewett and Dunlap, *J. Am. Chem. Soc.* **90**, 809 (1968).

[44] Halevi and Margolin, *Proc. Chem. Soc.* 174 (1964).

[45] Shiner, Buddenbaum, Murr, and Lamaty, Ref. 40; Harris, Hall, and Schleyer, *J. Am. Chem. Soc.* **93**, 2551 (1971).

[46] For a reported exception, see Tanaka, Kaji, and Hayami, *Chem. Lett.* 1223 (1972).

[47] Shiner and Dowd, *J. Am. Chem. Soc.* **93**, 1029 (1971); Shiner and Fisher, *J. Am. Chem. Soc.* **93**, 2553 (1971); Willi, Ho, and Ghanbarpour, *J. Org. Chem.* **37**, 1185 (1972); and references cited in these papers.

Another kind of isotope effect is the *solvent isotope effect*.[50] Reaction rates often change when the solvent is changed from H_2O to D_2O or from ROH to ROD. These changes may be due to any of three factors or a combination of all of them:

1. The solvent may be a reactant. If an O—H bond of the solvent is broken in the rate-determining step, there will be a primary isotope effect. If the molecules involved are D_2O or D_3O^+ there may also be a secondary effect caused by the O—D bonds which are not breaking.
2. The substrate molecules may become labeled with deuterium by rapid hydrogen exchange, and then the newly labeled molecule may become cleaved in the rate-determining step.
3. The extent or nature of solvent-solute interactions may be different in the deuterated and nondeuterated solvents; and this may change the energies of the transition state and hence the activation energy of the reaction. These are secondary isotope effects. Two physical models for this third factor have been constructed.[51] It is obvious that in many cases the first and third factors at least, and often the second, are working simultaneously. Attempts have been made to separate them.[52]

The methods described in this chapter are not the only means of determining mechanisms. In an attempt to elucidate a mechanism, the investigator is limited only by his ingenuity.

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[48] Streitwieser, Jagow, Fahey, and Suzuki, *J. Am. Chem. Soc.* **80,** 2326 (1958).

[49] Leffek, Llewellyn, and Robertson, *J. Am. Chem. Soc.* **82,** 6315 (1960); *Chem. Ind. (London)* 588 (1960); Werstiuk, Timmins, and Cappelli, *Can. J. Chem.* **51,** 3473 (1973).

[50] For reviews, see Schowen, *Prog. Phys. Org. Chem.* **9,** 275–332 (1972); Gold, *Adv. Phys. Org. Chem.* **7,** 259–331 (1969); and Laughton and Robertson, in Coetzee and Ritchie, "Solute-Solvent Interactions," pp. 399–538, Marcel Dekker, Inc., New York, 1969. For a review of the effect of isotopic changes in the solvent on the properties of nonreacting solutes, see Arnett and McKelvey, in Coetzee and Ritchie, cited above, pp. 343–398.

[51] Swain and Bader, *Tetrahedron* **10,** 182 (1960); Swain, Bader, and Thornton, *Tetrahedron* **10,** 200 (1960); Bunton and Shiner, *J. Am. Chem. Soc.* **83,** 42, 3207, 3214 (1961); Swain and Thornton, *J. Am. Chem. Soc.* **83,** 3884, 3890 (1961). See also Mitton, Gresser, and Schowen, *J. Am. Chem. Soc.* **91,** 2045 (1969).

[52] More O'Ferrall, Koeppl, and Kresge, *J. Am. Chem. Soc.* **93,** 9 (1971).

Seven
Photochemistry

Most reactions carried out in organic chemistry laboratories take place between molecules all of which are in their ground electronic states. In a *photochemical reaction*,[1] however, a reacting molecule has previously been promoted by absorption of light to an electronically excited state. A molecule in an excited state must lose its extra energy in some manner; it cannot remain in the excited condition for long. However, a chemical reaction is not the only possible means of relinquishing the extra energy. In this chapter we shall first discuss electronically excited states and the processes of promotion to these states. Then we shall examine the possible pathways open to the excited molecule, first the physical and then the chemical pathways. The subject of electronic spectra is closely related to photochemistry.

Excited States and the Ground State

In Chapter 1 it was mentioned that electrons can move from the ground-state energy level to a higher one and that outside energy is required for this. In a photochemical process this energy is in the form of light. Light of any wavelength has associated with it an energy value given by $E = h\nu$, where ν is the frequency of the light (ν = velocity of light c divided by the wavelength λ) and h is Planck's constant. Since the energy levels of a molecule are quantized, the amount of energy required to raise an electron in a given molecule from one level to a higher one is a fixed quantity. Only light with exactly the frequency corresponding to this amount of energy will cause the electron to move to the higher level. If light of another frequency is sent through a sample, it will pass out without a loss in intensity, since the molecules will not absorb it. However, if light of the correct frequency is passed in, the energy will be used by the molecules for electron promotion and hence the light that leaves the sample will be diminished in intensity or altogether gone. A *spectrophotometer* is a device which allows light of a given frequency to pass through a sample and which detects (by means of a phototube) the amount of light which has been transmitted, i.e., not absorbed. The instrument compares the intensity of the transmitted light with that of the incident light. The user of a manual spectrophotometer may select visible or uv light of any frequency, pass it through the sample, and read the amount of absorption. Automatic instruments gradually and continuously change the frequency, and an automatic recorder plots a graph of absorption versus frequency or wavelength.

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[1] For a treatise, see Calvert and Pitts, "Photochemistry," John Wiley & Sons, Inc., New York, 1966. For monographs, see Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, 1965; Kan, "Organic Photochemistry," McGraw-Hill Book Company, New York, 1966; Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corporation, New York, 1967; Cox and Kemp, "Introductory Photochemistry," McGraw-Hill Book Company, New York, 1971; Simons "Photochemistry and Spectroscopy," Wiley-Interscience, New York, 1971; Cundall and Gilbert, "Photochemistry," Appleton-Century-Crofts, New York, 1970; Coxon and Halton, "Organic Photochemistry," Cambridge University Press, London, 1974; and Arnold, Baird, Bolton, Brand, Jacobs, de Mayo, and Ware, "Photochemistry," Academic Press, Inc., New York, 1974. See also the series *Advances in Photochemistry*, *Organic Photochemistry*, and *Excited States*.

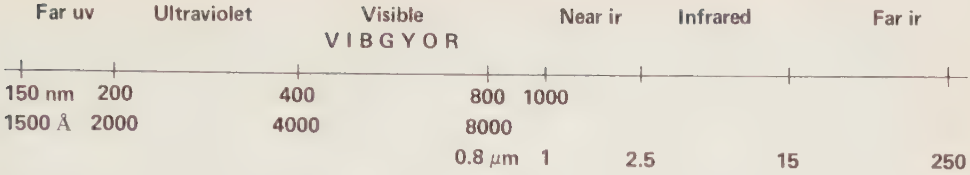

Figure 1 The uv, visible, and ir portions of the spectrum.

The energy of electronic transitions corresponds to light in the visible, uv, and far-uv regions of the spectrum (Figure 1). Absorption positions are normally expressed in wavelength units; either in angstroms (Å) or in nanometers (nm).[2] If a compound absorbs in the visible, it is colored, possessing a color complementary to that which is absorbed. Thus a compound absorbing in the violet is yellow. The far-uv region is studied by organic chemists less often than the visible or ordinary uv regions because special vacuum instruments are required owing to the fact that oxygen and nitrogen absorb in these regions.

From these considerations it would seem that an electronic spectrum should consist of one or more sharp peaks, each corresponding to the transfer of an electron from one electronic level to another. In practice the peaks are seldom sharp. In order to understand why, it is necessary to realize that molecules are constantly vibrating and rotating and that these motions are also quantized. A molecule at any time is in a given electronic state but also in a given vibrational and rotational state. The difference between two adjacent vibrational levels is much smaller than the difference between adjacent electronic levels, and the difference between adjacent rotational levels is smaller still. A typical situation is shown in Figure 2. When an electron moves from one electronic level to another, it moves from a given vibrational and rotational level within that electronic level to some vibrational and rotational level at the next electronic level. A given sample contains a large number of molecules, and even if all of them are in the ground electronic state, they are still distributed among the vibrational and rotational states (though the ground vibrational state V_0 is most heavily populated). This means that not just one wavelength of light will be absorbed but a number of them close together, with the most probable transition causing the most intense peak. But in molecules containing more than a few atoms there are so many possible transitions and these are so close together that what is observed is a relatively broad band. The height of the peak depends on the number of molecules making the transition and is proportional to log ε, where ε is the *extinction coefficient*. The extinction coefficient may be expressed by $\varepsilon = E/cl$, where c is the concentration in moles per liter, l is the cell length in centimeters, and $E = \log I_0/I$, where I_0 is the intensity of the incident light and I of the transmitted light. The wavelength is usually reported as $\lambda_{\max}$, meaning that this is the top of the peak. Purely vibrational transitions, such as between V_0 and V_1 of E_1, which require much less energy, are found in the ir region and are the basis of ir spectra. Purely rotational transitions are found in the far-ir and microwave (beyond the far-ir) regions.[3]

A uv or visible absorption peak is caused by the promotion of an electron in one orbital (usually a ground-state orbital) to a higher orbital. Normally the amount of energy necessary to make this transition depends mostly on the nature of the two orbitals involved and much less on the rest of the molecule. Therefore, a simple functional group such as the C=C double bond always causes absorption in the same general area. A group which causes absorption is called a *chromophore*.

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[2] Formerly, millimicrons (mμ) were frequently used; numerically they are the same as nanometers.

[3] For a review of how chemical information is obtained from microwave spectra, see Lide, *Surv. Prog. Chem.* **5**, 95–127 (1969).

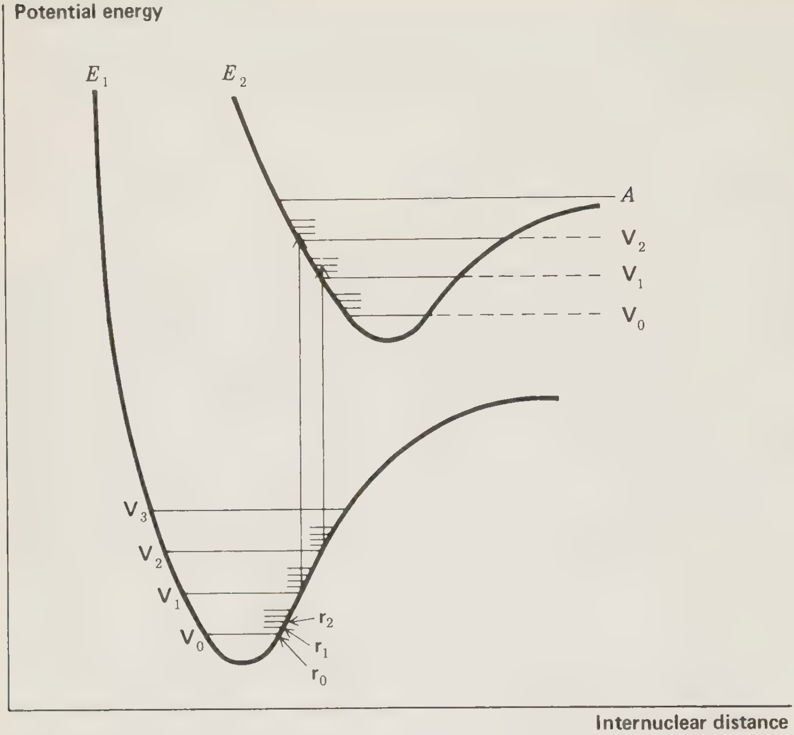

Figure 2 Energy curves for a diatomic molecule. Two possible transitions are shown. When an electron has been excited to the point marked *A*, the molecule may cleave (p. 214).

The amount of light energy necessary to raise an electron to a higher level is called a *quantum* or a *photon;* 1 mol of photons is 1 *einstein.* Obviously, an einstein of light represents a different amount of energy depending on which molecule absorbs it and which energy levels are involved.

Singlet and Triplet States. "Forbidden" Transitions

In most organic molecules all electrons in the ground state are paired, each member of a pair possessing opposite spin, as demanded by the Pauli principle. When one of a pair of electrons is promoted to an orbital of higher energy, however, the Pauli principle no longer applies because the two electrons are no longer sharing an orbital, and the promoted electron may, in principle, have the same spin as its former partner or the opposite spin. As we have seen in Chapter 5, a molecule in which two unpaired electrons have the same spin is called a *triplet*, while one in which all spins are paired is a *singlet*. Thus, at least in principle, for every excited singlet state there is a corresponding triplet state. In most cases, the triplet state has a lower energy than the corresponding singlet because of Hund's rule (p. 7). Therefore a different amount of energy and hence a different wavelength is required to promote an electron from the ground state (which is almost always a singlet) to an excited singlet than to the corresponding triplet state.

It would thus seem that promotion of a given electron in a molecule could result either in a singlet or a triplet excited state depending on the amount of energy added. However, this is often not the case because transitions between energy levels are governed by selection rules which state that certain transitions are "forbidden." There are several types of "forbidden" transitions, two of which are more important than the others.

1. *Spin-forbidden transitions.* Transitions in which the spin of an electron changes are not allowed, because a change from one spin to the opposite involves a change in angular momentum, and such a change would violate the law of conservation of angular momentum. Therefore singlet-triplet and triplet-singlet transitions are forbidden, whereas singlet-singlet and triplet-triplet transitions are allowed.
2. *Symmetry-forbidden transitions.* Among the transitions in this class are those in which a molecule has a center of symmetry. In such cases, a $g \rightarrow g$ or $u \rightarrow u$ transition (see p. 9) is "forbidden," while a $g \rightarrow u$ or $u \rightarrow g$ transition is allowed.

We have put the word "forbidden" into quotation marks because these transitions are not actually forbidden but only highly improbable. In most cases promotions from a singlet ground state to a triplet excited state are so improbable that they cannot be observed, and it is safe to state that in most molecules only singlet-singlet promotions take place. However, this rule does break down in certain cases, most often when a heavy atom (such as iodine) is present in the molecule, in which cases it can be shown from spectra that singlet-triplet promotions are occurring. Symmetry-forbidden transitions can frequently be observed, though usually with low intensity.

Types of Excitation

When an electron in a molecule is promoted (normally only one electron in any molecule), it usually goes into the lowest available vacant orbital, though promotion to higher orbitals is also possible if any are available. For most organic molecules there are consequently four types of electronic excitation:

1. $\sigma \rightarrow \sigma^*$. Alkanes, which have no n or π electrons, can be excited only in this way.[4]
2. $n \rightarrow \sigma^*$. Alcohols, amines, ethers, etc., can also be excited in this manner.
3. $\pi \rightarrow \pi^*$. This pathway is open to alkenes as well as to aldehydes, esters, etc.
4. $n \rightarrow \pi^*$. Aldehydes, ketones, esters, etc., can undergo this promotion as well as the other three.

The four excitation types above are listed in what is normally the order of decreasing energy. Thus light of the highest energy (in the far uv) is necessary for $\sigma \rightarrow \sigma^*$ excitation, while $n \rightarrow \pi^*$ promotions are caused by ordinary uv light. However, in some solvents the order may sometimes be altered.

In 1,3-butadiene (and other compounds with two conjugated double bonds) there are two π and two π^* orbitals (p. 32). The energy difference between the higher π (χ_2) and the lower π^* (χ_3) orbital is less than the difference between the π and π^* orbitals of ethylene. Therefore 1,3-butadiene requires less energy than ethylene, and thus light of a higher wavelength, to promote an electron. This is a general phenomenon, and it may be stated that, in general, *the more conjugation in a molecule, the more the absorption is displaced toward higher wavelengths* (see Table 1).[5] When a chromophore absorbs at a certain wavelength and the substitution of one group for another causes absorption at a higher wavelength, a *bathochromic shift* is said to have occurred. The opposite kind of shift is called *hypsochromic*.

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[4] An n electron is one in an unshared pair.

[5] Bohlmann and Mannhardt, *Chem. Ber.* **89**, 1307 (1956).

TABLE 1 Ultraviolet absorption[5] of $CH_3-(CH=CH)_n-CH_3$ for some values of n

n	nm
2	227
3	263
6	352
9	413

Of the four excitation types listed above, the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ are far more important in organic photochemistry than the other two. Compounds containing C=O groups can be excited in both ways, giving rise to at least two peaks in the uv. These are often easy to distinguish, because $\pi \rightarrow \pi^*$ transitions are found farther toward the far uv and are generally much more intense (ε for $\pi \rightarrow \pi^*$ is usually about 100 to 10,000 compared with $\varepsilon = 10$ to 1000 for $n \rightarrow \pi^*$). However, there are many cases in which it is difficult to tell them apart. In such cases there are several methods which can be used,[6] one of which involves the measurement of the spectrum in different solvents. An increase in solvent polarity usually causes a hypsochromic shift in $n \rightarrow \pi^*$ transitions and a bathochromic shift in $\pi \rightarrow \pi^*$ transitions. For the $n \rightarrow \pi^*$ transition the explanation is that hydrogen bonding between a hydrogen of the solvent and the oxygen of the C=O group lowers the energy of the ground state without doing the same for the excited state,[7] so that more energy is required for excitation. Acetone, for example, has an $n \rightarrow \pi^*$ peak at 265 nm in water but 279 nm in hexane. The bathochromic shift in the case of $\pi \rightarrow \pi^*$ transitions is more difficult to explain but may be caused by the formation of charge-transfer or π complexes.[8]

As we have seen, a chromophore is a group which causes a molecule to absorb light. Examples of chromophores in the visible or uv are C=O, N=N,[9] Ph, and NO_2. Some chromophores in the far uv (beyond 200 nm) are C=C, C≡C, Cl, and OH. An *auxochrome* is a group which displaces (through resonance) and usually intensifies the absorption of a chromophore present in the same molecule. Groups such as Cl, OH, and NH_2 are generally regarded as auxochromes since they shift (usually bathochromically) the uv and visible bands of chromophores such as Ph or C=O (see Table 2).[10] Since auxochromes are themselves chromophores (to be sure, generally in the far uv), it is sometimes difficult to decide which group in a molecule is an auxochrome and which a chromophore. For example, in acetophenone (PhCOMe) is the chromophore Ph or C=O? In such cases the distinction becomes practically meaningless.

Properties and Nomenclature of Excited States

An excited state of a molecule may be regarded as a distinct chemical species, different from the ground state of the same molecule and from other excited states. It is obvious that we need some method of naming excited states. Unfortunately, there are several methods in use, depending on

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[6] See Calvert and Pitts, Ref. 1, pp. 260–262.

[7] There is evidence that the energy of the initially formed excited state is actually *increased* by desolvation in more polar solvents: Haberfield, *J. Am. Chem. Soc.* **96,** 6526 (1974).

[8] For a discussion, see Jaffé and Orchin, "Theory and Applications of Ultraviolet Spectrosopy," John Wiley & Sons, Inc., New York, 1962, pp. 188–195.

[9] For a review of the azo group as a chromophore, see Rau, *Angew. Chem. Int. Ed. Engl.* **12,** 224–235 (1973) [*Angew. Chem.* **85,** 248–258].

[10] These values are from Ref. 8, p. 257.

TABLE 2 Some uv peaks of substituted benzenes in water, or water with a trace of methanol (for solubility)

Note how auxochromes shift and usually intensify the peaks[10]

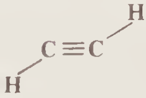
	Primary band		Secondary band	
	λ_{max}, nm	ε_{max}	λ_{max}, nm	ε_{max}
PhH	203.5	7,400	254	204
PhCl	209.5	7,400	263.5	190
PhOH	210.5	6,200	270	1,450
PhOMe	217	6,400	269	1,480
PhCN	224	13,000	271	1,000
PhCOOH	230	11,600	273	970
$PhNH_2$	230	8,600	280	1,430
PhO^-	235	9,400	287	2,600
PhAc	245.5	9,800		
PhCHO	249.5	11,400		
$PhNO_2$	268.5	7,800		

whether one is primarily interested in photochemistry, spectroscopy, or molecular-orbital theory.[11] One of the most common methods simply designates the original and newly occupied orbitals, with or without a superscript to indicate singlet or triplet. Thus the singlet state arising from promotion of a π to a π^* orbital in ethylene would be the $^1(\pi,\pi^*)$ state or the π,π^* singlet state. Another very common method may be used even in cases where one is not certain which orbitals are involved. The lowest-energy excited state is called S_1, the next S_2, etc., and triplet states are similarly labeled T_1, T_2, T_3, etc. In this notation the ground state is S_0. In another convention, the *symmetry notation*, the H_2 $\sigma \rightarrow \sigma^*$ transition is written

$$^1\Sigma_u^+ \leftarrow {}^1\Sigma_g^+$$

Here the superscript 1 means singlet, u and g refer to ungerade and gerade, respectively (p. 9), and the + means that reflection through a plane of symmetry leaves the sign of the wave function unaltered. A Σ state is one in which net orbital angular momentum about the molecular axis is zero. The ground state of ethylene in this notation is ^1A_g. In the symmetry notation the state of higher energy is written first, whether the process is absorption or emission. The arrow shows the direction of the transition. Other notational systems exist too, but in this book we shall confine ourselves to the $^1(\pi,\pi^*)$ type and the S_0, S_1, T_1 type.

The properties of excited states are not easy to measure because of their generally short lifetimes and low concentrations, but enough work has been done for us to know that they often differ from the ground state in geometry, dipole moment, and acid or base strength.[12] For example, acetylene, which is linear in the ground state, has a trans geometry



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[11] For discussions of excited-state notation and other terms in the photochemistry vocabulary, see Pitts, Wilkinson, and Hammond, *Adv. Photochem.* **1**, 1–21 (1963); Porter, Balzani, and Moggi, *Adv. Photochem.* **9**, 147–196 (1974).

[12] For a review of the structures of excited states, see Brand and Williamson, *Adv. Phys. Org. Chem.* **1**, 365–423 (1963).

TABLE 3 Typical energies for some covalent single bonds (see Table 6, Chapter 1) and the corresponding approximate wavelengths

Bond	E, kcal/mol	λ, nm
C—H	95	300
C—O	88	325
C—C	83	345
Cl—Cl	58	495
O—O	35	820

with approximately sp^2 carbons in the $^1(\pi,\pi^*)$ state.[13] Similarly, the $^1(\pi,\pi^*)$ and the $^3(\pi,\pi^*)$ states of ethylene have a perpendicular and not a planar geometry,[14] and the $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states of formaldehyde are both pyramidal.[15] Triplet species tend to stabilize themselves by distortion, which relieves interaction between the unpaired electrons. Obviously, if the geometry is different, the dipole moment will probably differ also; and the change in geometry and electron distribution often results in a change in acid or base strength.[15a] For example, the S_1 state of 2-naphthol is a much stronger acid (pK = 3.1) than the ground state (S_0) of the same molecule (pK = 9.5).[16]

Photolytic Cleavage

We have said that when a molecule absorbs a quantum of light, it is promoted to an excited state. Actually, that is not the only possible outcome. Because the energy of visible and uv light is of the same order of magnitude as that of covalent bonds (Table 3), another possibility is that the molecule may cleave into two parts, a process known as *photolysis*. There are three situations which may lead to cleavage.

1. The promotion may bring the molecule to a vibrational level so high that it lies above the right-hand portion of the E_2 curve (line A in Fig. 2). In such a case the excited molecule cleaves at its first vibration.

2. Even where the promotion is to a lower vibrational level, one which lies wholly within the E_2 curve (such as V_1 or V_2), the molecule may still cleave. As Figure 2 shows, equilibrium distances are greater in excited states than in the ground state. The *Franck-Condon principle* states that promotion of an electron takes place much faster than a single vibration (the promotion takes about 10^{-15} sec; a vibration about 10^{-12} sec). Therefore, when an electron is suddenly promoted, even to a low vibrational level, the distance between the atoms is essentially unchanged and the bond finds itself in a compressed condition, like a pressed-in spring; this condition may be relieved by an outward surge which is sufficient to break the bond.

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[13] Ingold and King, *J. Chem. Soc.* 2702, 2704, 2708, 2725, 2745 (1953).

[14] Merer and Mulliken, *Chem. Rev.* **69**, 639–656 (1969).

[15] Robinson and DiGiorgio, *Can. J. Chem.* **36**, 31 (1958); Buenker and Peyerimhoff, *J. Chem. Phys.* **53**, 1368 (1970); Garrison, Schaefer, and Lester, *J. Chem. Phys.* **61**, 3039 (1974). For a review of excited states of formaldehyde, see Moule and Walsh, *Chem. Rev.* **75**, 67–84 (1975).

[15a] For a review of acid-base properties of excited states, see Ireland and Wyatt, *Adv. Phys. Org. Chem.* **12**, 131–221 (1976).

[16] Weller, *Z. Phys. Chem. (Frankfurt am Main)* **3**, 238 (1955), *Discuss. Faraday Soc.* **27**, 28 (1959).

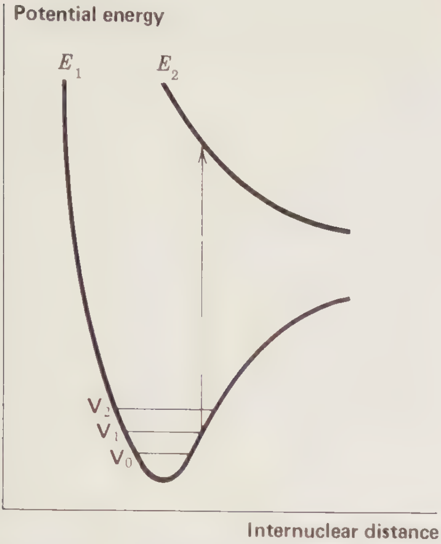

Figure 3 Promotion to a dissociative state results in bond cleavage

3. In some cases the excited state is entirely dissociative (Figure 3), i.e., there is no distance where attraction outweighs repulsion, and the bond must cleave. An example is the hydrogen molecule, where a $\sigma \rightarrow \sigma^*$ promotion always results in cleavage.

A photolytic cleavage may break the molecule into two smaller molecules or into two free radicals (see p. 220). Cleavage into two ions, though known, is much rarer. Once free radicals are produced by a photolysis, they behave like free radicals produced in any other way (Chapter 5) except that they may be in excited states, and this can cause differences in behavior.

The Fate of the Excited Molecule: Physical Processes

When a molecule has been photochemically promoted to an excited state, it does not remain there for long. Most promotions are from the S_0 to the S_1 state. As we have seen, promotions from S_0 to triplet states are "forbidden." Promotions to S_2 and higher singlet states take place, but in liquids and solids these higher states usually drop very rapidly to the S_1 state (about 10^{-13} to 10^{-11} sec). The energy which is lost when an S_2 or S_3 molecule drops to S_1 is given up in small increments to the environment by collisions with neighboring molecules. Such a process is called an *energy cascade*. In a similar manner, the initial excitation and the decay from higher singlet states initially populate many of the vibrational levels of S_1, but these also cascade, down to the lowest vibrational level of S_1. Therefore, in most cases, the lowest vibrational level of the S_1 state is the only important excited singlet state. This state can undergo various physical and chemical processes. In the following list, we shall describe the physical pathways open to molecules in the S_1 and excited triplet states. These pathways are also shown in a modified Jablonski diagram (Figure 4) and in Table 4.

1. A molecule in the S_1 state can cascade down through the vibrational levels of the S_0 state and thus return to the ground state by giving up its energy in small increments to the environment,

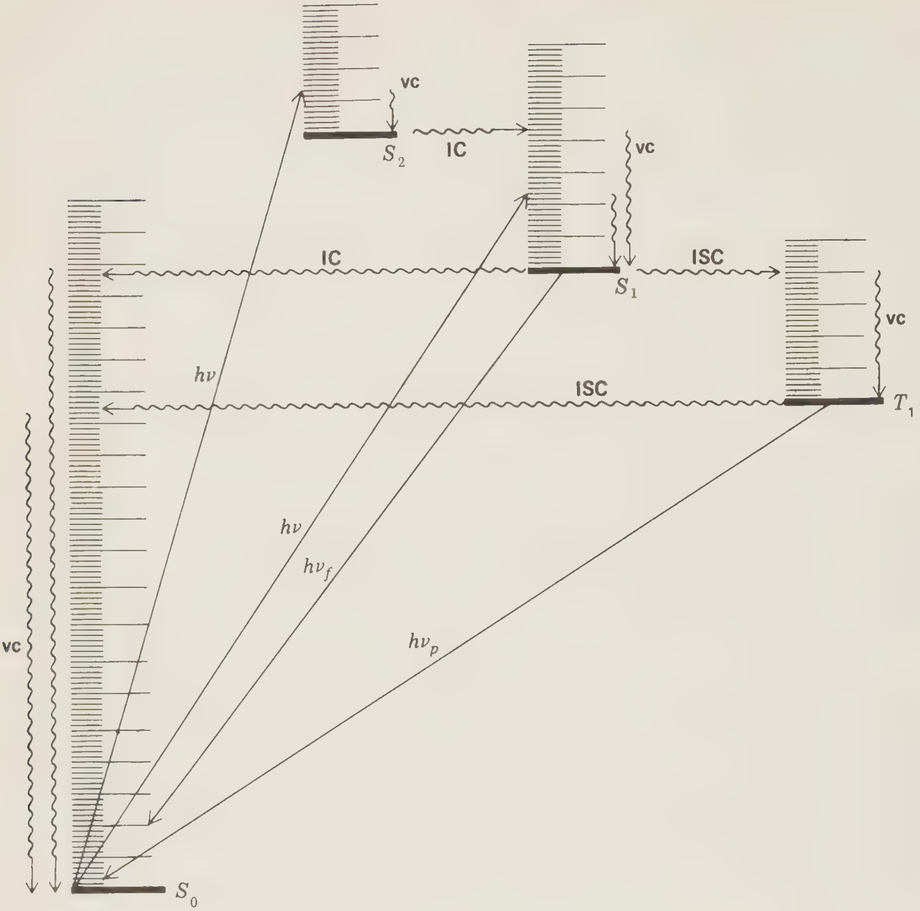

Figure 4 Modified Jablonski diagram showing transitions between excited states and the ground state. Radiative processes are shown by straight lines; radiationless processes by wavy lines. *IC* = internal conversion; *ISC* = intersystem crossing; *vc* = vibrational cascade; $h\nu_f$ = fluorescence; $h\nu_p$ = phosphorescence.

but this is generally quite slow because the amount of energy is large. The process is called *internal conversion* (IC). Because it is slow, most molecules in the S_1 state adopt other pathways.

2. A molecule in the S_1 state can drop to some low vibrational level of the S_0 state all at once by giving off the energy in the form of light. This process, which generally happens within 10^{-9} sec, is called *fluorescence*. This pathway is not very common either (because it is relatively slow) except for small molecules, e.g., diatomic, and rigid molecules, e.g., aromatic. For most other compounds fluorescence is very weak or undetectable. For compounds which do fluoresce, the fluorescence emission spectra are usually the approximate mirror images of the absorption spectra. This comes about because the fluorescing molecules all drop from the lowest vibrational level of the S_1 state to various vibrational levels of S_0, while excitation is from the lowest vibrational level of S_0 to various levels of S_1 (Figure 5). The only peak in common is the one resulting from transitions between the lowest vibrational levels of the two states. This peak is usually called the

TABLE 4 Physical processes undergone by excited molecules

The superscript v indicates vibrationally excited state: excited states higher than S_1 or T_1 are omitted

$S_0 + h\nu \rightarrow S_1{}^v$	Excitation
$S_1{}^v \rightsquigarrow S_1$ + heat	Vibrational relaxation
$S_1 \rightarrow S_0 + h\nu$	Fluorescence
$S_1 \rightsquigarrow S_0$ + heat	Internal conversion
$S_1 \rightsquigarrow T_1{}^v$	Intersystem crossing
$T_1{}^v \rightsquigarrow T_1$ + heat	Vibrational relaxation
$T_1 \rightarrow S_0 + h\nu$	Phosphorescence
$T_1 \rightsquigarrow S_0$ + heat	Intersystem crossing
$S_1 + \mathbf{A}_{(S_0)} \rightarrow S_0 + \mathbf{A}_{(S_1)}$	Singlet-singlet transfer (photosensitization)
$T_1 + \mathbf{A}_{(S_0)} \rightarrow S_0 + \mathbf{A}_{(T_1)}$	Triplet-triplet transfer (photosensitization)

0-0 peak, because the transition is from the V_0 level of one state to the V_0 level of another. In solution, even the 0-0 peak may be noncoincidental because the two states are solvated differently. Fluorescence nearly always arises from a $S_1 \rightarrow S_0$ transition, though azulene (p. 50) and its simple derivatives are exceptions,[17] emitting fluorescence from $S_2 \rightarrow S_0$ transitions.

Because of the possibility of fluorescence, any chemical reactions of the S_1 state must take place very fast, or fluorescence will occur before they can happen.

3. Most molecules (though by no means all) in the S_1 state can undergo an *intersystem crossing* (ISC) to the lowest triplet state T_1.[18] An important example is benzophenone, of which ap-

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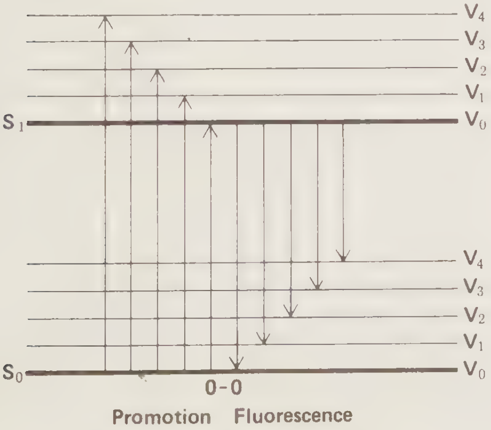
[17] For other exceptions see Hirayama, Gregory, and Lipsky, *J. Chem. Phys.* **58**, 4696 (1973); Gregory, Hirayama, and Lipsky, *J. Chem. Phys.* **58**, 4697 (1973); and references cited in these papers.

[18] Intersystem crossing from S_1 to T_2 and higher triplet states has also been reported in some aromatic molecules: Li and Lim, *J. Chem. Phys.* **57**, 605 (1972); Sharf and Silbey, *Chem. Phys. Lett.* **5**, 314 (1970). See also Schlag, Schneider, and Fischer, *Annu. Rev. Phys. Chem.* **22**, 465–526 (1971), pp. 490–494.

Figure 5 Promotion and fluorescence between S_1 and S_0 states.



proximately 100% of the molecules which are excited to the S_1 state cross over to the T_1.[19] Intersystem crossing from singlet to triplet is of course a "forbidden" pathway, since the angular-momentum problem (p. 211) must be taken care of, but this often takes place by compensations elsewhere in the system. Intersystem crossings take place without loss of energy. Since a singlet state usually has a higher energy than the corresponding triplet, this means that energy must be given up. One way for this to happen is for the S_1 molecule to cross to a T_1 state at a high vibrational level and then for the T_1 to cascade down to its lowest vibrational level (see Figure 4). This cascade is very rapid (10^{-12} sec). When T_2 or higher states are populated, they too rapidly cascade to the lowest vibrational level of the T_1 state.

4. A molecule in the T_1 state may return to the S_0 state by giving up heat (intersystem crossing) or light (this is called *phosphorescence*).[20] Of course the angular-momentum difficulty exists here, so that both intersystem crossing and phosphorescence are very slow ($\sim 10^{-3}$ to 10^1 sec). This means that T_1 states generally have much longer lifetimes than S_1 states. When they occur in the same molecule, phosphorescence is found at lower frequencies than fluorescence (because of the higher difference in energy between S_1 and S_0 than between T_1 and S_0) and is longer-lived (because of the longer lifetime of the T_1 state). Besides fluorescence and phosphorescence, there is a third type of emission, *slow fluorescence*. This has the same wavelength as fluorescence but occurs much more slowly. One way in which slow fluorescence is caused is when a molecule in the T_1 state acquires enough thermal energy to raise it to a higher vibrational level (equal in energy to the lowest S_1 level) and then crosses to S_1, which of course can then fluoresce. Slow fluorescence caused in this manner obviously increases with increasing temperature. Slow fluorescence can also be caused by a collision between two triplet molecules in which an excited singlet is produced.

5. If nothing else happens to it first, a molecule in an excited state (S_1 or T_1) may transfer its excess energy all at once to another molecule in the environment, in a process called *photosensitization*.[21] The excited molecule (which we shall call D for donor) thus drops to S_0 while the other molecule (A for acceptor) becomes excited:

$$\mathbf{D^* + A \longrightarrow A^* + D}$$

Thus there are *two* ways for a molecule to reach an excited state: by absorption of a quantum of light and by transfer from a previously excited molecule.[22] The donor D is also called a *photosensitizer*. This energy transfer is subject to the *Wigner spin-conservation rule*, which is actually a special case of the law of conservation of momentum we have encountered previously. According to the Wigner rule, the total electron spin does not change after the energy transfer. For example, when a triplet species interacts with a singlet the following are some allowed possibilities:[23]

$\underset{\mathbf{D^*}}{(\uparrow\uparrow)^*} + \underset{\mathbf{A}}{\uparrow\downarrow} \longrightarrow \underset{\mathbf{D}}{\uparrow\downarrow} + \underset{\mathbf{A^*}}{(\uparrow\uparrow)^*}$	singlet and triplet
$\longrightarrow \uparrow\uparrow\downarrow + \uparrow$	doublet and doublet (two free radicals)
$\longrightarrow \uparrow\uparrow + \downarrow + \uparrow$	triplet and two doublets
$\longrightarrow \uparrow\downarrow + \uparrow + \uparrow$	singlet and two doublets

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[19] Moore, Hammond, and Foss, *J. Am. Chem. Soc.* **83,** 2789 (1961).

[20] For a review of physical processes of triplet states, see Lower and El-Sayed, *Chem. Rev.* **66,** 199–241 (1966). For a review of physical and chemical processes of triplet states see Wagner and Hammond, *Adv. Photochem.* **5,** 21–156 (1968). For a review of phosphorescence, see Parker, *Adv. Photochem.* **2,** 305–383 (1964).

[21] For reviews, see Wilkinson, *Adv. Photochem.* **3,** 241–268 (1964); Turro, Dalton, and Weiss, *Org. Photochem.* **2,** 1–62 (1969).

[22] There is also a third way: in certain cases excited states can be produced directly in ordinary reactions. For a review, see White, Miano, Watkins, and Breaux, *Angew. Chem. Int. Ed. Engl.* **13,** 229–243 (1974) [*Angew. Chem.* **86,** 292–307].

[23] For additional tables of this kind, see Calvert and Pitts, Ref. 1, p. 89; and Cox and Kemp, Ref. 1, p. 22.

TABLE 5 Some triplet energies[25]

Compound	Energy, kcal/mol	Compound	Energy, kcal/mol
Benzene	85	Naphthalene	61
Phenol	82	Nitrobenzene	60
Aniline	77	Chrysene	57
Benzaldehyde	72	Biacetyl	55
Carbazole	70	Benzil	54
Benzophenone	69	Eosin	43
Fluorene	68	Anthracene	42
Quinoline	62	Naphthacene	29

In all these cases the products have three electrons spinning "up" and the fourth "down" (as do the starting molecules). However, formation of, say, two triplets ($\uparrow\uparrow + \downarrow\downarrow$) or two singlets ($\uparrow\downarrow + \uparrow\downarrow$), whether ground states or excited, would violate the rule.

In the two most important types of photosensitization, both of which are in accord with the Wigner rule, a triplet excited state generates another triplet, and a singlet generates a singlet:

$$\mathbf{D}_{T_1} + \mathbf{A}_{S_0} \longrightarrow \mathbf{A}_{T_1} + \mathbf{D}_{S_0} \qquad \text{triplet-triplet transfer}$$

$$\mathbf{D}_{S_1} + \mathbf{A}_{S_0} \longrightarrow \mathbf{A}_{S_1} + \mathbf{D}_{S_0} \qquad \text{singlet-singlet transfer}$$

Singlet-singlet transfer can take place over relatively long distances, e.g., 40 Å, but triplet transfer normally requires a collision between the molecules.[24] Both types of photosensitization can be useful for creating excited states when they are difficult to achieve by direct irradiation. Photosensitization is therefore an important method for carrying out photochemical reactions when a molecule cannot be brought to the desired excited state by direct absorption of light. Triplet-triplet transfer is especially important because triplet states are usually much more difficult to prepare by direct irradiation than singlet states (often impossible) and because triplet states, having longer lifetimes, are much more likely than singlets to transfer energy by photosensitization.

One way in which photosensitization can be detected is if the addition of a substance A to the original substance D quenches the fluorescence or phosphorescence of D. Another way is if A now exhibits fluorescence or phosphorescence or undergoes reactions which it would not in the absence of D.

Photosensitization is most efficient when the donor D* has a higher energy than the excited acceptor A*. The excess energy appears as kinetic energy of D and A*. Thus, before carrying out a photosensitization, one should know the energies of these states. Table 5 lists some triplet energies.[25] In choosing a photosensitizer one should avoid a compound which absorbs in the same region as the acceptor because the latter will then compete for the light.[26] For examples of the use of photosensitization to accomplish reactions, see pp. 753, 783.

It is also possible for an excited molecule D* to collide with a molecule A and for D* to drop to the ground state D, without A becoming excited, but with all the excess energy going into kinetic energy (translational, vibrational, rotational) of the recoiling A and D molecules. This, however, is relatively rare because the direct conversion of electronic to kinetic energy is a highly inefficient process.

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[24] Long-range triplet-triplet transfer has been observed in a few cases: Bennett, Schwenker, and Kellogg, *J. Chem. Phys.* **41**, 3040 (1964); Ermolaev and Sveshnikova, *Izv. Akad. Nauk SSSR, Ser. Fiz.* **26**, 29 (1962) [*C. A.* **57**, 1688 (1962)], *Opt. Spectrosc. (USSR)* **16**, 320 (1964).

[25] These values are taken from a much longer list in Turro, Ref. 1, p. 132, See also Calvert and Pitts, Ref. 1, pp. 297–298.

[26] For a review of other complications which may take place in photosensitized reactions, see Engel and Monroe, *Adv. Photochem.* **8**, 245–313 (1971).

TABLE 6 Primary photochemical reactions of an excited molecule **A—B—C**[28]

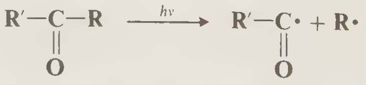
Examples are given in the text; the most common are (1), (2), *and, in the presence of a suitable acceptor molecule,* (7)

$(\mathrm{A{-}B{-}C}) \longrightarrow \mathrm{A{-}B}\cdot + \mathrm{C}\cdot$	Simple cleavage into free radicals	(1)
$(\mathrm{A{-}B{-}C}) \longrightarrow \mathrm{E} + \mathrm{F}$	Decomposition into molecules	(2)
$(\mathrm{A{-}B{-}C}) \longrightarrow \mathrm{A{-}C{-}B}$	Intramolecular rearrangement	(3)
$(\mathrm{A{-}B{-}C}) \longrightarrow \mathrm{A{-}B{-}C'}$	Photoisomerization	(4)
$(\mathrm{A{-}B{-}C}) \xrightarrow{\mathrm{RH}} \mathrm{A{-}B{-}C{-}H} + \mathrm{R}\cdot$	Hydrogen-atom abstraction	(5)
$(\mathrm{A{-}B{-}C}) \longrightarrow (\mathrm{ABC})_2$	Photodimerization	(6)
$(\mathrm{A{-}B{-}C}) \xrightarrow{\mathrm{A}} \mathrm{ABC} + \mathrm{A}^*$	Photosensitization	(7)

The Fate of the Excited Molecule: Chemical Processes

Although both excited singlet and triplet species can undergo chemical reactions, they are much more common for triplets, simply because these generally have much longer lifetimes. Excited singlet species, in most cases, have a lifetime of less than 10^{-10} sec and undergo one of the physical processes already discussed before they have a chance to react chemically. Therefore, photochemistry is largely the chemistry of triplet states.[27] Table 6[28] lists many of the possible chemical pathways which can be taken by an excited molecule.[28a] The first four of these are unimolecular reactions, and the others are bimolecular. In the case of bimolecular reactions it is rare for two excited molecules to react with each other (because the concentration of excited molecules at any one time is generally low); reactions are between an excited molecule and an unexcited molecule, either of the same or of another species. The reactions listed in Table 6 are primary processes. Secondary reactions often follow, since the primary products are frequently free radicals or carbenes; even if they are ordinary molecules, they are often in upper vibrational levels and so have excess energy. In almost all cases the primary products of photochemical reactions are in their ground states, though exceptions are known.[29] Of the reactions listed in Table 6, the most common are cleavage into free radicals (1), decomposition into molecules (2), and (in the presence of a suitable acceptor molecule) photosensitization (7), which we have already discussed. The following are some specific examples of reaction categories (1) to (6). Other examples are discussed in Part 2 of this book.

Category (1). Aldehydes and ketones absorb in the 230 to 330 nm region. This is assumed to result from an $n \rightarrow \pi^*$ singlet-singlet transition. The excited aldehyde or ketone can then cleave:[30]



$$\mathrm{R'{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R} \xrightarrow{h\nu} \mathrm{R'{-}\underset{\underset{\displaystyle O}{\|}}{C}\cdot + R\cdot}$$

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[27] For a review of the chemical reactions of triplet states, see Wagner and Hammond, Ref. 20. For other reviews of triplet states, see *Top. Curr. Chem.*, vols. 54 and 55 (1975).

[28] Adapted from Calvert and Pitts, Ref. 1, p. 367.

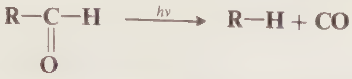
[28a] For a different kind of classification of photochemical reactions, see Dauben, Salem, and Turro, *Acc. Chem. Res.* **8,** 41–54 (1975).

[29] Turro, Lechtken, Lyons, Hautala, Carnahan, and Katz, *J. Am. Chem. Soc.* **95,** 2035 (1973).

[30] For full discussions of aldehyde and ketone photodissociative processes, see Calvert and Pitts, Ref. 1, pp. 368–427; Kan, Ref. 1, pp. 74–97; Coyle and Carless, *Chem. Soc. Rev.* **1,** 465–480 (1972); Pitts and Wan, in Patai, "The Chemistry of the Carbonyl Group," pp. 823–916, Wiley-Interscience, New York, 1966; Dalton and Turro, *Annu. Rev. Phys. Chem.* **21,** 499–560 (1970); Bérces, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 5, pp. 277–380, American Elsevier Publishing Company, New York, 1972; Turro, Dalton, Dawes, Farrington, Hautala, Morton, Niemczyk, and Shore, *Acc. Chem. Res.* **5,** 92–101 (1972); and Wagner and Hammond, Ref. 20, pp. 87–129. For reviews of the photochemistry of cyclic ketones, see Chapman and Weiss, *Org. Photochem.* **3,** 197–288 (1973); Morton and Turro, *Adv. Photochem.* **9,** 197–309 (1974). For reviews of the photochemistry of α-diketones, see Rubin, *Fortschr. Chem. Forsch.* **13,** 251–306 (1969); and Monroe, *Adv. Photochem.* **8,** 77–108 (1971).

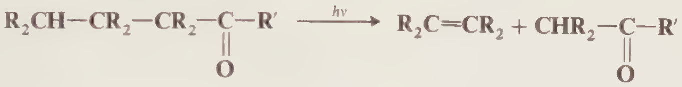
When applied to ketones, this is called *Norrish Type I cleavage* or often just *Type I cleavage*. In a secondary process, the acyl radical R′—CO• can then lose CO to give R′• radicals. Another example of a category (1) process is cleavage of Cl_2 to give two Cl atoms. Other bonds which are easily cleaved by photolysis are the O—O bonds of peroxy compounds and the C—N bonds of aliphatic azo compounds R—N=N—R. The latter is an important source of free radicals R•, since the other product is the very stable N_2.

Category (2). Aldehydes (though not generally ketones) can also cleave in this manner:



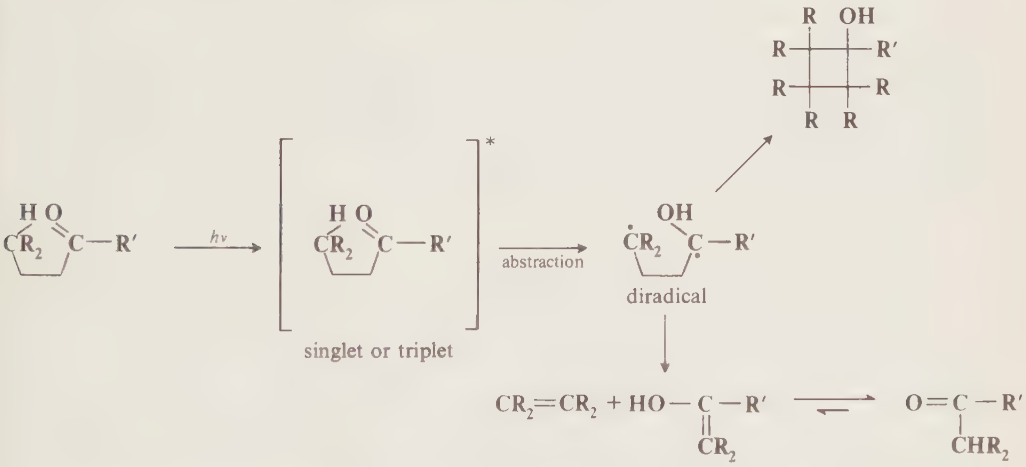
$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H} \xrightarrow{h\nu} \mathrm{R{-}H + CO}$$

This is an extrusion reaction (see Chapter 17). In another example of a process in category (2), aldehydes and ketones which have a γ-hydrogen can cleave in still another way (a β-elimination, see Chapter 17):



$$\mathrm{R_2CH{-}CR_2{-}CR_2{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'} \xrightarrow{h\nu} \mathrm{R_2C{=}CR_2 + CHR_2{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'}$$

This reaction, which is called *Norrish Type II cleavage*,[31] involves intramolecular abstraction of the γ-hydrogen followed by cleavage of the resulting diradical (a secondary reaction) to give an enol which tautomerizes to the aldehyde or ketone product:[32]



Both singlet and triplet n,π^* states undergo the reaction.[33] The intermediate diradical can also cyclize to a cyclobutanol, which is often a side product. Esters, anhydrides, and other carbonyl compounds can also give this reaction. The photolysis of ketene to CH_2 (p. 182) is still another example of a reaction in category (2). Both singlet and triplet CH_2 are generated, the latter in two ways:

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[31] For thorough discussions of the mechanism, see Dalton and Turro, Ref. 30, pp. 526–538; Wagner, *Acc. Chem. Res.* **4,** 168–177 (1971).

[32] This mechanism was proposed by Yang and Yang, *J. Am. Chem. Soc.* **80,** 2913 (1958). Among the evidence for this mechanism is the fact that the diradical intermediate has been trapped by the addition of mercaptans: Wagner and Zepp, *J. Am. Chem. Soc.* **94,** 287 (1972); Wagner, Kelso, and Zepp, *J. Am. Chem. Soc* **94,** 7480 (1972). See also Zepp and Wagner, *J. Chem. Soc., Chem. Commun.* 167 (1972).

[33] Wagner and Hammond, *J. Am. Chem. Soc.* **87,** 4009 (1965); Dougherty, *J. Am. Chem. Soc.* **87,** 4011 (1965); Ausloos and Rebbert, *J. Am. Chem. Soc.* **86,** 4512 (1964); Casey and Boggs, *J. Am. Chem. Soc.* **94,** 6457 (1972).

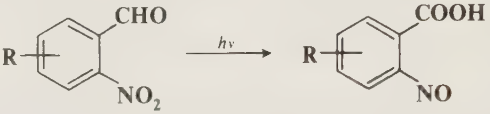
$$\begin{array}{llll} CH_2{=}C{=}O & \xrightarrow{h\nu} & CH_2{=}C{=}O\,(S_1) \rightarrow & \overline{C}H_2 + CO \\ & & \qquad\downarrow & \quad\downarrow \\ & & CH_2{=}C{=}O\,(T_1) \rightarrow & \cdot\dot{C}H_2 + CO \end{array}$$

A final example of category (2) is the irradiation of alkanes at 147 to 130 nm, whereby the predominant process is cleavage to carbenes and hydrogen:

$$RCH_3 \xrightarrow{h\nu} RCH + H_2$$

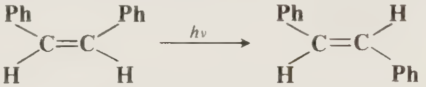
though other reactions of categories (1) and (2) also take place.

Category (3). When *o*-nitrobenzaldehydes are irradiated, *o*-nitrosobenzoic acids are products:[34]

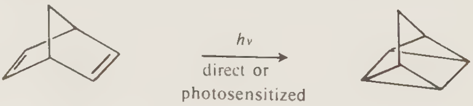


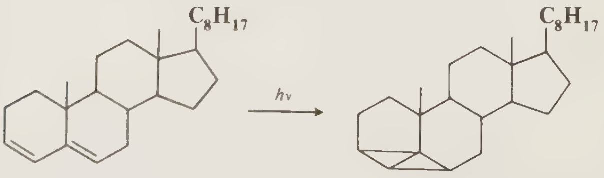
It is possible that this is not a one-step process but a cleavage from the NO_2 group of an oxygen, which then combines with the CHO group.

Category (4). The most common reaction in this category is photochemical cis-trans isomerization.[35] For example, *cis*-stilbene can be converted to the trans isomer:



The isomerization takes place because the excited states, both S_1 and T_1, of many olefins have a perpendicular instead of a planar geometry (p. 214), so that cis-trans isomerism disappears upon excitation. When the excited molecule drops back to the S_0 state, either isomer can be formed. A useful example is the photochemical conversion of *cis*-cyclooctene to the much less stable trans isomer.[36] Two other examples of category (4) reactions are[37]





Cholesta-3, 5-diene

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[34] For a review of this and closely related reactions, see Morrison, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 1, pp. 165–213, 185–191, Wiley-Interscience, New York, 1969.

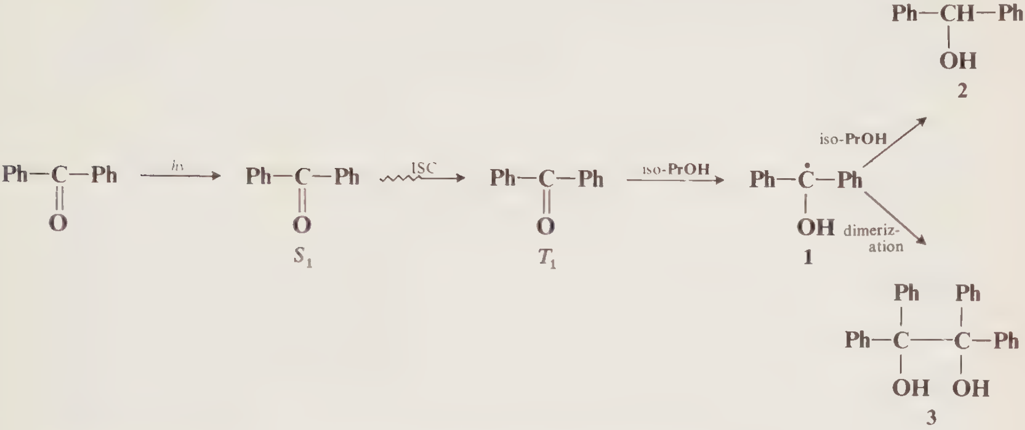
[35] For reviews, see Saltiel, Chang, Megarity, Rousseau, Shannon, Thomas, and Uriarte, *Pure Appl. Chem.* **41**, 559 579 (1975); Saltiel, D'Agostino, Megarity, Metts, Neuberger, Wrighton, and Zafiriou, *Org. Photochem.* **3**, 1–113 (1973); Saltiel, *Surv. Prog. Chem.* **2**, 239–328 (1964), pp. 254–264; and Schönberg, "Preparative Organic Photochemistry," pp. 56–64, Springer-Verlag New York Inc., New York, 1968.

[36] Deyrup and Betkouski, *J. Org. Chem.* **37**, 3561 (1972).

[37] Hammond, Turro, and Fischer, *J. Am. Chem. Soc.* **83**, 4674 (1961); Dauben and Cargill, *Tetrahedron* **15**, 197 (1961); Dauben and Willey, *Tetrahedron Lett.* 893 (1962); Dauben and Wipke, *Pure Appl. Chem.* **9**, 539 (1964).

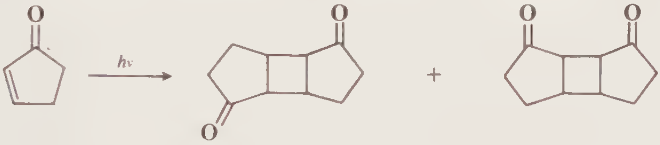
These examples illustrate that the use of photochemical reactions can make it very easy to obtain compounds which would be difficult to get in other ways. Reactions similar to these are discussed at reaction **5-52.**

Category (5). When benzophenone is irradiated in isopropyl alcohol, the initially formed S_1 state crosses to the T_1 state, which abstracts hydrogen from the solvent to give the ketyl radical **1. 1** then abstracts another hydrogen to give benzhydrol (**2**) or dimerizes to benzpinacol (**3**):



An example of intramolecular abstraction has already been given (p. 221).

Category (6). An example is dimerization of cyclopentenone:[38]



See p. 783 for a discussion of this and similar reactions.

The Determination of Photochemical Mechanisms[39]

Ideally, if one is to know a photochemical mechanism, one should know the states of all the molecules in the reaction and the energies and lifetimes of these states and all the side reactions which take place. In practice we usually know these things very imperfectly. "... to establish the exact fate of all the light-absorbing molecules and of all the free radicals formed in a photochemical system is an analytical task which to date has been nearly impossible to perform...."[40] The methods used for the determination of photochemical mechanisms are largely the same as those used for organic mechanisms in general (Chapter 6): product identification, isotopic tracing, the detection and trapping of intermediates, and kinetics, though there are a few new factors: (1) there are generally many products in a photochemical reaction, as many as 10 or 15; (2) in measuring kinetics, there are more variables, since we can study the effect on the rate of the intensity or the wavelength of light; (3) in the detection of intermediates by spectra we can use the technique of *flash photolysis*, which can detect extremely short-lived intermediates.

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[38] Eaton, *J. Am. Chem. Soc.* **84,** 2344, 2454 (1962), *Acc. Chem. Res.* **1,** 50 (1968).

[39] For a review, see Calvert and Pitts, Ref. 1, pp. 580–670.

[40] Calvert and Pitts, Ref. 1, p. 581.

In addition to these methods, there are two additional techniques.

1. The use of emission (fluorescence and phosphorescence) as well as absorption spectroscopy. From these spectra the presence of as well as the energy and lifetimes of singlet and triplet excited states can often be calculated.

2. The study of quantum yields. The *quantum yield* is the fraction of absorbed light which goes to produce a particular result. There are several types. A *primary quantum yield* (usually designated φ) for a particular process is the fraction of molecules absorbing light which undergo that particular process. Thus, if 10% of all the molecules which are excited to the S_1 state cross over to the T_1 state, the primary quantum yield for that process is 0.10. However, primary quantum yields are often difficult to measure. A *product quantum yield* Φ for a product P which is formed from a photoreaction of an initially excited molecule A may be expressed as

$$\Phi = \frac{\text{number of molecules of } \mathbf{P} \text{ formed}}{\text{number of quanta absorbed by } \mathbf{A}}$$

Product quantum yields are much easier to measure. The number of quanta absorbed can be determined by an instrument called an *actinometer*, which is actually a standard photochemical system whose quantum yield is known. An example of the information which can be learned from quantum yields is the following. If the quantum yield of a product is finite and invariant with changes in experimental conditions, it is likely that the product is formed in a primary rate-determining process. Another example: in some reactions, the product quantum yields are found to be well over 1 (perhaps as high as 1000). Such a finding indicates a chain reaction (see p. 619 for a discussion of chain reactions).

Eight

Acids and Bases

Two acid-base theories are in use today in organic chemistry, the Brönsted theory and the Lewis theory.[1] These theories are quite compatible, and are used for different purposes.[2]

Brönsted Theory

According to this theory, an acid is defined as a *proton donor* and a base as a *proton acceptor* (a base must have available a pair of electrons to share with the proton; this is usually present as an unshared pair, but sometimes is in a π orbital). An acid-base reaction is simply the transfer of a proton from an acid to a base. (Protons cannot exist free in solution but must be attached to an electron pair.) When the acid gives up a proton, the species remaining still retains the electron pair to which the proton was formerly attached. Thus the new species, in theory at least, can reacquire a proton and is therefore a base. It is referred to as the *conjugate base* of the acid. All acids have a conjugate base, and all bases have a *conjugate acid*. All acid-base reactions fit the equation

$$\underset{\text{Acid}_1}{\mathrm{A{-}H}} + \underset{\text{Base}_2}{\overline{\mathrm{B}}} \rightleftharpoons \underset{\text{Base}_1}{\overline{\mathrm{A}}} + \underset{\text{Acid}_2}{\mathrm{B{-}H}}$$

No charges are shown in this equation, but an acid always has a charge which is one positive unit higher than that of its conjugate base, whether the charge on the acid is positive, negative, or neutral. Many substances can be both bases and acids. Such species are called *amphoteric*.

Acid strength may be defined as the tendency to give up a proton and *base strength* as the tendency to accept a proton. Acid-base reactions occur because acids are not equally strong. If an acid, say HCl, is placed in contact with the conjugate base of a weaker acid, say acetate ion, the proton will be transferred because the HCl has a greater tendency to lose its proton than acetic acid does. That is, the equilibrium

$$\mathrm{HCl} + \mathrm{CH_3COO^-} \rightleftharpoons \mathrm{CH_3COOH} + \mathrm{Cl^-}$$

lies well over to the right. On the other hand, treatment of acetic acid with chloride ion gives essentially no reaction, since the weaker acid already has the proton.

This is always the case for any two acids, and by measuring positions of the equilibrium the relative strengths of acids and bases can be determined.[3] Of course, if the two acids involved are close to each other in strength, a measurable reaction will occur from both sides, although the position of equilibrium will still be over to the side of the weaker acid (unless the acidities are equal within experimental limits). In this manner it is possible to construct a table in which acids are listed in order of acid strength (Table 1).[4] Next to each acid in Table 1 is shown its conjugate

[1] For a monograph on acids and bases, see Bell, "The Proton in Chemistry," 2d ed., Cornell University Press, Ithaca, N.Y., 1973. For a review, see Gillespie, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 169-199, Interscience Publishers, New York, 1963.

[2] For discussion of the historical development of acid-base theory, see Bell, *Q. Rev., Chem. Soc.* **1**, 113–125 (1947); Bell, "The Proton in Chemistry," 1st ed., pp. 7–17, Cornell University Press, Ithaca, N.Y., 1959.

[3] Although in most acid-base reactions equilibrium is reached extremely rapidly (the rates of proton transfer between singly bonded oxygen and or nitrogen atoms are usually diffusion-controlled), some are slow (especially those in which the proton is given up by a carbon) and in these cases time must be allowed for the system to come to equilibrium.

[4] Table 1 is a thermodynamic acidity scale and applies only to positions of equilibria. For the distinction between thermodynamic and kinetic acidity, see p. 161.

base. It is obvious that if the acids in such a table are listed in *decreasing* order of acid strength, the bases must be listed in *increasing* order of base strength, since the stronger the acid, the weaker must be its conjugate base. The pK_a values in Table 1 are most accurate in the middle of the table. They are much harder to measure[5] for very strong and very weak acids, and these values must be regarded as approximate. Qualitatively, it can be determined that $HClO_4$ is a stronger acid than H_2SO_4, since a mixture of $HClO_4$ and H_2SO_4 in methyl isobutyl ketone may be titrated to an $HClO_4$ end point without interference by H_2SO_4.[6] Similarly, $HClO_4$ can be shown to be stronger than HNO_3 or HCl. However, this is not quantitative, and the value of -10 in the table is not much more than an educated guess. The values for RNO_2H^+, $ArNO_2H^+$, HI, $RCNH^+$, and $RSH_2{}^+$ must also be regarded as highly speculative.[7] A wide variety of pK_a values has been reported for the conjugate acids of even such simple bases as acetone (-0.24 to -7.2), diethyl ether (-0.30 to -6.2), ethanol (-0.33 to -4.8), methanol (-0.34 to -4.9), and 2-propanol (-0.35 to -5.2), depending on the method used to measure them.[8] Only for acids weaker than hydronium ion and stronger than water can very accurate values be obtained.

The bottom portion of Table 1, consisting of very weak acids[9] (pK_a above ~ 17) is known as the *MSAD scale*, in recognition of the work of McEwen, Streitwieser, Applequist, and Dessy, who made advances in this area. In most of these acids, the proton is lost from a carbon atom, and such acids are known as *carbon acids*. pK_a values for such weak acids are difficult to measure and are known only approximately. The methods used to determine the relative positions of these acids are discussed in Chapter 5.[10] The acidity of carbon acids is proportional to the stability of the carbanions which are their conjugate bases (see p. 160).

The extremely strong acids at the top of the table are known as *super acids* (see p. 161). The actual species present in the FSO_3H-SbF_5 mixture are probably $H[SbF_5(SO_3F)]$ and $H[SbF_2(SO_3F)_4]$.[11] The addition of SO_3 causes formation of the still stronger $H[SbF_4(SO_3F)_2]$, $H[SbF_3(SO_3F)_3]$, and $H[(SbF_5)_2(SO_3F)]$.[11]

By the use of tables such as Table 1, it is possible to determine whether a given acid will react with a given base. For tables in which acids are listed in order of decreasing strength, the rule is that *any acid will react with any base in the table which is below it but not with any above it.* The chart is most useful when the acid and the base are not close together, for the following reasons.

1. When an acid and a base are close together, the reaction will not be complete, though the position of equilibrium will be such that the weaker acid predominates.

2. The order can change with temperature. Thus, above 50°C the order of base strength is $BuOH > H_2O > Bu_2O$; from 1 to 50°C the order is $BuOH > Bu_2O > H_2O$; while below 1°C it becomes $Bu_2O > BuOH > H_2O$.[12] Other examples are that acetic acid is stronger than diethylacetic acid above 30°C but weaker below this temperature,[13] while propionic acid is weaker than butyric below 75 C but above 75°C the order is reversed.[14] Such inversions of acidity order with temperature are quite common when the acids are close together on the scale.

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[5] For a review of methods of determining pK_a values, see Cookson, *Chem. Rev.* **74,** 5–28 (1974).

[6] Kolthoff and Bruckenstein, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, pt. 1, pp. 475–542, 479, Interscience Publishers, Inc., New York, 1959.

[7] For reviews of organic compounds protonated at O, N, or S, see Olah, White, and O'Brien, *Chem. Rev.* **70,** 561–591 (1970); Olah, White, and O'Brien, in Olah and Schleyer, "Carbonium Ions," vol. 4, pp. 1697–1781, John Wiley & Sons, Inc., New York, 1973.

[8] Rochester, "Acidity Functions," Academic Press, Inc., New York, 1970. For a discussion of the basicity of such compounds, see Liler, "Reaction Mechanisms in Sulfuric Acid," pp. 118–139, Academic Press, Inc., New York, 1971.

[9] For discussions of acidity of very weak acids, see Cram, "Fundamentals of Carbanion Chemistry," pp. 1–45, Academic Press, Inc., New York, 1965; and Streitwieser and Hammons, *Prog. Phys. Org. Chem.* **3,** 41–80 (1965).

[10] For reviews of the methods used to measure the acidity of carbon acids, see Reutov, Butin, and Beletskaya, *Russ. Chem. Rev.* **43,** 17–31 (1974); Jones, *Q. Rev., Chem. Soc.* **25,** 365–378 (1971); Fischer and Rewicki, *Prog. Org. Chem.* **7,** 116–161 (1968); and Ref. 5.

[11] Gillespie, *Acc. Chem. Res.* **1,** 202–209 (1968).

[12] Gerrard and Macklen, *Chem. Rev.* **59,** 1105–1123 (1959).

[13] Calder and Barton, *J. Chem. Educ.* **48,** 338 (1971).

[14] Hambly, *Rev. Pure Appl. Chem.* **15,** 87–100 (1965), p. 88.

TABLE 1 pK_a values for many types of acids
The values in boldface are exact values; the others are approximate, especially above 18 and below −2[15]

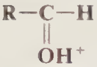
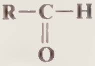
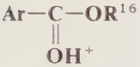
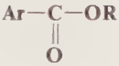
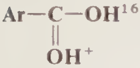
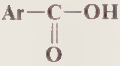
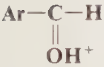
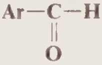
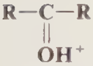
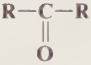
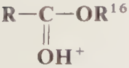
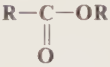
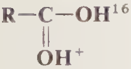
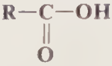
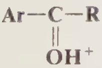
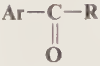
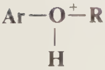
Acid	Base	Approximate pK_a (relative to water)	Ref.
Super acids:			
$HF–SbF_5$	SbF_6^-		18
$FSO_3H–SbF_5–SO_3$			11
$FSO_3H–SbF_5$			11, 18
FSO_3H	FSO_3^-		11
RNO_2H^+	RNO_2	−12	19
$ArNO_2H^+$	$ArNO_2$	−11	19
$HClO_4$	ClO_4^-	−10	20
HI	I^-	−10	20
$RCNH^+$	RCN	−10	21
 $R-\underset{\overset{\|}{OH^+}}{C}-H$	 $R-\underset{\overset{\|}{O}}{C}-H$	−10	22
H_2SO_4	HSO_4^-		
HBr	Br^-	−9	20
 $Ar-\underset{\overset{\|}{OH^+}}{C}-OR$[16]	 $Ar-\underset{\overset{\|}{O}}{C}-OR$	−7.4	19
HCl	Cl^-	−7	20
$ArOH_2^+$	ArOH	−7	23
RSH_2^+	RSH	−7	19
 $Ar-\underset{\overset{\|}{OH^+}}{C}-OH$[16]	 $Ar-\underset{\overset{\|}{O}}{C}-OH$	−7	24
 $Ar-\underset{\overset{\|}{OH^+}}{C}-H$	 $Ar-\underset{\overset{\|}{O}}{C}-H$	−7	25
 $R-\underset{\overset{\|}{OH^+}}{C}-R$	 $R-\underset{\overset{\|}{O}}{C}-R$	−7	21, 26
$ArSO_3H$	$ArSO_3^-$	−6.5	26a
 $R-\underset{\overset{\|}{OH^+}}{C}-OR$[16]	 $R-\underset{\overset{\|}{O}}{C}-OR$	−6.5	19
 $R-\underset{\overset{\|}{OH^+}}{C}-OH$[16]	 $R-\underset{\overset{\|}{O}}{C}-OH$	−6	19
 $Ar-\underset{\overset{\|}{OH^+}}{C}-R$	 $Ar-\underset{\overset{\|}{O}}{C}-R$	−6	25, 27
 $Ar-\underset{\overset{\mid}{H}}{\overset{+}{O}}-R$	$Ar-O-R$	−6	23, 28
$CH(CN)_3$	$^-C(CN)_3$	−5	29
Ar_3NH^+	Ar_3N	−5	30

TABLE 1 pK_a values for many types of acids (*Continued*)

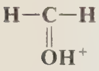
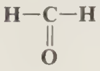
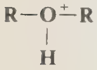
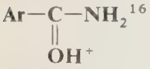
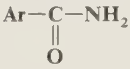
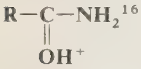
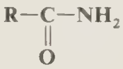
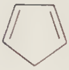
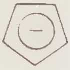
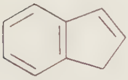
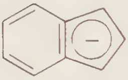
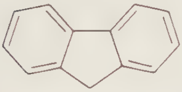
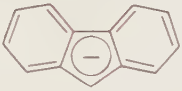
Acid	Base	Approximate pK_a (relative to water)	Ref.
 $H-\underset{\underset{OH^+}{\|}}{C}-H$	 $H-\underset{\underset{O}{\|}}{C}-H$	−4	31
 $R-\underset{\underset{H}{\mid}}{\overset{+}{O}}-R$	$R-O-R$	−3.5	21, 28, 32
$R_3COH_2^+$	R_3COH	−2	32
$R_2CHOH_2^+$	R_2CHOH	−2	32
$RCH_2OH_2^+$	RCH_2OH	−2	21, 32, 33
H_3O^+	H_2O	**−1.74**	
 $Ar-\underset{\underset{OH^+}{\|}}{C}-NH_2$[16]	 $Ar-\underset{\underset{O}{\|}}{C}-NH_2$	−1.5	19, 34
HNO_3	NO_3^-	−1.4	20
 $R-\underset{\underset{OH^+}{\|}}{C}-NH_2$[16]	 $R-\underset{\underset{O}{\|}}{C}-NH_2$	−0.5	21, 34
$Ar_2NH_2^+$	Ar_2NH	1	30
HSO_4^-	SO_4^{2-}	**1.99**	35
HF	F^-	**3.17**	35
$HONO$	NO_2^-	**3.29**	35
$ArNH_3^+$	$ArNH_2$	3–5	36
$ArNR_2H^+$	$ArNR_2$	3–5	36
$RCOOH$	$RCOO^-$	4–5	36
$HCOCH_2CHO$	$HCO\overset{\ominus}{\bar{C}}HCHO$	5	37
H_2CO_3[17]	HCO_3^-	**6.35**	35
H_2S	HS^-	**7.00**	35
$ArSH$	ArS^-	6–8	37a
$CH_3COCH_2COCH_3$	$CH_3CO\overset{\ominus}{\bar{C}}HCOCH_3$	9	37
NH_4^+	NH_3	**9.24**	35
$ArOH$	ArO^-	8–11	38
RCH_2NO_2	$R\overset{\ominus}{\bar{C}}HNO_2$	10	39
R_3NH^+	R_3N	10–11	36
RNH_3^+	RNH_2	10–11	36
HCO_3^-	CO_3^{2-}	**10.33**	35
RSH	RS^-	10–11	37a
$R_2NH_2^+$	R_2NH	11	36
$NCCH_2CN$	$NC\overset{\ominus}{\bar{C}}HCN$	11	37, 40
CH_3COCH_2COOR	$CH_3CO\overset{\ominus}{\bar{C}}HCOOR$	11	37

TABLE 1 pK_a values for many types of acids (*Continued*)

Acid	Base	Approximate pK_a (relative to water)	Ref.
$CH_3SO_2CH_2SO_2CH_3$	$CH_3SO_2\overset{\ominus}{\bar{C}}HSO_2CH_3$	12.5	41
$EtOOCCH_2COOEt$	$EtOOC\overset{\ominus}{\bar{C}}HCOOEt$	13	37
H_2O	OH^-	**15.74**	42
		16	43
$RCONH_2$	$RCONH^-$	17	44
RCH_2OH	RCH_2O^-	18	45
R_2CHOH	R_2CHO^-	18	45
R_3COH	R_3CO^-	19	45
$ArCOCH_2R$	$ArCO\overset{\ominus}{\bar{C}}HR$	19	46
$RCOCH_2R$	$RCO\overset{\ominus}{\bar{C}}HR$	20–21	46
		20	47, 48
		23	47, 48
$ROOCCH_2R$	$ROOC\overset{\ominus}{\bar{C}}HR$	24.5	37
RCH_2CN	$R\overset{\ominus}{\bar{C}}HCN$	25	37
$HC\equiv CH$	$HC\equiv C^-$	25	49
$ArNH_2$	$ArNH^-$	25	50
Ar_3CH	Ar_3C^-	31.5	47, 51
Ar_2CH_2	Ar_2CH^-	33.5	47, 51
NH_3	NH_2^-	34	50
$ArCH_3$	$ArCH_2^-$	35	49, 52
$CH_3CH{=}CH_2$	$[CH_2{=}CH{=}CH_2]^-$	35.5	49
$CH_2{=}CH_2$	$CH_2{=}CH^-$	36.5	49, 53
PhH	Ph^-	37	49, 53
cyclo-C_3H_6	cyclo-$C_3H_5^-$	39	49
CH_4	CH_3^-	40	49
C_2H_6	$C_2H_5^-$	42	49
$(CH_3)_2CH_2$	$(CH_3)_2CH^-$	44	49
cyclo-C_6H_{12}	cyclo-$C_6H_{11}^-$	45	49

[15] In this table it has not been possible to give pK_a values for individual compounds (with a few exceptions) but only average values for functional groups. Extensive tables of pK values for many carboxylic and other acids and amines are given in Ref. 36. Kortüm, Vogel, and Andrussow, *Pure Appl. Chem.* **1,** 190–536 (1960), give values for 631 carboxylic acids and 110 phenols. Ref. 19 gives hundreds of values for very strong acids (very weak bases). Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth & Co., Ltd., London, 1965, and Supplement, 1972, list pK values for more than 7000 amines and other bases. Collumeau, *Bull. Soc. Chim. Fr.* 5087–5112 (1968) gives pK values for about 800 acids and bases. Perrin, *Pure Appl. Chem.* **20,** 133–236 (1969) lists values for 217 inorganic acids and bases.

[16] Acids, esters, and amides are shown in this table to be protonated on the carbonyl oxygen. There has been some controversy on this point, but the weight of evidence today is in that direction. See Katritzky and Jones, *Chem. Ind. (London)* 722 (1961); Ottenheym, van Raayen, Smidt, Groenewege, and Veerkamp, *Recl. Trav. Chim. Pays-Bas* **80,** 1211 (1961); Stewart and Muenster, *Can. J. Chem.* **39,** 401 (1961); Casadevall, Cauquil, and Corriu, *Bull. Soc. Chim. Fr.* 187 (1964); Olah, O'Brien, and White, *J. Am. Chem. Soc.* **89,** 5694 (1967); Smith and Yates, *Can. J. Chem.* **50,** 771 (1972); Henriksen and Baltzer, *Tetrahedron Lett.* 2485 (1972); Martin, *J. Chem. Soc., Chem. Commun.* 793 (1972); Benderly and Rosenheck, *J. Chem. Soc., Chem. Commun.* 179 (1972); Kresge, Fitzgerald, and Chiang, *J. Am. Chem. Soc.* **96,** 4698 (1974); Homer and Johnson, in Zabicky, "The Chemistry of Amides," pp. 188–197, Interscience Publishers, New York, 1970; Ref. 7. For a review of alternative proton sites, see Liler, *Adv. Phys. Org. Chem.* **11,** 267–392 (1975).

[17] This value includes the CO_2 usually present. The value for H_2CO_3 alone is 3.9 (Ref. 20).

[18] Brouwer and van Doorn, *Recl. Trav. Chim. Pays-Bas* **91,** 895 (1972).

[19] Arnett, *Prog. Phys. Org. Chem.* **1,** 223–403 (1963), pp. 324–325.

[20] Bell, Ref. 1.

[21] Deno and Wisotsky, *J. Am. Chem. Soc.* **85,** 1735 (1963); Deno, Gaugler, and Wisotsky, *J. Org. Chem.* **31,** 1967 (1966).

[22] Levy, Cargioli, and Racela, *J. Am. Chem. Soc.* **92,** 6238 (1970). See, however, Brouwer and van Doorn, *Recl. Trav. Chim. Pays-Bas* **90,** 1010 (1971).

[23] Arnett and Wu, *J. Am. Chem. Soc.* **82,** 5660 (1960).

[24] Stewart and Granger, *Can. J. Chem.* **39,** 2508 (1961).

[25] Yates and Stewart, *Can. J. Chem.* **37,** 664 (1959); Stewart and Yates, *J. Am. Chem. Soc.* **80,** 6355 (1958).

[26] Lee, *Can. J. Chem.* **48,** 1919 (1970).

[26a] Cerfontain, Koeberg-Telder, and Kruk, *Tetrahedron Lett.* 3639 (1975).

[27] Fischer, Grigor, Packer, and Vaughan, *J. Am. Chem. Soc.* **83,** 4208 (1961).

[28] Arnett and Wu, *J. Am. Chem. Soc.* **82,** 4999 (1960).

[29] Boyd, *J. Phys. Chem.* **67,** 737 (1963).

[30] Arnett, Quirk, and Burke, *J. Am. Chem. Soc.* **92,** 1260 (1970).

[31] McTigue and Sime, *Aust. J. Chem.* **16,** 592 (1963).

[32] Deno and Turner, *J. Org. Chem.* **31,** 1969 (1966).

[33] Lee and Cameron, *J. Am. Chem. Soc.* **93,** 4724 (1971).

[34] Homer and Johnson, Ref. 16, p. 210.

[35] Bruckenstein and Kolthoff, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, pt. 1, pp. 432–433, Interscience Publishers, Inc., New York, 1959.

[36] Brown, McDaniel, and Häflinger, in Braude and Nachod, "Determination of Organic Structures by Physical Methods," vol. 1, pp. 567–662, Academic Press, Inc., New York, 1955.

[37] Pearson and Dillon, *J. Am. Chem. Soc.* **75,** 2439 (1953).

[37a] Crampton, in Patai, "The Chemistry of the Thiol Group," pt. 1, pp. 396–410, John Wiley & Sons, Inc., New York, 1974.

[38] Rochester, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, p. 374, Interscience Publishers, New York, 1971.

[39] Cram, *Chem. Eng. News* **41**(33), 94 (Aug. 19, 1963).

[40] Bowden and Stewart, *Tetrahedron* **21,** 261 (1965).

[41] Hine, Philips, and Maxwell, *J. Org. Chem.* **35,** 3943 (1970).

[42] Harned and Robinson, *Trans. Faraday Soc.* **36,** 973 (1940).

[43] Streitwieser and Nebenzahl, *J. Am. Chem. Soc.* **98,** 2188 (1976).

[44] Homer and Johnson, Ref. 16, pp. 238–240.

[45] McEwen, *J. Am. Chem. Soc.* **58,** 1124 (1936).

[46] Zook, Kelly, and Posey, *J. Org. Chem.* **33,** 3477 (1968).

[47] Streitwieser, Ciuffarin, and Hammons, *J. Am. Chem. Soc.* **89,** 63 (1967).

[48] Streitwieser, Hollyhead, Pudjaatmaka, Owens, Kruger, Rubenstein, MacQuarrie, Brokaw, Chu, and Niemeyer. *J. Am. Chem. Soc.* **93,** 5088 (1971).

[49] Cram, "Fundamentals of Carbanion Chemistry," p. 19, Academic Press, Inc., New York, 1965. Also see Dessy, Kitching, Psarras, Salinger, Chen, and Chivers, *J. Am. Chem. Soc.* **88,** 460 (1966).

[50] These values are based on those of Ref. 39 but corrected to the newer scales of Ref. 49.

[51] Streitwieser, Hollyhead, Sonnichsen, Pudjaatmaka, Chang, and Kruger, *J. Am. Chem. Soc.* **93,** 5096 (1971).

[52] See also Streitwieser, Granger, Mares, and Wolf, *J. Am. Chem. Soc.* **95,** 4257 (1973).

[53] See also Maskornick and Streitwieser, *Tetrahedron Lett.* 1625 (1972); Streitwieser, Scannon, and Niemeyer, *J. Am. Chem. Soc.* **94,** 7936 (1972).

3. For acids stronger than hydronium ion and weaker than water, not only are the pK_a values uncertain, but in many cases so are the relative positions.

It must be emphasized that the order of acid strength in Table 1 applies when a given acid and base react without a solvent or, when possible, in water. In other solvents the order may be greatly different (see pp. 233, 243). In the gas phase, where solvation effects are completely or almost completely absent, acidity orders may also differ greatly. For example, in the gas phase, toluene is a stronger acid than water, and *t*-butoxide ion is a weaker base than methoxide ion[54] (see also pp. 243–244).

Acidic and Basic Solvents[55]

One way to determine the position of an acid in a table such as Table 1 is simply to measure the position of equilibrium with a number of appropriate bases. This method is not always easy in practice. Another way is to make use of a solvent which is itself an acid or a base. An acidic solvent (SH) may be used in the following manner: a base placed in such a solvent will take protons from the solvent if it is stronger than S^-. We may imagine two bases B_1 and B_2, which are weaker than S^-, and two others, B_3 and B_4, which are stronger. Then a list similar to Table 1 will be

HB_2^+	B_2
HB_1^+	B_1
SH	S^-
HB_3^+	B_3
HB_4^+	B_4

If the base is B_3 or B_4, the concentrations of S^- and HB_3^+ (or HB_4^+) will be greater than those of SH and B_3 (or B_4). For B_1 and B_2 the reverse will be true. Now if the $[SH]/[S^-]$ or $[HB^+]/[B]$ ratios can be measured, this is a means of telling not only whether each B is stronger or weaker than S^- but also whether B_1 is stronger or weaker than B_2. From these measurements quantitative scales can be set up.[56] When the solvent is water, this is the pK_b scale.

However, if two bases, say B_3 and B_4, are so strong that $[HB_3^+]/[B_3]$ and $[HB_4^+]/[B_4]$ are both greater than, say, 100, then all that can be said is that they are both essentially completely protonated and it is not possible to tell the difference between a ratio of, say, 10^3 and one of 10^6. This is called the *leveling effect* of the solvent, since, to the solvent SH, the bases B_3 and B_4 are equally strong, even though their actual strengths may be greatly different. Similarly, if the two bases are so weak in relation to SH that the two ratios are both less than, say, $\frac{1}{100}$, the solvent cannot distinguish between their basicities. A similar argument holds for basic solvents.

In water, which is both an acidic and a basic solvent, it is very easy to measure S^- accurately (or SH^+ for measuring acid strengths), since H_3O^+ (and consequently OH^-) can be quite accurately measured between about 10 and 10^{-15} mol/liter; hence the pK of acids stronger than water and weaker than hydronium ion can be accurately determined. But outside this range, water is useless as a solvent because of two kinds of leveling effect. When an acid is stronger than H_3O^+, then it is converted essentially completely to H_3O^+. Although 1 mol each of two strong acids will give, say, 0.9990 mol H_3O^+ and 0.9999 mol H_3O^+, it is not possible to tell the difference, since the activity is what is actually being measured and the difference between activity and concentration is greater than the difference between 0.9990 and 0.9999. The second kind of leveling effect is found with acids weaker than water, since the amount of H_3O^+ produced by the acid is less than that produced by the autoprotolysis of the water and thus cannot be measured. Another way of saying this is that the base water would rather take a proton from the acid water than from an acid weaker than water. Similarly, in water, pK_b can be measured only for bases stronger than water and weaker than OH^-.

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[54] Brauman and Blair, *J. Am. Chem. Soc.* **92,** 5986 (1970); Bohme, Lee-Ruff, and Young, *J. Am. Chem. Soc.* **94,** 4608, 5153 (1972).

[55] For fuller treatments, see Kolthoff, in Kolthoff and Elving, "Treatise on Analytical Chemistry," vol. 1, pt. 1, pp. 407–420, Interscience Publishers, Inc., New York, 1959; King, in Covington and Dickinson, "Physical Chemistry of Organic Solvent Systems," pp. 331–403, Plenum Press, New York, 1973; and Bykova and Petrov, *Russ. Chem. Rev.* **41,** 975–990 (1972).

[56] Actually, $[SH]/[S^-]$ cannot be accurately measured, since the amount of SH is overwhelming. But if $[S^-]$ can be accurately measured, then the value of $[BH^+]$ is known, since it must be equal to $[S^-]$. If the initial concentration B_0 of B was known, this gives the $[HB^+]/[B]$ ratio, since $B_0 = [B] + [BH^+]$.

Other amphoteric solvents may be used in a similar manner to measure other areas of the chart. In acetic acid, it is possible to distinguish acidities of acids which in water would have pK_a between about -10 and $+5$; i.e., in acetic acid, it is possible to distinguish HBr and HCl but not H_2O and phenol. Conversely, in ammonia, the carboxylic acids are as strong as HCl, while the acidities of methanol and ethanol may be differentiated. The pK_a range in this solvent, relative to water, is about 3 to 23. In solvents such as these, we must measure, not $[H_3O^+]$ or $[OH^-]$, but analogously, $[CH_3COOH_2{}^+]$ or $[CH_3COO^-]$, or $[NH_4{}^+]$ or $[NH_2{}^-]$. These are usually much more difficult to measure than pH. Therefore many methods have been devised, e.g., freezing-point depressions, ir spectra, vapor-pressure measurements, etc.; still the values obtained are seldom as accurate as values in water. Of course, values obtained in other solvents must be corrected to the water scale. As a first approximation, this can be done by simple subtraction if the pK_a of any acid is known in both water and the other solvent, since differences in pK values of two acids of the same charge type should not be greatly affected by the solvent. However, when acids of different charge types are compared, there are no simple correlations.

Solvents which are not amphoteric may also be used. For basic solvents, such as diethyl ether or pyridine, there is a limit only on the strong-acid side, since on the weak-acid side there is no autoprotolysis to supply Et_2OH^+ or $C_5H_5NH^+$ to compete with that formed from even a weak acid and the solvent. Similarly, for acidic solvents such as HCN, there is a limit only on the other side. In aprotic solvents, such as benzene or chloroform, there are no limits, since the solvent merely serves as a diluent, and it is only necessary to measure the concentrations of two of the four participants in the equilibrium. However, most acid-base systems are not very soluble in aprotic solvents, and ion-pairing and complexing often become troublesome.

Measurements of Solvent Acidity[57]

So far we have seen that acid or base strength depends on the acidity or basicity of the solvent, but other characteristics of the solvent are also important. One of these is the dielectric constant, and it is important because it is a measure of the ion-solvating ability of the solvent. Solvents with high dielectric constants (e.g., H_2O) completely solvate each ion. When the dielectric constant is lower, then ions aggregate, so that ion pairs and larger aggregations are present. This usually makes little difference when the equation has the same total charge on both sides, as in $HA^+ + B \rightleftharpoons HB^+ + A$, but when the total charge increases, as, for example, in $HA + B \rightleftharpoons HB^+ + A^-$, a solvent with high dielectric constant pushes the equilibrium farther to the right than does one with a lower constant. Even when the charge is unchanged, the dielectric constant of the solvent may still make a difference if the ion (or ions) on the left are more solvated than the ones on the right. Also the solvent may cause differential solvation in another way, quite different from the effect of dielectric constant, arising from the difference in solvation of anions by a protic solvent (which can form hydrogen bonds) and an aprotic one.[58] The effect can be extreme: in dimethylformamide, picric acid is stronger than HBr.[59] This particular result can be attributed to size. That is, the large ion $(O_2N)_3C_6H_2O^-$ is better solvated by dimethylformamide than the smaller ion Br^-; while in a protic solvent like water the solvation of an anion is by the small unshielded proton.[60]

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[57] For fuller treatments, see Hammett, "Physical Organic Chemistry," 2d ed., pp. 263–313, McGraw-Hill Book Company, New York, 1970; Ref. 6, pp. 485–499; Deno, *Surv. Prog. Chem.* **2**, 155–187 (1964), pp. 169–178; and Arnett, *Prog. Phys. Org. Chem.* **1**, 223–403 (1963), pp. 233–258.

A measurement of solvent acidity is thus needed which takes into account factors such as dielectric constant and which applies to mixed solvents as well. The Hammett acidity function[61] is a measurement which is used for acidic solvents of high dielectric constant.[62] For any solvent, including mixtures of solvents (but the proportions of the mixture must be specified), a value H_0 is defined as

$$H_0 = \mathrm{p}K_{\mathrm{BH}_w^+} - \log \frac{[\mathbf{BH}^+]}{[\mathbf{B}]}$$

H_0 is measured by using "indicators" which are weak bases and so are partly converted in these acidic solvents. Typical indicators are *o*-nitroanilinium ion, with a pK in water of -0.29, and 2,4-dinitroanilinium ion, with a pK in water of -4.53. For a given solvent, $[BH^+]/[B]$ is measured for one indicator, usually by spectrophotometric means. Then, using the known pK in water for that indicator, H_0 can be calculated for that solvent system. In practice, several indicators are used, so that an average H_0 is taken. Once H_0 is known for a given solvent system, pK_a values in it can be calculated for any other acid-base pair.

H_0 is defined only for neutral bases, whose conjugate acids therefore have a charge of $+1$. An analogous function for bases with a charge of -1 is called H_-, but results with this function are less consistent than with H_0:

$$H_- = \mathrm{p}K_{\mathrm{BH}_w} - \log \frac{[\mathbf{BH}]}{[\mathbf{B}^-]}$$

The symbol h_0 is defined as

$$h_0 = \frac{a_{\mathrm{H}^+} f_{\mathrm{I}}}{f_{\mathrm{HI}^+}}$$

where a_{H^+} is the activity of the proton and f_{I} and f_{HI^+} are the activity coefficients of the indicator and conjugate acid of the indicator, respectively. H_0 is related to h_0 by

$$H_0 = -\log h_0$$

so that H_0 is analogous to pH, and h_0 to $[H^+]$, and indeed in dilute aqueous solution H_0 and $H_- = \mathrm{pH}$.

H_0 and H_- reflect the ability of the solvent system to donate protons, but they can be applied only to acidic solutions of high dielectric constant, mostly mixtures of water with acids like nitric, sulfuric, perchloric, etc. It is apparent that the H_0 treatment is valid only when $f_{\mathrm{I}}/f_{\mathrm{HI}^+}$ is independent of the nature of the base (the indicator). Since this is so only when the bases are structurally similar, the treatment is limited. Even when similar bases are compared, many devia-

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[58] For a review, see Parker, *Q. Rev., Chem. Soc.* **16,** 163–187 (1962).

[59] Sears, Wolford, and Dawson, *J. Electrochem. Soc.* **103,** 633 (1956).

[60] Miller and Parker, *J. Am. Chem. Soc.* **83,** 117 (1961).

[61] Hammett and Deyrup, *J. Am. Chem. Soc.* **54,** 2721 (1932).

[62] For a monograph on acidity functions, see Rochester, Ref. 8. For reviews, see Ref. 57; Boyd, in Coetzee and Ritchie, "Solute-Solvent Interactions," pp. 97–218, Marcel Dekker, Inc., New York, 1969, Paul and Long, *Chem. Rev.* **57,** 1–45 (1957); Long and Paul, *Chem. Rev.* **57,** 935–1010 (1957); Vinnik, *Russ. Chem. Rev.* **35,** 802–817 (1966); and Liler, Ref. 8, pp. 26–58.

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tions are found.[63] Other acidity scales have been set up, among them H_R for aryl carbinols,[64] $H_{R'}$ for aryl olefins and other molecules whose conjugate acids are stable carbonium ions which do not form hydrogen bonds with the solvent,[65] H_C for bases which protonate on carbon,[66] H_E for aliphatic esters,[67] and H_A for unsubstituted amides.[68] It is now clear that there is no single acidity scale which can be applied to a series of solvent mixtures irrespective of the bases employed.[69]

Although most acidity functions have been applied only to acidic solutions, some work has also been done with strongly basic solutions. The H_- function, which is used for highly acidic solutions when the base has a charge of -1, can also be used for strongly basic solvents, in which case it measures the ability of these solvents to abstract a proton from a neutral acid BH.[70]

Another approach to the acidity-function problem was proposed by Bunnett and Olsen,[71] who derived the equation

$$\log \frac{[\mathrm{SH}]^+}{[\mathrm{S}]} + H_0 = \phi(H_0 + \log [\mathrm{H}^+]) + \mathrm{p}K_{\mathrm{SH}^+}$$

where S is a base which is protonated by an acidic solvent. Thus the slope of a plot of $\log([\mathrm{SH}^+]/[\mathrm{S}]) + H_0$ against $H_0 + \log[\mathrm{H}^+]$ is the parameter ϕ, while the intercept is the $\mathrm{p}K_a$ of the acid SH^+ (referred to infinite dilution in water). The value of ϕ expresses the response of the equilibrium $\mathrm{S} + \mathrm{H}^+ \rightleftharpoons \mathrm{SH}^+$ to changing acid concentration. A negative ϕ indicates that the log of the ionization ratio $[\mathrm{SH}^+]/[\mathrm{S}]$ increases, as the acid concentration increases, more rapidly than does $-H_0$. A positive ϕ value indicates the reverse. The Bunnett-Olsen equation given above is a linear free-energy relationship (see p. 254) which pertains to acid-base equilibria. A corresponding equation which applies to kinetic data is

$$\log k_\psi + H_0 = \phi(H_0 + \log [\mathrm{H}^+]) + \log k_2^\circ$$

where k_ψ is the pseudo-first-order rate constant for a reaction of a weakly basic substrate taking place in an acidic solution and k_2° is the second-order rate constant at infinite dilution in water. In this case ϕ characterizes the response of the reaction rate to changing acid concentration of the solvent. The Bunnett-Olsen treatment has also been applied to basic media, where, in a group of nine reactions in concentrated NaOMe solutions, no correlation was found between reaction rates and either H_- or stoichiometric base concentration but where the rates were successfully correlated by a linear free-energy equation similar to those given above.[72]

For a number of years it was believed that when log k (the rate constant) for an acid-catalyzed reaction was linear with $-H_0$, the transformation of the protonated substrate AH^+ to the transition state did not involve a molecule of water, but when log k was linear with log [HA], a molecule of water was required. This was known as the Zucker-Hammett hypothesis.[73] However, in most cases the rates did not follow either line, and the Zucker-Hammett hypothesis has now been shown to be invalid.[74] A new classification system has been devised by Bunnett[75] for reactions occurring in moderately concentrated acid solutions. $\log k_\psi + H_0$ is plotted against $\log a_{H_2O}$, where k_ψ is the pseudo-first-order rate constant for the protonated species and a_{H_2O} is the activity of water. Most such plots are linear or nearly so. According to Bunnett, the slope of this plot w tells something about the mechanism. Where w is between -2.5 and 0, water is not involved in the rate-determining step; where w is between 1.2 and 3.3, water is a nucleophile in the rate-determining step; and where w is between 3.3 and 7 water is a proton-transfer agent. These rules hold for acids in which the proton is attached to oxygen or nitrogen.[76]

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[63] For example, see Kresge, Barry, Charles, and Chiang, *J. Am. Chem. Soc.* **84,** 4343 (1962); Katritzky, Waring, and Yates, *Tetrahedron* **19,** 465 (1963); Arnett and Mach, *J. Am. Chem. Soc.* **86,** 2671 (1964); Jorgenson and Hartter, *J. Am. Chem. Soc.* **85,** 878 (1963); Kreevoy and Baughman, *J. Am. Chem. Soc.* **95,** 8178 (1973); and Ref. 30. Also see the discussion in Arnett, Ref. 57, pp. 236–242.

[64] Deno, Jaruzelski, and Schriesheim, *J. Am. Chem. Soc.* **77,** 3044 (1955); Deno, Berkheimer, Evans, and Peterson, *J. Am. Chem. Soc.* **81,** 2344 (1959).

[65] Deno, Groves, and Saines, *J. Am. Chem. Soc.* **81,** 5790 (1959); Deno, Groves, Jaruzelski, and Lugasch, *J. Am. Chem. Soc.* **82,** 4719 (1960).

[66] Reagan, *J. Am. Chem. Soc.* **91,** 5506 (1969).

[67] Lee and Sadar, *J. Am. Chem. Soc.* **96,** 2862 (1974).

[68] Yates, Stevens, and Katritzky, *Can J. Chem.* **42,** 1957 (1964); Yates and Riordan, *Can. J. Chem.* **43,** 2328 (1965).

[69] Hammett, Ref. 57, p. 278; Rochester, Ref. 8, p. 21.

[70] For reviews, see Rochester, *Q. Rev., Chem. Soc.* **20,** 511–525 (1966); Rochester, Ref. 8, pp. 234–264; and Bowden, *Chem. Rev.* **66,** 119–131 (1966) (the last review is reprinted in Coetzee and Ritchie, Ref. 62, pp. 186–215).

[71] Bunnett and Olsen, *Can. J. Chem.* **44,** 1899, 1917 (1966); Bunnett, McDonald, and Olsen, *J. Am. Chem. Soc.* **96,** 2855 (1974).

[72] More O'Ferrall, *J. Chem. Soc., Perkin Trans. 2* 976 (1972).

Acid and Base Catalysis[77]

The old idea that a catalyst is something which merely increases the rate of a reaction which would proceed without the catalyst, only more slowly, has been found to be invalid for most reactions which are acid- or base-catalyzed. In these cases there is no reaction at all without at least some catalyst. Older workers were deceived because often only a trace of catalyst is necessary. The catalyst is involved in a fundamental way in the mechanism. Nearly always the first step of such a reaction is a proton transfer between the catalyst and the substrate.

Reactions may be catalyzed by acid or base in two different ways, called *general* and *specific catalysis*. If the rate of an acid-catalyzed reaction run in a solvent S is proportional to $[SH^+]$, the reaction is said to be subject to *specific acid catalysis*, the acid being SH^+. The acid which is put into the solvent may be stronger or weaker than SH^+, but the rate is proportional only to the $[SH^+]$ that is actually present in the solution (derived from $S + HA \rightleftharpoons SH^+ + A^-$) and the identity of HA makes no difference except insofar as it determines the position of equilibrium and hence the $[SH^+]$. Most measurements have been made in water, where SH^+ is H_3O^+.

In *general acid catalysis*, the rate is increased not only by an increase in $[SH^+]$ but also by an increase in the concentration of other acids (e.g., in water by phenols or carboxylic acids). These other acids increase the rate even when $[SH^+]$ is held constant. In this type of catalysis the strongest acids catalyze best, so that, in the example given, an increase in the phenol concentration would catalyze the reaction much less than a similar increase in $[H_3O^+]$. This relationship between acid strength of the catalyst and its catalytic ability may be expressed by the *Brönsted catalysis equation*[78]

$$\log k = \alpha \log K_a + C$$

where k is the rate constant for a reaction catalyzed by an acid of ionization constant K_a. According to this equation, when log k is plotted against log K_a for catalysis of a given reaction by a series of acids, a straight line should be obtained with slope α and intercept C. Although straight lines are obtained in many cases, this is not always the case. The relationship usually fails when acids of different types are being compared. For example, it is much more likely to hold for a group of substituted phenols than for a collection of acids which contains both phenols and carboxylic acids. The Brönsted equation is another linear free-energy relationship (see p. 254).

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[73] Zucker and Hammett, *J. Am. Chem. Soc.* **61**, 2791 (1939).

[74] Koskikallio and Whalley, *Trans. Faraday Soc.* **55**, 815 (1959), *Can. J. Chem.* **37**, 788 (1959).

[75] Bunnett, *J. Am. Chem. Soc.* **83**, 4956, 4968, 4973, 4978 (1961).

[76] The Bunnett w treatment has been criticized by Long and Bakule, *J. Am. Chem. Soc.* **85**, 2313 (1963).

[77] For reviews, see Hammett, Ref. 57, pp. 315–345; Bell, Ref. 1, pp. 159–193; Jencks, "Catalysis in Chemistry and Enzymology," pp. 163–242, McGraw-Hill Book Company, New York, 1969; and Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," pp. 19–144, John Wiley & Sons, Inc., New York, 1971.

[78] For a review, see Kresge, *Chem. Soc. Rev.* **2**, 475–503 (1973).

Analogously, there are *general* and *specific* (S^- from an acidic solvent SH) *base-catalyzed reactions*. The Brönsted law for bases is

$$\log k = \beta \log K_b + C$$

A knowledge of whether a reaction is subject to general or specific acid catalysis supplies information about the mechanism. For any acid-catalyzed reaction we may write

Step 1 $$\mathrm{A} \xrightleftharpoons{\mathrm{SH}^+} \mathrm{AH}^+$$

Step 2 $$\mathrm{AH}^+ \longrightarrow \text{products}$$

If the reaction is catalyzed only by the specific acid SH^+, it means that step 1 is rapid and step 2 is rate-controlling, since an equilibrium has been rapidly established between A and the strongest acid present in the solution, namely, SH^+ (since this is the strongest acid which can be present in S). On the other hand, if step 2 is faster, there is no time to establish equilibrium and the rate-determining step must be step 1. This step will be affected by all the acids present, and the rate will reflect the sum of the effects of each acid (general acid catalysis). General acid catalysis is also observed if the slow step is reaction of a hydrogen-bond complex $A \cdots\cdots HB$, since each complex will react with a base at a different rate. A comparable discussion may be used for general and specific base catalysis. Further information may be obtained from the values α and β in the Brönsted catalysis equations, since these are approximate measures of the extent of proton transfer in the transition state. In most cases values of α and β are between 1 and 0. A value of α or β near 0 is generally taken to mean that the transition state resembles the reactants; i.e., the proton has been transferred very little when the transition state has been reached. A value of α or β near 1 is taken to mean the opposite; i.e., in the transition state the proton has been almost completely transferred. However, cases are known in which these generalizations are not followed.[79] In general, the proton in the transition state lies closer to the weaker base.

Lewis Acids and Bases. Hard and Soft Acids and Bases

At about the same time that Brönsted proposed his acid-base theory, Lewis put forth a broader one. A base in the Lewis theory is the same as in the Brönsted one, namely, a compound with an available pair of electrons, either unshared or in a π orbital. A *Lewis acid*, however, is any species which has a vacant orbital. In a Lewis acid-base reaction the unshared pair of the base forms a covalent bond with the vacant orbital of the acid, as represented by the general equation

$$\mathrm{A} + \overline{\mathrm{B}} \longrightarrow \mathrm{A{-}B}$$

in which charges are not shown, since they may differ. A specific example is

$$\mathrm{BF_3} + \overline{\mathrm{N}}\mathrm{H_3} \longrightarrow \mathrm{F_3}\overset{\ominus}{\mathrm{B}}{-}\overset{\oplus}{\mathrm{N}}\mathrm{H_3}$$

In the Brönsted picture, the acid is a proton donor, but in the Lewis picture the proton itself is the acid since it has a vacant orbital. A Brönsted acid becomes, in the Lewis picture, the compound that gives up the actual acid. The advantage of the Lewis theory is that it correlates the behavior of many more processes. For example, $AlCl_3$ and BF_3 are Lewis acids because they have only six electrons in the outer shell and have room for eight. $SnCl_4$ and SO_3 have eight, but their central elements, not being in the first row of the periodic table, have room for ten or twelve. Other Lewis acids are simple cations, like Ag^+. The simple reaction $A + \overline{B} \rightarrow A{-}B$ is not very common in organic chemistry, but the scope of the Lewis picture is much larger because reactions of the types

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[79] See for example Bordwell and Boyle, *J. Am. Chem. Soc.* **94,** 3907 (1972); Davies, *J. Chem. Soc., Perkin Trans. 2* 1018 (1974); Hanna, Jermini, Loewenschuss, and Zollinger, *J. Am. Chem. Soc.* **96,** 7222 (1974).

$$\begin{array}{rcl} \mathbf{A^1 + A^2{-}B} & \longrightarrow & \mathbf{A^1{-}B + A^2} \\ \mathbf{B^1 + A{-}B^2} & \longrightarrow & \mathbf{A{-}B^1 + B^2} \\ \mathbf{A^1{-}B^1 + A^2{-}B^2} & \longrightarrow & \mathbf{A^1{-}B^2 + A^2{-}B^1} \end{array}$$

which are very common in organic chemistry, are also Lewis acid-base reactions. In fact, all reactions in which a covalent bond is formed through one species contributing a filled and the other a vacant orbital may be regarded as Lewis acid-base reactions.

When a Lewis acid combines with a base to give a negative ion in which the central atom has a higher-than-normal valence, the resulting salt is called an *ate complex*.[79a] Examples are

$$\mathbf{Me_3B + LiMe} \longrightarrow \underset{\text{Ate complex}}{\mathbf{Me_4B^-\quad Li^+}}$$

$$\mathbf{Ph_5Sb + LiPh} \longrightarrow \underset{\text{Ate complex}}{\mathbf{Ph_6Sb^-\quad Li^+}}$$

Ate complexes are analogous to the onium salts formed when a Lewis base expands its valence; e.g.,

$$\mathbf{Me_3N + MeI} \longrightarrow \underset{\text{Onium salt}}{\mathbf{Me_4N^+\quad I^-}}$$

Far fewer quantitative measurements have been made of Lewis acid strength compared with that of Brönsted acids.[80] A simple table of Lewis acidities based on some quantitative measurement (such as that given for Brönsted acids in Table 1) is not feasible because Lewis acidity depends on the nature of the base. Qualitatively, the following approximate sequence of acidity of Lewis acids of the type MX_n has been suggested, where X is a halogen atom or an inorganic radical:[80] $BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > InX_3 > SnX_4 > AsX_5 > ZnX_2 > HgX_2$.

The facility with which an acid-base reaction takes place depends of course on the strengths of the acid and of the base. But it also depends on quite another quality, called the *hardness* or *softness* of the acid or base.[81] This quality cannot be precisely measured, only qualitatively described. The characteristics are as follows:

Soft bases. The donor atoms are of low electronegativity and high polarizability and are easy to oxidize. They hold their valence electrons loosely.

Hard bases. The donor atoms are of high electronegativity and low polarizability and are hard to oxidize. They hold their valence electrons tightly.

Soft acids. The acceptor atoms are large, have low positive charge, and contain unshared pairs of electrons (*p* or *d*) in their valence shells. They have high polarizability and low electronegativity.

Hard acids. The acceptor atoms are small, have high positive charge, and do not contain unshared pairs in their valence shells. They have low polarizability and high electronegativity.

[79a] For a review of ate complexes, see Wittig, *Q. Rev., Chem. Soc.* **20,** 191–210 (1966).

[80] For reviews of the quantitative aspects of Lewis acidity, see Satchell and Satchell, *Q. Rev., Chem. Soc.* **25,** 171–199 (1971), *Chem. Rev.* **69,** 251–278 (1969).

[81] Pearson, *J. Am. Chem. Soc.* **85,** 3533 (1963), *Science* **151,** 172 (1966); Pearson and Songstad, *J. Am. Chem. Soc.* **89,** 1827 (1967). For reviews of the hard and soft acid-base concept, see Pearson, in Chapman and Shorter, "Advances in Linear Free-Energy Relationships," pp. 281–319, Plenum Press, New York, 1972; Pearson, *Surv. Prog. Chem.* **5,** 1–52 (1969) [portions of this article, slightly modified, also appear in Pearson, *J. Chem. Educ.* **45,** 581–587, 643–648 (1968)]; Ho, *Chem. Rev.* **75,** 1–20 (1975); Garnovskii, Osipov, and Bulgarevich, *Russ. Chem. Rev.* **41**, 341–359 (1972); Seyden-Penne, *Bull. Soc. Chim. Fr.* 3871 (1968).

TABLE 2 Hard and soft acids and bases[82]

Hard bases	Soft bases	Borderline bases
H_2O OH^- F^-	R_2S RSH RS^-	$ArNH_2$ C_5H_5N
AcO^- SO_4^{2-} Cl^-	I^- R_3P $(RO)_3P$	N_3^- Br^-
CO_3^{2-} NO_3^- ROH	CN^- RCN CO	NO_2^-
RO^- R_2O NH_3	C_2H_4 C_6H_6	
RNH_2	H^- R^-	
Hard acids	**Soft acids**	**Borderline acids**
H^+ Li^+ Na^+	Cu^+ Ag^+ Pd^{2+}	Fe^{2+} Co^{2+} Cu^{2+}
K^+ Mg^{2+} Ca^{2+}	Pt^{2+} Hg^{2+} BH_3	Zn^{2+} Sn^{2+} Sb^{3+}
Al^{3+} Cr^{2+} Fe^{3+}	$GaCl_3$ I_2 Br_2	Bi^{3+} BMe_3 SO_2
BF_3 $B(OR)_3$ $AlMe_3$	CH_2 carbenes	R_3C^+ NO^+ GaH_3
$AlCl_3$ AlH_3 SO_3		$C_6H_5^+$
RCO^+ CO_2		
HX (hydrogen-bonding molecules)		

Acids and bases can be ranked in (approximate) order of hardness or softness (e.g., base softness decreases in the order $I^- > Br^- > Cl^- > F^-$, and in the order $CH_3^- > NH_2^- > OH^- > F^-$), but since the quality is not precisely defined, it seems more appropriate to divide them each into three groups: hard, soft, and borderline. Such a listing is found in Table 2.[82] Note that the proton, which is involved in all Brönsted acid-base reactions, is classified as a hard acid.

Once acids and bases have been classified as hard or soft, a simple rule can be given: *hard acids prefer to bond to hard bases, and soft acids prefer to bond to soft bases.* The rule has nothing to do with acid or base *strength* but merely says that the complex A—B will have extra stability if both A and B are hard or if both are soft. The rule is not a theory but a generalization based on experimental facts.

One application of the rule is found in complexes between alkenes or aromatic compounds and metal ions (p. 79). Alkenes and aromatic rings are soft bases and should prefer to complex with soft acids. Thus, Ag^+, Pt^{2+}, and Hg^{2+} complexes are common, but complexes of Na^+, Mg^{2+}, or Al^{3+} are rare. Chromium complexes are also common, but in such complexes the chromium is in a low or zero oxidation state (which softens it) or attached to other soft ligands. Another application of the rule is discussed on p. 323.

The Effects of Structure on the Strengths of Acids and Bases[83]

The structure of a molecule may affect its acidity or basicity in a number of ways. Unfortunately, in most molecules two or more of these effects (as well as solvent effects) are operating, and it is usually very difficult or impossible to say how much each effect contributes to the acid or base strength. Small differences in acidity or basicity between similar molecules are particularly difficult to interpret, and it is well to be cautious when attributing them to any particular effect.

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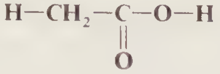
[82] Taken from larger listings in Pearson, Ref. 81.

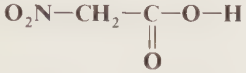
[83] For a monograph, see Hine, "Structural Effects on Equilibria in Organic Chemistry," John Wiley & Sons, Inc., New York, 1975. For reviews, see Ref. 36; Bell, Ref. 1, pp. 86–110; Barlin and Perrin, in Bentley and Kirby, "Elucidation of Organic Structures by Physical and Chemical Methods," 2d ed. (vol. 4 of Weissberger, "Techniques of Chemistry"), pt. 1, pp. 611–676, John Wiley & Sons, Inc., New York, 1972. For discussions, see Bolton and Hepler, *Q. Rev., Chem. Soc.* **25,** 521–532 (1971); Clark and Perrin, *Q. Rev., Chem. Soc.* **18,** 295–320 (1964); Barlin and Perrin, *Q. Rev., Chem. Soc.* **20,** 75–101 (1966); Thirot, *Bull. Soc. Chim. Fr.* 3559 (1967); Liler, Ref. 8, pp. 59–144.

1. *Field effects.* These were discussed on p. 20. As an example of the influence of field effects on acidity, we may compare the acidity of acetic acid and nitroacetic acid:



$H{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}O{-}H$

$pK_a = 4.76$



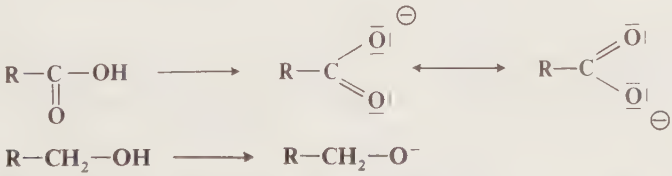
$O_2N{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}O{-}H$

$pK_a = 1.68$

The only difference in the structure of these molecules is the substitution of NO_2 for H. Since NO_2 is a strongly electron-withdrawing group, the electrons in the O—H bond of nitroacetic acid are closer to the oxygen than are the electrons in the O—H bond of acetic acid. The electron density is thus considerably greater on the oxygen (and hence lower on the hydrogen) in the former than in the latter. Since the electron cloud surrounds the hydrogen less, the proton of nitroacetic acid is more easily lost and, as the pK_a values indicate, nitroacetic acid is about 1000 times stronger than acetic.

Another way to look at it is the following: the NO_2 group in the anion of nitroacetic acid withdraws electron density from the negatively charged COO^- group (compared with the anion of acetic acid). Any effect which results in electron withdrawal from a negatively charged center is a stabilizing effect because it spreads the charge. Thus, $-I$ groups increase the acidity of uncharged acids like acetic because they spread the negative charge of the anion. However, $-I$ groups also increase the acidity of any acid, no matter what the charge. For example, if the acid has a charge of $+1$ (and its conjugate base is therefore uncharged), a $-I$ group destabilizes the positive center (by increasing and concentrating the positive charge) of the acid, a destabilization which will be relieved when the proton is lost. Similarly, if the acid has a charge of -1, then the $-I$ group stabilizes the conjugate base (with a charge of -2) more than it does the acid. In general we may say that *groups which withdraw electrons by the field effect increase acidity and decrease basicity, while electron-donating groups act in the opposite direction.* Another example is the molecule $(C_6F_5)_3CH$, with three strongly electron-withdrawing C_6F_5 groups, which has a pK_a of 16[84] compared with Ph_3CH, with a pK_a of 31.5 (Table 1), an acidity enhancement of about 10^{15}. Table 3 shows pK_a values for some acids,[85] and an approximate idea of field effects can be obtained from this table. In the case of the chlorobutyric acids note how the effect decreases with distance. It must be remembered, however, that field effects are not the sole cause of the acidity differences noted and that in fact solvation effects may be more important in many cases (see pp. 243–245).

2. *Resonance effects.* Resonance which stabilizes an acid but not its conjugate base results in the acid's having a lower acidity than otherwise expected, and vice versa. An example is found in the higher acidity of carboxylic acids compared with primary alcohols.



The $RCOO^-$ ion is stabilized by resonance not available to the RCH_2O^- ion (or to RCOOH). Note that the $RCOO^-$ is stabilized not only by the fact there are two equivalent canonical forms

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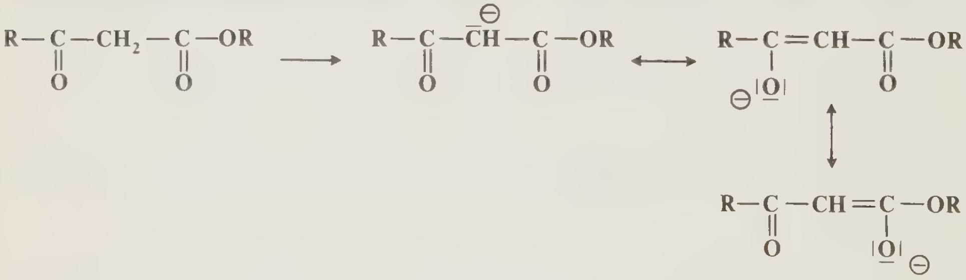
[84] Filler and Wang, *Chem. Commun.* 287 (1968).

[85] These values are from Ref. 36.

TABLE 3 pK values for some acids[85]

Acid	pK	Acid	pK
HCOOH	3.77	$ClCH_2COOH$	2.86
CH_3COOH	4.76	$Cl_2CHCOOH$	1.29
CH_3CH_2COOH	4.88	Cl_3CCOOH	0.65
$CH_3(CH_2)_nCOOH$[86]	4.82–4.95		
		O_2NCH_2COOH	1.68
$(CH_3)_2CHCOOH$	4.86	$(CH_3)_3\overset{\oplus}{N}CH_2COOH$	1.83
$(CH_3)_3CCOOH$	5.05	$HOOCCH_2COOH$	2.83
		$PhCH_2COOH$	4.31
FCH_2COOH	2.66	$\overset{\ominus}{O}OCCH_2COOH$	5.69
$ClCH_2COOH$	2.86		
$BrCH_2COOH$	2.86	$\overset{\ominus}{O}_3SCH_2COOH$	4.05
ICH_2COOH	3.12	$HOCH_2COOH$	3.83
		$H_2C{=}CHCH_2COOH$	4.35
$ClCH_2CH_2CH_2COOH$	4.52		
$CH_3CHClCH_2COOH$	4.06		
$CH_3CH_2CHClCOOH$	2.84		

but also by the fact that the negative charge is spread over both oxygen atoms and is therefore less concentrated than it is in RCH_2O^-. The same effect is found in other compounds containing a C=O (or C≡N) group. Thus amides $RCONH_2$ are more acidic than amines RCH_2NH_2; esters RCH_2COOR' than ethers RCH_2CH_2OR'; and ketones RCH_2COR' than alkanes RCH_2CH_2R' (Table 1). The effect is enhanced when two carbonyl groups are attached to the same carbon (because of additional resonance and spreading of charge); and, for example, β-keto esters are more acidic than simple ketones or esters (Table 1). Extreme examples of this effect are found in



the molecules tricyanomethane $(NC)_3CH$, with a pK_a of −5, and 2-(dicyanomethylene)-1,1,3,3-tetracyanopropene $(NC)_2C{=}C[CH(CN)_2]_2$, whose first pK_a is below −8.5 and whose second pK_a is −2.5.[29]

Resonance effects are also important in aromatic amines. *m*-Nitroaniline is a weaker base than aniline, a fact which can be accounted for by the −*I* effect of the nitro group. But *p*-nitroaniline is weaker still, though the −*I* effect should be less, because of the greater distance. We can explain this result by taking into account the canonical form **1**. Because **1** contributes to the resonance hybrid, the electron density of the unshared pair is lower in *p*-nitroaniline than it is in *m*-

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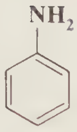
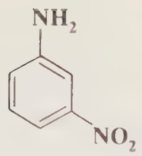
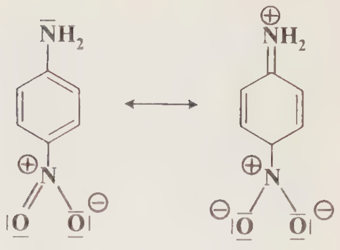
[86] $n = 2$ to 7.







1

pK_a of conjugate[87] acid	4.60	2.47	1.11

nitroaniline, where a canonical form such as **1** is impossible. The basicity is lower in the para compound for two reasons, both caused by the same effect: (1) the unshared pair is less available for attack by a proton, and (2) when the conjugate acid is formed, the resonance stabilization afforded by **1** is no longer available because the previously unshared pair is now being shared by the proton. The acidity of phenols is affected by substituents in a similar manner.

In general, resonance effects act in the same direction as field effects. That is, here too, electron-withdrawing groups increase acidity and decrease basicity, and electron-donating groups act in the opposite manner. As a result of both resonance and field effects, charge dispersal leads to greater stability.

3. *Periodic-table correlations.* When comparing Brönsted acids and bases which differ in the position of an element in the periodic table:

a. Acidity increases and basicity decreases in going from left to right across a row of the periodic table. Thus acidity increases in the order $CH_4 < NH_3 < H_2O < HF$, and basicity decreases in the order $CH_3^- > NH_2^- > OH^- > F^-$. This behavior can be explained by the increase in electronegativity upon going from left to right across the table. It is this effect which is responsible for the great differences in acidity between carboxylic acids, amides, and ketones: $RCOOH \gg RCONH_2 \gg RCOCH_3$.

b. Acidity increases and basicity decreases in going down a column of the periodic table, despite the decrease in electronegativity. Thus acidity increases in the order $HF < HCl < HBr < HI$, and $H_2O < H_2S$, and basicity decreases in the order $NH_3 > PH_3 > AsH_3$. This behavior is related to the size of the species involved. Thus, for example, F^-, which is much smaller than I^-, attracts a proton much more readily because its negative charge occupies a smaller volume and is therefore more concentrated (note that F^- is also much harder than I^- and is thus more attracted to the hard proton; see p. 238).

Lewis acidity is also affected by periodic-table considerations. In comparing acid strengths of Lewis acids of the form MX_n:[80]

a. Acids which require only one electron pair to complete an outer shell are stronger than those which require two. Thus $GaCl_3$ is stronger than $ZnCl_2$. This results from the relatively smaller energy gain in adding an electron pair which does not complete an outer shell and from the buildup of negative charge if two pairs come in.

b. Other things being equal, the acidity of MX_n decreases in going down the periodic table because as the size of the molecule increases, the attraction between the positive nucleus and the incoming electron pair is weaker. Thus BCl_3 is a stronger acid than $AlCl_3$.[88]

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[87] Smith, in Patai, "The Chemistry of the Amino Group," pp. 161–204, Interscience Publishers, New York, 1968.

[88] Note that Lewis acidity *decreases*, whereas Brönsted acidity *increases*, on going down the table. There is no contradiction here when we remember that in the Lewis picture the actual acid in all Brönsted acids is the same, namely the proton. In comparing, say, HI and HF, we are not comparing different Lewis acids but only how easily F^- and I^- give up the proton.

TABLE 4 Bases listed in increasing order of base strength when compared with certain reference acids[91]

Increasing order of base strength	Reference acid			
	H^+ or BMe_3	BMe_3	$B(CMe_3)_3$	
↓	NH_3	Et_3N	Me_3N	Et_3N
	Me_3N	NH_3	Me_2NH	Et_2NH
	$MeNH_2$	Et_2NH	NH_3	$EtNH_2$
	Me_2NH	$EtNH_2$	$MeNH_2$	NH_3

c. As has been noted, some MX_n compounds in which M already possesses an octet can still be Lewis acids by using empty *d* orbitals to bond with the incoming base (e.g., $SnCl_4$). These *d* orbitals become more readily available as we go down the periodic table, thus resulting in an increase in Lewis acidity. This factor contradicts factor **b**, to some extent, and the two effects must be added together. The Lewis acidity order given on p. 237 is in accord with these principles.

d. For cations, increased charge and decreased radius increase acidity. Thus the Lewis acids $Al(H_2O)_5{}^{3+}$, $Al(H_2O)_4Cl^{2+}$, and $Al(H_2O)_3Cl_2{}^+$ decrease steadily in acid strength. For anions, increased charge and decreased radius increase basicity, and O^{2-} is a stronger base than either OH^- or Se^{2-}.

4. *Statistical effects.* In a symmetrical dibasic acid, the first dissociation constant is twice as large as expected, since there are two equivalent ionizable hydrogens, while the second constant is only one-half as large as expected because the conjugate base can accept a proton at two equivalent sites. So K_1/K_2 should be 4, and approximately this value is found for dicarboxylic acids where the two groups are sufficiently far apart in the molecule that they do not influence each other. A similar argument holds for molecules with two equivalent basic groups.[89]

5. *Hydrogen bonding.* Internal hydrogen bonding can greatly influence acid or base strength. For example, the p*K* for *o*-hydroxybenzoic acid is 2.98, while the value for the para isomer is 4.58. Internal hydrogen bonding between the OH and COO^- groups of the conjugate base of the ortho isomer stabilizes it and results in an increased acidity.

6. *Steric effects.*[90] The proton itself is so small that direct steric hindrance is seldom encountered in proton transfers. Steric effects are much more common in Lewis acid-base reactions in which larger acids are used. Spectacular changes in the order of base strength have been demonstrated when the size of the acid was changed. Table 4 shows the order of base strength of simple amines when compared against acids of various size.[91] It may be seen that the usual order of basicity of amines (when the proton is the reference acid) may be completely inverted by using a large enough acid. The strain caused by formation of a covalent bond when the two atoms involved each have three large groups is called *face strain* or *F strain.* When the reference acids were boranes, the order of basicity was determined by measurements of dissociation pressures.

Steric effects may indirectly affect acidity or basicity by affecting the resonance (see p. 38). For example, *o-t*-butylbenzoic acid is about 10 times as strong as the para isomer, because the carboxyl group is forced out of the plane by the *t*-butyl group. Indeed, virtually all ortho benzoic acids are stronger than the corresponding para isomers, regardless of whether the group on the ring is electron-donating or electron-withdrawing.

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[89] The effect discussed here is an example of a symmetry factor. For an extended discussion, see Eberson, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 211–293, Interscience Publishers, New York, 1969.

[90] For a review, see Gold, *Prog. Stereochem.* **3**, 169–201 (1962).

[91] Brown, *J. Am. Chem. Soc.* **67**, 378, 1452 (1945), "Boranes in Organic Chemistry," pp. 53–64, Cornell University Press, Ithaca, N.Y., 1972.

7. *Hybridization.* An *s* orbital has a lower energy than a *p* orbital. Therefore the energy of a hybrid orbital is lower the more *s* character it contains. It follows that a carbanion at an *sp* carbon is more stable than a corresponding carbanion at an sp^2 carbon. Thus $HC{\equiv}C^-$, which has more *s* character in its unshared pair than $CH_2{=}CH^-$ or $CH_3CH_2^-$ (*sp* versus sp^2 versus sp^3, respectively), is a much weaker base. This explains the relatively high acidity of acetylenes and of HCN. Another example is that alcohol and ether oxygens, where the unshared pair is sp^3, are more strongly basic than carbonyl oxygens, where the unshared pair is sp^2 (Table 1).

The Effects of the Medium on Acid and Base Strength

Structural features are not the only factors which affect acidity or basicity. The same compound may have its acidity or basicity changed when the conditions are changed. The effects of temperature (p. 226) and some effects of solvent (p. 233) have already been discussed. Another way in which the solvent may influence acid and base strength is by differential solvation. If a base is more solvated than its conjugate acid, its stability is increased relative to the conjugate acid. For example, Table 4 shows that, toward the proton, where steric effects are absent, methylamine is a stronger base than ammonia, and dimethylamine stronger still,[92] results which are easily explainable if one assumes that methyl groups are electron-donating. However, trimethylamine, which should be even stronger, is a weaker base than dimethylamine or methylamine. This apparently anomalous behavior may be explained by differential hydration.[93] Thus, NH_4^+ is much better hydrated (by hydrogen bonding to the water solvent) than NH_3 because of its positive charge.[94] It has been estimated that this effect contributes about 11 p*K* units to the base stength of ammonia.[95] When methyl groups replace hydrogen, this difference in hydration decreases until, for trimethylamine, it contributes only about 6 p*K* units to the base strength.[95] Thus two effects act in opposite directions, the field effect increasing the basicity as the number of methyl groups increases and the hydration effect decreasing it. When the effects are added, the strongest base is dimethylamine and the weakest is ammonia. If alkyl groups are electron-donating, one would expect that in the gas phase,[96] where the solvation effect does not exist, the basicity order of amines toward the proton should be $R_3N > R_2NH > RNH_2 > NH_3$, and this has indeed been confirmed, for R = Me as well as R = Et and Pr.[97] Aniline too, in the gas phase, is a stronger base than NH_3,[98] so that its much lower basicity in aqueous solution (pK_a of $PhNH_3^+$ 4.60, compared with pK_a of 9.24 for aqueous NH_4^+), is caused by similar solution effects and not by resonance and field electron-withdrawing effects of a phenyl group, as had been generally believed. Similarly, pyridine[99] and pyrrole[100] are both much less basic than NH_3 in aqueous solution

[92] For a review of the basicity of amines, see Ref. 87.

[93] Trotman-Dickenson, *J. Chem. Soc.* 1293 (1949); Pearson, *J. Am. Chem. Soc.* **70,** 204 (1948); Pearson and Williams, *J. Am. Chem. Soc.* **76,** 258 (1954); Hall, *J. Am. Chem. Soc.* **79,** 5441 (1957); Arnett, Jones, Taagepera, Henderson, Beauchamp, Holtz, and Taft, *J. Am. Chem. Soc.* **94,** 4724 (1972); Aue, Webb, and Bowers, *J. Am. Chem. Soc.* **94,** 4726 (1972); **98,** 311, 318 (1976).

[94] For discussions of the solvation of ammonia and amines, see Jones and Arnett, *Prog. Phys. Org. Chem.* **11,** 263–420 (1974); Grunwald and Ralph, *Acc. Chem. Res.* **4,** 107–113 (1971).

[95] Condon, *J. Am. Chem. Soc.* **87,** 4481, 4485 (1965).

[96] For a discussion of basicities in the gas phase, see Arnett, *Acc. Chem. Res.* **6,** 404–409 (1973).

[97] Munson, *J. Am. Chem. Soc.* **87,** 2332 (1965); Brauman, Riveros, and Blair, *J. Am. Chem. Soc.* **93,** 3914 (1971); Briggs, Yamdagni, and Kebarle, *J. Am. Chem. Soc.* **94,** 5128 (1972); Aue, Webb, and Bowers, Ref. 93.

[98] Briggs, Yamdagni, and Kebarle, Ref. 97; Dzidic, *J. Am. Chem. Soc.* **94,** 8333 (1972).

[99] Taagepera, Henderson, Brownlee, Beauchamp, Holtz, and Taft, *J. Am. Chem. Soc.* **94,** 1369 (1972); Taft, Taagepera, Summerhays, and Mitsky, *J. Am. Chem. Soc.* **95,** 3811 (1973); Briggs, Yamdagni, and Kebarle, Ref. 97.

[100] Yamdagni and Kebarle, *J. Am. Chem. Soc.* **95,** 3504 (1973).

TABLE 5 Thermodynamic values for the ionizations of acetic and chloroacetic acids in H_2O at 25°C[105]

Acid	pK_a	ΔG, kcal/mol	ΔH, kcal/mol	$T\,\Delta S$, kcal/mol
CH_3COOH	4.76	+6.5	−0.1	−6.6
$ClCH_2COOH$	2.86	+3.9	−1.1	−5.0
Cl_3CCOOH	0.65	+0.9	+1.5	+0.6

(pyrrole is neutral in aqueous solution) but *more* basic in the gas phase. These examples in particular show how careful one must be in attributing relative acidities or basicities to any particular effect.

For simple alcohols the order of gas-phase *acidity* is completely reversed from that in aqueous solution. In solution the acidity is in the order $H_2O > CH_3OH > MeCH_2OH > Me_2CHOH > Me_3COH$, but in the gas phase the order is precisely the opposite.[101] Once again solvation effects can be invoked to explain the differences. Comparing the two extremes, H_2O and Me_3COH, we see that the OH^- ion is very well solvated by water while the bulky Me_3CO^- is much more poorly solvated because the water molecules cannot get as close to the oxygen. Thus in solution H_2O gives up its proton more readily. When solvent effects are absent, however, the intrinsic acidity is revealed and Me_3COH is a stronger acid than H_2O. This result demonstrates that simple alkyl groups cannot be simply regarded as electron-donating. If methyl is an electron-donating group, then Me_3COH should be a weaker acid (intrinsically) than H_2O; yet it is stronger. The evidence in this and other cases[102] is that alkyl groups may be electron-donating when connected to unsaturated systems but in other systems may have either no effect or actually be electron-withdrawing. The explanation given for the gas-phase (intrinsic) acidity order of alcohols, as well as the basicity order of amines, is that alkyl groups, because of their polarizability, can spread both positive and negative charges.[103]

An important aspect of solvent effects is the effect on the orientation of solvent molecules when an acid or base is converted to its conjugate. For example, consider an acid RCOOH converted to $RCOO^-$ in aqueous solution. The solvent molecules, by hydrogen bonding, arrange themselves around the COO^- group in a much more orderly fashion than they had been arranged around the COOH group (because they are more strongly attracted to the negative charge). This represents a considerable loss of freedom and a decrease in entropy. Thermodynamic measurements show that for simple aliphatic and halogenated aliphatic acids in aqueous solution at room temperature, the entropy ($T\,\Delta S$) usually contributes much more to the total free-energy change ΔG than does the enthalpy ΔH.[104] Two examples are shown in Table 5.[105] Resonance and field effects of functional groups therefore affect the acidity of RCOOH in two distinct ways. They affect the enthalpy (electron-withdrawing groups increase acidity by stabilizing $RCOO^-$ by charge dispersal), but they also affect the entropy (by lowering the charge on the COO^- group and by changing the electron-density distribution in the COOH group, electron-withdrawing groups alter the solvent orientation patterns around both the acid and the ion, and consequently change ΔS).

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[101] Baird, *Can. J. Chem.* **47,** 2306 (1969); Brauman and Blair, Ref. 54; Arnett, Small, McIver, and Miller, *J. Am. Chem. Soc.* **96,** 5638 (1974); Blair, Isolani, and Riveros, *J. Am. Chem. Soc.* **95,** 1057 (1973); McIver, Scott, and Riveros, *J. Am. Chem. Soc.* **95,** 2706 (1973). See also Graffeuil, Labarre, Leibovici, *J. Mol. Struct.* **23,** 65 (1974).

[102] Brauman and Blair, *J. Am. Chem. Soc.* **93,** 4315 (1971); Kwart and Takeshita, *J. Am. Chem. Soc.* **86,** 1161 (1964); Fort and Schleyer, *J. Am. Chem. Soc.* **86,** 4194 (1964); Holtz and Stock, *J. Am. Chem. Soc.* **87,** 2404 (1965); Laurie and Muenter, *J. Am. Chem. Soc.* **88,** 2883 (1966).

[103] Brauman and Blair, Ref. 54; Munson, Ref. 97; Brauman, Riveros, and Blair, Ref. 97; Huheey, *J. Org. Chem.* **36,** 204 (1971); Radom, *Aust. J. Chem.* **28,** 1 (1975).

[104] Bolton and Hepler, Ref. 83; Refs. 13 and 14.

[105] Bolton and Hepler, Ref. 83, p. 529; Hambly, Ref. 14, p. 92.

As an example, the data in Table 5 show that more than half of the acid-strengthening effect of the Cl in $ClCH_2COOH$ comes from entropy and less than half is caused by ΔH. A more extreme example is trichloroacetic acid, which is about 10,000 times stronger than acetic acid but which actually would be a weaker acid if enthalpy factors were all that mattered (Table 5). In this case it is the very large entropy change which makes the difference. Because the field effect spreads the negative charge of Cl_3CCOO^- all over the molecule, solvent molecules are less strongly attracted than they are to CH_3COO^-; they have much more freedom and consequently a higher entropy. There are other carboxylic acids in which enthalpy and entropy effects act in opposite directions, but in general, whether they act in the same or in opposite directions, entropy effects are more important.

The solvent may affect acidity or basicity even when it is aprotic. For example, the order of base strength against 2,4-dinitrophenol was $Bu_3N > Bu_2NH > BuNH_2$ in chlorobenzene; $Bu_2NH > Bu_3N > BuNH_2$ in benzene; and $Bu_2NH > BuNH_2 > Bu_3N$ in dibutyl ether.[106] The ionic strength of the solvent also influences acidity or basicity, since it has an influence on activity coefficients.

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[106] Bayles and Taylor, *J. Chem. Soc.* 417 (1961).

Nine

Effects of Structure on Reactivity

It is customary in writing the equation for a reaction of, say, carboxylic acids, to use the formula RCOOH, implying that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice will be used in this book. It enables a large number of individual reactions to be classified together and serves as an aid both to the memorization and the understanding of them. Organic chemistry would be a huge morass of facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way no matter what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be so great as to stop the reaction completely or to make it take an entirely unexpected course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when functional groups are present in addition to the one reacting.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric. In most cases two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

Resonance and Field Effects

It is often particularly difficult to separate these two, and they are frequently grouped together under the heading of *electrical effects*.[1] Field effects were discussed on pp. 20–22. Table 3 in Chapter 1 (p. 21) contains a list of some $+I$ and some $-I$ groups. As for resonance effects, on p. 38 it was shown how the electron-density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups which contain an unshared pair on an atom connected to an unsaturated system display a similar effect; i.e., the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron-donating by the resonance effect ($+M$ groups).[2] Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

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[1] On p. 20 we showed that there are two types of inductive effects: bond and field effects. Similarly, it is possible to define several types of resonance effects. Dewar and Grisdale, *J. Am. Chem. Soc.* **84,** 3539 (1962) recognize at least five distinct types of electrical effects, and Katritzky and Topsom, *J. Chem. Educ.* **48,** 427 (1971), point out at least seven. However, quantitatively (see p. 255) only two variables are necessary to account for the total electrical effects of substituents, one an overall field and one an overall resonance contribution: Hammett, "Physical Organic Chemistry," 2d ed., p. 376, McGraw-Hill Book Company, New York, 1970; Swain and Lupton, *J. Am. Chem. Soc.* **90,** 4328 (1968).

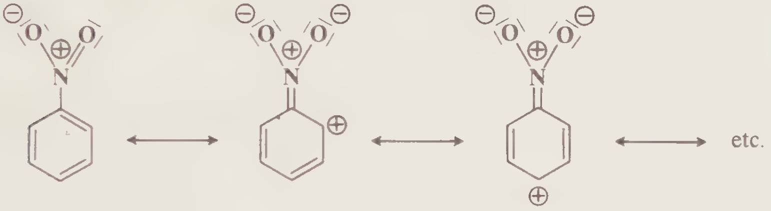
[2] The letters T and R are occasionally used instead of M.

TABLE 1 Some groups with $+M$ and $-M$ effects, not listed in order of strength of effect

Ar appears in both lists because it is capable of both kinds of effect

$+M$ groups		$-M$ groups	
O^-	SR	NO_2	CHO
S^-	SH	CN	COR
NR_2	Br	COOH[4]	SO_2R
NHR	I	COOR[4]	SO_2OR
NH_2	Cl	$CONH_2$	NO
NHCOR	F[3]	CONHR	Ar
OR	R	$CONR_2$	
OH	Ar		
OCOR			

On the other hand, groups which have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases we can draw canonical forms in which electrons have been taken from the unsaturated system into the group; e.g.,



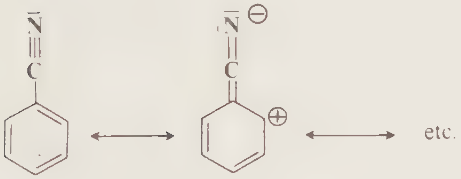


Table 1 contains a list of some $+M$ and $-M$ groups.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $CH_3OCH_2CH_2COOH$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient to use (and we shall use them). As a result of both effects the electron-density distribution is not the same as it would be without the effect (see pp. 21, 38).

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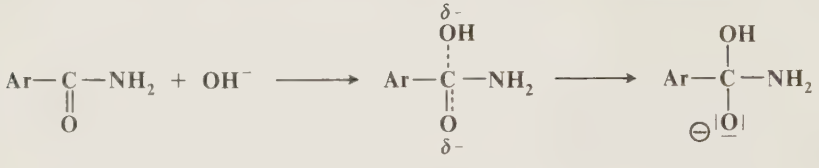
[3] For a review of the effects of F, see Yagupol'skii, Il'chenko, and Kondratenko, *Russ. Chem. Rev.* **43**, 32–47 (1974).

[4] For a review of the effects of the COOH, COOR, and COO^- groups, see Kohnstam and Williams, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 765–869, Interscience Publishers, 1969.

One thing which complicates the study of these effects is that a given group may have an effect in the transition state which is considerably more or less than it has in the unreacting molecule. For example, consider a molecule $C_6H_5CH_2Y$, where Y is the reaction site. The replacement of, say, a para hydrogen by a group X gives $XC_6H_4CH_2Y$, in which the electron density at the CH_2 group is greater or less, depending on the resonance or field effects of X. However, when the molecule undergoes reaction, the bond between CH_2 and Y begins to break, causing the CH_2 to have partial carbanion, carbonium-ion, or free-radical character, depending on the nature of the reaction. The group X, which in the unreacting molecule may have donated only slightly, may now donate electron density a good deal more or a good deal less. A given group X may even be electron-donating in one reaction and electron-withdrawing in another.

An example will show the nature of electrical effects (resonance and field) on reactivity. In the alkaline hydrolysis of aromatic amides (reaction **0-12**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon:



transition state

intermediate

1

2

In the transition state, which has a structure somewhere between that of the starting amide (**1**) and the intermediate (**2**), the electron density on the carbonyl carbon has been increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **1.** Since G is lowered for the transition state but not substantially for **1,** $\Delta G^{\ddagger}$ is lowered, and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

Steric Effects[5]

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. Very often in these cases it can be shown that steric effects are influencing the rate. For example, Table 2 lists relative rates for the SN2 ethanolysis of certain alkyl halides (see p. 266).[5] All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 266). The great decrease in rate may be attributed to *steric hindrance*, a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze (for another example, see p. 150).

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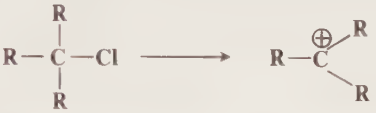
[5] Hughes, *Q. Rev., Chem. Soc.* **2,** 107–131 (1948).

TABLE 2 Relative rates of reaction of RBr with ethanol[5]

R	Relative rate
CH_3	17.6
CH_3CH_2	1
$CH_3CH_2CH_2$	0.28
$(CH_3)_2CHCH_2$	0.030
$(CH_3)_3CCH_2$	4.2×10^{-6}

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an SN1 mechanism (see p. 270), the first step, which is rate-determining, involves ionization of the alkyl chloride to a carbonium ion:



The central carbon in the alkyl chloride is sp^3-hybridized and thus has angles of about 109.5°, but when it is converted to the carbonium ion, the hybridization becomes sp^2 and the preferred angle is 120°. If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 148). This type of strain is called *B strain*[6] (for back strain), and it can be relieved by ionization to the carbonium ion. The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain would therefore be expected to be larger than in cases where B strain is not present. Table 3 shows that this is so.[7] Substitution of ethyl groups for the methyl groups of *t*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased tenfold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases solvolysis rates is found with the highly crowded molecules tri-*t*-butylcarbinol, di-*t*-butylneopentylcarbinol, *t*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters were faster than that of *t*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.[8]

Another type of strain, which can affect rates of cyclic compounds, is called *I strain* (internal strain).[9] This type of strain results from changes in ring strain on going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, SN1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from about 109.5° to about 120°. This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (p. 145); thus this compound undergoes solvolysis in 80% ethanol at 25°C 43.7 times faster than

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[6] For a discussion, see Brown, "Boranes in Organic Chemistry," pp. 114–121, Cornell University Press, Ithaca, N.Y., 1972.

[7] Brown and Fletcher, *J. Am. Chem. Soc.* **71**, 1845 (1949).

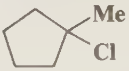
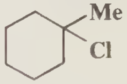
[8] Bartlett and Tidwell, *J. Am. Chem. Soc.* **90**, 4421 (1968).

[9] For discussions, see Gol'dfarb and Belen'kii, *Russ. Chem. Rev.* **29**, 214–235 (1960), pp. 221–228; and Ref. 6, pp. 105–107, 126–128.

TABLE 3 Rates of hydrolysis of tertiary alkyl chlorides at 25°C in 80% aqueous ethanol[7]

Halide	Rate	Halide	Rate
Me_3CCl	0.033	Et_3CCl	0.099
Me_2EtCCl	0.055	Me_2(iso-Pr)CCl	0.029
$MeEt_2CCl$	0.086	Me(iso-Pr)$_2$CCl	0.45

the reference compound *t*-butyl chloride.[10] In the corresponding cyclohexyl compound this factor is absent because the substrate does not have eclipsing strain (p. 144), and this compound undergoes the reaction at about one-third the rate of *t*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction: in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7 to 11 members exhibit eclipsing and transannular strain, and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.

	t-BuCl		
Relative solvolysis rates	1.0	43.7	0.35

Cyclopropyl substrates are extremely *unreactive* in cases where a tetrahedral carbon must become trigonal. For example, cyclopropyl tosylate solvolyzes about 10^6 times more slowly than cyclobutyl tosylate in acetic acid at 60°C.[11] The lack of reactivity here may be caused in part by I strain, since the ring bond angle cannot change much when the carbonium ion is formed. In the original compound, the preferred angle was about 109.5° and the real angle 60°, so the strain is about 50°; but in the carbonium ion the preferred angle has increased to 120°, yet the real angle is still about 60°, so the strain is now about 60°. Another factor which may contribute to the lack of reactivity in cyclopropyl substrates is the fact that the σ bonds have considerable π character (p. 141), so that we should expect cyclopropyl halides to resemble vinyl halides in reactivity. As shown on p. 317, vinyl halides are very unreactive to SN1 substitutions.

Conformational effects on reactivity may be considered under the heading of steric effects, although in these cases we are considering not the effect of a group X and that of another group X′ upon reactivity at a site Y but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of N-benzoylnorephedrine. The two diastereomers of this compound behave very differently when treated with alcoholic HCl. In one of the isomers nitrogen-to-oxygen migration takes place, while the other does not react at all.[12] In order for the migration to take place, the nitrogen must be near the oxygen (gauche to it). When **3** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **4** has the nitrogen gauche to the oxygen, the methyl must be gauche to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C

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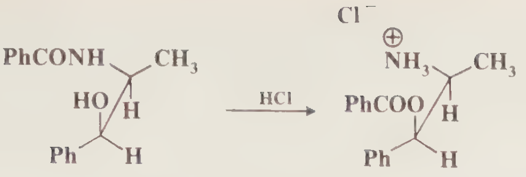
[10] Brown and Borkowski, *J. Am. Chem. Soc.* **74**, 1894 (1952).
[11] Roberts and Chambers, *J. Am. Chem. Soc.* **73**, 5034 (1951).
[12] Fodor, Bruckner, Kiss, and Óhegyi, *J. Org. Chem.* **14**, 337 (1949).



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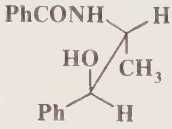
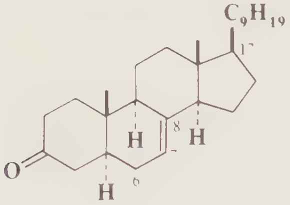


4

double bonds (see p. 673) and E2 elimination reactions (see p. 896). Also, many examples are known where axial and equatorial groups behave differently.[13]

In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**5**) and cholest-6-en-3-one (**6**), where **6** condenses with



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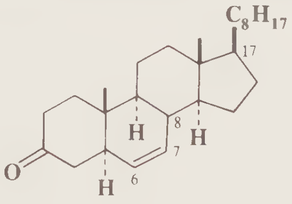

6

benzaldehyde 15 times faster than **5**.[14] The reaction site in both cases is the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate).

Quantitative Treatments of the Effect of Structure on Reactivity[15]

Suppose that the substitution of a group X for H in a reaction of $XCH{=}CHCH_2Y$ (the reaction taking place at the Y group) results in a rate increase by a factor of, say, 10. We would like to be able to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors which seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.[16] For the cases of *m*- and *p*-XC_6H_4Y, Hammett set up the equation

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[13] For a discussion, see Eliel, "Stereochemistry of Carbon Compounds," pp. 219–234, McGraw-Hill Book Company, New York, 1962.

[14] Barton, McCapra, May, and Thudium, *J. Chem. Soc.* 1297 (1960).

[15] For monographs, see Johnson, "The Hammett Equation," Cambridge University Press, Cambridge, 1973; Shorter, "Correlation Analysis in Organic Chemistry," Clarendon Press, Oxford, 1973; Chapman and Shorter, "Advances in Linear Free Energy Relationships," Plenum Press, New York, 1972; and Wells, "Linear Free Energy Relationships," Academic Press, Inc., New York, 1968. For reviews, see Hammett, Ref. 1, pp. 347–390; Fuchs and Lewis, in Lewis, "Investigation of Rates and Mechanisms of Reactions" (vol. 6 of Weissberger, "Techniques of Chemistry"), 3d ed., pp. 777–824, John Wiley & Sons, Inc., New York, 1974; Charton, *Chem. Technol.* 502–511 (1974), 245–255 (1975); Hine, "Structural Effects in Organic Chemistry," pp. 55–102, John Wiley & Sons, Inc., New York, 1975; Afanas'ev, *Russ. Chem. Rev.* **40,** 216–232 (1971), Laurence and Wojtkowiak, *Ann. Chim. (Paris)* [14] **5,** 163–191 (1970); Thirot, *Bull. Soc. Chim. Fr.* 739–744 (1967); Leffler and Grunwald, "Rates and Equilibria of Organic Reactions," pp. 171–235, John Wiley & Sons, Inc., New York, 1963; Wells, *Chem. Rev.* **63,** 171–218 (1963); Ritchie and Sager, *Prog. Phys. Org. Chem.* **2,** 323–400 (1964); Taft, in Newman, "Steric Effects in Organic Chemistry," pp. 556–675, John Wiley & Sons, Inc., New York, 1956; Taft, *J. Phys. Chem.* **64,** 1805–1815 (1960); and Pal'm, *Russ. Chem. Rev.* **30,** 471–498 (1961). For a theoretical discussion, see Ehrenson, *Prog. Phys. Org. Chem.* **2,** 195–251 (1964).

$$\log \frac{k}{k_0} = \sigma\rho$$

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation.*

The value of ρ was originally set at 1.00 for dissociation of XC_6H_4COOH at 25°C, and σ_m and σ_p values were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was so obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated and the known σ values for other groups, rates may be predicted for reactions which have not yet been run.

The σ values are numbers which sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. In a review article by Jaffé[16] are listed ρ values for 204 reactions,[17] many of them having different ρ values for different conditions. Among them are reactions as disparate as the following:

Rate constants for

$$\mathbf{ArCOOMe + OH^- \longrightarrow ArCOO^-}$$

$$\mathbf{ArCH_2OCOMe + OH^- \longrightarrow ArCH_2OH}$$

$$\mathbf{ArCH_2Cl + I^- \longrightarrow ArCH_2I}$$

$$\mathbf{ArNH_2 + PhCOCl \longrightarrow ArNHCOPh}$$

$$\mathbf{ArH + NO_2{}^+ \longrightarrow ArNO_2}$$

$$\mathbf{ArCO_2OCMe_3} \longrightarrow \text{decomposition (a free-radical process)}$$

Equilibrium constants for

$$\mathbf{ArCOOH + H_2O \rightleftharpoons ArCOO^- + H_3O^+}$$

$$\mathbf{ArCHO + HCN \rightleftharpoons ArCH(CN)OH}$$

The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts. The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be constant *within* a given reaction series.

However, there are many reactions which do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group is one which can enter into direct resonance interaction with the reaction site in the transition state. For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H. C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this

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[16] For a review, see Jaffé, *Chem. Rev.* **53,** 191 (1953).

[17] Additional ρ values are given in Wells, Ref. 15; and in van Bekkum, Verkade, and Wepster, *Recl. Trav. Chim. Pays-Bas* **78,** 821–827 (1959).

TABLE 4 σ, σ^+, and σ^- values for some common groups[19]

Group	σ_p	σ_m	$\sigma_p^{\ +}$	$\sigma_m^{\ +}$	$\sigma_p^{\ -}$
NH_2	−0.66	−0.16	−1.3	−0.16	
NMe_2	−0.60	−0.21	−1.7		
O^-	−0.52	−0.71			
OH	−0.36	−0.002	−0.92		
OMe	−0.27	0.12	−0.78	0.05	
CMe_3	−0.20	−0.12	−0.26	−0.06	
Me	−0.17	−0.07	−0.31	−0.10	
H	0	0	0	0	0
Ph	0.01	0.22	−0.18	0.11	
F	0.06	0.34	−0.07	0.35	
COO^-	0.13	0.10	−0.02	−0.03	
$CONH_2$		0.28			0.63
Cl	0.23	0.37	0.11	0.40	
Br	0.23	0.39	0.15	0.41	
COOH	0.27	0.36	0.42	0.32	0.73
I	0.28	0.35	0.14	0.36	
CHO	0.45	0.36			1.13
COOEt	0.52	0.40	0.48	0.37	0.68
$COCH_3$	0.52	0.31			0.87
CN	0.63	0.68	0.66	0.56	1.00
$NH_3^{\ +}$		0.63			
NO_2	0.78	0.71	0.79	0.67	1.27
$NMe_3^{\ +}$	0.86	0.90	0.41	0.36	
$N_2^{\ +}$	1.8	1.7			

includes the important case of electrophilic aromatic substitutions; see Chapter 11) and σ^- values,[18] where electron-withdrawing groups interact with a developing negative charge. Table 4 gives σ, σ^+, and σ^- values for some common X groups.[19] As shown in the table, σ is essentially the same as σ^+ for most electron-withdrawing groups.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group. The constant ρ measures the susceptibility of the reaction to electrical effects. Reactions with a positive ρ are helped by electron-withdrawing groups, and vice versa.

Similar calculations have been made for compounds with two groups X and X′ on one ring, where the σ values have been found to be sometimes additive and sometimes not,[20] for other ring systems such as naphthalene[21] and heterocyclic rings, and for ethylenic and acetylenic systems.[22]

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[18] These were formerly called σ^* values, but this designation is now used for the field-effect values mentioned in footnote 25.

[19] σ values are taken from Jaffé, Ref. 16, except for the values for $N_2^{\ +}$, which are from Lewis and Johnson, *J. Am. Chem. Soc.* **81,** 2070 (1959), and the σ_p value for CHO, which is from Humffray, Ryan, Warren, and Yung, *Chem. Commun.* 610 (1965). σ^- values are also from Jaffé. σ^+ values are from Okamoto, Inukai, and Brown, *J. Am. Chem. Soc.* **80,** 4969 (1958), and Brown and Okamoto, *J. Am. Chem. Soc.* **80,** 4979 (1958), except for the $\sigma_m^{\ +}$ value for Me, which is from Glyde and Taylor, *J. Chem. Soc., Perkin Trans. 2* 1463 (1975). See also the extensive table in Ritchie and Sager, Ref. 15, pp. 334–337.

[20] Stone and Pearson, *J. Org. Chem.* **26,** 257 (1961).

The Hammett equation is a *linear free-energy relationship*. This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with $\Delta G^{\ddagger}$ instead of ΔG). For each reaction, where X is any group,

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

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation may be rewritten

$$\log K - \log K_0 = \sigma\rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma\rho$$

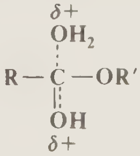
and

$$-\Delta G = \sigma\rho 2.3RT - \Delta G_0$$

For a given reaction under a given set of conditions, ρ, R, T, and ΔG_0 are all constant, so that σ is linear with ΔG.

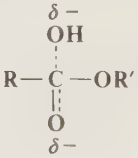
The Hammett equation is not the only linear free-energy relationship. About five or six are known at this time. Some of them, like the Hammett equation, correlate structural changes in reactants, but the Grunwald-Winstein relationship (see p. 334) correlates changes in solvent, and the Brönsted relation (see p. 235) relates acidity to catalysis. The Taft equation is a structure-reactivity equation which correlates only field effects.[23]

Taft, following Ingold,[24] assumed that for the hydrolysis of esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester-hydrolysis mechanisms, reaction **0-11**). Rate differences would therefore be caused only by the field effects of R and R′ in RCOOR′. This is reasonable because the transition state for acid-catalyzed hydrolysis (**7**) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (**8**) has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a



$$R-\overset{\overset{\delta+}{OH_2}}{\underset{\underset{\delta+}{OH}}{C}}-OR'$$

7



$$R-\overset{\overset{\delta-}{OH}}{\underset{\underset{\delta-}{O}}{C}}-OR'$$

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[21] Berliner and Winikov, *J. Am. Chem. Soc.* **81,** 1630 (1959); see also Wells, Ehrenson, and Taft, Ref. 28.

[22] For example, see Charton, *J. Org. Chem.* **26,** 735 (1961), **30,** 552, 557, 969, 974 (1965), **37,** 3684 (1972), *Can. J. Chem.* **48,** 1748 (1970); Hine and Bailey, *J. Am. Chem. Soc.* **81,** 2075 (1959); Charton and Charton, *J. Org. Chem.* **38,** 1631 (1973); Charton and Meislich, *J. Am. Chem. Soc.* **80,** 5940 (1958). For a review of the application of the Hammett treatment to nonaromatic unsaturated systems, see Charton, *Prog. Phys. Org. Chem.* **10,** 81–204 (1973).

[23] For a discussion of Taft's work on the separation of resonance, field, and steric effects, see Shorter, *Q. Rev., Chem. Soc.* **24,** 433–453 (1970), *Chem. Br.* **5,** 269–274 (1969).

[24] Ingold, *J. Chem. Soc.* 1032 (1930).

series XCH_2COOR', where R′ would be held constant. From these rate constants, a value σ_I could be determined by the equation

$$\sigma_I \equiv 0.181 \left[\log \left(\frac{k}{k_0}\right)_B - \log \left(\frac{k}{k_0}\right)_A\right]$$

In this equation $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR', $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, which reflects only field effects.[25] Once a set of σ_I values was obtained, it was found that the equation

$$\log \frac{k}{k_0} = \rho_I \sigma_I$$

holds for a number of reactions, among them:[26]

$$\mathbf{RCH_2OH} \longrightarrow \mathbf{RCH_2O^-}$$

$$\mathbf{RCH_2Br + PhS^-} \longrightarrow \mathbf{RCH_2SPh + Br^-}$$

$$\text{Acetone} + \mathbf{I_2}\text{, catalyzed by } \mathbf{RCOOH} \longrightarrow$$

$$o\text{-Substituted-}\mathbf{ArNH_2 + PhCOCl} \longrightarrow \mathbf{ArNHCOPh}$$

As with the Hammett equation, ρ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and final (or transition) states. A list of some σ_I values is given in Table 5. The σ_I values are about what we would expect for pure field-effect values (see p. 21) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (compare the values of R and RCH_2 in Table 5 for R = Ph and CH_3CO).

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect portion.[27] The resonance contribution σ_R[28] is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.[29] In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome the problem of varying σ_R values

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[25] There is another set of values (called σ^* values) which are also used to correlate field effects. These are related to σ_I values by $\sigma_{I(X)} = 0.45\sigma^*_{XCH_2}$. Following the suggestion by Ritchie and Sager (Ref. 15), we discuss only σ_I and not σ^* values. See also footnote 18.

[26] Wells, *Chem. Rev.*, Ref. 15, p. 196.

[27] Roberts and Moreland, *J. Am. Chem. Soc.* **75,** 2167 (1953); Taft, *J. Am. Chem. Soc.* **79,** 1045 (1957), *J. Phys. Chem.* **64,** 1805 (1960); Taft and Lewis, *J. Am. Chem. Soc.* **80,** 2436 (1958); Taft, Deno, and Skell, *Annu. Rev. Phys. Chem.* **9,** 287–314 (1958), pp. 290–293.

[28] For reviews of the σ_R and σ_I concept as applied to benzenes and naphthalenes, respectively, see Ehrenson, Brownlee, and Taft, *Prog. Phys. Org. Chem.* **10,** 1–80 (1973); and Wells, Ehrenson, and Taft, *Prog. Phys. Org. Chem.* **6,** 147–322 (1968).

[29] Taft and Lewis, *J. Am. Chem. Soc.* **81,** 5343 (1959).

TABLE 5 σ_I, σ_R°, and σ_p° values for some groups[31]

Group	σ_I	σ_R°	σ_p°
CMe_3	−0.07	−0.17	−0.24
Me	−0.05	−0.10	−0.15
H	0	0	0
$PhCH_2$	0.04		
NMe_2	0.05	−0.52	−0.47
NH_2	0.10	−0.48	−0.38
Ph	0.10	−0.10	0
CH_3COCH_2	0.10		
MeS	0.19	−0.17	0.02
NHAc	0.26	−0.22	0.04
OMe	0.26	−0.41	−0.15
OH	0.27	−0.44	−0.17
CH_3CO	0.28	0.19	0.47
COOR	0.31	0.15	0.46
I	0.39	−0.12	0.27
CF_3	0.41	0.13	0.54
Br	0.45	−0.16	0.29
Cl	0.47	−0.20	0.27
F	0.51	−0.34	0.17
CN	0.52	0.14	0.66
NO_2	0.64	0.19	0.83
NMe_3^+	0.86		

by using a special set of σ_p values, called σ_p°, for reactions which take place at some site effectively insulated from the π electrons of the benzene rings.[30] By means of these values, we can define a new set of values σ_R° as

$$\sigma_R^{\circ} = \sigma_p^{\circ} - \sigma_I$$

σ_R° vary much less with the nature of the reaction. Table 5 lists some values of σ_R° and σ_p°[31] based on this equation. According to this definition of σ_R°, both σ_I and σ_R° contribute equally to σ_p°. Exner[32] has shown that if one assumes that they do not contribute equally, the data give a better fit. His equation is

$$\sigma_p^{\circ} = 1.14\sigma_I + \sigma_R^{\circ}$$

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[30] Taft, Ehrenson, Lewis, and Glick, *J. Am. Chem. Soc.* **81,** 5352 (1959).

[31] These values are from Wells, Ehrenson, and Taft, Ref. 28, except for the values for H, Ph, CMe_3, and NMe_3^+, which are from Ref. 30; Taft, Deno, and Skell, Ref. 27; and Seth-Paul, de Meyer–van Duyse, and Tollenaere, *J. Mol. Struct.* **19,** 811 (1973). The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in footnote 25.

[32] Exner, *Collect. Czech. Chem. Commun.* **31,** 65 (1966); Exner and Lakomý, *Collect. Czech. Chem. Commun.* **35,** 1371 (1970).

TABLE 6 $\mathfrak{F}$ and $\mathfrak{R}$ values for some common groups[34]

Group	$\mathfrak{F}$	$\mathfrak{R}$	Group	$\mathfrak{F}$	$\mathfrak{R}$
COO	−0.221	0.124	COOEt	0.552	0.140
Me_3C	−0.104	−0.138	CF_3	0.631	0.186
Et	−0.065	−0.114	I	0.672	−0.197
Me	−0.052	−0.141	Cl	0.690	−0.161
H	0	0	F	0.708	−0.336
NH_2	0.037	−0.681	Br	0.727	−0.176
Ph	0.139	−0.088	CN	0.847	0.184
OMe	0.413	−0.500	NO_2	1.109	0.155
OH	0.487	−0.643	NMe_3^+	1.460	0.000
COOH	0.552	0.140	N_2^+	2.760	0.360

According to Exner, σ_I and σ_R° contribute to σ_m in the proportion

$$\sigma_m = \sigma_I + 0.33\sigma_R^\circ$$

Another attempt to divide σ values into resonance and field contributions[33] is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m, σ_p, σ_p^-, σ_p^+, σ_I, σ_R°, etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values $\mathfrak{F}$ (which expresses the field-effect contribution) and $\mathfrak{R}$ (the resonance contribution) satisfactorily express 43 sets of σ values.[34] Each set is expressed as

$$\sigma = f\mathfrak{F} + r\mathfrak{R}$$

where f and r are weighting factors. Some $\mathfrak{F}$ and $\mathfrak{R}$ values for common groups are given in Table 6. From the calculated values of f and r, Swain and Lupton have calculated that the importance of resonance, % $\mathfrak{R}$, is 22% for σ_m, 53% for σ_p, 66% for σ_p^+, and 92% for $\sigma_p - \sigma_m$. The Swain-Lupton approach has been extended by other workers.[35]

Another way of measuring resonance effects is by use of ^{19}F nmr of *m*- and *p*-XC_6H_4F. The chemical shift of the fluorine is taken to be a measure of the electron density around the fluorine. The field effect is regarded as the same for the meta and para positions, so that the difference in chemical shifts should be proportional to the resonance effect of X.[36] Chemical-shift differences obtained from these measurements have been converted, by a general formula, into σ_R values[37] which agree in general tendency, though not exactly, with those in Table 5. It has been shown[38] that electron density on fluorine cannot always be correlated with ^{19}F chemical shifts.

Taft was also able to isolate steric effects. For the acid-catalyzed hydrolysis of esters in aqueous acetone, log (k/k_0) was shown to be insensitive to polar effects. In cases where resonance interaction

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[33] See also Dewar and Grisdale, *J. Am. Chem. Soc.* **84**, 3548 (1962).

[34] Swain and Lupton, *J. Am. Chem. Soc.* **90**, 4328 (1968). The values in Table 6 are from a longer list in this paper.

[35] Godfrey, *J. Chem. Soc. B* 1534, 1537, 1540, 1545 (1971), *Tetrahedron Lett.* 753 (1972); Hansen and Hepler, *Can. J. Chem.* **50**, 1030 (1972); Williams and Norrington, *J. Am. Chem. Soc.* **98**, 508 (1976). For another approach, see Bancroft and Howe, *J. Chem. Soc. B* 1221 (1971).

[36] Taft, Glick, Lewis, Fox, and Ehrenson, *J. Am. Chem. Soc.* **82**, 756 (1960).

[37] Taft, Price, Fox, Lewis, Andersen, and Davis, *J. Am. Chem. Soc.* **85**, 3146 (1963); Brownlee and Taft, *J. Am. Chem. Soc.* **92**, 7007 (1970).

[38] Holmes and Gallagher, *Inorg. Chem.* **2**, 433 (1963).

TABLE 7 E_s values for some groups[39]

Group	E_s	Group	E_s	Group	E_s
H	1.24	ICH_2	−0.37	*t*-Bu	−1.54
Me	0	$PhOCH_2$	−0.38	Neopentyl	−1.85
Et	−0.07	iso-Pr	−0.47	Cl_3C	−2.06
$ClCH_2$	−0.24	Cyclohexyl	−0.79	Br_3C	−2.43
$BrCH_2$	−0.27	*sec*-Bu	−1.13	$(Me_3CCH_2)_2CH$	−3.18
Pr	−0.36	F_3C	−1.16	Et_3C	−3.8

was absent, this value was proportional only to steric effects (and any others which are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

The methyl group is taken as standard, with the value 0. Some E_s values are given in Table 7.[39] This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X, CHX_2, and CX_3 are linear functions of the van der Waals radii for these groups.[40] Another set of E_s values, called E_s^*, has been developed based on rates of hydroboration (reaction **5-15**).[41] The E_s^* scale is similar to the E_s scale except that the values are larger for tertiary systems.

An equation taking into account both field-effect and steric factors is the Pavelich-Taft equation:[42]

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \delta E_s$$

where δ is analogous to ρ. However, not much work has been done on this.

Since the Hammett equation has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that much work has been done in attempting to apply it to ortho positions also.[43] The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.[44] It has generally been believed that ortho substituents are not amenable to simple Hammett treatment because steric effects are important here. Therefore much of the work on the ortho effect has involved equations which attempt to separate steric from electrical effects. In an analysis of a vast amount of data, by means of such equations, Charton[45] reached the unexpected conclusion that the effect of ortho substituents is independent of steric effects[46] except for bulky substituents, such as I, Ph, or *t*-Bu. According to his analysis, ortho effects (except for bulky substituents and for groups which are capable of intramolecular hydrogen bonding) are linear combinations of σ_I and σ_R, and the usual Hammett treatment fails for ortho substituents because σ_I and σ_R can make vastly different contributions to the hypothetical σ_o, depending on which reaction is being studied. For some reactions, "σ_o" is completely made up of σ_I; for others only σ_R contributes; while for still others combinations of σ_I and σ_R in any proportion may be involved. Thus, according to Charton, the search for "true" ortho substituents σ_o must be fruitless because they do not exist. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC_6H_4Y is separated from the ring; e.g., ionization constants of *o*-$XC_6H_4OCH_2COOH$ can be successfully correlated.[47] Another way in which the ortho effect differs from σ_p or σ_m is in sensitivity to solvent changes. σ_p and σ_m do not vary when the solvent is changed, but ortho effects are sensitive to the solvent; Charton and Charton report that the relative contributions of σ_I and σ_R change when the solvent changes.[48]

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[39] Taft, in Newman, Ref. 15, p. 598.

[40] Charton, *J. Am. Chem. Soc.* **91,** 615 (1969). See also Charton, *J. Am. Chem. Soc.* **97,** 1552, 3691, 3694 (1975).

[41] Fellous and Luft, *J. Am. Chem. Soc.* **95,** 5593 (1973).

[42] Pavelich and Taft, *J. Am. Chem. Soc.* **79,** 4935 (1957).

[43] For a review, see Charton, *Prog. Phys. Org. Chem.* **8,** 235–317 (1971).

[44] This is not the same as the ortho effect discussed on p. 466.

[45] Charton, *J. Am. Chem. Soc.* **91,** 615, 619, 624, 6649 (1969). See also Ref. 43.

[46] A small steric effect has been found in one reaction: Charton, *J. Org. Chem.* **40,** 407 (1975).

Linear free-energy relationships may have mechanistic implications. If $\log (k/k_0)$ is linear with the appropriate σ, it is likely that the same mechanism is operating throughout the series. If not, then a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,[49] though nonlinear plots can also be due to other causes, such as complications arising from side reactions. Information can also be obtained from the magnitude and sign of ρ. For example, a strongly negative value of ρ indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbonium ion, is involved. Conversely, a positive value of ρ is associated with a developing negative charge in the transition state. The $\sigma\rho$ relationship even applies to free-radical reactions, because free radicals can have some polar character (p. 627), though ρ values here are usually small (less than about 1.5) whether positive or negative. Reactions involving cyclic transition states (p. 188) also exhibit very small ρ values.

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[47] Charton, *Can. J. Chem.* **38**, 2493 (1960).

[48] Charton and Charton, *J. Org. Chem.* **33**, 3872 (1968).

[49] For a discussion, see Schreck, *J. Chem. Educ.* **48**, 103–107 (1971).

PART TWO

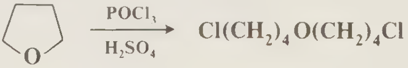
In Part 2 of this book we shall be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type and not on mechanism. These types are substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation-reduction reactions. Five chapters have been devoted to substitutions, and these are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Similarly, Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions, both aromatic and aliphatic, are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon-carbon multiple bonds are dealt with in Chapter 15, while in Chapter 16 we treat additions to other multiple bonds. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; and Chapter 19, oxidation-reduction reactions. This last chapter considers only those oxidation-reduction reactions which could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type there are a number of possible mechanisms. These are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors which cause one mechanism rather than another to prevail in a given reaction. Following the discussion of mechanisms, there is in each chapter a section on reactivity including, where pertinent, a consideration of orientation and of the factors affecting it.

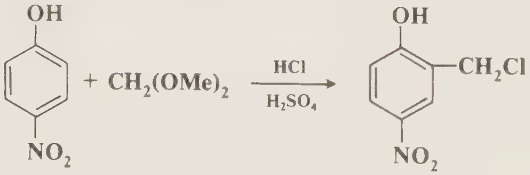
The second main section in each chapter is a treatment of reactions belonging to the category indicated by the title of the chapter. It is not possible—nor indeed would it be wise even if it were possible—to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry which may be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions which are traditionally discussed in textbooks, a number of reactions which do not fit into the above category have been included. The scope of the coverage is apparent from the fact that more than 90% of the individual preparations given in *Organic Syntheses* are treated in this book. However, certain special areas have been covered only lightly or not at all. Among these are electrochemical and polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated. Even with these omissions, however, some 610 reactions are treated in this book.

Each reaction is discussed in its own numbered section.[1] These are numbered consecutively within a chapter. The *first* digit in each number is the *second* digit of the chapter number. Thus, reaction **6-1** is the first reaction of Chapter 16, and reaction **3-21** is the twenty-first reaction of Chapter 13. The second part of the reaction number has no other significance. The order in which the reactions are presented is not arbitrary but is based on an orderly outline which depends on the reaction type. The placement of each reaction in a separate numbered section serves as an aid to both memory and understanding by setting clear boundary lines between one reaction and another, even if these boundary lines must be arbitrary, and by clearly showing the relationship of each reaction to all the others. Within each section, the scope and utility of the reaction are discussed, and references are given to review articles, if any. If there are features of the mechanism which especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

At the end of each numbered section there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**2-3, 2-20, 2-21,** and **2-37**) the list includes *all Organic Syntheses* references for each reaction. The volumes of *Organic Syntheses* which have been covered are Collective Volumes **I** to **V** and individual volumes **50** to **55.** Where no *Organic Syntheses* references are listed at the end of a section, the reaction has not been reported in *Organic Syntheses* through volume **55.** These listings thus constitute a kind of index to *Organic Syntheses.*[2] Certain ground rules were followed in assembling these lists. A reaction in which two parts of a molecule independently undergo simultaneous reaction is listed under both reactions. Similarly, if two reactions happen (or might happen) rapidly in succession without the isolation of an intermediate, the reactions are listed in both places. For example, at OS **IV,** 266 is



This reaction is treated as reaction **0-68** followed by reaction **0-18** and is listed at both places. However, certain reactions are not listed because they are trivial examples. An instance of this is the reaction found at OS **III,** 468:



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[1] The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction (for example, $CH_3Cl + CN^- \rightarrow CH_3CN$ and $C_2H_5Cl + CN^- \rightarrow C_2H_5CN$) is different, and custom generally decides how we group them together. Individual preferences also play a part. Some chemists would say that $C_6H_5N_2^+ + CuCN \rightarrow C_6H_5CN$ and $C_6H_5N_2^+ + CuCl \rightarrow C_6H_5Cl$ are examples of the "same" reaction, and others would say that they are not, but that $C_6H_5N_2^+ + CuCl \rightarrow C_6H_5Cl$ and $C_6H_5N_2^+ + CuBr \rightarrow C_6H_5Br$ are examples of the "same" reaction. No claim is made that the classification system used in this book is more valid than any other.

[2] A comprehensive index to Collective Volumes I to V has been published as part of the series: Shriner and Shriner, "Organic Syntheses Collective Volumes I, II, III, IV, V, Cumulative Indices," John Wiley & Sons, New York, 1976. For another index to *Organic Syntheses* (through volume **45**), see Sugasawa and Nakai, "Reaction Index of Organic Syntheses," John Wiley & Sons, New York, 1967.

This is a chloromethylation reaction and is consequently listed at reaction **1-27.** However, in the course of the reaction formaldehyde is generated from the acetal. This reaction is not listed at **0-7** (hydrolysis of acetals), because it is not really a preparation of formaldehyde. Another instance comes from OS **III,** 841:

$$Ph_3COH + CH_3COCl \longrightarrow Ph_3CCl + CH_3COOH$$

In this case, an acyl halide is converted to the corresponding acid (reaction **0-9**), but the reaction is not listed at **0-9,** because it is obviously designed to prepare triphenylmethyl chloride and not acetic acid. Thus the reaction is listed only at **0-67.**

Ten

Aliphatic Nucleophilic Substitution

In nucleophilic substitution the attacking reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with an electron pair:

$$\mathrm{R}\overset{\curvearrowright}{-}\mathrm{X} + \overline{\mathrm{Y}} \longrightarrow \mathrm{R{-}Y} + \overline{\mathrm{X}}$$

This equation says nothing about charges. Y may be neutral or negatively charged; RX may be neutral or positively charged; so that there are four charge types, examples of which are

$$\begin{array}{llcl}
\text{Type I} & \mathrm{R{-}I} + \mathrm{OH}^- & \longrightarrow & \mathrm{R{-}OH} + \mathrm{I}^- \\
\text{Type II} & \mathrm{R{-}I} + \mathrm{NMe_3} & \longrightarrow & \mathrm{R{-}}\overset{\oplus}{\mathrm{N}}\mathrm{Me_3} + \mathrm{I}^- \\
\text{Type III} & \mathrm{R{-}}\overset{\oplus}{\mathrm{N}}\mathrm{Me_3} + \mathrm{OH}^- & \longrightarrow & \mathrm{R{-}OH} + \mathrm{NMe_3} \\
\text{Type IV} & \mathrm{R{-}}\overset{\oplus}{\mathrm{N}}\mathrm{Me_3} + \mathrm{H_2S} & \longrightarrow & \mathrm{R{-}}\overset{\oplus}{\mathrm{S}}\mathrm{H_2} + \mathrm{NMe_3}
\end{array}$$

In all cases, Y must have an unshared pair of electrons, so that all nucleophiles are Lewis bases. When Y is the solvent, the reaction is called *solvolysis*. Nucleophilic substitution at an aromatic carbon is considered in Chapter 13.

Nucleophilic substitution at an alkyl carbon is said to *alkylate* the nucleophile. For example, the reaction above between RI and $\mathrm{NMe_3}$ is an *alkylation* of trimethylamine. Similarly, nucleophilic substitution at an acyl carbon is an *acylation* of the nucleophile.

MECHANISMS

Several distinct mechanisms are possible for aliphatic nucleophilic substitution reactions, depending on the substrate, nucleophile, leaving group, and reaction conditions, but in all of them the attacking reagent carries the electron pair with it, so that the similarities are greater than the differences. Mechanisms that occur at a saturated carbon atom are considered first.[1] By far the most common are the SN1 and SN2 mechanisms.

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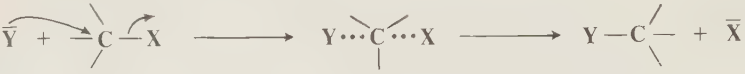
[1] For monographs on this subject, see Hartshorn, "Aliphatic Nucleophilic Substitution," Cambridge University Press, Cambridge, 1973; Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," American Elsevier Publishing Company, New York, 1963; Thornton, "Solvolysis Mechanisms," The Ronald Press Company, New York, 1964. For reviews, see de la Mare and Swedlund, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 1, pp. 409–490, John Wiley & Sons, New York, 1973; Streitwieser, *Chem. Rev.* **56,** 571–752 (1956). The latter review has been reprinted and more recent material added, in Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Company, New York, 1962.

The SN2 Mechanism

SN2 stands for *substitution nucleophilic bimolecular*. In this mechanism there is *backside attack:* the nucleophile approaches the substrate from a position 180° away from the leaving group. The reaction is a one-step process with no intermediate (see, however, p. 276). The C—Y bond is formed as the C—X bond is broken:



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The energy necessary to break the C—X bond is supplied by simultaneous formation of the C—Y bond. The position of the atoms at the top of the curve of free energy of activation can be represented as **1**. Of course the reaction does not stop here: this is the transition state. The group X must leave as the group Y comes in, because at no time can the carbon have more than eight electrons in its outer shell. In molecular-orbital terms, the transition state can be described as a point at which the previously unshared orbital of Y overlaps with the carbon orbital to about the same extent as the soon-to-be unshared orbital of X. When the transition state is reached, the central carbon atom has gone from its initial sp^3 hybridization to an sp^2 state with an approximately perpendicular p orbital. One lobe of this p orbital overlaps with the nucleophile, and the other with the leaving group. It is because of this that a frontside SN2 mechanism has never been observed. In a hypothetical frontside transition state, both the nucleophile and the leaving group would have to overlap with the same lobe of the p orbital. The backside mechanism involves the maximum amount of overlap throughout the course of the reaction.[2] During the transition state the three nonreacting groups and the central carbon are approximately coplanar. They will be exactly coplanar if both the entering and the leaving group are the same. Otherwise, they will deviate slightly from planarity, depending on whether bond making or bond breaking is more important in the transition state.

There is a large amount of evidence for the SN2 mechanism. First we consider the kinetic evidence. Since both the nucleophile and the substrate are involved in the rate-determining step (the only step, in this case), the reaction should be first order in each component, second order overall, and satisfy the rate expression

$$\text{Rate} = k[\mathbf{RX}][\mathbf{Y}] \tag{1}$$

This rate law has been found to apply in many cases. It has been noted that the 2 in SN2 stands for bimolecular. It must be remembered that this is not always the same as second order (see p. 201). If a large excess of nucleophile is present—for example, if it is the solvent—the mechanism may still be bimolecular, though the experimentally determined kinetics will be first order:

$$\text{Rate} = k[\mathbf{RX}] \tag{2}$$

As previously mentioned (p. 201), such kinetics are called *pseudo first order*.

The kinetic evidence is a necessary but not a sufficient condition, since other mechanisms may be devised which would also be consistent with these data. Much more convincing evidence is obtained from the fact that the mechanism predicts inversion of configuration when the substrate is optically active, and this has been observed many times. This inversion of configuration (see p. 102) is called the *Walden inversion* and was observed long before the SN2 mechanism was formulated by Hughes and Ingold.[3]

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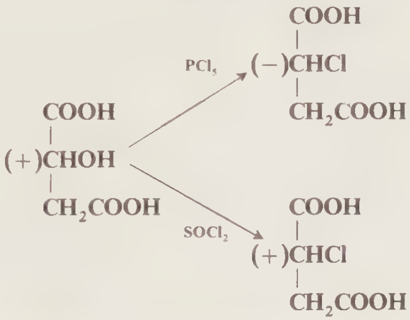
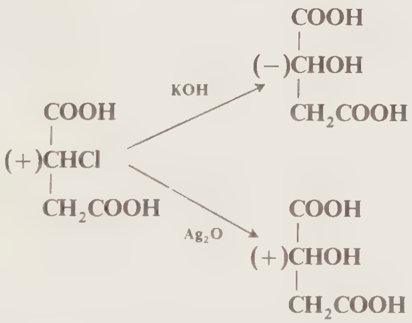
[2] For molecular-orbital calculations, see Allinger, Tai, and Wu, *J. Am. Chem. Soc.* **92,** 579 (1970).

At this point it is desirable for us to see just how it was originally proved that a given substitution reaction proceeds with inversion of configuration even before the mechanism was known. Walden presented a number of examples[4] in which inversion *must* have taken place. For example, (+)-malic acid could be converted to (+)-chlorosuccinic acid by thionyl chloride, and to (−)-chlorosuccinic acid by phosphorus pentachloride:



One of these must be an inversion and the other a retention of configuration, but the question is, which is which? The signs of rotation are of no help in answering this question since, as we have seen in Chapter 4 (p. 98), rotation need not be related to configuration. Another example discovered by Walden is



Once again, one reaction and only one must be an inversion, but which?[5] It may also be noticed [illustrated by the use of thionyl chloride on (+)-malic acid and treatment of the product with KOH] that it is possible to convert an optically active compound into its enantiomer.[6]

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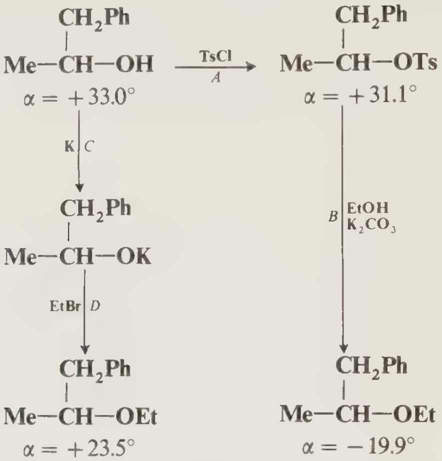
[3] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J. Chem. Soc.* 1252 (1937). The idea that the addition of one group and removal of the other are simultaneous was first suggested by Lewis in "Valence and the Structure of Atoms and Molecules," p. 113, Chemical Catalog Company, New York, 1923. The idea that a one-step substitution leads to inversion was proposed by Olsen, *J. Chem. Phys.* **1**, 418 (1933).

[4] Walden, *Ber.* **26**, 210 (1893), **29**, 133 (1896), **32**, 1855 (1899).

[5] For a discussion of these cycles, see Kryger and Rasmussen, *Acta Chem. Scand.* **26**, 2349 (1972).

[6] The student may wonder just what the mechanism is in cases where retention of configuration is involved, since it certainly is not simple SN2. As we shall see later, the reaction between malic acid and thionyl chloride is an SNi process (p. 302), while a neighboring-group mechanism (p. 279) is involved in the treatment of chlorosuccinic acid with silver oxide.

A series of experiments designed to settle the matter of exactly where inversion takes place was performed by Phillips, Kenyon, and coworkers. In 1923, Phillips carried out the following cycle:[7]



In this cycle, (+)-1-phenyl-2-propanol is converted to its ethyl ether by two routes, path *AB* giving the (−) ether, and path *CD* giving the (+) ether. Therefore, at least one of the four steps must be an inversion. It is extremely unlikely that there is inversion in step *A*, *C*, or *D*, since in all these steps the C—O bond is unbroken, and in none of them could the oxygen of the bond have come from the reagent. There is therefore a high probability that *A*, *C*, and *D* proceeded with retention of configuration, leaving *B* as the step involving inversion. A number of other such cycles were carried out, always with nonconflicting results.[8] These experiments not only definitely showed that certain specific reactions proceed with inversion, but also established the configurations of many compounds.

Walden inversion has been found at a primary carbon atom by the use of an optically active substrate containing a deuterium and a hydrogen atom at the carbon bearing the leaving group.[9] Inversion of configuration has also been found for S_N2 reactions proceeding in the gas phase.[10]

Another kind of evidence for the S_N2 mechanism comes from compounds with potential leaving groups at bridgehead carbons. If the S_N2 mechanism is correct, these compounds should not be able to react by this mechanism, since the nucleophile cannot approach from the rear. Among the many known examples of unsuccessful reaction attempts at bridgeheads under S_N2 conditions[11] are treatment of the [2.2.2] system **2** with ethoxide ion[12] and treatment of the [3.3.1] system **3** with sodium iodide in acetone.[13] In these cases, open-chain analogs underwent the

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[7] Phillips, *J. Chem. Soc.* **123**, 44 (1923). For analyses of such cycles and general descriptions of more complex ones, see Garwood and Cram, *J. Am. Chem. Soc.* **92**, 4575 (1970); Cram and Cram, *Fortschr. Chem. Forsch.* **31**, 1–43 (1972).

[8] For example, see Kenyon, Phillips, and Turley, *J. Chem. Soc.* **127**, 399 (1925); Kenyon, Phillips, and Taylor, *J. Chem. Soc.* 173 (1933); Kenyon, Phillips, and Shutt, *J. Chem. Soc.* 1663 (1935).

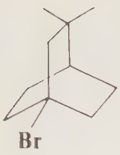
[9] Streitwieser, *J. Am. Chem. Soc.* **75**, 5014 (1953).

[10] Lieder and Brauman, *J. Am. Chem. Soc.* **96**, 4028 (1974).

[11] For reviews of reactions at bridgehead carbons, see Fort and Schleyer, *Adv. Alicyclic Chem.* **1**, 283–370 (1966); Applequist and Roberts, *Chem. Rev.* **54**, 1065–1089 (1954).

[12] Doering, Levitz, Sayigh, Sprecher, and Whelan, *J. Am. Chem. Soc.* **75**, 1008 (1953). Actually, a slow substitution was observed in this case, but not by an S_N2 mechanism.

[13] Cope and Synerholm, *J. Am. Chem. Soc.* **72**, 5228 (1950).



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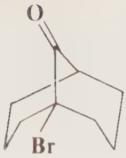

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reactions readily. As a final example of evidence for the SN2 mechanism, the reaction between optically active 2-octyl iodide and radioactive iodide ion may be mentioned:

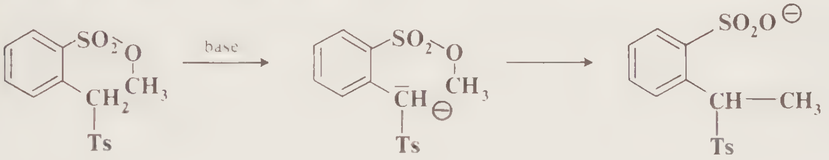
$$C_6H_{13}CHMeI + {}^*I^- \longrightarrow C_6H_{13}CHMe^*I + I^-$$

In this reaction, racemization is expected, since if we start with the pure *R* isomer, at first each exchange will produce an *S* isomer, but with increasing concentration of *S* isomer, *it* will begin to compete for I^- with the *R* isomer, until at the end a racemic mixture will be left, which will then remain at equilibrium. The point investigated was a comparison of the rate of inversion with the rate of uptake of radioactive ${}^*I^-$. It was found[14] that the rates were identical within experimental error:

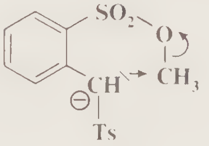
Rate of inversion	$2.88 \pm 0.03 \times 10^{-5}$
Rate of exchange	$3.00 \pm 0.25 \times 10^{-5}$

What was actually measured was the rate of racemization, which is twice the rate of inversion, since each inversion creates, in effect, two racemic molecules. The significance of this result is that it shows that every act of exchange is an act of inversion.

Eschenmoser and coworkers have provided strong evidence that the transition state in an SN2 reaction must be linear.[15] Base treatment of methyl α-tosyl-*o*-toluenesulfonate (**4**) gives the *o*-(1-tosylethyl)benzenesulfonate ion (**6**). The role of the base is to remove the α-proton to give the ion **5**. It might be supposed that the negatively charged carbon of **5** attacks the methyl group in an internal SN2 process:



4 **5** **6**



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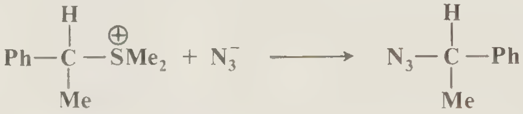
[14] Hughes, Juliusburger, Masterman, Topley, and Weiss, *J. Chem. Soc.* 1525 (1935).

[15] Tenud, Farooq, Seibl, and Eschenmoser, *Helv. Chim. Acta* **53**, 2059 (1970).

but this is not the case. Crossover experiments[15] (p. 506) have shown that the negatively charged carbon attacks the methyl group of another molecule rather than the nearby one in the same molecule; that is, the reaction is intermolecular and not intramolecular, despite the more favorable entropy of the latter pathway (p. 193). The obvious conclusion is that intramolecular attack does not take place because complete linearity cannot be attained. This behavior is in sharp contrast to that in cases in which the leaving group is not constrained (p. 279), where intramolecular SN2 mechanisms operate freely.

It has now been shown that the SN2 mechanism can operate in reactions of all four of the charge types shown on p. 265, even in the case of type III, where a negatively charged nucleophile must attack a positively charged substrate at a position in the molecule farthest away from the positive charge.[16] For example, the reaction between azide ion and dimethyl-1-phenylethylsulfonium chloride proceeds with complete inversion:



$$\mathrm{Ph{-}}\overset{\mathrm{H}}{\underset{\mathrm{Me}}{\mathrm{C}}}\mathrm{{-}\overset{\oplus}{S}Me_2} + \mathrm{N_3^-} \longrightarrow \mathrm{N_3{-}}\overset{\mathrm{H}}{\underset{\mathrm{Me}}{\mathrm{C}}}\mathrm{{-}Ph}$$

In reactions of type III it might have been expected that the negative nucleophile would directly attack the side occupied by the positively charged group.

The SN1 Mechanism

The most ideal version of the SN1 mechanism (*substitution nucleophilic unimolecular*) consists of two steps (once again, possible charges on the substrate and nucleophile are not shown):

Step 1 $\quad \mathrm{R{-}X} \xrightleftharpoons{\text{slow}} \mathrm{R^+ + X}$

Step 2 $\quad \mathrm{R^+ + Y} \xrightarrow{\text{fast}} \mathrm{R{-}Y}$

The first step is a slow ionization of the substrate and is the rate-determining step. The second step is a rapid reaction between the intermediate carbonium ion and the nucleophile. The ionization is always assisted by the solvent, since the energy necessary to break the bond is largely recovered by solvation of R^+ and of X. For example, the ionization of t-BuCl to $t\text{-Bu}^+$ and Cl^- in the gas phase without a solvent requires 150 kcal/mol. In the absence of a solvent such a process simply would not take place, except at very high temperatures. In water this ionization requires only 20 kcal/mol. The difference is solvation energy. In cases where the role of the solvent is solely to assist in departure of the leaving group from the frontside, that is, where there is a complete absence of backside (SN2) participation by solvent molecules, the mechanism is called *limiting SN1*, or often just *limiting*.

In looking for evidence for the SN1 reaction, the first thought is that it should be a first-order reaction following the rate law

$$\text{Rate} = k[\mathbf{RX}] \qquad (3)$$

Since the slow step involves only the substrate, the rate should be dependent only on that. Although the solvent is necessary to assist in the process of ionization, it does not enter the rate expression, since it is present in large excess. However, the simple rate law given [Eq. (3)] is not sufficient to account for all the data. Many cases are known where pure first-order kinetics are followed, but in many other cases more complicated kinetics are found. We can explain this by taking into account the reversibility of the first step of the reaction. The X formed in this step competes with Y for the substrate, and the rate law must be modified as follows (see Chapter 6):

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[16] Harvey, Hoye, Hughes, and Ingold, *J. Chem. Soc.* 800 (1960); Hughes and Whittingham, *J. Chem. Soc.* 806 (1960); Hoffmann and Hughes, *J. Chem. Soc.* 1252, 1259 (1964).

$$\mathbf{RX} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{R}^+ + \mathbf{X}$$

$$\mathbf{R}^+ + \mathbf{Y} \xrightarrow{k_2} \mathbf{RY}$$

$$\text{Rate} = \frac{k_1 k_2[\mathbf{RX}][\mathbf{Y}]}{k_{-1}[\mathbf{X}] + k_2[\mathbf{Y}]} \tag{4}$$

At the beginning of the reaction, when the concentration of X is very small, $k_{-1}[X]$ is negligible compared with $k_2[Y]$, and the rate law is reduced to Eq. (3). Indeed, SN1 reactions generally do display simple first-order kinetics in their initial stages. Most kinetic studies of SN1 reactions have been carried out on solvolytic reactions, since most SN1 reactions fall into this category. In the later stages of SN1 solvolyses, [X] becomes large, and Eq. (4) predicts that the rate should decrease. This is found to be the case for diarylmethyl halides,[17] though not for *t*-butyl halides which follow Eq. (3) for the entire reaction.[18] An explanation for this difference is that *t*-butyl cations are more reactive than the relatively stable diarylmethyl type (p. 155) and hence less selective. Although halide ion is a much more powerful nucleophile than water, there is much more water available since it is the solvent.[19] The selective diphenylmethyl cation survives many collisions with solvent molecules before combining with a reactive halide, but the less selective *t*-butyl ion cannot wait for a reactive but relatively rare halide ion and combines with the solvent.

If the X formed during the reaction can decrease the rate, at least in some cases, it should be possible to *add* X from the outside and further decrease the rate in that way. This retardation of rate by addition of X is called the *common-ion effect* or the *mass-law effect*. Once again, addition of halide ions decreases the rate for diphenylmethyl but not for *t*-butyl halides. Evidence that the common-ion effect operates even with *t*-butyl halides is that, when *t*-butyl chloride was hydrolyzed in the presence of $^{36}\text{Cl}^-$ (which is radioactive), radioactive *t*-butyl chloride was detected.[20]

One factor which complicates the kinetic picture is the *salt effect*. An increase in ionic strength of the solution usually increases the rate of an SN1 reaction (p. 333). But when the reaction is of charge type II, where both Y and RX are neutral, so that X is negatively charged (and most solvolyses are of this charge type), then the ionic strength increases as the reaction proceeds and this increases the rate. This effect must be taken into account in studying the kinetics. Incidentally, the fact that the addition of outside ions *increases* the rate of most SN1 reactions makes especially impressive the *decrease* in rate caused by the common ion.

It may be noted that the pseudo-first-order rate law for an SN2 reaction in the presence of a large excess of Y [Eq. (2)] is the same as that for an ordinary SN1 reaction [Eq. (3)]. It is thus not possible to tell these cases apart by simple kinetic measurements. However, we can often distinguish between them by the common-ion effect, mentioned above. Addition of a common ion will not markedly affect the rate of an SN2 reaction beyond the effect caused by other ions. Unfortunately, as we have seen above, not all SN1 reactions show the common-ion effect, and this test fails for *t*-butyl and similar cases.

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[17] Benfey, Hughes, and Ingold, *J. Chem. Soc.* 2488 (1952).

[18] Bateman, Hughes, and Ingold, *J. Chem. Soc.* 960 (1940).

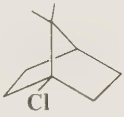
[19] Actually, in the experiments mentioned the solvent was "70%" or "80%" aqueous acetone. "80%" aqueous acetone consists of 4 vol of dry acetone and 1 vol of water.

[20] Bunton and Nayak, *J. Chem. Soc.* 3854 (1959).

The role of the solvent in assisting the ionization of the substrate may be illustrated by experiments involving ethanolysis of benzhydryl chloride to give benzhydryl ethyl ether. The addition of small amounts of water linearly increases the rate of the reaction, but the product is still almost entirely the ether.[21] The added water clearly cannot be attacking the substrate from the rear (or a proportionate amount of benzhydrol would be found in the product). It must be helping the chloride ion to leave and obviously performs this task better than does ethanol.

Kinetic studies also provide other evidence for the SN1 mechanism. If this mechanism operates essentially as shown on p. 270 then the rate should be the same for a given substrate under a given set of conditions, *regardless of the identity of the nucleophile or of its concentration.* One experiment which demonstrated this was carried out by Bateman, Hughes, and Ingold.[22] In this experiment benzhydryl chloride was treated in SO_2 with the nucleophiles fluoride ion, pyridine, and triethylamine at several concentrations of each nucleophile. In each case the initial rate of the reaction was approximately the same when corrections were made for the salt effect. The same type of behavior has been shown in a number of other cases, even when the reagents are as different in their nucleophilicities (see p. 322) as H_2O and OH^-.

Further evidence for the SN1 mechanism is that reactions run under SN1 conditions fail, or proceed very slowly, at bridgehead positions.[23] SN2 reactions also fail with these substrates (p. 268), though for a different reason. If SN1 reactions require carbonium ions and if carbonium ions must be planar or nearly planar, then it is no surprise that bridgehead carbon atoms, which cannot assume planarity, do not become the seat of carbonium ions. As an example, 1-chloroapocamphane (**7**) boiled 21 hr with 30% KOH in 80% ethanol, or 48 hr with aqueous ethanolic silver nitrate, gave no reaction in either case,[24] although analogous open-chain systems reacted readily. According to this theory, if the rings are large enough, SN1 reactions should be possible, since near-planar carbonium ions might be expected there. This turns out to be the case. For example, [2.2.2] bicyclic systems undergo SN1 reactions much faster than smaller bicyclic systems, though the reaction is still slower than with open-chain systems. Proceeding to a still larger system, the bridgehead 1-bicyclo[3.2.2]nonyl cation (**8**) is actually stable enough to be kept in solution in SbF_5–SO_2ClF at temperatures below −50°C.[25]



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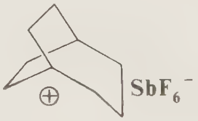


8

Certain nucleophilic substitution reactions which normally involve carbonium ions can take place at [2.2.1] bridgeheads[26] (though it is not certain that carbonium ions are actually involved in all cases) if the leaving group used is of the type which cannot function as a nucleophile (and thus come back) once it has gone, e.g.,

[21] Farinacci and Hammett, *J. Am. Chem. Soc.* **59,** 2542 (1937), **60,** 3097 (1938).

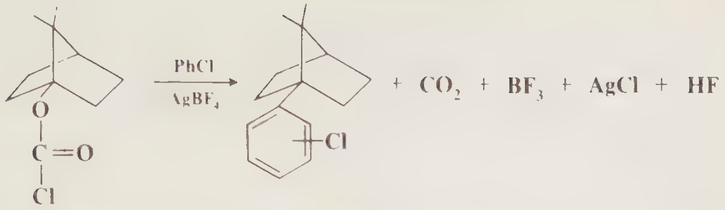
[22] Bateman, Hughes, and Ingold, *J. Chem. Soc.* 1011 (1940).

[23] For a review, see Fort, in Olah and Schleyer, "Carbonium Ions," vol. 4, pp. 1783–1835, John Wiley & Sons, New York, 1973.

[24] Bartlett and Knox, *J. Am. Chem. Soc.* **61,** 3184 (1939).

[25] Olah, Liang, Wiseman, and Chong, *J. Am. Chem. Soc.* **74,** 4927 (1972).

[26] Ref. 24; Beak and Trancik, *J. Am. Chem. Soc.* **90,** 2714 (1968); White, Tiwari, and Todd, *J. Am. Chem. Soc.* **90,** 4734 (1968); Clive and Denyer, *Chem. Commun.* 1112 (1971); White, McGirk, Aufdermarsh, Tiwari, and Todd, *J. Am. Chem. Soc.* **95,** 8107 (1973); Beak and Harris, *J. Am. Chem. Soc.* **96,** 6363 (1974).



In this example, chlorobenzene is the nucleophile (see reaction **1-13**). Halogen exchange at a bridgehead [2.2.1] position has also been reported.[27]

In certain reactions where an SN1 mechanism would seem to be obviously indicated, it has been shown (by esr detection of the intermediate) that free radicals are actually involved.[28] These are cases where a carbonium ion is a good electron acceptor and the nucleophile a good electron donor. An example is the reaction between the triphenylmethyl cation and the *t*-butoxide ion, which proceeds in this manner:[29]

$$\mathrm{Ph_3C^+} + t\text{-}\mathrm{BuO^-} \longrightarrow \mathrm{Ph_3C\cdot} + t\text{-}\mathrm{BuO\cdot} \longrightarrow t\text{-}\mathrm{BuOCPh_3}$$

Ion Pairs in the SN1 Mechanism[30]

Like the kinetic evidence, the stereochemical evidence for the SN1 mechanism is also less clear-cut than it is for the SN2 mechanism. If there is a free carbonium ion, it is planar (p. 157), and the nucleophile should attack with equal facility from either side of the plane, resulting in complete racemization. Although many first-order substitutions do give complete racemization, many others do not. Typically there is 5 to 20% inversion, though in a few cases a small amount of retention of configuration has been found. These and other results have led to the conclusion that in many SN1 reactions at least some of the products are not formed from free carbonium ions but rather from *ion pairs*. According to this concept,[31] SN1 reactions proceed in this manner:

$$\mathrm{R{-}X} \rightleftharpoons \underset{\mathbf{9}}{\mathrm{R^+\,X^-}} \rightleftharpoons \underset{\mathbf{10}}{\mathrm{R^+\,\|\,X^-}} \rightleftharpoons \underset{\mathbf{11}}{\mathrm{R^+ + X^-}}$$

where **9** is an *intimate, contact*, or *tight* ion pair, **10** a solvent-separated ion pair, and **11** the dissociated ions (each surrounded by molecules of solvent). In **9** and **10**, X^- is called the *counterion*. The reaction in which the intimate ion pair recombines to give the original substrate is referred to as *internal return*. The reaction products can result from attack by the nucleophile at any stage. In the intimate ion pair **9**, R^+ does not behave like the free cation of **11**. There is probably significant bonding between R^+ and X^-, and asymmetry can well be maintained.[32] X^- "solvates" the cation on the side from which it departed, while solvent molecules near **9** can only solvate it from the opposite side. Nucleophilic attack by a solvent molecule on **9** will thus lead to inversion.

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[27] McKinley, Pincock, and Scott, *J. Am. Chem. Soc.* **95**, 2030 (1973).

[28] Similar behavior has been reported for "SN2" reactions: Bank and Noyd, *J. Am. Chem. Soc.* **95**, 8203 (1973).

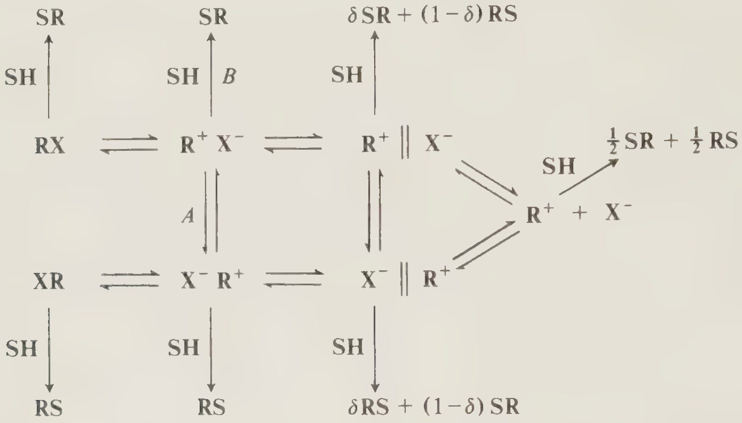
[29] Bilevitch, Bubnov, and Okhlobystin, *Tetrahedron Lett.* 3465 (1968).

[30] For reviews of ion pairs in SN reactions, see Harris, *Prog. Phys. Org. Chem.* **11**, 89–173 (1974); Raber, Harris, and Schleyer, in Szwarc, "Ions and Ion Pairs in Organic Reactions," vol. 2, pp. 247–374, John Wiley & Sons, New York, 1974.

[31] Proposed by Winstein, Clippinger, Fainberg, Heck, and Robinson, *J. Am. Chem. Soc.* **78**, 328 (1956).

[32] Fry, Lancelot, Lam, Harris, Bingham, Raber, Hall, and Schleyer, *J. Am. Chem. Soc.* **92**, 2538 (1970).

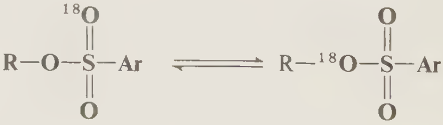
A complete picture of the possibilities for solvolysis reactions in a solvent SH (ignoring, however, the possibilities of elimination or rearrangement—see Chapters 17, 18) is the following,[33] though in any particular case it is unlikely that all these reactions occur:



In this scheme RS and SR represent enantiomers, etc., and δ represents some fraction. The following are the possibilities: (1) Direct attack by SH on RX gives SR (complete inversion) in a straight SN2 process. (2) If the intimate ion pair $R^+ X^-$ is formed, then the solvent can attack at this stage. This can lead to total inversion if reaction *A* does not take place, or to a combination of inversion and racemization if there is competition between *A* and *B*. (3) If the solvent-separated ion pair is formed, SH can attack here. The stereochemistry is not maintained as tightly, and more racemization (perhaps total) is expected. (4) Finally, if free R^+ is formed, it is planar, and attack by SH gives complete racemization.

The ion-pair concept thus predicts that SN1 reactions can display either complete racemization or partial inversion, and the fact that this behavior is generally found is evidence that ion pairs are involved in many SN1 reactions. There is much other evidence for the intervention of ion pairs:[34]

1. The compound 2-octyl brosylate was labeled at the sulfone oxygen with ^{18}O and solvolyzed. The unreacted brosylate recovered at various stages of solvolysis was shown to have the ^{18}O considerably, though not completely, scrambled:[35]



$$R{-}O{-}\overset{\overset{^{18}O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}Ar \rightleftharpoons R{-}{}^{18}O{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}Ar$$

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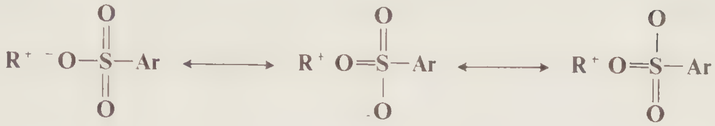
[33] Shiner and Fisher, *J. Am. Chem. Soc.* **93,** 2553 (1971).

[34] For further evidence beyond that given here, see Winstein, Baker, and Smith, *J. Am. Chem. Soc.* **86,** 2072 (1964); Streitwieser and Walsh, *J. Am. Chem. Soc.* **87,** 3686 (1965); Sommer and Carey, *J. Org. Chem.* **32,** 800, 2473 (1967); Kwart, Givens, and Collins, *J. Am. Chem. Soc.* **91,** 5532 (1969); Kwart and Irvine, *J. Am. Chem. Soc.* **91,** 5541 (1969); Harris, Clark, Becker, and Fagan, *J. Am. Chem. Soc.* **96,** 4478 (1974); Harris, Becker, Fagan, and Walden, *J. Am. Chem. Soc.* **96,** 4484 (1974); Bunton, Huang, and Paik, *J. Am. Chem. Soc.* **97,** 6262 (1975); Ref. 30.

[35] Diaz, Lazdins, and Winstein, *J. Am. Chem. Soc.* **90,** 1904 (1968).

In an intimate ion pair the three oxygens may become equivalent:



$$R^+\ {}^-O-\overset{O}{\underset{O}{S}}-Ar \longleftrightarrow R^+\ O{=}\overset{O}{\underset{{}^-O}{S}}-Ar \longleftrightarrow R^+\ O{=}\overset{O}{\underset{O}{S}}-Ar$$

Similar results were obtained with several other sulfonate esters.[36] The possibility must be considered that the scrambling resulted from ionization of one molecule of $ROSO_2Ar$ to R^+ and $ArSO_2O^-$ followed by attack by the $ArSO_2O^-$ ion on *another* carbonium ion (or perhaps on a molecule of $ROSO_2Ar$ in an SN2 process). However, this was ruled out by solvolyzing unlabeled substrate in the presence of labeled $HOSO_2Ar$. These experiments showed that there was some intermolecular exchange (3 to 20%), but not nearly enough to account for the amount of scrambling found in the original experiments. Similar scrambling was found in solvolysis of labeled esters $R{-}^{18}O{-}COR'$, where the leaving group is $R'COO^-$.[37] In this case also, the external addition of $RCOO^-$ did not result in significant exchange. Since the oxygen atoms of the intimate ion pair are not always completely equivalent (R^+ may remain closer to the oxygen from which it cleaved), such experiments provide a lower limit for ion-pair formation and internal return. In any given case, they could be a good deal higher.[37a]

2. The *special salt effect*. The addition of $LiClO_4$ or LiBr in the acetolysis of certain tosylates produced an initial steep rate acceleration which then decreased to the normal linear acceleration (caused by the ordinary salt effect).[38] This is interpreted as follows: the ClO_4^- (or Br^-) traps the solvent-separated ion pair to give $R^+\ \ ClO_4^-$ which, being unstable under these conditions, goes to product. Hence, the amount of solvent-separated ion pair which would have returned to the starting material is reduced, and the rate of the overall reaction is increased. This is an example of shifting the position of the equilibrium by removing a product.

3. We have previously discussed the possibilities of racemization or inversion of the *product* RS of a solvolysis reaction. However, the formation of an ion pair followed by internal return may also affect the stereochemistry of the *substrate* molecule RX. Cases have been found where internal return racemizes an original optically active RX, an example being solvolysis in aqueous acetone of α-*p*-anisylethyl *p*-nitrobenzoate,[39] while in other cases partial or complete retention is found, for example, solvolysis in aqueous acetone of *p*-chlorobenzhydryl *p*-nitrobenzoate.[40] Racemization of RX is presumably caused by the pathway: $RX \rightleftharpoons R^+\ X^- \rightleftharpoons X^-\ R^+ \rightleftharpoons XR$. Evidence for ion pairs is that, in some cases where internal return involves racemization, it has been shown that such racemization is *faster* than solvolysis. For example, optically active *p*-chlorobenzhydryl chloride racemizes about 30 times faster than it solvolyzes in acetic acid.[41]

In a few cases, SN1 reactions have been found to proceed with partial retention (20 to 50%)

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[36] Goering and Thies, *J. Am. Chem. Soc.* **90,** 2967, 2968 (1968).

[37] Goering and Levy, *J. Am. Chem. Soc.* **84,** 3853 (1962); **86,** 120 (1964); Goering, Briody, and Levy, *J. Am. Chem. Soc.* **85,** 3059 (1963); Goering and Chang, *Tetrahedron Lett.* 3607 (1965); Goering, Briody, and Sandrock, *J. Am. Chem. Soc.* **92,** 7401 (1970); Goering and Hopf, *J. Am. Chem. Soc.* **93,** 1224 (1971).

[37a] See for example Goering and Humski, *J. Org. Chem.* **40,** 920 (1975).

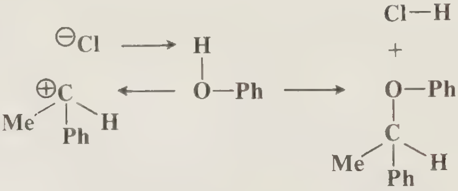
[38] Ref. 31; Winstein, Klinedinst, and Clippinger, *J. Am. Chem. Soc.* **83,** 4986 (1961); Cristol, Noreen, and Nachtigall, *J. Am. Chem. Soc.* **94,** 2187 (1972).

[39] Goering, Briody, and Sandrock, Ref. 37.

[40] Goering, Briody, and Levy, Ref. 37.

[41] Winstein, Gall, Hojo, and Smith, *J. Am. Chem. Soc.* **82,** 1010 (1960). See also Winstein, Hojo, and Smith, *Tetrahedron Lett.*, no. 22, 12 (1960); Winstein and Gall, *Tetrahedron Lett.* no. 2, 31 (1960); Shiner, Hartshorn, and Vogel, *J. Org. Chem.* **38,** 3604 (1973).

of configuration. Ion pairs have been invoked to explain some of these.[42] For example, it has been proposed that the phenolysis of optically active α-phenylethyl chloride, in which the ether of net retained configuration is obtained, involves a four-center mechanism:



This conclusion is strengthened by the fact that partial retention was obtained in this system only with chloride or other neutral leaving groups; but with leaving groups bearing a positive charge, which are much less likely to hydrogen-bond with the solvent, no retention was found.[43] Partial retention can also arise when the ion pair is shielded at the backside by an additive such as acetonitrile or acetone.[44]

The difference between the SN1 and SN2 mechanisms is in the timing of the steps. In the SN1 mechanism, first X leaves, then Y attacks. In the SN2 case, the two things happen simultaneously. One could imagine a third possibility: first the attack of Y, and then the removal of X. This is not possible at a saturated carbon, since it would mean more than eight electrons in the outer shell of carbon. However, this type of mechanism is possible and indeed occurs at other types of substrate (p. 307; Chapter 13).

Mixed SN1 and SN2 Mechanisms

Some reactions of a given substrate under a given set of conditions display all the characteristics of SN2 mechanisms; other reactions seem to proceed by SN1 mechanisms, but often cases are found which cannot be characterized so easily. There seems to be something in between, a mechanistic "borderline" region. At least two broad theories have been devised to explain these phenomena. One theory holds that intermediate behavior is caused by a mechanism which is neither "pure" SN1 nor "pure" SN2, but some "in-between" type. According to the second theory, there is no intermediate mechanism at all, and borderline behavior is caused by simultaneous operation, in the same flask, of both the SN1 and SN2 mechanisms; that is, some molecules react by the SN1, while others react by the SN2 mechanism.

One formulation of the intermediate-mechanism theory is that of Sneen.[45] The formulation is in fact very broad and applies not only to borderline behavior but to all nucleophilic substitution at a saturated carbon.[46] According to Sneen, all SN1 and SN2 reactions can be accommodated by one basic mechanism (the *ion-pair mechanism*). The substrate first ionizes to an intermediate ion pair which is then converted to products:

$$\mathrm{RX} \underset{}{\overset{k_1}{\rightleftharpoons}} \mathrm{R^+\,X^-} \overset{k_2}{\rightleftharpoons} \text{products}$$

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[42] Okamoto, Yamada, Nitta, and Shingu, *Bull. Chem. Soc. Jpn.* **39**, 299 (1966); Okamoto, Hayashi, Komatsu, and Shingu, *Bull. Chem. Soc. Jpn.* **40**, 624 (1967); Okamoto, Komatsu, and Shingu, *Bull. Chem. Soc. Jpn.* **40**, 1677 (1967); Okamoto, Kinoshita, and Osada, *J. Chem. Soc., Perkin Trans. 2* 253 (1975).

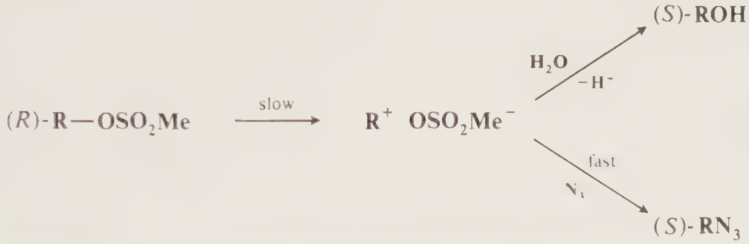
[43] Okamoto, Kinoshita, and Shingu, *Bull. Chem. Soc. Jpn.* **43**, 1545 (1970).

[44] Okamoto, Nitta, Dohi, and Shingu, *Bull. Chem. Soc. Jpn.* **44**, 3220 (1971).

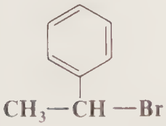
[45] Weiner and Sneen, *J. Am. Chem. Soc.* **87**, 292 (1965); Sneen and Larsen, *J. Am. Chem. Soc.* **91**, 362, 6031 (1969); Sneen, Felt, and Dickason, *J. Am. Chem. Soc.* **95**, 638 (1973); Sneen, *Acc. Chem. Res.* **6**, 46–53 (1973).

[46] Including substitution at an allylic carbon; see Sneen and Bradley, *J. Am. Chem. Soc.* **94**, 6975 (1972); Sneen and Kay, *J. Am. Chem. Soc.* **94**, 6983 (1972); Sneen and Carter, *J. Am. Chem. Soc.* **94**, 6990 (1972); Bordwell and Mecca, *J. Am. Chem. Soc.* **97**, 123, 127 (1975); Bordwell, Wiley, and Mecca, *J. Am. Chem. Soc.* **97**, 132 (1975).

The difference between the SN1 and SN2 mechanisms is that in the former case the *formation* of the ion pair (k_1) is rate-determining, while in the SN2 mechanism its *destruction* (k_2) is rate-determining. Borderline behavior is found where the rates of formation and destruction of the ion pair are of the same order of magnitude. Evidence that ion pairs intervene in at least some reactions which would generally be called SN2 reactions is the following: solvolysis of optically active 2-octyl methanesulfonate in 25% aqueous dioxane gave 2-octanol with about 95% inversion of configuration. From this fact the mechanism is regarded as SN2, though it cannot be shown to be second order, because the nucleophile is present in large excess. Addition of 0.0462 *M* azide ions had no effect on the rate of solvolysis (the rate of disappearance of the starting sulfonate), even though 31% of the product was now 2-octyl azide (the other 69% was inverted alcohol).[47] This means that azide ion is not involved in the rate-determining step, so it would seem that the mechanism of azide formation could not be SN2. *Yet the configuration of the 2-octyl azide was about 81% inverted.* It may be concluded that the rate-determining step is formation of the ion pair, which in this case maintains its configuration, and that this is what is attacked either by azide or by the solvent water. Consequently, not only is azide absent from the transition state, but so is water:



Other evidence for the ion-pair mechanism comes from a linear free-energy relationship which was discovered to hold between the stability of a carbonium ion and its selectivity.[48] The stability of R^+ was measured by the rate of $RX \rightarrow R^+$ hydrolysis in the absence of an added nucleophile. The selectivity of R^+ was measured by adding the nucleophile N_3^- and measuring the ratio of ROH to RN_3 produced. As might be expected, there is a direct relationship between the stability of R^+ and its selectivity, but this relationship holds only where free carbonium ions are present[49] and breaks down in the case of compounds for which borderline behavior is found. Further evidence was obtained in a study of the reactions of **12**, **13**, and **14** with solvent and



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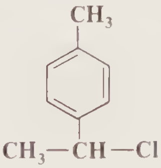

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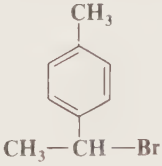

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added nucleophiles. In these three molecules only small changes in structure have been made, and yet in going from **12** to **13** to **14** the mechanism shifts not abruptly, but gradually, from SN2-like, to borderline, to SN1-like.[50] Linear free-energy relationships have also been used to support the contention that the ion-pair mechanism operates not only on secondary but also on primary substrates,[51] which have traditionally been regarded as showing "pure" SN2 behavior.[52] A number of investigators have raised objections to the ion-pair mechanism of Sneen and have asserted that these results could also be explained in other ways.[53]

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[47] Weiner and Sneen, Ref. 45.

[48] Sneen, Carter, and Kay, *J. Am. Chem. Soc.* **88**, 2594 (1966); Raber, Harris, Hall, and Schleyer, *J. Am. Chem. Soc.* **93**, 4821 (1971).

[49] Kovačević, Majerski, Borčić, and Sunko, *Tetrahedron* **28**, 2469 (1972).

Among the experiments that have been cited for the viewpoint that borderline behavior results from simultaneous SN1 and SN2 mechanisms is the behavior of 4-methoxybenzyl chloride in 70% aqueous acetone.[54] In this solvent, hydrolysis (that is, conversion to 4-methoxybenzyl alcohol) occurs by an SN1 mechanism. When azide ions are added, the alcohol is still a product, but now 4-methoxybenzyl azide is another product. Addition of azide ions increases the rate of ionization (by the salt effect) but *decreases* the rate of hydrolysis. If more carbonium ions are produced but fewer go to the alcohol, then some azide must be formed by reaction with carbonium ions—an SN1 process. However, the rate of ionization is always *less* than the total rate of reaction, so that some azide must also form by an SN2 mechanism.[54] Thus, the conclusion is that SN1 and SN2 mechanisms operate simultaneously.[55]

Some nucleophilic substitution reactions which seem to involve a "borderline" mechanism actually do not. Thus, one of the principal indications that a "borderline" mechanism is taking place has been the finding of partial racemization and partial inversion. However, Weiner and Sneen have demonstrated that this type of stereochemical behavior is quite consistent with a strictly SN2 process. These workers studied the reaction of optically active 2-octyl brosylate in 75% aqueous dioxane, under which conditions inverted 2-octanol was obtained in 77% optical purity.[56] When sodium azide was added, 2-octyl azide was obtained along with the 2-octanol, *but the latter was now 100% inverted.* It is apparent that, in the original case, 2-octanol was produced by two different processes, an SN2 reaction leading to inverted product, and another process in which some intermediate leads to racemization or retention. When azide ions were added, they scavenged this intermediate, so that the entire second process now went to produce azide, while the SN2 reaction, unaffected by addition of azide, still went on to give inverted 2-octanol. What is the nature of the intermediate in the second process? At first thought we might suppose that it is a carbonium ion, so that this would be another example of simultaneous SN1 and SN2 reactions. However, solvolysis of 2-octyl brosylate in pure methanol, or of 2-octyl methanesulfonate in pure water, in the absence of azide ions, gave methyl 2-octyl ether, or 2-octanol, respectively, *with 100% inversion of configuration,* indicating that the mechanism in these solvents was pure SN2. Since methanol and water are more polar than 75% aqueous dioxane and since an increase in polarity of solvent increases the rate of SN1 reactions at the expense of SN2 (p. 331), it is extremely unlikely that any SN1 process could occur in 75% aqueous dioxane. The intermediate in the second process is thus not a carbonium ion. What it is, is suggested by the fact that, in the absence of azide ions, the amount of inverted 2-octanol decreased with an increasing percentage of dioxane in the solvent. Thus the intermediate is an oxonium ion formed by an SN2 attack *by dioxane*. This ion is not a stable product but reacts with water in another SN2 process to produce 2-octanol with retained configuration. The entire process may be shown as follows:

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[50] Sneen and Robbins, *J. Am. Chem. Soc.* **94,** 7868 (1972).

[51] Scott, *Can. J. Chem.* **48,** 3807 (1970). See, however, Abraham, *J. Chem. Soc., Chem. Commun.* 51 (1973); *J. Chem. Soc., Perkin Trans. 2* 1893 (1973). See also Koskikallio, *Acta Chem. Scand.* **26,** 1201 (1972).

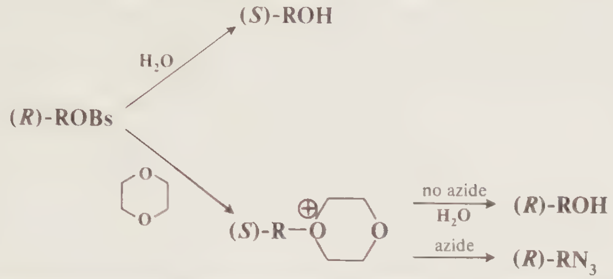
[52] For additional evidence for the ion-pair mechanism, see Graczyk and Taylor, *J. Am. Chem. Soc.* **96,** 3255 (1974); Stein, *Tetrahedron Lett.* 4145 (1974); Peeters and Anteunis, *J. Org. Chem.* **40,** 312 (1975); Pross and Koren, *Tetrahedron Lett.* 3613 (1975).

[53] See Gregory, Kohnstam, Paddon-Row, and Queen, *Chem. Commun.* 1032 (1970); Gregory, Kohnstam, Queen, and Reid, *Chem. Commun.* 797 (1971); Kurz and Harris, *J. Am. Chem. Soc.* **92,** 4117 (1970); Raber, Harris, Hall, and Schleyer, Ref. 48; McLennan, *J. Chem. Soc., Perkin Trans. 2* 1577 (1972), 481 (1974), *Acc. Chem. Res.* **9,** 281 287 (1976), *Tetrahedron Lett.* 4689 (1975); McLennan and Martin, *Tetrahedron Lett.* 4215 (1973); Raaen, Juhlke, Brown, and Collins, *J. Am. Chem. Soc.* **96,** 5928 (1974); Gregoriou, *Tetrahedron Lett.* 233 (1974); Queen and Matts, *Tetrahedron Lett.* 1503 (1975); Stein, *J. Org. Chem.* **41,** 519 (1976). For a reply to some of these objections, see Ref. 50.

[54] Kohnstam, Queen, and Shillaker, *Proc. Chem. Soc.* 157 (1959). For other evidence supporting the concept of simultaneous mechanisms, see Pocker, *J. Chem. Soc.* 3939, 3944 (1959); Casapieri and Swart, *J. Chem. Soc.* 4342 (1961); 1254 (1963); Fava, Iliceto, and Ceccon, *Tetrahedron Lett.* 685 (1963); Ceccon, Papa, and Fava, *J. Am. Chem. Soc.* **88,** 4643 (1966); Okamoto, Uchida, Saitô, and Shingu, *Bull. Chem. Soc. Jpn.* **39,** 307 (1966); Guinot and Lamaty, *Chem. Commun.* 960 (1967); Gregory, Kohnstam, Paddon-Row, and Queen, Ref. 53.

[55] These data have also been explained as being in accord with the ion-pair mechanism: Sneen and Larsen, *J. Am. Chem. Soc.* **91,** 6031 (1969).

[56] Weiner and Sneen, *J. Am. Chem. Soc.* **87,** 287 (1965).



That part of the original reaction which resulted in retention of configuration is thus seen to stem from two successive SN2 reactions and not from any "borderline" behavior.[57] In another investigation, Streitwieser, Walsh, and Wolfe showed that the racemization accompanying inversion in the acetolysis of optically active 2-octyl tosylate stems from processes other than the actual solvolytic displacement: from reaction of the product 2-octyl tosylate with the *p*-toluenesulfonic acid also formed, from addition of acetic acid to 2-octene (formed from the substrate by a competing elimination reaction), and from racemization of the starting tosylate.[58] The actual nucleophilic substitution

$$\mathrm{ROTs + HOAc \longrightarrow ROAc}$$

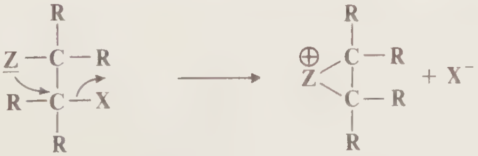
proceeds with essentially complete inversion of configuration.

The mechanisms so far considered can, in theory at least, operate on any type of saturated (or for that matter unsaturated) substrate. There are other mechanisms which are more limited in scope.

The Neighboring-Group Mechanism[59]

It is occasionally found with certain substrates that (1) the rate of reaction is greater than expected, and (2) the configuration at a chiral carbon is *retained* and not inverted or racemized. In these cases there is usually a group with an unshared pair of electrons β to the leaving group (or sometimes farther away). The mechanism operating in such cases is called the *neighboring-group mechanism* and consists essentially of two SN2 substitutions, each causing an inversion, so that the net result is retention of configuration. In the first step of this reaction the neighboring group acts as a nucleophile, pushing out the leaving group but still retaining attachment to the molecule. In the second step the external nucleophile pushes out the neighboring group:

Step 1



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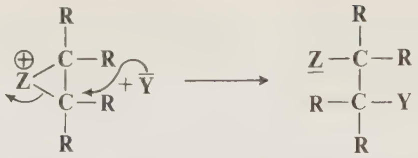
[57] According to this scheme, the configuration of the isolated RN$_3$ should be retained. It was, however, largely inverted, owing to a competing SN2 reaction where N$_3^-$ directly attacks ROBs.

[58] Streitwieser, Walsh, and Wolfe, *J. Am. Chem. Soc.* **87**, 3682 (1965); Streitwieser and Walsh, *J. Am. Chem. Soc.* **87**, 3686 (1965). For another example, see Beronius, Nilsson, and Holmgren, *Acta Chem. Scand.* **26**, 3173 (1972).

[59] For a review, see Capon, *Q. Rev., Chem. Soc.* **18**, 45–111 (1964).

Step 2

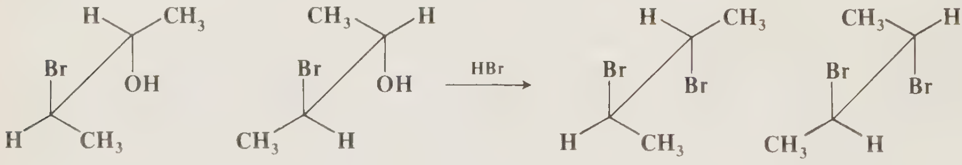


The reaction obviously must go faster than if Y were attacking directly, since if the latter process were faster, *it* would be happening. The neighboring group Z is said to be lending *anchimeric assistance*. The rate law followed in the neighboring-group mechanism is the first-order law shown in Eq. (2) or (3); that is, Y does not take part in the rate-determining step.

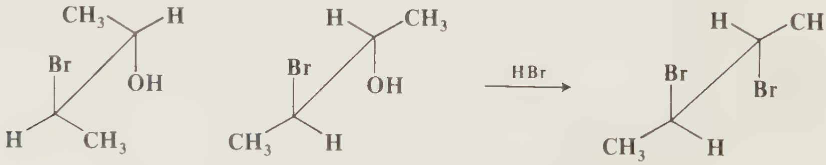
The question may be asked as to why attack by Z is faster than that by Y. The answer is that the group Z is more available. In order for Y to react, it must collide with the substrate, but Z is immediately available by virtue of its position. A reaction between the substrate and Y involves a large decrease in entropy of activation ($\Delta S^\ddagger$), since the reactants are far less free in the transition state than before. Reaction of Z involves a much smaller loss of $\Delta S^\ddagger$ (see p. 193).[60]

It is not always easy to determine when a reaction rate has been increased by anchimeric assistance. In order to be certain, it is necessary to know what the rate would be without participation by the neighboring group. The obvious way to examine this question is to compare the rates of the reaction with and without the neighboring group, for example, $HOCH_2CH_2Br$ versus CH_3CH_2Br. However, this will certainly not give an accurate determination of the extent of participation, since the steric and field effects of H and OH are not the same. Furthermore, no matter what the solvent, the shell of solvent molecules which surrounds the polar protic OH group must differ greatly from that which surrounds the nonpolar H. Because of these considerations, it is desirable to have a large increase in the rate, preferably more than fiftyfold, before a rate increase is attributed to neighboring-group participation.

The first important evidence for the existence of this mechanism was the demonstration that retention of configuration can occur if the substrate is suitable. It was shown that the threo DL pair of 3-bromo-2-butanol when treated with HBr gave DL-2,3-dibromobutane, while the erythro pair gave the meso isomer:[61]



threo DL pair DL pair



erythro DL pair meso

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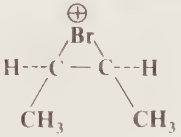
[60] For a review of the energetics of neighboring-group participation, see Page, *Chem. Soc. Rev.* **2**, 295–323 (1973).

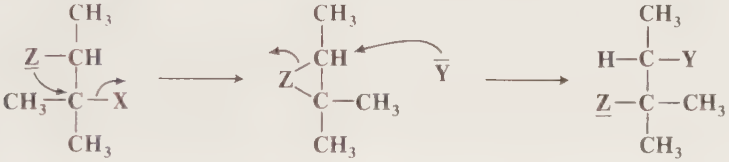
[61] Winstein and Lucas, *J. Am. Chem. Soc.* **61**, 1576, 2845 (1939).

This indicated that retention had taken place. Note that both products are optically inactive and so cannot be told apart by differences in rotation. The meso and DL dibromides have different boiling points and indexes of refraction and were identified by these properties. Even more convincing evidence was that either of the two threo isomers alone gave not just one of the enantiomeric dibromides, but the DL pair. The reason for this is that the intermediate present after the attack by the neighboring group (**15**) is symmetrical, so that the external nucleophile, Br$^-$, could equally well attack both carbon atoms. **15** is a bromonium ion, the existence of which has been demonstrated in several types of reactions.[62]



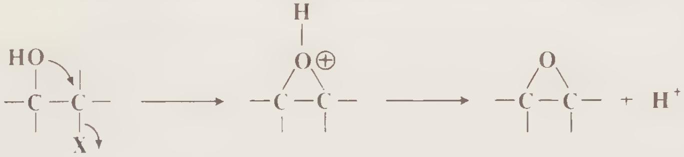
15

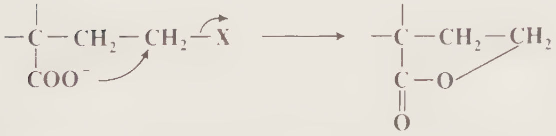
Although **15** is symmetrical, intermediates in most neighboring-group mechanisms are not, and it is therefore possible to get not a simple substitution product but a rearrangement. This will happen if Y attacks not the carbon atom from which X left, but the one to which Z was originally attached:



In such cases substitution and rearrangement products are often produced together. For a discussion of rearrangements, see Chapter 18.

Another possibility is that the intermediate may be stable or may find some other way to stabilize itself. In such cases, Y never attacks at all, and the product is cyclic. These are simple internal SN2 reactions. Two examples are formation of epoxides and lactones:





The fact that acetolysis of both 4-methoxy-1-pentyl brosylate (**16**) and 5-methoxy-2-pentyl brosylate (**17**) gave the same mixture of products is further evidence for participation by a neighboring group.[63] In this case the intermediate **18** is common to both substrates. Evidence has

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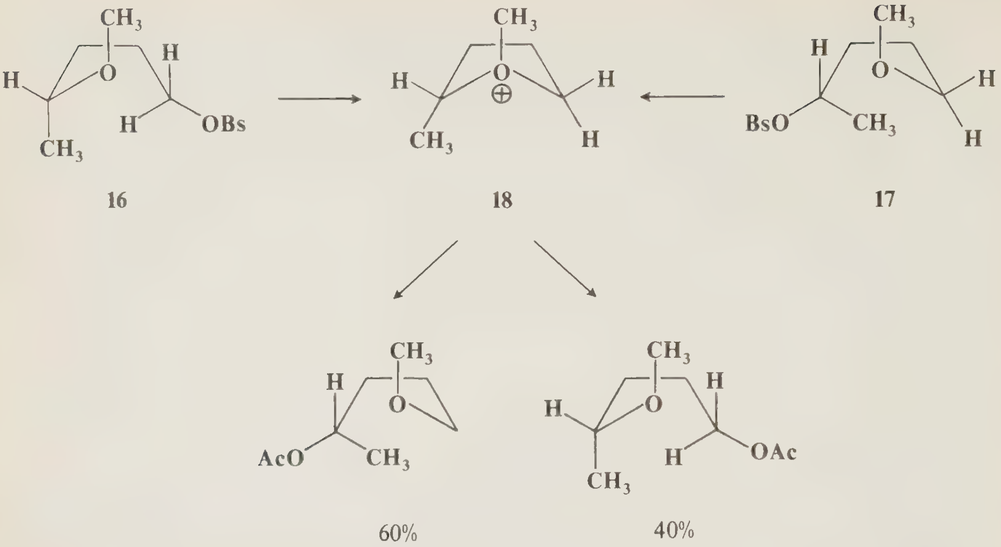
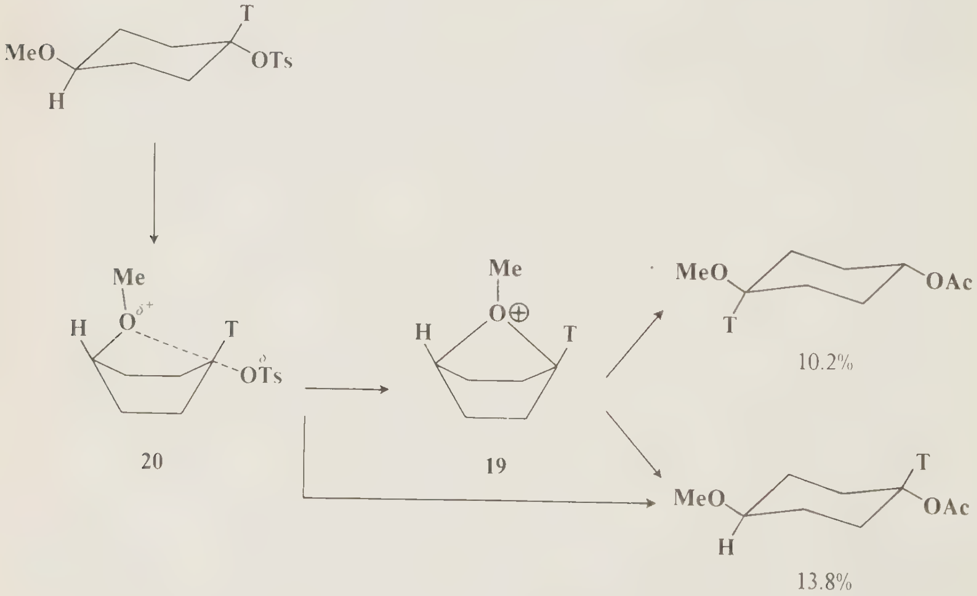
[62] See Traynham, *J. Chem. Educ.* **40**, 392 (1963).

[63] Allred and Winstein, *J. Am. Chem. Soc.* **89**, 3991, 3998 (1967).



been obtained from special salt effects that **18** is present both as the free ion and as ion pairs (with OBs$^-$ as the counterion).[63]

There is evidence that a neighboring group need not form a completely covalent bond with the substrate carbon in order to lend anchimeric assistance. Thus Noyce and coworkers showed that *trans*-4-methoxy-1-^{3}H-cyclohexyl tosylate when subjected to acetolysis gave 24% *trans*-4-methoxycyclohexyl acetate with 35% more tritium in the 1 position than in the 4 position.[64]



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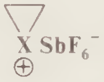
[64] Noyce, Thomas, and Bastian, *J. Am. Chem. Soc.* **82**, 885 (1960); Noyce and Bastian, *J. Am. Chem. Soc.* **82**, 1246 (1960).

If all the trans product came from the intermediate **19**, which is fully covalently bonded, then the tritium would have been equally distributed between the 1 and the 4 positions, except for the small isotope effect by which, if anything, more tritium would be expected in the 4 position. The excess 1-tritiated acetate could not have come from an ordinary SN2 reaction, since in that case the configuration would have been inverted. Indeed, 9.6% of *cis*-4-methoxycyclohexyl acetate (all labeled in the 1 position) was isolated in this reaction, formed by a concurrent SN2 reaction. Noyce and coworkers were thus led to postulate the intermediacy of an ion pair (**20**) which could go to **19** or directly to the substitution product. Similarly, in the hydrolysis of the anions of several α-bromoarylacetic and β-bromoarylpropionic acids, it was concluded that the action of the COO$^-$ group in assisting the departure of the Br is through electrostatic repulsion only, and that a covalent O—C bond is not being formed in the transition state.[65]

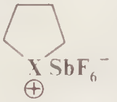
The neighboring-group mechanism operates only when the ring size is right for a particular type of Z. For example, for MeO(CH$_2$)$_n$OBs, neighboring-group participation was important for $n = 4$ or 5 (corresponding to a five- or six-membered intermediate) but not for $n = 2$, 3, or 6.[66] However, optimum ring size is not the same for all reactions, even with a particular Z. In general, the most rapid reactions occur when the ring size is three, five, or six, depending on the reaction type.

The following are some of the more important neighboring groups: COO$^-$ (but not COOH), OCOR, COOR, COAr,[67] OR, OH, O$^-$,[68] NH$_2$, NHR, NR$_2$, NHCOR, SH, SR, S$^-$,[69] I, Br, and Cl. The effectiveness of halogens as neighboring groups decreases in the order I > Br > Cl.[70] Cl is a very weak neighboring group and can be shown to act in this way only when the solvent does not interfere. For example, when 5-chloro-2-hexyl tosylate is solvolyzed in acetic acid, there is little participation by the Cl; but when the solvent is changed to trifluoroacetic acid, which is much less nucleophilic, neighboring-group participation by the Cl becomes the major reaction pathway.[71] Thus, Cl acts a neighboring group *only when there is need for it* (for other examples of this principle, see pp. 284, 288).

A number of intermediates of halogen participation (halonium ions),[71a] e.g., **21** and **22**, have been prepared as stable salts in SbF$_5$–SO$_2$ or SbF$_5$–SO$_2$ClF solutions.[72] Some of them have even



21



22

X = Br, Cl, or I

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[65] Kemp and Metzger, *J. Org. Chem.* **33,** 4165 (1968); Bordwell and Knipe, *J. Org. Chem.* **35,** 2956, 2959 (1970).

[66] Winstein, Allred, Heck, and Glick, *Tetrahedron* **3,** 1 (1958); Allred and Winstein, *J. Am. Chem. Soc.* **89,** 4012 (1967).

[67] For example, see Ward and Sherman, *J. Am. Chem. Soc.* **90,** 3812 (1968); Temnikova, Venediktova, and Karavan, *J. Org. Chem. USSR* **8,** 1229 (1972).

[68] For a review of oxygen functions as neighboring groups, see Perst, "Oxonium Ions in Organic Chemistry," pp. 100–127, Verlag Chemie, Weinheim/Bergstrasse, 1971.

[69] For a review of sulfur-containing neighboring groups, see Gundermann, *Angew. Chem. Int. Ed. Engl.* **2,** 674–683 (1963) [*Angew. Chem.* **75,** 1194–1203].

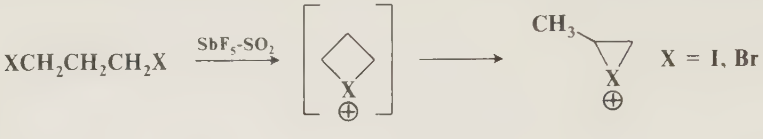
[70] Peterson, *Acc. Chem. Res.* **4,** 407–413 (1971), and references cited therein.

[71] Peterson, Bopp, Chevli, Curran, Dillard, and Kamat, *J. Am. Chem. Soc.* **89,** 5902 (1967). See also Reich and Reich, *J. Am. Chem. Soc.* **96,** 2654 (1974).

[71a] For a monograph, see Olah, "Halonium Ions," John Wiley & Sons, New York, 1975.

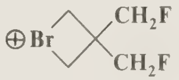
[72] Olah and Bollinger, *J. Am. Chem. Soc.* **89,** 4744 (1967), **90,** 947 (1967); Olah and Peterson, *J. Am. Chem. Soc.* **90,** 4675 (1968); Olah, Bollinger, and Brinich, *J. Am. Chem. Soc.* **90,** 2587, 6988 (1968); Peterson, Clifford, and Slama, *J. Am. Chem. Soc.* **92,** 2840 (1970); Peterson and Bonazza, *J. Am. Chem. Soc.* **94,** 5017 (1972); Peterson, Bonazza, and Henrichs, *J. Am. Chem. Soc.* **95,** 2222 (1973); Bonazza and Peterson, *J. Org. Chem.* **38,** 1015 (1973); Henrichs and Peterson, *J. Am. Chem. Soc.* **95,** 7449 (1973), *J. Org. Chem.* **41,** 362 (1976); Olah, Beal, and Westerman, *J. Am. Chem. Soc.* **95,** 3387 (1973); Olah, Westerman, Melby, and Mo, *J. Am. Chem. Soc.* **96,** 3565 (1974); Olah, Liang, and Staral, *J. Am. Chem. Soc.* **96,** 8112 (1974).

been crystallized. Attempts to prepare four-membered homologs of **21** and **22** did not bear fruit, as only three- or five-membered rings were obtained,[73] presumably by rearrangement, e.g.,

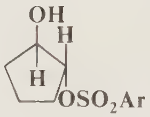


23

The fact that **23** (X = I or Br) forms in this reaction, but not the corresponding chloro analog, is further evidence for the low effectiveness of Cl as a neighboring group. In the case of 1,3-dichloropropane, the nmr spectrum of the product indicated the presence of an equilibrating mixture of **23** (X = Cl) and the open-chain ions $CH_3CH_2\overset{+}{C}HCl$ and $CH_3\overset{+}{C}HCH_2Cl$.[73] However, the four-membered bromonium ion **24** has been prepared.[74] There is no evidence that F can act as a neighboring group.[70]



24



25

The principle that a neighboring group lends assistance in proportion to the need for such assistance also applies to differences in leaving-group ability. Thus, *p*-$NO_2C_6H_4SO_2O$ (the nosylate group) is a better leaving group than *p*-$MeC_6H_4SO_2O$ (the tosylate group). Experiments have shown that the OH group in *trans*-2-hydroxycyclopentyl arenesulfonates (**25**) acts as a neighboring group when the leaving group is tosylate but not when it is nosylate, apparently because the nosylate group leaves so rapidly that it does not require assistance.[75]

Neighboring-Group Participation by π and σ Bonds. Nonclassical Carbonium Ions[76]

For all the neighboring groups listed in the preceding section, the internal nucleophilic attack is made by an atom with an unshared pair of electrons. In this section we shall consider neighboring-group participation by C=C π bonds and C—C and C—H σ bonds. There has been a great deal of controversy over whether such bonds can act as neighboring groups and about the existence and structure of the intermediates involved. These intermediates are called *nonclassical* (or *bridged*) carbonium ions. In classical carbonium ions (Chapter 5) the positive charge is localized on one carbon atom, or delocalized by resonance involving an unshared pair of electrons or a double or triple bond in the allylic position. In a nonclassical carbonium ion the positive charge is delocalized by a double or triple bond which is not in the allylic position, or by a

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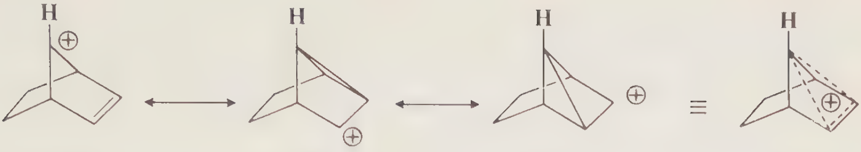
[73] Olah, Bollinger, Mo, and Brinich, *J. Am. Chem. Soc.* **94**, 1164 (1972).

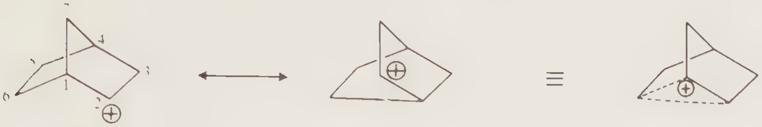
[74] Exner, Kershner, and Evans, *J. Chem. Soc., Chem. Commun.* 361 (1973).

[75] Haupt and Smith, *Tetrahedron Lett.* 4141 (1974).

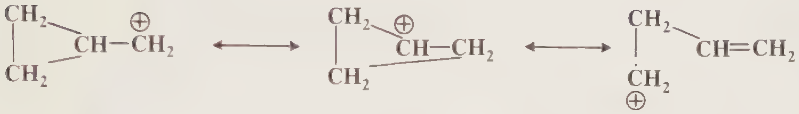
[76] For monographs, see Olah and Schleyer, "Carbonium Ions," vol. 3, John Wiley & Sons, New York, 1972; Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, 1965. For reviews, see McManus and Pittman, in McManus, "Organic Reactive Intermediates," pp. 302 321, Academic Press, New York, 1973; Bethell and Gold, "Carbonium Ions," p. 222–282, Academic Press, New York, 1967.



26a **26b** **26c** **26d**

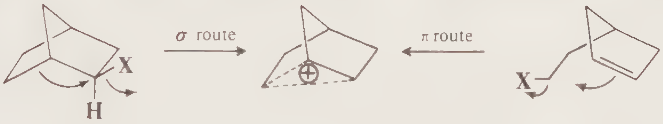


27a **27b** **27c**



28a **28b** **28c**

single bond. Examples are the 7-norbornenyl cation (**26**),[77] the norbornyl cation (**27**), and the cyclopropylmethyl cation (**28**). **26** is called a *homoallylic* carbonium ion, because in **26a** there is one carbon atom between the positively charged carbon and the double bond. Many nonclassical carbonium ions can be produced in more than one way if the proper substrates are chosen. For example, **27** can be generated by departure of a leaving group from **29** or from **30**.[78] The first of



29 **27** **30**

these pathways is called the σ route to a nonclassical carbonium ion, because participation of a σ bond is involved. The second is called the π route.[79] The argument against the existence of nonclassical carbonium ions is essentially that the structures **26a**, **26b**, **26c** (or **27a**, **27b**, etc.) are not canonical forms but real structures, and that there is rapid equilibration among them.

In the arguments for and against nonclassical carbonium ions, the distinction between neighboring-group participation and the existence of nonclassical carbonium ions has not always been kept clear.[80] If a nonclassical carbonium ion exists in any reaction, then an ion with electron delocalization, as shown in the above examples, is a discrete reaction intermediate. If a carbon-carbon double or single bond participates in the departure of the leaving group to form a carbonium ion, it may be that a nonclassical carbonium ion is involved, but there is no necessary relation. There are four possibilities:

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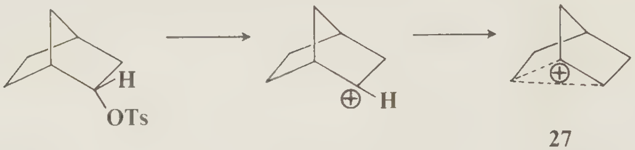
[77] There is evidence that **26d** is not the best representation of this ion. See p. 297.

[78] Lawton, *J. Am. Chem. Soc.* **83**, 2399 (1961); Bartlett, Bank, Crawford, and Schmid, *J. Am. Chem. Soc.* **87**, 1288 (1965).

[79] Winstein and Carter, *J. Am. Chem. Soc.* **83**, 4485 (1961).

[80] This has been pointed out by Cram, *J. Am. Chem. Soc.* **86**, 3767 (1964).

1. The leaving group may depart without assistance, and *then* a nonclassical ion may form, e.g.,



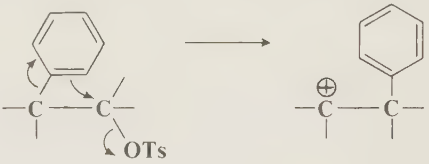
27

Classical carbonium ion

Nonclassical carbonium ion

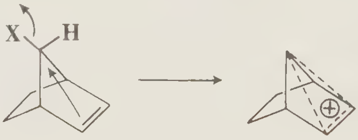
In this case there is no rate enhancement (compared, say, to the same reaction run on cyclopentyl tosylate, where no nonclassical ion is involved at any time).

2. A carbon-carbon double or single bond may lend assistance but may nonetheless give a classical open carbonium ion, e.g.,



In this case the rate *would* be enhanced, though no bridged ion is involved.

3. Both assistance and a nonclassical ion may be involved, e.g.,



31 **26d**

4. And, of course, there may be unassisted ionization to a classical carbonium ion.

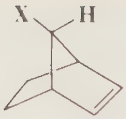
Enhanced rates are usually evidence for neighboring-group assistance but are not *always* evidence for the existence of nonclassical carbonium ions.

In the following pages we shall consider some of the evidence bearing on the questions of the participation of π and σ bonds and on the existence of nonclassical carbonium ions,[81] though a thorough discussion would be beyond the scope of this book.[76]

1. C=C *as a neighboring group*.[82] The most striking evidence that C=C can act as a neighboring group is that acetolysis of **31**-OTs is 10^{11} times faster than that of **32**-OTs and *proceeds with*

[81] For summaries of the arguments for nonclassical carbonium ions, see Winstein, *Aromaticity, Chem. Soc. Spec. Publ.* no. 21, 5–45 (1967), *Q. Rev., Chem. Soc.* **23,** 141–176 (1969). [The latter article is reprinted in Olah and Schleyer, Ref. 76, vol. 3, pp. 965–1005, 1972.] For summaries of the arguments against them, see Brown, *Chem. Br.* **2,** 199–208 (1966), "Boranes in Organic Chemistry," pp. 131–205, Cornell University Press, Ithaca, N.Y., 1972, *Acc. Chem. Res.* **6,** 377–386 (1973), *Tetrahedron* **32,** 179–204 (1976); Hückel, *Justus Liebigs Ann. Chem.* **711,** 1–18 (1968).

[82] For reviews, see Story and Clark, in Olah and Schleyer, Ref. 76, vol. 3, pp. 1007–1060, 1972; Richey, in Zabicky, "The Chemistry of Alkenes," vol. 2, pp. 77–101, Interscience Publishers, New York, 1970.



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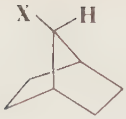
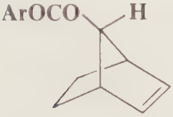


32

retention of configuration.[83] The rate data alone do not necessarily prove that acetolysis of **31**-OTs involves a nonclassical intermediate (**26d**), but it is certainly strong evidence that the C=C group assists in the departure of the OTs. It had been suggested that a pair of rapidly equilibrating classical carbonium ions (**26b** and **26c**) could also account for the results.[84] However, evidence against this view was obtained by a comparison of the rates of acetolysis of **33, 34,** and **35** at 140°C, which were found to be 1 : 13.3 : 148.[85] This ratio is in accord with the intermediate **26d,**



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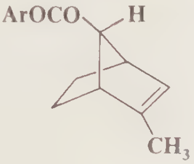

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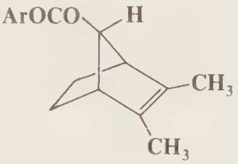
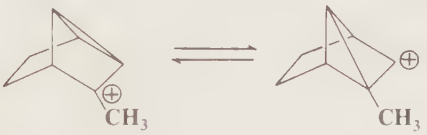


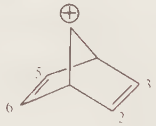
35

Ar = p-$NO_2C_6H_4$

since this intermediate has a partial positive charge at both carbons and should be stabilized by the first methyl group and then further stabilized by the second. If, however, an equilibrium between **26b** and **26c** were involved, then each of these ions would have a positive charge at only one carbon. Introduction of one methyl group would increase the rate, because the charge would then be at a tertiary carbon, but this would mean that **36** would be greatly favored at the



36 **37**



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expense of **37**. The introduction of a second methyl group should have little effect on the rate, since it has to be located on a carbon atom which bears no charge.

Further evidence that **26** is indeed a nonclassical ion comes from an nmr study of the relatively stable norbornadienyl cation (**38**). The spectrum shows that the 2 and 3 protons are not equivalent to the 5 and 6 protons.[86] Thus there is interaction between the charged carbon and one double bond, which is evidence for the existence of **26d.**[87] In the case of **31** the double bond is geometrically fixed in an especially favorable position for backside attack on the carbon bearing the leaving group (hence the very large rate enhancement), but there is much evidence that other double bonds in the homoallylic position,[88] as well as in positions farther away,[89] can also lend anchimeric assistance, though generally with much lower rate ratios. One example of the latter is the compound β-(*syn*-7-norbornenyl)ethyl brosylate (**39**) which undergoes acetolysis at 25°C about 140,000 times faster than the saturated analog **40**.[90] Triple bonds[91] and allenes[92] can also act as neighboring groups.

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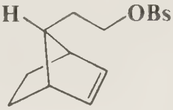
[83] Winstein and Shatavsky, *J. Am. Chem. Soc.* **78,** 592 (1956).

[84] Brown and Bell, *J. Am. Chem. Soc.* **85,** 2324 (1963). See, however, Brown, Peters, and Ravindranathan, *J. Am. Chem. Soc.* **97,** 2900 (1975).

[85] Gassman and Patton, *J. Am. Chem. Soc.* **91,** 2160 (1969).

[86] Story and Saunders, *J. Am. Chem. Soc.* **84,** 4876 (1962); Story, Snyder, Douglass, Anderson, and Kornegay, *J. Am. Chem. Soc.* **85,** 3630 (1963). For a discussion, see Story and Clark, Ref. 82, pp. 1026–1041. See also Lustgarten, Brookhart, and Winstein, *J. Am. Chem. Soc.* **94,** 2347 (1972).

[87] For further evidence for the nonclassical nature of **26,** see Winstein and Ordronneau, *J. Am. Chem. Soc.* **82,** 2084 (1960); Diaz, Brookhart, and Winstein, *J. Am. Chem. Soc.* **88,** 3133 (1966); Brooknart, Diaz, and Winstein, *J. Am. Chem. Soc.* **88,** 3135 (1966). Richey and Lustgarten, *J. Am. Chem. Soc.* **88,** 3136 (1966). Lustgarten, Brookhart, Winstein, Gassman, Patton, Richey, and Nichols, *Tetrahedron Lett.* 1699 (1970); Richey, Nichols, Gassman, Fentiman, Winstein, Brookhart, and Lustgarten, *J. Am. Chem. Soc.* **92,** 3783 (1970).



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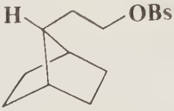
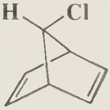


40

An interesting fact is that a second double bond, suitably placed, can increase solvolysis rates still further. Thus, solvolysis of 7-chloronorbornadiene (**41**) was 10^3 times faster than that of **31**-Cl,[93] while **42** (which has a [2.2.1] bicyclic system fused to a 7-norbornenyl system) solvolyzed about 10^3 times faster than the *p*-nitrobenzoate ester of **31**-OH.[94] Thus both these systems solvolyze about 10^{14} times faster than the saturated 7-norbornyl system.



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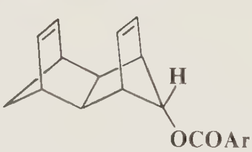

Ar = p-$NO_2C_6H_4$

42

We have already seen evidence that participation by a potential neighboring group can be reduced or eliminated if an outside nucleophile is present which is more effective than the neighboring group in attacking the central carbon (p. 283), or if a sufficiently good leaving group is present (p. 284). In another example of this principle, Gassman and coworkers have shown that neighboring-group participation can also be reduced if the stability of the potential carbonium ion is increased. They found that the presence of a *p*-anisyl group at the 7 position of **31** and **32** exerts a powerful leveling effect on the rate differences. Thus, solvolysis in acetone-water at 85°C of *syn*-7-*p*-anisyl-*anti*-7-norborn-2-enyl *p*-nitrobenzoate (**43**) was only about 2.5 times faster than

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[88] For examples, see Shoppee, *J. Chem. Soc.* 1147 (1946); LeBel and Huber, *J. Am. Chem. Soc.* **85**, 3193 (1963); Closson and Kwiatkowski, *Tetrahedron* **21**, 2779 (1965); Cristol and Nachtigall, *J. Am. Chem. Soc.* **90**, 7132 (1968); Masamune, Takada, Nakatsuka, Vukov, and Cain, *J. Am. Chem. Soc.* **91**, 4322 (1969); Hess, *J. Am. Chem. Soc.* **91**, 5657 (1969); Lambert and Holcomb, *J. Am. Chem. Soc.* **93**, 3952 (1971); Brown, Peters, and Ravindranathan, *J. Am. Chem. Soc.* **97**, 7449 (1975).

[89] For examples, see LeNy, *C. R. Acad. Sci.* **251**, 1526 (1960); Goering and Closson, *J. Am. Chem. Soc.* **83**, 3511 (1961); Bartlett, Trahanovsky, Bolon, and Schmid, *J. Am. Chem. Soc.* **87**, 1314 (1965); Bly and Swindell, *J. Org. Chem.* **30**, 10 (1965); Marvell, Sturmer, and Knutson, *J. Org. Chem.* **33**, 2991 (1968); Cogdell, *J. Org. Chem.* **37**, 2541 (1972); Gream, *Aust. J. Chem.* **25**, 1051 (1972); Ref. 79. See also Ref. 78.

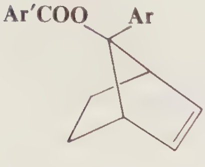
[90] Bly, Bly, Bedenbaugh, and Vail, *J. Am. Chem. Soc.* **89**, 880 (1967).

[91] See, for example, Closson and Roman, *Tetrahedron Lett.* 6015 (1966); Hanack, Herterich, and Vött, *Tetrahedron Lett.* 3871 (1967); Peterson and Kamat, *J. Am. Chem. Soc.* **91**, 4521 (1969); Lambert, Papay, and Mark, *J. Org. Chem.* **40**, 633 (1975).

[92] Jacobs and Macomber, *Tetrahedron Lett.* 4877 (1967); Bly and Koock, *J. Am. Chem. Soc.* **91**, 3292, 3299 (1969); Von Lehman and Macomber, *J. Am. Chem. Soc.* **97**, 1531 (1975).

[93] Winstein and Ordronneau, Ref. 87.

[94] Allred and Hinshaw, *Tetrahedron Lett.* 1293 (1968). See also Paquette and Dunkin, *J. Am. Chem. Soc.* **96**, 1220 (1974).



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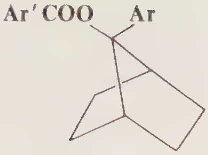

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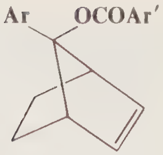
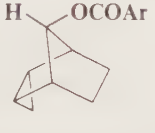


45

$\mathrm{Ar} = p\text{-}\mathrm{MeOC_6H_4}$
$\mathrm{Ar'} = p\text{-}\mathrm{NO_2C_6H_4}$

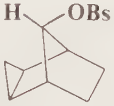
that of the saturated compound **44**.[95] Furthermore, both **43** and its stereoisomer **45** gave the same mixture of solvolysis products, showing that the stereoselectivity in the solvolysis of **31** is not present here. The difference between **43** and **31** is that in the case of **43** the positive charge generated at the 7 position in the transition state is greatly stabilized by the *p*-anisyl group. Apparently the stabilization by the *p*-anisyl group is so great that further stabilization which would come from participation by the C═C bond is not needed. The use of a phenyl instead of a *p*-anisyl group is not sufficient to stop participation by the double bond completely, though it does reduce it.[96] These results permit us to emphasize our previous conclusion, that *a neighboring group lends anchimeric assistance only when there is sufficient demand for it.*

2. *Cyclopropyl*[97] *as a neighboring group.*[98] On p. 141 we saw that the properties of a cyclopropane ring are in some ways similar to those of a double bond. Therefore it is not surprising that a suitably placed cyclopropyl ring can also be a neighboring group. Thus *endo-anti*-tricyclo-[3.2.1.0^{2,4}]octan-8-yl *p*-nitrobenzoate (**46**) solvolyzed about 10^{14} times faster than the *p*-nitrobenzoate of **32**-OH.[99] Obviously, a suitably placed cyclopropyl ring can be even more effective[100] as a neighboring group than a double bond.[101] The need for suitable placement is emphasized by the fact that **48** solvolyzed only about five times faster than **32**-OBs,[102] while **47** solvolyzed three



$\mathrm{Ar} = p\text{-}\mathrm{NO_2C_6H_4}$

46



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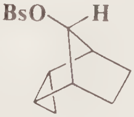

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[95] Gassman, Zeller, and Lamb, *Chem. Commun.* 69 (1968).

[96] Gassman and Fentiman, *J. Am. Chem. Soc.* **91**, 1545 (1969), **92**, 2549 (1970).

[97] In this section we consider systems in which at least one carbon separates the cyclopropyl ring from the carbon bearing the leaving group. For a discussion of systems in which the cyclopropyl group is directly attached to the leaving-group carbon, see p. 298.

[98] For a review, see Haywood-Farmer, *Chem. Rev.* **74**, 315–350 (1974).

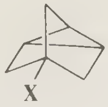
[99] Tanida, Tsuji, and Irie, *J. Am. Chem. Soc.* **89**, 1953 (1967); Battiste, Deyrup, Pincock, and Haywood-Farmer, *J. Am. Chem. Soc.* **89**, 1954 (1967).

[100] For a competitive study of cyclopropyl versus double-bond participation, see Lambert, Jovanovich, Hamersma, Koeng, and Oliver, *J. Am. Chem. Soc.* **95**, 1570 (1973).

[101] For other evidence for anchimeric assistance by cyclopropyl, see Sargent, Lowry, and Reich, *J. Am. Chem. Soc.* **89**, 5985 (1967); Battiste, Haywood-Farmer, Malkus, Seidl, and Winstein, *J. Am. Chem. Soc.* **92**, 2144 (1970); Gassman and Fentiman, *J. Am. Chem. Soc.* **92**, 2551 (1970); Coates and Kirkpatrick, *J. Am. Chem. Soc.* **92**, 4883 (1970); Coates and Yano, *Tetrahedron Lett.* 2289 (1972); Masamune, Vukov, Bennett, and Purdham, *J. Am. Chem. Soc.* **94**, 8239 (1972); Gassman and Creary, *J. Am. Chem. Soc.* **95**, 2729 (1973).

[102] Battiste, Deyrup, Pincock, and Haywood-Farmer, Ref. 99; Haywood-Farmer and Pincock, *J. Am. Chem. Soc.* **91**, 3020 (1969).

times *slower* than **32**-OBs.[103] In the case of **46** and of all other cases known where cyclopropyl lends considerable anchimeric assistance, the developing *p* orbital of the carbonium ion is orthogonal to the participating bond of the cyclopropane ring.[104] An experiment designed to test whether a developing *p* orbital which would be parallel to the participating bond would be assisted by that bond showed no rate enhancement.[104] This is in contrast to the behavior of cyclopropane rings directly attached to positively charged carbons, where the *p* orbital is parallel to the plane of the ring (pp. 155, 299). Another geometrical situation in which rate enhancement is not found is where the developing *p* orbital is directly over the face of a cyclopropane ring, as in **49**.[105]



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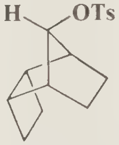

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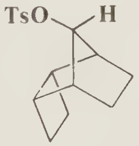
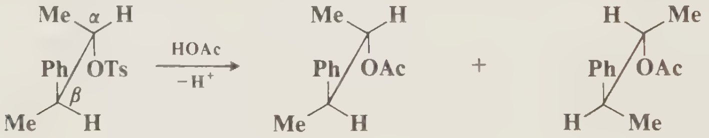


51

Rate enhancements, though considerably smaller, have also been reported for suitably placed cyclobutyl rings. For example, acetolysis of **50** was about 2×10^4 times faster than that of **32**-OTs.[106] Suitable placement is essential in this case also, as shown by the fact that there was essentially no rate enhancement at all in acetolysis of **51**, compared with that of **32**-OTs.

3. *Aromatic rings as neighboring groups.*[107] There is a great deal of evidence that aromatic rings in the *β*-position can function as neighboring groups. Stereochemical evidence was obtained by solvolysis of L-*threo*-3-phenyl-2-butyl tosylate (**52**) in acetic acid.[108] Of the acetate product 96%



52 **53** **54**

was the threo isomer and only about 4% was erythro. Moreover, both the D and L threo isomers (**53** and **54**) were produced in approximately equal amounts (a racemic mixture). When solvolysis was conducted in formic acid, even less erythro isomer was obtained. This result is similar to that found on reaction of 3-bromo-2-butanol with HBr (p. 280) and leads to the conclusion that configuration is retained because phenyl acts as a neighboring group. However, evidence from rate studies is not so simple. If β-aryl groups assist the departure of the leaving group, then solvolysis rates should be enhanced. In general they are not. However, solvolysis rate studies in 2-arylethyl systems are complicated by the fact that, for primary and secondary systems, two pathways can exist.[109] In one of these (designated k_Δ), the aryl, behaving as a neighboring group, pushes out the leaving group to give a bridged carbonium ion, called a *phenonium ion* (**55**), and is in turn pushed out by the solvent SOH, so that the net result is substitution with retention of configuration (or rearrangement, if **55** is opened from the other side). The other pathway (k_s) is simple S$_N$2 attack by the solvent at the leaving-group carbon. The net result here is substitution with inversion and no possibility of rearrangement. Whether the leaving group is located at a primary or a secondary carbon,[110] there is no crossover between these pathways; they are completely independent.[111] The overall rate constant k_t (which is determined by titration of the departed leaving group) is then given by

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[103] Haywood-Farmer, Pincock, and Wells, *Tetrahedron* **22**, 2007 (1966); Haywood-Farmer and Pincock, Ref. 102. For other cases where there was little or no rate enhancement by cyclopropyl, see Wiberg and Wenzinger, *J. Org. Chem.* **30**, 2278 (1965); Colter and Musso, *J. Org. Chem.* **30**, 2462 (1965); Sargent, Taylor, and Demisch, *Tetrahedron Lett.* 2275 (1968); Muneyuki, Yano, and Tanida, *J. Am. Chem. Soc.* **91**, 2408 (1969); Rhodes and Takino, *J. Am. Chem. Soc.* **92**, 4469 (1970); Dewar and Harris, *J. Am. Chem. Soc.* **92**, 6557 (1970); Diaz, Harris, Sakai, and Winstein, *Tetrahedron Lett.* 303 (1971); Hanack and Krause, *Justus Liebigs Ann. Chem.* **760**, 17 (1972).

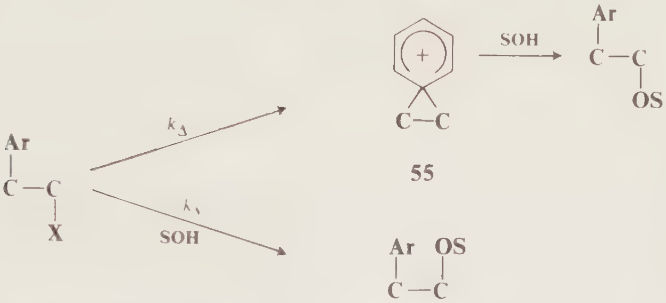
[104] Gassman, Seter, and Williams, *J. Am. Chem. Soc.* **93**, 1673 (1971). For a discussion, see Haywood-Farmer and Pincock, Ref. 102.

[105] Sherrod, Bergman, Gleicher, and Morris, *J. Am. Chem. Soc.* **92**, 3469 (1970), **94**, 4615 (1972); Bingham, Sliwinski, and Schleyer, *J. Am. Chem. Soc.* **92**, 3471 (1970).

[106] Sakai, Diaz, and Winstein, *J. Am. Chem. Soc.* **92**, 4452 (1970). See also Battiste and Nebzydoski, *J. Am. Chem. Soc.* **92**, 4450 (1970); Schipper, Driessen, de Haan, and Buck, *J. Am. Chem. Soc.* **96**, 4706 (1974).

[107] For a review, see Lancelot, Cram, and Schleyer, in Olah and Schleyer, Ref. 76, vol. 3, pp. 1347–1483, 1972.

[108] Cram, *J. Am. Chem. Soc.* **71**, 3863 (1949), **74**, 2129 (1952).



55

$$k_t = Fk_\Delta + k_s$$

where F is the fraction of **55** which goes to product. This factor is needed because **55** may be present as an ion pair and consequently may undergo partial internal return to the starting compound. Which of the two pathways predominates in any given case depends on the solvent and on the nature of the aryl group. As expected from the results we have seen for Cl as a neighboring group (p. 283), the k_Δ/k_s ratio is highest for solvents which are poor nucleophiles and so compete very poorly with the aryl group. For several common solvents the k_Δ/k_s ratio increases in the order EtOH < CH_3COOH < HCOOH < CF_3COOH.[112] In accord with this, the following percentages of retention were obtained in solvolysis of 1-phenyl-2-propyl tosylate at 50°C: solvolysis in EtOH 7%, CH_3COOH 35%, HCOOH 85%.[112] This indicates that k_s predominates in EtOH (phenyl participates very little), while k_Δ predominates in HCOOH. Trifluoroacetic acid is a solvent of particularly low nucleophilic power, and in this solvent the reaction proceeds entirely by k_Δ;[113] deuterium labeling showed 100% retention.[114] This case provides a clear example of neighboring-group rate enhancement by phenyl: the rate of solvolysis of $PhCH_2CH_2OTs$ at 75°C in CF_3COOH is 3040 times the rate for CH_3CH_2OTs.[113] The presence of special salt effects

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[109] Winstein and Heck, *J. Am. Chem. Soc.* **78,** 4801 (1956); Brookhart, Anet, Cram, and Winstein, *J. Am. Chem. Soc.* **88,** 5659 (1966); Lee, Unger, and Vassie, *Can. J. Chem.* **50,** 1371 (1972).

[110] Both the k_Δ and the k_s pathways are unimportant when the leaving group is at a tertiary carbon. In these cases the mechanism is S$_N$1 and open carbonium ions $ArCH_2CR_2^+$ are intermediates. This pathway is designated k_c.

[111] Harris, Schadt, Schleyer, and Lancelot, *J. Am. Chem. Soc.* **91,** 7508 (1969); Brown, Kim, Lancelot, and Schleyer, *J. Am. Chem. Soc.* **92,** 5244 (1970); Brown and Kim, *J. Am. Chem. Soc.* **93,** 5765 (1971).

[112] Diaz, Lazdins, and Winstein, *J. Am. Chem. Soc.* **90,** 6546 (1968); Diaz and Winstein, *J. Am. Chem. Soc.* **91,** 4300 (1969). See also Schadt and Schleyer, *J. Am. Chem. Soc.* **95,** 7860 (1973).

[113] Nordlander and Deadman, *J. Am. Chem. Soc.* **90,** 1590 (1968); Nordlander and Kelly, *J. Am. Chem. Soc.* **91,** 996 (1969).

[114] Jablonski and Snyder, *J. Am. Chem. Soc.* **91,** 4445 (1969).

TABLE 1 Approximate k_Δ/k_s ratios for acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ at 90°C[117]

Z	k_Δ/k_s
MeO	30
Me	11
H	1.3
Cl	0.3

during solvolysis of $PhCH_2CH_2OTs$ in CF_3COOH shows that under these conditions **55** and its counterion exist as intimate ion pairs, as solvent-separated ion pairs, and as dissociated ions.[115]

With respect to the aromatic ring, the k_Δ pathway is an electrophilic aromatic substitution (Chapter 11), and we would predict that groups on the ring which activate that reaction (p. 459) will increase, and deactivating groups will decrease, the rate of this pathway. This prediction has been borne out by several investigations. The p-nitro derivative of L-*threo*-**52** solvolyzed in acetic acid 190 times slower than **52**, and there was much less retention of configuration: the acetate produced was only 7% threo and 93% erythro.[116] At 90°C, acetolysis of p-$ZC_6H_4CH_2CH_2OTs$ gave the rate ratios shown in Table 1.[117] Throughout this series k_s is fairly constant, as it should be since it is affected only by the rather remote field effect of Z. It is k_Δ which changes substantially as Z is changed from activating to deactivating. The evidence is thus fairly clear that participation by aryl groups depends greatly on the nature of the group, and that for some groups, e.g., p-nitrophenyl, in some solvents, e.g., acetic acid, there is essentially no neighboring-group participation at all,[118] while for others, e.g., p-methoxyphenyl, neighboring-group participation is substantial. The combined effect of solvent and structure is shown in Table 2, where the figures shown were derived by three different methods.[119]

For some years there was controversy about the structure of phenonium ions **55**,[120] but several

TABLE 2 Percent of product formed by the k_Δ pathway in solvolysis of p-$ZC_6H_4CH_2CHMeOTs$[119]

Z	Solvent	Percent by k_Δ
H	CH_3COOH	35–38
H	HCOOH	72–79
MeO	CH_3COOH	91–93
MeO	HCOOH	99

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[115] Reich, Diaz, and Winstein, *J. Am. Chem. Soc.* **94,** 2256 (1972).

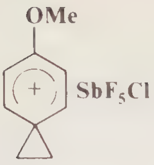
[116] Thompson and Cram, *J. Am. Chem. Soc.* **91,** 1778 (1969). See also Tanida, Tsuji, Ishitobi, and Irie, *J. Org. Chem.* **34**, 1086 (1969); Kingsbury and Best, *Bull. Chem. Soc. Jpn.* **45,** 3440 (1972).

[117] Coke, McFarlane, Mourning, and Jones, *J. Am. Chem. Soc.* **91,** 1154 (1969); Jones and Coke, *J. Am. Chem. Soc.* **91**, 4284 (1969). See also Harris, Schadt, Schleyer, and Lancelot, Ref. 111.

[118] The k_Δ pathway is important for p-nitrophenyl in CF_3COOH: Ando, Shimizu, Kim, Tsuno, and Yukawa, *Tetrahedron Lett.* 117 (1973).

[119] Lancelot and Schleyer, *J. Am. Chem. Soc.* **91,** 4291, 4296 (1969); Lancelot, Harper, and Schleyer, *J. Am. Chem. Soc.* **91,** 4294 (1969); Schleyer and Lancelot, *J. Am. Chem. Soc.* **91,** 4297 (1969).

[120] For discussions, see Brown, Morgan, and Chloupek, *J. Am. Chem. Soc.* **87,** 2137 (1965); Brown, Bernheimer, Kim, and Scheppele, *J. Am. Chem. Soc.* **89,** 370 (1966); Brown and Kim, *J. Am. Chem. Soc.* **90,** 2082 (1968); Kim and Brown, *J. Am. Chem. Soc.* **94,** 5043, 5051 (1972); Thompson and Cram, Ref. 116; Ref. 80.



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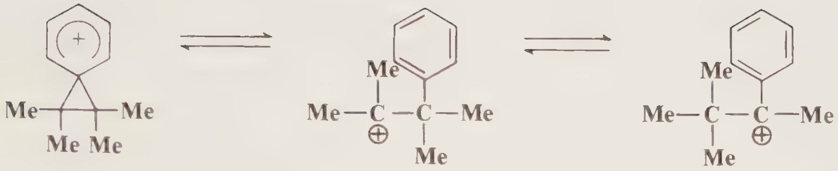
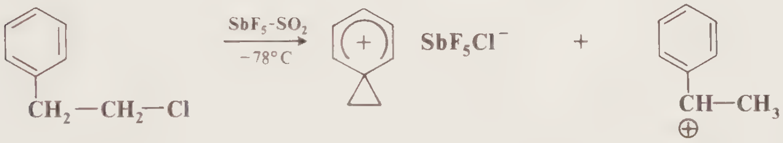


57 **58** **59**

of these have now been prepared as stable ions in solution where they can be studied by nmr, among them **56**,[121] **57**,[122] and the unsubstituted **55**.[123] These were prepared by the method shown for **55**: treatment of the corresponding β-arylethyl chloride with SbF_6–SO_2 at low temperatures. These conditions are even more extreme than the solvolysis in CF_3COOH mentioned earlier. The absence of any nucleophile at all eliminates not only the k_s pathway but also nucleophilic



55 **60**

attack on **55**. The 1-phenylethyl cation (**60**) is formed along with **55**, but the two ions are formed by separate pathways and do not interconvert. **60** is produced by a hydride shift. Although **55** is not in equilibrium with the open-chain ion $PhCH_2CH_2^+$ (which is primary and hence unstable), **57** is in equilibrium with the open-chain tertiary ions **58** and **59**, though only **57** is present in appreciable concentration. Proton and ^{13}C nmr show that **55**, **56**, and **57** are classical carbonium ions where the only resonance is in the six-membered ring. The three-membered ring is a normal cyclopropane ring which is influenced only to a relatively small extent by the positive charge on

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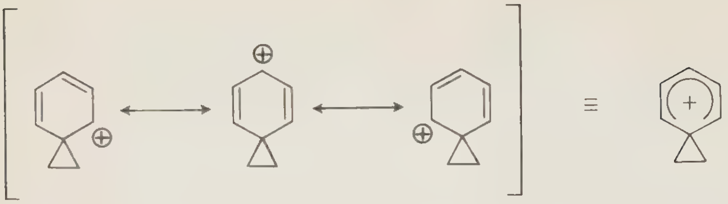
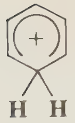
[121] Olah, Comisarow, Namanworth, and Ramsey, *J. Am. Chem. Soc.* **89**, 5259 (1967); Ramsey, Cook, and Manner, *J. Org. Chem.* **37**, 3310 (1972).

[122] Olah, Comisarow, and Kim, *J. Am. Chem. Soc.* **91**, 1458 (1969). See, however, Ramsey, Cook, and Manner, Ref. 121.

[123] Olah and Porter, *J. Am. Chem. Soc.* **93**, 6877 (1971). See also Eberson, Petrovich, Baird, Dyckes, and Winstein, *J. Am. Chem. Soc.* **87**, 3504 (1965); Olah and Liang, *J. Am. Chem. Soc.* **97**, 2236 (1975).





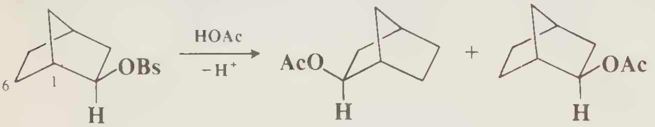
61

the adjacent ring. Nmr spectra show that the six-membered rings have no aromatic character but are similar in structure to those carbonium ions, e.g., **61**, which are intermediates in electrophilic aromatic substitution (Chapter 11). These ions can be quenched with an added nucleophile to give normal nucleophilic substitution products. For example, the addition of K_2CO_3-buffered ice in SO_2ClF to solutions containing mixtures of **55** and **60** gave a mixture of α- and β-phenylethyl alcohols.[123]

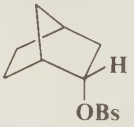
It is thus clear that β-aryl groups can function as neighboring groups.[124] Much less work has been done on aryl groups located in positions farther away from the leaving group, but there is evidence that these too can lend anchimeric assistance.[125]

4. *The carbon-carbon single bond as a neighboring group.*[126]

a. *The 2-norbornyl system.* In the investigations to determine whether a C—C σ bond can act as a neighboring group, by far the greatest attention has been paid to the 2-norbornyl system.[127] Winstein and Trifan found that solvolysis in acetic acid of optically active *exo*-2-norbornyl brosylate (**62**) gave a racemic mixture of the two exo acetates;[128] no endo isomers were formed:[129]



62 **63** **64**



65

Furthermore, **62** solvolyzed about 350 times faster than its endo isomer **65**. Similar high exo/endo rate ratios have been found in many other 2.2.1 systems. These two results, (1) that solvolysis of an optically active exo isomer gave only racemic exo isomers and (2) the high exo/endo rate ratio, were interpreted by Winstein and Trifan as indicating that the 1,6 bond assists in the departure of the leaving group and that a nonclassical intermediate (**66**) is involved. They reasoned that

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[124] For additional evidence, see Tanida, *Acc. Chem. Res.* **1,** 239–245 (1968); Kingsbury and Best, *Tetrahedron Lett.* 1499 (1967); Braddon, Wiley, Dirlam, and Winstein, *J. Am. Chem. Soc.* **90,** 1901 (1968); Tanida, Ishitobi, and Irie, *J. Am. Chem. Soc.* **90,** 2688 (1968); Brown and Tritle, *J. Am. Chem. Soc.* **90,** 2689 (1968); Cristol and Nachtigall, *J. Am. Chem. Soc.* **90,** 7133 (1968); Bentley and Dewar, *J. Am. Chem. Soc.* **92,** 3996 (1970); McDonald and Curtis, *J. Am. Chem. Soc.* **93,** 2530 (1971); Raber, Harris, and Schleyer, *J. Am. Chem. Soc.* **93,** 4829 (1971). For a discussion of evidence obtained from isotope effects, see Scheppele, *Chem. Rev.* **72,** 511–532 (1972), pp. 522–525.

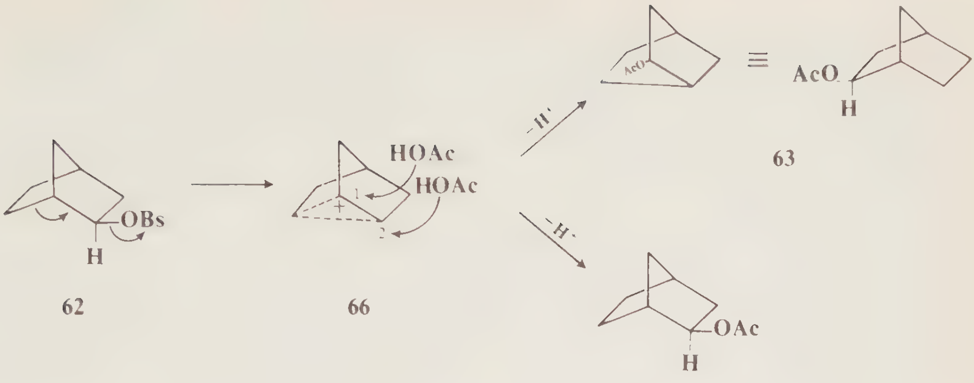
[125] Heck and Winstein, *J. Am. Chem. Soc.* **79,** 3105 (1957); Muneyuki and Tanida, *J. Am. Chem. Soc.* **90,** 656 (1968); Ouellette, Papa, Attea, and Levin, *J. Am. Chem. Soc.* **92,** 4893 (1970); Jackman and Haddon, *J. Am. Chem. Soc.* **96,** 5130 (1974); Gates, Frank, and von Felten, *J. Am. Chem. Soc.* **96,** 5138 (1974).

[126] For a review pertaining to studies of this topic at low temperatures, see Olah, *Angew. Chem. Int. Ed. Engl.* **12,** 173–212 (1973), pp. 192–198 [*Angew. Chem.* **85,** 183–225].

[127] For reviews, see Sargent, in Olah and Schleyer, Ref. 76, vol. 3, pp. 1099–1200 (1972); Sargent, *Q. Rev., Chem. Soc.* **20,** 301–371 (1966); Gream, *Rev. Pure Appl. Chem.* **16,** 25–60 (1966); Ref. 76.

[128] Winstein and Trifan, *J. Am. Chem. Soc.* **74,** 1147, 1154 (1952).

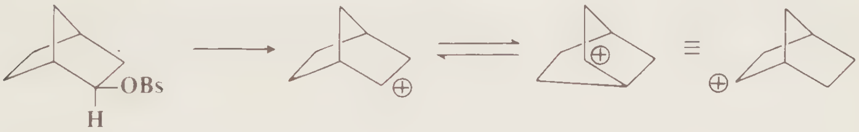
[129] It has been shown that the endo content is definitely less than 0.02%: Winstein, Clippinger, Howe, and Vogelfanger, *J. Am. Chem. Soc.* **87,** 376 (1965).



62 66 63 64

solvolysis of the endo isomer **65** is not assisted by the 1,6 bond because it is not in a favorable position for backside attack, and that consequently solvolysis of **65** takes place at a "normal" rate. Therefore the much faster rate for the solvolysis of **62** must be caused by anchimeric assistance. The stereochemistry of the product is also explained by the intermediacy of **66**, since in **66** the 1 and 2 positions are equivalent and would be attacked by the nucleophile with equal facility, but only from the exo direction in either case. There is the possibility that the 1,6 bond assists (accounting for the rate increase), but that **66** is not an intermediate. However, if this were the case, then every act of assistance would be an act of rearrangement (case 2, p. 286), and an optically active product would have been obtained. Incidentally, acetolysis of **65** also leads exclusively to the exo acetates (**63** and **64**), so that in this case Winstein and Trifan postulated that a classical ion (**67**) is first formed and then converted to the more stable **66**. Evidence for this interpretation is that the product from solvolysis of **65** is not racemic but contains somewhat more **64** than **63** (corresponding to 3 to 13% inversion, depending on the solvent),[129] suggesting that, when **67** is formed, some of it goes to give **64** before it can collapse to **66**.

The concepts of σ participation and of the nonclassical ion **66** have been challenged by H. C. Brown,[81] who has suggested that the two results can also be explained by postulating that **62** solvolyzes without participation of the 1,6 bond to give the classical ion **67** which is in rapid equilibrium with **68**. This rapid interconversion has been likened to the action of a windshield wiper. Obviously, in going from **67** to **68** and back again, **66** must be present, but in Brown's view it is only a transition state and not an intermediate. Brown's explanation for the stereochemical result is that exclusive exo attack is a property to be expected from any 2-norbornyl system, not only for the cation but even for reactions not involving cations, because of steric hindrance to attack from the endo side, and there is a large body of data which shows that exo attack on norbornyl systems is fairly general in many reactions. As for the obtention of a racemic mixture, this will obviously happen if **67** and **68** are present in equal amounts, since they are equivalent and exo attack on **67** and **68** gives, respectively, **64** and **63**. Brown explains the high



62 67 68

exo/endo rate ratios by contending that it is not the endo rate which is normal and the exo rate abnormally high, but the exo rate which is normal and the endo rate abnormally *low*, because of steric hindrance to removal of the leaving group in that direction. Schleyer has proposed that *torsional effects* are at least partly responsible for the high exo/endo rate ratios.[130] That is, when an exo leaving group departs, eclipsing and other nonbonded interactions decrease but, when an endo group departs, these interactions increase. However, there is evidence that torsional effects in this system are minor.[131]

A vast amount of work has been done[132] on solvolysis of the 2-norbornyl system in efforts to determine whether the 1,6 bond participates and whether **66** is an intermediate, but the question is still not settled.[133] However, there is general agreement on two points: (1) *endo*-2-norbornyl substrates solvolyze without participation (though some workers believe that formation of **66** may follow), and (2) substituents in the 2 position which stabilize a positive charge (e.g., methyl or phenyl) either entirely eliminate σ participation or at least greatly decrease it[134] (by the principle that the extent of neighboring-group participation depends on the need for it). The fact that high exo/endo rate and product ratios are also found in these systems[135] lends support to the statement that these phenomena are not caused by σ participation.

Though the intermediacy of **66** under solvolysis conditions remains to be proven or disproven, it has been stated that a nonclassical 2-norbornyl cation does exist under some conditions. Olah and coworkers have prepared the 2-norbornyl cation in stable solutions at temperatures below −150°C in SbF_5–SO_2 and FSO_3H–SbF_5–SO_2, where the structure is static and hydride shifts are absent.[136] Studies by proton and ^{13}C nmr, as well as by laser Raman spectra and x-ray electron spectroscopy,[137] led to the conclusion that under these conditions the ion is definitely nonclassical,[138] though this conclusion has been challenged.[138a] Olah and coworkers represented the structure as a corner-protonated nortricyclane (**69**); the symmetry is better seen when the

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[130] Schleyer, *J. Am. Chem. Soc.* **89,** 699, 701 (1967).

[131] Salmon and Whittaker, *Chem. Commun.* 491 (1967); Brown and Rei, *J. Am. Chem. Soc.* **90,** 6216 (1968); Werstiuk and Taillefer, *Can. J. Chem.* **48,** 3966 (1970); Jindal and Tidwell, *Tetrahedron Lett.* 783 (1971).

[132] For thorough discussions, see Refs. 76, 81, and 127.

[133] For some evidence in favor of a nonclassical **66,** see Hartman and Traylor, *J. Am. Chem. Soc.* **97,** 6147 (1975); Battiste and Fiato, *Tetrahedron Lett.* 1255 (1975); Harris and McManus, *J. Am. Chem. Soc.* **96,** 4693 (1974); Lenoir, *Tetrahedron Lett.* 1563 (1974); Nordlander, Gruetzmacher, Kelly, and Jindal, *J. Am. Chem. Soc.* **96,** 181 (1974); Kaplan, Cross, and Prinstein, *J. Am. Chem. Soc.* **92,** 1445 (1970); Muneyuki and Yano, *J. Am. Chem. Soc.* **92,** 746 (1970); Goering and Fickes, *J. Am. Chem. Soc.* **90,** 2848, 2856, 2862 (1968); Jefford, Hill, and Gunsher, *J. Am. Chem. Soc.* **89,** 6881 (1967); le Noble, Yates, and Scaplehorn, *J. Am. Chem. Soc.* **89,** 3751 (1967); Corey and Glass, *J. Am. Chem. Soc.* **89,** 2600 (1967); Berson, Hammons, McRowe, Bergman, Remanick, and Houston, *J. Am. Chem. Soc.* **89,** 2590 (1967). For some evidence against it, see Brown, Ravindranathan, Takeuchi, and Peters, *J. Am. Chem. Soc.* **97,** 2899 (1975); Brown and Liu, *J. Am. Chem. Soc.* **97,** 2469 (1975); Brown and Kawakami, *J. Am. Chem. Soc.* **97,** 5221 (1975); Brown, Gnedin, Takeuchi, and Peters, *J. Am. Chem. Soc.* **97,** 610 (1975); Brown, Ravindranathan, and Peters, *J. Am. Chem. Soc.* **96,** 7351 (1974); Peters and Brown, *J. Am. Chem. Soc.* **96,** 263, 265 (1974); Gream, Wege, and Mular, *Aust. J. Chem.* **27,** 567 (1974); Rothberg and Garnick, *J. Chem. Soc., Perkin Trans. 2* 457 (1974); Gassman and Hornback, *J. Am. Chem. Soc.* **94,** 7010 (1972); Goering and Clevenger, *J. Am. Chem. Soc.* **94,** 1010 (1972); Collins and Benjamin, *J. Am. Chem. Soc.* **92,** 3182 (1970); Benjamin and Collins, *J. Am. Chem. Soc.* **92,** 3183 (1970); Brown and Vander Jagt, *J. Am. Chem. Soc.* **91,** 6850 (1969); Gassman, Marshall, and Macmillan, *J. Am. Chem. Soc.* **91,** 4282 (1969); Brown and Ikegami, *J. Am. Chem. Soc.* **90,** 7122 (1968); Ikegami, Vander Jagt, and Brown, *J. Am. Chem. Soc.* **90,** 7124 (1968); Brown and Hammar, *J. Am. Chem. Soc.* **89,** 6378 (1967); Brown, Rothberg and Vander Jagt, *J. Am. Chem. Soc.* **89,** 6380 (1967); Brown, Hammar, Kawakami, Rothberg, and Vander Jagt, *J. Am. Chem. Soc.* **89,** 6381 (1967); Banerjee and Werstiuk, *Can. J. Chem.* **54,** 678 (1976).

[134] Brown and Rei, *J. Am. Chem. Soc.* **86,** 5004 (1964), **90,** 6216 (1968); Goering and Humski, *J. Am. Chem. Soc.* **90,** 6213 (1968); Goering, Brown, and Schewene, *J. Am. Chem. Soc.* **90,** 6214 (1968); Goering and Clevenger, Ref. 133.

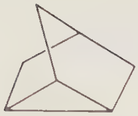
[135] Peters and Brown, *J. Am. Chem. Soc.* **95,** 2397, 2398 (1973); Brown, Vander Jagt, Schleyer, Fort, and Watts, *J. Am. Chem. Soc.* **91,** 6848 (1969); Carey and Tremper, *J. Org. Chem.* **34,** 4 (1969); Brown and Takeuchi, *J. Am. Chem. Soc.* **88,** 5336 (1966), **90,** 2691, 5268 (1968); Takeuchi and Brown, **90,** 2693, 5270 (1968); Rei and Brown, *J. Am. Chem. Soc.* **88,** 5335 (1966); Brown, Chloupek, and Rei, *J. Am. Chem. Soc.* **86,** 1248 (1964).

[136] The presence of hydride shifts (p. 980) under solvolysis conditions has complicated the interpretation of the data.

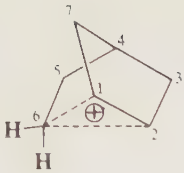
[137] Olah, Liang, Mateescu, and Riemenschneider, *J. Am. Chem. Soc.* **95,** 8698 (1973).

[138] Olah, White, DeMember, Commeyras, and Lui, *J. Am. Chem. Soc.* **92,** 4627 (1970); Olah, *J. Am. Chem. Soc.* **94,** 808 (1972); *Acc. Chem. Res.* **9,** 41–52 (1976).

[138a] Fong, *J. Am. Chem. Soc.* **96,** 7638 (1974); Kramer, *Adv. Phys. Org. Chem.* **11,** 177–224 (1975).



Nortricyclane



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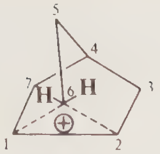

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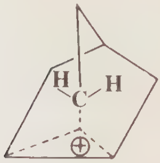
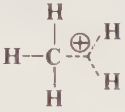


71

ion is drawn as in **70**. Almost all the positive charge resides on C-1 and C-2 and very little on the bridging carbon C-6. Because this means that C-6 is essentially tetrahedral, Olah has suggested[139] that a still better representation is **71**, which involves a two-electron, three-center



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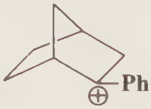


73

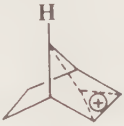
bond similar to the bonding found in the methanonium ion CH_5^+ (**72**)[140] (see p. 532). By measuring the rate of reaction of the stable (at low temperatures) 2-norbornyl cation with H_2 and

$$R^+ + H_2 \longrightarrow RH + H^+$$

comparing this with the rate for other cations, Hogeveen has concluded that the 2-norbornyl cation (which is of course a secondary cation) is almost as stable as typical tertiary cations (e.g., *t*-butyl, methylcyclohexyl) and much more stable than typical secondary cations (e.g., cyclopentyl, isopropyl).[141]

The spectra of other norbornyl cations have also been investigated under these conditions. Spectra of the tertiary 2-methyl- and 2-ethylnorbornyl cations show less delocalization,[142] and the 2-phenylnorbornyl cation (**73**) is essentially classical,[143] as are the 2-methoxy-[144] and 2-chloronorbornyl cations.[145] We may recall (p. 156) that methoxy and halo groups also stabilize a positive charge.

Note that in the 7-norbornenyl cation (**26**) there is also a corner-protonated cyclopropane ring. The similarity of the nmr spectra of **26** and **70** shows that in **26** also there is very little charge on the bridging carbon, which means that **26a** contributes very little to the hybrid; thus the structure is better represented as **74** rather than as **26d**.[145a]



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[139] Olah, Ref. 138.

[140] For discussions of pentacoordinated cations, see Olah, *Chem. Technol.* **1,** 566–573 (1971); *Chem. Br.* **8,** 281–287 (1972); Ref. 138.

[141] Hogeveen and Gaasbeek, *Recl. Trav. Chim. Pays-Bas* **88,** 719 (1969); Hogeveen, *Recl. Trav. Chim. Pays-Bas* **89,** 74 (1970). See also Solomon and Field, *J. Am. Chem. Soc.* **98,** 1567 (1976).

[142] Olah, DeMember, Lui, and White, *J. Am. Chem. Soc.* **91,** 3958 (1969).

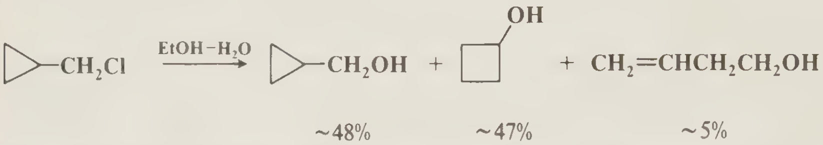
[143] Olah and Liang, *J. Am. Chem. Soc.* **96,** 195 (1974); Olah, White, DeMember, Commeyras, and Lui, Ref. 138; Farnum and Mehta, *J. Am. Chem. Soc.* **91,** 3256 (1969); Ref. 142. See also Schleyer, Kleinfelter, and Richey, *J. Am. Chem. Soc.* **85,** 479 (1963); Farnum and Wolf, *J. Am. Chem. Soc.* **96,** 5166 (1974).

[144] Nickon and Lin, *J. Am. Chem. Soc.* **91,** 6861 (1969).

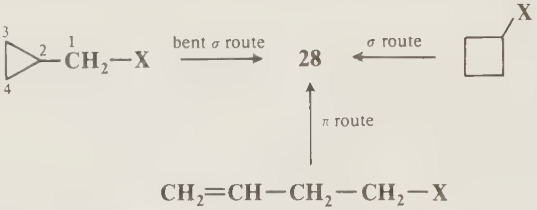
[145] Fry and Farnham, *J. Org. Chem.* **34,** 2314 (1969).

[145a] Olah and Liang, *J. Am. Chem. Soc.* **97,** 6803 (1975). See also Ref. 138.

b. *The cyclopropylmethyl system.* Apart from the 2-norbornyl system, the greatest amount of effort in the search for C—C participation has been devoted to the cyclopropylmethyl system.[146] It has long been known that cyclopropylmethyl substrates solvolyze with abnormally high rates, and that the products often include not only unrearranged cyclopropylmethyl but also cyclobutyl and homoallylic compounds. An example is:[147]

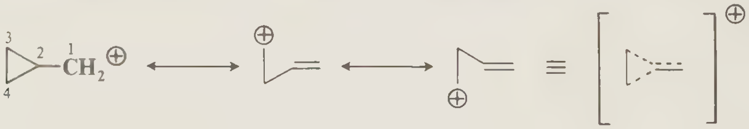


Cyclobutyl substrates also solvolyze abnormally rapidly and give similar products. Furthermore, when the reactions are carried out with labeled substrates, considerable, though not complete, scrambling is observed. For these reasons it has been suggested that a common intermediate (some kind of nonclassical intermediate, e.g., **28**, p. 285) is present in these cases. This could then be obtained by three routes:



In recent years much work has been devoted to the study of these systems, and it is apparent that matters are not so simple. Though there is much that is still not completely understood, some conclusions can be drawn.

i. In solvolysis of simple primary cyclopropylmethyl systems the rate is enhanced because of participation by the σ bonds of the ring. The ion which forms initially is an unrearranged cyclopropylmethyl cation[148] which is *symmetrically* stabilized; that is, both the 2,3 and the 2,4 σ bonds help to stabilize the positive charge. We have already seen (p. 155) that a cyclopropyl group stabilizes an adjacent positive charge even better than a phenyl group. One way of representing the structure of this cation is as shown in **75**. Among the evidence that **75** is a symmetrical



75

ion is that substitution of one or more methyl groups in the 3 and 4 positions increases the rate of solvolysis of cyclopropylcarbinyl 3,5-dinitrobenzoates by approximately a factor of 10 for *each* methyl group.[149] As we saw on p. 287, if only one of the σ bonds (say the 2,3 bond) stabilizes the cation, then methyl substitution at the 3 position should increase the rate, and a second methyl group at the 3 position should increase it still more, but a second methyl group at the 4 position should have little effect.[150] However, in bicyclic systems where there may be geometrical constraints, there is evidence that the cyclopropylmethyl cations formed are stabilized by the 2,3 or the 2,4 bond but not by both.

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[146] For reviews, see, in Olah and Schleyer, Ref. 76, vol. 3, 1972, the articles by Richey, pp. 1201–1294, and by Wiberg, Hess, and Ashe, pp. 1295-1345; Hanack and Schneider, *Fortschr. Chem. Forsch.* **8**, 554–607 (1967); *Angew. Chem. Int. Ed. Engl.* **6**, 666–677 (1967) [*Angew. Chem.* **79**, 709-720]; Sarel, Yovell, and Sarel-Imber, *Angew. Chem. Int. Ed. Engl.* **7**, 577–588 (1968) [*Angew. Chem.* **80**, 592–603].

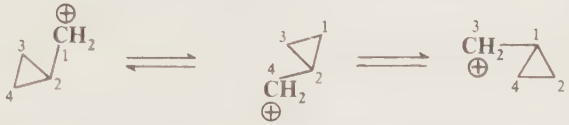
[147] Roberts and Mazur, *J. Am. Chem. Soc.* **73**, 2509 (1951).

[148] Wiberg and Ashe, *J. Am. Chem. Soc.* **90**, 63 (1968).

[149] Schleyer and Van Dine, *J. Am. Chem. Soc.* **88**, 2321 (1966).

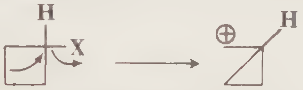
ii. The most stable geometry of simple cyclopropylmethyl cations is the bisected one shown on p. 156. There is much evidence that in systems where this geometry cannot be obtained, solvolysis is greatly slowed.[151]

iii. Once a cyclopropylmethyl cation is formed, it can rearrange to two other cyclopropylmethyl cations:



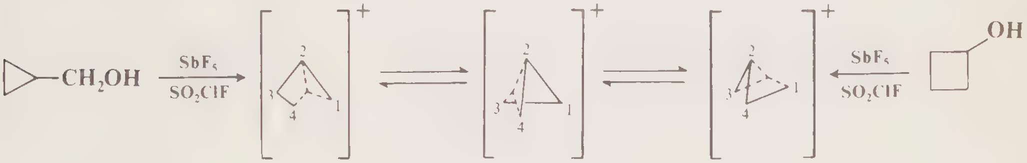
This rearrangement, which accounts for the scrambling found, is completely stereospecific.[152] The rearrangements probably take place through a nonplanar cyclobutyl cation intermediate or transition state. The formation of cyclobutyl and homoallylic products from a cyclopropylmethyl cation is also completely stereospecific. These products may arise by direct attack of the nucleophile on **75**, or on the cyclobutyl cation intermediate or transition state.[152] A planar cyclobutyl cation is ruled out in both cases, because it would be symmetrical and the stereospecificity would be lost.

iv. The rate enhancement in the solvolysis of secondary cyclobutyl substrates is probably caused by participation by a σ bond leading directly to **75**, which accounts for the fact that solvolysis of



cyclobutyl and of cyclopropylmethyl substrates often gives similar product mixtures. There is no evidence which requires that cyclobutyl cations be intermediates in most secondary systems. An exception is the 3-ethoxycyclobutyl cation which does form in solvolysis of 3-ethoxycyclobutyl tosylates and in deamination of the corresponding amine.[153] In this case there may be participation by the ethoxy group. However, tertiary cyclobutyl cations can be solvolysis intermediates.

v. The unsubstituted cyclopropylmethyl cation has been generated in super-acid solutions at low temperatures, where it has been represented as existing as an equilibrium mixture of three equivalent unsymmetrical cations, shown as **76**, **77**, and **78**.[154] In **76** there is a two-electron, three-center bond (p. 297) in which C-1 bridges the C-2, C-4 bond (or, equivalently, C-4 bridges the



76 **77** **78**

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[150] For a summary of additional evidence for the symmetrical nature of cyclopropylmethyl cations, see Wiberg, Hess, and Ashe, Ref. 146, pp. 1300–1303.

[151] For example, see Ree and Martin, *J. Am. Chem. Soc.* **92**, 1660 (1970); Rhodes and DiFate, *J. Am. Chem. Soc.* **94**, 7582 (1972). See, however, Brown and Peters, *J. Am. Chem. Soc.* **97**, 1927 (1975).

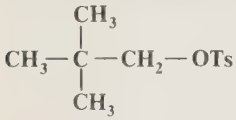
[152] Wiberg and Szeimies, *J. Am. Chem. Soc.* **90**, 4195 (1968), **92**, 571 (1970); Majerski and Schleyer, *J. Am. Chem. Soc.* **93**, 665 (1971).

[153] Lillien, *Chem. Commun.* 1009 (1968); Wiberg and Nelson, *Tetrahedron Lett.* 4385 (1969).

[154] Olah, Jeuell, Kelly, and Porter, *J. Am. Chem. Soc.* **94**, 146 (1972). See, however, Hehre and Hiberty, *J. Am. Chem. Soc.* **96**, 302 (1974); Kelly and Brown, *J. Am. Chem. Soc.* **97**, 3897 (1975).

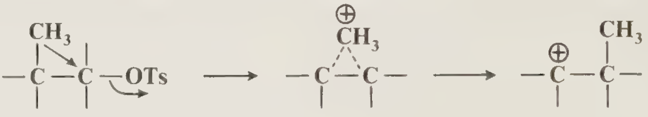
C-1, C-2 bond); in **77** and **78** there is analogous bridging. Evidence for this structure comes from proton and ^{13}C nmr spectra which show that C-1, C-3, and C-4 are completely equivalent (^{13}C chemical shift, 138; for C-2 it is 85), and that the six protons connected to these three atoms exist as two sets. One set is made up of the three equivalent protons at $\delta = 4.21$, and the other of the three equivalent protons at $\delta = 4.64$. The fact that the same mixture of cyclopropylmethyl cations is generated whether one starts with cyclopropylmethyl or cyclobutyl substrates is evidence that secondary cyclobutyl cations are much less stable than primary cyclopropylmethyl cations, which was also implicit in the results of the solvolytic studies. However, the tertiary cation 1-phenylcyclobutyl is stable at low temperatures in super-acid solutions.[154]

c. *Methyl as a neighboring group.* Both the 2-norbornyl and cyclopropylmethyl systems contain a σ bond which is geometrically constrained to be in a particularly favorable position for participation as a neighboring group. However, there have been a number of investigations to determine whether a C—C bond can lend anchimeric assistance even in a simple open-chain compound such as neopentyl tosylate (**79**). On solvolysis, neopentyl systems undergo almost exclusive rearrangement, and **80** must lie on the reaction path, but the two questions which have been asked are: (1) Is the departure of the leaving group concerted with the formation of the CH_3—C bond (that is, does the methyl participate)? (2) Is **80** an intermediate or only a transition state? There is no clear answer to the first question. Though evidence has been presented that under some conditions the methyl group in the neopentyl system does indeed participate,[155] other investigations have failed to find such participation.[156] As to the second question, evidence that **80** is an intermediate is that small amounts of cyclopropanes (10 to 15%) can be isolated in these reactions.[157] **80** is a protonated cyclopropane and would give a cyclopropane on loss of a proton.[158] This of course does not answer question 1 since even if **80** is an intermediate, it is possible that the leaving group departs first and then the CH_3—C bond forms. In an effort to isolate a species which would have the structure **80**, the dimethyl-*t*-butylcarbonium ion was prepared in super-acid solutions at low temperatures.[159] However, proton and ^{13}C nmr, as well as Raman spectra, showed this to be a pair of rapidly equilibrating open ions. Of course, **81** must

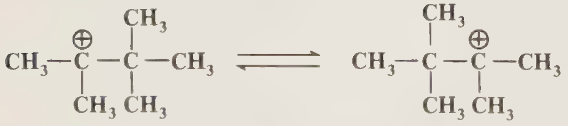


$CH_3-C(CH_3)_2-CH_2-OTs$

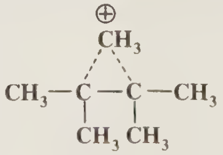
79



80



$(CH_3)_2\overset{\oplus}{C}-C(CH_3)_3 \rightleftharpoons (CH_3)_3C-\overset{\oplus}{C}(CH_3)_2$



81

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[155] For example, see Dauben and Chitwood, *J. Am. Chem. Soc.* **90**, 6876 (1968).

[156] For example, see Schubert and Henson, *J. Am. Chem. Soc.* **93**, 6299 (1971).

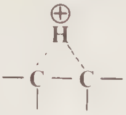
[157] Skell and Starer, *J. Am. Chem. Soc.* **82**, 2971 (1960); Silver, *J. Am. Chem. Soc.* **82**, 2971 (1960); Friedman and Bayless, *J. Am. Chem. Soc.* **91**, 1790 (1969); Friedman, Jurewicz, and Bayless, *J. Am. Chem. Soc.* **91**, 1795 (1969); Friedman and Jurewicz, *J. Am. Chem. Soc.* **91**, 1800, 1803 (1969); Dupuy, Hudson, and Karam, *Tetrahedron Lett.* 3193 (1971); Silver and Meek, *Tetrahedron Lett.* 3579 (1971); Dupuy and Hudson, *J. Chem. Soc., Perkin Trans. 2* 1715 (1972). See also Meek, Martin, Nadworny, and Silver, *J. Org. Chem.* **41**, 323 (1976).

[158] For a further discussion of protonated cyclopropanes, see pp. 693, 967.

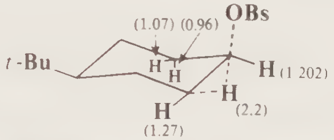
[159] Olah and White, *J. Am. Chem. Soc.* **91**, 5801 (1969); Olah, Comisarow, and Kim, *J. Am. Chem. Soc.* **91**, 1458 (1969); Olah, DeMember, Commeyras, and Bribes, *J. Am. Chem. Soc.* **93**, 459 (1971).

lie on the reaction path connecting the two open ions, but it is evidently only a transition state.

5. *Hydrogen as a neighboring group.* The questions relating to hydrogen are similar to those relating to methyl. There is no question that hydride can migrate, but the two questions are: (1) Does the hydrogen participate in the departure of the leaving group? (2) Is **82** an intermediate or only a transition state? Evidence that a β-hydrogen can participate comes from isotope-effect studies.[160] Solvolysis was carried out on *cis*-4-*t*-butylcyclohexyl brosylate substituted with deuterium in the α-position or in one or more of the β-positions.[161] In this compound, the large *t*-butyl group forces the brosylate group to be in the axial position. The isotope effect of one of the β-hydrogens, an axial one, was much greater than that of a hydrogen at any other position, even the other axial β-hydrogen. This indicates that this hydrogen participates in the transition state:

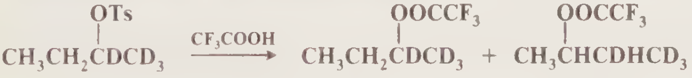


82



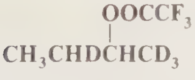
The two axial β-hydrogens are equivalent, but only one gives rise to a large isotope effect when substituted for by deuterium. This was determined by calculations using isotope-effect data from mono- and polydeuterated substrates. The isotope effect (k_H/k_D) at each position is indicated on the diagram.[162] There is also evidence that a hydrogen can participate from a more distant position if the geometry is suitable.[163]

Evidence that **82** can be an intermediate in solvolysis reactions comes from a study of the solvolysis in trifluoroacetic acid of deuterated *sec*-butyl tosylate **83**. In this solvent of very low nucleophilic power, the products were an equimolar mixture of **84** and **85**,[164] but *no* **86** or **87** was found. If this reaction did not involve neighboring hydrogen at all (pure S_N2 or S_N1), the



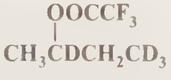
$$\underset{\textbf{83}}{CH_3CH_2\overset{OTs}{\overset{|}{C}}DCD_3} \xrightarrow{CF_3COOH} \underset{\textbf{84}}{CH_3CH_2\overset{OOCCF_3}{\overset{|}{C}}DCD_3} + \underset{\textbf{85}}{CH_3\overset{OOCCF_3}{\overset{|}{C}}HCDHCD_3}$$

83 **84** **85**



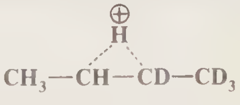
$$CH_3CHD\overset{OOCCF_3}{\overset{|}{C}}HCD_3$$

86



$$CH_3\overset{OOCCF_3}{\overset{|}{C}}DCH_2CD_3$$

87



88

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[160] For a discussion, see Scheppele, Ref. 124, pp. 531–532.

[161] Shiner and Jewett, *J. Am. Chem. Soc.* **87,** 1382 (1965).

[162] For other evidence for participation by β-hydrogen, see Pánková, Sicher, Tichý, and Whiting, *J. Chem. Soc. B* 365 (1968); Tichý, Hapala, and Sicher, *Tetrahedron Lett.* 3739 (1969); Myhre and Evans, *J. Am. Chem. Soc.* **91,** 5641 (1969); Inomoto, Robertson, and Sarkis, *Can. J. Chem* **47,** 4599 (1969); Shiner and Stoffer, *J. Am. Chem. Soc.* **92,** 3191 (1970); Krapcho and Johanson, *J. Org. Chem.* **36,** 146 (1971); Chuit, Felkin, Le Ny, Lion, and Prunier, *Tetrahedron* **28,** 4787 (1972).

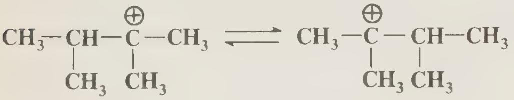
[163] Stéhelin, Lhomme, and Ourisson, *J. Am. Chem. Soc.* **93,** 1650 (1971); Stéhelin, Kanellias, and Ourisson, *J. Org. Chem.* **38,** 847, 851 (1973).

[164] Dannenberg, Weinwurzel, Dill, and Goldberg, *Tetrahedron Lett.* 1241 (1972).

product would be only **84**. On the other hand, if hydrogen does migrate, but only open cations are involved, then there should be an equilibrium among these four cations:

$$CH_3CH_2\overset{\oplus}{C}DCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}HCDHCD_3 \rightleftharpoons CH_3CD\overset{\oplus}{C}HCD_3 \rightleftharpoons CH_3\overset{\oplus}{C}DCH_2CD_3$$

leading not only to **84** and **85**, but also to **86** and **87**. The results are most easily compatible with the intermediacy of the bridged ion **88** which can then be attacked by the solvent equally at the 2 and 3 positions. Attempts to prepare **82** as a stable ion in super-acid solutions at low temperatures have not been successful. Spectral results indicate that both the dimethylisopropylcarbonium ion (**89**) and the 2-butyl cation (**90**) exist under these conditions as equilibrating pairs of ions,[159] where **82** is only a transition state.



$$CH_3-\underset{CH_3}{CH}-\overset{\oplus}{\underset{CH_3}{C}}-CH_3 \rightleftharpoons CH_3-\overset{\oplus}{\underset{CH_3}{C}}-\underset{CH_3}{CH}-CH_3$$

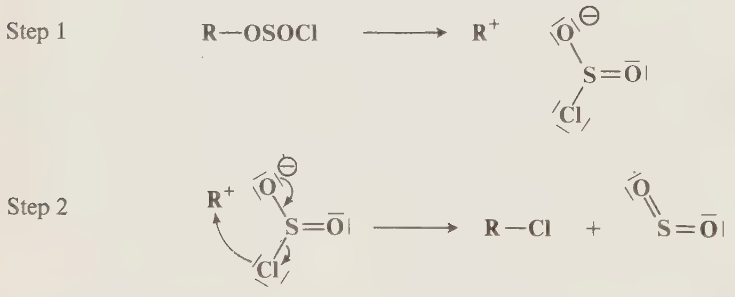
89

$$CH_3CH_2\overset{\oplus}{C}HCH_3 \rightleftharpoons CH_3\overset{\oplus}{C}HCH_2CH_3$$

90

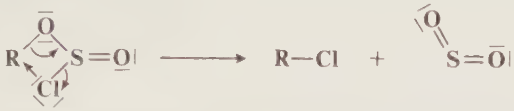
The SNi Mechanism

In a few reactions, nucleophilic substitution proceeds with retention of configuration even where there is no possibility of a neighboring-group effect. In the SNi mechanism (*substitution nucleophilic internal*) part of the leaving group must be able to attack the substrate, detaching itself from the rest of the leaving group in the process. The first step is the same as the very first step of the SN1 mechanism: dissociation into an intimate ion pair. But in the second step part of the leaving group attacks, necessarily from the front, since it is unable to get to the rear. This results in retention of configuration:

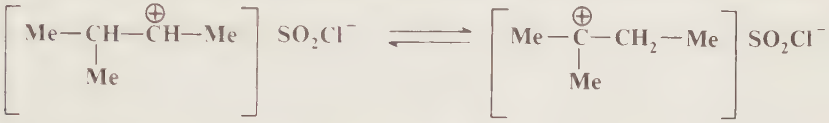


The example shown is the most important case of this mechanism yet discovered, since the reaction of alcohols with thionyl chloride to give alkyl halides usually proceeds in this way, with the first step in this case being $ROH + SOCl_2 \rightarrow ROSOCl$ (these alkyl chlorosulfites can be isolated).

Evidence for this mechanism is as follows: the addition of pyridine to the mixture of alcohol and thionyl chloride results in the formation of alkyl halide with *inverted* configuration. Inversion results because the pyridine reacts with ROSOCl to give $ROSO\overset{\oplus}{N}C_5H_5$ before anything further can take place. The Cl^- freed in this process now attacks from the rear. The reaction between alcohols and thionyl chloride is second order, which is predicted by this mechanism, but the decomposition by simple heating of ROSOCl is first order.[165] It was previously believed that the reaction was a one-step process:



However, the fact that $Me_2CHCHMeOSOCl$ gave, on heating, Me_2CClCH_2Me[166] indicated that an ion pair must have been present, since there is no other way to account for the rearrangement:

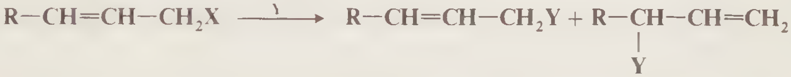


$$\left[\underset{\displaystyle Me}{\mathrm{Me{-}\underset{|}{C}H{-}\overset{\oplus}{C}H{-}Me}}\right] SO_2Cl^- \rightleftharpoons \left[\mathrm{Me{-}\underset{\underset{\displaystyle Me}{|}}{\overset{\oplus}{C}}{-}CH_2{-}Me}\right] SO_2Cl^-$$

The SNi mechanism is relatively rare, another example of it being the decomposition of ROCOCl (alkyl chloroformates) into RCl and CO_2.[167]

Nucleophilic Substitution at an Allylic Carbon. Allylic Rearrangements[168]

Allylic substrates undergo nucleophilic substitution reactions especially rapidly (see p. 318), but we discuss them in a separate section because they are usually accompanied by a certain kind of rearrangement known as an *allylic rearrangement* or an *allylic shift*. When allylic substrates are treated with nucleophiles under SN1 conditions, two products are usually obtained: the normal one and a rearranged one.



$$R{-}CH{=}CH{-}CH_2X \xrightarrow{Y} R{-}CH{=}CH{-}CH_2Y + R{-}\underset{\underset{\displaystyle Y}{|}}{CH}{-}CH{=}CH_2$$

Two products are formed because an allylic type of carbonium ion is a resonance hybrid

$$R{-}CH{=}CH{-}CH_2^{\oplus} \longleftrightarrow R{-}\overset{\oplus}{C}H{-}CH{=}CH_2$$

so that C-1 and C-3 each carry a partial positive charge, and both are attacked by Y. Of course an allylic rearrangement is undetectable in the case of symmetrical allylic carbonium ions, as in the case where R = H, unless isotopic labeling is used. This mechanism has been called the SN1′ mechanism.

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[165] Lewis and Boozer, *J. Am. Chem. Soc.* **74**, 308 (1952).

[166] Lee and Finlayson, *Can. J. Chem.* **39**, 260 (1961); Lee, Clayton, Lee, and Finlayson, *Tetrahedron* **18**, 1395 (1962).

[167] Lewis and Herndon, *J. Am. Chem. Soc.* **83**, 1955 (1961); Lewis, Herndon, and Duffey, *J. Am. Chem. Soc.* **83**, 1959 (1961); Lewis and Witte, *J. Chem. Soc. B* 1198 (1968). For other examples, see Hart and Elia, *J. Am. Chem. Soc.* **83**, 985 (1961); Stevens, Munk, Ash, and Elliott, *J. Am. Chem. Soc.* **85**, 3390 (1963); Stevens, Dittmer, and Kovacs, *J. Am. Chem. Soc.* **85**, 3394 (1963); Kice, Scriven, Koubek, and Barnes, *J. Am. Chem. Soc.* **92**, 5608 (1970); Kice and Hanson, *J. Org. Chem.* **38**, 1410 (1973); Prokipcak and Breckles, *Can. J. Chem.* **50**, 1770 (1972); Cohen and Solash, *Tetrahedron Lett.* 2513 (1973).

[168] For reviews, see DeWolfe, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 417–437, American Elsevier Publishing Company, New York, 1973; DeWolfe and Young, *Chem. Rev.* **56**, 753–901 (1956); Young, *J. Chem. Educ.* **39**, 455–460 (1962); de la Mare, in Mayo, "Molecular Rearrangements," vol. 1, pp. 27–110, Interscience Publishers, New York, 1963; in Patai, "The Chemistry of Alkenes," Interscience Publishers, New York, 1964, the sections by Mackenzie, pp. 436–453, and DeWolfe and Young, pp. 681–738.

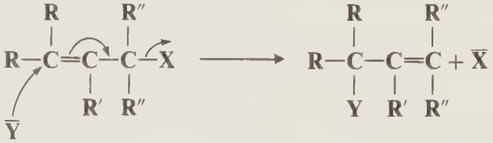
As with other SN1 reactions, there is clear evidence that SN1′ reactions may involve ion pairs. If the intermediate attacked by the nucleophile is a completely free carbonium ion, then, say,

$$\underset{\textbf{91}}{CH_3CH{=}CHCH_2Cl} \qquad \text{and} \qquad \underset{\textbf{92}}{CH_3CHClCH{=}CH_2}$$

should give the same mixture of alcohols when reacting with hydroxide ion, since the carbonium ion from each should be the same. When treated with 0.8 *N* aqueous NaOH at 25°C, **91** gave 60% $CH_3CH{=}CHCH_2OH$ and 40% $CH_3CHOHCH{=}CH_2$, while **92** gave these products in yields of 38% and 62%, respectively.[169] This phenomenon is called the *product spread.* In this case, and in most others, the product spread is in the direction of the starting compound. With increasing polarity of solvent, the product spread decreases and in some cases is entirely absent. It is evident that in such cases the high polarity of the solvent stabilizes completely free carbonium ions. There is other evidence for the intervention of ion pairs in many of these reactions. When $H_2C{=}CHCMe_2Cl$ was treated with acetic acid, both acetates were obtained, but also some $ClCH_2CH{=}CMe_2$,[170] and the isomerization was faster than the acetate formation. This could not have arisen from a completely free Cl^- returning to the carbonium ion, since the rate of formation of the rearranged chloride was unaffected by the addition of external Cl^-. All these facts indicate that the first step in these reactions is the formation of an unsymmetrical intimate ion pair which undergoes a considerable amount of internal return and in which the counterion remains close to the carbon from which it departed. Thus, **91** and **92,** for example, give rise to two *different* intimate ion pairs. The field of the anion polarizes the allylic cation, making the nearby carbon atom more electrophilic, so that it has a greater chance of attracting the nucleophile.[171] In fact, the first published suggestion[170] that ion pairs are involved in any nucleophilic substitution arose from work done on an allylic system.

Nucleophilic substitution at an allylic carbon may also take place by an SN2 mechanism, in which case *no allylic rearrangement usually takes place.* However, allylic rearrangements can also take place under SN2 conditions, and the following mechanism has been proposed, in which the nucleophile attacks at the γ-carbon rather than at the usual position:

SN2′ mechanism



This mechanism is an allylic rearrangement which is second order; it usually comes about where SN2 conditions hold but where α substitution sterically retards the normal SN2 mechanism. There are thus few well-established cases of the SN2′ mechanism on substrates of the type $C{=}C{-}CH_2X$, while compounds of the form $C{=}C{-}CR_2X$ give the SN2′ rearrangement almost exclusively when they give bimolecular reactions at all.[172] The SN2′ mechanism as shown above involves the simultaneous movement of three pairs of electrons. Bordwell has contended that there is no evidence that requires that this bond making and bond breaking be in fact concerted,[173] and that a true SN2′ mechanism is a myth. However, questions involving the timing of bond-making and bond-breaking steps can be studied by isotope effects. Evidence for a true SN2′ mechanism in the reaction between diethylamine and 3-chloro-1-butene was obtained by the principle of successive-labeling isotope effects.[174] According to this principle, isotope effects should be observed for the molecule successively labeled at each position which undergoes a bond change in going from the reactants to the transition state. If the SN2′ mechanism is correct in this case,

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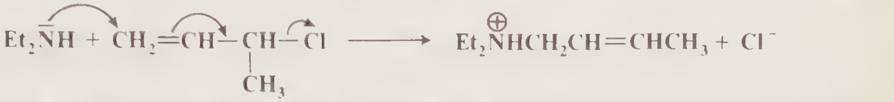
[169] DeWolfe and Young, Ref. 168, give several dozen such examples.

[170] Young, Winstein, and Goering, *J. Am. Chem. Soc.* **73,** 1958 (1951).

[171] For additional evidence for the involvement of ion pairs in SN1′ reactions, see Goering and Linsay, *J. Am. Chem. Soc.* **91,** 7435 (1969); Goering, Koermer, and Linsay, *J. Am. Chem. Soc.* **93,** 1230 (1971); d'Incan and Viout, *Bull. Soc. Chim. Fr.* 3312 (1971); Ref. 46.

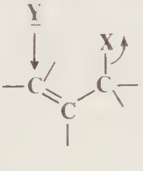
[172] For a discussion of this mechanism, with examples, see DeWolfe and Young, Ref. 168, pp. 769–784.

[173] Bordwell and Schexnayder, *J. Org. Chem.* **33,** 3240 (1968); Bordwell and Mecca, *J. Am. Chem. Soc.* **94,** 5829 (1972); Bordwell, *Acc. Chem. Res.* **3,** 281–290 (1970), pp. 282–285. See also de la Mare and Vernon, *J. Chem. Soc. B* 1699 (1971).

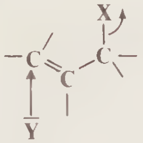


$$Et_2\overline{N}H + CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}Cl \longrightarrow Et_2\overset{\oplus}{N}HCH_2CH{=}CHCH_3 + Cl^-$$

then labeling at the nitrogen, the 1, 2, and 3 carbons, and the chlorine should all produce isotope effects. The nitrogen isotope effect was not studied, but labeling at the three carbons and at the chlorine produced an isotope effect in each instance. The stereochemistry of reactions generally



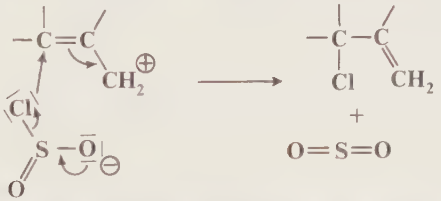
synfacial



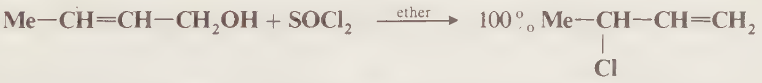
apofacial

considered to have SN2′ mechanisms has been investigated and is most often *synfacial*;[175] that is, the nucleophile enters from the same side as the leaving group departs.[176] However, *apofacial* reactions have also been reported.[177]

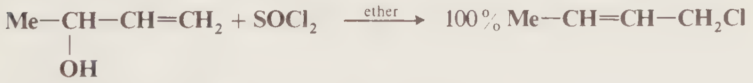
When a molecule has in an allylic position a leaving group capable of giving the SNi reaction, then it is possible for the nucleophile to attack at the γ-position instead of the α-position. This



is called the SNi′ mechanism and has been demonstrated on 2-buten-1-ol and 3-buten-2-ol.[178]



$$Me{-}CH{=}CH{-}CH_2OH + SOCl_2 \xrightarrow{\text{ether}} 100\%\ Me{-}CH{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}CH{=}CH_2$$



$$Me{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH{=}CH_2 + SOCl_2 \xrightarrow{\text{ether}} 100\%\ Me{-}CH{=}CH{-}CH_2Cl$$

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[174] Fry, *Pure Appl. Chem.* **8,** 409 (1964).

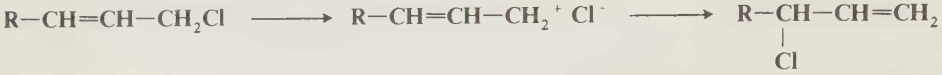
[175] Jefford, Sweeney, Hill, and Delay, *Helv. Chim. Acta* **54,** 1691 (1971).

[176] See for example, Stork and White, *J. Am. Chem. Soc.* **78,** 4609 (1956); Jefford, Mahajan, and Gunsher, *Tetrahedron* **24,** 2921 (1968); Jefford, Sweeney, and Delay, *Helv. Chim. Acta* **55,** 2214 (1972).

[177] Borden and Corey, *Tetrahedron Lett.* 313 (1969); Takahashi and Satoh, *Bull. Chem. Soc. Jpn.* **48,** 69 (1975); Staroscik and Rickborn, *J. Am. Chem. Soc.* **93,** 3046 (1971); Wieland and Johnson, *J. Am. Chem. Soc.* **93,** 3047 (1971). See also Liotta, *Tetrahedron Lett.* 523 (1975).

[178] Young, Ref. 168, p. 456. For other examples, see Pegolotti and Young, *J. Am. Chem. Soc.* **83,** 3251 (1961); Mark, *Tetrahedron Lett.* 281 (1962); Czernecki, Georgoulis, Labertrande, and Prévost, *Bull. Soc. Chim. Fr.* 3568 (1969); Lewis and Witte, Ref. 167.

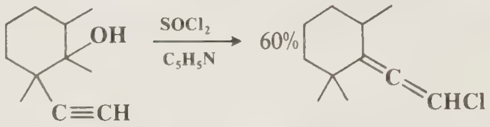
Ordinary allylic rearrangements (SN1′) or SN2′ mechanisms could not be expected to give 100% rearrangement in *both* cases. In the case shown, the nucleophile is only part of the leaving group, not the whole. But it is also possible to have reactions in which a simple leaving group, such as Cl, comes off to form an ion pair and then returns not to the position from whence it came but to the allylic position:



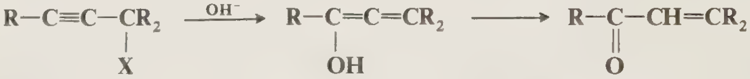
$$R{-}CH{=}CH{-}CH_2Cl \longrightarrow R{-}CH{=}CH{-}CH_2^{+}\ Cl^{-} \longrightarrow R{-}\underset{\displaystyle Cl}{\underset{|}{C}H}{-}CH{=}CH_2$$

Most SNi′ reactions are of this type.

Allylic rearrangements have also been demonstrated in propargyl systems, for example,[179]

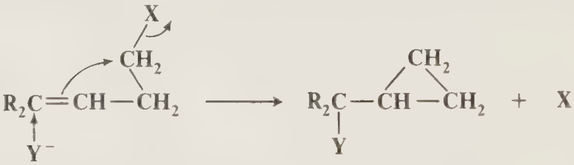


The product in this case is an allene,[180] but such shifts may also give triple-bond compounds or, if Y = OH, an enol will be obtained which will tautomerize to an α,β-unsaturated aldehyde or ketone.



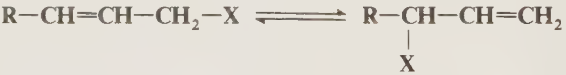
$$R{-}C{\equiv}C{-}\underset{\displaystyle X}{\underset{|}{C}}R_2 \xrightarrow{OH^-} R{-}C{=}C{=}\underset{\displaystyle OH}{\underset{|}{C}}R_2 \longrightarrow R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH{=}CR_2$$

When X = OH, this conversion of acetylenic alcohols to unsaturated aldehydes or ketones is called the *Meyer-Schuster rearrangement*.[181] An unusual type of "allylic shift" can occur in homoallylic systems where cyclopropyl rings may be formed, perhaps by an SN2′ type of mechanism:[182]



$$\underset{\displaystyle Y^-}{\underset{\uparrow}{R_2C}}{=}CH{-}CH_2{-}CH_2{-}X \longrightarrow \underset{\displaystyle Y}{\underset{|}{R_2C}}{-}\overset{CH_2}{CH{-}CH_2} + X^-$$

An allylic rearrangement in which the nucleophile is the same as the leaving group is an isomerization:[183]



$$R{-}CH{=}CH{-}CH_2{-}X \rightleftharpoons R{-}\underset{\displaystyle X}{\underset{|}{C}H}{-}CH{=}CH_2$$

This type of isomerization may proceed by any of the three mechanisms mentioned: SN1′, SN2′, or, as we have seen, SNi′. Examples are known where X = halide, OCOR, and OH (actually OH_2^+, the protonated OH group). It is of interest to examine the question of the direction of such isomerizations. When the reaction is permitted to proceed to equilibrium, the product will be thermodynamically controlled: the isomer of lower energy will predominate. Olefin stability increases with increasing alkyl substitution, so that where only alkyl groups are involved the more stable isomer will have the X on the less highly substituted carbon, e.g.,[184]

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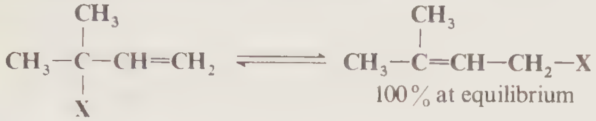
[179] Bhatia, Landor, and Landor, *J. Chem. Soc.* 24 (1959); Evans, Landor, and Smith, *J. Chem. Soc.* 1506 (1963).

[180] For reviews of such rearrangements, see Taylor, *Chem. Rev.* **67,** 317–359 (1967), pp. 324–328; Sandler and Karo, "Organic Functional Group Preparations," vol. 2, pp. 16–31, Academic Press, Inc., New York, 1971.

[181] For a review, see Swaminathan and Narayanan, *Chem. Rev.* **71,** 429–438 (1971).

[182] For examples, see Cope, Moon, and Peterson, *J. Am. Chem. Soc.* **84,** 1935 (1962); Hanack and Görler, *Chem. Ber.* **96,** 2121 (1963).

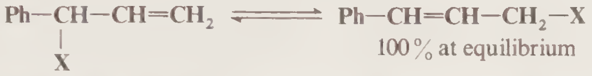
[183] For a review, see Braude, *Q. Rev., Chem. Soc.* **4,** 404–425 (1950).



$$CH_3-\overset{CH_3}{\underset{X}{C}}-CH=CH_2 \rightleftharpoons CH_3-\overset{CH_3}{C}=CH-CH_2-X$$

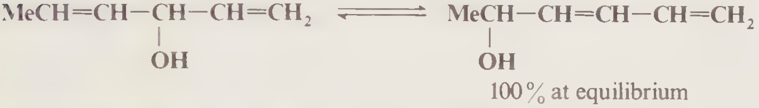
100% at equilibrium

If the double bond in one isomer can be in conjugation with an aromatic ring, a triple bond, another double bond, or a carbonyl group, then that isomer is more stable and will predominate at equilibrium, e.g.,[185]



$$Ph-\underset{X}{CH}-CH=CH_2 \rightleftharpoons Ph-CH=CH-CH_2-X$$

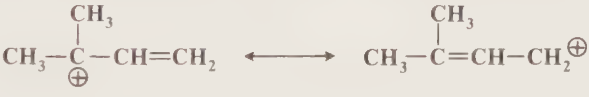
100% at equilibrium



$$MeCH=CH-\underset{OH}{CH}-CH=CH_2 \rightleftharpoons \underset{OH}{MeCH}-CH=CH-CH=CH_2$$

100% at equilibrium

It might be expected from this that, say, in an SN1′ reaction of $Me_2C{=}CHCH_2Cl$ with water, the predominant product would be the unrearranged $Me_2C{=}CHCH_2OH$ with only a smaller amount of the rearranged $Me_2COHCH{=}CH_2$. However, the main product here (85%) is the tertiary alcohol, although thermodynamically it is the less stable isomer. Equilibrium is not reached, and the product is kinetically controlled (see p. 194). In SN1′ reactions the thermodynamically less stable product is almost always formed in greater than the equilibrium proportion, because the relative rates of the two reactions are determined by the relative magnitudes of the positive charges on the two carbons. For example, in the case mentioned, **A** contributes more to the



$$CH_3-\overset{CH_3}{\underset{\oplus}{C}}-CH=CH_2 \longleftrightarrow CH_3-\overset{CH_3}{C}=CH-CH_2^{\oplus}$$

A **B**

resonance hybrid than **B** (because tertiary carbons are more stable than primary carbons), so that the charge on the tertiary carbon is greater than that on the primary carbon. However, whether one isomer or the other will predominate is usually not easy to predict in a given case. The solvent exerts a great effect. For example, the substrate mentioned gave 85% of the tertiary product when water was the solvent, but only 45% in acetic acid containing silver acetate. Increasing solvent polarity favors the formation of product resulting from attack at the more positive carbon. The existence of the product spread further complicates the picture.

Nucleophilic Substitution at an Aliphatic Trigonal Carbon.[186] The Tetrahedral Mechanism

All the mechanisms so far discussed take place at a saturated carbon atom. Nucleophilic substitution is also important at trigonal carbons, especially when the carbon is double-bonded to an oxygen, a sulfur, or a nitrogen. Nucleophilic substitution at vinyl carbons is considered in the next section; at aromatic carbons in Chapter 13.

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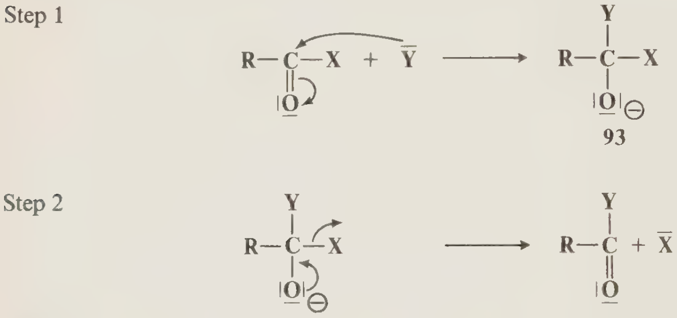
[184] Claisen, *J. Prakt. Chem.* **105**, 65 (1922).

[185] Pocker, *J. Chem. Soc.* 4318 (1958); Braude and Timmons, *J. Chem. Soc.* 2000, 2007 (1950).

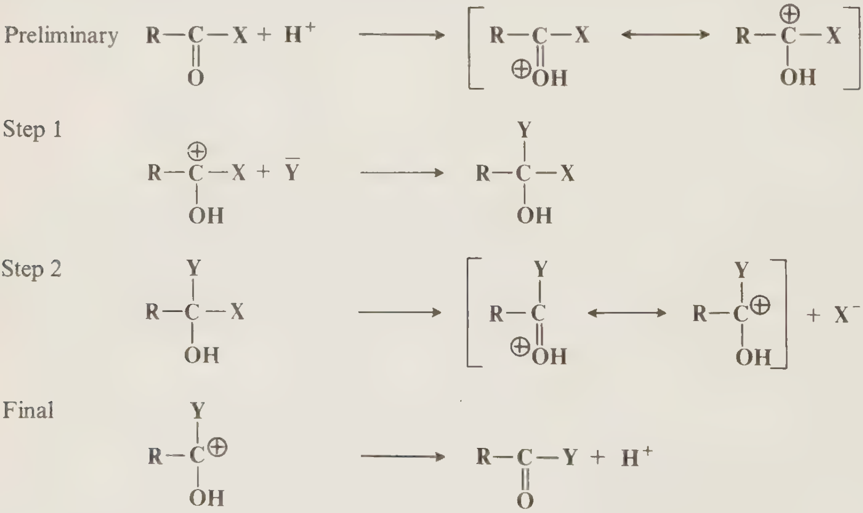
[186] For a review, see Satchell, *Q. Rev., Chem. Soc.* **17**, 160–203 (1963).

At a carbonyl group (or the corresponding nitrogen and sulfur analogs) substitution most often proceeds by a second-order mechanism, which in this book is called the *tetrahedral*[187] *mechanism.*[188] SN1 mechanisms, involving carbonium ions, are sometimes found with these substrates, especially with essentially ionic compounds such as $RCO^+ \ \ BF_4^-$, but the tetrahedral mechanism is far more prevalent. Although this mechanism displays second-order kinetics, it is not the same as the SN2 mechanism previously discussed. Simple SN2 mechanisms have seldom if ever been demonstrated for carbonyl substrates[189] (see, however, p. 355). In the tetrahedral mechanism, first Y attacks to give an intermediate containing both X and Y, and then X leaves. This sequence, impossible at a saturated carbon, is possible at an unsaturated one because the central carbon can release a pair of electrons to the oxygen and so preserve its octet:



93

When reactions are carried out in acid solution, there may be in addition a preliminary and a final step:



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[187] This mechanism has also been called the "addition-elimination mechanism," but in this book we limit this term to the type of mechanism shown on p. 311.

[188] For reviews of this mechanism, see Talbot, in Bamford and Tipper, Ref. 168, vol. 10, pp. 209-223, 1972; Jencks, "Catalysis in Chemistry and Enzymology," pp. 463-554, McGraw-Hill Book Company, New York, 1969; Satchell and Satchell, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 375-452, Interscience Publishers, New York, 1969; Johnson, *Adv. Phys. Org. Chem.* **5**, 237-330 (1967); Bender, *Chem. Rev.* **60**, 53-113 (1960).

[189] For example, see Kevill and Foss, *J. Am. Chem. Soc.* **91,** 5054 (1969); Haberfield and Trattner, *Chem. Commun.* 1481 (1971); Kevill, Daum, and Sapre, *J. Chem. Soc., Perkin Trans. 2* 963 (1975).

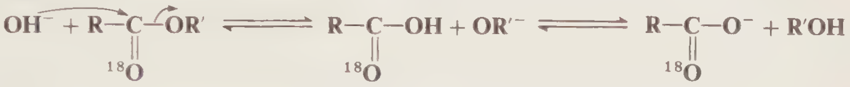
The hydrogen ion is a catalyst. The reaction rate is increased because it is easier for the nucleophile to attack the carbon when the electron density of the latter has been decreased.[190]

Evidence for the existence of the tetrahedral mechanism is as follows:

1. The kinetics are first order each in the substrate and in the nucleophile, as predicted by the mechanism.

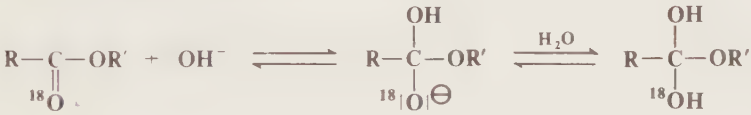
2. There is other kinetic evidence in accord with a tetrahedral intermediate. For example, the rate "constant" for the reaction between acetamide and hydroxylamine is not constant but decreases with increasing hydroxylamine concentration.[191] This is not a smooth decrease; there is a break in the curve. A straight line is followed at low hydroxylamine concentration and another straight line at high concentration. This means that the identity of the rate-determining step is changing. Obviously, this cannot happen if there is only one step: there must be two steps, and hence an intermediate. Similar kinetic behavior has been found in other cases as well,[192] in particular, plots of rate against pH are often bell-shaped.

3. Basic hydrolysis has been carried out on esters labeled with ^{18}O in the carbonyl group.[193] If this reaction proceeded by the normal SN2 mechanism, then all the ^{18}O would remain in the carbonyl group, even if, in an equilibrium process, some of the acid formed went back to the starting material:



$$\mathrm{OH^- + R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OR' \rightleftharpoons R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OH + OR'^- \rightleftharpoons R{-}\underset{\overset{\|}{^{18}O}}{C}{-}O^- + R'OH}$$

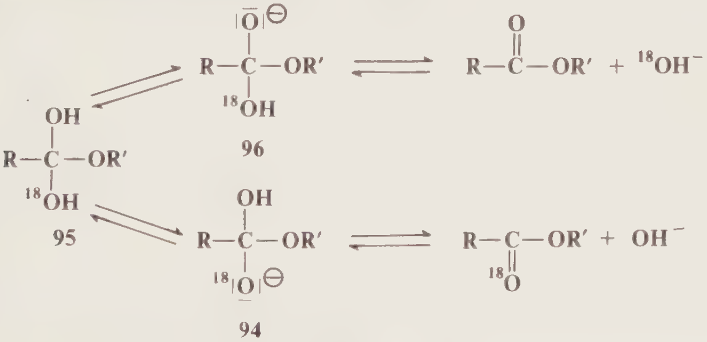
On the other hand, if the tetrahedral mechanism operates,



$$\mathrm{R{-}\underset{\overset{\|}{^{18}O}}{C}{-}OR' + OH^- \rightleftharpoons R{-}\overset{OH}{\underset{^{18}O^{\ominus}}{C}}{-}OR' \xrightarrow{H_2O} R{-}\overset{OH}{\underset{^{18}OH}{C}}{-}OR'}$$

94 95

then the intermediate **94**, by picking up a proton, becomes converted to the symmetrical intermediate **95**. In this intermediate the OH groups are equivalent, and (except for the small $^{18}O/^{16}O$ isotope effect) either one can lose a proton with equal facility:



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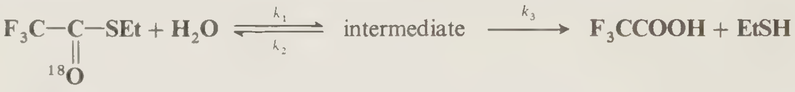
[190] For a discussion of general acid and base catalysis of reactions at a carbonyl group, see Jencks, *Chem. Rev.* **72**, 705–718 (1972).

[191] Jencks and Gilchrist, *J. Am. Chem. Soc.* **86**, 5616 (1964).

[192] Hand and Jencks, *J. Am. Chem. Soc.* **84**, 3505 (1962); Bruice and Fedor, *J. Am. Chem. Soc.* **86**, 4886 (1964); Johnson, *J. Am. Chem. Soc.* **86**, 3819 (1964); Fedor and Bruice, *J. Am. Chem. Soc.* **86**, 5697 (1964), **87**, 4138 (1965); Kevill and Johnson, *J. Am. Chem. Soc.* **87**, 928 (1965); Leinhard and Jencks, *J. Am. Chem. Soc.* **87**, 3855 (1965); Schowen, Jayaraman, and Kershner, *J. Am. Chem. Soc.* **88**, 3373 (1966).

[193] Bender, *J. Am. Chem. Soc.* **73**, 1626 (1951); Bender and Thomas, *J. Am. Chem. Soc.* **83**, 4183, 4189 (1961).

The intermediates **94** and **96** can now lose OR′ to give the acid (not shown in the equations given), or they can lose OH to regenerate the ester. If **94** goes back to ester, the ester will still be labeled, but if **96** reverts to ester, the ^{18}O will be lost. A test of the two possible mechanisms then is to stop the reaction before completion and to analyze the recovered ester for ^{18}O. This is just what was done by Bender, who found that, in alkaline hydrolysis of methyl, ethyl, and isopropyl benzoates, the esters had lost ^{18}O. A similar experiment carried out for acid-catalyzed hydrolysis of ethyl benzoate showed that here too the ester lost ^{18}O. However, alkaline hydrolysis of substituted benzyl benzoates showed *no* ^{18}O loss.[194] This result does not necessarily mean that no tetrahedral intermediate is involved in this case. If **94** and **96** do not revert to ester, but go entirely to acid, then no ^{18}O loss will be found even with a tetrahedral intermediate. In the case of benzyl benzoates this may very well be happening, because formation of the acid relieves steric strain. Even the experiments which *do* show ^{18}O loss do not *prove* the existence of the tetrahedral intermediate, since it is possible that ^{18}O is lost by some independent process not leading to ester hydrolysis. To deal with this possibility, Bender and Heck[195] measured the rate of ^{18}O loss in the hydrolysis of ethyl trifluorothioloacetate-^{18}O (**97**). This reaction had previously been shown[196] to involve an intermediate by the kinetic methods mentioned on p. 309. Bender and Heck showed that the rate of ^{18}O loss and the value of the partitioning ratio k_2/k_3 as determined by the oxygen exchange technique were exactly in accord with these values as previously determined by kinetic methods. Thus the original ^{18}O-exchange measurements showed that there is a tetrahedral species present, though not necessarily on the reaction path; while the kinetic experiments showed that there is some intermediate present, though not necessarily tetrahedral. However, the results of Bender and Heck demonstrate that there is a tetrahedral intermediate and that it lies on the reaction pathway.

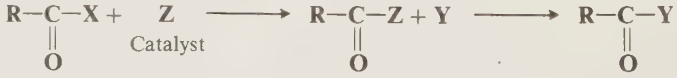


$$\mathrm{F_3C{-}\underset{\underset{^{18}O}{\|}}{C}{-}SEt + H_2O} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k_3} \mathrm{F_3CCOOH + EtSH}$$

97

4. In a few cases, tetrahedral intermediates have been isolated[197] or detected spectrally.[198]

Some nucleophilic substitutions at a carbonyl carbon are *catalyzed* by nucleophiles.[199] There occur, in effect, two tetrahedral mechanisms:



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}X} + \underset{\text{Catalyst}}{\mathrm{Z}} \longrightarrow \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}Z + Y} \longrightarrow \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}Y}$$

For an example, see page 348. When this happens internally, we have an example of a neighboring-group mechanism at a carbonyl carbon.[200] For example, the hydrolysis of phthalamic acid takes place as follows:

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[194] Bender, Matsui, Thomas, and Tobey, *J. Am. Chem. Soc.* **83**, 4193 (1961). See also Shain and Kirsch, *J. Am. Chem. Soc.* **90**, 5848 (1968).

[195] Bender and Heck, *J. Am. Chem. Soc.* **89**, 1211 (1967).

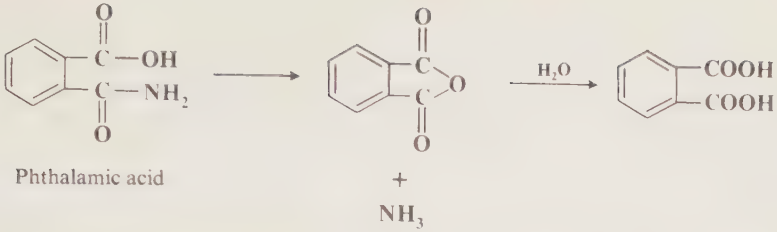
[196] Fedor and Bruice, *J. Am. Chem. Soc.* **87**, 4138 (1965).

[197] Rogers and Bruice, *J. Am. Chem. Soc.* **96**, 2481 (1974); Bender, Ref. 188, pp. 58–59.

[198] For example, see Robinson, *J. Am. Chem. Soc.* **92**, 3138 (1970); Fodor, Letourneau, and Mandava, *Can. J. Chem.* **48**, 1465 (1970); Fersht and Jencks, *J. Am. Chem. Soc.* **92**, 5432 (1970); Gravitz and Jencks, *J. Am. Chem. Soc.* **96**, 489, 499, 507 (1974); Fraenkel and Watson, *J. Am. Chem. Soc.* **97**, 231 (1975).

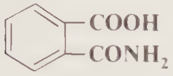
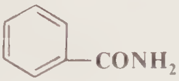
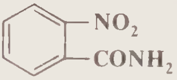
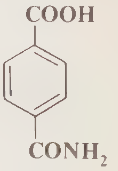
[199] For reviews of nucleophilic catalysis, see Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," pp. 147–179, John Wiley & Sons, New York, 1971; Jencks, Ref. 188, pp. 67–77; Johnson, Ref. 188, pp. 271–318.

[200] For reviews, see Kirby and Fersht, *Prog. Bioorg. Chem.* **1**, 1–82 (1971); Capon, *Essays Chem.* **3**, 127–156 (1972).



Phthalamic acid

Evidence comes from comparative rate studies.[201] Thus phthalamic acid was hydrolyzed about 10^5 times faster than benzamide ($PhCONH_2$) at about the same concentration of hydrogen ions. That this enhancement of rate was not caused by the resonance or field effects of COOH (an electron-withdrawing group) was shown by the fact that both *o*-nitrobenzamide and terephthalamic acid were hydrolyzed more slowly than benzamide:

Rate ratio: 10^5 1 0.1 Less than 1

Many other examples of neighboring-group participation at a carbonyl carbon have been reported.[202] It is likely that nucleophilic catalysis is involved in enzyme catalysis of ester hydrolysis.

The attack of a nucleophile on a carbonyl group may result in substitution or addition (Chapter 16), though the first step of each mechanism is the same. The principal factor which determines the product is the identity of the group X in RCOX. When X is alkyl or hydrogen, addition usually takes place. When X is halogen, OH, OCOR, NH_2, etc., the usual reaction is substitution.

Nucleophilic Substitution at a Vinyl Carbon[203]

Nucleophilic substitution at a vinyl carbon is difficult (see p. 317), but many examples are known. The most common mechanisms are the tetrahedral mechanism and the closely related *addition-elimination mechanism*. Both of these mechanisms are impossible at a saturated substrate. The addition-elimination mechanism has been demonstrated for the reaction between 1,1-dichloroethylene (**98**) and ArS^-, catalyzed by EtO^-.[204] The product was not the 1,1-dithiophenoxy compound **99**, but the "rearranged" compound **100**. Isolation of **101** and **102** showed that an addition-elimination mechanism had taken place. In the first step ArSH adds to the double bond (nucleophilic addition, p. 678) to give the saturated **101**. The second step is an E2 elimination

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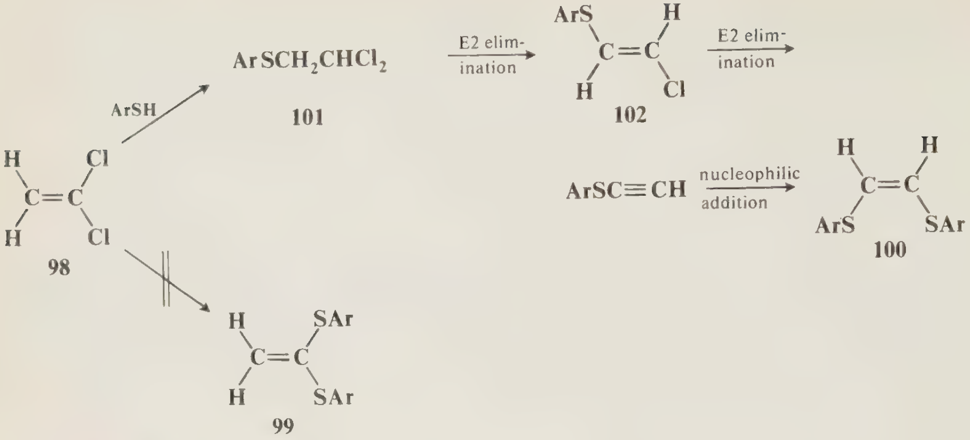
[201] Bender, Chow, and Chloupek, *J. Am. Chem. Soc.* **80,** 5380 (1958).

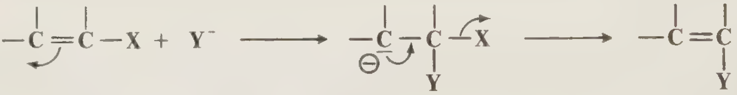
[202] For examples, see Bruice and Pandit, *J. Am. Chem. Soc.* **82,** 5858 (1960); Zimmering, Westhead, and Morawetz, *Biochim. Biophys. Acta* **25,** 376 (1957); Snell, Kwok, and Kim, *J. Am. Chem. Soc.* **89,** 6728 (1967); Burrows and Topping, *Chem. Commun.* 904 (1969), 1389 (1970); Kirby and Meyer, *J. Chem. Soc., Perkin Trans. 2* 1446 (1972); Kirby, McDonald, and Smith, *J. Chem. Soc., Perkin Trans. 2* 1495 (1974); Martin, Skovron, and Yiu, *J. Chem. Soc., Perkin Trans. 2* 125 (1974); Martin and Tan, *J. Chem. Soc., Perkin Trans. 2* 129 (1974).

[203] For reviews, see Rappoport, *Adv. Phys. Org. Chem.* **7,** 1–114 (1969); Modena, *Acc. Chem. Res.* **4,** 73–80 (1971); Patai and Rappoport, in Patai, "The Chemistry of Alkenes," pp. 525–546, Interscience Publishers, New York, 1964. The nomenclature in the first and third of these reviews differs from that used in this book. Rappoport and Patai use the term "addition-elimination" to refer to three mechanisms: those we call tetrahedral, SN2, and addition-elimination.

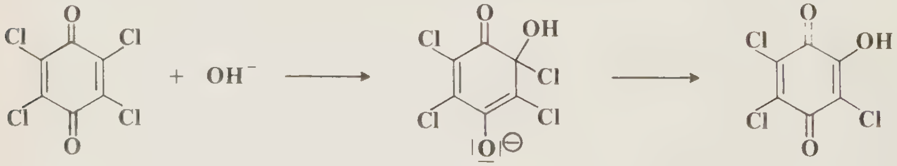
[204] Truce and Boudakian, *J. Am. Chem. Soc.* **78,** 2748 (1956).



reaction (p. 896) to give the alkene **102.** A second elimination and addition follow to give **100.** The tetrahedral mechanism, often also called addition-elimination (*Ad*N-*E*), takes place with much less facility than with carbonyl groups, since the negative charge of the intermediate must be borne by a carbon, which is less electronegative than oxygen, sulfur, or nitrogen:



Such an intermediate can also stabilize itself by combining with a positive species, and when it does, the reaction is nucleophilic addition to a C=C double bond (see Chapter 15). It is not surprising that with vinyl substrates addition and substitution often compete. For chloroquinones, where the charge is spread by resonance, tetrahedral intermediates have been isolated:[205]



Isolated

Since both the tetrahedral and addition-elimination mechanisms begin in the same way, it is usually difficult to tell them apart, and often no attempt is made to do so. The strongest kind of evidence for the addition-elimination sequence is the occurrence of a "rearrangement" (as in the conversion of **98** to **100**), but of course the mechanism could still take place even if no rearrangement is found. Evidence that a tetrahedral or an addition-elimination mechanism takes place in certain cases (as opposed, for example, to an SN1 or SN2 mechanism) is that the reaction rate increases when the leaving group is changed from Br or Cl to F (this is called the *element effect*).[206] This clearly demonstrates that the carbon-halogen bond does not break in the rate-determining step (as it would have to in both the SN1 and SN2 mechanisms), because fluorine is by far the poorest leaving group among the halogens in both the SN1 and SN2 reactions (p. 325). The rate is faster with fluorides in the cases cited, because the superior electron-withdrawing character of the fluorine makes the carbon of the C—F bond more positive and thus more susceptible to nucleophilic attack. However, there is evidence that the tetrahedral mechanism at a vinyl substrate can also take place with the second step being rate-determining.[207]

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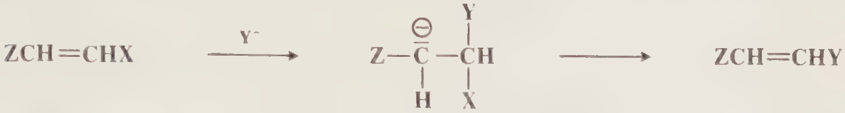
[205] Hancock, Morrell, and Rhom, *Tetrahedron Lett.* 987 (1962).
[206] Beltrame, Favini, Cattania, and Guella, *Gazz. Chim. Ital.* **98,** 380 (1968).

Ordinary vinylic substrates react very poorly if at all by these mechanisms, but substitution is greatly enhanced in substrates of the type ZCH=CHX, where Z is an electron-withdrawing group such as HCO, RCO,[208] EtOOC, $ArSO_2$, NC, F,[209] etc., since these β-groups stabilize the carbanion:



$$\mathrm{ZCH{=}CHX} \xrightarrow{Y^-} \mathrm{Z}-\underset{\mathrm{H}}{\overset{\ominus}{\bar{\mathrm{C}}}}-\underset{\mathrm{X}}{\overset{\mathrm{Y}}{\mathrm{C}}}\mathrm{H} \longrightarrow \mathrm{ZCH{=}CHY}$$

Many such examples are known. In most cases where the stereochemistry has been investigated, retention of configuration is observed.[210]

Vinyl substrates are in general very reluctant to undergo SN1 reactions, but they can be made to do so in two ways:[211] (1) By the use of an α-group which stabilizes the vinyl cation. For example, α-aryl vinyl halides $ArCBr{=}CR'_2$ have often been shown to give SN1 reactions.[212] SN1 reactions have also been demonstrated with other stabilizing groups: cyclopropyl,[213] vinyl,[214] and an adjacent double bond ($R_2C{=}C{=}CR'X$).[215] (2) Even without α stabilization, by the use of a very good leaving group, e.g., OSO_2CF_3 (triflate).[216] The stereochemical outcome of SN1 reactions at a vinyl substrate is often randomization;[217] that is, either a cis or a trans substrate gives a 1 : 1 mixture of cis and trans products, indicating that the vinyl cation is linear. Another indication that vinyl cations prefer to be linear is the fact that reactivity in cycloalkenyl systems decreases with decreasing ring size.[218] However, a linear vinyl cation need not give random

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[207] Rappoport, Ref. 203.

[208] For a review, see Rybinskaya, Nesmeyanov, and Kochetkov, *Russ. Chem. Rev.* **38**, 433–456 (1969).

[209] Sauvetre and Normant, *Bull. Soc. Chim. Fr.* 3202 (1972).

[210] Rappoport, Ref. 203, pp. 31–62.

[211] For reviews of the SN1 mechanism at a vinyl substrate, see Subramanian and Hanack, *J. Chem. Educ.* **52**, 80–86 (1975); Stang, *Prog. Phys. Org. Chem.* **10**, 205–325 (1973); Hanack, *Acc. Chem. Res.* **3**, 209–216 (1970); Modena and Tonellato, *Adv. Phys. Org. Chem.* **9**, 185–280 (1971), pp. 231–253, Grob, *Chimia* **25**, 87–91 (1971); Rappoport, Bässler, and Hanack, *J. Am. Chem. Soc.* **92**, 4985–4987 (1970).

[212] For example, see Grob and Cseh, *Helv. Chim. Acta* **47**, 194 (1964); Grob and Pfaendler, *Helv. Chim. Acta* **54**, 2060 (1971); Miller and Kaufman, *J. Am. Chem. Soc.* **90**, 7282 (1968); Rappoport and Gal, *J. Am. Chem. Soc.* **91**, 5246 (1969), *Tetrahedron Lett.* 3233 (1970), *J. Org. Chem.* **37**, 1174 (1972), *J. Chem. Soc., Perkin Trans. 2* 301 (1973); Rappoport and Kaspi, *J. Am. Chem. Soc.* **92**, 3220 (1970), **96**, 4518 (1974), *Tetrahedron Lett.* 4039 (1971), *J. Chem. Soc., Perkin Trans. 2* 1102 (1972); Rappoport and Apeloig, *J. Am. Chem. Soc.* **97**, 821, 836 (1975); Jones and Maness, *J. Am. Chem. Soc.* **92**, 5457 (1970); Derocque, Sundermann, Youssif, and Hanack, *Justus Liebigs Ann. Chem.* 419 (1973); Yates and Périé, *J. Org. Chem.* **39**, 1902 (1974).

[213] Sherrod and Bergman, *J. Am. Chem. Soc.* **91**, 2115 (1969), **93**, 1925 (1971); Kelsey and Bergman, *J. Am. Chem. Soc.* **92**, 238 (1970), **93**, 1941 (1971); Hanack and Bässler, *J. Am. Chem. Soc.* **91**, 2117 (1969); Heyd and Hanack, *Angew. Chem. Int. Ed. Engl.* **12**, 318 (1973) [*Angew. Chem.* **85**, 309]; Hanack, Bässler, Eymann, Heyd, and Kopp, *J. Am. Chem. Soc.* **96**, 6686 (1974).

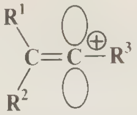
[214] Grob and Spaar, *Tetrahedron Lett.* 1439 (1969), *Helv. Chim. Acta* **53**, 2119 (1970).

[215] Schiavelli, Gilbert, Boynton, and Boswell, *J. Am. Chem. Soc.* **94**, 5061 (1972). See also Bässler and Hanack, *Tetrahedron Lett.* 2171 (1971).

[216] Stang and Summerville, *J. Am. Chem. Soc.* **91**, 4600 (1969); Martinez, Hanack, Summerville, Schleyer, and Stang, *Angew. Chem. Int. Engl.* **9**, 302 (1970) [*Angew. Chem.* **82**, 323]; Imhoff, Summerville, Schleyer, Martinez, Hanack, Dueber, and Stang, *J. Am. Chem. Soc.* **92**, 3802 (1970); Lamparter and Hanack, *Chem. Ber.* **105**, 3789 (1972), **106**, 3216 (1973); Clarke, Kelsey, and Bergman, *J. Am. Chem. Soc.* **94**, 3626 (1972); Clarke and Bergman, *J. Am. Chem. Soc.* **94**, 3627 (1972), **96**, 7934 (1974); Summerville and Schleyer, *J. Am. Chem. Soc.* **94**, 3629 (1972), **96**, 1110 (1974); Eckes, Subramanian, and Hanack, *Tetrahedron Lett.* 1967 (1973); Summerville, Senkler, Schleyer, Dueber, and Stang, *J. Am. Chem. Soc.* **96**, 1100 (1974). See also Jones and Miller, *J. Am. Chem. Soc.* **89**, 1960 (1967); Peterson and Indelicato, *J. Am. Chem. Soc.* **91**, 6194 (1969).

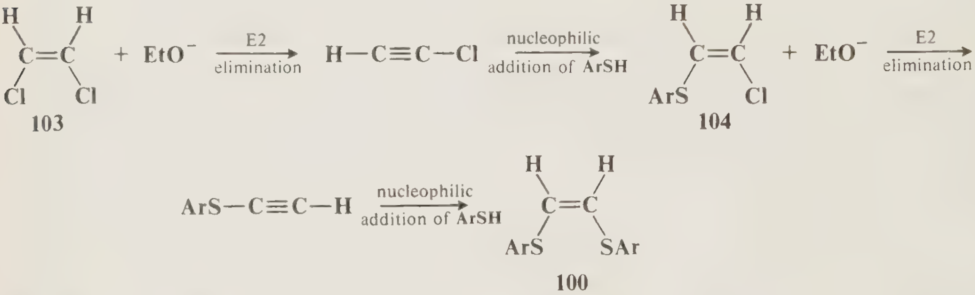
[217] Rappoport and Apeloig, *J. Am. Chem. Soc.* **91**, 6734 (1969); Kelsey and Bergman, Ref. 213.

[218] Pfeifer, Bahn, Schleyer, Bocher, Harding, Hummel, Hanack, and Stang, *J. Am. Chem. Soc.* **93**, 1513 (1971).



products.[219] The empty *p* orbital lies in the plane of the double bond, so entry of the nucleophile can be and often is influenced by the relative size of R^1 and R^2.[220] It must be emphasized that even where vinyl substrates do give S_N1 reactions, the rates are generally lower than those of the corresponding saturated compounds.

Besides the mechanisms already discussed, another mechanism, involving an *elimination-addition* sequence, has also been observed in vinyl systems (a similar mechanism is known for aromatic substrates, p. 588). An example of a reaction involving this mechanism is the reaction of 1,2-dichloroethane (**103**) with ArS^- and OEt^- to produce **100.** The mechanism may be formulated as:



The steps are the same as in the addition-elimination mechanism, but are in the reverse order. In the first step ethoxide ion causes E2 elimination to produce chloroacetylene. The E2 mechanism is stereoselective and proceeds rapidly when the hydrogen and halogen are trans, as they are in this case. In the second step the thiol adds to the acetylene by a nucleophilic addition mechanism to give **104.** This reaction is also stereoselective, with ArS and H adding from opposite sides (anti addition). Thus **104** still has a hydrogen trans to a halogen, and the two steps are repeated to give the cis product **100.** Evidence for this sequence[221] is as follows: (1) The reaction does not proceed without ethoxide ion, and the rate is dependent on the concentration of this ion and not on that of ArS^-. (2) *trans*-1,2-Dichloroethylene does not react under these conditions. There is no hydrogen trans to either chlorine, so that the rate of an E2 reaction is greatly reduced (**102** underwent elimination, though slowly, because strong conditions were used). (3) Under the same reaction conditions, chloroacetylene gave **104** and **100.** (4) **104** treated with ArS^- gave no reaction but, when EtO^- was added, **100** was obtained. It is interesting that the elimination-addition mechanism has even been shown to occur in five- and six-membered cyclic systems, where triple bonds are greatly strained.[222] Note that both the addition-elimination and elimination-addition sequences, as shown above, lead to overall retention of configuration, since in each case both addition and elimination are anti.

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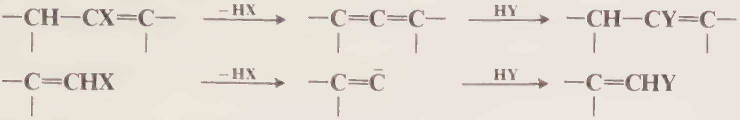
[219] For examples of inversion, see Clarke and Bergman, Ref. 216; Summerville and Schleyer, Ref. 216.

[220] Maroni, Melloni, and Modena, *J. Chem. Soc., Chem. Commun.* 857 (1972).

[221] Truce, Boudakian, Heine, and McManimie, *J. Am. Chem. Soc.* **78,** 2743 (1956); Flynn, Badiger, and Truce, *J. Org. Chem.* **28,** 2298 (1963).

[222] Montgomery, Scardiglia, and Roberts, *J. Am. Chem. Soc.* **87,** 1917 (1965); Montgomery and Applegate, *J. Am. Chem. Soc.* **89,** 2952 (1967); Montgomery, Clouse, Crelier, and Applegate, *J. Am. Chem. Soc.* **89,** 3453 (1967); Caubere and Brunet, *Tetrahedron* **27,** 3515 (1971); Bottini, Corson, Fitzgerald, and Frost, *Tetrahedron* **28,** 4883 (1972).

We have shown the elimination-addition sequence as operating through an acetylenic intermediate, but in some cases it can also take place with an allene- or a carbene-type intermediate:[223]



$$-\underset{|}{\text{CH}}-\text{CX}=\underset{|}{\text{C}}- \xrightarrow{-\text{HX}} -\underset{|}{\text{C}}=\text{C}=\underset{|}{\text{C}}- \xrightarrow{\text{HY}} -\underset{|}{\text{CH}}-\text{CY}=\underset{|}{\text{C}}-$$

$$-\underset{|}{\text{C}}=\text{CHX} \xrightarrow{-\text{HX}} -\underset{|}{\text{C}}=\bar{\text{C}} \xrightarrow{\text{HY}} -\underset{|}{\text{C}}=\text{CHY}$$

The elimination-addition sequence has also been demonstrated for certain reactions of saturated substrates, for example, $ArSO_2CH_2CH_2SO_2Ar$.[224] Treatment of this with ethoxide proceeds as follows:

$$\text{ArSO}_2\text{CH}_2\text{CH}_2\text{SO}_2\text{Ar} \xrightarrow[\text{E2 elimination}]{\text{EtO}} \text{ArSO}_2\text{CH}=\text{CH}_2 \xrightarrow[\text{addition}]{\text{EtO}} \text{ArSO}_2\text{CH}_2\text{CH}_2\text{OEt}$$

Mannich bases (see reaction **6-17**) of the type $RCOCH_2CH_2NR_2$ similarly undergo nucleophilic substitution by the elimination-addition mechanism.[225] The nucleophile replaces the NR_2 group.

The simple SN2 mechanism has never been demonstrated for vinyl substrates.[226]

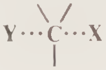
REACTIVITY

A large amount of work has been done on this subject. Many small effects have been examined. However, though a great deal is known, much is still poorly understood, and many results are anomalous and hard to explain. In this section only approximate generalizations are attempted.

The Effect of Substrate Structure

The effect on the reactivity of a change in substrate structure depends on the mechanism.

1. *Branching at the α- and β- carbons.* For the SN2 mechanism, branching at either the α- or the β-carbon decreases the rate. Tertiary systems seldom[227] react by the SN2 mechanism, and neopentyl systems react so slowly as to make such reactions, in general, synthetically useless.[228] Table 3 shows average relative rates for some alkyl substrates.[229] The reason for these low rates is almost certainly steric.[230] The transition state **1** is more crowded when larger groups are close to the central carbon. It was pointed out on page 304 that allylic substrates undergo SN2′ reactions only when there is branching at the α-position. Ordinary SN2 reactions are so slowed by this α branching that the nucleophile attacks the allylic position.



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[223] Rappoport, Ref. 203, pp. 91–98.

[224] Kader and Stirling, *J. Chem. Soc.* 3686 (1962).

[225] For an example, see Andrisano, Angeloni, De Maria, and Tramontini, *J. Chem. Soc. C* 2307 (1967).

[226] For a report of an "SN2" reaction at a vinyl carbon with retention of configuration, see Klein and Levene, *J. Am. Chem. Soc.* **94**, 2520 (1972). See also Stohrer, *Tetrahedron Lett.* 207 (1975).

[227] For a reported example, see Edwards and Grieco, *Can. J. Chem.* **52**, 3561 (1974).

[228] SN2 reactions on neopentyl tosylates have been conveniently carried out in the solvents hexamethylphosphoric triamide (HMPT) and dimethyl sulfoxide: Lewis, Gustafson, and Erman, *Tetrahedron Lett.* 401 (1967). Paquette and Phillips, *Tetrahedron Lett.* 4645 (1967); Stephenson, Solladié, and Mosher, *J. Am. Chem. Soc.* **94**, 4184 (1972); Anderson, Stephenson, and Mosher, *J. Am. Chem. Soc.* **96**, 3171 (1974).

[229] This table is from Streitwieser, Ref. 1, p. 13. Also see Table 2, Chapter 9 (p. 249).

[230] For a review on this point, see Ingold, *Q. Rev., Chem. Soc.* **11**, 1–14 (1957).

TABLE 3 Average relative SN2 rates for some alkyl substrates[229]

R	Relative rate
Methyl	30
Ethyl	1
Propyl	0.4
Butyl	0.4
Isopropyl	0.025
Isobutyl	0.03
Neopentyl	10^{-5}
Allyl	40
Benzyl	120

The tetrahedral mechanism for substitution at a carbonyl carbon is also slowed or blocked completely by α or β branching for similar reasons. For example, esters of the formula R_3CCOOR' cannot generally be hydrolyzed by the tetrahedral mechanism (see reaction **0-11**), nor can acids R_3CCOOH be easily esterified. Synthetic advantage can be taken of this fact, for example, when in a molecule containing two ester groups only the less hindered one is hydrolyzed.

For the SN1 mechanism, α branching increases the rate, as shown in Table 4.[231] We may explain this by the stability order of carbonium ions (tertiary > secondary > primary). Of course, the rates are not actually dependent on the stability of the carbonium ions, but on the difference in free energy between the starting compounds and the transition states, but we may use the Hammond postulate (p. 194) to make the assumption that the transition states resemble the carbonium ions and that anything (such as α branching) which lowers the free energy of the carbonium ions also lowers it for the transition states. For simple alkyl groups, the SN1 mechanism is important under all conditions only for tertiary substrates. As previously indicated (p. 279), secondary substrates generally react by the SN2 mechanism,[232] except that the SN1 mechanism may become important at high solvent polarities. Table 4 shows that isopropyl bromide reacts less than twice as fast as ethyl bromide in the relatively nonpolar 60% ethanol (compare this with the 10^4 ratio for *t*-butyl bromide, where the mechanism is certainly SN1), but in the more polar water the rate ratio is 11.6. The 2-adamantyl system is an exception: this is a secondary system which reacts by the SN1 mechanism because backside attack is hindered for steric reasons.[233] Because there is no SN2 component, this system provides an opportunity for comparing the pure SN1 reactivity of secondary and tertiary substrates. It has been found that substitution of a methyl group for the 2 α-hydrogen of 2-adamantyl substrates (thus changing a secondary to a tertiary system) increases solvolysis rates by a factor of about 10^8.[234] Simple primary substrates react by the SN2 mechanism (or with participation by neighboring alkyl or hydrogen)

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[231] These values are from Streitwieser, Ref. 1, p. 43, where values are also given for other conditions. Methyl bromide reacts faster than ethyl bromide (and in the case of 60% ethanol, isopropyl bromide) because some of it (probably most of it) reacts by the SN2 mechanism.

[232] See Raber and Harris, *J. Chem. Educ.* **49**, 60 (1972); Lambert, Putz, and Mixan, *J. Am. Chem. Soc.* **94**, 5132 (1972); Nordlander and McCrary, *J. Am. Chem. Soc.* **94**, 5133 (1972); Ref. 32.

[233] Fry, Harris, Bingham, and Schleyer, *J. Am. Chem. Soc.* **92**, 2540 (1970); Schleyer, Fry, Lam, and Lancelot, *J. Am. Chem. Soc.* **92,** 2542 (1970); Ref. 32.

[234] Fry, Engler, and Schleyer, *J. Am. Chem. Soc.* **94**, 4628 (1972). See also Gassman and Pascone, *J. Am. Chem. Soc.* **95**, 7801 (1973).

TABLE 4 Relative rates of solvolysis of RBr in two solvents[231]

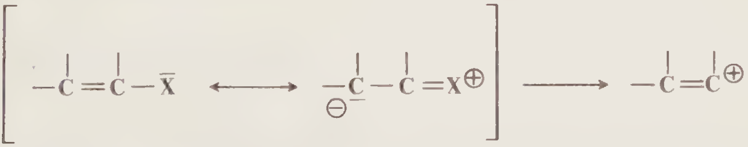
RBr substrate	In 60% ethanol at 55°C	In water at 50°C
MeBr	2.08	1.05
EtBr	1.00	1.00
iso-**PrBr**	1.78	11.6
t-**BuBr**	2.41×10^4	1.2×10^6

but not by the SN1 mechanism, even when solvolyzed in solvents of very low nucleophilicity, e.g., trifluoroacetic acid or trifluoroethanol.[235]

For some tertiary substrates, the rate of SN1 reaction is greatly increased by the relief of B strain in the formation of the carbonium ion (see p. 249). Except where B strain is involved, β branching has little effect on the SN1 mechanism, except that carbonium ions with β branching undergo rearrangements readily. Of course, isobutyl and neopentyl are primary substrates, and for this reason react very slowly by the SN1 mechanism, but not more slowly than the corresponding ethyl or propyl compounds.

To sum up, primary and secondary substrates generally react by the SN2 mechanism, and tertiary by the SN1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nucleophilic substitutions (wherever a β-hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value.

2. *Unsaturation at the α-carbon.* Vinyl, acetylenic,[236] and aryl substrates are very unreactive toward nucleophilic substitutions. For these systems both the SN1 and SN2 mechanisms are greatly slowed or stopped altogether. This may be attributed to several factors. The first of these is that sp^2 (and even more, sp) carbons have a higher electronegativity than sp^3 carbons and thus have a greater attraction for the electrons of the bond. As we have seen (p. 243), an sp—H bond has a higher acidity than an sp^3—H bond, with that of an sp^2—H bond in between. This is reasonable: the carbon retains the electrons when the proton is lost, and an sp carbon, which has the greatest hold on the electrons, loses the proton most easily. But in nucleophilic substitution, the leaving group *carries off* the electron pair, so that the situation is reversed, and it is the sp^3 carbon which loses the leaving group and the electron pair most easily. Another factor holds only where the leaving group has one or more unshared pairs (of course, most of them do) and applies only to SN1 reactions. When X has an unshared pair, the *molecule* is stabilized by resonance in which some of the electron density of the leaving group is transferred into the C—X bond, greatly strengthening it:



$$\left[-\overset{|}{C}=\overset{|}{C}-\bar{X} \longleftrightarrow \underset{\ominus}{-\overset{|}{C}}-\overset{|}{C}=X^{\oplus} \right] \longrightarrow -\overset{|}{C}=\overset{|}{C}^{\oplus}$$

This resonance is lost on going to the carbonium ion, and there is no resonance there for a compensating gain. It may be recalled (p. 23) that bond distances decrease with increasing *s*

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[235] Dafforn and Streitwieser, *Tetrahedron Lett.* 3159 (1970).

[236] For a summary of SN reactions which have been reported for acetylenic substrates, see Dickstein and Miller, *J. Org. Chem.* **37**, 2168, 2175 (1972).

TABLE 5 Relative rates for the SN1 reaction between ROTs and ethanol at 25°C[237]

Group	Relative rate
Et	0.26
iso-Pr	0.69
$CH_2{=}CHCH_2$	8.6
$PhCH_2$	100
Ph_2CH	$\sim 10^5$
Ph_3C	$\sim 10^{10}$

character. Thus the bond length for a vinyl or aryl C—Cl bond is 1.73 Å, as compared with 1.78 Å for a saturated C—Cl bond. Other things being equal, a shorter bond is a stronger bond.

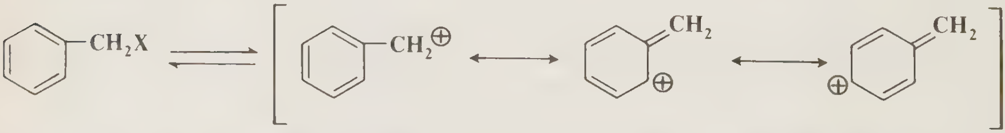
Both of the explanations given above relate to the stability of the original substrate. It is now known that vinyl cations are about as stable as simple alkyl cations (p. 157), so that lack of stability of vinyl cations cannot be the main reason for the greatly decreased SN1 reactivity of vinyl substrates. Of course we have seen (p. 313) that SN1 reactions at vinyl substrates can be accelerated by α-substituents which stabilize the cation, and that reactions by the tetrahedral mechanism can be accelerated by β-substituents which stabilize the carbanion. Also, reactions at vinyl substrates may in certain cases proceed by addition-elimination or elimination-addition sequences (pp. 311, 314).

In contrast to such systems, substrates of the type RCOX are usually much *more* reactive than the corresponding RCH_2X. Of course, the mechanism here is almost always the tetrahedral one, and there are three reasons for the enhanced reactivity of RCOX: (1) The carbonyl carbon has a sizable partial positive charge which makes it very attractive to nucleophiles. (2) In an SN2 reaction a σ bond must break in the rate-determining step, which requires more energy than the shift of a pair of π electrons, which is what happens in a tetrahedral mechanism. (3) A trigonal carbon offers less steric hindrance to a nucleophile than a tetrahedral carbon.

For reactivity in aryl systems, see Chapter 13.

3. *Unsaturation at the β-carbon.* SN1 rates are greatly increased when there is a double bond in the β-position, so that allylic and benzylic substrates react rapidly (Table 5).[237] This is because the carbonium ion is stabilized by resonance:

$$CH_2{=}CH{-}CH_2{-}X \rightleftharpoons \left[CH_2{=}CH{-}CH_2^{\oplus} \longleftrightarrow \overset{\oplus}{C}H_2{-}CH{=}CH_2\right]$$



In sharp contrast to the case of α unsaturation, where there was resonance stabilization of the molecule but not of the ion, here there is resonance stabilization of the ion but not of the molecule, since in the molecule the X group and the unsaturation are too far apart for resonance interaction. As shown in Table 5, a second and a third phenyl group increase the rate still more, because these carbonium ions are more stable yet. It should be remembered that, with allylic systems, allylic rearrangements are possible.

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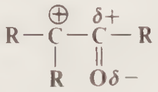
[237] Streitwieser, Ref. 1, p. 75. Actually, the figures for Ph_2CHOTs and Ph_3COTs are estimated from the general reactivity of these substrates. Solvolysis rates in ethanol have not been measured for these compounds.

In general, SN1 rates at an allylic substrate are increased by any substituent in the 1 or 3 position which can stabilize the carbonium ion by resonance or hyperconjugation.[238] Among these are alkyl, aryl, and halo groups.

SN2 rates for allylic and benzylic systems are also increased (see Table 3), probably owing to resonance possibilities in the transition state. Triple bonds in the β position (in propargyl systems) have about the same effect as double bonds.[239] Alkyl, aryl, halo, and cyano groups, among others, in the 3 position of allylic substrates increase SN2 rates, owing to increased resonance in the transition state, but alkyl and halo groups in the 1 position decrease the rates, because of steric hindrance.

4. *α substitution.* Compounds of the formula ZCH_2X, where Z = RO, RS, or R_2N, undergo SN1 reactions very rapidly,[240] because of the increased resonance in the carbonium ion. These groups have an unshared pair on an atom directly attached to the positive carbon, which greatly stabilizes the carbonium ion (p. 156). The field effects of these groups would be expected to decrease SN1 rates (see section 6, p. 320), so that the resonance effect is far more important.

When Z in ZCH_2X is RCO, HCO, ROCO, NH_2CO, or NC, SN1 rates are decreased compared to CH_3X, owing to the electron-withdrawing effects of these groups. Furthermore, carbonium ions with an α-CO or CN group[241] are greatly destabilized because of the partial positive charge on the adjacent carbon (**105**). However, the presence in the α-position of one of these groups *increases* SN2 rates, an example being α-chloroacetophenone which reacts with KI in acetone at 75 C about 32,000 times faster than *n*-butyl chloride.[242] A number of reasons[243] have been suggested for this, among them that the transition state is stabilized by simultaneous overlap of the nucleophile with the central carbon and the carbonyl carbon (**106**), and that the CO group polarizes the nucleophile as it approaches, making the incoming end of the nucleophile more negative and hence more nucleophilic. Another possibility is that the CO oxygen or CN nitrogen lends anchimeric assistance.[244] When Z is SOR or SO_2R (e.g., α-halo sulfoxides and sulfones), nucleophilic substitution is retarded.[245] The SN1 mechanism is slowed by the electron-withdrawing effect of the SOR or SO_2R group, and the SN2 mechanism presumably by the steric effect.



$$\mathrm{R}-\underset{\mathrm{R}}{\overset{\oplus}{\mathrm{C}}}-\underset{\mathrm{O}\delta-}{\overset{\delta+}{\mathrm{C}}}-\mathrm{R}$$

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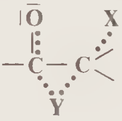

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5. *β substitution.* For compounds of the type ZCH_2CH_2X, where Z is any of the groups listed in the previous section as well as halogen or phenyl, SN1 rates are lower than for unsubstituted systems, because the resonance effects mentioned in section 4 are absent, but the field effects are still there, though smaller. These groups in the β-position do not have much effect on SN2 rates unless they behave as neighboring groups and enhance the rate through anchimeric assistance, or unless their size causes the rates to decrease for steric reasons.[246]

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[238] For discussions of the relative reactivities of different allylic substrates, see de la Mare, in Mayo, Ref. 168, vol. 1, pp. 42–47, 58–62, Interscience Publishers, New York, 1963; DeWolfe and Young, in Patai, Ref. 203, pp. 683–688, 695–697, Interscience Publishers, New York, 1964.

[239] Hatch and Chiola, *J. Am. Chem. Soc.* **73**, 360 (1951); Jacobs and Brill, *J. Am. Chem. Soc.* **75**, 1314 (1953).

[240] For a review of the reactions of α-haloamines, sulfides, and ethers, see Gross and Höft, *Angew. Chem. Int. Ed. Engl.* **6**, 335–355 (1967) [*Angew. Chem.* **79**, 358–378]. For a review restricted to α-halo ethers, see Summers, *Chem. Rev.* **55**, 301–353 (1955), pp. 319–333.

[241] For a review of such carbonium ions, see Charpentier-Morize, *Bull. Soc. Chim. Fr.* 343–351 (1974).

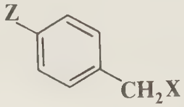
[242] Bordwell and Brannen, *J. Am. Chem. Soc.* **86**, 4645 (1964). For some other examples, see Conant, Kirner, and Hussey, *J. Am. Chem. Soc.* **47**, 488 (1925); Sisti and Lowell, *Can. J. Chem.* **42**, 1896 (1964).

[243] For a discussion, see Thorpe and Warkentin, *Can. J. Chem.* **51**, 927 (1973).

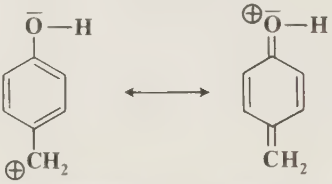
[244] For evidence favoring this possibility, see Masuike, Furukawa, and Oae, *Bull. Chem. Soc. Jpn.* **44**, 448 (1971).

[245] Bordwell and Jarvis, *J. Org. Chem.* **33**, 1182 (1968); Loeppky and Chang, *Tetrahedron Lett.* 5415 (1968); Cinquini, Landini, and Maia, *J. Chem. Soc., Chem. Commun.* 734 (1972).

6. *The effect of electron-donating and -withdrawing groups.* If substitution rates of a series of compounds



are measured, it is possible to study the electronic effects of groups Z on the reaction. Steric effects of Z are minimized or eliminated, because Z is so far from the reaction site. For SN1 reactions electron-withdrawing Z decrease the rate and electron-donating Z increase it, because the latter decrease the energy of the transition state (and of the carbonium ion) by spreading the positive charge, e.g.,

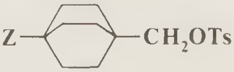


while electron-withdrawing groups concentrate the charge. The Hammett σ-ρ relationship (see p. 252) correlates fairly successfully the rates of many of these reactions (with σ^+ instead of σ). ρ values are generally about -4, which is to be expected for a reaction where a positive charge is created in the transition state.

For SN2 reactions no such simple correlations are found.[247] In this mechanism bond breaking is about as important as bond making in the rate-determining step, and substituents have an effect on both processes, often in opposite directions.

For Z = alkyl, the Baker-Nathan order (p. 70) is usually observed both for SN1 and SN2 reactions.

In para-substituted benzyl systems, steric effects have been removed, but resonance and field effects are still present. However, Holtz and Stock studied a system which removes not only steric effects but also resonance effects. This is the 4-substituted bicyclo[2.2.2]octylmethyl tosylate system (**107**).[248] In this system steric effects are completely absent, owing to the rigidity of the molecules, and only field effects operate. By this means Holtz and Stock showed that electron-withdrawing groups increase the rate of SN2 reactions. This can be ascribed to stabilization of the transition state by withdrawal of some of the electron density.



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For substrates which react by the tetrahedral mechanism, electron-withdrawing groups increase the rate and electron-donating groups decrease it.

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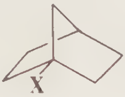
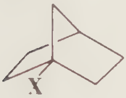
[246] See for example, Okamoto, Kita, Araki, and Shingu, *Bull. Chem. Soc. Jpn.* **40**, 1913 (1967).

[247] See Sugden and Willis, *J. Chem. Soc.* 1360 (1951); Baker and Nathan, *J. Chem. Soc.* 840 (1935); Hayami, Tanaka, Kurabayashi, Kotani, and Kaji, *Bull. Chem. Soc. Jpn.* **44**, 3091 (1971).

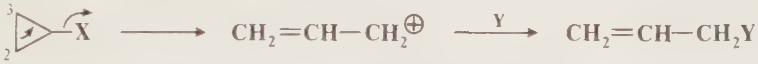
[248] Holtz and Stock, *J. Am. Chem. Soc.* **87**, 2404 (1965).

TABLE 6 List of groups in approximately descending order of reactivity toward SN1 and SN2 reactions

Z is RCO, HCO, ROCO, NH_2CO, NC, or a similar group

SN1 reactivity	SN2 reactivity
Ar_3CX	Ar_3CX
Ar_2CHX	Ar_2CHX
$ROCH_2X$, $RSCH_2X$, R_2NCH_2X	$ArCH_2X$
R_3CX	ZCH_2X
$ArCH_2X$	$-\overset{\vert}{C}=\overset{\vert}{C}CH_2X$
$-\overset{\vert}{C}=\overset{\vert}{C}CH_2X$	$RCH_2X \approx RCHDX \approx RCHDCH_2X$
R_2CHX	R_2CHX
$RCH_2X \approx R_3CCH_2X$	R_3CX
$RCHDX$	ZCH_2CH_2X
$RCHDCH_2X$	R_3CCH_2X
ZCH_2X	$-\overset{\vert}{C}=\overset{\vert}{C}X$
ZCH_2CH_2X	ArX
$-\overset{\vert}{C}=\overset{\vert}{C}X$	
ArX	
	

7. *Cyclic substrates.* Cyclopropyl substrates are extremely resistant to nucleophilic attack (p. 250). When such attack does take place, the result is generally not normal substitution (though exceptions are known[249]) but ring opening:[250]



There is much evidence that the ring opening is concerted with the departure of the leaving group[251] (as in the similar case of cyclobutyl substrates, p. 299), from which we can conclude that, if the 2,3 bond of the cyclopropane ring did not assist, the rates would be lower still. It has been estimated[252] that without this assistance the rates of these already slow reactions would be further reduced by a factor of 10^4 to 10^7. For a discussion of the stereochemistry of the ring opening, see p. 1034. For larger rings, we have seen (p. 250) that, because of I strain, cyclohexyl substrates solvolyze slower than analogous compounds in which the leaving group is attached to a ring of 5 or of from 7 to 11 members.

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[249] For example, see Kirmse and Schütte, *J. Am. Chem. Soc.* **89**, 1284 (1967); Landgrebe and Becker, *J. Am. Chem. Soc.* **89**, 2505 (1967); Howell and Jewett, *J. Am. Chem. Soc.* **93**, 798 (1971); Ledlie and Nelson, *Tetrahedron Lett.* 1175 (1969).

[250] Roberts and Chambers, *J. Am. Chem. Soc.* **73**, 5034 (1951); DePuy, Schnack, and Hausser, *J. Am. Chem. Soc.* **88**, 3343 (1966).

[251] For example, see Schleyer, Van Dine, Schöllkopf, and Paust, *J. Am. Chem. Soc.* **88**, 2868 (1966); Jefford and Medary, *Tetrahedron* **23**, 4123 (1967); Jefford and Wojnarowski, *Tetrahedron* **25**, 2089 (1969); Hausser and Uchic, *J. Org. Chem.* **37**, 4087 (1972); DePuy, Schnack, and Hausser, Ref. 250.

[252] Schleyer, Sliwinski, Van Dine, Schöllkopf, Paust, and Fellenberger, *J. Am. Chem. Soc.* **94**, 125 (1972); Sliwinski, Su, and Schleyer, *J. Am. Chem. Soc.* **94**, 133 (1972).

8. *Bridgeheads.* Nucleophilic substitution at bridgeheads is impossible or very slow, except that SN1 reactions can take place readily when the rings are large enough (pp. 268, 272).

9. *Deuterium substitution.* α and β secondary isotope effects affect the rate in various ways (p. 206). The measurement of α secondary isotope effects provides a means of distinguishing between SN1 and SN2 mechanisms, since for SN2 reactions the values range from 0.95 to 1.06 per α-D, while for SN1 reactions the values are higher.[33] This method is especially good, because it provides the minimum of perturbation of the system under study: changing from α-H to α-D hardly affects the reaction, while other probes, such as changing a substituent or the polarity of the solvent, may have a much more complex effect.

Table 6 is an approximate listing of groups in order of SN1 and SN2 reactivity.

The Effect of the Attacking Nucleophile[253]

Any species which has an unshared pair (i.e., any Lewis base) may be a nucleophile, whether it is neutral or has a negative charge. The rates of SN1 reactions are independent of the identity of the nucleophile, since it does not appear in the rate-determining step.[254] This may be illustrated by the effect of changing the nucleophile from H_2O to OH^- for a primary and a tertiary substrate. For methyl bromide, which reacts by an SN2 mechanism, the rate is multiplied by more than 5000 by the change to the more powerful nucleophile OH^-, but for *t*-butyl bromide, which reacts by an SN1 mechanism, the rate is unaffected.[255] A change in nucleophile may, however, change the *product* of an SN1 reaction. Thus solvolysis of benzyl tosylate in methanol gives benzyl methyl ether (the nucleophile is the solvent methanol). If the more powerful nucleophile Br^- is added, the rate is unchanged, but the product is now benzyl bromide.

For SN2 reactions there are four main principles which govern the effect of the nucleophile on the rate, though the nucleophilicity order is not invariant but depends on substrate, solvent, leaving group, etc.

1. A nucleophile with a negative charge is always a more powerful nucleophile than its conjugate acid (assuming the latter is also a nucleophile). Thus OH^- is more powerful than H_2O, NH_2^- more powerful than NH_3, etc. See the example given above.

2. In comparing nucleophiles whose attacking atom is in the same row of the periodic table, nucleophilicity is roughly in order of basicity, though basicity is thermodynamically controlled and nucleophilicity is kinetically controlled. So an approximate order of nucleophilicity is $NH_2^- > RO^- > OH^- > R_2NH > ArO^- > NH_3 >$ pyridine $> F^- > H_2O > ClO_4^-$, and another is $R_3C^- > R_2N^- > RO^- > F^-$ (see Table 1 in Chapter 8, p. 227). This type of correlation works best when the structures of the nucleophiles being compared are similar, as with a set of substituted phenoxides.[256]

3. Going down the periodic table, nucleophilicity increases, though basicity decreases. Thus the usual order of halide nucleophilicity is $I^- > Br^- > Cl^- > F^-$ (though as we shall see below, this order is solvent-dependent). Similarly, any sulfur nucleophile is more powerful than its oxygen analog, and the same is true for phosphorus versus nitrogen. The principal reason for this distinction between basicity and nucleophilic power is that the smaller negatively charged nucleophiles are more solvated by the usual polar solvents; that is, because the negative charge of Cl^- is more concentrated than the charge of I^-, the former is more tightly surrounded by a shell of solvent molecules which constitute a barrier between it and the substrate. This is most important for protic polar solvents in which the solvent may hydrogen-bond to small nucleophiles. Evidence for this is that many nucleophilic substitutions with small negatively charged nucleophiles are much more rapid in aprotic polar solvents than in protic ones[257] and that, in dimethylformamide, an aprotic solvent, the order of nucleophilicity was $Cl^- > Br^- > I^-$.[258] Another experiment was the use of $Bu_4N^+\ X^-$ and LiX as nucleophiles in acetone, where X^- was a halide ion. The halide ion in the former salt is much less associated than in LiX. The relative rates with LiX were Cl^-, 1; Br^-, 5.7; I^-, 6.2, which is in the normal order, while with $Bu_4N^+\ X^-$, where X^- is much freer, the relative rates were Cl^-, 68; Br^-, 18; I^-, 3.7.[259] In a further experiment halide ions were allowed to react with the molten salt $(n\text{-}C_5H_{11})_4N^+\ X^-$ at 180°C in the absence of a solvent.[260] Under these conditions, where the ions are unsolvated and unassociated, the relative rates were Cl^-, 620; Br^-, 7.7; I^-, 1. Further evidence that differences in the solvation of the nucleophile is the major cause of the nucleophilicity order comes from a study of ^{37}Cl ^{35}Cl isotope effects in reactions of RCl with nucleophiles RO^- and RS^-.[261]

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[253] For reviews, see Hudson, in Klopman, "Chemical Reactivity and Reaction Paths," pp. 167–252, John Wiley & Sons, New York, 1974; Bunnett, *Annu. Rev. Phys. Chem.* **14**, 271–290 (1963); and Edwards and Pearson, *J. Am. Chem. Soc.* **84**, 16 (1962).

[254] It is, however, possible to measure the rates of reaction of nucleophiles with fairly stable carbonium ions: see Ritchie, *Acc. Chem. Res.* **5**, 348–354 (1972); Ritchie and Virtanen, *J. Am. Chem. Soc.* **95**, 1882 (1973).

[255] Bateman, Cooper, Hughes, and Ingold, *J. Chem. Soc.* 925 (1940).

[256] Within such a series, linear relationships can often be established between nucleophilic rates and p*K* values: see for example, Jokinen, Luukkonen, Ruostesuo, Virtanen, and Koskikallio, *Acta Chem. Scand.* **25**, 3367 (1971).

However, solvation is not the entire answer since, even for *uncharged* nucleophiles, nucleophilicity increases going down a column in the periodic table, These nucleophiles are not so greatly solvated, and changes in solvent do not greatly affect their nucleophilicity.[262] Even with the charged nucleophiles ArO^- and ArS^-, changes in solvent did not affect the order. To explain these cases we may use the principle of hard and soft acids and bases (p. 237).[263] The proton is a hard acid, but an alkyl substrate (which may be considered to act as a Lewis acid toward the nucleophile considered as a base) is a good deal softer. According to the principle given on p. 238, we may then expect the alkyl group to prefer softer nucleophiles than the proton does. Thus the larger, more polarizable (softer) nucleophiles have a greater (relative) attraction toward an alkyl carbon than toward a proton. Another way of looking at this is that the more polarizable the nucleophile, the more easily the electron cloud is distorted, and thus large nucleophiles can actually bring a greater degree of electron density to the substrate than the small nucleophiles whose electron clouds are more tightly held.

4. The freer the nucleophile, the greater the rate.[263a] We have already seen one instance of this.[259] Another is that the rate of attack by $(EtOOC)_2CBu^-\ Na^+$ in benzene was increased by the addition of substances (for example, 1,2-dimethoxyethane, adipamide) which specifically solvated the Na^+ and thus left the anion freer.[264] In a nonpolar solvent such as benzene, salts such as $(EtOOC)_2CBu^-\ Na^+$ usually exist as ion-pair aggregations of molecular weights of at least 10,000.

[257] Parker, *J. Chem. Soc.* 1328 (1961), has a list of about 20 such reactions.

[258] Weaver and Hutchison, *J. Am. Chem. Soc.* **86**, 261 (1964). See also Rodewald, Mahendran, Bear, and Fuchs, *J. Am. Chem. Soc.* **90**, 6698 (1968); Fuchs and Mahendran, *J. Org. Chem* **36**, 730 (1971); Müller and Siegfried, *Helv. Chim. Acta* **54**, 2675 (1971); Liotta, Grisdale, and Hopkins, *Tetrahedron Lett.* 4205 (1975). For a contrary result in liquid SO_2, see Lichtin, Puar, and Wasserman, *J. Am. Chem. Soc.* **89**, 6677 (1967).

[259] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Lett.* no. 9, 24 (1960).

[260] Gordon and Varughese, *Chem. Commun.* 1160 (1971). See also Ford, Hauri, and Smith, *J,. Am. Chem. Soc.* **96**, 4316 (1974).

[261] Grimsrud and Taylor, *J. Am. Chem. Soc.* **92**, 739 (1970).

[262] Parker, *J. Chem. Soc.* 4398 (1961).

[263] Pearson, *Surv. Prog. Chem.* **5**, 1–52 (1969), pp. 21–38.

[263a] For a review of the effect of nucleophile association on nucleophilicity, see Guibe and Bram, *Bull. Soc. Chim. Fr.* 933–948 (1975).

[264] Zaugg, Horrom, and Borgwardt, *J. Am. Chem. Soc.* **82**, 2895 (1960); Zaugg, *J. Am. Chem. Soc.* **82**, 2903 (1960); Barlow and Zaugg, *J. Org. Chem.* **37**, 2246 (1972); Zaugg, Ratajczyk, Leonard, and Schaefer, *J. Org. Chem.* **37**, 2249 (1972); Zaugg and Leonard, *J. Org. Chem.* **37**, 2253 (1972). See also Chastrette and Gauthier-Countani, *Bull. Soc. Chim. Fr.* 363 (1973).

Similarly, it was shown that the half-life of the reaction between $C_6H_5COCHEt^-$ and ethyl bromide depended on the positive ion; K^+, 4.5×10^{-3}; Na^+, 3.9×10^{-5}; Li^+, 3.1×10^{-7}.[265] Presumably, the potassium ion leaves the negative ion most free to attack most rapidly. In Chapter 3 we saw that crown ethers specifically solvate the alkali metal portion of salts like KF, KBr, KI, KOAc, and KCN, leaving the negative ions much freer. This has been turned to synthetic use, where suitable crown ethers have been used to increase greatly the rates of reactions where F^-, Br^-, I^-, OAc^-, and CN^- are nucleophiles.[266]

In the gas phase, where nucleophilic ions are totally free, without solvation or counterions, the ions F^-, OH^-, and NH_2^- were all equally reactive toward CH_3Cl.[267] This does not mean that these ions have intrinsic nucleophilicities of about equal magnitude. The rates were about equal because nearly every collision led to nucleophilic substitution. This is a kind of leveling effect, similar to diffusion control in solution.

However, the four rules given above do not always hold. One reason is that steric influences often play a part. For example, the *t*-butoxide ion Me_3CO^- is a stronger base than OH^- or OEt^-, but a much poorer nucleophile because its large bulk hinders it from closely approaching a substrate. Another example was given on p. 150, where it was shown that 2,6-di-*t*-butylpyridine is a poorer nucleophile than 2,6-dimethylpyridine.

The following overall nucleophilicity order for S_N2 mechanisms (in protic solvents) was given by Edwards and Pearson:[253] $RS^- > ArS^- > I^- > CN^- > OH^- > N_3^- > Br^- > ArO^- > Cl^- >$ pyridine $> AcO^- > H_2O$. A quantitative relationship has been worked out by Swain and Scott[268] similar to the linear free-energy equations considered in Chapter 9:[269]

$$\log \frac{k}{k_0} = sn$$

where n is the nucleophilicity of a given group, s is the sensitivity of a substrate to nucleophilic attack, and k_0 is the rate for H_2O, which is taken as the standard and for which n is assigned a value of zero. s is defined as 1.0 for methyl bromide. Table 7 contains values of n for some common nucleophiles.[270] The order is similar to that of Edwards and Pearson.

For substitution at a carbonyl carbon, the nucleophilicity order is not the same but follows the basicity order more closely. This is presumably because the carbonyl carbon, with its partial positive charge, resembles a proton more than does the carbon at a saturated center. That is, a carbonyl carbon is a much harder acid than a saturated carbon. The following nucleophilicity order for these substrates has been determined:[271] $Me_2C{=}NO^- > EtO^- > MeO^- > OH^- > OAr^- > N_3^- > F^- > H_2O > Br^- \sim I^-$. Soft bases are quite ineffective at a carbonyl carbon.

If adjacent to the attacking atom on the nucleophile there is an atom containing one or more unshared pairs, the nucleophilicity is enhanced. Examples of such nucleophiles are HO_2^-,

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[265] Zook and Gumby, *J. Am. Chem. Soc.* **82,** 1386 (1960).

[266] Liotta and Harris, *J. Am. Chem. Soc.* **96,** 2250 (1974); Sam and Simmons, *J. Am. Chem. Soc.* **96,** 2252 (1974); Cook, Bowers, and Liotta, *J. Org. Chem.* **39,** 3416 (1974); Liotta, Harris, McDermott, Gonzalez, and Smith, *Tetrahedron Lett.* 2417 (1974); Durst, *Tetrahedron Lett.* 2421 (1974). See also Knöchel and Rudolph, *Tetrahedral Lett.* 3739 (1974); Mąkosza and Ludwikow, *Angew. Chem. Int. Ed. Engl.* **13,** 665 (1974) [*Angew. Chem.* **86,** 744]; Kurts, Sakembaeva, Beletskaya, and Reutov, *J. Org. Chem. USSR* **10,** 1588 (1974).

[267] Young, Lee-Ruff, and Bohme, *J. Chem. Soc., Chem. Commun.* 35 (1973). See also Bohme, Mackay, and Payzant, *J. Am. Chem. Soc.* **96,** 4027 (1974); Brauman, Olmstead, and Lieder, *J. Am. Chem. Soc.* **96,** 4030 (1974).

[268] Swain and Scott, *J. Am. Chem. Soc.* **75,** 141 (1953).

[269] This is not the only equation which has been devised in an attempt to correlate nucleophilic reactivity. For reviews of attempts to express nucleophilic power quantitatively, see Duboc, *Bull. Soc. Chim. Fr.* 1768–1781 (1970); Ibne-Rasa, *J. Chem. Educ.* **44,** 89–94 (1967). See also Pearson, Sobel, and Songstad, *J. Am. Chem. Soc.* **90,** 319 (1968).

[270] From Wells, *Chem. Rev.* **63,** 171–219 (1963), p. 212. See also Koskikallio, *Acta Chem. Scand.* **23,** 1477, 1490 (1969).

[271] Hudson and Green, *J. Chem. Soc.* 1055 (1962); Bender and Glasson, *J. Am. Chem. Soc.* **81,** 1590 (1959); Jencks and Gilchrist, *J. Am. Chem. Soc.* **90,** 2622 (1968).

TABLE 7 Nucleophilicities of some common reagents[270]

Nucleophile	n	Nucleophile	n
SH^-	5.1	Br^-	3.5
CN^-	5.1	PhO^-	3.5
I^-	5.0	AcO^-	2.7
$PhNH_2$	4.5	Cl^-	2.7
OH^-	4.2	NO_3^-	1.0
N_3^-	4.0	H_2O	0.0
Pyridine	3.6		

$Me_2C{=}NO^-$, NH_2NH_2, etc. This is called the *alpha effect*,[272] and the reasons for it are not completely understood,[273] though it is likely that the effect is caused not by one factor alone but by the sum of several factors,[274] one of which is repulsion between the adjacent pairs of electrons.[275] The alpha effect is substantial for substitution at a carbonyl or other unsaturated carbon, at some inorganic atoms,[276] and for reactions of a nucleophile with a carbonium ion,[277] but is generally smaller or absent entirely for substitution at a saturated carbon.[278] The magnitude of the alpha effect correlates with β in the Brönsted equation (p. 236).[274] β is dependent on the position of the transition state (p. 236); hence the alpha effect is greatest where considerable bond formation has taken place in the transition state.[279]

The Effect of the Leaving Group

1. *At a saturated carbon.* The leaving group comes off more easily the more stable it is as a free entity. This is usually inverse to its basicity, and the best leaving groups are the weakest bases. Thus iodide is the best leaving group among the halides, and fluoride the poorest.[280] Since XH is always a weaker base than X^-, nucleophilic substitution is always easier at a substrate RXH^+ than at RX. An example of this effect is that OH and OR are not leaving groups from ordinary alcohols and ethers but can come off when the groups are protonated, that is, converted to ROH_2^+ or $RORH^+$.[281] Reactions in which the leaving group does not come off until it has been protonated are called SN1cA or SN2cA, depending on whether the reaction, after protonation, is an SN1 or SN2 process (sometimes these designations are shortened to A1 and A2). The cA stands for conjugate acid, since the substitution takes place on the conjugate acid of the substrate. The ions ROH_2^+ and $RORH^+$ can be observed as stable entities at low temperatures in super-acid solutions.[282] At higher temperatures they cleave to give carbonium ions. It is obvious that many of the best nucleophiles (e.g., NH_2^-, OH^-) cannot take part in SN1cA or SN2cA processes, because they would be converted to their conjugate acids under the acidic conditions necessary to protonate the leaving groups. Because SN1 reactions do not require powerful nucleophiles but do require good leaving groups, most of them take place under acidic conditions. In contrast, SN2 reactions, which do require powerful nucleophiles (which are generally strong bases), most often take place under basic conditions.

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[272] Fina and Edwards, *Int. J. Chem. Kinet.* **5**, 1–26 (1973); Ref. 253.

[273] See Bruice, Donzel, Huffman, and Butler, *J. Am. Chem. Soc.* **89**, 2106 (1967).

[274] Sander and Jencks, *J. Am. Chem. Soc.* **90**, 6154 (1968); Dixon and Bruice, *J. Am. Chem. Soc.* **94**, 2052 (1972).

[275] Ibne-Rasa and Edwards, *J. Am. Chem. Soc.* **84**, 763 (1962); Aubort and Hudson, *Chem. Commun.* 937, 938, 1378 (1970); Filippini and Hudson, *J. Chem. Soc., Chem. Commun.* 522 (1972); Pratt and Bruice, *J. Org. Chem.* **37**, 3563 (1972). For another explanation, see Liebman and Pollack, *J. Org. Chem.* **38**, 3444 (1973).

[276] For example, see Kice and Legan, *J. Am. Chem. Soc.* **95**, 3912 (1973).

[277] Dixon and Bruice, *J. Am. Chem. Soc.* **93**, 3248, 6592 (1971).

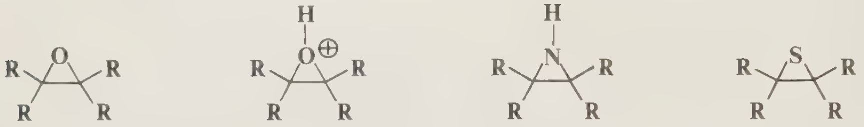
[278] Gregory and Bruice, *J. Am. Chem. Soc.* **89**, 4400 (1967); Oae, Kadoma, and Yano, *Bull. Chem. Soc. Jpn.* **42**, 1110 (1969); McIsaac, Subbaraman, Subbaraman, Mulhausen, and Behrman, *J. Org. Chem.* **37**, 1037 (1972). See, however, Beale, *J. Org. Chem.* **37**, 3871 (1972).

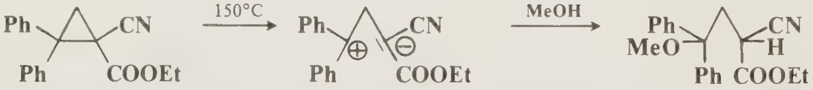
[279] See also Klopman, Tsuda, Louis, and Davis, *Tetrahedron* **26**, 4549 (1970).

[280] For a discussion of F as a leaving group, see Parker, *Adv. Fluorine Chem.* **3**, 63–91 (1963).

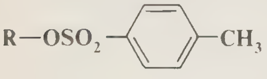
[281] For a review of ORH^+ as a leaving group, see Staude and Patat, in Patai, "The Chemistry of the Ether Linkage," pp. 22–46, Interscience Publishers, New York, 1967.

Another circumstance that increases leaving-group power is ring strain. Ordinary ethers do not cleave at all, and protonated ethers only under strenuous conditions, but epoxides are cleaved quite easily, and protonated epoxides even more easily. Aziridines and episulfides, three-membered rings containing, respectively, nitrogen and sulfur, are also easily cleaved (see p. 340). Even cyclopropane rings can be cleaved in a similar manner if they contain groups which can stabilize the positive and negative charges.[282a] An example is found in the treatment of ethyl 1-cyano-2,2-diphenylcyclopropanecarboxylate with methanol at 150°C for 3 days.[283] Similar reactions have been carried out photochemically.[284]



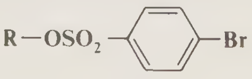


Although halides are the most common leaving groups in nucleophilic substitution for synthetic purposes, it is often more convenient to use alcohols. Since OH does not leave from ordinary alcohols, it must be converted to a group which does leave. One way is protonation, mentioned above. Another is conversion to a reactive ester, most commonly a sulfonic ester. The sulfonic ester groups *tosylate*, *brosylate*, *nosylate*, and *mesylate* are better leaving groups than halides and are frequently used. In recent years still better leaving groups have been found, and compounds containing these groups make powerful alkylating agents. Among them are oxonium ions



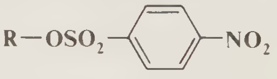
ROTs

p-Toluenesulfonates
Tosylates



ROBs

p-Bromobenzenesulfonates
Brosylates



RONs

p-Nitrobenzenesulfonates
Nosylates

$R-OSO_2CH_3$

ROMs

Methanesulfonates
Mesylates

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[282] Olah and O'Brien, *J. Am. Chem. Soc.* **89**, 1725 (1967); Olah, Sommer, and Namanworth, *J. Am. Chem. Soc.* **89**, 3576 (1967); Olah and Olah, in Olah and Schleyer, Ref. 76, vol. 2, pp. 743–747, 1970.

[282a] Cram and Ratajczak, *J. Am. Chem. Soc.* **90**, 2198 (1968); Yankee, Spencer, Howe, and Cram, *J. Am. Chem. Soc.* **95**, 4220 (1973); Howe, Yankee, and Cram, *J. Am. Chem. Soc.* **95**, 4230 (1973); Chmurny and Cram, *J. Am. Chem. Soc.* **95**, 4237 (1973).

[283] Yankee, Badea, Howe, and Cram, *J. Am. Chem. Soc.* **95**, 4210 (1973).

[284] Irving, Petterson, Sarkar, Kristinsson, Aaron, Griffin, and Boudreaux, *J. Am. Chem. Soc.* **88**, 5675 (1966); Hixson, *J. Am. Chem. Soc.* **93**, 5293 (1971); Hixson and Garrett, *J. Am. Chem. Soc.* **93**, 5294 (1971).

(ROR_2^+),[285] alkyl perchlorates ($ROClO_3$),[286] alkyl fluorosulfonates ($ROSO_2F$),[287] and the fluorinated compounds *triflates*[288] and *nonaflates*.[289] *Tresylates* are about 400 times less reactive

$R{-}OSO_2CF_3$	**$R{-}OSO_2C_4F_9$**	**$R{-}OSO_2CH_2CF_3$**
Trifluoromethanesulfonates	Nonafluorobutanesulfonates	2,2,2-Trifluoroethanesulfonates
Triflates	Nonaflates	Tresylates

than triflates, but still about 100 times more reactive than tosylates.[290] Halonium ions ($RClR^+$, $RBrR^+$, RIR^+), which can be prepared in super-acid solutions (p. 283) and isolated as solid SbF_6^- salts, are also extremely reactive in nucleophilic substitution.[291] NH_2, NHR, and NR_2 are extremely poor leaving groups, but the leaving-group ability of NH_2 can be greatly improved by converting a primary amine RNH_2 to the ditosylate $RNTs_2$. The NTs_2 group has been successfully replaced by a number of nucleophiles.[292] Ordinary NR_2 groups are very good leaving groups when the substrate is a Mannich base (these are compounds of the form $RCOCH_2CH_2NR_2$; see reaction **6-17**).[293] The elimination-addition mechanism applies in this case.

Probably the best leaving group is N_2 from the species RN_2^+, which can be generated in several ways,[294] of which the two most important are the treatment of primary amines with nitrous acid (see p. 578 for this reaction)

$$\mathbf{RNH_2 + HONO \longrightarrow RN_2^+}$$

and the protonation of diazo compounds[295]

$$\mathbf{R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} + H^+ \longrightarrow R_2CHN_2^+}$$

No matter how produced, RN_2^+ are too unstable to be isolable,[296] reacting presumably by the SN1 or SN2 mechanism.[297] Actually, the exact mechanisms are in doubt because the rate laws, stereochemistry, and products have proved difficult to interpret.[298] If there are free carbonium ions, they should give the same ratio of substitution to elimination to rearrangements, etc., as carbonium ions generated in other SN1 reactions, but they often do not. "Hot" carbonium ions (unsolvated and/or chemically activated) which can hold their configuration have been postulated,[299] as have ion pairs, in which OH^- (or OAc^-, etc., depending on how the diazonium ion is generated) is the counterion.[300] Many of these carbonium ions have very short lifetimes, even when compared to what are formally the same carbonium ions generated in other ways, and the products are determined not by the same factors but largely by the conformation of the original molecule. A series of experiments which demonstrated this was carried out by Chérest and coworkers.[301] They showed, by the use of conformationally rigid molecules, that deamination is highly stereoselective. The four isomeric 4-*t*-butyl-2-aminocyclohexanols were treated with nitrous acid, and in each case only one product was obtained:

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[285] For a monograph, see Perst, Ref. 68. For a review, see Granik, Pyatin, and Glushkov, *Russ. Chem. Rev.* **40,** 747–759 (1971). For a discussion of their use, see Curphey, *Org. Synth.* **51,** 144 (1971). See also Copson, Heaney, Logun, and Sharma, *J. Chem. Soc., Chem. Commun.* 315 (1972).

[286] Baum and Beard, *J. Am. Chem. Soc.* **96,** 3233 (1974).

[287] Ahmed, Alder, James, Sinnott, and Whiting, *Chem. Commun.* 1533 (1968); Ahmed and Alder, *Chem. Commun.* 1389 (1969); Alder, *Chem. Ind. (London)* 983 (1973).

[288] Burdon and McLoughlin, *Tetrahedron* **21,** 1 (1965); Hansen, *J. Org. Chem.* **30,** 4322 (1965); Streitwieser, Wilkins, and Kiehlmann, *J. Am. Chem. Soc.* **90,** 1598 (1968); Su, Sliwinski, and Schleyer, *J. Am. Chem. Soc.* **91,** 5386 (1969); Beard, Baum, and Grakauskas, *J. Org. Chem.* **38,** 3673 (1973).

[289] Subramanian and Hanack, *Chem. Ber.* **105,** 1465 (1972); Subramanian, Bentz, and Hanack, *Synthesis* 293 (1973).

[290] Crossland, Wells, and Shiner, *J. Am. Chem. Soc.* **93,** 4217 (1971).

[291] Peterson, Clifford, and Slama, Ref. 72; Olah, DeMember, Schlosberg, and Halpern, *J. Am. Chem. Soc.* **94,** 156 (1972); Olah and Melby, *J. Am. Chem. Soc.* **94,** 6220 (1972); Peterson and Bonazza, Ref. 72; Peterson and Waller, *J. Am. Chem. Soc.* **94,** 5024 (1972); Olah and Svoboda, *Synthesis* 203 (1973); Olah, DeMember, Mo, Svoboda, Schilling, and Olah, *J. Am. Chem. Soc.* **96,** 884 (1974); Olah and Mo, *J. Am. Chem. Soc.* **96,** 3560 (1974).

[292] DeChristopher, Adamek, Lyon, Galante, Haffner, Boggio, and Baumgarten, *J. Am. Chem. Soc.* **91,** 2384 (1969). See also Hendrickson, Bergeron, Giga, and Sternbach, *J. Am. Chem. Soc.* **95,** 3412 (1973).

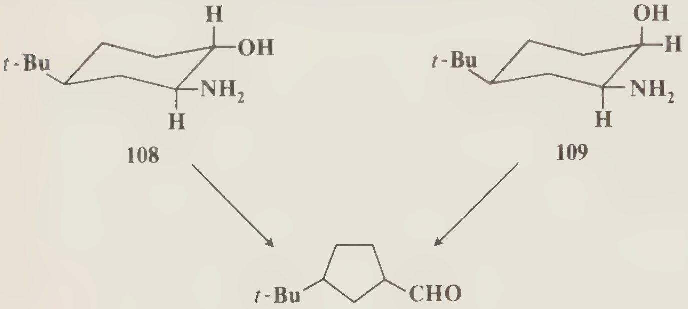
[293] For a review of Mannich bases, see Tramontini, *Synthesis* 703–775 (1973).

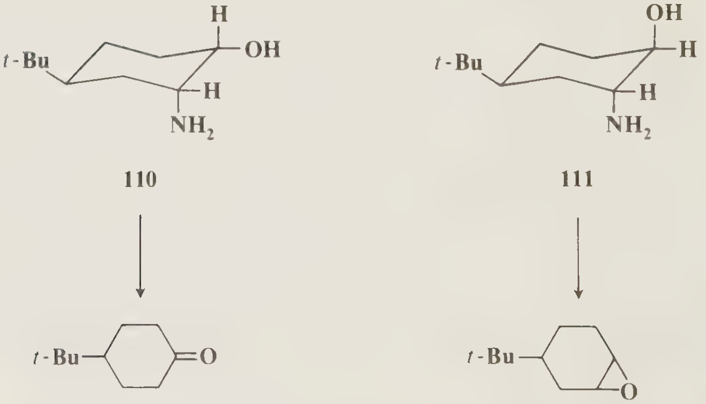
[294] For reviews, see Kirmse, *Angew. Chem. Int. Ed. Engl.* **15,** 251–261 (1976) [*Angew. Chem.* **88,** 273–283]; Collins, *Acc. Chem. Res.* **4,** 315–322 (1971); Moss, *Chem. Eng. News* **49** (48), 28–36 (Nov. 22, 1971).

[295] For a review of the reactions of aliphatic diazo compounds with acids, see More O'Ferrall, *Adv. Phys. Org. Chem.* **5,** 331–399 (1967). For a review of the structures of these compounds, see Studzinskii and Korobitsyna, *Russ. Chem. Rev.* **39,** 834–843 (1970).

[296] *Aromatic* diazonium salts can of course be isolated (see Chapter 13), but only a few aliphatic diazonium salts have been prepared. For examples, see Reimlinger, *Angew. Chem. Int. Ed. Engl.* **2,** 482 (1963) [*Angew. Chem.* **75,** 788]; Bott, *Angew Chem. Int. Ed. Engl.* **3,** 804 (1964) [*Angew. Chem.* **76,** 992], *Tetrahedron* **22,** 1251 (1966), *Angew. Chem. Int. Ed. Engl.* **9,** 954 (1970) [*Angew. Chem.* **82,** 953], *Tetrahedron Lett.* 2227 (1971), *Chem. Ber.* **108,** 402 (1975); Mohrig and Keegstra, *J. Am. Chem. Soc.* **89,** 5492 (1967).

[297] For an example of a diazonium ion reacting by an SN2 mechanism, see Mohrig, Keegstra, Maverick, Roberts, and Wells, *J. Chem. Soc., Chem. Commun.* 780 (1974).





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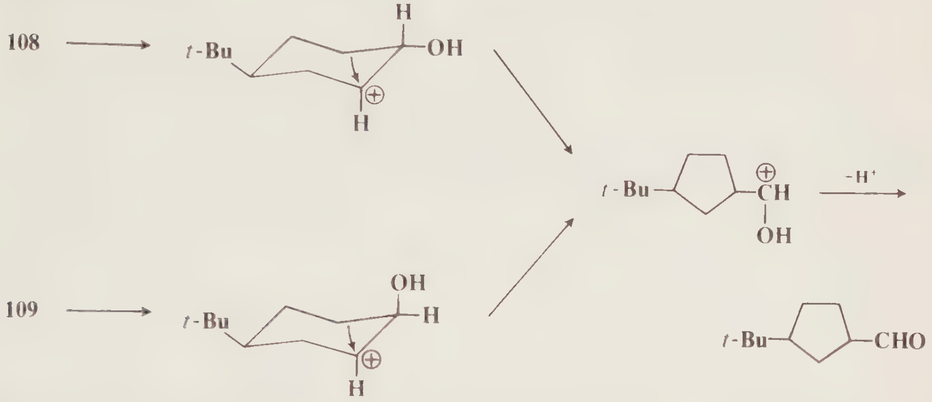
[298] For reviews of the mechanism, see Saunders and Cockerill, "Mechanisms of Elimination Reactions," pp. 280–317, John Wiley & Sons, New York, 1973; in Olah and Schleyer, Ref. 76, vol. 2, 1970, the articles by Keating and Skell, pp. 573–653; and by Friedman, pp. 655–713; White and Woodcock, in Patai, "The Chemistry of the Amino Group," pp. 440–483, Interscience Publishers, New York, 1968; Ref. 294.

[299] Semenow, Shih, and Young, *J. Am. Chem. Soc.* **80**, 5472 (1958). For a review of "hot" or "free" carbonium ions, see Keating and Skell, Ref. 298.

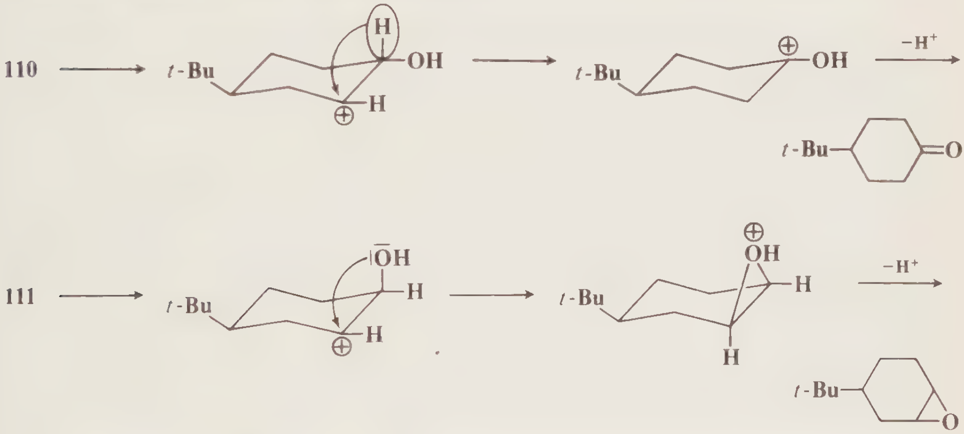
[300] Collins, Ref. 294; Collins and Benjamin, *J. Org. Chem.* **37**, 4358 (1972); Collins, Glover, Eckart, Raaen, Benjamin, and Benjaminov, *J. Am. Chem. Soc.* **94**, 899 (1972); Cohen and Daniewski, *J. Am. Chem. Soc.* **91**, 533 (1969); Cohen, Daniewski, Deeb, and Shaw, *J. Am. Chem. Soc.* **94**, 1786 (1972); White and Field, *J. Am. Chem. Soc.* **97**, 2148 (1975).

[301] Chérest, Felkin, Sicher, Šipoš, and Tichý, *J. Chem. Soc.* 2513 (1965).

For **108** and **109** the 2 hydrogen of the carbonium ion remains axial, and the different positions of the hydroxyl group and of the 1 hydrogen do not affect the product:



For **110** and **111** the 2 hydrogen remains equatorial and prevents ring contraction. In each of these cases, the axial group at the 1 position forms a bond with the carbonium-ion carbon:



It is obvious that the carbonium ion does not reach its maximum stability before the product-determining step occurs.

Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[302]

It has been suggested[303] that the reaction between aliphatic amines and nitrous acid may lead to carbonium ions *without* the intermediacy of diazonium ions. This could happen if the

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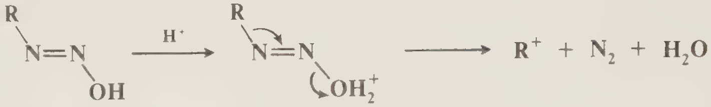
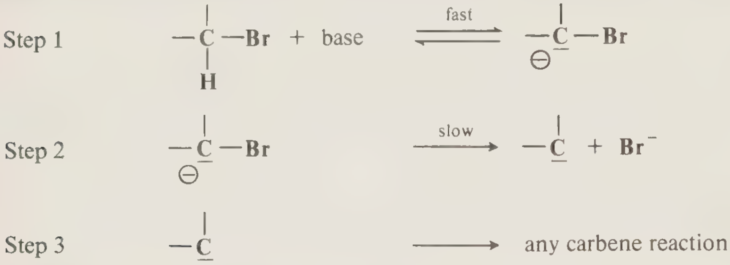
[302] Whitmore and Langlois, *J. Am. Chem. Soc.* **54,** 3441 (1932); Streitwieser and Schaeffer, *J. Am. Chem. Soc.* **79,** 2888 (1957).

[303] Ref. 301. Also see Cram and Sahyun, *J. Am. Chem. Soc.* **85,** 1257 (1963); Maskill, Southam, and Whiting, *Chem. Commun.* 496 (1965).

C—N bond of the diazohydroxide (see p. 579 for the mechanism of diazonium-ion formation) is cleaved at the same time as the N—O bond:



In the SN1cA and SN2cA mechanisms (p. 325) there is a preliminary step, the addition of a proton, before the normal SN1 or SN2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions there is a carbene intermediate:



Once formed by this process, the carbene may give any of the normal carbene reactions (see p. 182). When the net result is substitution, this mechanism may be called the SN1cB (for conjugate base) mechanism.[304] Though the slow step is an SN1 step, the reaction is second order: first order in substrate and first order in base.

Table 8 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for SN1 and SN2 reactions.

2. *At a carbonyl carbon.* In both the SN1 and SN2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density of the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C, and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium.* In the intermediate **93** (p. 308) there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **93** will revert to the starting compounds. Thus there is a partitioning factor between **93** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be $RCOCl > RCOOCOR' > RCOOAr > RCOOR' > RCONH_2 > RCONR'_2 > RCOO^-$.[305] Note that this order is approximately the order of decreasing stability of the leaving-group anion. If the leaving group is bulky, it may exert a steric effect and retard the rate for this reason.

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[304] Pearson and Edgington, *J. Am. Chem. Soc.* **84,** 4607 (1962).

[305] RCOOH would belong in this sequence just after RCOOAr, but it fails to undergo many reactions for a special reason. Many nucleophiles, instead of attacking the C=O group, are basic enough to take a proton from the acid, converting it to the unreactive $RCOO^-$.

[306] ROTs, etc., includes esters of sulfuric and sulfonic acids in general, for example, $ROSO_2OH$, $ROSO_2OR$, $ROSO_2R$, etc. $RONO_2$, etc., includes inorganic-ester leaving groups, such as $ROPO(OH)_2$, $ROB(OH)_2$, etc.

[307] Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates [2,4,6-$ROC_6H_2(NO_2)_3$] react at rates comparable to tosylates: Sinnott and Whiting, *J. Chem. Soc. B* 965 (1971). See also Page, Pritt, and Whiting, *J. Chem. Soc., Perkin Trans. 2* 906 (1972).

TABLE 8 Leaving groups listed in approximate order of decreasing ability to leave. Groups which are common leaving groups at saturated and carbonyl carbons are indicated

Substrate RX	Common leaving groups At saturated carbon	 At carbonyl carbon
RN_2^+	×	
$ROR_2'^+$		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	×	
$ROSO_2F$		
ROTs, etc.[306]	×	
RI	×	
RBr	×	
ROH_2^+	× (conjugate acid of alcohol)	
RCl	×	× (acyl halides)
$RORH^+$	× (conjugate acid of ether)	
$RONO_2$, etc.[306]	×	
$RSR_2'^+$		
$RNR_3'^+$	×	
RF		
ROCOR′	×	× (anhydrides)
RNH_3^+		
ROAr[307]		× (aryl esters)
ROH		× (carboxylic acids)
ROR		× (alkyl esters)
RH		
RNH_2		× (amides)
RAr		
RR		

The Effect of the Reaction Medium

The effect of solvent polarity on the rate of SN1 reactions depends on whether the substrate is neutral or positively charged. For neutral substrates, which constitute the majority of cases, the more polar the solvent, the faster the reaction, since there is a greater charge in the transition state than in the starting compound (Table 9) and the energy of an ionic transition state is reduced by polar solvents. However, when the substrate is positively charged, then the charge is more spread out in the transition state than in the starting ion, and a greater solvent polarity slows the reaction. Even for solvents with about the same polarity, there is a difference between protic and aprotic solvents. SN1 reactions of un-ionized substrates are more rapid in protic solvents, which can hydrogen-bond with the leaving group. Examples of protic solvents are

TABLE 9 Transition states for SN1 reactions of charged and uncharged substrates, and for SN2 reactions of the four charge types[308]

	Reactants and transition states	Change in the transition state relative to starting materials	How an increase in solvent polarity affects the rate
SN2	Type I $RX + Y^- \longrightarrow Y^{\delta-}\cdots\cdots R\cdots\cdots X^{\delta-}$	Dispersed	Small decrease
	Type II $RX + Y \longrightarrow Y^{\delta+}\cdots\cdots R\cdots\cdots X^{\delta-}$	Increased	Large increase
	Type III $RX^+ + Y^- \longrightarrow Y^{\delta-}\cdots\cdots R\cdots\cdots X^{\delta+}$	Decreased	Large decrease
	Type IV $RX^+ + Y \longrightarrow Y^{\delta+}\cdots\cdots R\cdots\cdots X^{\delta+}$	Dispersed	Small decrease
SN1	$RX \longrightarrow R^{\delta+}\cdots\cdots X^{\delta-}$	Increased	Large increase
	$RX^+ \longrightarrow R^{\delta+}\cdots\cdots X^{\delta+}$	Dispersed	Small decrease

water, alcohols, and carboxylic acids, while some polar aprotic solvents are dimethylformamide, dimethyl sulfoxide,[309] acetonitrile, acetone, nitrobenzene, sulfur dioxide, and hexamethylphosphoric triamide [$(Me_2N)_3PO$, HMPT, also called hexamethylphosphoramide, HMPA].[310]

For SN2 reactions, the effect of the solvent depends on which of the four charge types the reaction belongs to (p. 265). In types I and IV, an initial charge is dispersed in the transition state, so that the reaction is hindered by polar solvents. In type III initial charges are *decreased* in the transition state, so that the reaction is even more hindered by polar solvents. Only type II, where the reactants are uncharged but the transition state has built up a charge, is aided by polar solvents. These effects are summarized in Table 9.[308] For SN2 reactions also, the difference between protic and aprotic solvents must be considered.[311] For reactions of types I and III the transition state is more solvated in polar aprotic solvents than in protic ones, while (as we saw on p. 323) the original charged nucleophile is less solvated in aprotic solvents[312] (the second factor is generally much greater than the first[313]). So the change from, say, methanol to dimethyl sulfoxide should greatly increase the rate. As an example, the relative rates at 25°C for the reaction between methyl iodide and Cl^- were[257] in MeOH, 1; in $HCONH_2$ (still protic though a weaker acid), 12.5; in HCONHMe, 45.3; and in $HCONMe_2$, 1.2×10^6. The change in rate in going from a protic to an aprotic solvent is also related to the *size* of the attacking anion. Small ions are solvated best in protic solvents, since hydrogen bonding is most important for them, while large anions are solvated best in aprotic solvents (protic solvents have highly developed structures held together by hydrogen bonds; aprotic solvents have much looser structures, and it is easier for a large anion to be fitted in). So the rate of attack by small anions is most greatly increased by the change from a protic to an aprotic solvent. This may have preparative significance. The review articles in Ref. 311 have lists of several dozen reactions of charge types I and III in which yields are improved and reaction times reduced in polar

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[308] This analysis is due to Ingold, "Structure and Mechanism in Organic Chemistry," 2d ed., pp. 457–463, Cornell University Press, Ithaca, N.Y., 1969.

[309] For a review of reactions in dimethyl sulfoxide, see Martin, Weise, and Niclas, *Angew. Chem. Int. Ed. Engl.* **6**, 318–334 (1967) [*Angew. Chem.* **79**, 340–357].

[310] For reviews of HMPT, see Normant, *Russ. Chem. Rev.* **39**, 457–484 (1970), *Bull. Soc. Chim. Fr.* 791–826 (1968), *Angew. Chem. Int. Ed. Engl.* **6**, 1046–1067 (1967) [*Angew. Chem.* **79**, 1029–1050].

[311] For reviews of the effects of protic and aprotic solvents, see Parker, *Chem. Rev.* **69**, 1–32 (1969), *Adv. Phys. Org. Chem.* **5**, 173–235 (1967), *Adv. Org. Chem.* **5**, 1–46 (1965), *Q. Rev., Chem. Soc.* **16**, 163–187 (1962); Madaule-Aubry, *Bull. Soc. Chim. Fr.* 1456 (1966).

[312] See for example Fuchs and Cole, *J. Am. Chem. Soc.* **95**, 3194 (1973).

[313] See, however, Haberfield, Clayman, and Cooper, *J. Am. Chem. Soc.* **91**, 787 (1969).

TABLE 10 Relative rates of ionization of *p*-methoxyneophyl toluenesulfonate in various solvents[317]

Solvent	Relative rate	Solvent	Relative rate
HCOOH	153	Ac_2O	0.020
H_2O	39	Pyridine	0.013
80% EtOH-H_2O	1.85	Acetone	0.0051
AcOH	1.00	EtOAc	6.7×10^{-4}
MeOH	0.947	Tetrahydrofuran	5.0×10^{-4}
EtOH	0.370	Et_2O	3×10^{-5}
Me_2SO	0.108	$CHCl_3$	Lower still
Octanoic acid	0.043	Benzene	
MeCN	0.036	Alkanes	
$HCONMe_2$	0.029		

aprotic solvents.[314] Reaction types II and IV are much less susceptible to the difference between protic and aprotic solvents. In these cases the original nucleophile is about equally solvated by protic and polar aprotic solvents, though the transition state is still solvated better by polar aprotic solvents.[315] Even for types I and III, there is a difference in susceptibility between primary and secondary substrates. Primary substrates are more greatly accelerated by the change from a protic to an aprotic solvent than secondary substrates. This has been attributed to a "looser" transition state for secondary substrates than for primary, "looser" meaning that bond forming lags behind bond breaking.[316]

Since for most reactions SN1 rates go up and SN2 rates go down in solvents of increasing polarity, it is quite possible for the same reaction to go by the SN1 mechanism in one solvent and the SN2 in another.

Table 10 is a list of solvents in order of ionizing power;[317] a solvent high on the list is a good solvent for SN1 reactions. Trifluoroacetic acid, which was not studied by Smith, Fainberg, and Winstein, has greater ionizing power than any solvent listed in Table 10.[318] Because it also has very low nucleophilicity, it is an excellent solvent for SN1 solvolyses. Other good solvents for this purpose are 1,1,1-trifluoroethanol CF_3CH_2OH, and 1,1,1,3,3,3-hexafluoro-2-propanol $(F_3C)_2CHOH$.[319]

We have seen how the polarity of the solvent influences the rates of SN1 and SN2 reactions. The ionic strength of the medium has similar effects. In general, the addition of an external salt affects the rates of SN1 and SN2 reactions in the same way as an increase in solvent polarity, though this is not quantitative: different salts have different effects.[320] However, there are exceptions: although the rates of SN1 reactions are usually increased by the addition of salts (this is called the *salt effect*), addition of the leaving-group ion often decreases the rate (the common-ion effect, p. 271). Also, there is the special salt effect of $LiClO_4$, mentioned on p. 275. In addition to these effects, SN1 rates are also greatly accelerated when there are ions present which specifically help in pulling off the leaving group. Especially important are Ag^+, Hg^{2+}, and $Hg_2{}^{2+}$, but H^+ helps to pull off F (hydrogen bonding).[321] This does not mean, however, that reactions in the presence of metallic ions invariably proceed by the SN1 mechanism. It has been shown that alkyl halides can react with $AgNO_2$ and $AgNO_3$ by the SN1 or SN2 mechanism, depending on the reaction conditions.[322]

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[314] See also Alexander, Ko, Parker, and Broxton, *J. Am. Chem. Soc.* **90,** 5049 (1968).

[315] Haberfield, Nudelman, Bloom, Romm, and Ginsberg, *J. Org. Chem.* **36,** 1792 (1971); Abraham, *J. Chem. Soc. B* 299 (1971).

[316] Ko and Parker, *J. Am. Chem. Soc.* **90,** 6447 (1968).

[317] Smith, Fainberg, and Winstein, *J. Am. Chem. Soc.* **83,** 618 (1961).

[318] Refs. 71, 113; Streitwieser and Dafforn, *Tetrahedron Lett.* 1263 (1969).

[319] Schadt, Schleyer, and Bentley, *Tetrahedron Lett.* 2335 (1974).

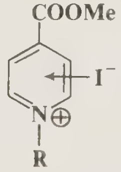
[320] See for example Duynstee, Grunwald, and Kaplan, *J. Am. Chem. Soc.* **82,** 5654 (1960); Bunton and Robinson, *J. Am. Chem. Soc.* **90,** 5965 (1968).

The effect of solvent has been treated quantitatively (for SN1 mechanisms, in which the solvent pulls off the leaving group) by a linear free-energy relationship[323]

$$\log \frac{k}{k_0} = mY$$

where m is characteristic of the substrate (defined as 1.00 for *t*-BuCl) and is usually near unity, Y is characteristic of the solvent and measures its "ionizing power," and k_0 is the rate in a standard solvent, 80% aqueous ethanol at 25°C. This is known as the Grunwald-Winstein equation, and its utility is at best limited. Y values can of course be measured for solvent *mixtures* too, and this is one of the principal advantages of the treatment, since it is not easy otherwise to assign a polarity arbitrarily to a given mixture of solvents. The treatment is most satisfactory for different proportions of a given solvent pair. For wider comparisons the treatment is not so good quantitatively, although the Y values do give a reasonably good idea of solvolyzing power. Table 11 contains a list of some Y values.[324] At least in some cases, even where the Grunwald-Winstein equation holds, it is the result of a fortuitous combination of effects. Thus, if the substrate (and hence m) is held constant, the equation holds if $\Delta G^‡$ is proportional to the Y value of the solvent (p. 254). But $\Delta G^‡$ is the sum of $\Delta H^‡$ and $-T\Delta S^‡$, and it has been shown that in the solvolysis of *t*-butyl chloride in ethanol-water mixtures, $\Delta H^‡$ and $-T\Delta S^‡$ fluctuate wildly, though their sum (fortuitously) does vary linearly with Y.[325]

In order to include a wider range of solvents than those in which Y values can be conveniently measured, other attempts have been made at correlating solvent polarities.[326] Kosower found that the position of the charge-transfer peak (see p. 79) in the uv spectrum of the complex (**112**)



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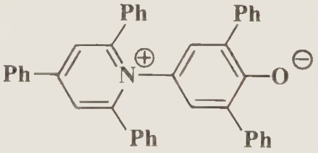
R = Me or Et



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[321] For a review of assistance by metallic ions, see Rudakov, Kozhevnikov, and Zamashchikov, *Russ. Chem. Rev.* **43**, 305–316 (1974). For an example of assistance in removal of F by H^+, see Coverdale and Kohnstam, *J. Chem. Soc.* 3906 (1960).

[322] Kornblum, Jones, and Hardies, *J. Am. Chem. Soc.* **88**, 1704 (1966); Kornblum and Hardies, *J. Am. Chem. Soc.* **88**, 1707 (1966).

[323] Grunwald and Winstein, *J. Am. Chem. Soc.* **70**, 846 (1948).

[324] Y values are from Fainberg and Winstein, *J. Am. Chem. Soc.* **78**, 2770 (1956), except for the value for CF_3COOH, which is from Shiner, Dowd, Fisher, Hartshorn, Kessick, Milakofsky, and Rapp, *J. Am. Chem. Soc.* **91**, 4838 (1969). Z values are from Ref. 327. E_T values are from Reichardt and Dimroth, *Fortschr. Chem. Forsch.* **11**, 1–73 (1969). Values for additional solvents are given in Reichardt, *Justus Liebigs Ann. Chem.* **752**, 64 (1971).

[325] Winstein and Fainberg, *J. Am. Chem. Soc.* **79**, 5937 (1957); Arnett, Bentrude, Burke, and Duggleby, *J. Am. Chem. Soc.* **87**, 1541 (1965). See also Abraham, Buisson, and Schulz, *J. Chem. Soc., Chem. Commun.* 693 (1975).

[326] For reviews of solvent polarity scales, see Abraham, *Prog. Phys. Org. Chem.* **11**, 1–87 (1974); Koppel and Palm, in Chapman and Shorter, "Advances in Linear Free Energy Relationships," pp. 203–280, Plenum Press, New York, 1972; Reichardt and Dimroth, Ref. 324; Reichardt, *Angew. Chem. Int. Ed. Engl.* **4**, 29 40 (1965) [*Angew Chem.* **77**, 30 40]; Kosower, "An Introduction to Physical Organic Chemistry," pp. 293–333, John Wiley & Sons, New York, 1968. See also Fowler, Katritzky, and Rutherford, *J. Chem. Soc. B* 460 (1971).

TABLE 11 *Y*, *Z*, and E_T values for some solvents[324]

Solvent	Y	Z	E_T
CF_3COOH			
H_2O	3.5	94.6	63.1
$(CF_3)_2CHOH$			
HCOOH	2.1		
H_2O–EtOH (1 : 1)	1.7	90	55.6
CF_3CH_2OH	1.0		
$HCONH_2$	0.6	83.3	56.6
80% EtOH	0.0	84.8	53.7
MeOH	−1.1	83.6	55.5
AcOH	−1.6	79.2	51.2
EtOH	−2.0	79.6	51.9
90% dioxane	−2.0	76.7	46.7
iso-PrOH	−2.7	76.3	48.6
95% acetone	−2.8	72.9	48.3
t-BuOH	−3.3	71.3	43.9
MeCN		71.3	46.0
Me_2SO		71.1	45.0
$HCONMe_2$		68.5	43.8
Acetone		65.7	42.2
Pyridine		64.0	40.2
$CHCl_3$		63.2	39.1
PhCl			37.5
THF			37.4
Dioxane			36.0
Et_2O			34.6
C_6H_6		54	34.5
CCl_4			32.5
n-Hexane			30.9

between iodide ion and 1-methyl- or 1-ethyl-4-carbomethoxypyridinium ion was dependent on the polarity of the solvent.[327] From these peaks, which are very easy to measure, Kosower calculated transition energies which he called *Z* values. *Z* values are thus measures of solvent polarity analogous to *Y* values. Another scale is based on the position of electronic spectra peaks of the pyridinium-*N*-phenolbetaine **113** in various solvents.[328] Solvent polarity values on this scale are called E_T values. E_T values are related to *Z* values by the expression[329]

$$Z = 1.41E_T + 6.92$$

Table 11 shows that *Z* and E_T values are generally in the same order as *Y* values.

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[327] Kosower, *J. Am. Chem. Soc.* **80,** 3253, 3261, 3267 (1958); Kosower and Wu, *J. Am. Chem. Soc.* **83,** 3142 (1961); Kosower, Wu, and Sorensen, *J. Am. Chem. Soc.* **83,** 3147 (1961).

[328] Dimroth, Reichardt, Siepmann, and Bohlmann, *Justus Liebergs Ann. Chem.* **661,** 1 (1963); Dimroth and Reichardt, *Justus Liebigs Ann. Chem.* **727,** 93 (1969).

[329] Reichardt and Dimroth, Ref. 324, p. 32.

The effect of solvent on nucleophilicity has already been discussed (p. 323).

It has been proposed[268] that if the Grunwald-Winstein equation, which applies only to removal of the leaving group, is combined with the nucleophilicity relationship (p. 324), which applies only to pushing by the nucleophile, an equation can be obtained which correlates both effects:

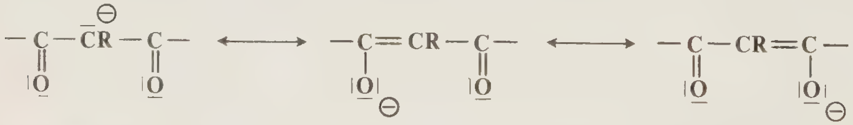
$$\log\frac{k}{k_0} = sn + s'e$$

In this equation, s and n are as defined on page 324, s' is analogous to m, and e is analogous to Y. In solvolysis reactions, the solvent may be both pushing and pulling, so that n and e are different functions of the same compound. This equation has not proved very satisfactory, and numerous attempts have been made to improve it.[330]

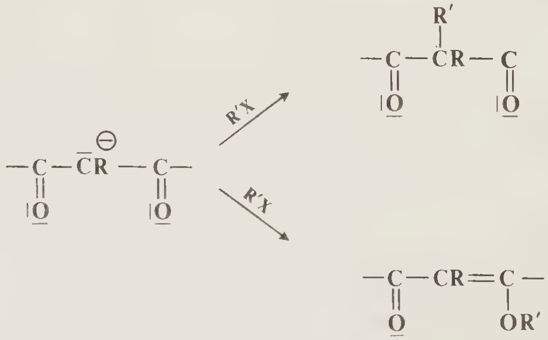
Ambident Nucleophiles. Regiospecificity

Some nucleophiles have a pair of electrons on each of two or more atoms, or canonical forms may be drawn in which two or more atoms bear an unshared pair. In these cases the nucleophile may attack in two or more different ways to give different products. Such reagents are called *ambident nucleophiles.* In most cases a nucleophile with two potentially attacking atoms can attack with either of them, depending on conditions, and mixtures are often obtained, though this is not always the case. For example, the nucleophile NCO^- usually gives only isocyanates RNCO and not the isomeric cyanates ROCN.[331] When a reaction can potentially give rise to two or more structural isomers (e.g., ROCN or RNCO) but actually produces only one, the reaction is said to be *regiospecific*[332] (compare the definition of stereospecific, p. 123). Some important ambident nucleophiles are:

1. *Ions of the type* $-\text{CO}-\overset{-\ominus}{\text{C}}\text{R}-\text{CO}-$. These ions, which are derived by removal of a proton from malonic esters, β-keto esters, β-diketones, etc., are resonance hybrids:



They can thus attack a saturated carbon with their carbon atoms (C-alkylation) or with their oxygen atoms (O-alkylation):



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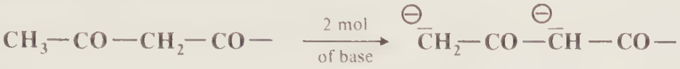
[330] See for example, Bentley, Schadt, Schleyer, Peterson, and Waller, *J. Am. Chem. Soc.* **94,** 991 (1972).

[331] Both cyanates and isocyanates have been isolated in treatment of secondary alkyl iodides with NCO^-: Holm and Wentrup, *Acta Chem. Scand.* **20,** 2123 (1966).

[332] This term was introduced by Hassner, *J. Org. Chem.* **33,** 2684 (1968).

With unsymmetrical ions, three products are possible, since either oxygen may attack. With a carbonyl substrate the ion may analogously undergo C-acylation or O-acylation.

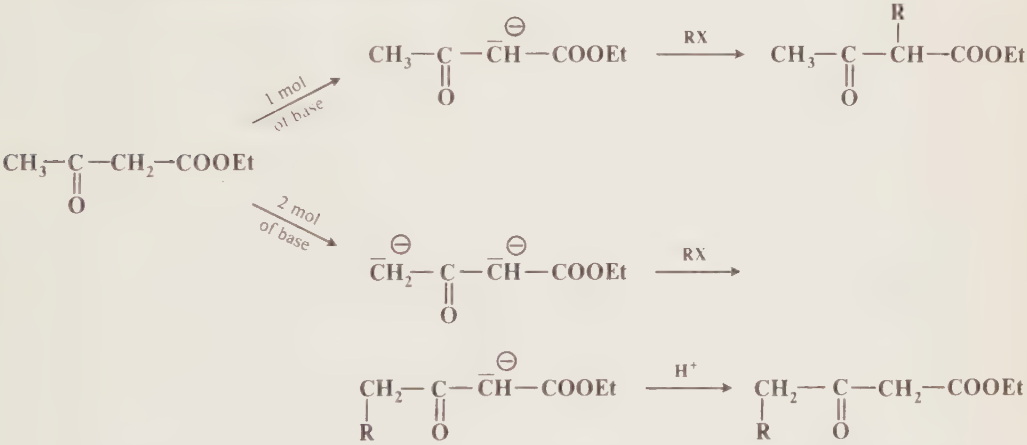
2. Compounds of the type $CH_3CO{-}CH_2{-}CO{-}$ can give up two protons, if treated with 2 moles of a strong enough base, to give dicarbanions:



$$CH_3{-}CO{-}CH_2{-}CO{-} \xrightarrow[\text{of base}]{\text{2 mol}} \overset{\ominus}{\bar{C}}H_2{-}CO{-}\overset{\ominus}{\bar{C}}H{-}CO{-}$$

114

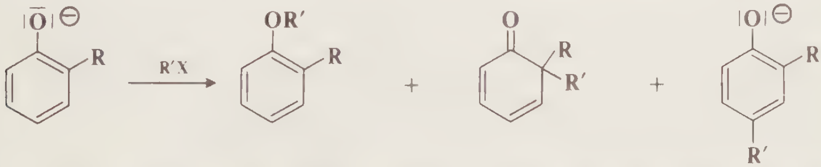
Such ions are ambident nucleophiles, since they have two possible attacking carbon atoms, aside from the possibility of attack by oxygen. In such cases, the attack is always by the more basic carbon. Since the hydrogen of a carbon bonded to two carbonyl groups is more acidic than that of a carbon bonded to just one (see Chapter 8), the CH group of **114** is less basic than the CH_2 group, so that the latter attacks the substrate. This gives rise to a useful general principle: whenever it is desired to remove a proton at a given position for use as a nucleophile, but there is a stronger acidic group in the molecule, it may be possible to take off both protons; if it is, then attack is always by the desired position, since it is the ion of the weaker acid. On the other hand, if it is desired to attack with the more acidic position, all that is necessary is to remove just one proton.[333] For example, ethyl acetoacetate may be alkylated at will, either at the methyl or at the methylene group (reaction **0-96**):



3. *The* CN⁻ *ion.* This nucleophile may give nitriles RCN (reaction **0-103**) or isonitriles RN≡C.

4. *The nitrite ion.* This ion may give nitrite esters R—O—N=O (reaction **0-33**) or nitro compounds RNO_2 (reaction **0-62**), which are not esters.

5. Phenoxide ions (which are analogous to enolate ions) may undergo C-alkylation or O-alkylation:



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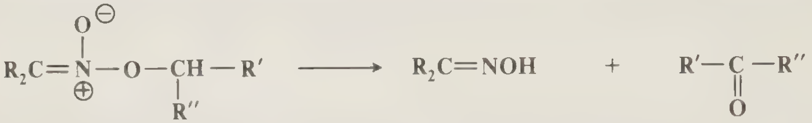
[333] The use of this principle was first reported by Hauser and Harris, *J. Am. Chem. Soc.* **80**, 6360 (1958). It has since been applied many times by Hauser, Harris, and coworkers. For a review, see Harris and Harris, *Org. React.* **17**, 155–211 (1969).

6. Removal of a proton from an aliphatic nitro compound gives a carbanion ($R_2C^{\ominus}{-}NO_2$) which can be alkylated at oxygen or carbon.[334] O-Alkylation gives nitronic esters, which are generally unstable to heat but break down to give an oxime and an aldehyde or ketone.



$$R_2C{=}\overset{\overset{\displaystyle O^{\ominus}}{|}}{\underset{\oplus}{N}}{-}O{-}\underset{\underset{\displaystyle R''}{|}}{CH}{-}R' \longrightarrow R_2C{=}NOH + R'{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R''$$

There are many other ambident nucleophiles. An interesting case is that of β-amino-α, β-unsaturated ketones, which may be alkylated on a carbon, oxygen, or nitrogen atom.[335]

It would be useful to have general rules as to which atom of an ambident nucleophile will attack a given substrate under a given set of conditions.[336] Unfortunately, the situation is complicated by the large number of variables which must be considered. It might be expected that the more electronegative atom would always attack, but this is often not the case. Where the products are determined by thermodynamic control (p. 194), the principal product is usually the one in which the atom of higher basicity has attacked (i.e., $C > N > O > S$). However, in most reactions the products are kinetically controlled and matters are much less simple. Nevertheless, the following generalizations can be made, while recognizing that there are many exceptions and unexplained results. As in the discussion of nucleophilicity in general (p. 323), there are two major factors: the polarizability (hard-soft character) of the nucleophile and solvation effects.

1. The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (p. 238). In an SN1 mechanism the nucleophile attacks a carbonium ion, which is a hard acid. In an SN2 mechanism the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from SN1-like to SN2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom.[337] Therefore, changing from SN1 to SN2 conditions should favor C attack by CN^-, N attack by NO_2^-, C attack by enolate or phenoxide ions, etc. As an example, primary alkyl halides are attacked (in protic solvents) by the carbon atom of the anion of CH_3COCH_2COOEt, while α-chloro ethers, which react by the SN1 mechanism, are attacked by the oxygen atom. However, this does not mean that attack is by the less electronegative atom in all SN2 reactions and by the more electronegative atom in all SN1 reactions. The position of attack also depends on the nature of the nucleophile, the solvent, the leaving group, and other conditions. The rule merely states that increasing the SN2 character of the transition state makes attack by the less electronegative atom more likely.

2. All negatively charged nucleophiles must of course have a positive counterion. If this ion is Ag^+ (or some other ion which specifically helps in removing the leaving group, p. 334), rather than the more usual Na^+ or K^+, then the transition state is more SN1-like. Therefore the use of Ag^+ promotes attack at the more electronegative atom. For example, alkyl halides treated with NaCN generally give mostly RCN, but the use of AgCN increases the yield of isonitriles RNC.[338]

[334] For a review, see Erashko, Shevelev, and Fainzil'berg, *Russ. Chem. Rev.* **35**, 719–732 (1966).

[335] Leonard and Adamcik, *J. Am. Chem. Soc.* **81**, 595 (1959).

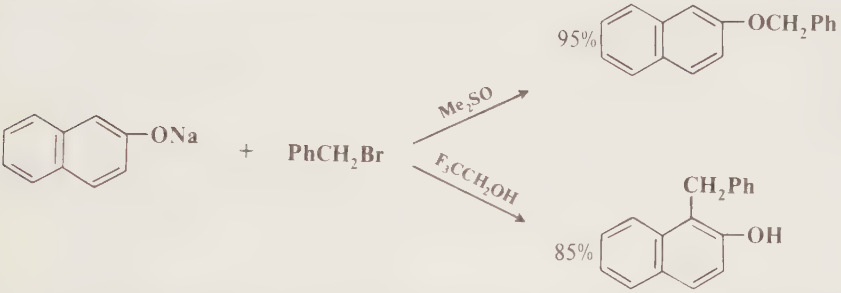
[336] For reviews, see Shevelev, *Russ. Chem. Rev.* **39**, 844–858 (1970); Gompper, *Angew. Chem. Int. Ed. Engl.* **3**, 560–570 (1964) [*Angew. Chem.* **76**, 412–423]. For discussions, see Kornblum, Smiley, Blackwood, and Iffland, *J. Am. Chem. Soc.* **77**, 6269 (1955); Kurts and Beletskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 781 (1970).

[337] This principle, sometimes called *Kornblum's rule*, was first stated by Kornblum, Smiley, Blackwood, and Iffland, Ref. 336.

[338] Actually, this reaction is more complicated than it seems on the surface; see Austad, Songstad, and Stangeland, *Acta Chem. Scand.* **25**, 2327 (1971).

3. An increase in the electron-withdrawing character of the X in RX gives the carbon atom a higher partial positive charge, making it a harder acid. Thus such a change increases the extent of attack by the more electronegative atom of the nucleophile. For example, the O/C ratio increased in the order RI < RBr < RCl < ROTs (R and other conditions held constant) for a series of alkylations of the sodium salt of acetylacetone $CH_3COCH_2COCH_3$.[339]

4. In many cases the solvent influences the position of attack. The freer the nucleophile, the more likely it is to attack with its more electronegative atom, but the more this atom is encumbered by either solvent molecules or by positive counterions, the more likely is attack by the less electronegative atom. In protic solvents, the more electronegative atom is better solvated by hydrogen bonds than the less electronegative atom. In polar aprotic solvents, neither atom of the nucleophile is greatly solvated, but these solvents are very effective in solvating cations. Thus in a polar aprotic solvent the more electronegative end of the nucleophile is freer from entanglement by both the solvent and the cation, so that a change from a protic to a polar aprotic solvent often increases the extent of attack by the more electronegative atom. An example is attack by sodium β-naphthoxide on benzyl bromide, which resulted in 95% O-alkylation in dimethyl sulfoxide and 85% C-alkylation in 2,2,2-trifluoroethanol.[340] However, all polar aprotic solvents are not equal in their effects; for example, in alkylation of the anion of $CH_3COCH_2COCH_3$ with ethyl tosylate, the O/C alkylation ratio varied greatly with the identity of the dipolar aprotic solvent; ranging from 90 : 10 in $MePO(NMe_2)_2$ to 11 : 77 in sulfolane.[341] Changing the cation from Li^+ to Na^+ to K^+ (in nonpolar solvents) also favors O- over C-alkylation[342] for similar reasons (K^+ leaves the nucleophile much freer than does Li^+), as does the use of crown ethers, which are good at solvating cations (p. 82).[343]



5. In some cases steric influences control. Thus the 2,6-di-*t*-butylphenoxide ion gave 88% O-alkylation and 6% C-alkylation with methyl iodide, 11% O- and 59% C-alkylation with ethyl iodide, and 100% C-alkylation with isopropyl iodide:

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[339] Kurts, Genkina, Masias, Beletskaya, and Reutov, *Tetrahedron* **27**, 4777 (1971). For a similar result, see Sarthou, Guibé, and Bram, *J. Chem. Soc., Chem. Commun.* 377 (1974).

[340] Kornblum, Berrigan, and le Noble, *J. Chem. Soc.* **85**, 1141 (1963); Kornblum, Seltzer, and Haberfield, *J. Am. Chem. Soc.* **85**, 1148 (1963). For other examples, see le Noble and Puerta, *Tetrahedron Lett.* 1087 (1966); Brieger and Pelletier, *Tetrahedron Lett.* 3555 (1965); Heiszwolf and Kloosterziel, *Recl. Trav. Chim. Pays-Bas* **89**, 1153, 1217 (1970); Kurts, Masias, Beletskaya, and Reutov, *J. Org. Chem. USSR* **7**, 2323 (1971).

[341] Kurts, Masias, Genkina, Beletskaya, and Reutov, *Doklad. Chem.* **187**, 595 (1969). See also le Noble and Morris, *J. Org. Chem.* **34**, 1969 (1969); Kurts, Sakembaeva, Beletskaya, and Reutov, *Doklad. Chem.* **211**, 590 (1973).

[342] Kornblum, Seltzer, and Haberfield, Ref. 340; Kurts, Beletskaya, Masias, and Reutov, *Tetrahedron Lett.* 3679 (1968).

[343] Smith and Hanson, *J. Org. Chem.* **36**, 1931 (1971); Kurts, Dem'yanov, Beletskaya, and Reutov, *J. Org. Chem. USSR* **9**, 1341 (1973). See also Zook, Russo, Ferrand, and Stotz, *J. Org. Chem.* **33**, 2222 (1968); le Noble and Palit, *Tetrahedron Lett.* 493 (1972).

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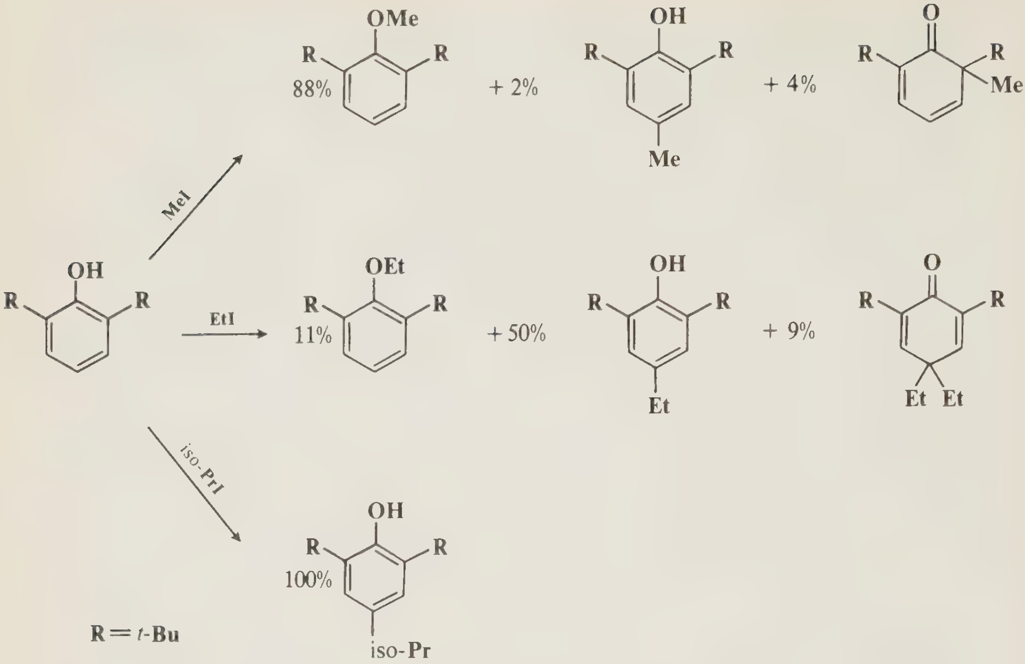
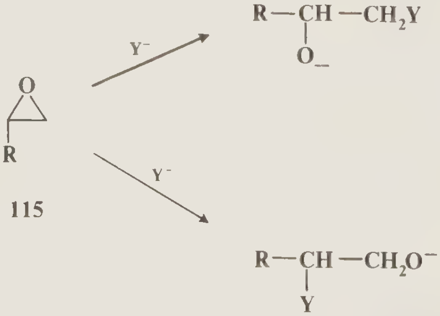


though the unsubstituted phenoxide ion gave only O-alkylation with all three alkyl halides.[344]

Ambident Substrates

Some substrates (for example, 1,3-dichlorobutane) may be attacked at two or more positions. We may call these *ambident substrates*. In the example given, there happen to be two leaving groups in the molecule, but there are two kinds of substrates which are inherently ambident (unless symmetrical). One of these, the allylic type, has already been discussed (p. 303). The other is the epoxy (or the similar aziridine[345] or episulfide) substrate.[346]



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[344] Kornblum and Seltzer, *J. Am. Chem. Soc.* **83**, 3668 (1961).

[345] For a review of SN reactions at an aziridine substrate, see Dermer and Ham, "Ethylenimine and Other Aziridines," pp. 206–273, Academic Press, Inc., New York, 1969.

[346] For reviews of substitution at this type of substrate, see Wohl, *Chimia* **28**, 1–5 (1974); Kirk, *Chem. Ind.* (*London*) 109–116 (1973); Buchanan and Sable, *Sel. Org. Transform.* **2**, 1 95 (1972); Akhrem, Moiseenkov, and Dobrynin, *Russ. Chem. Rev.* **37**, 448–462 (1968); Gritter, in Patai, Ref. 281, pp. 390–400; Parker and Isaacs, *Chem. Rev.* **59**, 737–799 (1959).

Substitution of the free epoxide, which generally occurs under basic or neutral conditions, usually involves an SN2 mechanism. Since primary substrates undergo SN2 attack more readily than secondary, compounds of the type **115** are attacked in neutral or basic solution at the less highly substituted carbon, and stereospecifically, with inversion at that carbon. Under acidic conditions, it is the protonated epoxide which undergoes the reaction. Under these conditions the mechanism may be either SN1 or SN2. In SN1 mechanisms, which favor tertiary carbons, we might expect that attack would be at the more highly substituted carbon, and this is indeed the case. However, even when protonated epoxides react by the SN2 mechanism, attack is usually at the more highly substituted position.[347] Thus, it is often possible to change the direction of ring opening by changing the conditions from basic to acidic, or vice versa. When an epoxide ring is fused to a cyclohexane ring, SN2 ring opening invariably gives diaxial rather than diequatorial ring opening.[348]

REACTIONS

The reactions in this chapter are classified according to the attacking atom of the nucleophile in the order O, S, N, halogen, H, C. For a given nucleophile, reactions are classified by the substrate and leaving group, with alkyl substrates usually considered before acyl ones. Nucleophilic substitutions at a sulfur atom are treated at the end.

Not all the reactions in this chapter are actually nucleophilic substitutions. In some cases the mechanisms are not known with enough certainty even to decide whether a nucleophile, an electrophile, or a free radical is attacking. In other cases (such as **0-77**) conversion of one compound to another may occur by two or even all three of these possibilities, depending on the reagent and on the reaction conditions. However, one or more of the nucleophilic mechanisms previously discussed do hold for the overwhelming majority of the reactions in this chapter.

Oxygen Nucleophiles

A. Attack by OH at an Alkyl Carbon

0-1 Hydrolysis of Alkyl Halides

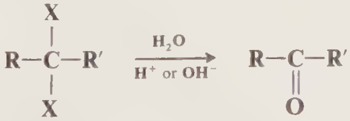
$$\mathrm{RX + H_2O \longrightarrow ROH_2^+ \xrightarrow{-H^+} ROH + H^+}$$

$$\mathrm{RX + OH^- \longrightarrow ROH}$$

Alkyl halides can be hydrolyzed to alcohols. Hydroxide ion is usually required, except that especially active substrates, such as allylic or benzylic types, may be hydrolyzed by water. In contrast to most nucleophilic substitutions at saturated carbons, this reaction can be performed on tertiary substrates without significant interference from elimination side reactions. The reaction is not frequently used for synthetic purposes, because alkyl halides are usually obtained from alcohols.

OS **II,** 408; **III,** 434; **IV,** 128; **51,** 60.

0-2 Hydrolysis of *gem*-Dihalides



$$\mathrm{R{-}\overset{X}{\underset{X}{C}}{-}R' \xrightarrow[H^+\ \text{or}\ OH^-]{H_2O} R{-}\underset{\|}{\overset{}{C}}{-}R'}\quad(\mathrm{C{=}O})$$

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[347] Addy and Parker, *J. Chem. Soc.* 915 (1963); Biggs, Chapman, Finch, and Wray, *J. Chem. Soc. B* 55 (1971).

[348] Murphy, Alumbaugh, and Rickborn, *J. Am. Chem. Soc.* **91,** 2649 (1969).

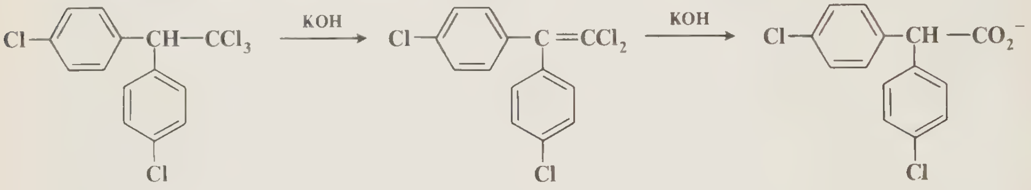
gem-Dihalides can be hydrolyzed, with either acid or basic catalysis, to give aldehydes or ketones.[349] Formally, the reaction may be regarded as first giving R—C(OH)XR′, which is unstable and loses HX to give the carbonyl compound. This is a very good reaction for the preparation of aromatic aldehydes, but for ketones and aliphatic aldehydes the starting dihalides are less easy to prepare. For aldehydes, strong bases cannot be used, because the product undergoes the aldol condensation (**6-40**) or the Cannizzaro reaction (**9-74**).

OS **I,** 95; **II,** 89, 133, 244, 549; **III,** 538, 788; **IV,** 110, 423, 807. Also see OS **III,** 737.

0-3 Hydrolysis of 1,1,1-Trihalides

$$RCX_3 + H_2O \longrightarrow RCOOH$$

This reaction is similar to the previous one. Formally, $RC(OH)X_2$ may be regarded as an intermediate which loses HX to give RCOX, which is easily hydrolyzed to the acid under the reaction conditions. However, in at least one case, that of treatment of DDT with KOH, elimination takes place first, since **116** can be isolated (OS **III,** 270):

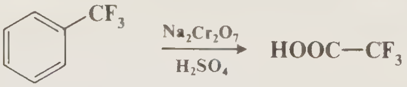


DDT

116

The utility of the method is limited by lack of availability of trihalides, though these compounds can be prepared by addition of CCl_4 and similar compounds to double bonds (reaction **5-37**), and by free-radical halogenation of methyl groups on aromatic rings (reaction **4-1**). When the hydrolysis is carried out in the presence of an alcohol, an ester can be obtained directly.[350] 1,1-Dichloroalkenes can also be hydrolyzed to carboxylic acids, by treatment with H_2SO_4.

In general 1,1,1-trifluorides do not undergo this reaction.[351] As an example of the remarkable stability of the C—F bond to nucleophilic substitution, α,α,α-trifluorotoluene, treated for 2 weeks with sodium dichromate and sulfuric acid, gave trifluoroacetic acid. However, some CF_3 groups



can be hydrolyzed to COOH groups, either by the α-proton mechanism shown above for DDT, or by strong acids[352] which assist in the removal of F by hydrogen bonding.

Chloroform is more rapidly hydrolyzed with base than is dichloromethane or carbon tetrachloride and gives not only formic acid but also carbon monoxide.[353] Hine[354] has shown that the mechanism of chloroform hydrolysis is quite different from that of dichloromethane or carbon tetrachloride, though superficially the three reactions appear similar. The first step is the loss of a proton to give CCl_3 which then loses Cl to give dichlorocarbene CCl_2, which is hydrolyzed to formic acid or carbon monoxide:

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[349] For a review, see Salomaa, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 177–210, Interscience Publishers, New York, 1966.

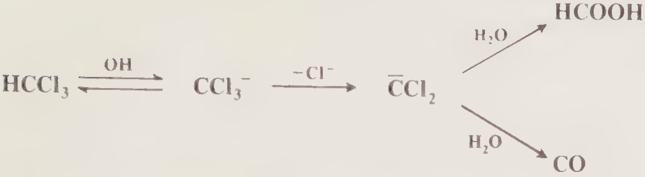
[350] See for example Le Fave and Scheurer, *J. Am. Chem. Soc.* **72,** 2464 (1950).

[351] Sheppard and Sharts, "Organic Fluorine Chemistry," pp. 410–411, W. A. Benjamin, Inc., New York, 1969; Hudlický, "Chemistry of Organic Fluorine Compounds," pp. 205–207. The Macmillan Company, New York, 1962.

[352] For an example, see Burmakov, Alekseeva, and Yagupol'skii, *J. Org. Chem. USSR* **6,** 143 (1970).

[353] For a review, see Kirmse, "Carbene Chemistry," 2d ed., pp. 129–141, Academic Press, Inc., New York, 1971.

[354] Hine, *J. Am. Chem. Soc.* **72,** 2438 (1950). Also see le Noble, *J. Am. Chem. Soc.* **87,** 2434 (1965).



This is an example of an SN1cB mechanism (p. 330). The other two compounds react by the normal mechanisms. Carbon tetrachloride cannot give up a proton, and dichloromethane is not acidic enough.

OS **III,** 270; **V,** 93. Also see OS **I,** 327.

0-4 Hydrolysis of Alkyl Esters of Inorganic Acids

$$\left.\begin{array}{l} R{-}OSO_2OH \\ R{-}OSO_2OR' \\ R{-}OSO_2R' \\ R{-}OSOOH \\ R{-}OSOOR' \\ R{-}OSOR' \\ R{-}ONO_2 \\ R{-}ONO \\ R{-}OPO(OH)_2 \\ R{-}OPO(OR')_2 \\ R{-}OB(OH)_2 \\ \text{and others} \end{array}\right\} \xrightarrow{H_2O} R{-}OH$$

Esters of inorganic acids, including those given above and others, can be hydrolyzed to alcohols. The reactions are most successful when the ester is that of a strong acid, but it can be done for esters of weaker acids by the use of hydroxide ion (a more powerful nucleophile) or acid conditions (which make the leaving group come off more easily). When vinyl substrates are hydrolyzed (p. 313), the products are aldehydes or ketones.

$$R_2C{=}CH{-}X \xrightarrow{H_2O} R_2C{=}CH{-}OH \rightleftharpoons R_2CH{-}CHO$$

These reactions are all considered at one place because they are formally similar, but though some of them involve R—O cleavage and are thus nucleophilic substitutions at a saturated carbon, others involve cleavage of the bond between the inorganic atom and oxygen and are thus nucleophilic substitutions at a sulfur, nitrogen, etc. It is even possible for the same ester to be cleaved at either position, depending on the conditions. Thus benzhydryl *p*-toluenesulfinate ($Ph_2CHOSOC_6H_4CH_3$) was found to undergo C—O cleavage in $HClO_4$ solutions and S—O cleavage in alkaline media.[355] In general, the weaker the corresponding acid, the less likely is C—O cleavage. Thus, sulfonic acid esters $ROSO_2R'$ generally give C—O cleavage,[356] while nitrous acid esters RONO usually give N—O cleavage.[357] Esters of sulfonic acids which are frequently hydrolyzed are mentioned on p. 326. For hydrolysis of sulfonic acid esters, see also reaction **0-118.**

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[355] Bunton and Hendy, *J. Chem. Soc.* 627 (1963). For another example, see Batts, *J. Chem. Soc. B* 551 (1966).

[356] Barnard and Robertson, *Can. J. Chem.* **39,** 881 (1961).

[357] Allen, *J. Chem. Soc.* 1968 (1954); Kobayashi, *Chem. Lett.* 37 (1972).

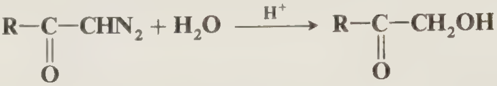
OS **50,** 88.

0-5 Diazotization of Primary Aliphatic Amines

$$RNH_2 + HONO \rightarrow [RN_2{}^+] \xrightarrow{H_2O} N_2 + ROH + \text{other products}$$

The diazotization of primary amines is not usually a good method for the preparation of alcohols, since it leads to a mixture of products (see p. 329). The reaction can be used, however, to measure the amount of NH_2 present in a sample, since nitrogen is evolved quantitatively.

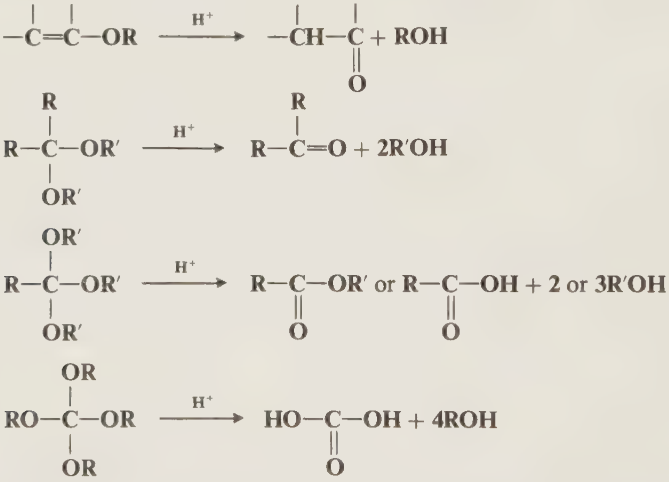
0-6 Hydrolysis of Diazo Ketones



$$R-\underset{\underset{O}{\|}}{C}-CHN_2 + H_2O \xrightarrow{H^+} R-\underset{\underset{O}{\|}}{C}-CH_2OH$$

Diazo ketones are relatively easy to prepare (see reaction **0-116**). When treated with acid, they add a proton to give diazonium salts, which are hydrolyzed to the alcohols by the SN1 or SN2 mechanism.[358] Relatively good yields of α-hydroxy ketones may be prepared in this way, since the diazonium ion is somewhat stabilized by the presence of the carbonyl group, which discourages N_2 from leaving since that would result in an unstable α-carbonyl carbonium ion.

0-7 Hydrolysis of Vinyl Ethers, Acetals, and Similar Compounds[359]



$$-\overset{|}{C}=\overset{|}{C}-OR \xrightarrow{H^+} -\overset{|}{CH}-\underset{\underset{O}{\|}}{\overset{|}{C}} + ROH$$

$$R-\overset{\overset{R}{|}}{\underset{\underset{OR'}{|}}{C}}-OR' \xrightarrow{H^+} R-\overset{\overset{R}{|}}{C}=O + 2R'OH$$

$$R-\overset{\overset{OR'}{|}}{\underset{\underset{OR'}{|}}{C}}-OR' \xrightarrow{H^+} R-\underset{\underset{O}{\|}}{C}-OR' \text{ or } R-\underset{\underset{O}{\|}}{C}-OH + 2 \text{ or } 3R'OH$$

$$RO-\overset{\overset{OR}{|}}{\underset{\underset{OR}{|}}{C}}-OR \xrightarrow{H^+} HO-\underset{\underset{O}{\|}}{C}-OH + 4ROH$$

The alkoxyl group OR is not a leaving group, and so these compounds must be converted to the conjugate acids before they can be hydrolyzed. Although 100% sulfuric acid and other concentrated strong acids readily cleave simple ethers,[360] the only acids used preparatively for this purpose are HBr and HI (reaction **0-68**). However, acetals, ketals, and ortho esters are easily cleaved by dilute acids. These compounds are hydrolyzed with greater facility because carbonium ions of the type $\mathrm{RO{-}\overset{\oplus}{\underset{|}{C}}{-}}$ are greatly stabilized by resonance (p. 156). The reactions therefore proceed by the SN1 mechanism, as shown for acetals:[361]

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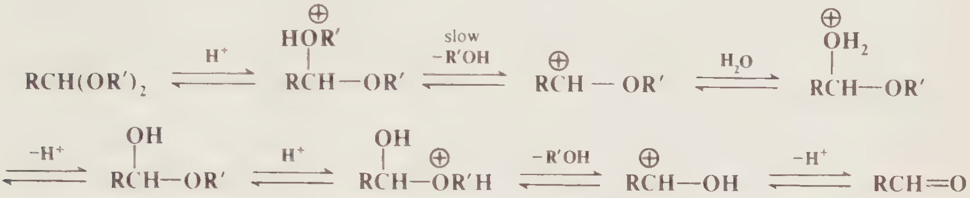
[358] Dahn and Gold, *Helv. Chim. Acta* **46,** 983 (1963); Dahn, Donzel, Merbach, and Gold, *Helv. Chim. Acta* **46,** 994 (1963); Dahn, Gold, Ballenegger, Lenoir, Diderich, and Malherbe, *Helv. Chim. Acta* **51,** 2065 (1968); Dahn and Ballenegger, *Helv. Chim. Acta* **52,** 2417 (1969); Aziz and Tillett, *Tetrahedron Lett.* 2321 (1968); *J. Chem. Soc. B* 1302 (1968); Diderich, *Helv. Chim. Acta* **55,** 2103 (1972); Engberson and Engberts, *Tetrahedron* **30,** 1215 (1974).

[359] For reviews, see Cordes and Bull, *Chem. Rev.* **74,** 581-603 (1974); Cordes, *Prog. Phys. Org. Chem.* **4,** 1-44 (1967); Salomaa, Ref. 349, pp. 184-198; Cordes, in Patai, Ref. 188, pp. 632-656, Interscience Publishers, New York, 1969 (ortho esters); DeWolfe, "Carboxylic Ortho Acid Derivatives," pp. 134-146, Academic Press, Inc., New York, 1970 (ortho esters); Rekasheva, *Russ. Chem. Rev.* **37,** 1009-1022 (1968) (vinyl ethers).

[360] Jaques and Leisten, *J. Chem. Soc.* 2683 (1964). See also Olah and O'Brien, *J. Am. Chem. Soc.* **89,** 1725 (1967).

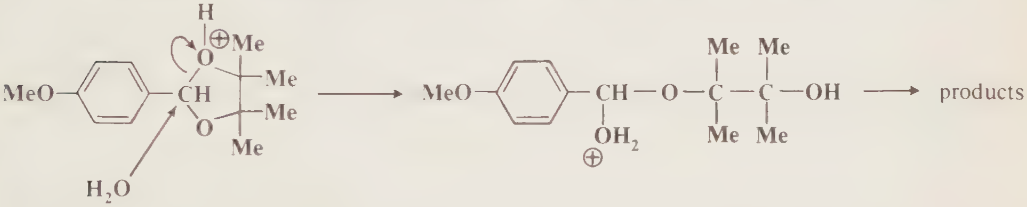


$$\mathrm{RCH(OR')_2} \xrightleftharpoons{\mathrm{H^+}} \overset{\overset{\oplus}{\mathrm{HOR'}}}{\mathrm{RCH{-}OR'}} \xrightleftharpoons[\mathrm{-R'OH}]{\text{slow}} \mathrm{R\overset{\oplus}{C}H-OR'} \xrightleftharpoons{\mathrm{H_2O}} \overset{\overset{\oplus}{\mathrm{OH_2}}}{\mathrm{RCH{-}OR'}}$$

$$\xrightleftharpoons{\mathrm{-H^+}} \overset{\mathrm{OH}}{\mathrm{RCH{-}OR'}} \xrightleftharpoons{\mathrm{H^+}} \overset{\mathrm{OH}\quad\oplus}{\mathrm{RCH{-}OR'H}} \xrightleftharpoons{\mathrm{-R'OH}} \mathrm{R\overset{\oplus}{C}H{-}OH} \xrightleftharpoons{\mathrm{-H^+}} \mathrm{RCH{=}O}$$

This mechanism (which is an SN1cA or A1 mechanism) is the reverse of that for acetal formation by reaction of an aldehyde and an alcohol (reaction **6-6**). Among the facts supporting the mechanism are:[362] (1) The reaction proceeds with *specific* H_3O^+ catalysis (see p. 236). (2) It is faster in D_2O. (3) Optically active ROH are not racemized. (4) Even with *t*-butyl alcohol the R—O bond does not cleave, as shown by ^{18}O labeling.[363] (5) Hydrolysis rates greatly increase in the order $CH_2(OR')_2 < RCH(OR')_2 < R_2C(OR')_2 < RC(OR')_3$, as would be expected for a carbonium-ion intermediate.

While the A1 mechanism shown above operates in most acetal hydrolyses, it has been shown that at least two other mechanisms can also take place with suitable substrates.[364] In one of these mechanisms the second and third of the above steps are concerted, so that the mechanism is SN2cA (or A2). This mechanism has been demonstrated for hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane.[365] In the second mechanism, the first and second steps are concerted. In the case of hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran, *general* acid catalysis was shown,[366] demonstrating that the substrate is protonated in the rate-determining step (p. 236). Reactions in which a substrate is protonated in the rate-determining step are called A-SE2 reactions.[367] However, if protonation of the substrate were all that happens in the slow step, then the proton in the transition state would be expected to lie closer to the weaker base (p. 236). Because the substrate is a much weaker base than water, the proton should be largely transferred. Since



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[361] Kreevoy and Taft, *J. Am. Chem. Soc.* **77,** 3146, 5590 (1955).

[362] For a discussion of these, and of other evidence, see Cordes, *Prog. Phys. Org. Chem.*, Ref. 359.

[363] Cawley and Westheimer, *Chem. Ind.* (*London*) 656 (1960).

[364] For a review, see Fife, *Acc. Chem. Res.* **5,** 264–272 (1972).

[365] Fife, *J. Am. Chem. Soc.* **89,** 3228 (1967).

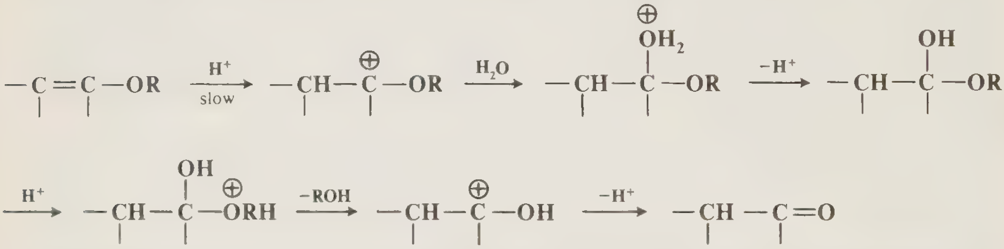
[366] Fife and Jao, *J. Am. Chem. Soc.* **90,** 4081 (1968); Fife and Brod, *J. Am. Chem. Soc.* **92,** 1681 (1970). For other examples, see Kankaanperä and Lahti, *Acta Chem. Scand.* **23,** 2465 (1969); Anderson and Capon, *J. Chem. Soc. B* 1033 (1969); Anderson and Fife, *J. Am. Chem. Soc.* **93,** 1701 (1971); Capon and Page, *J. Chem. Soc., Perkin Trans. 2* 522 (1972); Mori, Porzio, and Schaleger, *J. Am. Chem. Soc.* **94,** 5034 (1972); Mori and Schaleger, *J. Am. Chem. Soc.* **94,** 5039 (1972).

[367] For a review of A-SE2 reactions, see Williams and Kreevoy, *Adv. Phys. Org. Chem.* **6,** 63–101 (1968).

the Brönsted coefficient was found to be 0.5, the proton was actually transferred only about halfway (p. 236). This can be explained if the basicity of the substrate were increased by partial breaking of the C—O bond. The conclusion is thus drawn that steps 1 and 2 are concerted. The hydrolysis of ortho esters is also subject to general acid catalysis.

Although acetals, ketals, and ortho esters are easily hydrolyzed by acids, they are extremely resistant to hydrolyis by bases. An aldehyde or ketone can therefore be protected from attack by a base by conversion to the acetal or ketal (reaction **6-6**), and then can be later cleaved with acid. Thioacetals, thioketals, *gem*-diamines, and other compounds which contain any two of the groups OR, OCOR, NR_2, NHCOR, SR, and halogen on the same carbon can also be hydrolyzed to aldehydes or ketones, in most cases by acid treatment, though with some substrates this is insufficient and other catalysts must be used. For example, thioacetals $RCHSR'_2$ and thioketals $R_2CSR'_2$ have been converted to aldehydes and ketones, respectively, by treatment with $HgCl_2$,[368] with HgO-BF_3,[369] and with certain other reagents.[370]

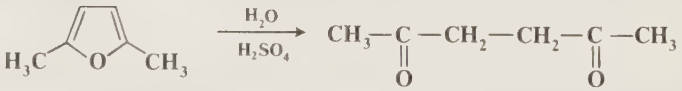
Vinyl ethers are readily hydrolyzed by acids; the rate-determining step is protonation of the substrate. However, protonation does not take place at the oxygen, but at the β-carbon.[371] After that the mechanism is similar to the A1 mechanism given above for the hydrolysis of acetals.



$$-\underset{|}{C}=\underset{|}{C}-OR \xrightarrow[\text{slow}]{H^+} -\underset{|}{CH}-\overset{\oplus}{\underset{|}{C}}-OR \xrightarrow{H_2O} -\underset{|}{CH}-\overset{\overset{\oplus}{OH_2}}{\underset{|}{C}}-OR \xrightarrow{-H^+} -\underset{|}{CH}-\overset{OH}{\underset{|}{C}}-OR$$

$$\xrightarrow{H^+} -\underset{|}{CH}-\overset{OH}{\underset{|}{C}}-\overset{\oplus}{O}RH \xrightarrow{-ROH} -\underset{|}{CH}-\overset{\oplus}{\underset{|}{C}}-OH \xrightarrow{-H^+} -\underset{|}{CH}-\underset{|}{C}=O$$

Among the facts supporting this mechanism (which is an A-SE2 mechanism because the substrate is protonated in the rate-determining step) are: (1) ^{18}O labeling shows that in $ROCH{=}CH_2$ it is the vinyl-oxygen bond and not the RO bond which cleaves;[372] (2) the reaction is subject to general acid catalysis;[373] and (3) there is a solvent isotope effect when D_2O is used.[373] Enamines are also hydrolyzed by acids (see reaction **6-2**); the mechanism is similar. Furans represent a special case of vinyl ethers which are cleaved by acid to give 1,4 diones. Thus



$$\xrightarrow[H_2SO_4]{H_2O} CH_3-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-CH_3$$

Mixed aryl alkyl ethers have been cleaved in 99.6% H_2SO_4 by a simple SN1 mechanism. Dialkyl ethers have also been cleaved in this medium, but in this case the ether first reacts with SO_3 to give **117**, so that the leaving group is $ROSO_2OH$.[374] *t*-Butyl ethers are readily cleaved with

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[368] Corey and Erickson, *J. Org. Chem.* **36**, 3553 (1971).

[369] Vedejs and Fuchs, *J. Org. Chem.* **36**, 366 (1971).

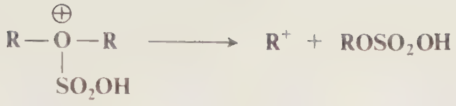
[370] For example, see Huurdeman, Wynberg, and Emerson, *Synth. Commun.* **2**, 7 (1972); Tamura, Sumoto, Fujii, Satoh, and Ikeda, *Synthesis* 312 (1973).

[371] Jones and Wood, *J. Chem. Soc.* 5400 (1964); Okuyama, Fueno, Nakatsuji, and Furukawa, *J. Am. Chem. Soc.* **89**, 5826 (1967); Fueno, Matsumura, Okuyama, and Furukawa, *Bull. Chem. Soc. Jpn.* **41**, 818 (1968); Okuyama, Fueno, and Furukawa, *Bull. Chem. Soc. Jpn.* **43**, 3256 (1970); Kreevoy and Eliason, *J. Phys. Chem.* **72**, 1313 (1969); Lienhard and Wang, *J. Am. Chem. Soc.* **91**, 1146 (1969). Kresge and Chen, *J. Am. Chem. Soc.* **94**, 2818 (1972).

[372] Kiprianova and Rekasheva, *Dokl. Akad. Nauk SSSR* **142**, 589 (1962).

[373] Fife, *J. Am. Chem. Soc.* **87**, 1084 (1965); Salomaa, Kankaanperä, and Lajunen, *Acta Chem. Scand.* **20**, 1790 (1966); Kresge and Chiang, *J. Chem. Soc. B* 53, 58 (1967).

[374] Jaques and Leisten, *J. Chem. Soc.* 4963 (1961).



$$\underset{SO_2OH}{R-\overset{\oplus}{O}-R} \longrightarrow R^+ + ROSO_2OH$$

117

perfluoroacetic acid.[375] This is not nucleophilic substitution, but elimination, the *t*-butyl group being converted to isobutylene (also see reaction **7-2**):

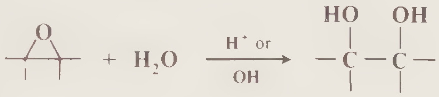
$$ROC(CH_3)_3 \xrightarrow{F_3COOH} ROH + (CH_3)_2C{=}CH_2$$

Oxonium ions are cleaved by water to give an alcohol and an ether:

$$R_3O^+ \quad BF_4^- + H_2O \longrightarrow R_2O + ROH + HBF_4$$

OS **I**, 67, 205; **II**, 302, 305, 323; **III**, 37, 127, 465, 470, 536, 541, 564, 641, 701, 731, 800; **IV**, 302, 499, 660, 816, 903; **V**, 91, 292, 294, 703, 716, 937, 967, 1088; **51**, 11, 24, 39, 76; **53**, 44, 48; **54**, 19, 42.

0-8 Hydrolysis of Epoxides



The hydrolysis of epoxides is a convenient method for the preparation of *vic*-glycols. The reaction is catalyzed by acids or bases (see discussion of the mechanism on p. 341). Among acid catalysts the reagent of choice is perchloric acid, since side reactions are minimized with this reagent.[376] Dimethyl sulfoxide is a superior solvent for the alkaline hydrolysis of epoxides.[377]

OS **V**, 414.

B. Attack by OH at an Acyl Carbon

0-9 Hydrolysis of Acyl Halides

$$RCOCl + H_2O \longrightarrow RCOOH$$

Acyl halides are so reactive that hydrolysis is easily carried out.[378] In fact, most simple acyl halides must be stored under anhydrous conditions lest they react with water in the air. Consequently, water is usually a strong enough nucleophile for the reaction, though in difficult cases hydroxide ion may be required. The reaction is seldom synthetically useful, because acyl halides are normally prepared from acids. The reactivity order is $F < Cl < Br < I$.[379] If a carboxylic acid is used as the nucleophile, an exchange reaction may take place (see reaction **0-75**). The mechanism[379] of hydrolysis may be either SN1 or tetrahedral, the former occurring in highly polar solvents and in the absence of strong nucleophiles.[380] The tetrahedral mechanism in this case may be formulated as

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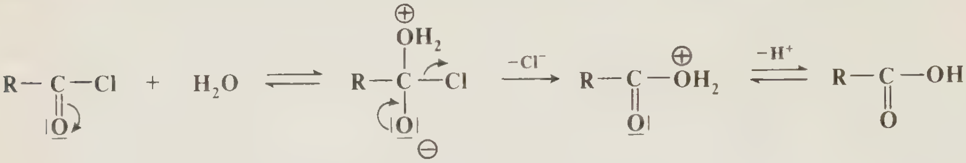
[375] Beyerman and Bontekoe, *Recl. Trav. Chim. Pays-Bas* **81**, 691 (1962); Beyerman and Heiszwolf, *Recl. Trav. Chim. Pays-Bas* **84**, 203 (1965); Callahan, Anderson, Paul, and Zimmerman, *J. Am. Chem. Soc.* **85**, 201 (1963).

[376] Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, p. 796, John Wiley & Sons, New York, 1967.

[377] Berti, Macchia, and Macchia, *Tetrahedron Lett.* 3421 (1965).

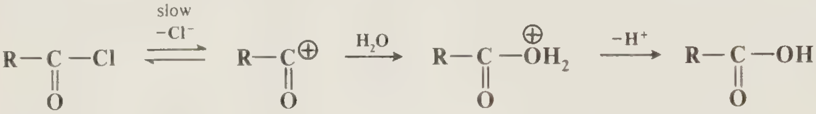
[378] For a review, see Sonntag, *Chem. Rev.* **52**, 237–416 (1953), pp. 251–258.

[379] For a review, see Talbot, Ref. 188, pp. 226–257. For a review of the mechanisms of reactions of acyl halides with water, alcohols, and amines, see Kivinen, in Patai, "The Chemistry of Acyl Halides," pp. 177–230, Interscience Publishers, New York, 1972.

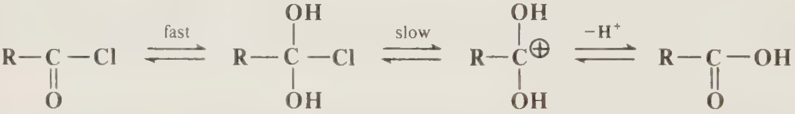


There are two possible paths for the SN1 mechanism:

Path 1



Path 2

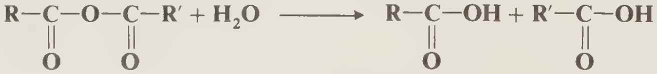


It is not easy to distinguish path 2 (which involves preliminary hydration) from path 1, but most evidence favors path 2.[381]

Hydrolysis of acyl halides is not usually catalyzed by acids, except for acyl fluorides, where hydrogen bonding can assist in the removal of F.[382]

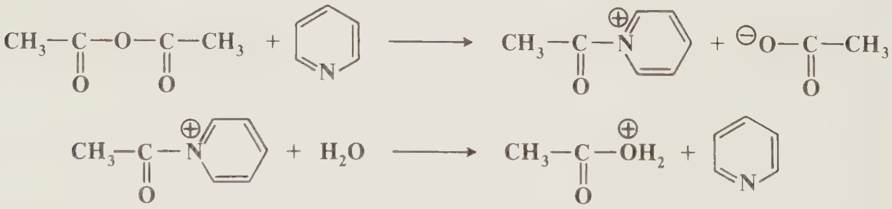
OS **II**, 74.

0-10 Hydrolysis of Anhydrides



$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R' + H_2O \longrightarrow R-\underset{\underset{O}{\|}}{C}-OH + R'-\underset{\underset{O}{\|}}{C}-OH$$

Anhydrides are somewhat more difficult to hydrolyze than acyl halides, but here too water is usually a strong enough nucleophile. The mechanism is usually tetrahedral. Only under acid catalysis does the SN1 mechanism occur, and seldom even then.[383] Anhydride hydrolysis can also be catalyzed by bases. Of course, OH^- attacks more readily than water, but other bases can also catalyze the reaction. This phenomenon, called *nucleophilic catalysis* (p. 310), is actually the result of *two* successive tetrahedral mechanisms. For example, pyridine catalyzes the hydrolysis of acetic anhydride in this manner:[384]



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[380] Bender and Chen, *J. Am. Chem. Soc.* **85**, 30 (1963).

[381] Hudson and Moss, *J. Chem. Soc.*, 5157 (1962).

[382] Bevan and Hudson, *J. Chem. Soc.* 2187 (1953); Satchell, *J. Chem. Soc.* 555 (1963).

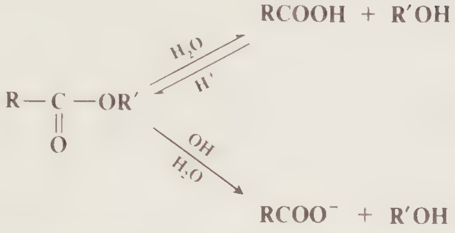
[383] Satchell, *Q. Rev., Chem. Soc.* **17**, 160–203 (1963), pp. 172–173. For a review of the mechanism, see Talbot, Ref. 188, pp. 280–287.

[384] Butler and Gold, *J. Chem. Soc.* 4362 (1961); Fersht and Jencks, *J. Am. Chem. Soc.* **92**, 5432, 5442 (1970).

Many other nucleophiles similarly catalyze the reaction.

OS **I**, 408; **II**, 140, 368, 382; **IV**, 766; **V**, 8, 813.

0-11 Hydrolysis of Esters



Ester hydrolysis is usually catalyzed by acids or bases. Since OR is a much poorer leaving group than halide or OCOR, water alone does not hydrolyze most esters. When bases catalyze the reaction, the attacking species is the more powerful nucleophile OH^-. This reaction is called *saponification* and gives the salt of the acid. Acids catalyze the reaction by making the carbonyl carbon more positive and therefore more susceptible to attack by the nucleophile. Both reactions are equilibrium reactions, so that they are practicable only when there is a way of shifting the equilibrium to the right. Since formation of the salt does just this, ester hydrolysis is almost always done for preparative purposes in basic solution, unless the compound is base-sensitive. Ester hydrolysis may also be catalyzed by metal ions, by enzymes, and by nucleophiles (see reaction **0-10**).[188] Methanesulfonic acid is also a good catalyst,[385] as is potassium superoxide KO_2 in benzene in the presence of 18-crown-6 (p. 82).[385a] Phenolic esters may be similarly cleaved; in fact the reaction is usually faster for these compounds. Lactones also undergo the reaction (though if the lactone is five- or six-membered, the hydroxy acid often spontaneously relactonizes); and thiol esters (RCOSR′) give mercaptans R′SH. Sterically hindered esters are hydrolyzed with difficulty (p. 316).

Ingold[386] has classified the acid- and base-catalyzed hydrolyses of esters (and the formation of esters, since these are reversible reactions and thus have the same mechanisms) into eight possible mechanisms (Table 12) depending on the following conditions: (1) acid- or base-catalyzed, (2) unimolecular or bimolecular, and (3) acyl cleavage or alkyl cleavage.[387] All eight of these are SN1, SN2, or tetrahedral mechanisms. The acid-catalyzed mechanisms are shown with reversible arrows. They are not only reversible but symmetrical; that is, the mechanisms for ester formation are exactly the same as for hydrolysis, except that H replaces R. Internal proton transfers, such as shown for **A** and **B** and for **C** and **D**, may not actually be direct but may take place through the solvent. There is much physical evidence to show that esters are initially protonated on the carbonyl and not on the alkyl oxygen (Chapter 8, Ref. 16). We have nevertheless shown the AAC1 mechanism as proceeding through the ether-protonated intermediate **A**, since it is difficult to envision OR′ as a leaving group here. It is of course possible for a reaction to proceed through an intermediate even if only a tiny concentration is present. The designations AAC1, etc., are those of Ingold. The AAC2 and AAC1 mechanisms are also called A2 and A1, respectively. It may be noted that the AAC1 mechanism is actually the same as the SN1cA mechanism for this type of substrate, and that AAL2 is analogous to SN2cA. Some authors use A1 and A2 to refer to all types

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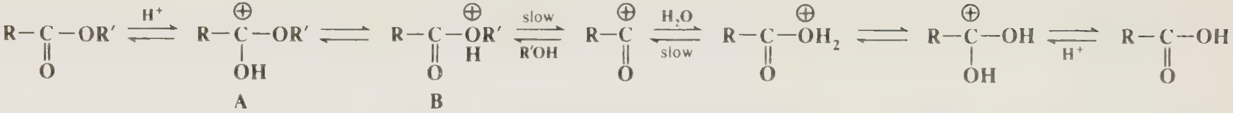
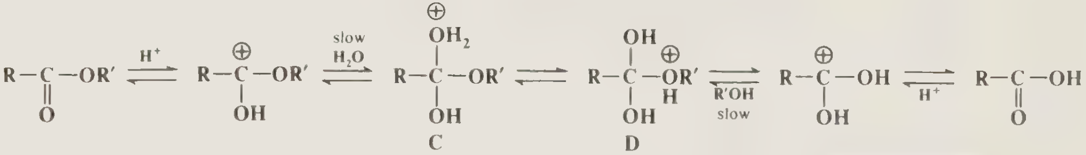
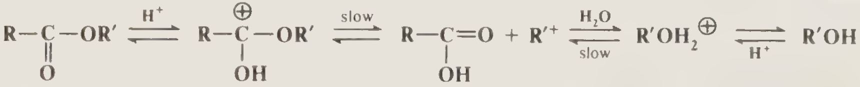
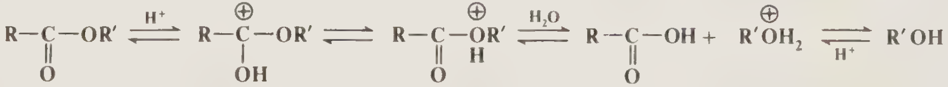
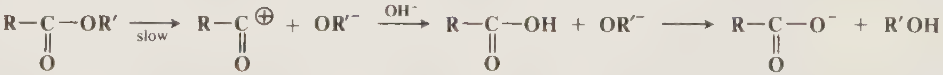
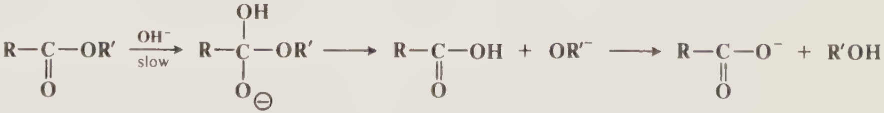
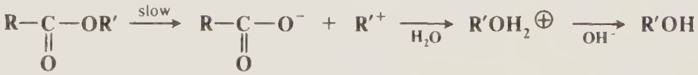
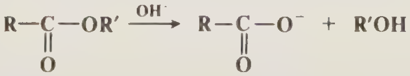
[385] Loev, *Chem. Ind.* (*London*) 193 (1964).

[385a] San Filippo, Romano, Chern, and Valentine, *J. Org. Chem.* **41**, 586 (1976).

[386] Ingold, Ref. 308, pp. 1129–1131.

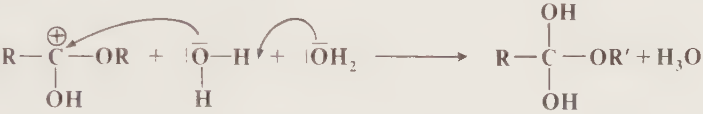
[387] For reviews of the mechanisms of ester hydrolysis and formation, see Kirby, in Bamford and Tipper, Ref. 168, vol. 10, pp. 57–207, 1972; Euranto, in Patai, Ref. 188, pp. 505–588.

TABLE 12 Classification of the eight mechanisms for ester hydrolysis and formation[386]

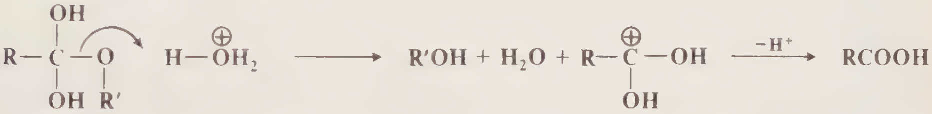
		Name	Type	
Acid catalysis	Acyl cleavage	AAC1	SN1	
		AAC2	Tetra-hedral	
	Alkyl cleavage	AAL1	SN1	
		AAL2	SN2	
Basic catalysis	Acyl cleavage	BAC1	SN1	
		BAC2	Tetra-hedral	
	Alkyl cleavage	BAL1	SN1	
		BAL2	SN2	

of nucleophilic substitution in which the leaving group first acquires a proton. The base-catalyzed reactions are not shown with reversible arrows, since they are reversible only in theory and not in practice. Hydrolyses taking place under neutral conditions are classified as B mechanisms.

Of the eight mechanisms, only six have actually been observed in hydrolysis of carboxylic esters. The two which have not been observed are the BAC1 and the AAL2 mechanisms. The BAC1 is an SN1 mechanism with OR′ as the leaving group, which does not happen, while the AAL2 requires water to be a nucleophile in an SN2 process.[387a] The most common mechanisms are the BAC2 for basic catalysis and the AAC2[388] for acid catalysis, that is, the two tetrahedral mechanisms. Both of these involve acyl-oxygen cleavage. Evidence for this is: (1) hydrolysis with $H_2{}^{18}O$ results in the ^{18}O appearing in the acid and not in the alcohol;[389] (2) esters with chiral R′ groups give alcohols with *retention* of configuration;[390] (3) allylic R′ gives no allylic rearrangement;[391] and (4) neopentyl R′ gives no rearrangement;[392] all these facts indicating that the O—R′ bond is not broken. It has been concluded that in the AAC2 mechanism two molecules of water are required.



If this is so, the protonated derivatives **C** and **D** would not appear at all. This conclusion stems from a value of *w* (see p. 235) of about 5, indicating that water acts as a proton donor here as well as a nucleophile.[393] Termolecular processes are rare, but in this case the two water molecules are already connected by a hydrogen bond. To maintain the symmetry of the process, the reaction would then continue as follows:



The other mechanism involving acyl cleavage is the AAC1 mechanism. This is rare, being found only where R is very bulky, so that bimolecular attack is sterically hindered, and only in ionizing solvents. The mechanism has been demonstrated for esters of 2,4,6-trimethylbenzoic acid (mesitoic acid). This acid depresses the freezing point of sulfuric acid four times as much as would be predicted from its molecular weight, which is evidence for the equilibrium

$$\mathrm{ArCOOH} + 2\mathrm{H_2SO_4} \rightleftharpoons \mathrm{ArCO}^{\oplus} + \mathrm{H_3O^+} + 2\mathrm{HSO_4^-}$$

In a comparable solution of benzoic acid the freezing point is depressed only twice the predicted amount, indicating only a normal acid-base reaction. Further, a sulfuric acid solution of methyl mesitoate when poured into water gave mesitoic acid, while a similar solution of methyl benzoate similarly treated did not.[394] The AAC1 mechanism is also found when acetates of phenols or of primary alcohols are hydrolyzed in concentrated (more than 90%) H_2SO_4 (the mechanism under the more usual dilute acid conditions is the normal AAC2).[395] This conclusion stems from kinetic investigations similar to those used in determining w values. Synthetic advantage can be taken of this: many aliphatic esters are conveniently hydrolyzed in concentrated H_2SO_4.[396]

[387a] There is evidence that the AAL2 mechanism can take place in the hydrolysis of imino esters RC(OR′)=NR″: McClelland, *J. Am. Chem. Soc.* **97**, 3177 (1975).

[388] For a discussion of this mechanism with specific attention to the proton transfers involved, see Zimmerman and Rudolph, *Angew. Chem. Int. Ed. Engl.* **4**, 40–49 (1965) [*Angew. Chem.* **77**, 65–74].

[389] For one of several examples, see Polanyi and Szabo, *Trans. Faraday Soc.* **30**, 508 (1934).

[390] Holmberg, *Ber.* **45**, 2997 (1912).

[391] Ingold and Ingold, *J. Chem. Soc.* 758 (1932).

[392] Norton and Quayle, *J. Am. Chem. Soc.* **62**, 1170 (1940).

[393] Martin, *J. Am. Chem. Soc.* **84**, 4130 (1962). See also Lane, *J. Am. Chem. Soc.* **86**, 2521 (1964); Lane, Cheung, and Dorsey, *J. Am. Chem. Soc.* **90**, 6492 (1968); Yates and McClelland, *J. Am. Chem. Soc.* **89**, 2686 (1967); Yates, *Acc. Chem. Res.* **6**, 136–144 (1971).

[394] Treffers and Hammett, *J. Am. Chem. Soc.* **59**, 1708 (1937). For other evidence for this mechanism, see Bender and Chen, *J. Am. Chem. Soc.* **85**, 37 (1963).

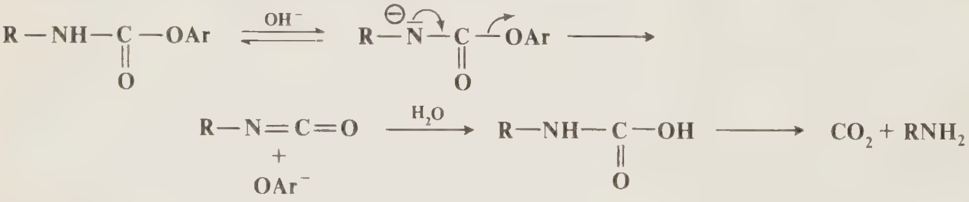
The mechanisms involving alkyl-oxygen cleavage[397] are ordinary SN1 and SN2 mechanisms in which OCOR (an acyloxy group) or its conjugate acid is the leaving group. Two of the three mechanisms, the BAL1 and AAL1 mechanisms, occur most readily when R′ comes off as a stable carbonium ion, that is, when R′ is tertiary alkyl, allyl, benzyl, etc. For acid catalysis, most esters with this type of alkyl group (especially tertiary alkyl) cleave by this mechanism, but even for these substrates, the BAL1 mechanism occurs only in neutral or weakly basic solution, where the rate of attack by OH^- is so slowed that the normally slow (by comparison) unimolecular cleavage takes over. These two mechanisms have been established by kinetic studies. ^{18}O labeling, and isomerization of R′.[398] Secondary and benzylic acetates hydrolyze by the AAC2 mechanism in dilute H_2SO_4, but in concentrated acid the mechanism changes to AAL1.[395] The remaining mechanism, BAL2, is very rare, because it requires OH^- to attack an alkyl carbon when an acyl carbon is also available, but it has been observed in the hydrolysis of β-lactones under neutral conditions[399] (because cleavage of the C—O bond in the transition state opens the four-membered ring and relieves strain), the alkaline hydrolysis of methyl 2,4,6-tri-*t*-butyl benzoate,[400] and in the unusual reaction[401]

$$\text{ArCOOMe} + \text{RO}^- \longrightarrow \text{ArCOO}^- + \text{ROMe}$$

When it does occur, the BAL2 mechanism is easy to detect, since it is the only one of the six observed mechanisms which requires inversion at R′. However, in the last example given, the mechanism is evident from the nature of the product, since the ether could have been formed in no other way.

To sum up the acid-catalysis mechanisms, AAC2 and AAL1 are the common mechanisms, the latter for R′ which give stable carbonium ions, the former for practically all the rest. AAC1 is rare, being found mostly with strong acids and sterically hindered R. AAL2 has not been observed. For basic catalysis, BAC2 is almost universal; BAL1 occurs only with R′ which give stable carbonium ions, and then only in weakly basic or neutral solution; BAL2 is very rare; and BAC1 has never been observed.

In the special case of alkaline hydrolysis of N-substituted aryl carbamates, there is another mechanism,[401a] involving elimination-addition:[402]



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[395] Yates, Ref. 393.

[396] van Bekkum, Buurmans, Wepster, and van Wijk, *Recl. Trav. Chim. Pays-Bas* **88**, 301 (1969).

[397] For a review of these, see Davies and Kenyon, *Q. Rev., Chem. Soc.* **9**, 203–228 (1955).

[398] For discussions, see Kirby, Ref. 387, pp. 86–101; Ingold, Ref. 308, pp. 1137–1142, 1157–1163.

[399] Cowdrey, Hughes, Ingold, Masterman, and Scott, *J. Chem. Soc.* 1264 (1937); Long and Purchase, *J. Am. Chem. Soc.* **73**, 3267 (1950).

[400] Barclay, Hall, and Cooke, *Can. J. Chem.* **40**, 1981 (1962).

[401] Sneen and Rosenberg, *J. Org. Chem.* **26**, 2099 (1961).

[401a] For a review of elimination-addition mechanisms at a carbonyl carbon, see Williams and Douglas, *Chem. Rev.* **75**, 627–649 (1975).

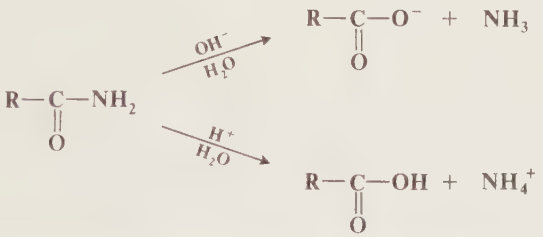
[402] Bender and Homer, *J. Org. Chem.* **30**, 3975 (1965); Vontor, Socha, and Večeřa, *Collect. Czech. Chem. Commun.* **37**, 2183 (1972); Williams, *J. Chem. Soc., Perkin Trans. 2* 808 (1972), 1244 (1973); Hegarty and Frost, *J. Chem. Soc., Perkin Trans. 2* 1719 (1973); Menger and Glass, *J. Org. Chem.* **39**, 2469 (1974); Sartore, Bergon, and Calmon, *Tetrahedron Lett.* 3133 (1974).

This mechanism does not apply to unsubstituted or N,N-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α-position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism, involving a ketene intermediate.[403]

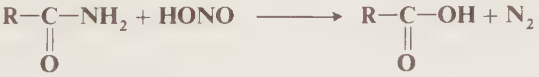
The acid-catalyzed hydrolysis of enol esters $RCOOCR'{=}CR''_2$ can take place either by the normal AAC2 mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of vinyl ethers given in reaction **0-7**, depending on reaction conditions.[404] In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone R''_2CHOR'.

OS **I**, 351, 360, 366, 379, 391, 418, 523; **II**, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; **III**, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS **V**, 1050), 833, 835; **IV**, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; **V**, 8, 445, 509, 687, 762, 887, 985, 1031; **50**, 94; **51**, 139; **52**, 39; **53**, 13; **55**, 67. Ester hydrolyses with concomitant decarboxylation are listed at reaction **2-39**.

0-12 Hydrolysis of Amides



Unsubstituted amides ($RCONH_2$) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion, or the salt of the acid and ammonia. N-Substituted (RCONHR′) and N,N-disubstituted ($RCONR'_2$) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, etc., also undergo the reaction. Water alone is not sufficient to hydrolyze most amides, since NH_2 is even a poorer leaving group than OR. Often prolonged heating is required even with acid or basic catalysts. In difficult cases, nitrous acid can be used (unsubstituted amides only) in a reaction similar to **0-5**:



$$R{-}\underset{\Large O}{\underset{\|}{C}}{-}NH_2 + HONO \longrightarrow R{-}\underset{\Large O}{\underset{\|}{C}}{-}OH + N_2$$

In contrast to reaction **0-5**, side reactions are not a problem here, and this reaction is much faster than ordinary hydrolysis: for benzamide the rate ratio was 2.5×10^7.[405] Another procedure for difficult cases involves treatment with aqueous sodium peroxide.[405a] Imidazolides (**118**) are particularly easy to hydrolyze,[406] and these are often used in synthesis (for an example, see p. 365).

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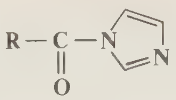
[403] Casanova, Werner, and Kiefer, *J. Am. Chem. Soc.* **89**, 2411 (1967); Bruice and Holmquist, *J. Am. Chem. Soc.* **90**, 7136 (1968); Holmquist and Bruice, *J. Am. Chem. Soc.* **91**, 2993, 3003 (1969); Pratt, and Bruice, *J. Am. Chem. Soc.* **92**, 5956 (1970); Campbell and Lawrie, *Chem. Commun.* 355 (1971). See also Tobias and Kézdy, *J. Am. Chem. Soc.* **91**, 5171 (1969).

[404] See for example Noyce and Pollack, *J. Am. Chem. Soc.* **91**, 119, 7158 (1969); Noyce and Myers, *J. Org. Chem.* **35**, 2460 (1970).

[405] Ladenheim and Bender, *J. Am. Chem. Soc.* **82**, 1895 (1960).

[405a] Vaughan and Robbins, *J. Org. Chem.* **40**, 1187 (1975).

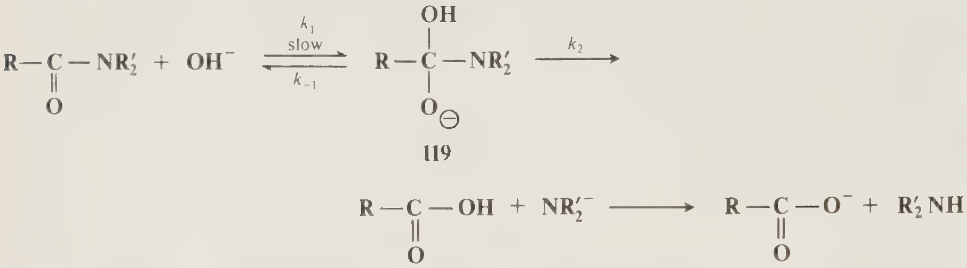
[406] For reviews, see Staab, *Angew. Chem. Int. Ed. Engl.* **1**, 351–367 (1962) [*Angew. Chem.* **74**, 407–423]; Staab and Rohr, *Newer Methods Prep. Org. Chem.* **5**, 61–108 (1968).



118

Amide hydrolysis can also be catalyzed by nucleophiles (see p. 310).

The same framework of eight possible mechanisms which were discussed for ester hydrolysis can also be applied to amide hydrolysis.[407] Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since in both cases salts are formed. For basic catalysis[408] the mechanism is BAC2.

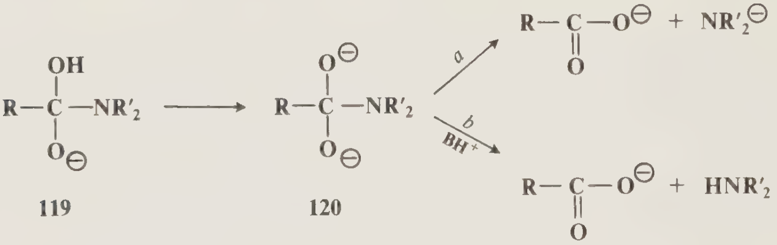


$$R-\underset{\underset{O}{\|}}{C}-NR'_2 + OH^- \underset{k_{-1}}{\overset{k_1\text{ slow}}{\rightleftharpoons}} R-\underset{\underset{O^{\ominus}}{|}}{\overset{\overset{OH}{|}}{C}}-NR'_2 \xrightarrow{k_2}$$

119

$$R-\underset{\underset{O}{\|}}{C}-OH + NR'^-_2 \longrightarrow R-\underset{\underset{O}{\|}}{C}-O^- + R'_2NH$$

There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. In certain cases, kinetic studies have shown that the reaction is second order in OH^-, indicating that **119** can lose a proton to give **120**.[409] Depending on the nature of R′, **120** can cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.[410] Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2, of substituents on the atomatic rings in a series of amides $CH_3CONHAr$ led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents, and path *b* when electron-donating groups are present.[411] The presence of electron-withdrawing groups helps to stabilize



119 **120**

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[407] For reviews, see O'Connor, *Q. Rev., Chem. Soc.* **24,** 553–564 (1970); Talbot, Ref. 188, pp. 257–280; Challis and Challis, in Zabicky, "The Chemistry of Amides," pp. 731–857, Interscience Publishers, New York, 1970.

[408] For a comprehensive list of references, see DeWolfe and Newcomb, *J. Org. Chem.* **36,** 3870 (1971).

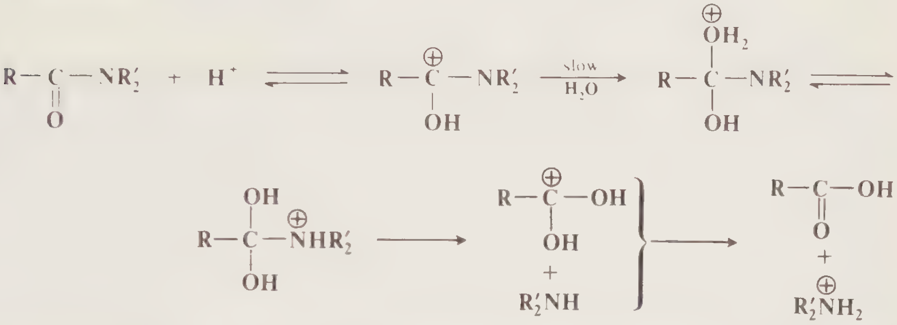
[409] Biechler and Taft, *J. Am. Chem. Soc.* **79,** 4927 (1957).

[410] Eriksson and Holst, *Acta Chem. Scand.* **20,** 1892 (1966); Eriksson and Bratt, *Acta Chem. Scand.* **21,** 1812 (1967); Eriksson, *Acta Chem. Scand.* **22,** 892 (1968); *Acta Pharm. Suec.* **6,** 139–162 (1969).

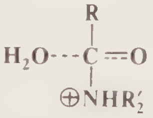
[411] Bender and Thomas, *J. Am. Chem. Soc.* **83,** 4183 (1961); Pollack and Bender, *J. Am. Chem. Soc.* **92,** 7190 (1970); Kershner and Schowen, *J. Am. Chem. Soc.* **93,** 2014 (1971); Schowen, Hopper, and Bazikian, *J. Am. Chem. Soc.* **94,** 3095 (1972). See also Ref. 408; Gani and Viout, *Tetrahedron Lett.* 5241 (1972); Menger and Donohue, *J. Am. Chem. Soc.* **95,** 432 (1973); Hopper, Schowen, Venkatasubban, and Jayaraman, *J. Am. Chem. Soc.* **95,** 3280 (1973); Pollack and Dumsha, *J. Am. Chem. Soc.* **95,** 4463 (1973).

the negative charge on the nitrogen, so that NR'_2 can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not NR'^-_2 but the conjugate NHR'_2 (path *b*). Though we have shown formation of **119** as the rate-determining step in the BAC2 mechanism, this is true only at high base concentrations. At lower concentrations of base, the cleavage of **119** or **120** becomes rate-determining.[412]

For acid catalysis, matters are less clear. The reaction is generally second order, and it is known that amides are primarily protonated on the oxygen (Chapter 8, Ref. 16). Because of these facts it has been generally agreed that most acid-catalyzed amide hydrolysis takes place by the AAC2 mechanism.



Further evidence for this mechanism is that a small but detectable amount of ^{18}O exchange (see p. 310) has been found in the acid-catalyzed hydrolysis of benzamide[413] (^{18}O exchange has also been detected for the base-catalyzed process,[414] in accord with the BAC2 mechanism). However, on the basis of certain kinetic results, it has been suggested[415] that acid-catalyzed amide hydrolysis in at least some cases takes place partially or exclusively on the small amount of N-protonated amide,[416] either with the transition state **121** or by simultaneous attack by H_2O



121

and departure of NHR'_2. The latter, if true, would be a rare example of an SN2 mechanism at a carbonyl carbon. Kinetic data have shown that three molecules of water are involved in the rate-determining step,[417] suggesting that, as in the AAC2 mechanism for ester hydrolysis (**0-11**), additional water molecules take part in a process such as

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[412] Schowen, Jayaraman, and Kershner, *J. Am. Chem. Soc.* **88,** 3373 (1966).

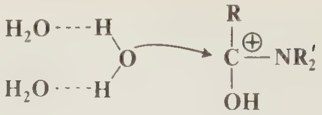
[413] McClelland, *J. Am. Chem. Soc.* **97,** 5281 (1975). For earlier negative results, see Bender, Ginger, and Kemp, *J. Am. Chem. Soc.* **76,** 3350 (1954), Bender and Ginger, *J. Am. Chem. Soc.* **77,** 348 (1955); Bunton, Farber, Milbank, O'Connor, and Turney, *J. Chem. Soc., Perkin Trans. 2* 1869 (1972).

[414] Bender and Thomas, Ref. 411; Bunton, Nayak, and O'Connor, *J. Org. Chem.* **33,** 572 (1968); Ref. 413.

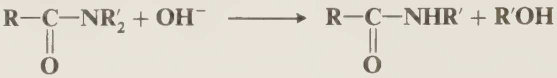
[415] Bunton, O'Connor, and Turney, *Chem. Ind.* (*London*) 1835 (1967); Smith and Yates, *J. Am. Chem. Soc.* **93,** 6578 (1971), **94,** 8811 (1972); Hyland and O'Connor, *J. Chem. Soc., Perkin Trans. 2* 1402 (1973); Challis and Jones, *J. Chem. Soc., Chem. Commun.* 748 (1974); Williams, *J. Am. Chem. Soc.* **97,** 6278 (1975).

[416] For evidence against this view, see Hall and Satchell, *Chem. Ind.* (*London*) 527 (1974), Kresge, Fitzgerald, and Chiang, *J. Am. Chem. Soc.* **96,** 4698 (1974).

[417] Moodie, Wale, and Whaite, *J. Chem. Soc.* 4273 (1963); Yates and Stevens, *Can. J. Chem.* **43,** 529 (1965); Yates and Riordan, *Can. J. Chem.* **43,** 2328 (1965).



The four mechanisms involving alkyl—N cleavage (the AL mechanisms) do not apply to this reaction. They are not possible for unsubstituted amides, since the only N—C bond is the acyl bond. They are possible for N-substituted and N,N-disubstituted amides, but in these cases they give entirely different products and are not amide hydrolyses at all.

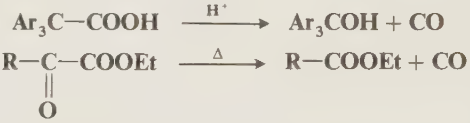


$$R-\underset{\underset{O}{\|}}{C}-NR'_2 + OH^- \longrightarrow R-\underset{\underset{O}{\|}}{C}-NHR' + R'OH$$

This reaction, while rare, has been observed for various N-*t*-butyl amides in 98% sulfuric acid, where the mechanism was the AAL1 mechanism,[418] and for certain amides containing an azo group, where a BAL1 mechanism was postulated.[419] Of the two first-order acyl cleavage mechanisms, only the AAC1 has been observed, in concentrated sulfuric acid solutions.[420] Of course, the diazotization of unsubstituted amides might be expected to follow this mechanism, and there is evidence that this is true.[405]

OS **I,** 14, 111, 194, 201, 286; **II,** 19, 25, 28, 49, 76, 208, 330, 374, 384, 457, 462, 491, 503, 519, 612; **III,** 66, 88, 154, 256, 410, 456, 586, 591, 661, 735, 768, 813; **IV,** 39, 42, 55, 58, 420, 441, 496, 664; **V,** 27, 96, 341, 471, 612, 627; **51,** 53; **55,** 114.

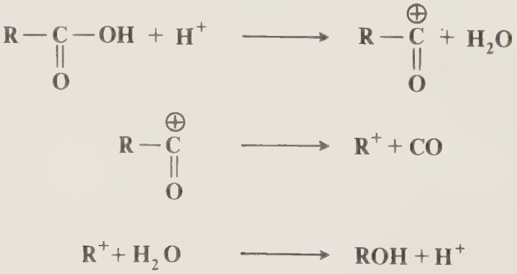
0-13 Decarbonylation of Esters and Acids



$$Ar_3C-COOH \xrightarrow{H^+} Ar_3COH + CO$$

$$R-\underset{\underset{O}{\|}}{C}-COOEt \xrightarrow{\Delta} R-COOEt + CO$$

Decarbonylations of esters and acids are not general reactions. Only certain acids can be decarbonylated in this manner: formic, oxalic, triarylacetic, α-hydroxy, and α-keto acids. Most but not all α-keto esters can be decarbonylated simply by heating. The mechanisms are little known,[421] and the reactions are included in this chapter because at least in some cases this mechanism has been demonstrated:[422]



$$R-\underset{\underset{O}{\|}}{C}-OH + H^+ \longrightarrow R-\overset{\oplus}{\underset{\underset{O}{\|}}{C}} + H_2O$$

$$R-\overset{\oplus}{\underset{\underset{O}{\|}}{C}} \longrightarrow R^+ + CO$$

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

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[418] Lacey, *J. Chem. Soc.* 1633 (1960).

[419] Stodola, *J. Org. Chem.* **37,** 178 (1972).

[420] Duffy and Leisten, *J. Chem. Soc.* 545, 853 (1960); Barnett and O'Connor, *J. Chem. Soc., Chem. Commun.* 525 (1972), *J. Chem. Soc., Perkin Trans. 2* 2378 (1972).

[421] See for example, Louw and Kooyman, *Recl. Trav. Chim. Pays-Bas* **86,** 1041 (1967).

[422] Ropp, *J. Am. Chem. Soc.* **82,** 842 (1960); Margolin and Samuel, *Chem. Commun.* 802 (1970). For a review, see Liler, "Reaction Mechanisms in Sulphuric Acid," pp. 254–259, Academic Press, Inc., New York, 1971.

This is an SN1 mechanism. The cleavage of the acyl cation is analogous to the cleavage of the diazonium ion RN_2^+.

OS **I,** 10; **II,** 279, 288, 531; **IV,** 141.

The oxidation of aldehydes to carboxylic acids can proceed by a nucleophilic mechanism, but more often it does not. The reaction is considered in Chapter 14 (reaction **4-6**). Basic cleavage of β-keto esters and the haloform reaction could be considered at this point, but they are also electrophilic substitutions and are treated in Chapter 12 (reactions **2-42** and **2-43**).

C. Attack by OR at an Alkyl Carbon

0-14 Alkylation with Alkyl Halides. The Williamson Reaction

$$\mathbf{RX + OR'^- \longrightarrow ROR'}$$

The *Williamson reaction*, discovered in 1850, is still the best general method for the preparation of unsymmetrical ethers or, for that matter, symmetrical ones.[423] The reaction can also be carried out with aromatic R′, though C-alkylation is sometimes a side reaction (see p. 337). The method is not successful for tertiary R (because of elimination), and low yields are obtained with secondary R. Many other functional groups may be present in the molecule without interference. Ethers in which one group is tertiary *can* be prepared by treatment of an alkyl halide or sulfate ester (reaction **0-16**) with a tertiary alkoxide $R'O^-$, which is prepared by removal of a proton from a tertiary alcohol with methylsulfinyl carbanion;[424] or with a copper(I) tertiary alkoxide.[425] Di-*t*-butyl ether was prepared in high yield by direct attack by *t*-BuOH on the *t*-butyl cation (at −80 C in SO_2ClF).[425a] Active halides such as Ar_3CX may react directly with the alcohol without need for the more powerful nucleophile alkoxide ion.[426] Even tertiary halides have been converted to ethers in this way, with no elimination.[427] The mechanism in these cases is of course SN1. *gem*-Dihalides react with alkoxides to give acetals, and 1,1,1-trihalides give ortho esters.[428]

Hydroxy groups may be protected by reaction of their salts with chloromethyl methyl ether.

$$\mathbf{RO^- + CH_3OCH_2Cl \longrightarrow ROCH_2OCH_3}$$

The resulting acetals are stable to bases and are easily cleaved with mild acid treatment (**0-7**).[429] Phenacyl bromides ($ArCOCH_2Br$) have also been used for this purpose.[430] The resulting ethers can easily be hydrolyzed with zinc and acetic acid. Aryl cyanates[431] can be prepared by reaction of phenols with cyanogen halides in the presence of a base: $ArO^- + ClCN \rightarrow ArOCN + Cl^-$.[432] This reaction has also been applied to certain alkyl cyanates.[433]

An efficient procedure for the synthesis of phenolic ethers by the Williamson reaction makes use of *phase-transfer catalysis*.[434] The phenol ArOH is added to a two-phase system consisting of water, CH_2Cl_2, a quaternary ammonium hydroxide $R'_4N^+\ \ OH^-$,[435] and the alkyl halide RX. The alkyl halide is soluble only in the CH_2Cl_2, and the $R'_4N^+\ \ OH^-$ only in the water. The phenol is soluble in both phases, but in the water it is converted by the base to ArO which has a small solubility in CH_2Cl_2. Once in this solvent it is quickly converted to the ether ArOR.[435] Phase-transfer-catalyzed Williamson reactions have also been used to prepare dialkyl ethers.[435a]

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[423] For a review, see Feuer and Hooz, in Patai, Ref. 281, pp. 446–450, 460–468.

[424] Sjöberg and Sjöberg, *Acta Chem. Scand.* **26,** 275 (1972).

[425] Whitesides, Sadowski, and Lilburn, *J. Am. Chem. Soc.* **96,** 2829 (1974).

[425a] Olah, Halpern, and Lin, *Synthesis* 315 (1975).

[426] For a review of reactions in which alcohols serve as nucleophiles, see Salomaa, Kankaanperä, and Pihlaja, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, pp. 454–466, Interscience Publishers, New York, 1971.

[427] Biordi and Moelwyn-Hughes, *J. Chem. Soc.* 4291 (1962).

[428] For a review of the formation of ortho esters by this method, see DeWolfe, Ref. 359, pp. 12–18.

[429] McOmie, *Adv. Org. Chem.* **3,** 191–294 (1963), pp. 232–233.

[430] Hendrickson and Kandall, *Tetrahedron Lett.* 343 (1970).

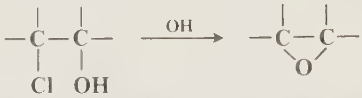
[431] For a review of alkyl and aryl cyanates, see Grigat and Pütter, *Angew. Chem. Int. Ed. Engl.* **6,** 206–218 (1967) [*Angew. Chem.* **79,** 219–231].

[432] Grigat and Pütter, *Chem. Ber.* **97,** 3012 (1964).

[433] Kauer and Henderson, *J. Am. Chem. Soc.* **86,** 4732 (1964).

OS **I,** 75, 205, 258, 296, 435; **II,** 260; **III,** 127, 140, 209, 418, 432, 544; **IV,** 427, 457, 558, 590, 836; **V,** 251, 258, 266, 403, 424, 684; **52,** 66; **54,** 19.

0-15 Epoxide Formation



This is a special case of reaction **0-14.** Many epoxides have been made in this way.[436] The method can also be used to prepare larger cyclic ethers: five- and six-membered rings. Additional treatment with base yields the glycol (reaction **0-8**). The base removes the proton from the OH group, and the epoxide then attacks in an internal SN2 reaction. There is much evidence for this mechanism.[437]

OS **I,** 185, 233; **II,** 256; **III,** 835.

0-16 Alkylation with Inorganic Esters

$$\mathbf{R{-}OSO_2OR'' + R'O^- \longrightarrow ROR'}$$

The reaction of alkyl sulfates with alkoxide ions is quite similar to reaction **0-14** in mechanism and scope. Other inorganic esters may also be used. However, the most common usage of this reaction is the formation of methyl ethers of alcohols and phenols by treatment of alkoxides or aroxides with methyl sulfate. Organic esters sometimes give ethers when treated with alkoxides (BAL2 mechanism, p. 352) in a very similar process (also see reaction **0-25**).

OS **I,** 58, 537; **II,** 387, 619; **III,** 127, 564, 800; **IV,** 588; **53,** 90. Also see OS **V,** 431.

0-17 Alkylation with Diazo Compounds[438]

$$\mathbf{R_2CN_2 + ArOH \longrightarrow R_2CHOAr}$$

$$\mathbf{CH_2N_2 + ROH \xrightarrow{HBF_4} CH_3OR}$$

Reaction with alcohols is general for diazo compounds, but it is most often performed with diazomethane to produce methyl ethers, or with diazo ketones to produce α-keto ethers, since these kinds of diazo compounds are most readily available. With diazomethane the method is expensive and requires great caution. It is used chiefly to methylate alcohols and phenols which are expensive or available in small amounts, since the conditions are mild and high yields are obtained. Hydroxy compounds react better as their acidity increases, and ordinary alcohols do not react at all unless HBF_4[439] or $AlCl_3$[440] is present as a catalyst. The more acidic phenols react very well in the absence of a catalyst. Oximes, and ketones which have substantial enolic contributions, give O-alkylation to form, respectively, O-alkyl oximes and enol ethers. The mechanism is as in reaction **0-6**:

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[434] For reviews of phase-transfer catalysts, see Dockx, *Synthesis* 441–456 (1973); Dehmlow, *Angew. Chem. Int. Ed. Engl.* **13,** 170–179 (1974) [*Angew. Chem.* **86,** 187–196], *Chem. Technol.* 210–218 (1975). See also Herriot and Picker, *J. Am. Chem. Soc.* **97,** 2345 (1975).

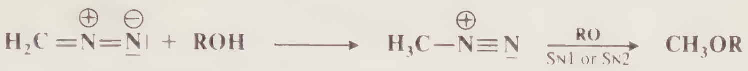
[435] McKillop, Fiaud, and Hug, *Tetrahedron* **30,** 1379 (1974).

[435a] Freedman and Dubois, *Tetrahedron Lett.* 3251 (1975).

[436] For a review, see Berti, *Top. Stereochem.* **7,** 93–251 (1973), pp. 187–209.

[437] See for example, Swain, Ketley, and Bader, *J. Am. Chem. Soc.* **81,** 2353 (1959); Knipe, *J. Chem. Soc., Perkin Trans. 2* 589 (1973).

[438] For reviews, see Zollinger, "Azo and Diazo Chemistry," pp. 68–71, 102–108, Interscience Publishers, Inc., New York, 1961; Ref. 423, pp. 478–484.



$$H_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{N}}| + ROH \longrightarrow H_3C{-}\overset{\oplus}{N}{\equiv}\underline{N} \xrightarrow[\text{SN1 or SN2}]{RO} CH_3OR$$

Diazoalkanes can also be converted to ethers by thermal or photochemical cleavage in the presence of an alcohol. In such cases there is a carbene intermediate and the mechanism is SN1cB (p. 330).[441] A carbene intermediate is also involved when diazoalkanes react with alcohols in the presence of *t*-BuOCl to give acetals:[442]

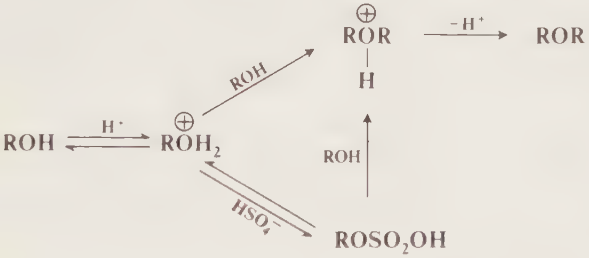
$$R_2CN_2 + 2R'OH \xrightarrow{t\text{-BuOCl}} R_2C(OR')_2$$

OS V, 245. Also see OS V, 1099.

0-18 Dehydration of Alcohols

$$2ROH \xrightarrow{H_2SO_4} ROR + H_2O$$

The dehydration of alcohols to form ethers[443] is analogous to reactions **0-14** and **0-16**, but the species from which the leaving group departs is ROH_2^+ or $ROSO_2OH$. The former is obtained directly on treatment of alcohols with sulfuric acid and may go, by an SN1 or SN2 pathway, directly to the ether if attacked by another molecule of alcohol. On the other hand, it may, again by either an SN1 or SN2 route, be attacked by the nucleophile HSO_4^-, in which case it is converted to $ROSO_2OH$, which in turn may be attacked by an alcohol molecule to give ROR. These processes are summarized:



Elimination is always a side reaction and, in the case of tertiary alkyl substrates, completely predominates.

The ether prepared is symmetrical. Mixed ethers can be prepared if one group is tertiary alkyl and the other primary or secondary, since the latter group is not likely to compete with the tertiary group in the formation of the carbonium ion, while a tertiary alcohol is a very poor nucleophile. If one group is not tertiary, then the reaction of a mixture of two alcohols leads to all three possible ethers. Glycols can be converted to cyclic ethers, though the reaction is most successful for five-membered rings. Thus, 1,6-hexanediol gives mostly 2-ethyltetrahydrofuran. This reaction is also important in preparing furfural derivatives from aldoses, with concurrent elimination:

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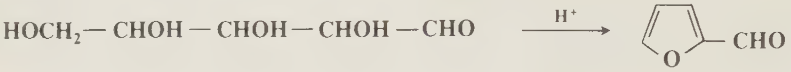
[439] Neeman, Caserio, Roberts, and Johnson, *Tetrahedron* **6**, 36 (1959).

[440] Müller, Heischkeil, and Bauer, *Justus Liebigs Ann. Chem.* **677**, 55 (1964).

[441] Bethell and Howard, *J. Chem. Soc. B* 745 (1969); Bethell, Newall, and Whittaker, *J. Chem. Soc. B* 23 (1971).

[442] Baganz and May, *Angew. Chem. Int. Ed. Engl.* **5**, 420 (1966) [*Angew. Chem.* **78**, 448].

[443] For a review, see Ref. 423, pp. 457–460, 468–470.



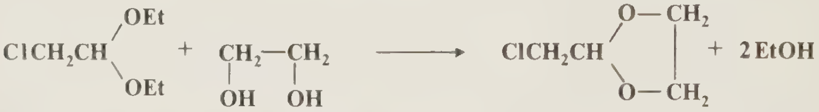
Phenols and primary alcohols form ethers when heated with dicyclohexylcarbodiimide[444] (see reaction **0-24**). 1,2-Glycols can be converted to epoxides by treatment with dimethylformamide dimethyl acetal $[(MeO)_2CHNMe_2]$,[445] or with the diaryldialkoxysulfurane $Ph_2S[OCPh(CF_3)_2]_2$.[446]

OS **I,** 280; **II,** 126; **IV,** 25, 72, 266, 350, 393, 534; **V,** 539, 1024. Also see OS **V,** 721.

0-19 Transetherification

$$ROR' + R''OH \longrightarrow ROR'' + R'OH$$

The exchange of one alkoxyl group for another is very rare for *ethers*, though it has been accomplished with reactive R, for example, diphenylmethyl, with *p*-toluenesulfonic acid as a catalyst,[447] and by treatment of alkyl aryl ethers with alkoxide ions: $ROAr + R'O^- \rightarrow ROR' + ArO^-$.[448] However, acetals and ortho esters undergo transetherification readily,[449] for example,[450]

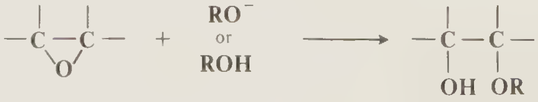


because, as we have seen (reaction **0-7**), departure of the leaving group from an acetal gives a particularly stable carbonium ion. These are equilibrium reactions, and most often the equilibrium is shifted by removing the lower-boiling alcohol by distillation. Enol ethers can be prepared by treating an alcohol with an enol ester or a different enol ether, with mercuric acetate as a catalyst,[451] e.g.,

$$ROCH{=}CH_2 + R'OH \xrightarrow{Hg(OAc)_2} R'OCH{=}CH_2 + ROH$$

OS **51,** 39; **53,** 116; **54,** 71, 74, 77. Also see OS **V,** 1080, 1096.

0-20 Alcoholysis of Epoxides



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[444] Vowinkel, *Chem. Ber.* **95,** 2997 (1962), **96,** 1702 (1963), **99,** 42 (1966).

[445] Neumann, *Chimia* **23,** 267 (1969).

[446] Martin, Franz, and Arhart, *J. Am. Chem. Soc.* **96,** 4604 (1974).

[447] Pratt and Draper, *J. Am. Chem. Soc.* **71,** 2846 (1949).

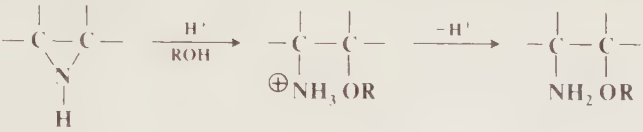
[448] Zoltewicz and Sale, *J. Org. Chem.* **35,** 3462 (1970).

[449] For reviews, see Ref. 426, pp. 458–463; DeWolfe, Ref. 359, pp. 18–29, 146–148.

[450] McElvain and Curry, *J. Am. Chem. Soc.* **70,** 3781 (1948).

[451] Watanabe and Conlon, *J. Am. Chem. Soc.* **79,** 2828 (1957); Büchi and White, *J. Am. Chem. Soc.* **86,** 2884 (1964). For a review, see Shostakovskii, Trofimov, Atavin, and Lavrov, *Russ. Chem. Rev.* **37,** 907–919 (1968).

This reaction is analogous to reaction **0-8**. It may be acid- or base-catalyzed and may occur by either an SN1 or SN2 mechanism. Many of the β-hydroxy ethers produced in this way are valuable solvents, for example, diethylene glycol, Cellosolve, etc. Aziridines may similarly be converted to β-amino ethers.[452]



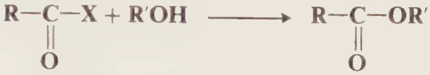
0-21 Alkylation with Onium Salts

$$R_3O^+ + R'OH \longrightarrow ROR' + R_2O$$

Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.[453] Quaternary ammonium salts can sometimes also be used.[454]

D. Attack by OR at an Acyl Carbon

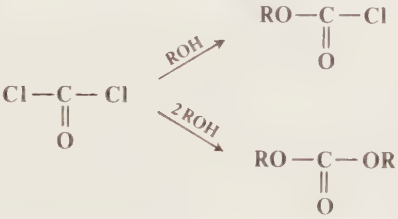
0-22 Alcoholysis of Acyl Halides



$$R-\underset{\underset{O}{\|}}{C}-X + R'OH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OR'$$

The reaction between acyl halides and alcohols is the best general method for the preparation of esters.[455] The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX which is formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Both R and R′ may be primary, secondary, or tertiary alkyl, or aryl. Enolic esters can also be prepared by this method, although C-acylation competes in these cases. In difficult cases, especially with hindered acids, or for tertiary R′, the alkoxide may be used instead of the alcohol.[456] Thallium salts of phenols give very high yields of phenolic esters.[457]

When phosgene is the acyl halide, haloformic esters[458] or carbonates may be obtained.



An important example is the preparation of carbobenzoxy chloride ($PhCH_2OCOCl$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis (see reaction **0-54**).

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[452] For a review, see Ref. 345, pp. 224–227, 256–257.

[453] Granik, Pyatin, and Glushkov, Ref. 285, p. 749.

[454] For an example, see Rodionov, *Bull. Soc. Chim. Fr.* **39**, 305 (1926).

[455] For a review, see Sonntag, *Chem. Rev.* **52**, 237–416 (1953), pp. 312–324.

[456] For an example, see Kaiser and Woodruff, *J. Org. Chem.* **35**, 1198 (1970).

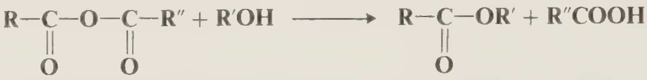
[457] Taylor, McLay, and McKillop, *J. Am. Chem. Soc.* **90**, 2422 (1968).

[458] For a review of this method as applied to the synthesis of chloroformates, see Matzner, Kurkjy, and Cotter, *Chem. Rev.* **64**, 645–687 (1964).

As with reaction **0-9**, the mechanism may be S_N1 or tetrahedral.[379] In the tetrahedral mechanism there is evidence (the reaction is second order or higher in ROH) that the OH proton is lost or partially lost in the rate-determining step.[459] Pyridine catalyzes the reaction by the nucleophilic catalysis route (see reaction **0-10**).

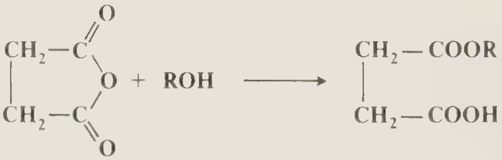
OS **I,** 12; **III,** 142, 144, 167, 187, 623, 714; **IV,** 84, 263, 478, 479, 608, 616, 788; **V,** 1, 166, 168, 171; **51,** 11, 96, 139.

0-23 Alcoholysis of Anhydrides



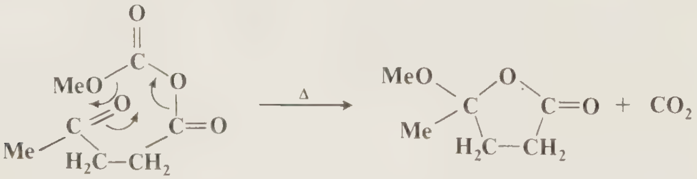
$$\underset{\overset{\|}{O}}{R-C}-O-\underset{\overset{\|}{O}}{C}-R'' + R'OH \longrightarrow \underset{\overset{\|}{O}}{R-C}-OR' + R''COOH$$

The scope of this reaction is similar to that of reaction **0-22**. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine. Catalysis by pyridine is of the nucleophilic type; that is, there are two tetrahedral mechanisms (see reaction **0-10**). 4-(N,N-Dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails.[460] Formic anhydride is not a stable compound (see p. 493), but esters of formic acid can be prepared by treating alcohols[461] or phenols[462] with acetic-formic anhydride. Cyclic anhydrides give mono-esterified dicarboxylic acids, for example,



Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as acetic-phosphoric anhydride $MeCOOPO(OH)_2$[463] (see reaction **0-34**).

Certain mixed anhydrides can be converted to esters simply by heating. An example is the mixed anhydride of levulinic and methylcarbonic acids, which gives pseudomethyl levulinate (**122**).[464] This reason takes place by a [3.2.1] bicyclic mechanism.



122

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[459] Ross, *J. Am. Chem. Soc.* **92,** 5998 (1970).

[460] Steglich and Höfle, *Angew. Chem. Int. Ed. Engl.* **8,** 981 (1969) [*Angew. Chem.* **81,** 1009]; Höfle and Steglich, *Chem. Ber.* **105,** 1368 (1972), *Synthesis* 619 (1972).

[461] For example, see Stevens and van Es, *Recl. Trav. Chim. Pays-Bas,* **83,** 1287 (1964); van Es and Stevens, *Recl. Trav. Chim. Pays-Bas,* **84,** 704 (1965).

[462] For example, see Stevens and van Es, *Recl. Trav. Chim. Pays-Bas,* **83,** 1294 (1964); Sōfuku, Muramatsu, and Hagitani, *Bull. Chem. Soc. Jpn.* **40,** 2942 (1967).

[463] Fatiadi, *Carbohydr. Res.* **6,** 237 (1968).

[464] Newman, Gill, and Darré, *J. Org. Chem.* **31,** 2713 (1966). For other examples, see Newman and Corduvelis, *J. Am. Chem. Soc.* **86,** 2942 (1964); Newman, Mladenovic, and Lala, *J. Am. Chem. Soc.* **90,** 747 (1968); Newman and Din, *J. Org. Chem.* **36,** 2740 (1971); Newman, Gupte, and Sankarrappa, *J. Org. Chem.* **35,** 2757 (1970); Newman and Gupte, *J. Org. Chem.* **35,** 4176 (1970).

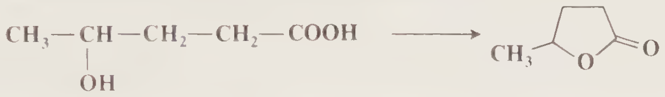
OS **I,** 285, 418; **II,** 69, 124; **III,** 11, 127, 141, 169, 237, 281, 428, 432, 452, 690, 833; **IV,** 15, 242, 304; **V,** 8, 459, 591, 887; **51,** 90; **52,** 39; **54,** 49.

0-24 Esterification of Acids

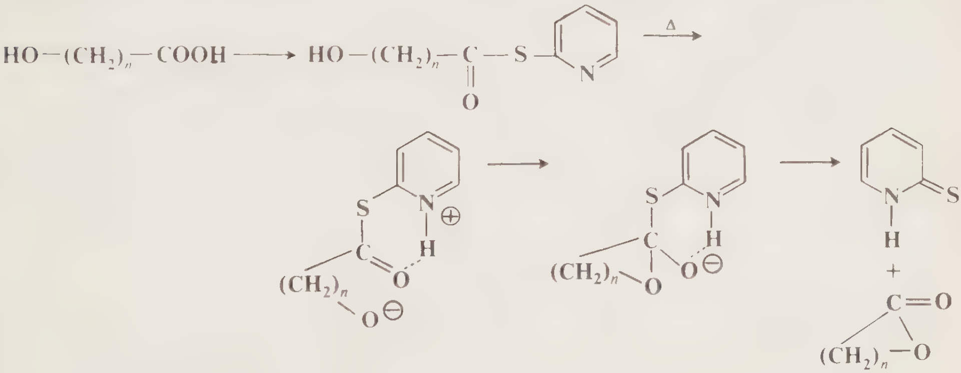
$$\mathrm{RCOOH + R'OH \xrightleftharpoons{H} RCOOR' + H_2O}$$

The esterification of acids with alcohols is the reverse of reaction **0-12** and can be accomplished only if a means is available to drive the equilibrium to the right. There are many ways of doing this, among which are: (1) addition of an excess of one of the reactants, usually the alcohol; (2) removal of the ester or the water by distillation; and (3) removal of water by use of a dehydrating agent or a molecular sieve.[465] When R′ is methyl, the most common way of driving the equilibrium is by adding excess MeOH; when R′ is ethyl, it is preferable to remove water by distillation.[466] The most common catalysts are H_2SO_4 and TsOH, though some reactive acids (e.g., formic) do not require a catalyst. Besides methyl and ethyl, R′ may be other primary or secondary alkyl groups, but tertiary alcohols usually give carbonium ions and elimination. Phenols can sometimes be used to prepare phenolic esters, but yields are generally very low.

γ- and δ-hydroxy acids are easily lactonized by treatment with acids, or often simply on standing, but larger and smaller lactone rings cannot generally be made in this manner, because



polyester formation occurs more readily. However, sometimes the polyester can be converted to the lactone. Often the conversion of a group such as keto or halogen, γ or δ to a carboxyl group, to a hydroxyl group gives the lactone directly, since the hydroxy acid cyclizes too rapidly for isolation. β-Substituted β-hydroxy acids can be converted to β-lactones by treatment with benzenesulfonyl chloride in pyridine at 0 to 5 C.[467] ε-Lactones (seven-membered rings) have been made by cyclization of ε-hydroxy acids at high dilution.[468] Macrocyclic lactones can be prepared indirectly in very good yields by conversion of the hydroxy acids to 2-pyridinethiol esters and adding these to refluxing xylene.[469]



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[465] For example, see Harrison, Haynes, Arthur, and Eisenbraun, *Chem. Ind.* (*London*) 1568 (1968).

[466] Newman, "An Advanced Organic Laboratory Course," pp. 8–10, The Macmillan Company, New York, 1972.

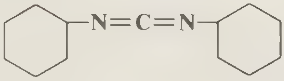
[467] Adam, Baeza, and Liu, *J. Am. Chem. Soc.* **94,** 2000 (1972). For other methods of converting β-hydroxy acids to β-lactones, see Merger, *Chem. Ber.* **101,** 2413 (1968); Blume, *Tetrahedron Lett.* 1047 (1969).

[468] Lardelli, Lamberti, Weller, and de Jonge, *Recl. Trav. Chim. Pays-Bas* **86,** 481 (1967).

[469] Corey and Nicolaou, *J. Am. Chem. Soc.* **96,** 5614 (1974); Corey, Nicolaou, and Melvin, *J. Am. Chem. Soc.* **97,** 653, 655 (1975); Gerlach and Thalmann, *Helv. Chim. Acta* **57,** 2661 (1974).

Esterification is catalyzed by acids (not bases) in ways that were discussed on p. 349.[387] The mechanisms are usually AAC2, but AAC1 and AAL1 have also been observed.[470] Certain acids, such as 2,6-di-ortho-substituted benzoic acids, cannot be esterified by the AAC2 mechanism, because of steric hindrance (p. 316). In such cases, esterification may be accomplished by dissolving the acid in 100% H_2SO_4 (forming the ion RCO^+) and pouring the solution into the alcohol (AAC1 mechanism). The reluctance of hindered acids to undergo the normal AAC2 mechanism can sometimes be put to advantage when, in a molecule containing two COOH groups, only the less hindered one is esterified. The AAC1 pathway cannot be applied to unhindered carboxylic acids.

Another way to esterify an acid is to treat it with an alcohol in the presence of a dehydrating agent. One of the most common of these is dicyclohexylcarbodiimide (**123**), which is converted in the process to dicyclohexylurea (**124**). The mechanism[471] has much in common with the nucleophilic catalysis mechanism: the acid is converted to a compound with a better leaving group. However, the conversion is not by a tetrahedral mechanism (as it is in nucleophilic catalysis), since the C—O bond remains intact during this step:



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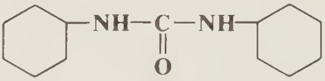

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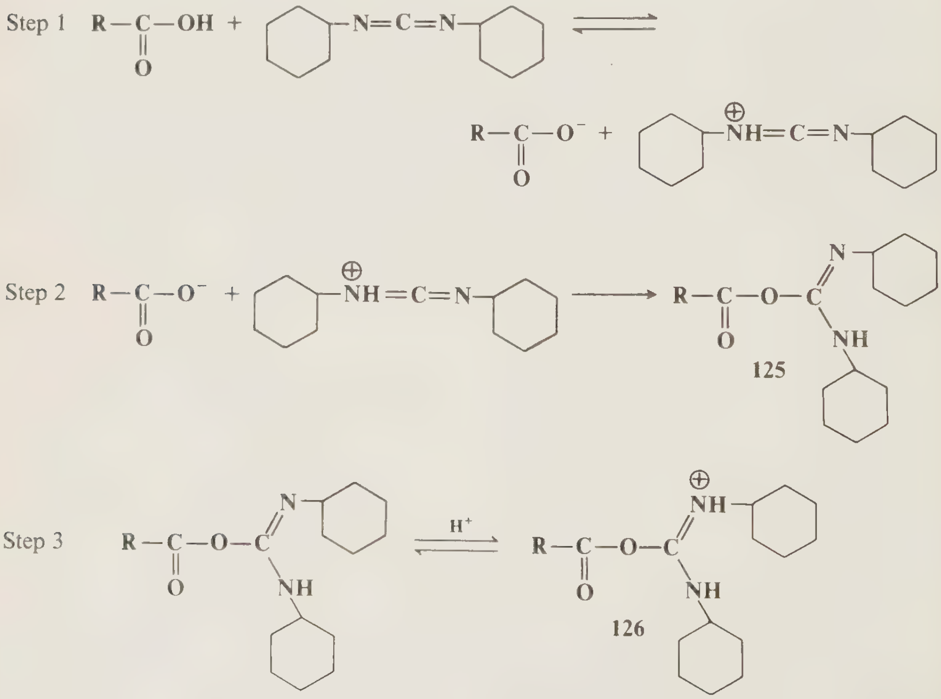

125

126

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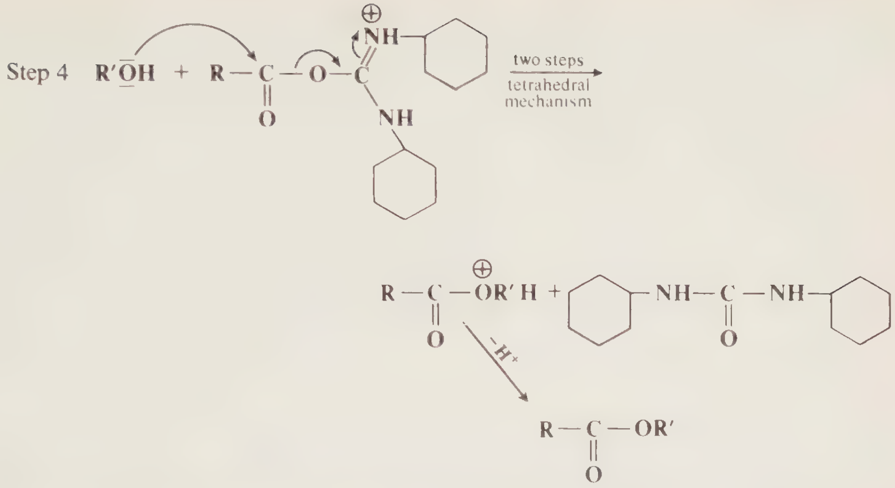
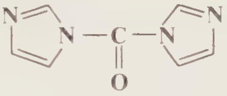
[470] For a review of aspects of the mechanism, see Ref. 426, pp. 466–481.

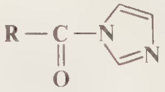
[471] Smith, Moffat, and Khorana, *J. Am. Chem. Soc.* **80**, 6204 (1958).



Evidence for this mechanism was the preparation of O-acylureas similar to **125** and the finding that when catalyzed by acids they react with alcohols to give esters.[472] Other reagents which promote the reaction are trifluoroacetic anhydride,[473] H_3BO_3–H_2SO_4,[474] polymer-protected $AlCl_3$,[475] pyridinium salts-Bu_3N,[475a] and N,N'-carbonyldiimidazole (**127**).[406] In the latter case easily alcoholyzed imidazolides (**118**) are intermediates. BF_3 promotes the esterification by converting the acid to RCO^+ BF_3OH^-, so that the reaction proceeds by an AAC1 type of mechanism. The use of BF_3-etherate is simple and gives high yields.[476] Carboxylic esters may also be prepared by treating carboxylic acids with *t*-butyl ethers and acid catalysts:[477]



127

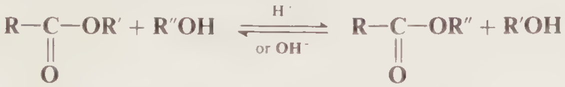


118

$$\mathbf{RCOOH} + t\text{-}\mathbf{Bu\text{-}OR'} \longrightarrow \mathbf{RCOOR'} + \mathbf{H_2C{=}CMe_2} + \mathbf{H_2O}$$

OS **I,** 42, 138, 237, 241, 246, 254, 261, 451; **II,** 260, 264, 276, 292, 365, 414, 526; **III,** 46, 203, 237, 381, 413, 526, 531, 610; **IV,** 169, 178, 302, 329, 390, 398, 427, 506, 532, 635, 677; **V,** 80, 762, 946; **55,** 45, 77. Also see OS **III,** 536, 742.

0-25 Alcoholysis of Esters. Transesterification



$$\underset{\displaystyle \mathrm{O}}{\overset{}{\mathrm{R{-}\underset{\|}{C}{-}OR'}}} + \mathrm{R''OH} \underset{\text{or OH}^-}{\overset{\mathrm{H}^+}{\rightleftharpoons}} \underset{\displaystyle \mathrm{O}}{\mathrm{R{-}\underset{\|}{C}{-}OR''}} + \mathrm{R'OH}$$

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[472] Doleschall and Lempert, *Tetrahedron Lett.* 1195 (1963).

[473] Parish and Stock, *J. Org. Chem.* **30,** 927 (1965).

[474] Lowrance, *Tetrahedron Lett.* 3453 (1971).

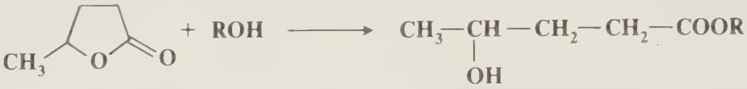
[475] Blossey, Turner, and Neckers, *Tetrahedron Lett.* 1823 (1973).

[475a] Mukaiyama, Usui, Shimida, and Saigo, *Chem. Lett.* 1045 (1975). See also Mukaiyama, Toda, and Kobayashi, *Chem. Lett.* 13 (1976); Mukaiyama, Usui, and Saigo, *Chem. Lett.* 49 (1976).

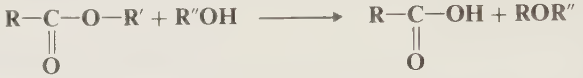
[476] For examples, see Marshall, Erickson, and Folsom, *Tetrahedron Lett.* 4011 (1970); Kadaba, *Synthesis* 628 (1972), *Synth. Commun.* 4, 167 (1974).

[477] Derevitskaya, Klimov, and Kochetkov, *Tetrahedron Lett.* 4269 (1970).

Transesterification is catalyzed by acids or bases. It is an equilibrium reaction and must be shifted in the desired direction. In many cases low-boiling esters may be converted to higher ones by distillation of the lower-boiling alcohol as fast as it is formed. Lactones are easily opened by treatment with alcohols to give open-chain hydroxy esters:



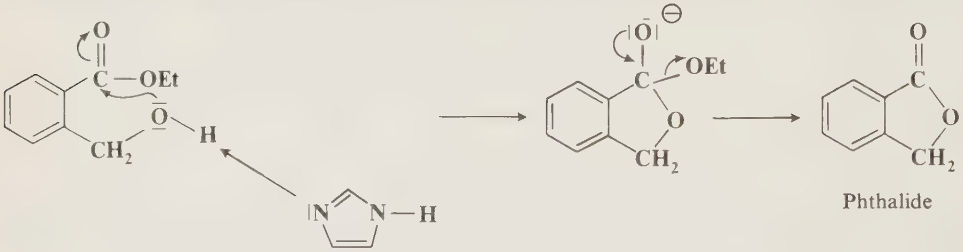
Transesterification occurs by mechanisms[478] which are identical with those of ester hydrolysis—except that ROH replaces HOH that is, by the acyl-oxygen fission mechanisms. When alkyl fission takes place, the products are the *acid* and the *ether*:



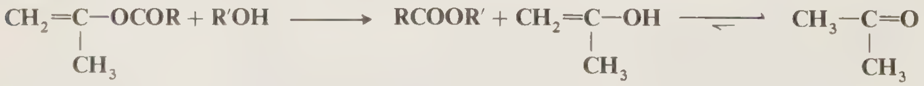
$$\mathrm{R-\underset{\overset{\|}{O}}{C}-O-R' + R''OH \longrightarrow R-\underset{\overset{\|}{O}}{C}-OH + ROR''}$$

Therefore, transesterification reactions frequently fail when R′ is tertiary, since this type of substrate most often reacts by alkyl-oxygen cleavage. In such cases, the reaction is of the Williamson type with OCOR as the leaving group (see reaction **0-16**).

It has been shown that intramolecular transesterification of ethyl 2-hydroxymethylbenzoate to give phthalide can be catalyzed by imidazole and other bases.[479] It is likely that the catalyst functions by assisting removal of the O—H proton in the rate-determining step (general base catalysis). Similar catalysis has been shown in the conversion of 2-hydroxymethylbenzamide to phthalide.[480] These reactions serve as a model for hydrolysis of esters and amides by α-chymotrypsin. This enzyme has a serine group [—NHCH(CH_2OH)CO—] in position 195. The OH group of the serine reacts with the ester or amide, releasing the alcohol or amine portion. This reaction is catalyzed by a histidine residue in the 57 position of the enzyme. Histidine contains an imidazole ring, and the catalysis is believed to follow the model shown above. Following this reaction, the acylated serine residue is deacylated to regenerate the active enzyme. Transesterification can also be catalyzed by CO_2.[481]



With enol esters, the free alcohol is the enol of a ketone, so such esters easily undergo the reaction



$$\mathrm{CH_2{=}\underset{CH_3}{\underset{|}{C}}-OCOR + R'OH \longrightarrow RCOOR' + CH_2{=}\underset{CH_3}{\underset{|}{C}}-OH \rightleftharpoons CH_3-\underset{CH_3}{\underset{|}{C}}{=}O}$$

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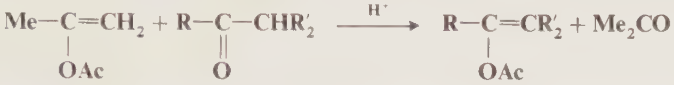
[478] For a review, see Koskikallio, in Patai, Ref. 188, pp. 103–136.

[479] Fife and Benjamin, *J. Am. Chem. Soc.* **95,** 2059 (1973). See also Kirby and Lloyd, *J. Am. Chem. Soc., Perkin Trans. 2* 637 (1974); Fife and Benjamin, *J. Chem. Soc., Chem. Commun.* 525 (1974); Pollack and Dumsha, *J. Am. Chem. Soc.* **97,** 377 (1975); Chiong, Lewis, and Shafer, *J. Am. Chem. Soc.* **97,** 418 (1975).

[480] Belke, Su, and Shafer, *J. Am. Chem. Soc.* **93,** 4552 (1971).

[481] Otsuji, Matsumura, and Imoto, *Bull. Chem. Soc. Jpn.* **44,** 852 (1971).

Hence, enol esters such as isopropenyl acetate are good acylating agents for alcohols.[482] Isopropenyl acetate can also be used to convert other ketones to the corresponding enol acetates in an exchange reaction:[483]



$$\underset{\text{OAc}}{\text{Me—C}}\text{=CH}_2 + \underset{\text{O}}{\underset{\|}{\text{R—C}}}\text{—CHR}'_2 \xrightarrow{\text{H}^+} \underset{\text{OAc}}{\text{R—C}}\text{=CR}'_2 + \text{Me}_2\text{CO}$$

Enol esters can also be prepared in the opposite type of exchange reaction, catalyzed by mercuric acetate[484] or by Pd(II) chloride,[485] e.g.,

$$\text{RCOOH} + \text{R}'\text{COOCH=CH}_2 \xrightleftharpoons[\text{H}_2\text{SO}_4]{\text{Hg(OAc)}_2} \text{RCOOCH=CH}_2 + \text{R}'\text{COOH}$$

A closely related reaction is equilibration of a dicarboxylic acid and its diester to produce monoesters:

$$\text{ROCO(CH}_2)_n\text{COOR} + \text{HOOC(CH}_2)_n\text{COOH} \rightleftharpoons 2\text{ROCO(CH}_2)_n\text{COOH}$$

OS **II**, 5, 122, 360; **III**, 123, 146, 165, 231, 281, 581, 605; **IV**, 10, 549, 630; 977; **V**, 155, 545, 863; **55**, 39.

Alcoholysis of amides is possible but is seldom performed, except for the imidazolide type of amide (p. 353).

E. Attack by OCOR at an Alkyl Carbon

0-26 Alkylation of Acid Salts

$$\text{RX} + \text{R}'\text{COO}^- \xrightarrow{\text{HMPT}} \text{R}'\text{COOR}$$

Sodium salts of carboxylic acids, including hindered acids such as mesitoic, rapidly react with primary and secondary bromides and iodides at room temperature in dipolar aprotic solvents, especially HMPT, to give high yields of carboxylic esters.[486] The mechanism is SN2. Another method uses potassium carboxylates in acetonitrile or benzene in the presence of a crown ether such as 18-crown-6 (p. 82). With this method good yields of esters are obtained from primary, secondary, benzylic, and phenacyl bromides.[487] When the reaction is carried out without crown ethers and in protic solvents, it is useful only for fairly active R, such as benzyl, allyl, etc. (SN1 mechanism), but not for tertiary alkyl, since elimination occurs instead. The salts used are often sodium, but potassium, silver, and substituted ammonium salts have also been used Lactones can be prepared from γ- and δ-halo acids by treatment with base (see reaction **0-24**).

Copper(I) carboxylates give esters with primary (including neopentyl without rearrangement), secondary, and tertiary alkyl, allylic, and vinylic halides.[488] A simple SN mechanism is obviously precluded in this case. Primary and secondary halides also give esters when treated directly with carboxylic acids in the presence of Cu_2O and an isonitrile.[489] A copper carboxylate is an intermediate here. Vinyl halides can be converted to vinyl acetates by treatment with sodium acetate if palladium(II) chloride is present.[490] A COOH group can be conveniently protected by reaction of its ion with a phenacyl bromide ($ArCOCH_2Br$).[430] The resulting ester is easily cleaved when desired with zinc and acetic acid.

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[482] Jeffery and Satchell, *J. Chem. Soc.* 1906 (1962); Rothman, Hecht, Pfeffer, and Silbert, *J. Org. Chem.* **37**, 3551 (1972).

[483] For examples, see Deghenghi and Engel, *J. Am. Chem. Soc.* **82**, 3201 (1960); House and Trost, *J. Org. Chem.* **30**, 2502 (1965).

[484] For example, see Hopff and Osman, *Tetrahedron* **24**, 2205, 3887 (1968); Mondal, van der Meer, German, and Heikens, *Tetrahedron* **30**, 4205 (1974).

[485] Henry, *J. Am. Chem. Soc.* **93**, 3853 (1971), *Acc. Chem. Res.* **6**, 16–24 (1973).

[486] Parker, *Adv. Org. Chem.* **5**, 1–46 (1965), p. 37; Alvarez and Watt, *J. Org. Chem.* **33**, 2143 (1968); Pfeffer, Foglia, Barr, Schmeltz, and Silbert, *Tetrahedron Lett.* 4063 (1972); Mehta, *Synthesis* 262 (1972); Shaw, Kunerth, and Sherry, *Tetrahedron Lett.* 689 (1973); Shaw and Kunerth, *J. Org. Chem.* **39**, 1968 (1974); Larock, *J. Org. Chem.* **39**, 3721 (1974).

[487] Liotta, Harris, McDermott, Gonzalez, and Smith, Ref. 266; Durst, Ref. 266. See also Akabori and Ohtomi, *Bull. Chem. Soc. Jpn.* **48**, 2991 (1975).

[488] Lewin and Goldberg, *Tetrahedron Lett.* 491 (1972); Klumpp, Bos, Schakel, Schmitz, and Vrielink, *Tetrahedron Lett.* 3429 (1975).

Other leaving groups may also be replaced by OCOR. Alkyl chlorosulfites (ROSOCl) and other derivatives of sulfuric, sulfonic, and other inorganic acids can be treated with carboxylate ions to give the corresponding esters. The use of dimethyl sulfate[491] or trimethyl phosphate[492] allows sterically hindered COOH groups to be methylated. With certain substrates, carboxylic acids are strong enough nucleophiles for the reaction. Examples of such substrates are trialkyl phosphites $P(OR)_3$[493] and acetals of dimethylformamide:[494]

$$(RO)_2CHNMe_2 + R'COOH \longrightarrow R'COOR + ROH + HCONMe_2$$

This is an SN2 process, since inversion is found at R. Tertiary amines containing one group which forms a stable carbonium ion (e.g., benzyl, *t*-butyl, triphenylmethyl) can be cleaved by acetic anhydride,[495] e.g.,

$$PhCH_2NMe_2 + Ac_2O \longrightarrow PhCH_2OAc + Me_2NCOCH_3$$

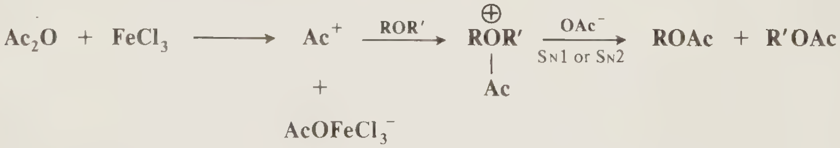
Amines which do not contain such groups do not react. Another good leaving group is NTs_2, and ditosylamines react quite well with acetate ion in dipolar aprotic solvents:[496] $RNTs_2 + OAc^- \rightarrow ROAc$. Quaternary ammonium salts can be cleaved by heating with AcO^- in an aprotic solvent.[497] Oxonium ions may also be used as substrates:[498] $R_3O^+ + R'COO^- \rightarrow R'COOR + R_2O$.

OS **II**, 5; **III**, 650; **IV**, 582; **V**, 580.

0-27 Cleavage of Ethers with Acetic Anhydride

$$R{-}O{-}R' + Ac_2O \xrightarrow{FeCl_3} ROAc + R'OAc$$

Dialkyl ethers can be cleaved by treatment with anhydrous ferric chloride in acetic anhydride.[499] In this reaction both R groups are converted to acetates. Yields are moderate to high. The mechanism has been formulated as



$$Ac_2O + FeCl_3 \longrightarrow \underset{\displaystyle AcOFeCl_3^-}{\underset{+}{Ac^+}} \xrightarrow{ROR'} \underset{\displaystyle Ac}{\overset{\oplus}{ROR'}} \xrightarrow[\text{SN1 or SN2}]{OAc^-} ROAc + R'OAc$$

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[489] Saegusa and Murase, *Synth. Commun.* **2**, 1 (1972); Saegusa, Murase, and Ito, *J. Org. Chem.* **38**, 1753 (1973).

[490] Kohll and van Helden, *Recl. Trav. Chim. Pays-Bas* **87**, 481 (1968); Volger, *Recl. Trav. Chim. Pays-Bas* **87**, 501 (1968); Yamaji, Fujiwara, Imanaka, and Teranishi, *Bull. Chem. Soc. Jpn.* **43**, 2659 (1970); Yamaji, Fujiwara, Asano, and Teranishi, *Bull. Chem. Soc. Jpn.* **46**, 90 (1973).

[491] Grundy, James, and Pattenden, *Tetrahedron Lett.* 757 (1972).

[492] Harris and Patel, *Chem. Ind.* (*London*) 1002 (1973).

[493] Szmuszkovicz, *Org. Prep. Proced. Int.* **4**, 51 (1972).

[494] Vorbrüggen, *Angew. Chem. Int. Ed. Engl.* **2**, 211 (1963) [*Angew. Chem.* **75**, 296]; Brechbühler, Büchi, Hatz, Schreiber, and Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **2**, 212 (1963) [*Angew. Chem.* **75**, 296].

[495] Mariella and Brown, *Can. J. Chem.* **49**, 3348 (1971), **51**, 2177 (1973). See also Gol'dfarb and Belen'kii, *Can. J. Chem.* **51**, 2174 (1973).

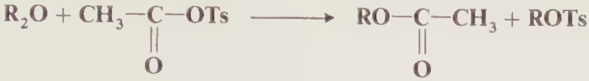
[496] Anderson and Uh, *Synth. Commun.* **2**, 297 (1972).

[497] Wilson and Joule, *Tetrahedron* 24, 5493 (1968).

[498] Raber and Gariano, *Tetrahedron Lett.* 4741 (1971).

[499] Ganem and Small, *J. Org. Chem.* **39**, 3728 (1974).

Ethers can also be cleaved by the mixed anhydride acetyl tosylate:[500]



$$R_2O + CH_3{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OTs \longrightarrow RO{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3 + ROTs$$

0-28 Alkylation of Acids with Diazo Compounds

$$R_2CN_2 + R'COOH \longrightarrow R'COOCHR_2$$

Acids can be converted to esters with diazo compounds in a reaction which is essentially the same as reaction **0-17**. In contrast to alcohols, carboxylic acids undergo the reaction quite well at room temperature, since the reactivity of the reagent increases with acidity. The reaction is used where high yields are important or where the acid is sensitive to higher temperatures. Because of availability, the diazo compounds most often used are diazomethane (for methyl esters)

$$CH_2N_2 + RCOOH \longrightarrow RCOOCH_3$$

and diazo ketones. The mechanism is as shown in reaction **0-17**.

OS **V**, 797.

F. Attack by OCOR at an Acyl Carbon

0-29 Acylation of Acids with Acyl Halides

$$RCOCl + R'COO^- \longrightarrow RCOOCOR'$$

Unsymmetrical as well as symmetrical anhydrides are often prepared by the treatment of an acyl halide with an acid salt. If a metallic salt is used, then Na^+, K^+, or Ag^+ are the most common cations, but more often pyridine or another tertiary amine is added to the free acid, and the salt thus formed is treated with the acyl halide. Thallium(I) salts are particularly effective and react with acyl halides to give anhydrides in high yield.[457] Anhydrides which are unaffected by cold water may be made in high yield by shaking an aqueous solution of the sodium salt of an acid with an acyl halide at room temperature in the presence of a tertiary amine.[501] Acyl halides may also be converted to anhydrides by treatment with esters (with a $ZnCl_2$ catalyst) or with anhydrides (an exchange reaction), but these methods are seldom used. Symmetrical anhydrides can be prepared by treatment of acyl halides with dry N_2O_4.[502] The mixed anhydride $RCOONO_2$ is probably an intermediate which reacts with another molecule of RCOCl.

OS **III**, 28, 422, 488; **IV**, 285; **50**, 1; **51**, 48.

0-30 Acylation of Acids with Acids

$$2RCOOH \xrightleftharpoons{P_2O_5} (RCO)_2O + H_2O$$

Anhydrides can be formed from two molecules of an ordinary acid only if a dehydrating agent is present so that the equilibrium can be driven to the right. Common dehydrating agents are acetic anhydride, trifluoroacetic anhydride, dicyclohexylcarbodiimide,[503] methoxyacetylene,[504] and P_2O_5. The method is very poor for the formation of mixed anhydrides, which in any case generally undergo disproportionation to the two simple anhydrides when they are heated. However, simple heating of dicarboxylic acids does give cyclic anhydrides, provided that the ring formed contains five, six, or seven members. Malonic acid and its derivatives, which would give four-membered cyclic anhydrides, do not give this reaction when heated but instead undergo decarboxylation (reaction **2-39**).

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[500] Karger and Mazur, *J. Am. Chem. Soc.* **90**, 3878 (1968). See also Coffi-Nketsia, Kergomard, and Tautou, *Bull. Soc. Chim. Fr.* 2788 (1967).

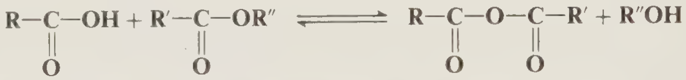
[501] Smalley and Suschitzky, *J. Chem. Soc.* 755 (1964).

[502] Svetlakov, Stepanova, and Shafigullin, *J. Org. Chem. USSR* **5**, 2183 (1969).

[503] For example, see Schüssler and Zahn, *Chem. Ber.* **95**, 1076 (1962); Rammler and Khorana, *J. Am. Chem. Soc.* **85**, 1997 (1963). See also Hata, Tajima, and Mukaiyama, *Bull. Chem. Soc. Jpn.* **41**, 2746 (1968).

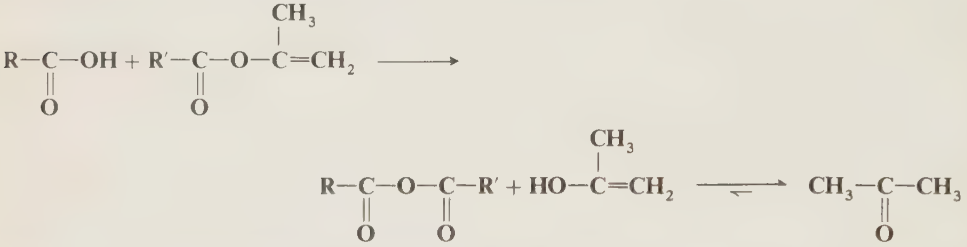
[504] See for example, Eglinton, Jones, Shaw, and Whiting, *J. Chem. Soc.* 1860 (1954); Arens and Doornbos, *Recl. Trav. Chim. Pays-Bas* **74**, 79 (1955).

Carboxylic acids exchange with amides and esters, and these methods are sometimes used to prepare anhydrides if the equilibrium can be shifted; e.g.,



$$\mathrm{R-\underset{\overset{\|}{O}}{C}-OH + R'-\underset{\overset{\|}{O}}{C}-OR'' \rightleftharpoons R-\underset{\overset{\|}{O}}{C}-O-\underset{\overset{\|}{O}}{C}-R' + R''OH}$$

Enolic esters are especially good for this purpose, since the equilibrium is shifted by formation of the ketone.



$$\mathrm{R-\underset{\overset{\|}{O}}{C}-OH + R'-\underset{\overset{\|}{O}}{C}-O-\overset{\overset{CH_3}{|}}{C}{=}CH_2 \longrightarrow}$$

$$\mathrm{R-\underset{\overset{\|}{O}}{C}-O-\underset{\overset{\|}{O}}{C}-R' + HO-\overset{\overset{CH_3}{|}}{C}{=}CH_2 \rightleftharpoons CH_3-\underset{\overset{\|}{O}}{C}-CH_3}$$

Acids also exchange with anhydrides; indeed, this is how acetic anhydride acts as a dehydrating agent in this reaction.

Anhydrides can be formed by treatment of the triethylammonium *salt* of a carboxylic acid with phosgene:[505]

$$\mathrm{2RCOO^{\ominus}\ \overset{\oplus}{N}HEt_3 \xrightarrow{COCl_2} RCOOCOR + 2\overset{\oplus}{N}HEt_3\ Cl^- + CO_2}$$

or of thallium(I) carboxylates with thionyl chloride,[457] or of mercury(II) carboxylates with a thioester.[506]

OS **I,** 91, 410; **II,** 194, 368, 560; **III,** 164, 449; **IV,** 242, 630, 790; **V,** 8, 822. Also see OS **54,** 79.

G. Other Oxygen Nucleophiles

0-31 Formation of Oxonium Salts

$$\mathrm{RX + R_2O \xrightarrow{AgBF_4} R_3O^+\ BF_4^- + AgX}$$

$$\mathrm{RX + R'_2CO \xrightarrow{AgBF_4} R'_2C{=}\overset{\oplus}{O}-R\quad BF_4^- + AgX}$$

Alkyl halides can be alkylated by ethers or ketones to give oxonium salts, if a very weak, negatively charged nucleophile is present to serve as a counterion and a Lewis acid is present to combine with X .[507] A typical procedure consists of treating the halide with the ether or the ketone in the presence of $AgBF_4$ or $AgSbF_6$. The Ag^+ serves to remove X^-, and the BF_4^- or SbF_6^- acts as the counterion. Another method involves treatment of the halide with a complex formed between the oxygen compound and a Lewis acid, e.g., $R_2O{-}BF_3 + RF \rightarrow R_3O^+ \; BF_4^-$, though this method is most satisfactory when the oxygen and halogen atoms are in the same molecule so that a cyclic oxonium ion is obtained. Ethers and oxonium ions also undergo exchange reactions:

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[505] Rinderknecht and Ma, *Helv. Chim. Acta* **47,** 152 (1964).

[506] Ellis, Frier, and Schibeci, *Aust. J. Chem.* **24,** 1527 (1971). See also Yamaguchi, Inomata, and Mukaiyama, *Bull. Chem. Soc. Jpn.* **41,** 673 (1968).

[507] Meerwein, Hederich, and Wunderlich, *Arch. Pharm.* **291/63,** 541 (1958). For a review, see Ref. 68, pp. 22–39.

$$2R_3O^+ \; BF_4^- + 3R'_2O \rightleftharpoons 2R'_3O^+ \; BF_4^- + 3R_2O$$

Other leaving groups have also been used.[508]

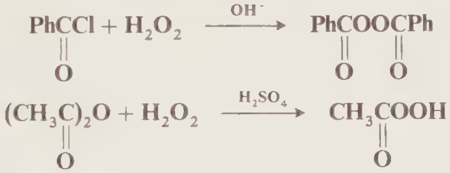
OS V 1080, 1096, 1099; **51**, 142.

0-32 Preparation of Peroxides and Hydroperoxides

$$2RX + O_2^{2-} \longrightarrow ROOR$$
$$RX + OOH^- \longrightarrow ROOH$$

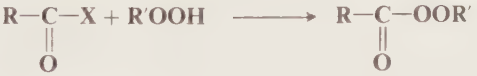
Hydroperoxides can be prepared by treatment of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in basic solution, where it is actually HO_2^-.[509] Sodium peroxide is similarly used to prepare dialkyl peroxides. For R = benzyl, the reaction has been shown to proceed by the S_N1cB mechanism with phenylcarbene (PhCH) as an intermediate.[510] Peroxides can also be prepared by treatment of alkyl bromides or tosylates with potassium superoxide KO_2 in the presence of crown ethers.[510a]

Acyl peroxides and hydroperoxides can be similarly prepared[511] from acyl halides or anhydrides,



$$\text{Ph}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{Cl} + \text{H}_2\text{O}_2 \xrightarrow{\text{OH}^-} \text{Ph}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{OO}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{Ph}$$
$$(\text{CH}_3\underset{\underset{\text{O}}{\|}}{\text{C}})_2\text{O} + \text{H}_2\text{O}_2 \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3\underset{\underset{\text{O}}{\|}}{\text{C}}\text{OOH}$$

from carboxylic acids,[512] and from amides of the imidazolide type (p. 353).[513] Diacyl peroxides can also be prepared by the treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarbodiimide,[514] H_2SO_4, methanesulfonic acid, or some other dehydrating agent. Mixed alkyl-acyl peroxides (peresters) can be made from acyl halides and hydroperoxides.



$$\text{R}{-}\underset{\underset{\text{O}}{\|}}{\text{C}}{-}\text{X} + \text{R}'\text{OOH} \longrightarrow \text{R}{-}\underset{\underset{\text{O}}{\|}}{\text{C}}{-}\text{OOR}'$$

OS **III,** 619, 649; **V,** 805, 904; **50,** 15.

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[508] For example, see Olah, Olah, and Svoboda, *Synthesis* 490 (1973).

[509] For a review, see Hiatt, in Swern, "Organic Peroxides," vol. 2, pp. 1-151, Interscience Publishers, New York, 1971.

[510] Pearson and Edgington, *J. Am. Chem. Soc.* **84,** 4607 (1962).

[510a] Johnson and Nidy, *J. Org. Chem.* **40,** 1681 (1975).

[511] For a review of the synthesis of acyl peroxides, see Hiatt, Ref. 509, vol. 2, pp. 799-929.

[512] For example, see Antonovskii, Lyashenko, and Lozovaya, *J. Org. Chem. USSR* **9,** 1172 (1973).

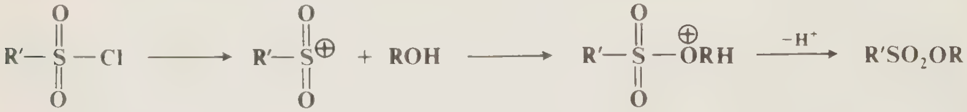
[513] Staab, Rohr, and Graf, *Chem. Ber.* **98,** 1122 (1965).

[514] Greene and Kazan, *J. Org. Chem.* **28,** 2168 (1963).

0-33 Preparation of Inorganic Esters

$$\begin{aligned}
&ROH + HONO_2 \xrightarrow{H^+} RONO_2\\
&ROH + HONO \xrightarrow{H^+} RONO\\
&ROH + SOCl_2 \longrightarrow ROSOOR\\
&ROH + POCl_3 \longrightarrow PO(OR)_3\\
&ROH + SO_3 \longrightarrow ROSO_2OH
\end{aligned}$$

The above reactions show a few of the many inorganic esters which can be prepared by attack of an inorganic acid or, better, its acid halide or anhydride, on an alcohol.[515] Although for convenience all these similar reactions are grouped together, the mechanism in many cases is not nucleophilic substitution at the alcoholic carbon. The other possible mechanism is nucleophilic substitution at the inorganic central atom:



$$R'-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-Cl \longrightarrow R'-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{}^{\oplus} + ROH \longrightarrow R'-\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}-\overset{\oplus}{O}RH \xrightarrow{-H^+} R'SO_2OR$$

or a corresponding SN2 type (see p. 449). In such cases there is no alkyl-O cleavage. Alkyl and aryl sulfates can be prepared by treatment of the alcohol or phenol with H_2SO_4 in the presence of dicyclohexylcarbodiimide.[516] Mono esters of sulfuric acid (alkylsulfuric acids), which are important industrially because their salts are used as detergents, can be prepared by treating alcohols with SO_3, H_2SO_4, $ClSO_2OH$, or SO_3 complexes.[517]

Alkyl halides are often used as substrates instead of alcohols. In such cases the *salt* of the inorganic acid is usually used, and the mechanism is nucleophilic substitution at the carbon atom. An important example is the treatment of alkyl halides with silver nitrate to form alkyl nitrates. This is often used as a test for alkyl halides. In some cases there is competition from the central atom. Thus nitrite ion is an ambident nucleophile which can give nitrites or nitro compounds (see reaction **0-62**). In some cases ethers may be substrates. Thus dialkyl or aryl alkyl ethers may be cleaved with anhydrous sulfonic acids:[518]

$$ROR' + R''SO_2OH \longrightarrow ROSO_2R'' + R'OH$$

R″ may be alkyl or aryl. For dialkyl ethers, the reaction does not end as indicated above, since R′OH is rapidly converted to R′OR′ by the sulfonic acid (reaction **0-18**), which in turn is further cleaved to $R'OSO_2R''$ so that the product is a mixture of the two sulfonates. For aryl alkyl ethers, cleavage always takes place to give the phenol, which is not converted to the ether under these conditions. Ethers can also be cleaved in a similar manner by mixed anhydrides of sulfonic and carboxylic acids[519] (prepared as in reaction **0-34**).

OS **II,** 106, 108, 109, 112, 204, 412; **III,** 148, 471; **IV,** 955; **V,** 839. Also see OS **II,** 111.

0-34 Preparation of Mixed Organic-Inorganic Anhydrides[520]

$$(RCO)_2O + HONO_2 \longrightarrow RCOONO_2$$

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[515] For a review, see Ref. 426, pp. 481-497.

[516] Hoiberg and Mumma, *J. Am. Chem. Soc.* **91,** 4273 (1969).

[517] For a review, see Sandler and Karo, Ref. 180, vol. 3, pp. 114-133 (1972).

[518] Klamann and Weyerstahl, *Chem. Ber.* **98,** 2070 (1965).

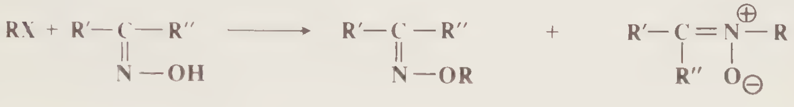
[519] Karger and Mazur, *J. Org. Chem.* **36,** 532, 540 (1971).

[520] For a review, see Satchell, *Q. Rev., Chem. Soc.* **17,** 160-203 (1963), pp. 179-181.

Mixed organic-inorganic anhydrides are seldom isolated, though they are often intermediates when acylation is carried out with acid derivatives catalyzed by inorganic acids. Sulfuric, perchloric, phosphoric, and other acids form similar anhydrides, most of which are unstable or not easily obtained because the equilibrium lies in the wrong direction. These intermediates are formed from amides, acids, and esters, as well as from anhydrides. Organic anhydrides of phosphoric acid are more stable than most others and, for example, $RCOOPO(OH)_2$ can be prepared in the form of its salts.[521] Mixed anhydrides of carboxylic and sulfonic acids ($RCOOSO_2R'$) are obtained in high yields by treatment of sulfonic acids with acyl halides or (less preferred) anhydrides.[522]

OS **I**, 495; **50**, 9.

0-35 Alkylation of Oximes



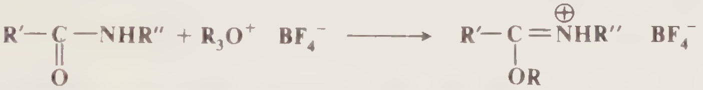
$$RX + R'-\underset{\underset{\displaystyle N-OH}{\|}}{C}-R'' \longrightarrow R'-\underset{\underset{\displaystyle N-OR}{\|}}{C}-R'' + R'-\underset{\underset{\displaystyle R''}{|}}{C}=\overset{\oplus}{\underset{\underset{\displaystyle O^{\ominus}}{|}}{N}}-R$$

A nitrone

Oximes may be alkylated by alkyl halides or sulfates. N-alkylation is a side reaction, yielding a nitrone. The relative yield of oxime ether and nitrone depends on the nature of the reagents, including the configuration of the oxime, and on the reaction conditions. For example, *anti*-benzaldoximes give nitrones, while the syn isomers give oxime ethers.[523]

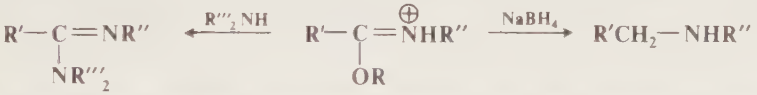
OS **III**, 172; **V**, 1031. Also see OS **V**, 269.

0-36 Alkylation of Amides and Other Carbonyl Compounds[524]



$$R'-\underset{\underset{\displaystyle O}{\|}}{C}-NHR'' + R_3O^+\ BF_4^- \longrightarrow R'-\underset{\underset{\displaystyle OR}{|}}{C}=\overset{\oplus}{N}HR''\ BF_4^-$$

The oxygen atom of amides can be alkylated by oxonium salts to give salts of N-alkylimino esters. These ions can then be treated with a variety of nucleophiles. For example, they can be reduced to amines with $NaBH_4$ or converted to amidines with secondary amines.[525] The reaction



$$R'-\underset{\underset{\displaystyle NR'''_2}{|}}{C}=NR'' \xleftarrow{R'''_2NH} R'-\underset{\underset{\displaystyle OR}{|}}{C}=\overset{\oplus}{N}HR'' \xrightarrow{NaBH_4} R'CH_2-NHR''$$

is also good for lactams, lactones, and esters of carbonic acid but is generally unsuccessful for aldehydes, ketones, and open-chain carboxylic esters.

0-37 Acylation at the Oxygen of Aldehydes (see reaction **6-58**)

Sulfur Nucleophiles

Sulfur compounds are better nucleophiles than their oxygen analogs (p. 322), so that in most cases these reactions take place faster and more smoothly than the corresponding reactions with oxygen nucleophiles.

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[521] Avison, *J. Chem. Soc.* 732 (1955).

[522] Karger and Mazur, *J. Org. Chem.* **36**, 528 (1971).

[523] Buehler, *J. Org. Chem.* **32**, 261 (1967).

[524] For reviews, see Ref. 68, pp. 128–137; Granik, Pyatin, and Glushkov, Ref. 285, pp. 749–755.

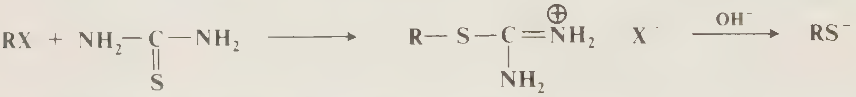
[525] Weintraub, Oles, and Kalish, *J. Org. Chem.* **33**, 1679 (1968).

0-38 Attack by SH at an Alkyl Carbon. Formation of Mercaptans[525a]

$$RX + H_2S \longrightarrow RSH_2^+ \longrightarrow RSH + H^+$$

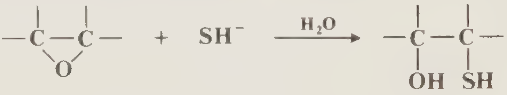
$$RX + HS^- \longrightarrow RSH$$

Sodium sulfhydride (NaSH) is a much better reagent for the formation of mercaptans from alkyl halides than H_2S and is much more often used.[526] It is easily prepared by bubbling H_2S into an alkaline solution. The reaction is most useful for primary halides. Secondary substrates give much lower yields, and the reaction fails completely for tertiary halides because elimination predominates. Sulfuric and sulfonic esters can be used instead of halides. Sulfides (RSR) are often side products. An indirect method for the conversion of an alkyl halide to a mercaptan consists of treatment with thiourea to give an isothiuronium salt, which with alkali or a high-molecular-weight amine is cleaved to the mercaptan:



$$RX + NH_2-\underset{\underset{S}{\|}}{C}-NH_2 \longrightarrow R-S-\underset{\underset{NH_2}{|}}{C}=\overset{\oplus}{N}H_2 \quad X^- \xrightarrow{OH^-} RS^-$$

Another indirect method is hydrolysis of Bunte salts (see reaction **0-42**). When epoxides are substrates, the products are β-hydroxy mercaptans:[526a]



OS **III,** 363, 440; **IV,** 401, 491; **V,** 1046. Also see OS **II,** 345, 411, 573; **IV,** 232; **V,** 223.

0-39 Attack by SR at an Alkyl Carbon. Formation of Sulfides

$$RX + R'S^- \longrightarrow RSR'$$

Sulfides may be prepared by treatment of alkyl halides with salts of mercaptans.[527] R′ may be alkyl or aryl. As in reaction **0-38,** RX cannot be a tertiary halide, and sulfuric and sulfonic esters can be used instead of halides. As in the Williamson reaction (**0-14**) yields are improved by phase-transfer catalysis.[527a] R may be tertiary if an alcohol is the substrate, e.g.,[528]

$$R_3COH + R'_3CSH \xrightarrow{H_2SO_4} R_3CSCR'_3$$

This reaction is analogous to reaction **0-18.** Compounds with other leaving groups have also been used, e.g., $ROPOX_2$ (X = R or OR)[529] and ROC(NHR′)=NR′ (R′ = cyclohexyl).[530]

Mercaptide ions are also useful for the demethylation of certain ethers, esters, and quaternary ammonium salts. Aryl methyl ethers can be cleaved by heating with EtS^- in the dipolar aprotic solvent dimethylformamide: $ROAr + EtS^- \rightarrow ArO^- + EtSR$.[531] Similarly, *n*-PrSLi in HMPT can be used to cleave methyl esters of sterically hindered acids, e.g., methyl mesitoate.[532] A good method for the demethylation of quaternary ammonium salts consists of refluxing them with PhS^- in butanone:[533]

[525a] For a review, see Wardell, in Patai, "The Chemistry of the Thiol Group," pt. 1, pp. 179–211, John Wiley & Sons, New York, 1974.

[526] For a review, see Reid, "Organic Chemistry of Bivalent Sulfur," vol. 1, pp. 21–29, 32–35, vol. 5, pp. 27–34, Chemical Publishing Company, New York, 1958, 1963.

[526a] For a review, see Ref. 525a, pp. 246–251.

[527] For reviews, see Ref. 526, vol. 2, pp. 16–21, 24–29, vol. 3, pp. 11–14 (1960); Peach, in Patai, Ref. 525a, pt. 2, pp. 721–735.

[527a] Herriott and Picker, *Synthesis* 447 (1975), *J. Am. Chem. Soc.* **97,** 2345 (1975).

[528] Fehnel and Carmack, *J. Am. Chem. Soc.* **71,** 84 (1949); Cain, Evans, and Lee, *J. Chem. Soc.* 1694 (1962).

[529] Savignac and Coutrot, *Synthesis* 818 (1974).

[530] Vowinkel, *Synthesis* 430 (1974).

[531] Feutrill and Mirrington, *Tetrahedron Lett.* 1327 (1970); *Aust. J. Chem.* **25,** 1719, 1731 (1972).

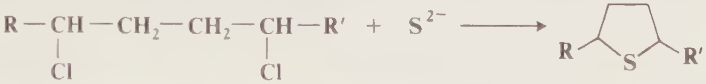
$$R_3\overset{\oplus}{N}Me + PhS^- \xrightarrow{MeCOEt} R_3N + PhSMe$$

A methyl group is cleaved more readily than other simple alkyl groups (such as ethyl), though loss of these groups competes, but benzyl and allyl groups cleave even more easily, and this is a useful procedure for the cleavage of benzyl and allyl groups from quaternary ammonium salts even if methyl groups are also present.[534]

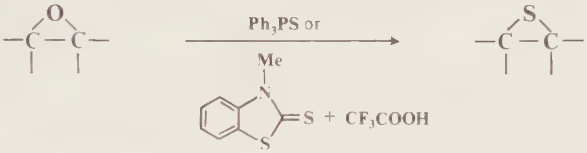
Symmetrical sulfides may also be prepared by treatment of an alkyl halide with sodium sulfide.

$$2RX + Na_2S \longrightarrow RSR$$

This reaction may be carried out internally, by addition of sulfide ions to 1,4- or 1,5-dihalides, to prepare five- and six-membered sulfur-containing heterocyclic rings.



Selenides and tellurides may be prepared similarly.[535] When epoxides are substrates, β-hydroxy sulfides are obtained in a manner analogous to that mentioned in reaction **0-38.** Epoxides can also be directly converted to episulfides,[535a] by treatment with a phosphine sulfide such as Ph_3PS[536] or with 3-methylbenzothiazole-2-thione and trifluoroacetic acid.[536a]

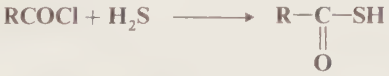


Alkyl halides, treated with sulfides, give sulfonium salts.[537]

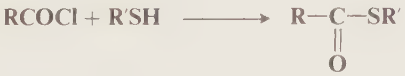
$$RCl + R'_2S \longrightarrow R'_2SR^+ \quad Cl^-$$

OS **II,** 31, 345, 547, 576; **III,** 332, 751, 763; **IV,** 396, 667, 892, 967; **V,** 562, 780, 1046; **50,** 31, 33, 72; **51,** 70; **53,** 1, 90; **54,** 19, 27. See also OS **55,** 127.

0-40 Attack by SH or SR at an Acyl Carbon[538]



$$RCOCl + H_2S \longrightarrow R-\underset{\displaystyle O}{\underset{\|}{C}}-SH$$



$$RCOCl + R'SH \longrightarrow R-\underset{\displaystyle O}{\underset{\|}{C}}-SR'$$

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[532] Bartlett and Johnson, *Tetrahedron Lett.* 4459 (1970).

[533] Shamma, Deno, and Remar, *Tetrahedron Lett.* 1375 (1966). For alternative procedures, see Hutchins and Dux, *J. Org. Chem.* **38,** 1961 (1973); Posner and Ting, *Synth. Commun.* **4,** 355 (1974).

[534] Kametani, Kigasawa, Hiiragi, Wagatsuma, and Wakisaka, *Tetrahedron Lett.* 635 (1969).

[535] Brandsma and Wijers, *Recl. Trav. Chim. Pays-Bas* **82,** 68 (1963).

[535a] For a review of episulfide formation, see Fokin and Kolomiets, *Russ. Chem. Rev.* **44,** 138–153 (1975).

[536] Chan and Finkenbine, *J. Am. Chem. Soc.* **94,** 2880 (1972).

[536a] Calō, Lopez, Marchese, and Pesce, *J. Chem. Soc., Chem. Commun.* 621 (1975).

[537] For a review, see Ref. 526, vol. 2, pp. 66–71 (1960).

[538] For a review, see Ref. 520, pp. 182–184.

Thiol acids and thiol esters may be prepared in this manner, which is analogous to reactions **0-9** and **0-25.**[539] Anhydrides and aryl esters (RCOOAr)[540] are also used as substrates, but the reagents in these cases are usually SH^- and SR^-. Thiol esters may also be prepared by treatment of carboxylic acids with trisalkylthioboranes $B(SR)_3$,[541] or with a mercaptan and diethyl phosphorocyanidate $NCPO(OEt)_2$ or diphenyl phosphorazidate $N_3PO(OPh)_2$ in dimethylformamide in the presence of Et_3N.[542] Esters RCOOR′ can be converted to thiol esters RCOSR″ by treatment with trimethylsilyl sulfides Me_3SiSR'' and $AlCl_3$.[543]

OS **III,** 116, 599; **IV,** 924, 928.

0-41 Formation of Disulfides

$$2RX + S_2{}^{2-} \longrightarrow RSSR + 2X^-$$

Disulfides[544] can be prepared by treatment of alkyl halides with disulfide ions and also indirectly by the reaction of Bunte salts (see reaction **0-42**) with acid solutions of iodide, thiocyanate ion, or thiourea,[545] or by pyrolysis, or by treatment with hydrogen peroxide.

There are no OS references, but a similar preparation of a polysulfide may be found in OS **IV,** 295.

0-42 Formation of Bunte Salts

$$RX + S_2O_3{}^{2-} \longrightarrow R{-}S{-}SO_3{}^- + X^-$$

Primary and secondary, but not tertiary, alkyl halides are easily converted to Bunte salts ($RSSO_3{}^-$) by treatment with thiosulfate ion.[546] Bunte salts may be hydrolyzed with acids to give the corresponding mercaptans,[547] or converted to disulfides, tetrasulfides, or pentasulfides.[548]

0-43 Alkylation of Sulfinic Acid Salts

$$RX + R'SO_2{}^- \longrightarrow R{-}SO_2{-}R' + X^-$$

Alkyl halides or alkyl sulfates, treated with the salts of sulfinic acids, give sulfones. Alkyl sulfinates R′SO—OR may be side products.[549]

OS **IV,** 674. See also OS **54,** 33.

0-44 Attack by Sulfite Ion

$$RX + SO_3{}^{2-} \longrightarrow R{-}SO_2O^- + X^-$$

Salts of sulfonic acids may be prepared by treatment of primary or secondary alkyl halides with sulfite ion.[550] Even tertiary halides have been used, though the yields are low. Epoxides treated with bisulfite give β-hydroxy sulfonic acids:[551]

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[539] For a review of these compounds, see Ref. 526, vol. 4, pp. 7–130 (1962).

[540] Hirabayashi, Mizuta, and Mazume, *Bull. Chem. Soc. Jpn.* **38,** 320 (1965).

[541] Pelter, Levitt, and Smith, *Chem. Commun.* 435 (1969).

[542] Yamada, Yokoyama, and Shioiri, *J. Org. Chem.* **39,** 3302 (1974).

[543] Mukaiyama, Takeda, and Atsumi, *Chem. Lett.* 187 (1974).

[544] For a review of disulfides, see Ref. 526, vol. 3, pp. 362–462 (1960).

[545] Milligan and Swan, *J. Chem. Soc.* 2172 (1962).

[546] For reviews of Bunte salts, see Milligan and Swan, *Rev. Pure Appl. Chem.* **12,** 72–94 (1962); Distler, *Angew. Chem. Int. Ed. Engl.* **6,** 544–553 (1967) [*Angew. Chem.* **79,** 520–529].

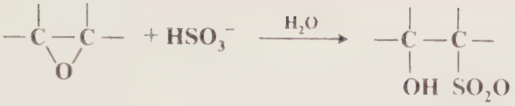
[547] Kice, *J. Org. Chem.* **28,** 957 (1963).

[548] Milligan, Saville, and Swan, *J. Chem. Soc.* 3608 (1963).

[549] Schank, *Justus Liebigs Ann. Chem.* **702,** 75 (1967), **714,** 117 (1968); Meek and Fowler, *J. Org. Chem.* **33,** 3422 (1968).

[550] For a review, see Gilbert, "Sulfonation and Related Reactions," pp. 136–148, 161–163, Interscience Publishers, New York, 1965.

[551] For a discussion, see Yoneda, Griffin, and Carlyle, *J. Org. Chem.* **40,** 375 (1975).



OS **II**, 558, 564; **IV**, 529.

0-45 Formation of Alkyl Thiocyanates

$$RX + SCN^- \longrightarrow RSCN + X^-$$

Alkyl halides or sulfuric or sulfonic esters can be heated with sodium or potassium thiocyanate to give alkyl thiocyanates,[552] though the attack by the analogous cyanate ion (reaction **0-64**) gives exclusive N-alkylation.

OS **II**, 366.

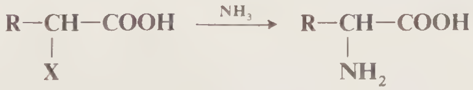
Nitrogen Nucleophiles

A. Attack by NH_2, NHR, or NR_2 at an Alkyl Carbon

0-46 Alkylation of Amines

$$\begin{array}{llllll}
3RX + NH_3 & \longrightarrow & R_3N & + RX & \longrightarrow & R_4N^+ \quad X^- \\
2RX + R'NH_2 & \longrightarrow & R_2R'N & + RX & \longrightarrow & R_3R'N^+ \quad X^- \\
RX + R'R''NH & \longrightarrow & RR'R''N & + RX & \longrightarrow & R_2R'R''N^+ \quad X^- \\
RX + R'R''R'''N & \longrightarrow & RR'R''R'''N^+ \quad X^- & & &
\end{array}$$

The reaction between alkyl halides and ammonia or primary amines is not usually a feasible method for the preparation of primary or secondary amines, since they are stronger bases than ammonia and preferentially attack the substrate. However, the reaction is very useful for the preparation of tertiary amines[553] and quaternary ammonium salts. If ammonia is the nucleophile, the three or four alkyl groups on the nitrogen of the product must be identical. If a primary, secondary, or tertiary amine is used, then different alkyl groups may be placed on the same nitrogen atom. The conversion of tertiary amines to quaternary salts is called the *Menschutkin reaction.*[554] It is sometimes possible to use this method for the preparation of a primary amine by the use of a large excess of ammonia, or a secondary amine by the use of a large excess of primary amine. However, the limitations of this approach can be seen in the reaction of a saturated solution of ammonia in 90% ethanol with ethyl bromide in a 16:1 molar ratio, under which conditions the yield of primary amine was 34.2% (at a 1:1 ratio the yield was 11.3%).[555] In some cases, where field or other effects cause the primary amine to be a weaker base than ammonia, it can easily be prepared in good yield. An important example is the conversion of α-halo acids to α-amino acids:



$$\underset{\displaystyle X}{\text{R—CH—COOH}} \xrightarrow{NH_3} \underset{\displaystyle NH_2}{\text{R—CH—COOH}}$$

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[552] For discussions, see Bacon, in Kharasch, "Organic Sulfur Compounds," pp. 306–309, Pergamon Press, New York, 1961; Ref. 526, vol. 6, pp. 34–37 (1965); Ref. 525a, pp. 230–231.

[553] For reviews of this reaction, see Gibson, in Patai, Ref. 298, pp. 45–55; Spialter and Pappalardo, "The Acyclic Aliphatic Tertiary Amines," pp. 14–29, The Macmillan Company, New York, 1965.

[554] For a review of stereoselectivity in this reaction, especially where the tertiary nitrogen is included in a ring, see Bottini, *Sel. Org. Transform.* **1**, 89–142 (1970).

[555] Werner, *J. Chem. Soc.* **113**, 899 (1918).

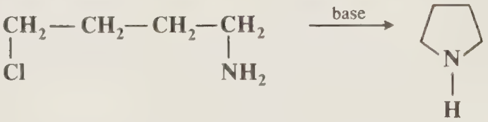
Primary amines can be prepared from alkyl halides by method **0-47** or, more commonly, by the Gabriel synthesis (**0-60**).

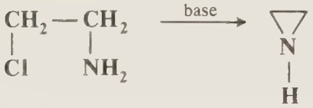
The immediate product in any particular step is the protonated amine, which, however, rapidly loses a proton to another molecule of ammonia or amine in an equilibrium process, e.g.,

$$\mathrm{RX} + \mathrm{R_2NH} \longrightarrow \mathrm{R_3\overset{\oplus}{N}H} + \mathrm{R_2NH} \rightleftharpoons \mathrm{R_3N} + \mathrm{R_2\overset{\oplus}{N}H_2}$$

When it is desired to convert a primary or secondary amine directly to the quaternary salt (*exhaustive alkylation*), then the rate can be increased by the addition of a nonnucleophilic strong base which serves to remove the proton from $RR'NH_2^+$ or $RR'R''NH^+$ and thus liberates the amine to attack another molecule of RX.[556]

The conjugate bases of ammonia and of primary and secondary amines (NH_2^-, RNH^-, R_2N^-) are sometimes used as nucleophiles. However, in most cases they offer no advantages over ammonia or the amines themselves, since the latter are basic enough. This is in contrast to the analogous methods **0-1, 0-14, 0-38,** and **0-39.** Primary arylamines are easily alkylated, but diaryl- and triarylamines are very poor nucleophiles. However, the reaction has been carried out with diarylamines.[557] Sulfates or sulfonates may be used instead of halides. The reaction may be carried out intramolecularly to give cyclic amines, with three-, five-, and six-membered (but not four-membered) rings being easily prepared. Thus, 4-chloro-1-aminobutane treated with base gives pyrrolidine, and 2-chloroethylamine gives aziridine[558] (analogous to reaction **0-15**):





As usual, tertiary substrates do not give the reaction at all but undergo preferential elimination. However, tertiary (but not primary or secondary) halides R_3CCl can be converted to primary amines R_3CNH_2 by treatment with NCl_3 and $AlCl_3$[559] in a reaction related to reaction **0-52.**

Phosphines behave similarly, and compounds of the type R_3P and $R_4P^+\ X^-$ can be so prepared.

OS **I,** 23, 48, 102, 300, 488; **II,** 85, 183, 290, 328, 374, 397, 419, 563; **III,** 50, 148, 254, 256, 495, 504, 523, 705, 753, 774, 813, 848; **IV,** 84, 98, 383, 433, 466, 582, 585, 980; **V,** 88, 124, 306, 361, 434, 499, 541, 555, 608, 736, 751, 758, 769, 825, 883, 985, 989, 1018, 1085, 1145; **51,** 53; **53,** 13; 111; **54,** 58, 60, 93; **55,** 3, 114. Also see OS **II,** 395; **IV,** 950.

0-47 Conversion of Alkyl Halides to Primary Amines with Hexamethylenetetramine

$$\mathrm{RX} + \mathrm{(CH_2)_6N_4} \longrightarrow \mathrm{N_3(CH_2)_6\overset{\oplus}{N}R\ X^-} \xrightarrow[\mathrm{EtOH}]{\mathrm{HCl}} \mathrm{RNH_2}$$

Primary amines can be prepared from alkyl halides by the use of hexamethylenetetramine followed by cleavage of the resulting salt with ethanolic HCl. The method, called the *Delépine reac-*

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[556] Sommer and Jackson, *J. Org. Chem.* **35**, 1558 (1970); Sommer, Lipp, and Jackson, *J. Org. Chem.* **36**, 824 (1971).

[557] Patai and Weiss, *J. Chem. Soc.* 1035 (1959).

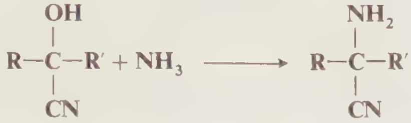
[558] For a review of aziridine formation by this method, see Ref. 345, pp. 1–59.

[559] Kovacic and Lowery, *J. Org. Chem.* **34**, 911 (1969); Strand and Kovacic, *J. Am. Chem. Soc.* **95**, 2977 (1973).

tion, is most successful for active halides such as allylic and benzylic halides and α-halo ketones, and for primary iodides.

OS V, 121.

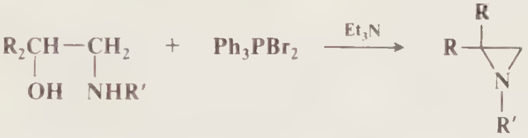
0-48 Replacement of a Hydroxy by an Amino Group



$$R{-}\underset{CN}{\overset{OH}{C}}{-}R' + NH_3 \longrightarrow R{-}\underset{CN}{\overset{NH_2}{C}}{-}R'$$

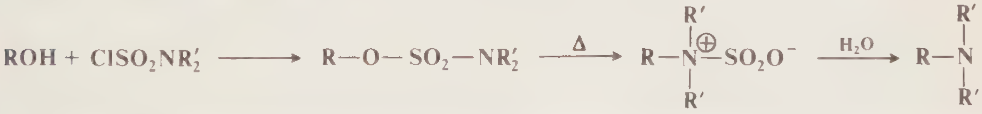
Cyanohydrins can be converted to amines by treatment with ammonia. The use of primary or secondary amines instead of ammonia leads to secondary and tertiary cyanoamines, respectively. It is more common to perform the conversion of an aldehyde or ketone directly to the cyanoamine without isolation of the cyanohydrin (see reaction **6-51**). α-Hydroxy ketones (acyloins and benzoins) behave similarly.[560] Allylic alcohols $RCH{=}CHCH_2OH$ (and their ethers and esters) can be converted to tertiary amines $RCH{=}CHCH_2NR'_2$ by treatment with a secondary amine in the presence of a palladium-triphenylphosphine complex catalyst.[561]

β-Amino alcohols give aziridines when treated with triphenylphosphine dibromide in the presence of triethylamine.[562]



The fact that inversion takes place at the OH carbon indicates that an S_N2 mechanism is involved, with $OPPh_3$ as the leaving group.

Alcohols can be converted to amines in an indirect manner.[563] The salt of the alcohol is treated with a sulfamoyl chloride to give a sulfonamate ester, which on heating rearranges to a zwitterion. Hydrolysis of this gives the amine:



$$ROH + ClSO_2NR'_2 \longrightarrow R{-}O{-}SO_2{-}NR'_2 \xrightarrow{\Delta} R{-}\underset{R'}{\overset{R'}{\overset{\oplus}{N}}}{-}SO_2O^- \xrightarrow{H_2O} R{-}\underset{R'}{\overset{R'}{N}}$$

The reaction has been carried out with R′ = methyl to give tertiary amines. The rearrangement step is an S_Ni process, as shown by retention of configuration at R. The success of the method increases with the stability of R^+ as a carbonium ion (compatible with the ion-pair nature of the S_Ni reaction, see p. 302). Therefore it is a particularly useful method for the preparation of tertiary alkylamines, which are difficult to prepare in other ways. On the other hand, primary (but not secondary or tertiary) alcohols can be converted to carbamates which can be hydrolyzed to amines by heating sodium or trialkylammonium salts of their N-carbalkoxy sulfamates, e.g.,[564]

$$R{-}O{-}SO_2{-}\overset{\ominus}{\bar{N}}{-}COOMe \quad \overset{\oplus}{N}HEt_3 \xrightarrow{95\,^\circ C} R{-}NHCOOMe \xrightarrow{\text{hydrol.}} RNH_2$$

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[560] For example, see Klemmensen, Schroll, and Lawesson, *Ark. Kemi* **28,** 405 (1968).

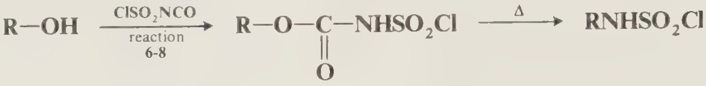
[561] Atkins, Walker, and Manyik, *Tetrahedron Lett.* 3821 (1970). For a similar reaction involving allylic or benzylic alcohols, see Murahashi, Shimamura, and Moritani, *J. Chem. Soc., Chem. Commun.* 931 (1975).

[562] Okada, Ichimura, and Sudo, *Bull. Chem. Soc. Jpn.* **43,** 1185 (1970).

[563] White and Ellinger, *J. Am. Chem. Soc.* **87,** 5261 (1965).

[564] Burgess, Penton, and Taylor, *J. Am. Chem. Soc.* **92,** 5224 (1970).

When the reaction is applied to the corresponding salts of secondary or tertiary alcohols, elimination is observed instead (p. 927). A similar method involves conversion of the alcohol to the N-chlorosulfonyl carbamate and heating of this compound:[565]



$$\text{R—OH} \xrightarrow[\substack{\text{reaction}\\ \textbf{6-8}}]{\text{ClSO}_2\text{NCO}} \text{R—O—}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{—NHSO}_2\text{Cl} \xrightarrow{\Delta} \text{RNHSO}_2\text{Cl}$$

However, this method is satisfactory only for tertiary R and others which give moderately stable carbonium ions. In another indirect method, primary alcohols are converted to alkyloxyphosphonium perchlorates which in dimethylformamide successfully *monoalkylate* not only secondary but also primary amines.[566]

$$\text{ROH} \xrightarrow[\text{2. NH}_4\text{ClO}_4]{\text{1. CCl}_4\text{-P(NMe}_2)_3} \text{RO}\overset{\oplus}{\text{P}}(\text{NMe}_2)_3 \quad \text{ClO}_4^- \xrightarrow[\text{R}'\text{R}''\text{NH}]{\text{DMF}} \text{RR}'\text{R}''\text{N} + \text{OP(NMe}_2)_3$$

Thus by this means secondary as well as tertiary amines can be prepared in good yields.

OS **II,** 29, 231; **IV,** 91, 283. Also see OS **I,** 473; **III,** 272, 471.

0-49 Transamination

$$\text{RNH}_2 + \text{R}'\text{NH}^- \longrightarrow \text{RR}'\text{NH} + \text{NH}_2^-$$

Where the nucleophile is the conjugate base of a primary amine, NH_2 can be a leaving group. The method has been used to prepare secondary amines.[567] Similar exchange, but with the attack by the amine itself, is observed with ethanolamine, where the substrate is a quaternary salt.[568]

$$\text{R}_4\text{N}^+ + \text{NH}_2\text{CH}_2\text{CH}_2\text{OH} \longrightarrow \text{R}_3\text{N} + \text{R}\overset{\oplus}{\text{N}}\text{H}_2\text{CH}_2\text{CH}_2\text{OH}$$

In this reaction, methyl groups are cleaved in preference to other saturated alkyl groups. A similar reaction takes place between a Mannich base (see reaction **6-17**) and a secondary amine, where the mechanism is elimination-addition[569] (see p. 315).

OS **V,** 1018.

0-50 Alkylation of Amines with Diazo Compounds

$$\text{CR}_2\text{N}_2 + \text{R}'_2\text{NH} \xrightarrow{\text{BF}_3} \text{CHR}_2\text{NR}'_2$$

The reaction of diazo compounds with amines is similar to reaction **0-17.**[570] The acidity of amines is not great enough for the reaction to proceed without a catalyst, but BF_3, which converts the amine to the $F_3B\text{-}NHR'_2$ complex, enables the reaction to take place. Cuprous cyanide can also be used as a catalyst.[571] The most common substrate is diazomethane, in which case this is a method for the methylation of amines. Ammonia has been used as the amine but, as in the case of reaction **0-46,** mixtures of primary, secondary, and tertiary amines are obtained. Primary aliphatic amines give mixtures of secondary and tertiary amines. Secondary amines give successful alkylation. Primary aromatic amines also give the reaction, but diaryl or arylalkylamines react very poorly.

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[565] Hendrickson and Joffee, *J. Am. Chem. Soc.* **95,** 4083 (1973).

[566] Castro and Selve, *Bull. Soc. Chim. Fr.* 4368 (1971). For a similar method, see Tanigawa, Murahashi, and Moritani, *Tetrahedron Lett.* 471 (1975).

[567] Baltzly and Blackman, *J. Org. Chem.* **28,** 1158 (1963).

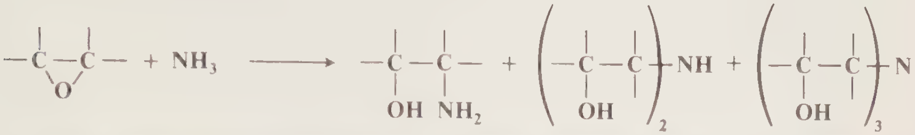
[568] Hünig and Baron, *Chem. Ber.* **90,** 395, 403 (1957).

[569] See, for example, Casy and Myers, *J. Chem. Soc.* 4639 (1964).

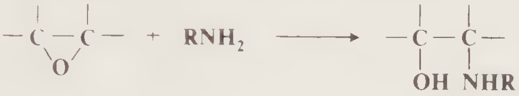
[570] Müller, Huber-Emden, and Rundel, *Justus Liebigs Ann. Chem.* **623,** 34 (1959).

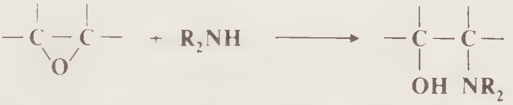
[571] Saegusa, Ito, Kobayashi, Hirota, and Shimizu, *Tetrahedron Lett.* 6131 (1966).

0-51 Amination of Epoxides



The reaction between epoxides and ammonia is a general and useful method for the preparation of β-hydroxyamines.[572] Ammonia gives largely the primary amine, but also some secondary and tertiary amines. The useful solvents, the ethanolamines, are prepared by this reaction. Primary and secondary amines give, respectively, secondary and tertiary amines:





Episulfides, which can be generated in situ in various ways, react similarly to give β-amino mercaptans,[573] and aziridines give 1,2-diamines.[574]

Triphenylphosphine similarly reacts with epoxides to give an intermediate which then undergoes elimination to give olefins (see the Wittig reaction, **6-47**).

0-52 Amination of Alkanes

$$R_3CH + NCl_3 \xrightarrow[0\text{–}10\,C]{AlCl_3} R_3CNH_2$$

Alkanes, arylalkanes, and cycloalkanes can be aminated, at tertiary positions only, by treatment with trichloroamine and aluminum chloride at 0 to 10 C.[575] For example, *p*-cymene (*p*-$MeC_6H_4CHMe_2$) gives *p*-$MeC_6H_4CMe_2NH_2$, methylcyclopentane gives 1-amino-1-methylcyclopentane, and adamantane gives 1-aminoadamantane, all in good yields. This is a useful reaction, since there are not many other methods for the preparation of *t*-alkylamines. The mechanism has been rationalized as an SN1 process with H^- as the leaving group:[575]

$$NCl_3 + AlCl_3 \longrightarrow (Cl_2N{-}AlCl_3)^- Cl^+$$

$$R_3CH \xrightarrow{Cl^+} R_3C^+ \xrightarrow{NCl_2^-} R_3CNCl_2 \xrightarrow[2H^+]{-2Cl^+} R_3CNH_2$$

OS V, 35.

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[572] For an example, see McManus, Larson, and Hearn, *Synth. Commun.* **3**, 177 (1973).

[573] Reynolds, Massad, Fields, and Johnson, *J. Org. Chem.* **26**, 5109 (1961); Reynolds, Fields, and Johnson, *J. Org. Chem.* **26**, 5111, 5116, 5119, 5125 (1961); Wineman, Gollis, James, and Pomponi, *J. Org. Chem.* **27**, 4222 (1962).

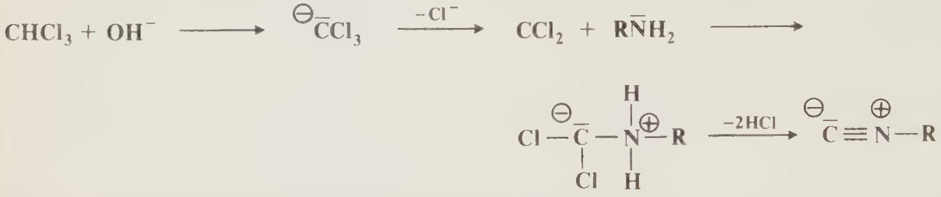
[574] For a review, see Ref. 345, pp. 262–268.

[575] Kovacic and Chaudhary, *Tetrahedron* **23**, 3563 (1967); Kovacic and Hopper, *Tetrahedron* **23**, 3965, 3977 (1967); Kovacic, Gormish, Hopper, and Knapczyk, *J. Org. Chem.* **33**, 4515 (1968); Kovacic and Roskos, *J. Am. Chem. Soc.* **91**, 6457 (1969); Field, Kovacic, and Herskovitz, *J. Org. Chem.* **35**, 2146 (1970); Strand and Kovacic, Ref. 559.

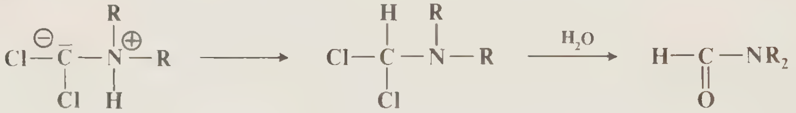
0-53 Formation of Isonitriles

$$\mathrm{CHCl_3 + RNH_2 \xrightarrow{OH^-} R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}}}$$

Reaction with chloroform under basic conditions is a common test for primary amines, both aliphatic and aromatic, since isonitriles have bad odors which are very strong. The reaction probably proceeds by an SN1cB mechanism with dichlorocarbene as an intermediate:



The reaction can also be used synthetically for the preparation of isonitriles, though yields are generally not high. An improved procedure has been reported.[576] When secondary amines are involved, the adduct cannot lose two moles of HCl. Instead it is hydrolyzed to an N,N-disubstituted formamide:[577]



OS **55**, 96.

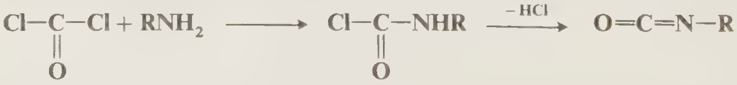
B. Attack by NH_2, NHR, or NR_2 at an Acyl Carbon[578]

0-54 Acylation of Amines by Acyl Halides

$$\mathrm{RCOX + NH_3 \longrightarrow RCONH_2 + HX}$$

The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.[579] The reaction is highly exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give N-substituted amides, and secondary amines give N,N-disubstituted amides. Arylamines may be similarly acylated. In some cases aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten-Baumann procedure* as it was in reaction **0-22.**

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides $RCONHNH_2$[580] and hydroxamic acids RCONHOH, and these compounds are often made in this way. When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides ClCONHR which lose HCl to give isocyanates RNCO. This is one of the most



$$\mathrm{Cl-\underset{\underset{O}{\|}}{C}-Cl + RNH_2 \longrightarrow Cl-\underset{\underset{O}{\|}}{C}-NHR \xrightarrow{-HCl} O{=}C{=}N-R}$$

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[576] Weber and Gokel, *Tetrahedron Lett.* 1637 (1972); Weber, Gokel, and Ugi, *Angew. Chem. Int. Ed. Engl.* **11,** 530 (1972) [*Angew. Chem.* **84,** 587].

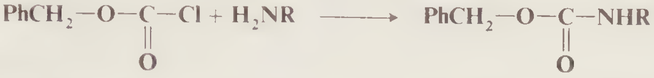
[577] Saunders and Murray, *Tetrahedron* **6,** 88 (1959); Frankel, Feuer, and Bank, *Tetrahedron Lett.* no. 7, 5 (1959).

[578] For a review, see Challis and Butler, in Patai, Ref. 298, pp. 279–290.

[579] For reviews, see Beckwith, in Zabicky, Ref. 407, pp. 73–185; Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 258–294.

[580] For a review of hydrazides, see Paulsen and Stoye, in Zabicky, Ref. 407, pp. 515–600.

common methods for the preparation of isocyanates.[581] Thiophosgene, similarly treated, gives isothiocyanates. When chloroformates ROCOCl are treated with primary amines, carbamates ROCONHR′ are obtained. An example of this reaction is the use of carbobenzoxy chloride to protect the amino group of amino acids and peptides:



$$PhCH_2-O-\underset{\underset{O}{\|}}{C}-Cl + H_2NR \longrightarrow PhCH_2-O-\underset{\underset{O}{\|}}{C}-NHR$$

Amino groups in general are often protected by conversion to amides. The treatment of acyl halides with lithium nitride gives N,N-diacyl amides (triacylamines):[582]

$$3RCOCl + Li_3N \longrightarrow (RCO)_3N$$

The nitrogen of dimethylformamide may also attack acyl halides in what amounts to an exchange reaction:[583]

$$ROCl + HCONMe_2 \longrightarrow RCONMe_2 + [HCOCl] \longrightarrow HCl + CO$$

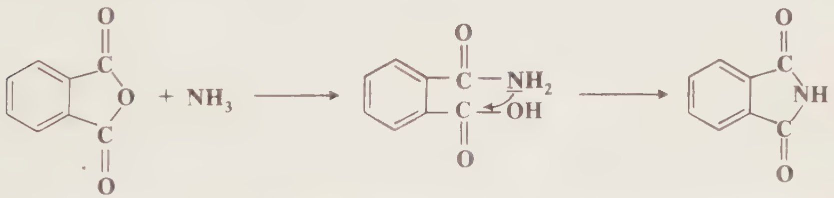
The reactions proceed by the tetrahedral mechanism.[584]

OS **I**, 99, 165; **II**, 76, 208, 278, 328, 453; **III**, 167, 375, 415, 488, 490, 613; **IV**, 339, 411, 521, 620, 780; **V**, 201, 336; **54**, 88.

0-55 Acylation of Amines by Anhydrides

$$R-\underset{\underset{O}{\|}}{C}-O-\underset{\underset{O}{\|}}{C}-R' + NH_3 \longrightarrow R-\underset{\underset{O}{\|}}{C}-NH_2 + R'COOH$$

This reaction, similar in scope and mechanism to reaction **0-54**, can be carried out with ammonia or primary or secondary amines.[585] However, ammonia and primary amines may also give imides, in which two acyl groups are attached to the nitrogen. This is especially easy with cyclic anhydrides which produce cyclic imides.[586]



The second step in this case, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic acid.

Even though formic anhydride is not a stable compound (see p. 493), amines can be formylated with the mixed anhydride of acetic and formic acids HCOOCOMe or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. When α-amino acids are treated with trifluoroacetic anhydride, the initial amide rapidly cyclizes and hydrolysis of the product gives an α-keto acid. This is a method of converting α-amino acids to α-keto acids.[587]

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[581] For recent examples, see Ozaki, *Chem. Rev.* **72**, 457–496 (1972), pp. 457–460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, *Chem. Soc. Rev.* **3**, 209–230 (1974).

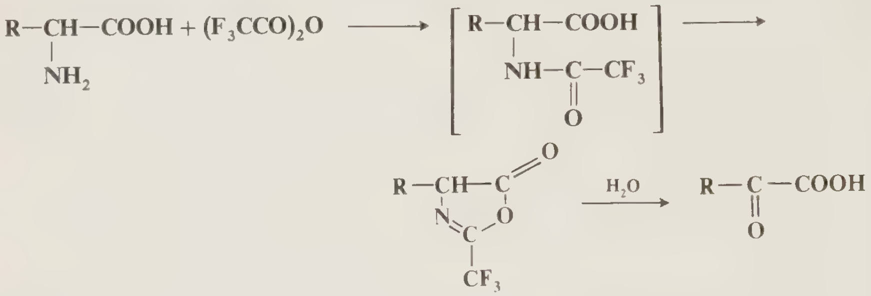
[582] Baldwin, Blanchard, and Koenig, *J. Org. Chem.* **30**, 671 (1965).

[583] Coppinger, *J. Am. Chem. Soc.* **76**, 1372 (1954).

[584] Kivinen, Ref. 379; Ref. 520, p. 185; Bender and Jones, *J. Org. Chem.* **27**, 3771 (1962).

[585] For a review, see Beckwith, in Zabicky, Ref. 407, pp. 86–96. For a review of peptide synthesis by means of treatment of an amino acid with a mixed anhydride of another amino acid, see Albertson, *Org. React.* **12**, 157–355 (1962).

[586] For reviews of imides, see Wheeler and Rosado, in Zabicky, Ref. 407, pp. 335–381; Hargreaves, Pritchard, and Dave, *Chem. Rev.* **70**, 439–469 (1970) (cyclic imides).

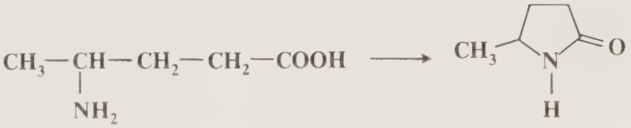


OS **I**, 457; **II**, 11; **III**, 151, 456, 661, 813; **IV**, 5, 42, 106, 657; **V**, 27, 373, 650, 944, 973.

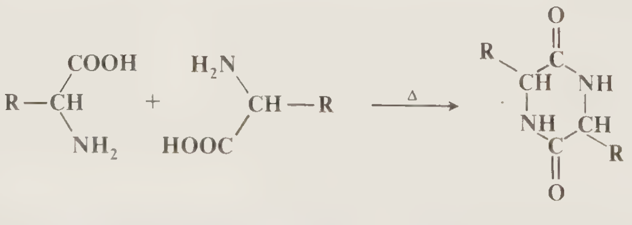
0-56 Acylation of Amines by Acids

$$\mathrm{RCOOH} + \mathrm{NH_3} \longrightarrow \mathrm{RCOO^- \ NH_4^+} \xrightarrow{\text{pyrolysis}} \mathrm{RCONH_2}$$

When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia or primary or secondary amines may be pyrolyzed to give amides,[588] but the method is less convenient than reactions **0-54**, **0-55**, and **0-57**[589] and is seldom of preparative value. Lactams are produced fairly easily from γ- or δ-amino acids, for example,



On heating, α-amino acids give diketopiperazines, an example of double amide formation:



Although treatment of acids with amines does not directly give amides, the reaction can be made to proceed in good yield at room temperature or slightly above by the use of coupling agents,[590] the most important of which is dicyclohexylcarbodiimide. This is very convenient and is used a great deal in peptide synthesis.[591] The mechanism is probably the same as in reaction

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[587] Weygand, Steglich, and Tanner, *Justus Liebigs Ann. Chem.* **658**, 128 (1962).

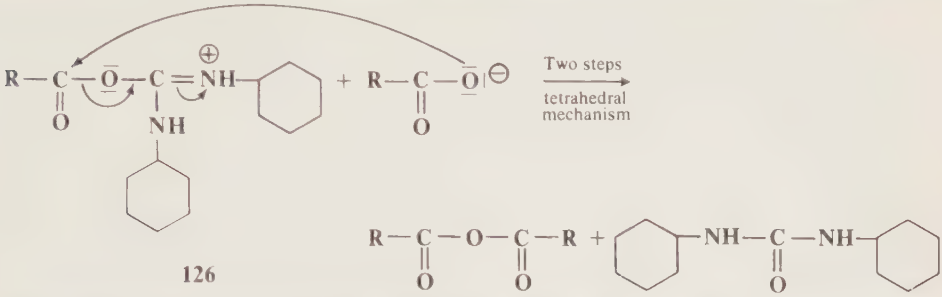
[588] For example, see Mitchell and Reid, *J. Am. Chem. Soc.* **53**, 1879 (1931).

[589] For a review of amide formation from carboxylic acids, see Beckwith, in Zabicky, Ref. 407, pp. 105–109.

[590] For reviews of peptide synthesis by means of dicyclohexylcarbodiimide and other coupling agents, see Albertson, Ref. 585, pp. 205–218; Klausner and Bodansky, *Synthesis* 453–463 (1972).

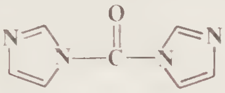
[591] It was first used in this way by Sheehan and Hess, *J. Am. Chem. Soc.* **77**, 1067 (1955).

0-24 up to the formation of **126.** This intermediate is then attacked by another molecule of $RCOO^-$ to give the anhydride $(RCO)_2O$, which is the actual species which reacts with the amine:

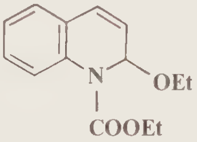


126

The anhydride has been isolated from the reaction mixture and then used to acylate an amine.[592] Other promoting agents are N,N′-carbonyldiimidazole (**127**),[406] which behaves as in reaction **0-24** and has been used for peptide synthesis,[593] N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline



127



EEDQ

(EEDQ),[594] BF_3-etherate,[594a] $POCl_3$,[595] $TiCl_4$,[596] pyridinium salts–Bu_3N,[596a] and a mixture of Ph_3P and $BrCCl_3$.[597] Certain dicarboxylic acids form amides simply on treatment with primary aromatic amines. In these cases the cyclic anhydride is an intermediate and is the species actually attacked by the amine.[598] Acids can also be converted to amides by heating with amides of carboxylic acids (exchange),[599] sulfonic acids, or phosphoric acids, for example,[600]

$$\mathrm{RCOOH + Ph_2PONH_2 \longrightarrow RCONH_2 + Ph_2POOH}$$

or by treatment with trisalkylaminoboranes $[B(NHR')_3]$ or trisdialkylaminoboranes $[B(NR'_2)_3]$.[601]

$$\mathrm{RCOOH + B(NR'_2)_3 \longrightarrow RCONR'_2}$$

OS **I,** 3, 82, 111, 172, 327; **II,** 65, 562; **III,** 95, 328, 475, 590, 646, 656, 768; **IV,** 6, 62, 513; **V,** 670, 1070. Also see OS **III,** 360.

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[592] Schüssler and Zahn, *Chem. Ber.* **95,** 1076 (1962); Rebek and Feitler, *J. Am. Chem. Soc.* **96,** 1606 (1974). There is evidence that some of the **126** is converted to products by another mechanism. See Rebek and Feitler, *J. Am. Chem. Soc.* **95,** 4052 (1973).

[593] Paul and Anderson, *J. Am. Chem. Soc.* **82,** 4596 (1960).

[594] Belleau and Malek, *J. Am. Chem. Soc.* **90,** 1651 (1968).

[594a] Tani, Oine, and Inoue, *Synthesis* 714 (1975).

[595] Klosa, *J. Prakt. Chem.* [4]**19,** 45 (1963).

[596] Wilson and Weingarten, *Can. J. Chem.* **48,** 983 (1970).

[596a] Bald, Saigo, and Mukaiyama, *Chem. Lett.* 1163 (1975). See also Mukaiyama, Aikawa, and Kobayashi, *Chem. Lett.* 57 (1976).

[597] Barstow and Hruby, *J. Org. Chem.* **36,** 1305 (1971).

[598] Higuchi, Miki, Shah, and Herd, *J. Am. Chem. Soc.* **85,** 3655 (1963).

[599] For example, see Schindlbauer, *Monatsh. Chem.* **99,** 1799 (1968).

[600] Zhmurova, Voitsekhovskaya, and Kirsanov, *J. Gen. Chem. USSR* **29,** 2052 (1959). See also Kopecký and Šmejkal, *Chem. Ind.* (*London*) 1529 (1966).

[601] Pelter, Levitt, and Nelson, *Tetrahedron* **26,** 1539 (1970); Pelter and Levitt, *Tetrahedron* **26,** 1545, 1899 (1970).

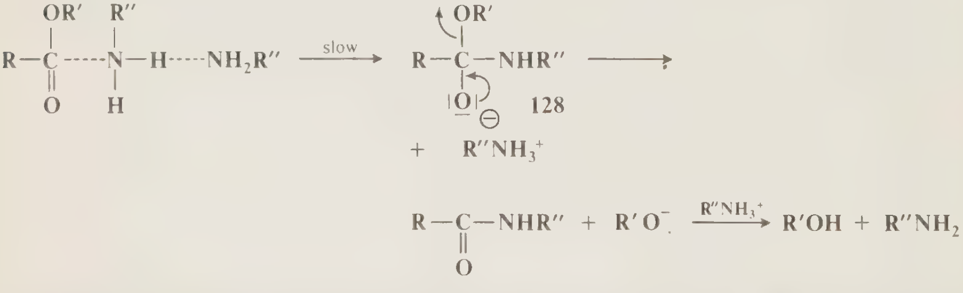
0-57 Acylation of Amines by Esters

$$\mathrm{RCOOR' + NH_3 \longrightarrow RCONH_2 + R'OH}$$

The conversion of esters to amides is a useful reaction, and unsubstituted, N-substituted, and N,N-disubstituted amides can be prepared in this way from the appropriate amine.[602] Both R and R′ may be alkyl or aryl. An especially good leaving group is *p*-nitrophenyl. The reaction is particularly useful because many esters are readily available or easy to prepare even in cases where the corresponding acyl halide or anhydride is not. As in reaction **0-54** hydrazides and hydroxamic acids can be prepared from esters, with hydrazine and hydroxylamine, respectively. Both hydrazine and hydroxylamine react more rapidly than ammonia or primary amines (the alpha effect, p. 325). Phenylhydrazides, prepared with phenylhydrazine, are often used as derivatives for esters, and the formation of hydroxamic acids, which form colored complexes in the presence of ferric ions, is often used as a test for esters. Imidates $\mathrm{RC({=}NH)OR'}$ give amidines $\mathrm{RC({=}NH)NH_2}$[603] (see reaction **0-36**). Lactones, when treated with ammonia or primary amines, give lactams. Lactams are also produced from γ- and δ-amino esters in an internal example of this reaction. The basicity of some amines (for example, arylamines) is so low that the reaction goes with difficulty. However, when arylamines are converted to their conjugate bases $\mathrm{ArNH^-}$ by a strong base such as ethoxide ion, the reaction proceeds at a convenient rate.[604] Isopropenyl formate is a useful compound for the formylation of primary and secondary amines.[605]

$$\mathrm{R_2NH + HCOOCMe{=}CH_2 \longrightarrow R_2NCHO + CH_2{=}CMeOH \rightleftharpoons MeCOMe}$$

Although more studies have been devoted to the mechanism of this reaction than to acylation of amines by other reagents, the mechanistic details are not yet entirely clear.[606] In its broad outlines, the mechanism appears to be essentially BAC2.[607] Under the normal basic conditions the reaction is general base-catalyzed,[608] indicating that a proton is being transferred in the rate-determining step and that two molecules of amine are involved.[609]



Alternatively, another base, such as H_2O or OH^-, can substitute for the second molecule of amine. With some substrates and under some conditions, especially at low pH, the breakdown of

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[602] For a review, see Beckwith, Ref. 579, pp. 96–105.

[603] For a review, see Sandler and Karo, Ref. 180, pp. 217–222 (1972).

[604] De Feo and Strickler, *J. Org. Chem.* **28**, 2915 (1963). See also Yang, Cannon, and Rose, *Tetrahedron Lett.* 1791 (1970); Singh, *Tetrahedron Lett.* 321 (1971).

[605] van Melick and Wolters, *Synth. Commun.* **2**, 83 (1972).

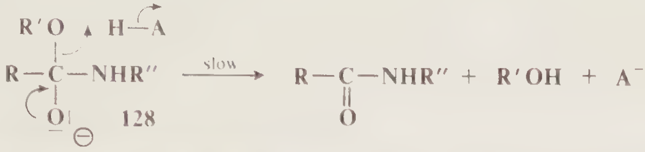
[606] For a discussion of the mechanism, see Satchell and Satchell, Ref. 188, pp. 410–431.

[607] Bunnett and Davis, *J. Am. Chem. Soc.* **82**, 665 (1960); Bruice, Donzel, Huffman, and Butler, *J. Am. Chem. Soc.* **89**, 2106 (1967).

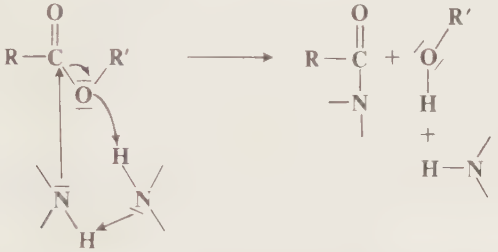
[608] Bunnett and Davis, Ref. 607; Jencks and Carriuolo, *J. Am. Chem. Soc.* **82**, 675 (1960); Bruice and Mayahi, *J. Am. Chem. Soc.* **82**, 3067 (1960).

[609] Blackburn and Jencks, *J. Am. Chem. Soc.* **90**, 2638 (1968); Bruice and Felton, *J. Am. Chem. Soc.* **91**, 2799 (1969); Felton and Bruice, *J. Am. Chem. Soc.* **91**, 6721 (1969).

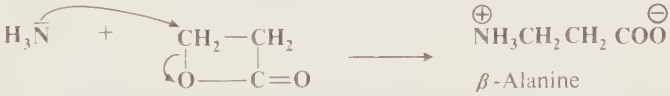
128 may become rate-determining.[610] The reaction also takes place under acidic conditions, and here the reaction is general acid-catalyzed, so that breakdown of **128** is rate-determining and proceeds as follows:[611]



HA may be $R''NH_3^+$ or another acid. **128** may or may not be further protonated on the nitrogen. Even under basic conditions, a proton donor may be necessary to assist leaving-group removal. Evidence for this is that the rate is lower with NR_2^- in liquid ammonia than with NHR_2 in water, apparently owing to the lack of acids to protonate the leaving oxygen.[612] It has been suggested[613] that under some conditions, particularly in aprotic solvents, all the steps can occur simultaneously,[614] with a second molecule of ammonia or amine both pulling a proton from the first molecule and supplying a proton to the leaving group:



In this mechanism, the ammonia or amine acts as an acid and a basic catalyst at the same time. In the special case of β-lactones, where small-angle strain is an important factor, alkyl-oxygen cleavage is observed (BAL2 mechanism, as in the similar case of hydrolysis of β-lactones, reaction **0-11**), and the product is not an amide but a β-amino acid:



A similar result has been found for certain sterically hindered esters.[615] This reaction is similar to reaction **0-46**, with OCOR as the leaving group.

OS **I,** 153, 179; **II,** 67, 85; **III,** 10, 96, 108, 404, 440, 516, 536, 751, 765; **IV,** 80, 357, 441, 486, 532, 566, 819; **V,** 168, 301, 645; **51,** 121; **53,** 25. Also see OS **I,** 5; **V,** 582.

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[610] Hansen, *Acta Chem. Scand.* **17,** 1307 (1963); Satterthwait and Jencks, *J. Am. Chem. Soc.* **96,** 7018, 7031 (1974); Blackburn and Jencks, Ref. 609.

[611] Blackburn and Jencks, Ref. 609.

[612] Bunnett and Davis, Ref. 607.

[613] Bruice and Mahayi, Ref. 608; Satchell and Secemski, *J. Chem. Soc. B* 130 (1969), 1013 (1970).

[614] For evidence against this view, see Anderson, Su, and Watson, *J. Am. Chem. Soc.* **91,** 482 (1969); Su and Watson, *J. Am. Chem. Soc.* **96,** 1854 (1974); Menger and Smith, *J. Am. Chem. Soc.* **94,** 3824 (1972); Menger and Vitale, *J. Am. Chem. Soc.* **95,** 4931 (1973).

[615] Zaugg, Helgren, and Schaefer, *J. Org. Chem.* **28,** 2617 (1963). See also Weintraub and Terrell, *J. Org. Chem.* **30,** 2470 (1965); Harada and Kinoshita, *Bull. Chem. Soc. Jpn.* **40,** 2706 (1967).

0-58 Acylation of Amines by Amides

$$\mathrm{RCONH_2} + \mathrm{R'}\overset{\oplus}{\mathrm{N}}\mathrm{H_3} \longrightarrow \mathrm{RCONHR'} + \mathrm{NH_4^+}$$

This is an exchange reaction and is usually carried out with the salt of the amine. The leaving group is usually NH_2 rather than NHR or NR_2, and primary amines (in the form of their salts) are the most common reagents. BF_3 can be added to complex with the leaving ammonia. The reaction is often used to convert urea to substituted ureas: $NH_2CONH_2 + RNH_3^+ \rightarrow NH_2CONHR + NH_4^+$. Dimethylformamide can be converted to other formamides by prolonged heating with a primary or secondary amine.[616]

OS **I,** 302 (but see **V,** 589), 450, 453; **II,** 461; **III,** 151, 404; **IV,** 52, 361.

0-59 Acylation of Amines by Other Acid Derivatives

Acid derivatives which can be converted to amides include thiol acids RCOSH, thiol esters RCOSR, silicic esters $(RCOO)_4Si$, 1,1,1-trihalo ketones $RCOCX_3$, α-keto nitriles, acyl azides, and non-enolizable ketones (see the Haller-Bauer reaction **2-32**).

OS **III,** 394; **IV,** 6, 569; **V,** 160, 166.

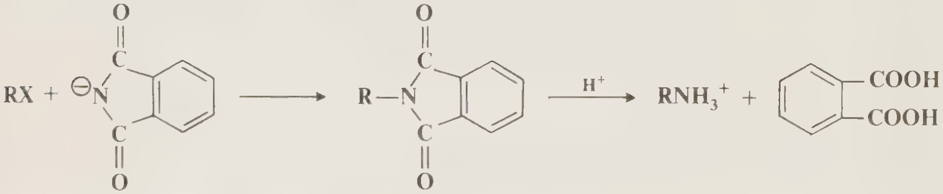
C. Attack by NHCOR

0-60 N-Alkylation of Amides and Imides

$$\mathrm{RX} + {}^{\ominus}\mathrm{NHCOR'} \longrightarrow \mathrm{RNHCOR'}$$

Amides are very weak bases, far too weak to attack alkyl halides, so that they must first be converted to their salts. By this method, unsubstituted amides can be converted to N-substituted, or N-substituted to N,N-disubstituted, amides. Esters of sulfuric or sulfonic acids can also be substrates. Tertiary substrates give elimination. O-alkylation is at times a side reaction.[617]

The *Gabriel synthesis*,[618] for converting halides to primary amines, is based on this reaction. The halide is treated with potassium phthalimide and the product hydrolyzed (reaction **0-12**):



It is obvious that the primary amines formed in this reaction will be uncontaminated by secondary or tertiary amines (unlike reaction **0-46**). The reaction is usually rather slow but can be conveniently speeded by the use of a dipolar aprotic solvent such as dimethylformamide.[619] Hydrolysis of the phthalimide, whether acid- or base-catalyzed (acid catalysis is used far more frequently), is also usually very slow, and a better way is to heat the phthalimide with hydrazine in an exchange reaction (the *Ing-Manske procedure*).[620] The Ing-Manske procedure has largely, though not entirely, superseded hydrolytic methods.

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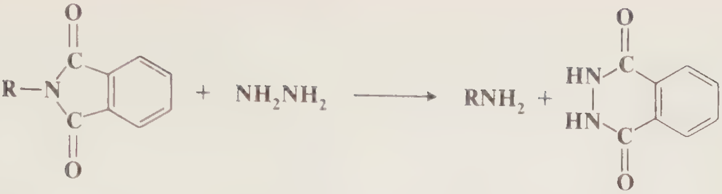
[616] Kraus, *Synthesis* 361 (1973). See also Otsuji, Matsumura, and Imoto, *Bull. Chem. Soc. Jpn.* **41,** 1485 (1968).

[617] For a review of alkylation of amides, see Challis and Challis, Ref. 407, pp. 734–754.

[618] For a review, see Gibson and Bradshaw, *Angew. Chem. Int. Ed. Engl.* **7,** 919–930 (1968) [*Angew. Chem.* **80,** 986–996].

[619] For example, see Sheehan and Bolhofer, *J. Am. Chem. Soc.* **72,** 2786 (1950).

[620] Ing and Manske, *J. Chem. Soc.* 2348 (1926).

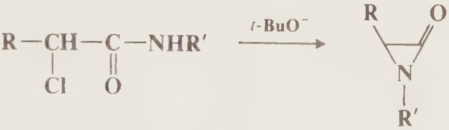


Vinyl bromides react with potassium phthalimide at 165 C in N,N-dimethylacetamide in the presence of CuI.[621] N-Alkylphthalimides can also be prepared starting from alcohols by treatment of the latter with equimolar amounts of phthalimide, triphenylphosphine, and diethyl azodicarboxylate (EtOOCN=NCOOEt) at room temperature.[622]

An alternative to the Gabriel synthesis, in which alkyl halides can be converted to primary amines in good yields, involves treatment of the halide with the strong base guanidine followed by alkaline hydrolysis.[623] In another alternative, alkyl bromides or tosylates are treated with $(PhS)_2NLi$ to give bisbenzenesulfenimides $(PhS)_2NR$ which can be hydrolyzed to RNH_2 by 3 *N* HCl or thiophenol.[624]

Amides can also be alkylated with diazo compounds, as in reaction **0-50**. Salts of sulfonamides ($ArSO_2NH^-$) may be used to attack alkyl halides to prepare N-alkyl sulfonamides ($ArSO_2NHR$) which may be further alkylated to $ArSO_2NRR'$. Hydrolysis of the latter is a good method for the preparation of secondary amines.

Internal N-alkylation has been used to prepare the highly strained compounds α-lactams.[625]



OS **I,** 119, 203, 271; **II,** 25, 83, 208; **III,** 151; **IV,** 810; **V,** 1064.

0-61 N-Acylation of Amides and Imides

$$\mathbf{RCOCl + H_2NCOR' \longrightarrow RCONHCOR'}$$

Imides may be prepared by the attack of amides or their salts on acyl halides, anhydrides, esters, or acids.[626] The best synthetic method for the preparation of acyclic imides is the reaction between an amide and an anhydride at 100 C, catalyzed by H_2SO_4.[627] When acyl chlorides are treated with amides in a 2:1 molar ratio at low temperatures in the presence of pyridine, the products are N,N-diacylamides $(RCO)_3N$.[628]

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[621] Bacon and Karim, *J. Chem. Soc., Perkin Trans. 1* 278 (1973).

[622] Mitsunobu, Wada, and Sano, *J. Am. Chem. Soc.* **94,** 679 (1972).

[623] Hebrard and Olomucki, *Bull. Soc. Chim. Fr.* 1938 (1970).

[624] Mukaiyama and Taguchi, *Tetrahedron Lett.* 3411 (1970); Mukaiyama, Taguchi, and Nishi, *Bull. Chem. Soc. Jpn.* **44,** 2797 (1971). For other alternatives, see Hendrickson, Bergeron, and Sternbach, *Tetrahedron* **31,** 2517 (1975); Hendrickson, Bergeron, Giga, and Sternbach, Ref. 292.

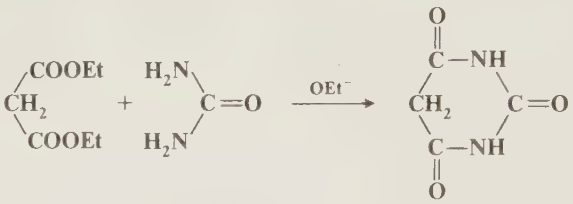
[625] Baumgarten, Fuerholzer, Clark, and Thompson, *J. Am. Chem. Soc.* **85,** 3303 (1963). For a review of α-lactams, see Lengyel and Sheehan, *Angew. Chem. Int. Ed. Engl.* **7,** 25–36 (1968) [*Angew. Chem.* **80,** 27–37].

[626] For a review, see Challis and Challis, Ref. 407, pp. 759–773.

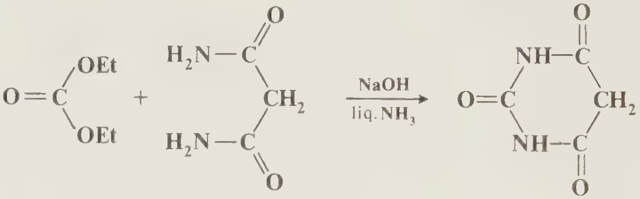
[627] Baburao, Costello, Petterson, and Sander, *J. Chem. Soc. C* 2779 (1968); Davidson and Skovronek, *J. Am. Chem. Soc.* **80,** 376 (1958).

[628] For example, see LaLonde and Davis, *J. Org. Chem.* **35,** 771 (1970).

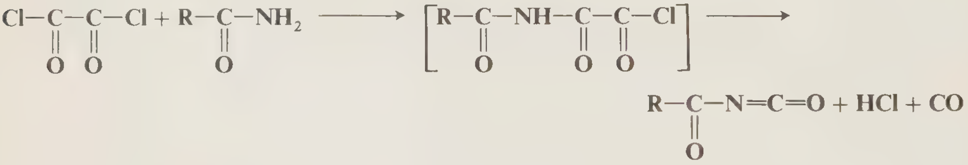
The reaction is often used to prepare urea derivatives, an important example being the preparation of barbituric acid:



It is also possible to prepare this compound in the reverse manner:[629]



When the substrate is oxalyl chloride (ClCOCOCl) and the reagent an unsubstituted amide, an acyl isocyanate is formed. The "normal" product (RCONHCOCOCl) does not form, or if it does, it rapidly loses CO and HCl:[630]



$$\mathrm{Cl{-}\underset{\overset{\|}{O}}{C}{-}\underset{\overset{\|}{O}}{C}{-}Cl + R{-}\underset{\overset{\|}{O}}{C}{-}NH_2 \longrightarrow \left[R{-}\underset{\overset{\|}{O}}{C}{-}NH{-}\underset{\overset{\|}{O}}{C}{-}\underset{\overset{\|}{O}}{C}{-}Cl\right] \longrightarrow R{-}\underset{\overset{\|}{O}}{C}{-}N{=}C{=}O + HCl + CO}$$

OS **II,** 60, 79, 422; **III,** 763; **IV,** 245, 247, 496, 566, 638, 662, 744; **V,** 204, 944.

D. Other Nitrogen Nucleophiles

0-62 Formation of Nitro Compounds[631]

$$RX + NO_2^- \longrightarrow RNO_2$$

Sodium nitrite can be used to form nitro compounds with primary or secondary alkyl bromides or iodides. Silver nitrite gives nitro compounds only when RX is a primary bromide or iodide. Nitrite esters are an important side product in all these cases (reaction **0-33**) and become the major product (by an SN1 mechanism) when secondary or tertiary halides are treated with silver nitrite.

gem-Dinitro compounds can be prepared, in a way which is not a nucleophilic substitution, from silver nitrite and salts of nitro compounds:[632]

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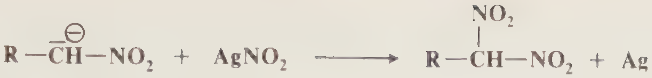
[629] Shimo and Wakamatsu, *J. Org. Chem.* **24,** 19 (1959).

[630] Speziale and Smith, *J. Org. Chem.* **27,** 3742 (1962); Speziale, Smith, and Fedder, *J. Org. Chem.* **30,** 4306 (1965). See also Goerdeler and Schenk, *Angew. Chem. Int. Ed. Engl.* **2,** 552 (1963) [*Angew. Chem.* **75,** 675]; *Chem. Ber.* **98,** 2954 (1965).

[631] For reviews, see Larson, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 1, pp. 325–339, Interscience Publishers, New York, 1969; Kornblum, *Org. React.* **12,** 101–156 (1962).

[632] Kaplan and Shechter, *J. Am. Chem. Soc.* **83,** 3535 (1961).



$$R-\overset{\ominus}{C}H-NO_2 + AgNO_2 \longrightarrow R-\overset{NO_2}{C}H-NO_2 + Ag$$

This is an oxidation-reduction reaction.

OS **I,** 410; **IV,** 368, 454, 724.

0-63 Formation of Azides

$$RX + N_3^- \longrightarrow RN_3$$

$$RCOX + N_3^- \longrightarrow RCON_3$$

Alkyl azides can be prepared by treatment of the appropriate halide with azide ion,[633] often in the form of sodium azide, though tetramethylguanidinium azide gives good yields.[634] Other leaving groups have also been used, for example, ONO_2.[635] Tertiary alkyl azides can be prepared by stirring tertiary alkyl chlorides with NaN_3 and $ZnCl_2$ in CS_2 for a period of 10 to 100 hr.[635a] Acyl azides, which can be used in the Curtius reaction (**8-18**), can be similarly prepared from acyl halides or anhydrides.[636]

OS **III,** 846; **IV,** 715; **V,** 273, 586; **50,** 9; **51,** 48; **55,** 32.

0-64 Formation of Isocyanates and Isothiocyanates

$$RX + NCO^- \longrightarrow RNCO$$

$$RX + NCS^- \longrightarrow RNCS$$

When the reagent is the thiocyanate ion, S-alkylation is an important side reaction (**0-45**), but the cyanate ion practically always gives exclusive N-alkylation.[331] When alkyl halides are treated with NCO^- in the presence of ethanol, carbamates can be prepared directly (see reaction **6-8**).[636a] Acyl halides give the corresponding acyl isocyanates and isothiocyanates.[637] For the formation of isocyanides, see reaction **0-103.**

OS **III,** 735.

Halogen Nucleophiles

A. Attack at an Alkyl Carbon

0-65 Halide Exchange. The Finkelstein Reaction

$$RX + X'^- \rightleftharpoons RX' + X^-$$

Halide exchange, sometimes called the *Finkelstein reaction*, is an equilibrium process, but it is often possible to shift the equilibrium. The reaction is most often applied to the preparation of iodides and fluorides. Iodides can be prepared from chlorides or bromides by taking advantage of the fact that sodium iodide, but not the bromide or chloride, is soluble in acetone. When an alkyl chloride or bromide is treated with a solution of sodium iodide in acetone, the equilibrium is shifted by the precipitation of sodium chloride or bromide. This is thus a method for the preparation of alkyl iodides. Since the mechanism is SN2, the reaction is much more successful for primary halides than for secondary or tertiary halides, and sodium iodide in acetone is often used as a test for primary bromides or chlorides. Tertiary chlorides can be converted to iodides by treatment with excess NaI in a nonpolar solvent containing a trace of $FeCl_3$.[638] This procedure is also successful for benzylic chlorides, but not for primary or secondary chlorides. Fluorides are prepared by treatment of other alkyl halides with any of a number of fluorinating agents, among them anhydrous HF (which is useful only for reactive substrates such as benzylic or allylic), AgF, HgF_2, and, for polyhalo compounds (such as chloroform), HF plus SbF_3.[639] A particularly effective reagent is KF in a polar aprotic solvent such as N-methylpyrrolidone or tetramethylene sulfone, or in acetonitrile or benzene in the presence of a crown ether.[640] The equilibria in these cases are shifted because the alkyl fluoride once formed has little tendency to react, owing to the extremely poor leaving-group ability of fluorine.

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[633] For reviews, see Biffin, Miller, and Paul, in Patai, "The Chemistry of the Azido Group," pp. 57–119, Interscience Publishers, New York, 1971; Boyer and Canter, *Chem. Rev.* **54,** 1–57 (1954).

[634] Papa, *J. Org. Chem.* **31,** 1426 (1966).

[635] Svetlakov, Mikheev, and Fedotov, *J. Org. Chem. USSR* **7,** 2304 (1971).

[635a] Miller, *Tetrahedron Lett.* 2959 (1975).

[636] For a review of acyl azides, see Lwowski, in Patai, Ref. 633, pp. 503–554.

[636a] Argabright, Rider, and Sieck, *J. Org. Chem.* **30,** 3317 (1965).

[637] For reviews of acyl isocyanates, see Nuridzhanyan, *Russ. Chem. Rev.* **39,** 130–139 (1970); Lozinskii and Pel'kis, *Russ. Chem. Rev.* **37,** 363–375 (1968).

Alkyl bromides can be converted to chlorides with silver difluorochloroacetate ($ClF_2CCOOAg$).[641] Alkyl chlorides or bromides may be prepared from iodides by treatment with HCl or HBr in the presence of HNO_3, making use of the fact that the leaving I^- is oxidized to I_2 by the HNO_3.[642]

Not only can one halogen be substituted for another, but the halogen exchange reaction can also be carried out with, say, radioactive chloride replacing chloride, for studying mechanisms (see p. 269). Alkyl halides also exchange with *halogens* (X_2 rather than X^-). This is a free-radical reaction.[643]

OS **II,** 476; **IV,** 84, 525.

0-66 Formation of Alkyl Halides from Esters of Sulfuric and Sulfonic Acids

$$\mathbf{ROSO_2R' + X^- \longrightarrow RX}$$

Alkyl sulfates, tosylates, and other esters of sulfuric and sulfonic acids can be converted to alkyl halides with any of the four halide ions. Neopentyl tosylate reacts with Cl^-, Br^-, or I^- without rearrangement in HMPT.[644] Similarly, allylic tosylates can be converted to chlorides without allylic rearrangement by reaction with LiCl in the same solvent.[645] Inorganic esters are intermediates in the conversion of alcohols to alkyl halides with $SOCl_2$, PCl_5, PCl_3, etc. (reaction **0-67**), but are seldom isolated.

OS **I,** 25; **II,** 111, 404; **IV,** 597, 753; **V,** 545.

0-67 Formation of Alkyl Halides from Alcohols

$$\mathbf{ROH + HX \longrightarrow RX}$$

$$\mathbf{ROH + SOCl_2 \longrightarrow RCl}$$

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[638] Miller and Nunn, *Tetrahedron Lett.* 2691 (1974).

[639] For reviews of the use of halogen exchange to prepare alkyl fluorides, see Sharts and Sheppard, *Org. React.* **21,** 125–406 (1974); Barbour, Belf, and Buxton, *Adv. Fluorine Chem.* **3,** 181–270 (1963); Hudlický, Ref. 351, pp. 87–112; Stephens and Tatlow, *Q. Rev., Chem. Soc.* **16,** 44–70 (1962); Henne, *Org. React.* **2,** 49–93 (1944). For a review of the introduction of fluorine into organic compounds, see Sheppard and Sharts, Ref. 351, pp. 52–184, 409–430.

[640] Liotta and Harris, Ref. 266. Crown ethers have also been used as phase-transfer catalysts (p. 358) in the conversion of RX to RI: Landini, Montanari, and Pirisi, *J. Chem. Soc., Chem. Commun.* 879 (1974).

[641] Vida, *Tetrahedron Lett.* 3447 (1970). For another method, see Bertin, Luche, Kagan, and Setton, *Tetrahedron Lett.* 763 (1974).

[642] Svetlakov, Moisak, and Averko-Antonovich, *J. Org. Chem. USSR* **5,** 971 (1969).

[643] Gazith and Noyes, *J. Am. Chem. Soc.* **77,** 6091 (1955); Gardner and Noyes, *J. Am. Chem. Soc.* **83,** 2409 (1961); Miller, Neiman, and Solovnikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 227 (1959).

[644] Stephenson, Solladié, and Mosher, Ref. 228.

[645] Stork, Grieco, and Gregson, *Tetrahedron Lett.* 1393 (1969).

Alcohols can be converted to alkyl halides with several reagents, the most common of which are halogen acids HX and inorganic acid halides such as $SOCl_2$, PCl_5, PCl_3, $POCl_3$, etc.[646] HBr is usually used for alkyl bromides and HI for alkyl iodides. These reagents are often generated in situ from the halide ion and an acid such as phosphoric or sulfuric. The use of HI sometimes results in reduction of the alkyl iodide to the alkane (reaction **0-77**) and, if the substrate is unsaturated, can also reduce the double bond.[647] The reaction can be used to prepare primary, secondary, or tertiary halides, but alcohols of the isobutyl or neopentyl type often give large amounts of rearrangement products. Tertiary chlorides are easily made with concentrated HCl, but primary and secondary alcohols react with HCl so slowly that a catalyst, usually zinc chloride, is required.[648] This behavior is the basis of the *Lucas test* for distinguishing among primary, secondary, and tertiary alcohols. The test consists of shaking the alcohol with a mixture of concentrated HCl and zinc chloride at room temperature. Tertiary alcohols react at once, secondary alcohols within 5 min, and primary alcohols do not react within this time. Primary alcohols give good yields of chlorides upon treatment with HCl in HMPT.[648a] The inorganic acid chlorides $SOCl_2$, PCl_3, etc., give primary, secondary, or tertiary alkyl chlorides with much less rearrangement than is observed with HCl, and these reagents are often preferred for the preparation of chlorides. Analogous bromides and iodides, especially PBr_3, have also been used, but they are more expensive and less often used than HBr or HI, though some of them, too, may be generated in situ (e.g., PBr_3 from red phosphorus and bromine). Secondary alcohols always give *some* rearranged bromides if another secondary position is available, even with PBr_3, PBr_5, or $SOBr_2$; thus 3-pentanol gives both 2- and 3-bromopentane. Such rearrangement can be avoided by converting the alcohol to a sulfonate and then using reaction **0-66**.[649] HF does not generally convert alcohols to alkyl fluorides.[650] Such conversions can be carried out with SF_4,[651] SeF_4,[652] with α-fluoroamines of the type $R'CF_2NR''_2$,[653] or, indirectly, by conversion to a sulfate or tosylate, etc. (reaction **0-66**). Dialkylaminosulfur trifluorides R_2NSF_3 and bis(dialkylamino)sulfur trifluorides $(R_2N)_2SF_2$ are reagents which convert alcohols to fluorides under mild conditions.[654] Primary fluorides can be made by heating 2-alkyl pseudouronium fluorides $[Ph_2C(OR)NH_2^+ \quad F^-]$ prepared from the alcohol and Ph_2NCN.[655] Secondary and tertiary alcohols can be converted to fluorides with an HF-pyridine mixture.[656] Primary, secondary, and tertiary alcohols can be converted to any of the four halides by treatment with the appropriate NaX, KX, or NH_4X in polyhydrogen fluoride–pyridine solution.[657] This method is even successful for neopentyl halides.

Other reagents have also been used, for example, $(RO)_3PRX$[658] and R_3PX_2[659] (made from R_3P and X_2), which give good yields of primary (including neopentyl), secondary, and tertiary halides without rearrangements, $Cl_2C{=}CClNEt_2$,[660] cyanuric chloride,[661] Me_2SBr_2[662] (prepared from Me_2S and Br_2), and a mixture of PPh_3 and CCl_4:[663]

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[646] For a review, see Brown, in Patai, Ref. 426, pt. 1, pp. 595–622.

[647] Jones and Pattison, *J. Chem. Soc. C* 1046 (1969).

[648] Phase-transfer catalysts (p. 358) have been used instead of $ZnCl_2$: Landini, Montanari, and Rolla, *Synthesis* 37 (1974).

[648a] Fuchs and Cole, *Can. J. Chem.* **53,** 3620 (1975).

[649] Cason and Correia, *J. Org. Chem.* **26,** 3645 (1961).

[650] For an exception, see Hanack, Eggensperger, and Hähnle, *Justus Liebigs Ann. Chem.* **652,** 96 (1962). See also Politanskii, Ivanyk, Sarancha, and Shevchuk, *J. Org. Chem. USSR* **10,** 697 (1974).

[651] For a review, see Boswell, Ripka, Scribner, and Tullock, *Org. React.* **21,** 1–124 (1974).

[652] Olah, Nojima, and Kerekes, *J. Am. Chem. Soc.* **96,** 925 (1974).

[653] Yarovenko and Raksha, *J. Gen. Chem. USSR* **29,** 2125 (1959); Kopecký, Šmejkal, and Hudlický, *Chem. Ind. (London)* 271 (1969). For a review, see Sharts and Sheppard, Ref. 639.

[654] Middleton, *J. Org. Chem.* **40,** 574 (1975).

[655] Amin, Newton, and Pattison, *Can. J. Chem.* **43,** 3173 (1965).

[656] Olah, Nojima, and Kerekes, *Synthesis* 786 (1973).

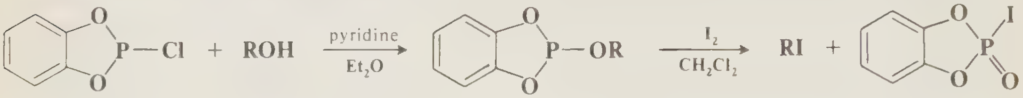
[657] Olah and Welch, *Synthesis* 653 (1974).

[658] Rydon, *Org. Synth.* **51,** 44 (1971).

[659] Wiley, Hershkowitz, Rein, and Chung, *J. Am. Chem. Soc.* **86,** 964 (1964); Wiley, Rein, and Hershkowitz, *Tetrahedron Lett.* 2509 (1964); Schaefer and Weinberg, *J. Org. Chem.* **30,** 2635 (1965); Kaplan, *J. Org. Chem.* **31,** 3454 (1966); Weiss and Snyder, *J. Org. Chem.* **36,** 403 (1971).

$$\mathbf{ROH + Ph_3P + CCl_4 \longrightarrow RCl + Ph_3PO + HCCl_3}$$

The latter method converts allylic alcohols to the corresponding halides without allylic rearrangements.[664] Another method which yields this result involves treatment of the allylic alcohol with a mixture of CH_3SO_2Cl, LiCl, and *s*-collidine (2,4,6-trimethylpyridine) in dimethylformamide at 0°C.[665] A simple indirect method for the conversion of alcohols to alkyl iodides consists of treating the alcohol with *o*-phenylene phosphorochlorodite (**129**, easily prepared from catechol and PCl_3), and then reaction of the resulting ester with I_2.[666] A simple method which is specific for benzylic and allylic alcohols (and does not give allylic rearrangement) involves reaction with N-chloro- or N-bromosuccinimide and methyl sulfide.[667] The specificity of this method is illustrated by the conversion, in 87% yield, of (*Z*)-$HOCH_2CH_2CMe{=}CHCH_2OH$ to (*Z*)-$HOCH_2CH_2CMe{=}CHCH_2Cl$. Only the allylic OH group was affected.



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When the reagent is HX, the mechanism is SN1cA or SN2cA; that is, the leaving group is not OH^-, but OH_2 (p. 325). The leaving group is not OH^- with the other reagents either, since in these cases the alcohol is first converted to an inorganic ester, for example, ROSOCl with $SOCl_2$ (reaction **0-33**). The leaving group is therefore $OSOCl^-$ or a similar group (reaction **0-66**). These may react by the SN1 or SN2 mechanism and, in the case of ROSOCl, by the SNi mechanism (p. 302).

OS **I,** 25, 36, 131, 142, 144, 292, 294, 533; **II,** 91, 136, 159, 246, 308, 322, 358, 399, 476; **III,** 11, 227, 370, 446, 698, 793, 841; **IV,** 106, 169, 323, 333, 576, 681; **V,** 1, 249, 608; **51,** 44; **53,** 13, 70; **54,** 63, 68. Also see OS **III,** 818; **IV,** 278, 383, 597.

0-68 Cleavage of Ethers

$$\mathbf{ROR' + HI \longrightarrow RI + R'OH}$$

Ethers can be cleaved by heating with concentrated HI or HBr.[668] HCl is seldom successful. HBr reacts more slowly than HI, but it is often a superior reagent, since it causes fewer side reactions. Dialkyl ethers and alkyl aryl ethers can be cleaved. In the latter case the alkyl-oxygen bond is the one broken. As in reaction **0-67** the actual leaving group is not OR'^-, but OHR'.

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[660] Speziale and Freeman, *J. Am. Chem. Soc.* **82,** 909 (1960).

[661] Sandler, *J. Org. Chem.* **35,** 3967 (1970).

[662] Furukawa, Inoue, Aida, and Oae, *J. Chem. Soc., Chem. Commun.* 212 (1973).

[663] Downie, Holmes, and Lee, *Chem. Ind. (London)* 900 (1966); Lee and Downie, *Tetrahedron* **23,** 359 (1967); Lee and Nolan, *Tetrahedron* **23,** 2789 (1967); Downie, Lee, and Matough, *Chem. Commun.* 1350 (1968); Brett, Downie, Lee, and Matough, *Chem. Ind. (London)* 1017 (1969); Weiss and Snyder, *Chem. Commun.* 1358 (1968); *J. Org. Chem.* **35,** 1627 (1970); Hooz and Gilani, *Can. J. Chem.* **46,** 86 (1968); Aneja, Davies, and Knaggs, *Tetrahedron Lett.* 67 (1974). For a review, see Appel, *Angew. Chem. Int. Ed. Engl.* **14,** 801–811 (1975) [*Angew. Chem.* **87,** 863–874]. See also Bose and Lal, *Tetrahedron Lett.* 3937 (1973); Hodge and Richardson, *J. Chem. Soc., Chem. Commun.* 622 (1975).

[664] Snyder, *J. Org. Chem.* **37,** 1466 (1972); Axelrod, Milne, and van Tamelen, *J. Am. Chem. Soc.* **92,** 2139 (1973).

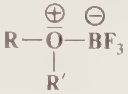
[665] Collington and Meyers, *J. Org. Chem.* **36,** 3044 (1971).

[666] Corey and Anderson, *J. Org. Chem.* **32,** 4160 (1967).

[667] Corey, Kim, and Takeda, *Tetrahedron Lett.* 4339 (1972).

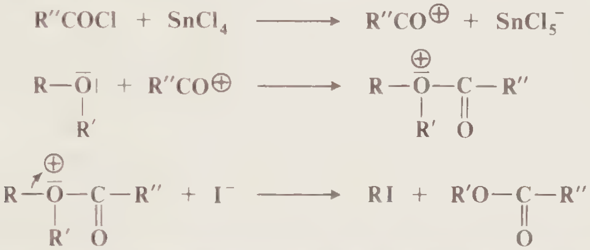
[668] For a review of this reaction, see Burwell, *Chem. Rev.* **54,** 615–685 (1954). For a review of ether cleavage in general, see Ref. 281.

The *Zeisel method* for determination of methoxy groups consists of running this reaction with HI and measuring the amount of methyl iodide formed. Although alkyl aryl ethers always cleave so as to give an alkyl halide and a phenol, there is no general rule for dialkyl ethers. Often cleavage occurs from both sides, and a mixture of two alcohols and two alkyl halides is obtained. However, methyl ethers are usually cleaved so that methyl iodide or bromide is a product. An excess of HI or HBr converts the alcohol product into alkyl halide, so that dialkyl ethers (but not alkyl aryl ethers) are converted to 2 moles of alkyl halide. This procedure is often carried out so that a mixture of only two products is obtained instead of four. Cyclic ethers (usually tetrahydrofuran derivatives) can be similarly cleaved (see reaction **0-69** for epoxides). Ethers have also been cleaved with Lewis acids such as BF_3, BCl_3, BBr_3,[669] or $AlCl_3$.[670] In such cases, the departure of the OR is assisted by complex formation with the Lewis acid:



$$\mathrm{R{-}\overset{\oplus}{\underset{|\atop R'}{\bar{O}}}{-}\overset{\ominus}{B}F_3}$$

Lewis acids are also used in conjunction with acyl halides. In such cases it is the acyl cation which assists in removal of the leaving group:



$$\mathrm{R''COCl + SnCl_4 \longrightarrow R''CO^{\oplus} + SnCl_5^-}$$

$$\mathrm{R{-}\underset{\displaystyle R'}{\bar{O}|} + R''CO^{\oplus} \longrightarrow R{-}\overset{\oplus}{\underset{\displaystyle R'}{\bar{O}}}{-}\underset{\displaystyle O}{\overset{}{C}}{-}R''}$$

$$\mathrm{R{-}\overset{\oplus}{\underset{\displaystyle R'}{\bar{O}}}{-}\underset{\displaystyle O}{C}{-}R'' + I^- \longrightarrow RI + R'O{-}\underset{\displaystyle O}{C}{-}R''}$$

Alkyl aryl ethers can also be cleaved with LiI to give alkyl iodides and salts of phenols[671] in a reaction similar to **0-70**. Triphenyldibromophosphorane (Ph_3PBr_2) cleaves dialkyl ethers to give 2 moles of alkyl bromide.[672]

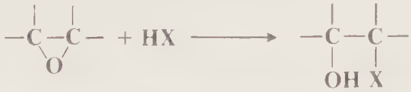
A closely related reaction is cleavage of oxonium salts:

$$\mathrm{R_3O^+ \;\; X^- \longrightarrow RX + R_2O}$$

For these substrates, HX is not required, and X may be any of the four halide ions.

OS **I,** 150; **II,** 571; **III,** 187, 432, 586, 692, 753, 774, 813; **IV,** 266, 321; **V,** 412.

0-69 Formation of Halohydrins from Epoxides



This is a special case of reaction **0-68** and is frequently used for the preparation of halohydrins. In contrast to the situation with open-chain ethers and with larger rings, many epoxides react with all four hydrohalic acids, though with HF[673] the reaction is unsuccessful with simple aliphatic and cycloalkyl epoxides.[674] HF does react with more rigid epoxides, such as those in steroid systems. Epoxides can be converted directly to 1,2-dichloro compounds by treatment with $SOCl_2$ and pyridine[675] or with Ph_3P and CCl_4.[676] These are two-step reactions in which a halohydrin is formed first and then converted by the reagents to the dihalide (reaction **0-67**). As expected, inversion is found at both carbons. HI reduces α-keto epoxides to olefins.

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[669] Manson and Musgrave, *J. Chem. Soc.* 1011 (1963); McOmie, Watts, and West, *Tetrahedron* **24,** 2289 (1968); Stehle, Brini, and Pousse, *Bull. Soc. Chim. Fr.* 1100 (1966), 2171 (1969); Egly, Pousse, and Brini, *Bull. Soc. Chim. Fr.* 1357 (1972).

[670] For a review, see Johnson, in Olah, "Friedel-Crafts and Related Reactions," vol. 4, pp. 1–109, Interscience Publishers, New York, 1965.

[671] Harrison, *Chem. Commun.* 616 (1969).

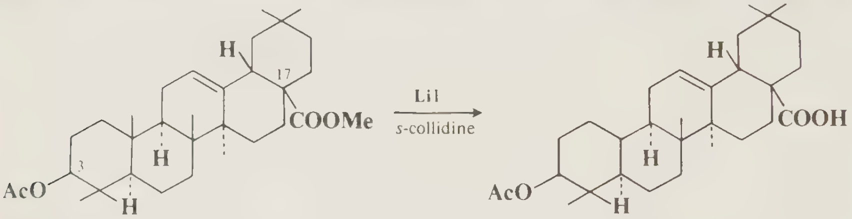
[672] Anderson and Freenor, *J. Org. Chem.* **37,** 626 (1972).

OS **I,** 117.

0-70 Cleavage of Esters with Lithium Iodide

$$\mathrm{R'COOR + LiI \xrightarrow[\Delta]{\text{pyridine}} RI + R'COOLi}$$

Carboxylic esters where R is methyl or ethyl can be cleaved by heating with lithium iodide in refluxing pyridine or a higher-boiling amine.[677] The reaction is useful where a molecule is sensitive to acid and base (so that **0-11** cannot be used), or where it is desired to cleave selectively only one ester group in a molecule containing two or more. For example, refluxing O-acetyloleanolic acid methyl ester with LiI in *s*-collidine cleaved only the 17-carbomethoxy group and not



the 3-acetyl group.[678] The reaction is an equilibrium, and the heat of reaction is such that relatively high temperatures are required to drive it to completion. However, the reaction temperature can be lowered if another nucleophile, e.g., OAc^- or CN^-, is added to react with the RI, thus preventing the reverse reaction from taking place.[679] Esters of salicylic acid (o-HOC_6H_4-COOR) are converted to alkyl chlorides RCl on treatment with PCl_5.[680]

0-71 Conversion of Diazo Ketones to α-Halo Ketones

$$\mathrm{RCOCHN_2 + HBr \longrightarrow RCOCH_2Br}$$

When diazo ketones are treated with HBr or HCl, they give the respective α-halo ketones. HI does not give the reaction, since it reduces the product to a methyl ketone (reaction **0-82**). α-Fluoro ketones can be prepared by addition of the diazo ketone to a 70% polyhydrogen fluoride–pyridine solution at 0°C.[681] This method is also successful for diazoalkanes. When a halide ion (Cl^-, Br^-, or I^-) or an N-halosuccinimide is added to this mixture, a mixed *gem*-dihalide is obtained, e.g.,

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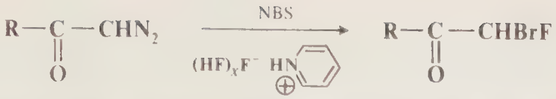
[673] For a review of reactions of HF with epoxides, see Sharts and Sheppard, Ref. 639.
[674] Shahak, Manor, and Bergmann, *J. Chem. Soc. C* 2129 (1968).
[675] Campbell, Jones, and Wolfe, *Can. J. Chem.* **44,** 2339 (1966).
[676] Isaacs and Kirkpatrick, *Tetrahedron Lett.* 3869 (1972).
[677] Taschner and Liberek, *Rocz. Chem.* **30,** 323 (1956) [*CA* **51,** 1039 (1957)].
[678] Elsinger, Schreiber, and Eschenmoser, *Helv. Chim. Acta* **43,** 113 (1960).
[679] Mc Murry and Wong, *Synth. Commun.* **2,** 389 (1972).
[680] Pinkus and Lin, *Synthesis* 279 (1974).
[681] Olah and Welch, *Synthesis* 896 (1974).



Diazotization of α-amino acids in the above solvent at room temperature gives α-fluoro acids.[682]

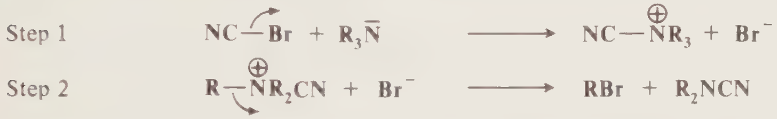
OS III, 119.

0-72 Conversion of Tertiary Amines to Cyanamides. The von Braun Reaction

$$R_3N + BrCN \longrightarrow R_2NCN + RBr$$

The *von Braun reaction*, which involves the cleavage of tertiary amines by cyanogen bromide to give an alkyl bromide and a disubstituted cyanamide, has been applied to many tertiary amines.[683] Usually, the R group which cleaves is the one which gives the most reactive halide (for example, benzyl or allyl). For simple alkyl groups, the smallest are the most readily cleaved. One or two of the groups on the amine may be aryl, but they do not cleave. Cyclic amines have been frequently cleaved by this reaction. Secondary amines also give the reaction, but the results are usually poor.[684]

The mechanism consists of two successive nucleophilic substitutions, with the tertiary amine as the first nucleophile and the liberated bromide ion as the second:



Step 1 $$NC{-}Br + R_3\bar{N} \longrightarrow NC{-}\overset{\oplus}{N}R_3 + Br^-$$

Step 2 $$R{-}\overset{\oplus}{N}R_2CN + Br^- \longrightarrow RBr + R_2NCN$$

The intermediate N-cyanoammonium bromide has been trapped, and its structure confirmed by chemical, analytical, and spectral data.[685]

OS III, 608.

0-73 Conversion of Amines to Halides

$$ArNR_2 + HBr \longrightarrow RBr + ArNHR$$
$$ArNHR + HBr \longrightarrow RBr + ArNH_2$$

Alkyl groups can be cleaved from secondary and tertiary aromatic amines by concentrated HBr in a reaction which is similar to reaction **0-68**.[686] Tertiary aliphatic amines are also cleaved by HI, but useful products are seldom obtained. Tertiary amines can be cleaved by reaction with phenyl chloroformate:[687] $R_3N + ClCOOPh \rightarrow RCl + R_2NCOOPh$. Primary aliphatic amines can be converted to alkyl halides indirectly by first sulfonating them with 2 moles of sulfonyl halide and then treating with I^- or Br^- in dimethylformamide,[292] e.g.,

$$RNH_2 + ArSO_2Cl \longrightarrow RNHSO_2Ar \xrightarrow[2.\ ArSO_2Cl]{1.\ NaH\ in\ DMF} RN(SO_2Ar)_2 \xrightarrow[DMF]{I^-} RI$$

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[682] Olah and Welch, *Synthesis* 652 (1974).

[683] For a review, see Hageman, *Org. React.* 7, 198–262 (1953).

[684] For a detailed discussion of the scope of the reaction and of the ease of cleavage of different groups, see Ref. 683, pp. 205–225.

[685] Fodor and Abidi, *Tetrahedron Lett.* 1369 (1971); Abidi, Fodor, Huber, Miura, and Nakanishi, *Tetrahedron Lett.* 355 (1972); Fodor, Abidi, and Carpenter, *J. Org. Chem.* **39**, 1507 (1974). See also Paukstelis and Kim, *J. Org. Chem.* **39**, 1494 (1974).

[686] Chambers and Pearson, *J. Org. Chem.* **28**, 3144 (1963).

[687] Hobson and McCluskey, *J. Chem. Soc. C* 2015 (1967). See also Gol'dfarb, Ispiryan, and Belen'kii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 839 (1969); Montzka, Matiskella, and Partyka, *Tetrahedron Lett.* 1325 (1974); Leclerc, Rouot, and Wermuth, *Tetrahedron Lett.* 3765 (1974).

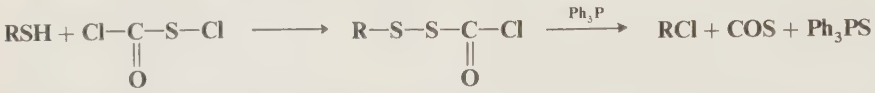
Alkyl halides may be formed when quaternary ammonium salts are heated: $\mathbf{R_4N^+ \quad X \rightarrow R_3N + RX}$.[688]

There are no OS references, but see OS **I,** 428, for a related reaction.

0-74 Replacement of Sulfur by Halogen

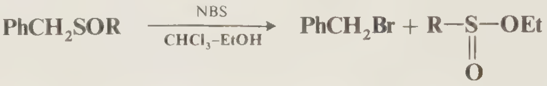
$$\mathrm{RSO_2X + Et_4N^+\,Br^- \xrightarrow{CH_2Cl_2} RBr + SO_2 + Et_4N^+\,X^-}$$

Phenylmethanesulfonyl bromide and chloride ($R = PhCH_2$), as well as methanesulfonyl bromide, can be cleaved by treatment at room temperature with tetraethylammonium bromide in CH_2Cl_2 or acetonitrile.[689] Mercaptans can be converted to chlorides by sequential treatment with chlorocarbonylsulfenyl chloride and Ph_3P.[690]



$$\mathrm{RSH + Cl{-}\underset{\underset{O}{\|}}{C}{-}S{-}Cl \longrightarrow R{-}S{-}S{-}\underset{\underset{O}{\|}}{C}{-}Cl \xrightarrow{Ph_3P} RCl + COS + Ph_3PS}$$

Benzyl and *t*-butyl alkyl or aryl sulfoxides react with N-chloro- or N-bromosuccinimide in $CHCl_3$–EtOH to give benzyl or *t*-butyl halides and sulfinic acid esters, e.g.,[691]



$$\mathrm{PhCH_2SOR \xrightarrow[CHCl_3\text{–}EtOH]{NBS} PhCH_2Br + R{-}\underset{\underset{O}{\|}}{S}{-}OEt}$$

Sulfides are in general resistant to cleavage by concentrated HI or HBr (which would be analogous to reaction **0-68**), but *β*-keto sulfides can be cleaved in this manner.[692]

B. Attack at an Acyl Carbon

0-75 Formation of Acyl Halides from Acids

$$\mathrm{RCOOH + SOCl_2 \longrightarrow RCOCl}$$

The same inorganic acid halides which convert alcohols to alkyl halides (reaction **0-67**) also convert acids to acyl halides.[693] The reaction is the best and the most common method for the preparation of acyl chlorides. Bromides and iodides are also made in this manner, but much less often. Thionyl chloride is the best reagent, since the by-products are gases and the acyl halide is thus easily isolated, but PX_3 and PX_5 ($X = Cl$ or Br) are also commonly used. However, hydrogen halides do not give the reaction. A particularly mild procedure, similar to one mentioned in reaction **0-67,** involves reaction of the acid with Ph_3P in CCl_4, whereupon acyl chlorides are produced without the obtention of any acidic compound as a by-product.[694] Acyl fluorides can be prepared by treatment of carboxylic acids with cyanuric fluoride.[695]

The reaction of acids with inorganic acid halides is unsuccessful for α-keto acids, since under the reaction conditions these compounds give decarbonylation, but if the keto group is protected by conversion to its enol ester, the reaction can be successfully carried out. Acid salts are also sometimes used as substrates. Acyl halides are also used as reagents in an exchange reaction:

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[688] For examples, see Leffek and Tsao, *Can. J. Chem.* **46,** 1215 (1968); Ko and Leffek, *Can. J. Chem.* **48,** 1865 (1970); 49, 129 (1971).

[689] King and Smith, *J. Am. Chem. Soc.* **89,** 4803 (1967).

[690] Clive and Denyer, *J. Chem. Soc., Chem. Commun.* 773 (1972).

[691] Jung and Durst, *J. Chem. Soc., Chem. Commun.* 4 (1973).

[692] For example, see Rappe and Gustafsson, *Acta Chem. Scand.* **22,** 2915 (1968).

[693] For a review, see Ansell, in Patai, Ref. 379, pp. 35–68.

[694] Lee, *J. Am. Chem. Soc.* **88,** 3440 (1966).

[695] Olah, Nojima, and Kerekes, *Synthesis* 487 (1973).

$$\mathrm{RCOOH + R'COCl \rightleftharpoons RCOCl + R'COOH}$$

which probably involves an anhydride intermediate. This is an equilibrium reaction which must be driven to the desired side. Oxalyl chloride and bromide are frequently used as the acyl halide reagent, since oxalic acid decomposes to CO and CO_2, and the equilibrium is thus driven to the side of the other acyl halide.

OS **I,** 12, 147, 394; **II,** 74, 156, 169, 569; **III,** 169, 490, 547, 555, 613, 623, 712, 714; **IV,** 34, 88, 154, 263, 339, 348, 554, 608, 616, 620, 715, 739, 900; **V,** 171, 258, 887; **52,** 36; **55,** 27.

0-76 Formation of Acyl Halides from Acid Derivatives

$$\mathrm{(RCO)_2O + HF \longrightarrow RCOF}$$

$$\mathrm{RCOCl + HF \longrightarrow RCOF}$$

These reactions are most important for the preparation of acyl fluorides. Anhydrides can be converted to acyl fluorides by treatment with liquid HF at −10°C.[696] Formyl fluoride, which is a stable compound, can be prepared in this manner from the mixed anhydride of formic and acetic acids.[697] Acyl fluorides can also be obtained by reaction of acyl chlorides with anhydrous HF[696] or with KF. Esters and anhydrides can be converted to acyl halides other than fluorides by the inorganic acid halides mentioned in **0-75,** as well as with Ph_3PX_2 ($X = Cl$ or Br),[698] but this is not often done. Halide exchange can be carried out in a similar manner. When halide exchange is done, it is always acyl bromides and iodides that are made from chlorides, since chlorides are by far the most readily available. As with reaction **0-75,** acyl halides are sometimes used as reagents in an exchange reaction. Acyl hydrazides $RCONHNH_2$ can be treated with chlorine and HCl to give acyl chlorides. This method is apparently unsuccessful for bromides and iodides.[699]

OS **II,** 528; **III,** 422; **V,** 66, 1103. See also OS **IV,** 307.

Hydrogen as Nucleophile

The reactions in this section (**0-77** to **0-85**) are reductions and could have been considered in Chapter 19. They are treated here because they involve replacement of a leaving group by hydrogen, which frequently attacks as the nucleophile hydride ion. However, not all the reactions in this section are true nucleophilic substitutions, and for some of them, more than one kind of mechanism may be involved, depending on the reagents and on the conditions. When cleavage of a carbon-hetero atom bond is accomplished by catalytic hydrogenation, the reaction is called *hydrogenolysis.*

A. Attack at an Alkyl Carbon

0-77 Reduction of Alkyl Halides

$$\mathrm{RX + LiAlH_4 \longrightarrow RH}$$

This type of reduction can be accomplished with many reducing agents, the most common being lithium aluminum hydride.[700] This reagent reduces almost all types of alkyl halide, including vinyl, bridgehead, and cyclopropyl halides.[701] Reduction with lithium aluminum deuteride serves to introduce deuterium into organic compounds. An even more powerful reducing agent, indeed reportedly the strongest SN2 nucleophile known, is lithium triethylborohydride $LiEt_3BH$. This reagent rapidly reduces primary, secondary, allylic, benzylic, and neopentyl halides, but not tertiary (these give elimination) or aryl halides.[702] Another powerful reagent, which reduces primary, secondary, tertiary, allylic, vinylic, aryl, and neopentyl halides, is a complex formed from lithium trimethoxyaluminum hydride $LiAlH(OMe)_3$ and CuI.[703] A milder reducing agent is $NaBH_4$ in a dipolar aprotic solvent such as dimethyl sulfoxide, dimethylformamide, or sulfolane,[704] which at room temperature or above reduces primary, secondary, and some tertiary[705] halides in good yield without affecting other functional groups which would be reduced by $LiAlH_4$, e.g., COOH, COOR, CN. Other reducing agents are HI, alkali metals in liquid ammonia, zinc (with acid or base), $SnCl_2$, and chromium(II) ion,[706] either in the form of simple chromous salts (for active substrates or *gem*-dihalides[707]) or complexed with ethylenediamine or ethanolamine (for ordinary alkyl halides[708]). Sodium arsenite and base, Et_3SiH in the presence of benzoyl peroxide,[709] phosphorus tris(dimethyl)amide $(Me_2N)_3P$,[710] or organotin hydrides R_nSnH_{4-n}[711] (chiefly Bu_3SnH)[712] can be used to reduce just one halogen of a *gem*-dihalide or a 1,1,1-trihalide. Reduction can also be effected by catalytic hydrogenation. A good reducing agent for the removal of all halogen atoms in a polyhalo compound (including vinyl, allylic, geminal, and even bridgehead halogens) is lithium[713] or sodium[714] and *t*-BuOH in tetrahydrofuran. Propargylic halides can often be reduced with allylic rearrangement to give allenes:[715]

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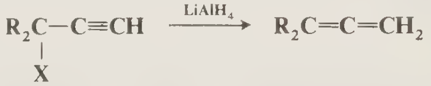
[696] Olah and Kuhn, *J. Org. Chem.* **26,** 237 (1961).

[697] Olah and Kuhn, *J. Am. Chem. Soc.* **82,** 2380 (1960).

[698] Burton and Koppes, *J. Chem. Soc., Chem. Commun.* 425 (1973), *J. Org. Chem.* **40,** 3026 (1975); Anderson and Kono, *Tetrahedron Lett.* 5121 (1973).

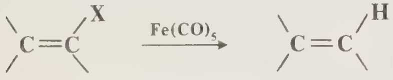
[699] Carpino, *J. Am. Chem. Soc.* **79,** 96 (1957).

[700] For a discussion of metallic hydrides as reducing agents in this reaction, see Gaylord, "Reduction with Complex Metal Halides," pp. 889–917, Interscience Publishers, Inc., New York, 1956.

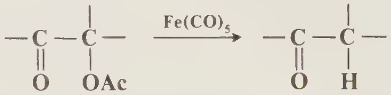


$$\underset{\displaystyle X}{R_2C}{-}C{\equiv}CH \xrightarrow{LiAlH_4} R_2C{=}C{=}CH_2$$

Another reagent which reduces vinyl chlorides (as well as vinyl acetates, α,β-unsaturated aldehydes, and α-acetoxy ketones) is iron pentacarbonyl.[716]



X = Cl, OAc, CHO



Usually the choice of a reducing agent depends on what other functional groups are present.

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[701] Jefford, Kirkpatrick, and Delay, *J. Am. Chem. Soc.* **94,** 8905 (1972).

[702] Brown and Krishnamurthy, *J. Am. Chem. Soc.* **95,** 1669 (1973).

[703] Masamune, Rossy, and Bates, *J. Am. Chem. Soc.* **95,** 6452 (1973); Masamune, Bates, and Georghiou, *J. Am. Chem. Soc.* **96,** 3686 (1974).

[704] Bell, Vanderslice, and Spehar, *J. Org. Chem.* **34,** 3923 (1969); Hutchins, Hoke, Keogh, and Koharski, *Tetrahedron Lett.* 3495 (1969); Vol'pin, Dvolaitzky, and Levitin, *Bull. Soc. Chim. Fr.* 1526 (1970).

[705] Hutchins, Bertsch, and Hoke, *J. Org. Chem.* **36,** 1568 (1971).

[706] For reviews, see Hanson, *Synthesis* 1–8 (1974), pp. 2–5; Hanson and Premuzic, *Angew. Chem. Int. Ed. Engl.* **7,** 247–252 (1968) [*Angew. Chem.* **80,** 271–276].

[707] Castro and Kray, *J. Am. Chem. Soc.* **88,** 4447 (1966).

[708] Kochi and Mocadlo, *J. Am. Chem. Soc.* **88,** 4094 (1966); Kochi and Powers, *J. Am. Chem. Soc.* **92,** 137 (1970).

[709] Nagai, Yamazaki, Shiojima, Kobori, and Hayashi, *J. Organomet. Chem.* **9,** P21 (1967); Nagai, Yamazaki, and Shiojima, *J. Organomet. Chem.* **9,** P25 (1967), *Bull. Chem. Soc. Jpn.* **40,** 2210 (1967).

[710] Downie and Lee, *Tetrahedron Lett.* 4951 (1968).

[711] Seyferth, Yamazaki, and Alleston, *J. Org. Chem.* **28,** 703 (1963).

[712] For reviews of organotin hydrides, see Kuivila, *Synthesis* 499–509 (1970), *Acc. Chem. Res.* **1,** 299–305 (1968).

[713] For example, see Bruck, Thompson, and Winstein, *Chem. Ind.* (*London*) 405 (1960); Gassman and Pape, *J. Org. Chem.* **29,** 160 (1964); Fieser and Sachs, *J. Org. Chem.* **29,** 1113 (1964); Nazer, *J. Org. Chem.* **30,** 1737 (1965).

[714] For example, see Gassman, Aue, and Patton, *J. Am. Chem. Soc.* **90,** 7271 (1968); Gassman and Marshall, *Org. Synth.* **V,** 424.

[715] For examples, see Jacobs and Wilcox, *J. Am. Chem. Soc.* **86,** 2240 (1964); Crandall, Keyton, and Kohne, *J. Org. Chem.* **33,** 3655 (1968). For a reduction of γ-bromo-α,β-unsaturated esters with allylic rearrangement to give β,γ-unsaturated esters (by Zn in acetic acid) see Moppett and Sutherland, *J. Chem. Soc. C* 3040 (1968).

[716] Nelson, Detre, and Tanabe, *Tetrahedron Lett.* 447 (1973).

Each reducing agent reduces certain groups and not others. For example, the use of $LiI-BF_3$,[717] CH_3SNa,[718] or aqueous $TiCl_3$[719] provides a means of reducing only the halogen of α-halo ketones, leaving the carbonyl group intact. Another highly selective reagent, for primary and secondary iodo and bromo groups, is sodium cyanoborohydride $NaBH_3CN$ in HMPT.[720] Still more selective is tetrabutylammonium cyanoborohydride, which is fairly specific for primary iodides.[721] Most of the reducing agents mentioned reduce chlorides, bromides, and iodides, but organotin hydrides also reduce fluorides. See page 1116 for a discussion of selectivity in reduction reactions.

With lithium aluminum hydride and most other metallic hydrides, the mechanism usually consists of simple nucleophilic substitution with attack by hydride ion which may or may not be completely free. The mechanism is SN2 rather than SN1, since primary halides react better than secondary or tertiary (tertiary generally give alkenes or do not react at all), and since Walden inversion has been demonstrated. However, rearrangements found in the reduction of bicyclic tosylates with $LiAlH_4$ indicate that the SN1 mechanism can take place.[722] The SN1 mechanism has also been shown for reduction by alkanes (such as isopentane) and aluminum chloride.[723] The aluminum chloride ionizes the substrate, and the resulting carbonium ion abstracts a hydride ion from the alkane:

$$RX + AlCl_3 \longrightarrow AlCl_3X^- + R^+ \xrightarrow{R'H} RH + R'^+$$

Reduction of halides by $NaBH_4$ in 80% aqueous diglyme[724] and by BH_3 in nitromethane[725] also takes place by an SN1 mechanism. $NaBH_4$ in sulfolane reduces tertiary halides possessing a β-hydrogen by an elimination-addition mechanism.[726]

With other reducing agents the mechanism is not always nucleophilic substitution. For example, reductions with organo tin halides generally[727] take place by free-radical mechanisms,[728] as do those with $Fe(CO)_5$[716] and Et_3SiH.[709] Alkyl halides, including fluorides and polyhalides, can be reduced with magnesium and a secondary or tertiary alcohol (most often isopropyl alcohol).[729] This is actually an example of the occurrence in one step of the sequence:

$$RX \longrightarrow RMgX \xrightarrow{H^+} RH$$

More often the process is carried out in two separate steps (reaction **2-37** and reaction **2-21**).

OS **I,** 357, 358, 548; **II,** 320, 393; **V,** 424; **51,** 60; **53,** 107; **54,** 11.

0-78 Reduction of Tosylates and Similar Compounds

$$RCH_2OTs + LiAlH_4 \longrightarrow RCH_3$$

Tosylates and other sulfonates can be reduced with $LiAlH_4$[730] or with $NaBH_4$ in a dipolar aprotic solvent.[731] The scope of the reaction seems to be similar to that of reaction **0-77.**

OS **52,** 109; **53,** 107.

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[717] Townsend and Spencer, *Tetrahedron Lett.* 137 (1971).

[718] Ōki, Funakoshi, and Nakamura, *Bull. Chem. Soc. Jpn.* **44,** 828 (1971).

[719] Ho and Wong, *Synth. Commun.* **3,** 237 (1973); Mc Murry, *Acc. Chem. Res.* **7,** 281–286 (1974), pp. 284–285.

[720] Hutchins, Maryanoff, and Milewski, *Chem. Commun.* 1097 (1971).

[721] Hutchins and Kandasamy, *J. Am. Chem. Soc.* **95,** 6131 (1973).

[722] Appleton, Fairlie, and McCrindle, *Chem. Commun.* 690 (1967); Kraus and Chassin, *Tetrahedron Lett.* 1443 (1970).

[723] Bartlett, Condon, and Schneider, *J. Am. Chem. Soc.* **66,** 1531 (1944); Necşoiu, Bârlădeanu, and Nenitzescu, *Chem. Ind.* (*London*) 1753 (1961).

[724] Bell and Brown, *J. Am. Chem. Soc.* **88,** 1473 (1966).

[725] Matsumura and Tokura, *Tetrahedron Lett.* 363 (1969).

[726] Jacobus, *Chem. Commun.* 338 (1970); Ref. 705.

[727] For an exception, see Carey and Tremper, *Tetrahedron Lett.* 1645 (1969).

[728] Kuivila and Menapace, *J. Org. Chem.* **28,** 2165 (1963); Menapace and Kuivila, *J. Am. Chem. Soc.* **86,** 3047 (1964).

[729] Bryce-Smith, Wakefield, and Blues, *Proc. Chem. Soc.* 219 (1963).

[730] For examples, see Rapoport and Bonner, *J. Am. Chem. Soc.* **73,** 2872 (1951); Eschenmoser and Frey, *Helv. Chim. Acta* **35,** 1660 (1952); Hardegger, Furter, and Kiss, *Helv. Chim. Acta* **41,** 2401 (1958).

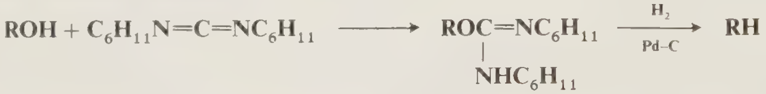
[731] Hutchins, Hoke, Keogh, and Koharski, Ref. 704.

0-79 Hydrogenolysis of Alcohols

$$\mathrm{ROH + H_2 \xrightarrow{catalyst} RH}$$

The hydroxyl groups of most alcohols can seldom be cleaved by catalytic hydrogenation, and alcohols are often used as solvents for hydrogenation of other compounds. However, benzyl-type alcohols undergo the reaction readily, and these have often been reduced.[732] The most common catalysts are copper chromite and palladium-on-charcoal. Diaryl and triarylcarbonols are similarly easy to reduce, and this has been accomplished with $LiAlH_4$–$AlCl_3$,[733] with alcohols and sulfuric or formic acid,[734] and with iodine, water, and red phosphorus (OS **I**, 224). Other reagents have been used, among them tin and hydrochloric acid. 1,3-Glycols are especially susceptible to hydrogenolysis. Tertiary alcohols can be reduced by catalytic hydrogenolysis when the catalyst is platinum bis(triphenylphosphine) dichloride.[734a]

Alcohols can also be reduced indirectly by conversion to a sulfonate and reduction of that compound (reaction **0-78**). The two reactions can be carried out without isolation of the sulfonate if the alcohol is treated with pyridine-SO_3 in tetrahydrofuran, and $LiAlH_4$ then added.[735] Another indirect method involves catalytic reduction of the O-alkyl isourea formed by treating the alcohol with dicyclohexylcarbodiimide.[736]

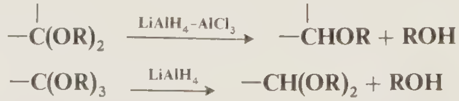


$$\mathrm{ROH + C_6H_{11}N{=}C{=}NC_6H_{11} \longrightarrow \underset{\displaystyle NHC_6H_{11}}{\underset{|}{ROC}}{=}NC_6H_{11} \xrightarrow[Pd\text{–}C]{H_2} RH}$$

Though the mechanisms of most alcohol reductions are obscure,[737] in at least some cases nucleophilic substitution has been demonstrated.[734] Hydrogenolysis of benzyl alcohols can give inversion or retention of configuration, depending on the catalyst.[738]

OS **I**, 224; **IV**, 25, 218, 482; **V**, 339.

0-80 Replacement of Alkoxyl by Hydrogen



$$\mathrm{-\overset{|}{C}(OR)_2 \xrightarrow{LiAlH_4\text{–}AlCl_3} -\overset{|}{C}HOR + ROH}$$

$$\mathrm{-C(OR)_3 \xrightarrow{LiAlH_4} -CH(OR)_2 + ROH}$$

Simple ethers are not normally cleaved by reducing agents, although such cleavage has sometimes been reported (for example, tetrahydrofuran treated with $LiAlH_4$–$AlCl_3$[739] or with a mixture of $LiAlH(O\text{-}t\text{-}Bu)_3$ and Et_3B[740] gave 1-butanol). Certain types of ethers can be cleaved quite well by reducing agents. Among these are allyl aryl,[741] vinyl aryl,[742] and benzyl ethers[732] (for epoxides, see reaction **0-81**). Acetals and ketals are resistant to $LiAlH_4$ and similar hydrides, and carbonyl groups are often converted to acetals or ketals for protection. However, a combination of $LiAlH_4$

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[732] For reviews, see Rylander, "Catalytic Hydrogenation over Platinum Metals," pp. 449–468, Academic Press, Inc., New York, 1967; Hartung and Simonoff, *Org. React.* **7**, 263–326 (1953). For a review of the stereochemistry of hydrogenolysis, see Klabunovskii, *Russ. Chem. Rev.* **35**, 546–558 (1966).

[733] Blackwell and Hickinbottom, *J. Chem. Soc.* 1405 (1961).

[734] Dar'eva and Miklukhin, *J. Gen. Chem. USSR* **29**, 620 (1959).

[734a] Parnes, Shaapuni, Kalinkin, and Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23**, 1592 (1974). See also Kalinkin, Parnes, Shaapuni, and Kursanov, *Dokl. Chem.* **219**, 888 (1974).

[735] Corey and Achiwa, *J. Org. Chem.* **34**, 3667 (1969).

[736] Vowinkel and Büthe, *Chem. Ber.* **107**, 1353 (1974).

[737] For discussions of the mechanisms of the hydrogenolysis of benzyl alcohols, see Khan, McQuillin, and Jardine, *Tetrahedron Lett.* 2649 (1966); *J. Chem. Soc. C* 136 (1967); Garbisch, Schreader, and Frankel, *J. Am. Chem. Soc.* **89**, 4233 (1967); Mitsui, Imaizumi, and Esashi, *Bull. Chem. Soc. Jpn.* **43**, 2143 (1970).

[738] Mitsui, Kudo, and Kobayashi, *Tetrahedron* **25**, 1921 (1969); Mitsui, Imaizumi, and Esashi, Ref. 737.

[739] Bailey and Marktscheffel, *J. Org. Chem.* **25**, 1797 (1960).

[740] Brown and Krishnamurthy, *J. Chem. Soc., Chem. Commun.* 868 (1972); Brown, Krishnamurthy, and Coleman, *J. Am. Chem. Soc.* **94**, 1750 (1972).

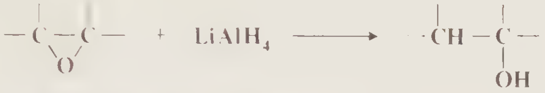
[741] Tweedie and Cuscurida, *J. Am. Chem. Soc.* **79**, 5463 (1957).

[742] Tweedie and Barron, *J. Org. Chem.* **25**, 2023 (1960).

and $AlCl_3$[743] does reduce acetals and ketals, removing one group, as shown above.[744] The actual reducing agents in this case are primarily chloroaluminum hydride AlH_2Cl and dichloroaluminum hydride Al_2HCl, which are formed from the reagents.[745] Ortho esters are easily reduced to acetals by $LiAlH_4$ alone,[746] offering a route to aldehydes, since these are easily prepared by hydrolysis of the acetals (reaction **0-7**). Acetals can also be reduced to ethers by treatment with BH_3 in tetrahydrofuran[747] or with trichlorosilane $SiHCl_3$ under γ irradiation.[748]

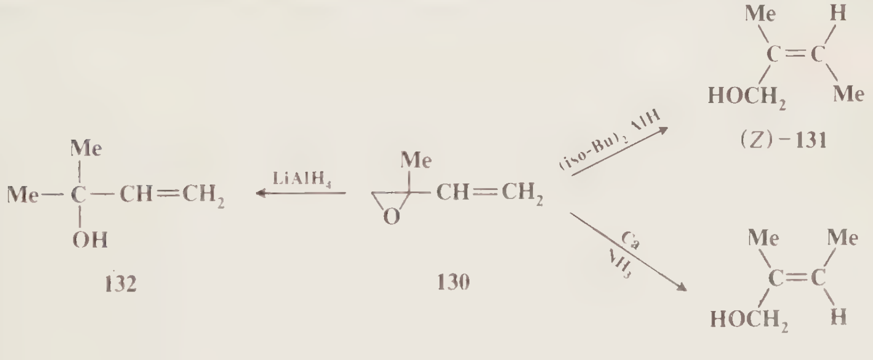
OS **III**, 693; **IV**, 798; **V**, 303. Also see OS **III**, 742.

0-81 Reduction of Epoxides



Reduction of epoxides is a special case of reaction **0-80** and is easily carried out. The most common reagent is $LiAlH_4$, which reacts by the S_N2 mechanism, giving inversion of configuration. An epoxide on a substituted cyclohexane ring cleaves in such a direction as to give an axial alcohol. As expected for an S_N2 mechanism, cleavage usually occurs so that a tertiary alcohol is formed if possible. If not, a secondary alcohol is preferred. However, for certain substrates, the epoxide ring can be opened the other way by reduction with BH_3 in tetrahydrofuran[749] in the presence of BF_3 (for aryl-substituted epoxides) or of BH_4^- (for trisubstituted epoxides).[750] The reaction has also been carried out with other reagents, for example, sodium amalgam in EtOH, and Li in ethylenediamine,[751] and by catalytic hydrogenation.[752] Highly hindered epoxides can be conveniently reduced, without rearrangement, with lithium triethylborohydride.[753] See reaction **9-48** for another type of epoxide reduction.

α,β-Unsaturated epoxides can be reduced with concomitant allylic rearrangement, the stereochemistry of the reaction depending on the reagent.[754] Thus, 2-methyl-1,2-oxido-3-butene (**130**)



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[743] For a review of reductions by metal hydride-Lewis acid combinations, see Rerick, in Augustine, "Reduction," pp. 1-94, Marcel Dekker, Inc., New York, 1968.

[744] Eliel, Badding, and Rerick, *J. Am. Chem. Soc.* **84**, 2371 (1962).

[745] Ashby and Prather, *J. Am. Chem. Soc.* **88**, 729 (1966); Diner, Davis, and Brown, *Can. J. Chem.* **45**, 207 (1967).

[746] Ref. 700, p. 690.

[747] Fleming and Bolker, *Can. J. Chem.* **52**, 888 (1974); Bolker and Fleming, *Can. J. Chem.* **53**, 2818 (1975).

[748] Nakao, Fukumoto, and Tsurugi, *J. Org. Chem.* **37**, 4349 (1972).

[749] For a review of epoxide reduction with BH_3, see Cragg, "Organoboranes in Organic Synthesis," pp. 345-348, Marcel Dekker, Inc., New York, 1973.

[750] Brown and Yoon, *Chem. Commun.* 1549 (1968); *J. Am. Chem. Soc.* **90**, 2686 (1968).

[751] Brown, Ikegami, and Kawakami, *J. Org. Chem.* **35**, 3243 (1970).

[752] For a review, see Rylander, Ref. 732, pp. 478-485.

[753] Krishnamurthy, Schubert, and Brown, *J. Am. Chem. Soc.* **95**, 8486 (1973).

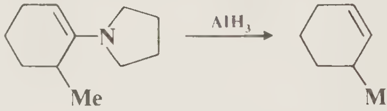
[754] Lenox and Katzenellenbogen, *J. Am. Chem. Soc.* **95**, 957 (1973).

gives 95% (*Z*)-2-methyl-2-buten-1-ol (**131**) when treated with (iso-Bu)$_2$AlH at 68°C in hexane, but 92% of the *E* isomer with calcium in liquid NH_3 at −33 C. Reduction of **130** with $LiAlH_4$ gives the normal nonrearranged product **132.**

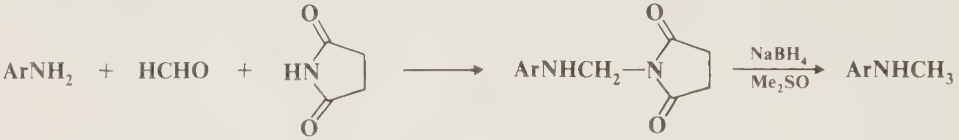
0-82 Reduction of the C—N Bond

$$3RNH_2 + HNF_2 \longrightarrow RH + 2RNH_3^+ \quad F^- + N_2$$

Primary amines have been reduced to alkanes with HNF_2. It is postulated that R—N=N—H is an intermediate,[755] so that the reaction proceeds through the carbonium ion. An indirect means of achieving the same result is conversion of the primary amine to the sulfonamide $RNHSO_2R'$ (reaction **0-120**) and treatment of this with hydroxylamine-O-sulfonic acid $(H_3\overset{\oplus}{N}OSO_3^{\ominus})$.[756] The same intermediate is postulated in this case. Another indirect method involves conversion to N,N-disulfonimides $RN(SO_2R')_2$ and reduction of these with $NaBH_4$ in HMPT.[756a] Allylic and benzylic amines[732] can be reduced by catalytic hydrogenation. Enamines are cleaved to olefins with alane AlH_3,[757] e.g.,



Since enamines can be prepared from ketones (**6-15**), this is a way of converting ketones to alkenes. A method for the monomethylation of arylamines consists of refluxing them with aqueous HCHO and succinimide to form arylaminomethylsuccinimides (a Mannich reaction, **6-17**), which are easily reduced with $NaBH_4$ in dimethyl sulfoxide.[758] Diazo ketones are reduced to methyl ketones by HI: $RCOCHN_2 + HI \rightarrow RCOCH_3$.[759]



Quaternary ammonium salts can be cleaved with $LiAlH_4$[760]

$$R_4N^+ + LiAlH_4 \longrightarrow R_3N + RH$$

as can quaternary phosphonium salts R_4P^+. Other reducing agents have also been used, for example, lithium triethylborohydride (which preferentially cleaves methyl groups)[761] and sodium in liquid ammonia. When quaternary salts are reduced with sodium amalgam in water, the reaction is known as the *Emde reduction*. However, this reagent is not applicable to the cleavage of ammonium salts with four *saturated* alkyl groups. Some tertiary amines have been cleaved with $LiAlH_4$.[762] Of course, aziridines[752] can be reduced in the same way as epoxides (reaction **0-81**).

OS **III,** 148; **IV,** 508.

For reduction of the C—S bond, see reaction **4-37.**

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[755] Bumgardner, Martin, and Freeman, *J. Am. Chem. Soc.* **85,** 97 (1963).

[756] Nickon and Hill, *J. Am. Chem. Soc.* **86,** 1152 (1964).

[756a] Hutchins, Cistone, Goldsmith, and Heuman, *J. Org. Chem.* **40,** 2018 (1975).

[757] Coulter, Lewis, and Lynch, *Tetrahedron* **24,** 4489 (1968).

[758] Kadin, *J. Org. Chem.* **38,** 1348 (1973).

[759] For example, see Pojer, Ritchie, and Taylor, *Aust. J. Chem.* **21,** 1375 (1968).

[760] For a review, see Ref. 700, pp. 781–793.

[761] Cooke and Parlman, *J. Org. Chem.* **40,** 531 (1975).

[762] Tweedie and Allabash, *J. Org. Chem.* **26,** 3676 (1961).

B. Attack at an Acyl Carbon

0-83 Reduction of Acyl Halides

$$\mathrm{RCOCl} \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{LiAlH(O\text{-}\mathit{t}\text{-}Bu)_3}} \mathrm{RCHO}$$

Acyl halides are conveniently reduced to aldehydes[763] by treatment with lithium tri-*t*-butoxyaluminum hydride in diglyme at −78°C.[764] R may be alkyl or aryl and may contain many types of substituents, including NO_2, CN, and EtOOC groups. The reaction stops at the aldehyde stage because steric hindrance prevents further reduction under these conditions. Acyl halides can also be reduced to aldehydes by hydrogenation with palladium-on-barium sulfate as catalyst. This is called the *Rosenmund reduction.*[765] It is sometimes necessary to "poison" the catalyst to prevent further reduction, although many successful reactions have been run without poisons. The most commonly used poison is "quinoline-sulfur," prepared by heating sulfur in refluxing quinoline. A more convenient hydrogenation procedure involves palladium-on-charcoal as the catalyst, with ethyldiisopropylamine as acceptor of the liberated HCl and acetone as the solvent.[766] The reduction of acyl halides to aldehydes has also been carried out with Bu_3SnH,[767] with Et_3SiH catalyzed by Pd/C,[768] with disodium tetracarbonyl ferrate $Na_2Fe(CO)_4$,[769] electrochemically,[770] and by irradiation in the presence of a hydrogen donor.[771] In some of these cases, the mechanisms are free-radical. There are several indirect methods for the conversion of acyl halides to aldehydes, most of them involving prior conversion of the halides to certain types of amides (see reaction **0-85**).[772] There is also a method in which the COOH group is replaced by a completely different CHO group (**0-113**). Also see reaction **9-47.**

OS **III,** 551, 627; **51,** 8; **53,** 52. Also see OS **III,** 818; **51,** 11.

0-84 Reduction of Carboxylic Acids, Esters, and Anhydrides to Aldehydes

$$\mathrm{RCOOH} \xrightarrow[\mathrm{MeNH_2}]{\mathrm{Li}} \mathrm{RCH{=}N{-}Me} \xrightarrow{\mathrm{H_2O}} \mathrm{RCHO}$$

With most reducing agents, reduction of carboxylic acids generally gives the primary alcohol (reaction **9-40**), and the isolation of aldehydes is not feasible. However, simple straight-chain carboxylic acids have been reduced to aldehydes by treatment with Li in $MeNH_2$ or NH_3 followed by hydrolysis of the resulting imine,[773] and by treatment with diaminoaluminum hydrides.[773a] Some aldehydes have also been prepared by heating carboxylic acids with formic acid and thorium oxide (this is actually an example of reaction **0-117**). Caproic and isovaleric acids have been reduced to aldehydes, in 50% yields or better, with $(\text{iso-Bu})_2AlH$ at −75 to −70°C.[774]

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[763] For a review of the formation of aldehydes from acid derivatives, see Fuson, in Patai, Ref. 349, pp. 211–232. For a review of the reduction of acyl halides, see Wheeler, in Patai, Ref. 379, pp. 231–251.

[764] Brown and McFarlin, *J. Am. Chem. Soc.* **80,** 5372 (1958); Brown and Subba Rao, *J. Am. Chem. Soc.* **80,** 5377 (1958).

[765] For reviews, see Rylander, Ref. 732, pp. 398–404; Mosettig and Mozingo, *Org. React.* **4,** 362–377 (1948).

[766] Peters and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **90,** 1323 (1971).

[767] Kuivila, *J. Org. Chem.* **25,** 284 (1960); Kuivila and Walsh, *J. Am. Chem. Soc.* **88,** 571 (1966); Walsh, Stoneberg, Yorke, and Kuivila, *J. Org. Chem.* **34,** 1156 (1969).

[768] Citron, *J. Org. Chem.* **34,** 1977 (1969); Dent, Eaborn, and Pidcock, *Chem. Commun.* 1703 (1970).

[769] Watanabe, Mitsudo, Tanaka, Yamamoto, Okajima, and Takegami, *Bull. Chem. Soc. Jpn.* **44,** 2569 (1971).

[770] Wagenknecht, *J. Org. Chem.* **37,** 1513 (1972).

[771] Schmidt, *Angew. Chem. Int. Ed. Engl.* **4,** 146 (1965) [*Angew. Chem.* **77,** 169]; Silhan and Schmidt, *Monatsh. Chem.* **102,** 1481 (1971).

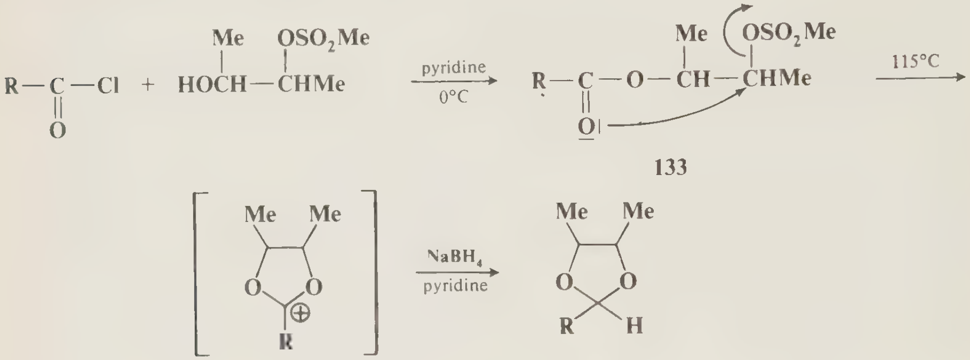
[772] For a review, see Mosettig, *Org. React.* **8,** 218–257 (1954). See also Doleschall, *Tetrahedron Lett.* 2649 (1974).

[773] Bedenbaugh, Bedenbaugh, Bergin, and Adkins, *J. Am. Chem. Soc.* **92,** 5774 (1970); Burgstahler, Worden, and Lewis, *J. Org. Chem.* **28,** 2918 (1963).

[773a] Muraki and Mukaiyama, *Chem. Lett* 1447 (1974), 215 (1975).

[774] Zakharkin and Khorlina, *J. Gen. Chem. USSR* **34,** 1021 (1964); Zakharkin and Sorokina, *J. Gen. Chem. USSR* **37,** 525 (1967).

Esters have been reduced to aldehydes with (iso-Bu)$_2$AlH at −70°C, with diaminoaluminum hydrides,[773a] and with NaAlH$_4$ at −65 to −45°C, and (for phenolic esters) with LiAlH(O-*t*-Bu)$_3$ at 0°C.[775] An unusual way of converting acyl halides to aldehydes through an ester is treatment of a 2,3-butanediol monomesylate ester (**133**) with NaBH$_4$ in pyridine at 115°C.[776] Hydrolysis of the acetal (**134**) gives the aldehyde RCHO.



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134

Anhydrides, both aliphatic and aromatic, as well as mixed anhydrides of carboxylic and carbonic acids, have been reduced to aldehydes in moderate yields with disodium tetracarbonylferrate Na$_2$Fe(CO)$_4$.[777]

Also see reactions **9-42** and **9-44**.

OS **51,** 11.

0-85 Reduction of Amides to Aldehydes

$$\mathbf{RCONR'_2 + LiAlH_4 \longrightarrow RCHO + NHR'_2}$$

N,N-Disubstituted amides can be reduced to amines with LiAlH$_4$ (see reaction **9-41**), but also to aldehydes.[778] Keeping the amide in excess gives the aldehyde rather than the amine. Sometimes it is not possible to prevent further reduction, and primary alcohols are obtained instead. Other reagents which give good yields of aldehydes are (iso-Bu)$_2$AlH,[779] LiAlH(O-*t*-Bu)$_3$, LiAlH$_4$-EtOH,[780] NaAlH$_4$,[781] and diaminoaluminum hydrides.[781a]

Aldehydes have been prepared from acids or acyl halides by first converting them to certain types of amides which are easily reducible. The following are some examples:

1. *Reissert compounds*[782] (**135**) are prepared from the acyl halide by treatment with quinoline and cyanide ion. Treatment of **135** with sulfuric acid gives the corresponding aldehyde.

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[775] Zakharkin and Khorlina, *Tetrahedron Lett.* 619 (1962); *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 288–290 (1963), 435 (1964); Zakharkin, Gavrilenko, Maslin, and Khorlina, *Tetrahedron Lett.* 2087 (1963); Zakharkin, Gavrilenko, and Maslin, *Bull. Acad. Sci., Div. Chem. Sci.* 867 (1964); Weissman and Brown, *J. Org. Chem.* **31,** 283 (1966).

[776] Johnson and Rickborn, *Org. Synth.* **51,** 11 (1971). See also Doleschall, *Tetrahedron Lett.* 681 (1975).

[777] Watanabe, Yamashita, Mitsudo, Igami, and Takegami, *Bull. Chem. Soc. Jpn.* **48,** 2490 (1975); Watanabe, Yamashita, Mitsudo, Igami, Tomi, and Takegami, *Tetrahedron Lett.* 1063 (1975).

[778] For reviews, see Fuson, Ref. 763, pp. 220–225; Ref. 700, pp. 575–590.

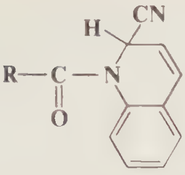
[779] Zakharkin and Khorlina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2046 (1959).

[780] Brown and Tsukamoto, *J. Am. Chem. Soc.* **86,** 1089 (1964).

[781] Zakharkin, Maslin, and Gavrilenko, *Tetrahedron* **25,** 5555 (1969).

[781a] Muraki and Mukaiyama, *Chem. Lett.* 875 (1975).

[782] For a review of Reissert compounds, see Popp, *Adv. Heterocycl. Chem.* **9,** 1–25 (1968).



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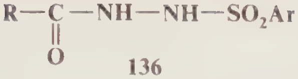
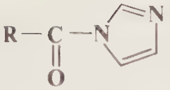


$$R-\underset{\underset{O}{\|}}{C}-NH-NH-SO_2Ar$$

136



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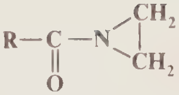

138

2. Acyl sulfonylhydrazides (**136**) are cleaved with base to give aldehydes. This is known as the *McFadyen-Stevens reduction*[782] and is applicable only to aromatic aldehydes or to aliphatic aldehydes with no α-hydrogen.[783] RCON=NH (see reaction **0-82**) has been proposed as an intermediate in this reaction.[784]

3. Imidazoles (**137**)[406] and N-acylaziridines (**138**)[785] can be reduced to aldehydes with $LiAlH_4$.

4. See also the Sonn-Müller method (reaction **6-30**).

See OS **IV**, 641, for the preparation of a Reissert compound.

Carbon Nucleophiles

In any ionic reaction in which a new carbon-carbon bond is formed, one carbon atom attacks as a nucleophile and the other as an electrophile. Whether to classify a given reaction as nucleophilic or electrophilic is a matter of convention and is usually based on analogy. Although not discussed in this chapter, reactions **1-13** to **1-31** and **2-15** to **2-18** are actually nucleophilic substitutions with respect to one reactant though, following convention, we classify them with respect to the other. Similarly, all the reactions in this section (**0-86** to **0-117**) would be called electrophilic substitutions (aromatic or aliphatic) if we were to consider the reagent as the substrate.

A. Attack at an Alkyl Carbon. In reactions **0-86** to **0-93** the nucleophile is a "carbanion" part of an organometallic compound, often a Grignard reagent. There is much that is still not known about the mechanisms of these reactions, and many of them are not nucleophilic substitutions at all. In those reactions which are nucleophilic substitutions, the attacking carbon brings a pair of electrons with it to the new C—C bond, whether or not free carbanions are actually involved. The connection of two alkyl or aryl groups is called *coupling*. Reactions **0-86** to **0-93** and **0-95** include both symmetrical and unsymmetrical coupling reactions. The latter are also called *cross-coupling reactions*. Other coupling reactions are considered in later chapters.

0-86 Coupling of Alkyl Halides. The Wurtz Reaction

$$2RX + Na \longrightarrow RR$$

The coupling of alkyl halides by treatment with sodium to give a symmetrical product is called the *Wurtz reaction*. Side reactions (elimination and rearrangement) are so common that the reaction is seldom used. Mixed Wurtz reactions of two alkyl halides are even less feasible, because of the number of products obtained. A somewhat more useful reaction (though still not very good) takes place when a mixture of an alkyl and an aryl halide is treated with sodium to give an alkylated aromatic compound (the *Wurtz-Fittig reaction*).[786] However, the coupling of two aryl halides with sodium is impractical (see, however, reaction **3-16**). Other metals have also been used to effect Wurtz reactions, notably silver, zinc,[787] iron,[788] and pyrophoric lead.[789] With the latter reagent, a COOH group may be present in the molecule without being affected; e.g., succinic acid was produced from chloroacetic acid. The complex $VCl_2(py)_4$ dimerizes benzyl halides to give $ArCH_2CH_2Ar$.[790] Benzal bromides ($ArCHBr_2$) can be coupled with CuCl in dimethyl sulfoxide (to give ArCHBrCHBrAr).[791] A zinc-copper couple in dimethylformamide has been used to couple α,α′-dibromo ketones, with concomitant reduction of the other bromines, e.g.,[792]

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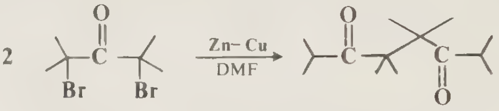
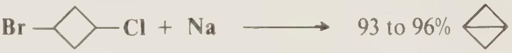
[783] Sprecher, Feldkimel, and Wilchek, *J. Org. Chem.* **26**, 3664 (1961); Babad, Herbert, and Stiles, *Tetrahedron Lett.* 2927 (1966).

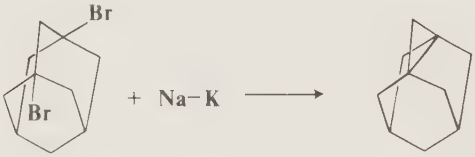
[784] For discussions, see Cacchi and Paolucci, *Gazz. Chem. Ital.* **104**, 221 (1974); Matin, Craig, and Chan, *J. Org. Chem.* **39**, 2285 (1974).

[785] Brown and Tsukamoto, *J. Am. Chem. Soc.* **83**, 4549 (1961).



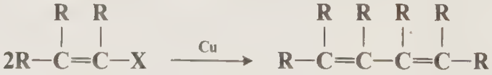
One type of Wurtz reaction which is quite useful is the closing of small rings, especially three-membered rings. For example, 1,3-dibromopropane can be converted to cyclopropane by Zn and NaI. Two highly strained molecules which have been prepared in this way are bicyclobutane[793] and tetracyclo[$3.3.1.1^{3,7}.0^{1,3}$]decane.[794] Three- and four-membered rings can also be closed in





this manner with certain other reagents,[795] including benzoyl peroxide,[796] ethylenediamine-chromium(II) reagent,[795] and lithium amalgam,[797] as well as electrochemically.[798]

Vinyl halides can be coupled to give 1,3-butadienes by treatment with activated copper powder in a reaction analogous to the Ullmann reaction (**3-16**).[799] This reaction is stereospecific,



$$2R-\overset{R}{\underset{|}{C}}=\overset{R}{\underset{|}{C}}-X \xrightarrow{\text{Cu}} R-\overset{R}{C}=\overset{R}{C}-\overset{R}{C}=\overset{R}{C}-R$$

with retention of configuration at both carbons. Vinyl halides can also be coupled with bis(1,5-

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[786] For an example, see Kwa and Boelhouwer, *Tetrahedron* **25,** 5771 (1970).

[787] See, for example, Nosek, *Collect. Czech. Chem. Commun.* **29,** 597 (1964).

[788] Nozaki and Noyori, *Tetrahedron* **22,** 2163 (1966).

[789] Mészáros, *Tetrahedron Lett.* 4951 (1967); Azoo and Grimshaw, *J. Chem. Soc. C* 2403 (1968).

[790] Cooper, *J. Am. Chem. Soc.* **95,** 4158 (1973).

[791] Nozaki, Shirafuji, and Yamamoto, *Tetrahedron* **25,** 3461 (1969).

[792] Chassin, Schmidt, and Hoffmann, *J. Am. Chem. Soc.* **96,** 606 (1974).

[793] Wiberg and Lampman, *Tetrahedron Lett.* 2173 (1963); Lampman and Aumiller, *Org. Synth.* **51,** 55 (1971).

[794] Pincock, Schmidt, Scott, and Torupka, *Can. J. Chem.* **50,** 3958 (1972).

[795] For a discussion, see Kochi and Singleton, *J. Org. Chem.* **33,** 1027 (1968).

[796] Kaplan, *J. Am. Chem. Soc.* **89,** 1753 (1967), *J. Org. Chem.* **32,** 4059 (1967).

[797] Connor and Wilson, *Tetrahedron Lett.* 4925 (1967).

[798] Rifi, *J. Am. Chem. Soc.* **89,** 4442 (1967), *Org. Synth.* **52,** 22 (1972).

[799] Cohen and Poeth, *J. Am. Chem. Soc.* **94,** 4363 (1972).

cyclooctadiene)nickel,[800] with CuCl,[801] and with Et_4NSnCl_3, $PtCl_2$, and CsF in dimethylformamide containing 2% H_2O.[802] Halides containing aryl groups (e.g., benzyl chloride) can be coupled with Grignard reagents if a small amount of a catalyst such as $CoCl_2$ or $FeCl_3$ is present.[803] The Grignard reagent is not found in the product. For example, benzyl chloride gives bibenzyl regardless of which Grignard reagent is used.

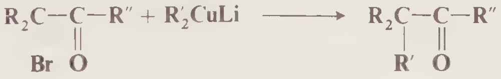
It seems likely that the mechanism of the Wurtz reaction consists of two basic steps. The first is halogen-metal exchange to give an organometallic compound ($RX + M \rightarrow RM$), which in many cases can be isolated (reaction **2-37**). Following this, the organometallic compound reacts with a second molecule of alkyl halide ($RX + RM \rightarrow RR$). This reaction and its mechanism are considered in the next section (**0-87**).

OS **III,** 157; **V,** 328, 1058; **51,** 55; **52,** 22.

0-87 The Reaction of Alkyl Halides with Organometallic Reagents

$$\mathbf{RX + R'_2CuLi \longrightarrow R{-}R'}$$

The reagents lithium dialkylcopper (which possibly have the structure $Li^+ \; R'_2Cu^-$) react with alkyl bromides, chlorides, and iodides in ether or tetrahydrofuran to give good yields of the cross-coupling products.[804] The reaction is of wide scope.[805] R may be primary (in some cases also secondary) alkyl, allylic, benzylic, aryl, vinyl, or allenic,[806] and may contain keto, COOH, COOR, or $CONR_2$ groups. The reaction at a vinyl substrate occurs stereospecifically, with retention of configuration.[807] Many *gem*-dihalides do not react, but when the two halogens are on a carbon α to an aromatic ring[808] or on a cyclopropane ring,[804] both halogens can be replaced by R; e.g., $PhCHCl_2 \rightarrow PhCHMe_2$. However, 1,2-dibromides give exclusive elimination[809] (reaction **7-27**). R′ in R'_2CuLi may be primary alkyl, vinyl, allyl, or aryl. However, secondary and tertiary alkyl coupling can be achieved (on primary RX) by the use of $R'_2CuLi \cdot PBu_3$[810] (though this procedure introduces problems in the workup) or by the use of PhS(R′)CuLi,[811] which selectively couples a secondary or tertiary R′ with a primary iodide RI to give RR′.[812] The fact that R'_2CuLi do not react with ketones provides a method for the alkylation of ketones[813] (see also



$$\mathbf{R_2C(Br){-}C({=}O){-}R'' + R'_2CuLi \longrightarrow R_2C(R'){-}C({=}O){-}R''}$$

reactions **0-97**, **0-101**), though halogen-metal exchange (**2-38**) is a side reaction and can become the main reaction.[814]

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[800] Semmelhack, Helquist, and Gorzynski, *J. Am. Chem. Soc.* **94,** 9234 (1972).

[801] Kauffmann and Sahm, *Angew. Chem. Int. Ed. Engl.* **6,** 85 (1967) [*Angew. Chem.* **79,** 101]; Toda and Takehira, *J. Chem. Soc., Chem. Commun.* 174 (1975).

[802] Jones, *J. Org. Chem.* **32,** 1667 (1967).

[803] Sayles and Kharasch, *J. Org. Chem.* **26,** 4210 (1961).

[804] Corey and Posner, *J. Am. Chem. Soc.* **89,** 3911 (1967), **90,** 5615 (1968); Whitesides, Fischer, San Filippo, Bashe, and House, *J. Am. Chem. Soc.* **91,** 4871 (1969); Bergbreiter and Whitesides, *J. Org. Chem.* **40,** 779 (1975).

[805] For a review of this reaction, see Posner, *Org. React.* **22,** 253–400 (1975). For a review of organocopper reagents, see Normant, *Synthesis* 63–80 (1972).

[806] Kalli, Landor, and Landor, *J. Chem. Soc., Perkin Trans. 1* 1347 (1973).

[807] Corey and Posner, Ref. 804; Klein and Levene, *J. Am. Chem. Soc.* **94,** 2520 (1972).

[808] Posner and Brunelle, *Tetrahedron Lett.* 293 (1972).

[809] Posner and Ting, *Synth. Commun.* **3,** 281 (1973).

[810] Whitesides, Fischer, San Filippo, Bashe, and House, Ref. 804.

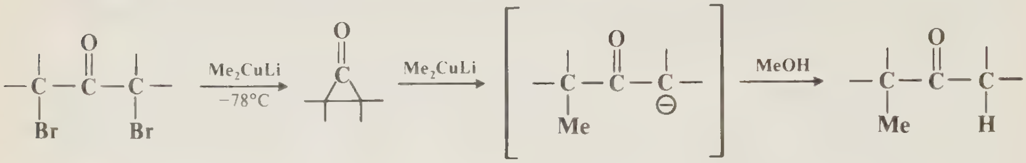
[811] Prepared as in Ref. 816, or by treatment of PhSCu with RLi: Posner, Brunelle, and Sinoway, *Synthesis* 662 (1974).

[812] Posner, Whitten, and Sterling, *J. Am. Chem. Soc.* **95,** 7788 (1973); Posner and Whitten, *Tetrahedron Lett.* 1815 (1973).

[813] Dubois, Lion, and Moulineau, *Tetrahedron Lett.* 177 (1971); Dubois and Lion, *Tetrahedron* **31,** 1227 (1975).

[814] See Corey and Posner, Ref. 804; Wakselman and Mondon, *Tetrahedron Lett.* 4285 (1973).

When α,α′-dibromo ketones are treated with Me_2CuLi in ether at −78°C and the mixture quenched with methanol, *mono*methylation takes place[815] (no dimethylation is observed). It has been suggested that the reaction involves initial cyclization (reaction **0-86**) to a cyclopropanone,



139 **140**

followed by nucleophilic attack to give the enolate ion **140** which is protonated by the methanol. If methyl iodide is added instead of methanol, an α,α′-dimethyl ketone is obtained, presumably from SN2 attack by **140** on methyl iodide (reaction **0-97**). Only halides which are highly reactive to SN2 attack (e.g., methyl and benzyl halides) react successfully with **140.** Primary, secondary, *and tertiary* monoalkylation of **139** can be achieved if **139** is treated with a lithium *t*-butoxy(alkyl)copper reagent[816] instead of Me_2CuLi. For example, 2,6-dibromocyclohexanone, treated with lithium *t*-butoxy(*t*-butyl)copper, gave 66% 2-*t*-butylcyclohexanone. This is one of the few methods for introducing a tertiary alkyl group α to a carbonyl group. With an unsymmetrical α,α′-dibromo ketone, monomethylation takes place predominantly on the less substituted side when the incoming group is large, but this predominance decreases with decreasing size until, with methyl, an approximately 1 : 1 mixture of both products is obtained.

R'_2CuLi reagents can be prepared by mixing 2 mol of RLi with 1 mol of cuprous halide in ether solution at low temperatures[816a] (reaction **2-34**), or by dissolving an alkylcopper compound in an alkyllithium solution. The analogous R_3MnLi and R_3FeLi also give coupling reactions but are less effective.[817]

A much older reaction is the coupling of alkyl halides with Grignard reagents.[818] Grignard reagents have the advantage that they are usually simpler to prepare than the corresponding R'_2CuLi, but the reaction is much narrower in scope. Grignard reagents couple only with active halides: allylic (though allylic rearrangements are common) and benzylic. They also couple with tertiary alkyl halides, but in low yields (30 to 50%). Aryl Grignard reagents usually give better yields in these reactions than alkyl Grignard reagents. Furthermore, because Grignard reagents react with the C=O group (reactions **6-31, 6-34**), they cannot be used to couple with halides containing ketone, COOH, or amide functions. Though the coupling of Grignard reagents with ordinary alkyl halides is usually not useful for synthetic purposes, small amounts of symmetrical coupling product are commonly formed while Grignard reagents are being prepared. The usual method for the preparation of Grignard reagents consists of the addition of the halide to magnesium in ether. The coupling products arise from reaction of some of the RMgX which is initially formed with fresh RX which is being added to the solution. Grignard reagents can be made to couple with alkyl halides in good yields by the use of certain catalysts. Among these are Cu(I) salts, which permit the coupling of Grignard reagents with primary alkyl halides in good yield[819]

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[815] Posner and Sterling, *J. Am. Chem. Soc.* **95,** 3076 (1973). See also Posner, Sterling, Whitten, Lentz, and Brunelle, *J. Am. Chem. Soc.* **97,** 107 (1975); Lion and Dubois, *Tetrahedron* **31,** 1223 (1975).

[816] Prepared by treating CuI with *t*-BuOLi in tetrahydrofuran at 0°C and adding RLi to this solution.

[816a] An improved method is given by House, Chu, Wilkens, and Umen, *J. Org. Chem.* **40,** 1460 (1975).

[817] Corey and Posner, *Tetrahedron Lett.* 315 (1970). See also Corey, Yamamoto, Herron, and Achiwa, *J. Am. Chem. Soc.* **92,** 6635 (1970).

[818] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 1046–1165, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

[819] Tamura and Kochi, *J. Am. Chem. Soc.* **91,** 1485 (1971), *Synthesis* 303 (1971), *J. Organomet. Chem.* **42,** 205 (1972); Onuma and Hashimoto, *Bull. Chem. Soc. Jpn.* **45,** 2582 (1972).

(organocopper salts are probably intermediates here), and iron(III) complexes, which allow the coupling of Grignard reagents and vinyl halides.[820] Grignard reagents couple with only one halogen of a dihalide, provided the second halogen is at least two carbons away, if the reaction is carried out in tetrahydrofuran in the presence of lithium tetrachlorocuprate.[821] Grignard reagents

$$\mathrm{RMgX + Br(CH_2)_nBr} \xrightarrow[\text{THF}]{\mathrm{Li_2CuCl_4}} \mathrm{R(CH_2)_nBr} \qquad n = 3 \text{ or more}$$

prepared from primary alkyl or aryl halides can be coupled with vinyl or aryl halides in high yields in the presence of a nickel(II) catalyst.[822] Among the catalysts used have been dichloro 1,2-bis(diphenylphosphine)ethane nickel(II) and nickel(II) acetonylacetonate. Grignard reagents prepared from secondary halides also give this reaction, but isomerization to a primary group competes.[823] When a chiral nickel(II) catalyst is used, optically active hydrocarbons can be prepared from achiral reagents.[824]

Other organometallic compounds have also been used to couple with alkyl halides. Organosodium and organopotassium compounds are more reactive than Grignard reagents and couple even with less reactive halides. The difficulty is in preparing and keeping them long enough for the alkyl halide to be added. With particularly stable organosodium or organopotassium reagents, such as triphenylmethylsodium, coupling can be accomplished even with primary and secondary halides. Alkenes can be prepared by the coupling of vinyllithium compounds with primary halides.[825] Organoaluminum compounds couple very well with tertiary (to give products containing a quaternary carbon) and benzylic halides at −78°C.[826] This reaction can also be applied to allylic, secondary, and some primary halides, but here several days standing at room temperature is required (see also reaction **0-90**). Vinylaluminum compounds couple with allylic halides to give 1,4-dienes.[827] Arylpalladium salts "ArPdX" prepared from arylmercury compounds and lithium palladium chloride couple with allylic chlorides in moderate yields, though allylic rearrangements can occur.[828] The advantage of this procedure is that the aryl group may contain nitro, ester, or aldehyde groups, etc., which cannot be present in a Grignard reagent.

Much study has been devoted to the mechanisms of these reactions, but firm conclusions are still lacking, in part because the mechanisms vary depending on the metal, the R group, the catalyst, if any, and the reaction conditions. Two basic pathways can be envisioned: a nucleophilic substitution process (which might be S_N1 or S_N2) and a free-radical mechanism:

$$\mathrm{RX + R'M} \longrightarrow \underset{\text{Solvent cage}}{\left|\begin{array}{c}\mathrm{R\cdot + R'\cdot} \\ \mathrm{+\ MX}\end{array}\right|} \longrightarrow \mathrm{RR'}$$

It is necessary to postulate the solvent cage because, if the radicals were completely free, the products would be about 50% RR′, 25% RR, and 25% R′R′, and this is generally not the case; in most of these reactions RR′ is the predominant or exclusive product.[829] An example where an Sn2 mechanism has been demonstrated (by the finding of inversion of configuration at R) is the reaction between allylic or benzylic lithium reagents with secondary halides.[830] Similarly, inversion has been shown in the reaction of 2-bromobutane with Ph_2CuLi.[810] The fact that in some of these cases the reaction may be successfully applied to aryl and vinyl substrates indicates that a simple Sn process cannot be the only mechanism. One possibility is that the reagents first undergo an exchange reaction: $ArX + RM \rightarrow RX + ArM$; and then a nucleophilic substitution takes place. On the other hand, there is much evidence that many coupling reactions involving organometallic reagents with simple alkyl groups occur by free-radical mechanisms. Among the evidence is the observation of CIDNP in reactions of alkyl halides with simple organolithium reagents[831] (see p. 171), the detection of free radicals by esr spectroscopy[832] (p. 170), and the formation of 2,3-dimethyl-2,3-diphenylbutane when the reaction was carried out in the presence of cumene[833] (this product is formed when a free-radical abstracts a hydrogen from cumene to give $Ph\dot{C}Me_2$, which dimerizes). Evidence for free-radical mechanisms has also been found for the coupling of alkyl halides with simple organosodium compounds (Wurtz),[834] and with Grignard reagents.[835] Free radicals have also been implicated in the metal-ion-catalyzed coupling of alkyl and aryl halides with Grignard reagents.[836]

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[820] Tamura and Kochi, *Synthesis* 303 (1971), *J. Am. Chem. Soc.* **91,** 1487 (1971); Neumann and Kochi, *J. Org. Chem.* **40,** 599 (1975); Smith and Kochi, *J. Org. Chem.* **41,** 502 (1976).

[821] Friedman and Shani, *J. Am. Chem. Soc.* **96,** 7101 (1974).

[822] Corriu and Masse, *J. Chem. Soc., Chem. Commun.* 144 (1972); Tamao, Sumitani, and Kumada, *J. Am. Chem. Soc.* **94,** 4374 (1972); Tamao, Zembayashi, Kiso, and Kumada, *J. Organomet. Chem.* **55,** C91 (1973). See also Davies, Done, and Hey, *J. Chem. Soc. C* 2506 (1969).

[823] Tamao, Kiso, Sumitani, and Kumada, *J. Am. Chem. Soc.* **94,** 9268 (1972); Kiso, Tamao, and Kumada, *J. Organomet. Chem.* **50,** C12 (1973).

[824] Consiglio and Botteghi, *Helv. Chim. Acta* **56,** 460 (1973).

[825] Linstrumelle, *Tetrahedron Lett.* 3809 (1974); Millon, Lorne, and Linstrumelle, *Synthesis* 434 (1975).

[826] Miller, *J. Org. Chem.* **31,** 908 (1966); Kennedy, *J. Org. Chem.* **35,** 532 (1970). See also Kennedy and Sivaram, *J. Org. Chem.* **38,** 2262 (1973).

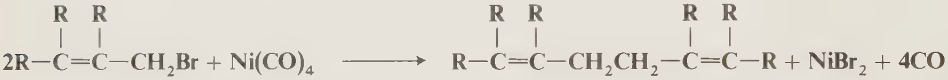
[827] Lynd and Zweifel, *Synthesis* 658 (1974).

[828] Heck, *J. Am. Chem. Soc.* **90,** 5531 (1968).

For symmetrical coupling of organometallic reagents ($2RM \rightarrow RR$), see reactions **4-34** to **4-36**.

OS **I,** 186; **III,** 121; **IV,** 748; **V,** 1092; **55,** 62, 103.

0-88 Allylic and Propargylic Coupling with a Halide Substrate



$$2R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2Br + Ni(CO)_4 \longrightarrow R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2CH_2-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-R + NiBr_2 + 4CO$$

Because of the presence of the 1,5-diene moiety in many naturally occurring compounds, a great deal of effort has been expended in searching for methods to couple allylic groups.[837] In one of these methods, allylic halides, tosylates, and acetates can be symmetrically coupled by treatment with nickel carbonyl at room temperature in a solvent such as tetrahydrofuran or dimethylformamide to give 1,5-dienes.[838] The order of halide reactivity is $I > Br > Cl$. With unsymmetrical allylic substrates, coupling nearly always takes place at the less substituted end. The reaction can be performed intramolecularly: large (11- to 20-membered) rings can be made in good yields (60 to 80%) by the use of high dilution. An example[839] is:

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[829] When a symmetrical distribution of products *is* found, this is evidence for a free-radical mechanism: the solvent cage is not efficient and breaks down.

[830] Sauer and Braig, *Tetrahedron Lett.* 4275 (1969); Sommer and Korte, *J. Org. Chem.* **35,** 22 (1970); Korte, Kinner, and Kaska, *Tetrahedron Lett.* 603 (1970). See also Schlosser and Fouquet, *Chem. Ber.* **107,** 1162, 1171 (1974).

[831] Ward, Lawler, and Cooper, *J. Am. Chem. Soc.* **91,** 746 (1969); Lepley and Landau, *J. Am. Chem. Soc.* **91,** 748 (1969); Leshina, Sagdeev, Kamkha, Shein, and Molin, *J. Org. Chem. USSR* **8,** 2412 (1972). For a review, see Ward, Lawler, and Cooper, in Lepley and Closs, "Chemically Induced Magnetic Polarization," pp. 281–322, John Wiley & Sons, New York, 1973.

[832] Russell and Lamson, *J. Am. Chem. Soc.* **91,** 3967 (1969).

[833] Bryce-Smith, *Bull. Soc. Chim. Fr.* 1418 (1963). See also D'yachkovskii and Shilov, *Russ. Chem. Rev.* **35,** 300–307 (1966), pp. 304–306.

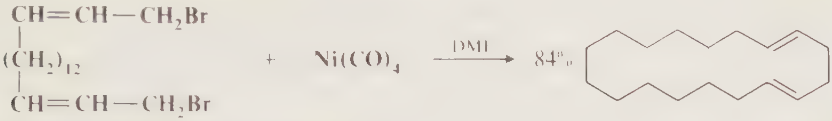
[834] Garst and Cox, *J. Am. Chem. Soc.* **92,** 6389 (1970); Kasukhin and Gragerov, *J. Org. Chem. USSR* **7,** 2087 (1971); Garst and Hart, *J. Chem. Soc., Chem. Commun.* 215 (1975).

[835] Gough and Dixon, *J. Org. Chem.* **33,** 2148 (1968); Ward, Lawler, and Marzilli, *Tetrahedron Lett.* 521 (1970); Kasukhin, Ponomarchuk, and Buteiko, *J. Org. Chem. USSR* **8,** 673 (1972); Singh, Tayal, and Nigam, *J. Organomet. Chem.* **42,** C9 (1972).

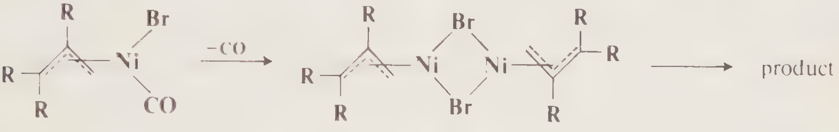
[836] Norman and Waters, *J. Chem. Soc.* 950 (1957); Frey, *J. Org. Chem.* **26,** 5187 (1961); Slaugh, *J. Am. Chem. Soc.* **83,** 2734 (1961); Davies, Hey, and Tiecco, *J. Chem. Soc.* 7062 (1965); Davies, Done, and Hey, *J. Chem. Soc. C* 1392, 2021, 2506 (1969); Abraham and Hogarth, *J. Organomet. Chem.* **12,** 1, 497 (1968); Tamura and Kochi, *J. Am. Chem. Soc.* **93,** 1483, 1485, 1487 (1971), *J. Organomet. Chem.* **31,** 289 (1971), **42,** 205 (1972); Allen, Lawler, and Ward, *J. Am. Chem. Soc.* **95,** 1692 (1973), *Tetrahedron Lett.* 3303 (1973).

[837] In this section are discussed methods in which one molecule is a halide. For other allylic coupling reactions, see **0-87**, **0-90**, **0-91**, and **4-32**.

[838] For reviews, see Semmelhack, *Org. React.* **19,** 115–198 (1972), pp. 162–170; Baker, *Chem. Rev.* **73,** 487–530 (1973), pp. 512–517; Heimbach, Jolly, and Wilke, *Adv. Organomet. Chem.* **8,** 29–86 (1970), pp. 30–39.



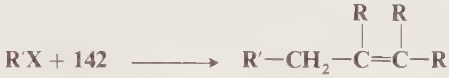
The mechanism is not completely understood, but it is likely that the allylic compound reacts with $Ni(CO)_4$ to give one or more π complexes, of which one may be **141**, which can then lose



141 **142**

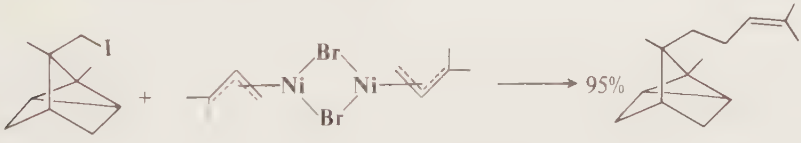
CO to give a π-allylnickel bromide (**142**) which then reacts further, perhaps with CO, to give the product. The complexes **142** can be isolated from the solution and crystallized as stable solids.

Unsymmetrical coupling can be achieved by treating an alkyl halide directly with **142**[840] in a



$$R'X + \mathbf{142} \longrightarrow R'{-}CH_2{-}\overset{\overset{\displaystyle R}{|}}{C}{=}\overset{\overset{\displaystyle R}{|}}{C}{-}R$$

polar aprotic solvent[841] (**142** do not react with alkyl halides in hydrocarbon or ether-type solvents). An example is the synthesis of α-santalene (**143**).[841]



143

Once again, as shown in the example, unsymmetrical allylic groups couple at the less substituted end. In this case too the mechanism is not completely known, but it cannot be simple nucleophilic substitution, since aryl and vinyl halides undergo the reaction as well as or better than simple primary bromides. The order of halide reactivity is I > Br > Cl and, for example, in a molecule containing both I and Cl it is possible for the I to react while the Cl is unaffected. Hydroxy or carbonyl groups in the alkyl halide do not interfere. When **142** reacts with an allylic halide, a mixture of three products is obtained, because of halogen-metal interchange. For example, allyl bromide treated with **142** prepared from methallyl bromide gave an approximately statistical mixture of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene.[842]

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[839] Corey and Wat, *J. Am. Chem. Soc.* **89**, 2757 (1967). See also Corey and Hamanaka, *J. Am. Chem. Soc.* **89**, 2758 (1967); Corey and Helquist, *Tetrahedron Lett.* 4091 (1975).

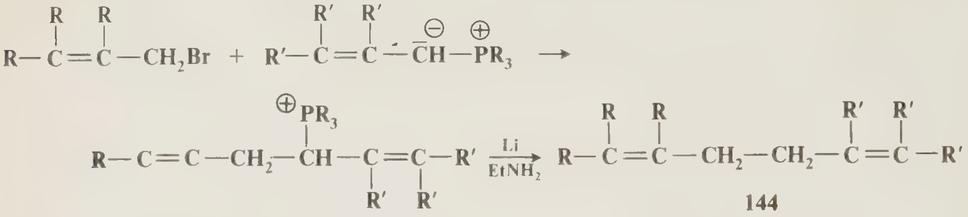
[840] For a discussion of the preparation and handling of π-allylnickel halides, see Semmelhack, Ref. 838, pp. 144–146.

[841] Corey and Semmelhack, *J. Am. Chem. Soc.* **89**, 2755 (1967). For a review, see Semmelhack, Ref. 838, pp. 147–162.

[842] Corey, Semmelhack, and Hegedus, *J. Am. Chem. Soc.* **90**, 2416 (1968).

Symmetrical coupling of allylic halides can also be accomplished by heating with magnesium in ether,[843] with a cuprous iodide–dialkylamide complex,[843a] or with iron powder in dimethylformamide.[844] The coupling of two different allyl groups has been achieved by treatment of an allylic bromide with an allyllithium (generated in situ from an allylic mesitoate) at 0°C in tetrahydrofuran,[845] or with an allylic Grignard reagent in tetrahydrofuran containing HMPT.[846]

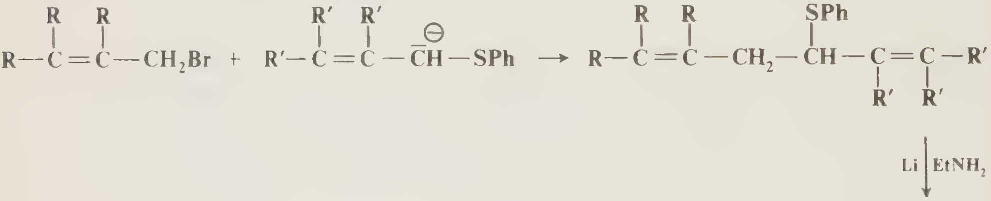
In another method for the coupling of two different allylic groups, a phosphorus ylide (p. 40) derived from one allylic halide combines with another allylic halide.[847] The product is a phosphonium salt which must be reduced (with lithium in ethylamine), but this method has the advantage that, unlike most of the methods previously discussed, the coupling preserves the original positions and configurations of the two double bonds: no allylic rearrangements take place. A similar method involves coupling of an allylic halide with a carbanion derived from a β,γ-unsaturated thioether.[848] In this case too the original positions and configurations of the double bonds are preserved, and a group (here the SPh group) must be removed to give the 1,5-diene.



$$R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2Br + R'-\overset{R'}{\overset{|}{C}}=\overset{R'}{\overset{|}{C}}-\overset{\ominus}{C}H-\overset{\oplus}{P}R_3 \longrightarrow$$

$$R-C=C-CH_2-\overset{\oplus PR_3}{\overset{|}{C}H}-\underset{R'}{\underset{|}{C}}=\underset{R'}{\underset{|}{C}}-R' \xrightarrow[EtNH_2]{Li} R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2-CH_2-\overset{R'}{\overset{|}{C}}=\overset{R'}{\overset{|}{C}}-R'$$

144



$$R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2Br + R'-\overset{R'}{\overset{|}{C}}=\overset{R'}{\overset{|}{C}}-\overset{\ominus}{C}H-SPh \longrightarrow R-\overset{R}{\overset{|}{C}}=\overset{R}{\overset{|}{C}}-CH_2-\overset{SPh}{\overset{|}{C}H}-\underset{R'}{\underset{|}{C}}=\underset{R'}{\underset{|}{C}}-R' \xrightarrow[EtNH_2]{Li}$$

144

In a method for propargylating an alkyl halide without allylic rearrangement, the halide is treated with lithio-1-trimethylsilylpropane (**145**) which is a lithium compound protected by an $SiMe_3$ group.[849] Attack by the ambident nucleophile at its 1 position, which gives an allene, takes place only to a small extent, because of steric blockage by the large $SiMe_3$ group. The $SiMe_3$ group is easily removed by treatment with Ag^+ followed by CN^-. **145** is prepared by treating propynyllithium with Me_3SiCl to give $MeC{\equiv}CSiMe_3$ from which a proton is removed with BuLi.

$$RX + Li\overset{3}{C}H_2-C{\equiv}\overset{1}{C}-SiMe_3 \longrightarrow RCH_2-C{\equiv}C-SiMe_3 \xrightarrow[2.\ CN^-]{1.\ Ag^+} R-CH_2-C{\equiv}CH$$

145

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[843] Turk and Chanan, *Org. Synth.* **III**, 121.

[843a] Kitagawa, Oshima, Yamamoto, and Nozaki, *Tetrahedron Lett.* 1859 (1975).

[844] Hall and Hurley, *Can. J. Chem.* **47**, 1238 (1969).

[845] Katzenellenbogen and Lenox, *J. Org. Chem.* **38**, 326 (1973).

[846] Stork, Grieco, and Gregson, *Tetrahedron Lett.* 1393 (1969); Grieco, *J. Am. Chem. Soc.* **91**, 5660 (1969).

[847] Axelrod, Milne, and van Tamelen, *J. Am. Chem. Soc.* **92**, 2139 (1970).

[848] Biellmann and Ducep, *Tetrahedron Lett.* 3707 (1969). See also Oshima, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **95**, 7926 (1973).

[849] Corey and Kirst, *Tetrahedron Lett.* 5041 (1968); Corey, Kirst, and Katzenellenbogen, *J. Am. Chem. Soc.* **92**, 6314 (1970).

R may be primary or allyl. In an alternative procedure,[850] the halide is treated with the propargyl Grignard reagent and the product subsequently trimethylsilylated.

OS **III,** 121; **IV,** 748; **52,** 115.

0-89 Coupling of Organometallic Reagents with Esters of Sulfuric and Sulfonic Acids

$$\mathbf{ROSO_2OR' + R''_2CuLi \longrightarrow RR''}$$

Lithium dialkylcopper reagents couple with alkyl tosylates.[851] High yields are obtained with primary tosylates; secondary tosylates give lower yields. Aryl tosylates do not react. Tosylates and other sulfonates and sulfates also couple with Grignard reagents,[852] most often those prepared from aryl or benzylic halides. Alkyl sulfates and sulfonates generally make better substrates in the reaction with Grignard reagents than the corresponding alkyl halides (reaction **0-87**). The method is useful for primary and secondary R. Allylic tosylates can be symmetrically coupled with $Ni(CO)_4$ (see reaction **0-88**).

OS **I,** 471; **II,** 47, 360.

0-90 Coupling Involving Alcohols

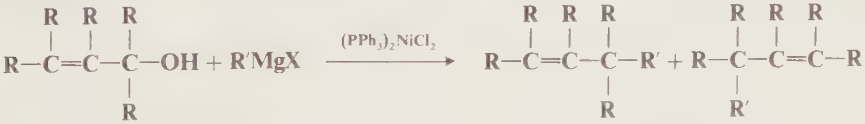
$$\mathbf{2ROH \xrightarrow[-78\text{ C}]{\text{MeLi–TiCl}_3} RR}$$

Allylic or benzylic alcohols can be symmetrically coupled by treatment with methyllithium and titanium trichloride at −78 C,[853] or by refluxing with $TiCl_3$ and $LiAlH_4$.[853a] When the substrate is an allylic alcohol, the reaction is not regiospecific, but a mixture of normal coupling and allylically rearranged products is found. Applying the reaction to a mixture of two different alcohols gives an approximately statistical mixture of RR, R′R, and R′R′, but better yields of RR′ can be obtained by the use of an excess of one alcohol. A free-radical mechanism is involved.[854]

Tertiary alcohols react with trimethylaluminum at 80 to 200 C to give methylation.[855] The

$$\mathbf{R_3COH + Me_3Al \xrightarrow{80\ 200\text{ C}} R_3CMe}$$

presence of side products from elimination and rearrangement, as well as the lack of stereospecificity,[856] indicate an S_N1 mechanism. The reaction can also be applied to primary and secondary alcohols if these contain an aryl group in the α-position. Higher trialkylaluminums are far less suitable, because reduction competes with alkylation (see also reactions of Me_3Al with ketones, **6-31,** and with carboxylic acids, **6-34**). Allylic alcohols couple with Grignard reagents in the presence of dichlorobis(triphenylphosphine)nickel.[857] Both normal products and products of allylic



$$\mathrm{R{-}\overset{R}{\overset{|}{C}}{=}\overset{R}{\overset{|}{C}}{-}\underset{\underset{R}{|}}{\overset{R}{\overset{|}{C}}}{-}OH + R'MgX \xrightarrow{(PPh_3)_2NiCl_2} R{-}\overset{R}{\overset{|}{C}}{=}\overset{R}{\overset{|}{C}}{-}\underset{\underset{R}{|}}{\overset{R}{\overset{|}{C}}}{-}R' + R{-}\underset{\underset{R'}{|}}{\overset{R}{\overset{|}{C}}}{-}\overset{R}{\overset{|}{C}}{=}\overset{R}{\overset{|}{C}}{-}R}$$

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[850] Ireland, Dawson, and Lipinski, *Tetrahedron Lett.* 2247 (1970).

[851] Johnson and Dutra, *J. Am. Chem. Soc.* **95,** 7777, 7783 (1973).

[852] For a review, see Ref. 818, pp. 1277–1286.

[853] Sharpless, Hanzlik, and van Tamelen, *J. Am. Chem. Soc.* **90,** 209 (1968).

[853a] Mc Murry and Silvestri, *J. Org. Chem.* **40,** 2687 (1975).

[854] van Tamelen, Åkermark, and Sharpless, *J. Am. Chem. Soc.* **91,** 1552 (1969).

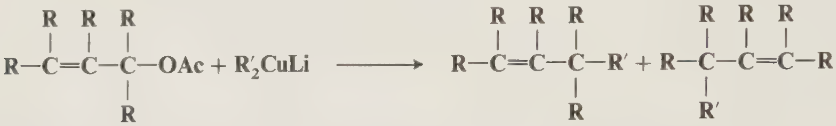
[855] Meisters and Mole, *J. Chem. Soc., Chem. Commun.* 595 (1972); Harney, Meisters, and Mole, *Aust. J. Chem.* **27,** 1639 (1974).

[856] Salomon and Kochi, *J. Org. Chem.* **38,** 3715 (1973).

[857] Chuit, Felkin, Frajerman, Roussi, and Swierczewski, *Chem. Commun.* 1604 (1968); Felkin and Swierczewski, *Tetrahedron Lett.* 1433 (1972).

rearrangement are produced. R′ may be alkyl or aryl, but must lack a β-hydrogen (e.g., Me, $PhCH_2$ give the reaction, but not Et), since otherwise the allylic alcohol is simply reduced to an alkene. A π complex between the nickel and the allylic compound is an intermediate.

0-91 Coupling of Organometallic Reagents with Carboxylic Esters



$$\mathrm{R{-}\overset{R}{C}{=}\overset{R}{C}{-}\underset{R}{\overset{R}{C}}{-}OAc + R'_2CuLi \longrightarrow R{-}\overset{R}{C}{=}\overset{R}{C}{-}\underset{R}{\overset{R}{C}}{-}R' + R{-}\underset{R'}{\overset{R}{C}}{-}\overset{R}{C}{=}\overset{R}{C}{-}R}$$

Lithium dialkylcopper reagents couple with allylic acetates to give normal coupling products, or those resulting from allylic rearrangement, depending on the substrate.[858] With propargyl substrates, the products are allenes.[859] Allenes are also obtained when propargyl acetates are treated

$$\mathrm{RC{\equiv}C{-}CR_2{-}OAc + R'_2CuLi \longrightarrow RR'C{=}C{=}CR_2}$$

with methylmagnesium iodide.[860] Lithium dialkylcopper reagents also give normal coupling products with enol acetates of β-dicarbonyl compounds.[861] Allylic acetates can be symmetrically coupled by treatment with $Ni(CO)_4$ (reaction **0-88**).

0-92 Coupling of Grignard Reagents with Compounds Containing the Ether Linkage[861a]

$$\mathrm{R_2C(OR')_2 + R''MgX \longrightarrow R_2CR''(OR') + R'OMgX}$$

$$\mathrm{RC(OR')_3 + R''MgX \longrightarrow RCR''(OR')_2 + R'OMgX}$$

Acetals, ketals, and ortho esters[862] react with Grignard reagents to give, respectively, ethers and acetals (or ketals). The latter can be hydrolyzed to aldehydes or ketones (reaction **0-7**). This procedure is a way of converting a halide R″X (which may be alkyl, aryl, vinyl, or alkynyl) to an aldehyde R″CHO, increasing the length of the carbon chain by one carbon. The ketone synthesis generally gives lower yields. Tertiary amines can be prepared by the reaction of amino ethers with Grignard reagents:[863]

$$\mathrm{R_2N{-}CH_2{-}OR' + R''MgX \longrightarrow R_2N{-}CH_2{-}R''}$$

Amino thioethers R_2NCH_2SAr behave similarly.[864] Alkynyl ethers can be alkylated with primary, secondary, or tertiary alkyl- or aryllithium reagents: $R'C{\equiv}COR'' + RLi \rightarrow R'C{\equiv}CR$.[865] An addition-elimination mechanism has been suggested for this reaction.

Ordinary ethers are not cleaved by Grignard reagents (in fact, diethyl ether and tetrahydrofuran are the most common solvents for Grignard reagents), though more active organometallic compounds often do cleave them.[866] Phenolic ethers have been cleaved by heating to a high temperature with Grignard reagents.

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[858] Rona, Tökes, Tremble, and Crabbé, *Chem. Commun.* 43 (1969); Anderson, Henrick, and Siddall, *J. Am. Chem. Soc.* **92,** 735 (1970).

[859] Rona and Crabbé, *J. Am. Chem. Soc.* **91,** 3289 (1969); Luche, Barreiro, Dollat, and Crabbé, *Tetrahedron Lett.* 4615 (1975).

[860] Roumestant and Gore, *Bull. Soc. Chim. Fr.* 591, 598 (1972).

[861] Casey, Marten, and Boggs, *Tetrahedron Lett.* 2071 (1973); Casey and Marten, *Synth. Commun.* **3,** 321 (1973), *Tetrahedron Lett.* 925 (1974). See also Posner and Brunelle, *J. Chem. Soc., Chem. Commun.* 907 (1973); Kobayashi, Takei, and Mukaiyama, *Chem. Lett.* 1097 (1973).

[861a] For a review, see Trofimov and Korostova, *Russ. Chem. Rev.* **44,** 41–55 (1975).

[862] For a review of the reaction with ortho esters, see DeWolfe, Ref. 359, pp. 44–45, 224–230.

[863] For example, see Miginiac and Mauzé, *Bull. Soc. Chim. Fr.* 2544 (1968).

[864] Pollak, Trifunac, and Grillot, *J. Org. Chem.* **32,** 272 (1967); Ref. 863.

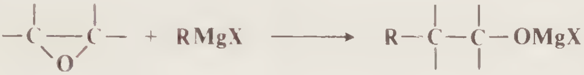
[865] Kooyman, Hendriks, Montijn, Brandsma, and Arens, *Recl. Trav. Chim. Pays-Bas* **87,** 69 (1968).

$$\mathrm{ROAr + R''MgX \longrightarrow RR'' + ArOMgX}$$

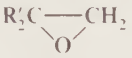
Also see reaction **0-93.**

OS **II,** 323; **III,** 701. Also see OS **V,** 431.

0-93 The Reaction of Organometallic Reagents with Epoxides



The reaction between Grignard reagents and epoxides is very valuable and is often used to increase the length of a carbon chain by two carbons.[867] The Grignard reagent may be aromatic or aliphatic, though tertiary Grignard reagents give low yields. As expected for an SN2 process, attack is at the less substituted carbon. Lithium dialkylcopper reagents also give the reaction, often producing higher yields, and have the additional advantage that they do not react with ester or ketone groups so that the epoxide ring of epoxy esters and ketones may be selectively attacked.[868]



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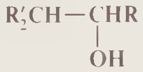
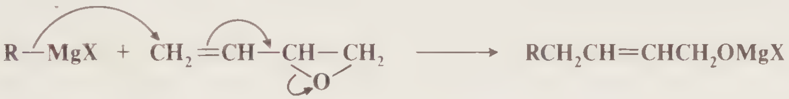


147

When *gem*-disubstituted epoxides (**146**) are treated with Grignard reagents (and sometimes other epoxides), the product may be **147;** that is, the new alkyl group may appear on the same carbon as the OH. In such cases, the epoxide is isomerized to an aldehyde or a ketone before reacting with the Grignard reagent. Halohydrins are often side products.

When the substrate is a vinyl epoxide, Grignard reagents generally give a mixture of the normal product and the product of allylic rearrangement:[869]



The latter often predominates. In the case of R_2CuLi, allylic rearrangement takes place almost exclusively.[869]

OS **I,** 306.

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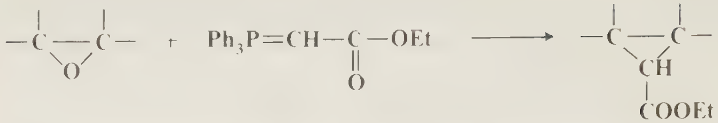
[866] For a review of the reactions of ethers with Grignard reagents, see Ref. 818, pp. 1013–1045.

[867] For reviews, see Gaylord and Becker, *Chem. Rev.* **49,** 413–533 (1951); and Ref. 818, pp. 961–1012. For a thorough discussion, see Schaap and Arens, *Recl. Trav. Chim. Pays-Bas* **87,** 1249 (1968).

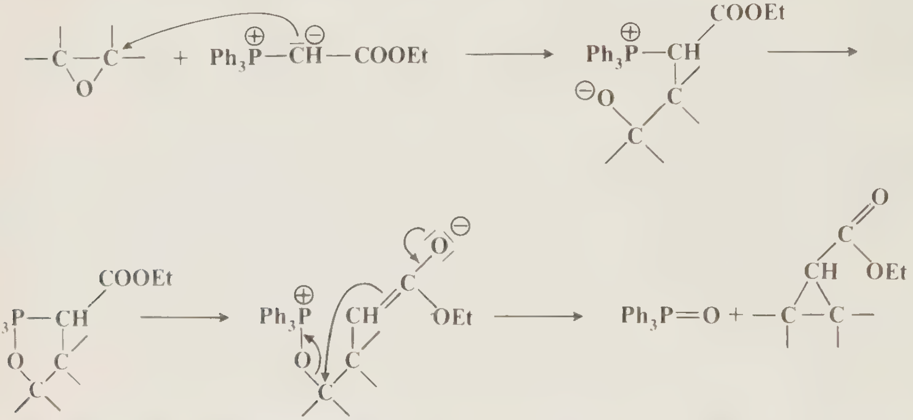
[868] Herr, Wieland, and Johnson, *J. Am. Chem. Soc.* **92,** 3813 (1970); Herr and Johnson, *J. Am. Chem. Soc.* **92,** 4979 (1970); Johnson, Herr, and Wieland, *J. Org. Chem.* **38,** 4263 (1973); Hartman, Livinghouse, and Rickborn, *J. Org. Chem.* **38,** 4346 (1973); Hudrlik, Peterson, and Rona, *J. Org. Chem.* **40,** 2265 (1975).

[869] Anderson, *J. Am. Chem. Soc.* **92,** 4978 (1970); Herr and Johnson, Ref. 868; Johnson, Herr, and Wieland, Ref. 868.

0-94 The Conversion of Epoxides to Cyclopropanes

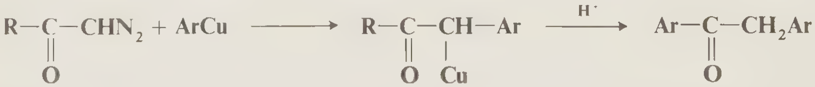


The treatment of epoxides with certain phosphorus ylides gives substituted cyclopropanes[870] in a reaction which is mechanistically related to reaction **0-93.** In this reaction the initial attack on the epoxide is similar to that of the Grignard reagent:



The final step is also a nucleophilic substitution, with $OPPh_3$ as the leaving group. The use of $Bu_3P{=}CHCOOEt$ instead of $Ph_3P{=}CHCOOEt$ led to the predominant formation of unsaturated esters instead of ester-substituted cyclopropanes.[871] Nucleophilic attack by phosphorus ylides is also found in reaction **0-114** and in the Wittig reaction **(6-47)**.

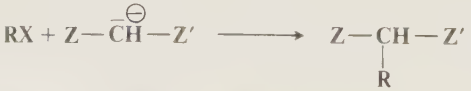
0-95 Arylation of Diazo Ketones and Diazo Esters



$$R-\underset{\underset{O}{\|}}{C}-CHN_2 + ArCu \longrightarrow R-\underset{\underset{O}{\|}}{C}-\underset{\underset{Cu}{|}}{CH}-Ar \xrightarrow{H^+} Ar-\underset{\underset{O}{\|}}{C}-CH_2Ar$$

Diazo ketones and diazo esters can be arylated by treatment with an arylcopper compound (prepared from ArLi or ArMgX and CuBr) followed by hydrolysis.[872] The reaction has also been performed on diazoalkanes.

0-96 Alkylation at a Carbon Bearing an Active Hydrogen



$$RX + Z-\overset{\ominus}{\underline{C}}H-Z' \longrightarrow Z-\underset{\underset{R}{|}}{CH}-Z'$$

Compounds which contain two (or three, but this is rare) strong electron-withdrawing groups on a carbon atom are more acidic than compounds without such groups (p. 240) and are easily converted to their corresponding enolate ions (p. 73). These enolate ions can attack alkyl halides, resulting in their alkylation.[873] Z and Z′ may be COOR′, CHO, COR′, $CONR'_2$, COO^-, CN,[874] NO_2, SOR′, SO_2R', SO_2OR', $SO_2NR'_2$, or similar groups. A carbon atom with any two of these, the same or different, will give up a proton (if it has one) to a suitable base. In the case where $Z = NO_2$, a second Z group is not required, since NO_2 is so powerful an electron-withdrawing group. Some commonly used bases are sodium ethoxide and potassium *t*-butoxide, each in its respective alcohol as solvent. With particularly acidic compounds (e.g., β-diketones Z, Z′ = COR′), sodium hydroxide in water or aqueous alcohol or acetone, or even sodium carbonate, is a strong enough base for the reaction. If at least one Z group is COOR′, saponification is a possible side reaction. In addition to the groups listed above, Z may also be phenyl, but if two phenyl groups are on the same carbon, the acidity is less than in the other cases and a stronger base must be used. However, the reaction can be successfully carried out with diphenylmethane, with $NaNH_2$ as the base.[875] The solvent used in the reaction must not be acidic enough to protonate either the enolate ion or the base, which in most cases rules out water. The use of polar aprotic solvents, e.g., dimethylformamide or dimethyl sulfoxide, markedly increases the rate of alkylation[876] but also increases the extent of alkylation at the oxygen rather than the carbon (p. 339).

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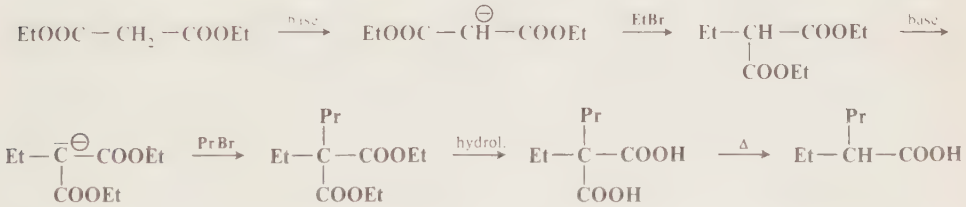
[870] Denney, Vill, and Boskin, *J. Am. Chem. Soc.* **84,** 3944 (1962). For reviews, see Johnson, "Ylid Chemistry," pp. 111–113, Academic Press, Inc., New York, 1966; Trippett, *Q. Rev., Chem. Soc.* **17,** 406–440 (1964), pp. 426–428.

[871] Gerkin and Rickborn, *J. Am. Chem. Soc.* **89,** 5850 (1967).

[872] Cairncross and Sheppard, *J. Am. Chem. Soc.* **90,** 2186 (1968); Sato and Watanabe, *Chem. Commun.* 515 (1969).

Usually the reaction is carried out on a CH_2 group connected to two Z groups. In such cases it is possible to alkylate twice, first removing the proton with a base, then alkylating with RX, then removing the proton from ZCHRZ′, and finally alkylating the resulting enolate ion with the same or a different RX. The reaction is successful for primary and secondary alkyl, allylic (with allylic rearrangement possible), and benzylic RX, but fails for tertiary halides, since these undergo elimination under the reaction conditions (see, however, p. 421). Various functional groups may be present in RX as long as they are not sensitive to base. Side reactions which may cause problems are the above-mentioned competing O-alkylation, elimination (if the enolate ion is a strong enough base), and dialkylation.

An important example of this reaction is the *malonic ester synthesis*, in which both Z groups are COOEt. The product can be hydrolyzed and decarboxylated (reaction **2-39**) to give a carboxylic acid. An illustration is the preparation of 2-ethylpentanoic acid from malonic ester:



$$EtOOC{-}CH_2{-}COOEt \xrightarrow{\text{base}} EtOOC{-}\overset{\ominus}{C}H{-}COOEt \xrightarrow{EtBr} Et{-}\underset{COOEt}{CH}{-}COOEt \xrightarrow{\text{base}}$$

$$Et{-}\underset{COOEt}{\overset{\ominus}{C}}{-}COOEt \xrightarrow{PrBr} Et{-}\underset{COOEt}{\overset{Pr}{C}}{-}COOEt \xrightarrow{\text{hydrol.}} Et{-}\underset{COOH}{\overset{Pr}{C}}{-}COOH \xrightarrow{\Delta} Et{-}\overset{Pr}{CH}{-}COOH$$

It is obvious that many carboxylic acids of the formulas RCH_2COOH and RR′CHCOOH can be synthesized by this method (for some other ways of preparing such acids, see reactions **0-98**, **0-100**, and **0-101**). Another important example is the *acetoacetic ester synthesis*, in which Z is COOEt and Z′ is $COCH_3$. In this case the product can be decarboxylated with acid or dilute base (reaction **2-39**) to give a ketone, or cleaved with concentrated base (reaction **2-42**) to give an ester and a salt of acetic acid:

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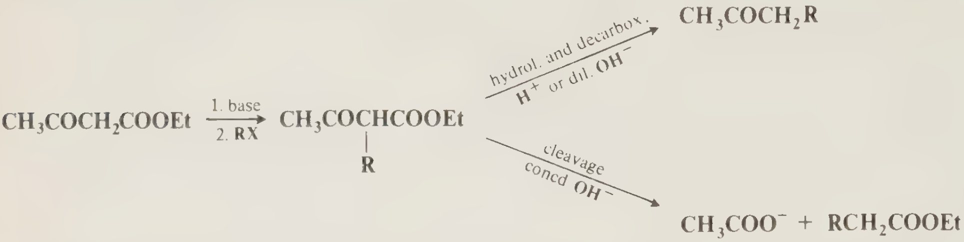
[873] For discussions of reactions **0-96** and **0-97**, see House, "Modern Synthetic Reactions," 2d ed., pp. 492–570, 586–595, W. A. Benjamin, Inc., Menlo Park, Calif., 1972; Carruthers, "Some Modern Methods of Organic Synthesis," pp. 1–29, Cambridge University Press, London, 1971.

[874] For a review of the reactions of malononitrile $CH_2(CN)_2$, see Freeman, *Chem. Rev.* **69**, 591–624 (1969).

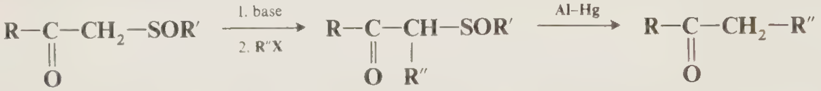
[875] Murphy, Hamrick, and Hauser, *Org. Synth.* **V**, 523.

[876] Zaugg, Horrom, and Borgwardt, Ref. 264; Zaugg, Ref. 264; Zaugg, Dunnigan, Michaels, Swett, Wang, Sommers, and DeNet, *J. Org. Chem.* **26**, 644 (1961).



$$CH_3COCH_2COOEt \xrightarrow[2.\ RX]{1.\ \text{base}} \underset{\underset{R}{|}}{CH_3COCHCOOEt} \begin{cases} \xrightarrow[H^+ \text{ or dil. } OH^-]{\text{hydrol. and decarbox.}} CH_3COCH_2R \\ \xrightarrow[\text{concd } OH^-]{\text{cleavage}} CH_3COO^- + RCH_2COOEt \end{cases}$$

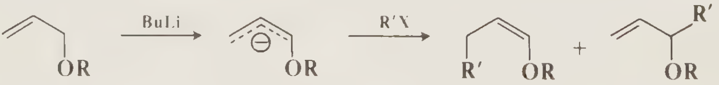
Another way of preparing ketones involves alkylation with primary halides of β-keto sulfoxides[877] or sulfones,[878] e.g.,



$$R-\underset{\underset{O}{\|}}{C}-CH_2-SOR' \xrightarrow[2.\ R''X]{1.\ \text{base}} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{R''}{|}}{CH}-SOR' \xrightarrow{\text{Al-Hg}} R-\underset{\underset{O}{\|}}{C}-CH_2-R''$$

since the product in this case is easily reduced to a ketone in high yields with aluminum amalgam or by electrolysis.[879] The β-keto sulfoxides or sulfones are easily prepared (reaction **0-112**). Other examples of the reaction are the *cyanoacetic ester synthesis*, in which Z is COOEt and Z′ is CN (as in the malonic ester synthesis, the product here can be hydrolyzed and decarboxylated), and the *Sorensen* method of amino acid synthesis, in which the reaction is applied to N-acetylaminomalonic ester $(EtOOC)_2CHNHCOCH_3$. Hydrolysis and decarboxylation of the product in this case gives an α-amino acid. The amino group is also frequently protected by conversion to a phthalimido group.

The reaction is not limited to $Z-CH_2-Z'$ compounds. Other acidic C—H hydrogens, which include, for example, the methyl hydrogens of α-aminopyridines, the methyl hydrogens of ynamines of the form $CH_3C{\equiv}CNR_2$[880] (the product in this case can be hydrolyzed to an amide $RCH_2CH_2CONR_2$), the CH_2 hydrogens of cyclopentadiene and its derivatives (p. 46), hydrogens connected to a triple-bond carbon (reaction **0-102**), and the hydrogen of HCN (reaction **0-103**), can also be removed with a base and the resulting ion alkylated (see also reactions **0-97** to **0-100**). A proton can be removed from an allylic ether by treatment with an alkyllithium at about -70 C (at higher temperatures the Wittig rearrangement—**8-26**—takes place) to give the ion **148** which reacts with alkyl halides to give the products **149** and/or **150**.[881]



148 **149** **150**

Alkylation always takes place at the most acidic position of a reagent molecule; for example, acetoacetic ester (CH_3COCH_2COOEt) is alkylated at the methylene and not at the methyl group, because the former is more acidic than the latter and hence gives up its proton to the base.

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[877] Gassman and Richmond, *J. Org. Chem.* **31**, 2355 (1966). Such sulfoxides can be alkylated on the other side of the C=O group by the use of two moles of base (p. 337): Kuwajima and Iwasawa, *Tetrahedron Lett.* 107 (1974).

[878] House and Larson, *J. Org. Chem.* **33**, 61 (1968).

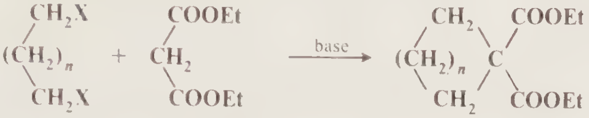
[879] Lamm and Samuelsson, *Acta Chem. Scand.* **23**, 691 (1969).

[880] Corey and Cane, *J. Org. Chem.* **35**, 3405 (1970).

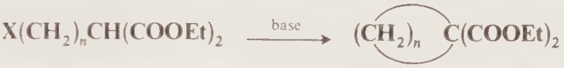
[881] Evans, Andrews, and Buckwalter, *J. Am. Chem. Soc.* **96**, 5560 (1974); Still and Macdonald, *J. Am. Chem. Soc.* **96**, 5561 (1974).

However, if 2 moles of base are used, then not only is the most acidic proton removed but also the second most acidic. Alkylation of this doubly charged anion then takes place at the less acidic position (see p. 337). This technique has been used to alkylate many compounds in the second most acidic position.[333]

When ω,ω′-dihalides are used, ring closures may be effected:



The method has been used to close rings of from three ($n = 0$) to seven members, although five-membered-ring closures proceed in highest yields. Another ring-closing method involves internal alkylation.[882]

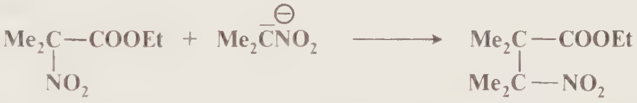


The mechanism of these reactions is usually S_N2, with inversion taking place at a chiral RX, though in certain instances there is evidence that a radical-anion mechanism is involved.[883] Tertiary alkyl groups can be introduced by an S_N1 mechanism if the ZCH_2Z' compound (not the enolate ion) is treated with a tertiary carbonium ion generated in situ from an alcohol or alkyl halide and BF_3 or $AlCl_3$,[884] or with a tertiary alkyl perchlorate.[885]

Other leaving groups are sometimes used. Sulfates, sulfonates, and epoxides give the expected products. Acetals can behave as substrates, one OR group being replaced by ZCHZ′ in a reaction similar to **0-92.**[886] Ortho esters behave similarly, but the product loses R′OH to give an enol ether.[887] The NR_2 group from Mannich bases such as $RCOCH_2CH_2NR_2$ can also act as a

$$ZCH_2Z' + RC(OR')_3 \xrightarrow{Ac_2O} ZZ'C{=}CROR'$$

leaving group in this reaction[888] (elimination-addition mechanism, p. 315). A nitro group can be displaced from α-nitro esters, ketones, nitriles, and α,α-dinitro compounds by salts of nitro paraffins, e.g.,[889]



$$\underset{\displaystyle NO_2}{Me_2C}{-}COOEt + Me_2\overset{\ominus}{C}NO_2 \longrightarrow \begin{array}{l}Me_2C{-}COOEt\\ \quad|\\ Me_2C{-}NO_2\end{array}$$

but this is probably not nucleophilic substitution. A radical-ion mechanism has been suggested.[890] However, with α-nitro sulfones it is the sulfone group which is displaced, rather than the nitro group.[891] Palladium can be the leaving atom if the substrate is a π-allylpalladium complex. The ion of malonic ester reacts with such complexes in the presence of triphenylphosphine,[892] e.g.,

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[882] For example, see Knipe and Stirling, *J. Chem. Soc. B* 67 (1968); Winkler and Gosselck, *Tetrahedron Lett.* 2433 (1970); Gosselck and Winkler, *Tetrahedron Lett.* 2437 (1970). For a review of this method as applied to the synthesis of β-lactams, see Bose, Manhas, Chatterjee, and Abdulla, *Synth. Commun.* **1**, 51-73 (1971).

[883] Kerber, Urry, and Kornblum, *J. Am. Chem. Soc.* **87**, 4520 (1965); Kornblum, Michel, and Kerber, *J. Am. Chem. Soc.* **88**, 5660, 5662 (1966); Russell and Danen, *J. Am. Chem. Soc.* **88**, 5663 (1966). See also Suama, Sugita, and Ichikawa, *Bull. Chem. Soc. Jpn.* **44**, 1999 (1971).

[884] For example, see Boldt and Militzer, *Tetrahedron Lett.* 3599 (1966); Crimmins and Hauser, *J. Org. Chem.* **32**, 2615 (1967); Boldt, Militzer, Thielecke, and Schulz, *Justus Liebigs Ann. Chem.* **718**, 101 (1968).

[885] Boldt and Thielecke, *Angew. Chem. Int. Ed. Engl.* **5**, 1044 (1966) [*Angew Chem.* **78**, 1058]; Boldt, Ludwieg, and Militzer, *Chem. Ber.* **103**, 1312 (1970).

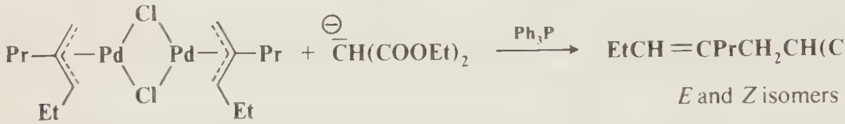
[886] Yufit, Krasnaya, Levchenko, and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 123 (1967); Aleskerov, Yufit, and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **21**, 2279 (1972).

[887] For a review, see DeWolfe, Ref. 359, pp. 231-266.

[888] For a review, see Brewster and Eliel, *Org. React.* **7**, 99-197 (1953).

[889] For a review, see Kornblum, *Angew. Chem. Int. Ed. Engl.* **14**, 734-745 (1975) [*Angew. Chem.* **87**, 797-808].

[890] Russell and Danen, *J. Am. Chem. Soc.* **90**, 347 (1968); Ref. 889. See also Kornblum and Stuchal, *J. Am. Chem. Soc.* **92**, 1804 (1970).

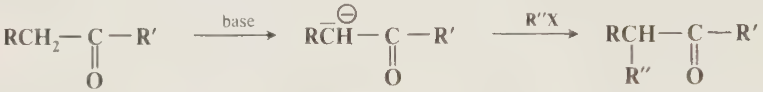


$$+ \ \overset{\ominus}{C}H(COOEt)_2 \xrightarrow{Ph_3P} EtCH{=}CPrCH_2CH(COOEt)_2$$

E and *Z* isomers

OS **I,** 248, 250; **II,** 262, 279, 384, 474; **III,** 213, 219, 397, 405, 495, 705; **IV,** 10, 55, 288, 291, 623, 641, 962; **V,** 76, 187, 514, 523, 559, 743, 767, 785, 848, 1013; **53,** 21, 70; **54,** 97; **55,** 57.

0-97 Alkylation of Ketones, Nitriles, and Esters



$$RCH_2-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{\text{base}} R\overset{\ominus}{\underline{C}}H-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{R''X} R\underset{\underset{R''}{|}}{C}H-\underset{\underset{O}{\|}}{C}-R'$$

Ketones, nitriles, and esters can be alkylated[893] in the α-position in a reaction similar to **0-96,**[873] but a stronger base must be employed, since only one activating group is present. Some typical bases are *t*-BuOK, sodium *t*-pentoxide, $NaNH_2$, Et_2NLi, $(iso\text{-}Pr)_2NLi$, and Ph_3CNa. The base lithium N-isopropyl-N-cyclohexylamide is particularly successful for esters[894] and for nitriles.[895] Some of these bases are strong enough to convert the ketone, nitrile, or ester completely to its conjugate base; others (especially *t*-BuOK) convert a significant fraction of the molecules. In the latter case, aldol condensation (**6-40**) or Claisen condensation (**0-111**) may be a side reaction, since both the free molecule and its conjugate base are present at the same time. In general, it is better to use a base strong enough to convert the starting compound completely. Protic solvents are generally not suitable because they protonate the base (though of course this is not a problem with a conjugate pair, such as *t*-BuOK in *t*-BuOH). Some common solvents are 1,2-dimethoxyethane, dimethylformamide, tetrahydrofuran, and liquid ammonia. Good results can be obtained by the use of butylmagnesium bromide as the base in the solvent HMPT.[896]

As in reaction **0-96,** the alkyl halide may be primary or secondary. Tertiary halides give elimination. Even primary and secondary halides give predominant elimination if the enolate ion is a strong enough base (e.g., the enolate ion from Me_3CCOMe).[897] Also as in **0-96,** this reaction can be used to close rings.[898]

The reaction can be applied to aldehydes, indirectly, by alkylating an imine derivative of the aldehyde.[899] The derivative is easily prepared (**6-15**), and the product easily hydrolyzed to the aldehyde (**6-2**). Either or both R groups may be hydrogen, so that mono-, di-, and trisubstituted

[891] Kornblum, Boyd, and Ono, *J. Am. Chem. Soc.* **96,** 2580 (1974).

[892] Trost and Fullerton, *J. Am. Chem. Soc.* **95,** 292 (1973); Trost and Dietsche, *J. Am. Chem. Soc.* **95,** 8200 (1973); Trost, Dietsche, and Fullerton, *J. Org. Chem.* **39,** 737 (1974); Trost and Weber, *J. Am. Chem. Soc.* **97,** 1611 (1975).

[893] For a review of alkylation of esters and nitriles, see Cope, Holmes, and House, *Org. React.* **9,** 107–331 (1957).

[894] Rathke and Lindert, *J. Am. Chem. Soc.* **93,** 2319 (1971). See also Cregge, Herrmann, Lee, Richman, and Schlessinger, *Tetrahedron Lett.* 2425 (1973).

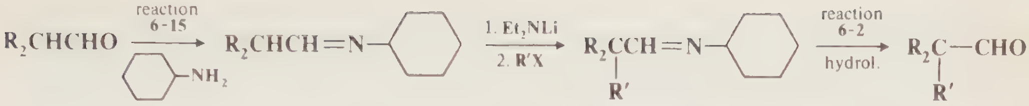
[895] Watt, *Tetrahedron Lett.* 707 (1974).

[896] Fauvarque and Fauvarque, *Bull. Soc. Chim. Fr.* 160 (1969).

[897] Zook, Kelly, and Posey, *J. Org. Chem.* **33,** 3477 (1968).

[898] For example, see Etheredge, *J. Org. Chem.* **31,** 1990 (1966); Wilcox and Whitney, *J. Org. Chem.* **32,** 2933 (1967); Bird and Stirling, *J. Chem. Soc. B* 111 (1968); Stork, Gardner, Boeckman, and Parker, *J. Am. Chem. Soc.* **95,** 2014 (1973); Stork and Boeckman, *J. Am. Chem. Soc.* **95,** 2016 (1973); Stork, Cama, and Coulson, *J. Am. Chem. Soc.* **96,** 5268 (1974); Stork and Cohen, *J. Am. Chem. Soc.* **96,** 5270 (1974). In the latter case, the substrate moiety is an epoxide function.

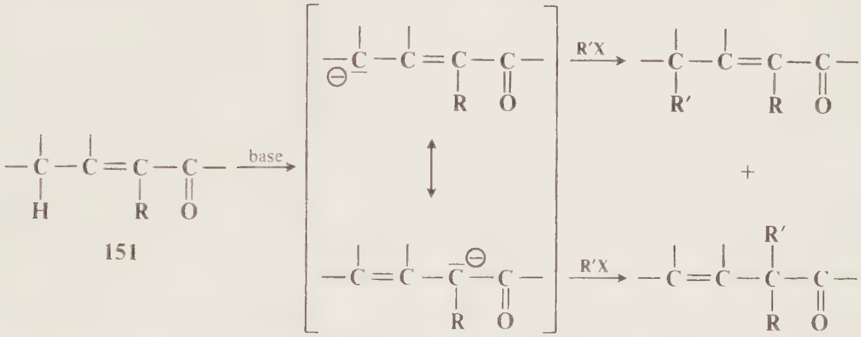
[899] Cuvigny and Normant, *Bull. Soc. Chim. Fr.* 3976 (1970); Cuvigny, Le Borgne, Larchevêque, and Normant, *J. Organomet. Chem.* **70,** C5 (1974), *Synthesis* 237 (1976); Cuvigny, Larchevêque, and Normant, *Justus Liebigs Ann. Chem.* 719 (1975).



acetaldehydes can be prepared by this method. R' may be primary alkyl, allylic, or benzylic. Direct alkylation of aldehydes is not generally possible because base treatment of aldehydes normally gives rapid aldol condensation (**6-40**), though aldehydes bearing only one α-hydrogen have been alkylated in moderate yield by the use of a phase-transfer catalyst[900] (p. 358).

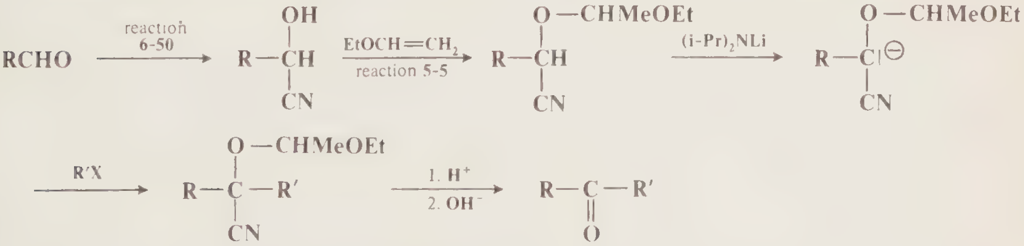
A convenient method for the alkylation of acetonitrile[901] or ethyl acetate[902] involves treatment of an allylic halide with cyanomethylcopper $CuCH_2CN$ prepared by treating MeCN with *n*-BuLi (to give $LiCH_2CN$) followed by CuI, or ethoxymethylcarbonylcopper $CuCH_2COOEt$ prepared from ethyl acetate in a similar manner. This procedure permits preparation of γ,δ-unsaturated nitriles and esters in good yield. These organocopper reagents do not react with ordinary alkyl halides or even with benzyl halides but react smoothly with allylic halides.

In α,β-unsaturated ketones, nitriles, and esters (e.g., **151**), the γ-hydrogen assumes the acidity normally held by the position α to the carbonyl group, especially when R is not hydrogen and


151

so cannot compete. This principle, called *vinylology*, operates because the resonance effect is transmitted through the double bond. However, because of the resonance, alkylation at the α-position (with allylic rearrangement) competes with alkylation at the γ-position and often predominates.[903]

α-Hydroxynitriles (cyanohydrins), protected by conversion to acetals with ethyl vinyl ether (reaction **5-5**), can be easily alkylated with primary or secondary alkyl, or allylic, halides.[904]



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[900] Dietl and Brannock, *Tetrahedron Lett.* 1273 (1973). See also de Graaf, Oosterhoff, and van der Gen, *Tetrahedron Lett.* 1653 (1974).

[901] Corey and Kuwajima, *Tetrahedron Lett.* 487 (1972).

[902] Kuwajima and Doi, *Tetrahedron Lett.* 1163 (1972).

[903] A method for ensuring alkylation at the γ position, but with rather special R'X, is described by Melvin and Trost, *J. Am. Chem. Soc.* **94,** 1790 (1972); Trost and Melvin, *J. Am. Chem. Soc.* **98,** 1204 (1976).

[904] Stork and Maldonado, *J. Am. Chem. Soc.* **93,** 5286 (1971); Stork, Depezay, and d'Angelo, *Tetrahedron Lett.* 389 (1975). See also Deuchert, Hertenstein, and Hünig, *Synthesis* 777 (1973); Hünig and Wehner, *Synthesis* 180 (1975).

Since the cyanohydrins are easily formed from aldehydes (reaction **6-50**) and the product is easily hydrolyzed to a ketone, this is a method for converting an aldehyde RCHO to a ketone RCOR′ (for other methods, see reactions **0-99, 8-10**). R may be aryl or saturated or unsaturated alkyl.

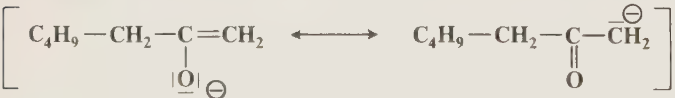
When the compound to be alkylated is a nonsymmetrical ketone, the question arises as to which side will be alkylated. If an α-phenyl or α-vinyl group is present on one side, alkylation goes predominantly on that side. When only alkyl groups are present, the reaction is generally not regiospecific; mixtures are obtained in which sometimes the more alkylated and sometimes the less alkylated side is predominantly alkylated. Which product is found in higher yield depends on the nature of the substrate, the cation, and the solvent. In any case, di- and trisubstitution are frequent, and it is often difficult to stop with the introduction of just one alkyl group. One method for achieving high yields of monoalkylated products is to convert an initial Li or K enolate to an Al enolate by adding Et_3Al to the mixture before adding the alkyl halide.[905] In this case, however, HMPT must be added to the mixture for alkylation to occur in a reasonable amount of time.

Several methods have been developed for ensuring that alkylation takes place regiospecifically on the *desired* side of a ketone.[906] Among these are:

1. Block one side of the ketone by introducing a removable group. Alkylation takes place on the *other* side; the blocking group is then removed.[907] A common reaction for this purpose is formylation with ethyl formate (reaction **0-112**); this generally blocks the less hindered side. The formyl group is easily removed by alkaline hydrolysis (reaction **2-42**).

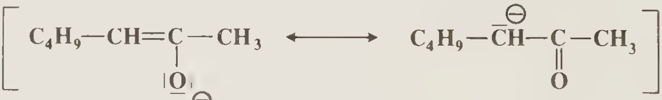
2. Introduce an activating group on one side; alkylation then takes place on *that* side (reaction **0-96**); the activating group is then removed.[907]

3. Prepare the desired one of the two possible enolate ions. The two ions, e.g. **152** and **153** for 2-heptanone, interconvert rapidly only in the presence of the parent ketone or of any stronger acid.[908] In the absence of such acids, it is possible to prepare either **152** or **153** and thus achieve selective alkylation on either the more or less highly alkylated side of the ketone.[909] The desired enolate ion can be obtained by treatment of the corresponding enol acetate with two equivalents of methyllithium in 1,2-dimethoxyethane. Each enol acetate gives the corresponding enolate, e.g.,



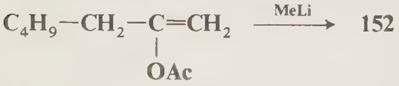
$$\left[C_4H_9-CH_2-\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}=CH_2 \longleftrightarrow C_4H_9-CH_2-\underset{O}{\underset{\|}{C}}-\overset{\ominus}{C}H_2 \right]$$

152

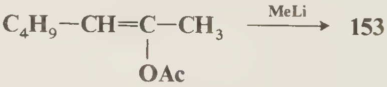


$$\left[C_4H_9-CH=\underset{|\underline{O}|^{\ominus}}{\underset{|}{C}}-CH_3 \longleftrightarrow C_4H_9-\overset{\ominus}{C}H-\underset{O}{\underset{\|}{C}}-CH_3 \right]$$

153



$$C_4H_9-CH_2-\underset{OAc}{\underset{|}{C}}=CH_2 \xrightarrow{MeLi} \mathbf{152}$$



$$C_4H_9-CH=\underset{OAc}{\underset{|}{C}}-CH_3 \xrightarrow{MeLi} \mathbf{153}$$

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[905] Tardella, *Tetrahedron Lett.* 1117 (1969).

[906] For a review, see House, *Rec. Chem. Prog.* **28**, 99–120 (1968).

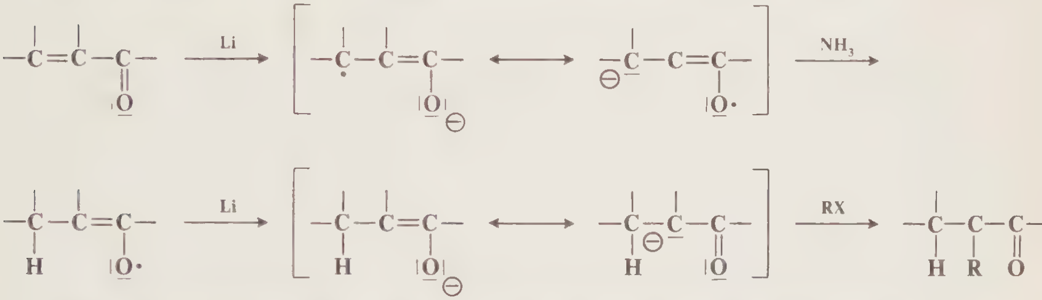
[907] For examples, see House, Ref. 873, pp. 561–563; Carruthers, Ref. 873, pp. 22–23.

[908] House and Trost, *J. Org. Chem.* **30**, 1341 (1965).

[909] House and Trost, *J. Org. Chem.* **30**, 2502 (1965); Whitlock and Overman, *J. Org. Chem.* **34**, 1962 (1969); House, Gall and Olmstead, *J. Org. Chem.* **36**, 2361 (1971). See also Kuwajima and Nakamura, *J. Am. Chem. Soc.* **97**, 3257 (1975).

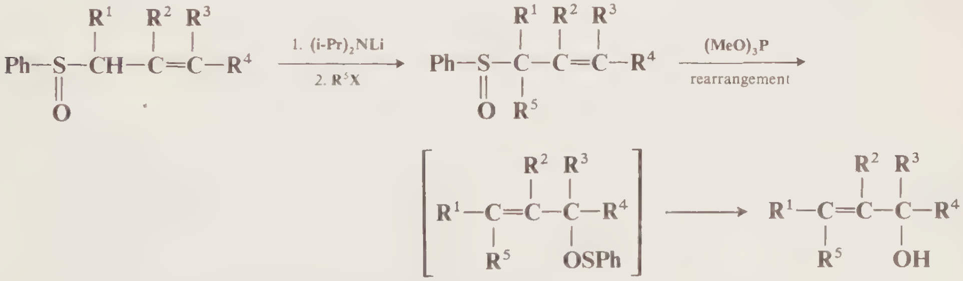
The enol acetates, in turn, can be prepared by treatment of the parent ketone with an appropriate reagent.[909] Such treatment generally gives a mixture of the two enol acetates in which one or the other predominates, depending on the reagent. The mixtures are easily separable.[909] An alternate procedure involves conversion of a trialkylsilyl enol ether[910] or a dialkylboron enol ether[911] (an enol borinate, see p. 434) to the corresponding enolate ion.

4. Begin not with the ketone itself, but with an α,β-unsaturated ketone in which the double bond is present on the side where alkylation is desired. Upon treatment with lithium in liquid NH_3, such a ketone is reduced to an enolate ion. When the alkyl halide is added, it must react with the enolate ion on the side where the double bond was.[912] Of course, this method is not actually an alkylation of the ketone, but of the α,β-unsaturated ketone, though the product is the same as if the saturated ketone had been alkylated on the desired side.



Among other methods for the preparation of alkylated ketones are: (1) the Stork enamine reaction (**2-17**), (2) the acetoacetic ester synthesis (**0-96**), (3) alkylation of β-keto sulfones or sulfoxides (**0-96**), (4) acylation of $CH_3SOCH_2^-$ followed by reductive cleavage (**0-112**), (5) treatment of α-halo ketones with lithium dialkylcopper reagents (**0-87**), and (6) treatment of α-halo ketones with trialkylboranes (**0-101**).

Sulfones and sulfonic esters can also be alkylated in the α-position if strong enough bases are used.[913] The alkylation of allylic sulfoxy compounds followed by a [2,3] sigmatropic rearrangement (reaction **8-40**) is a means for the preparation of allylic alcohols:[914]



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[910] Stork and Hudrlik, *J. Am. Chem. Soc.* **90,** 4462 (1968). See also House, Czuba, Gall, and Olmstead, *J. Org. Chem.* **34,** 2324 (1969); Binkley and Heathcock, *J. Org. Chem.* **40,** 2156 (1975).

[911] Pasto and Wojtkowski, *J. Org. Chem.* **36,** 1790 (1971).

[912] Stork, Rosen, Goldman, Coombs, and Tsuji, *J. Am. Chem. Soc.* **87,** 275 (1965); Smith, Huff, Powers, and Caine, *J. Org. Chem.* **32,** 2851 (1967). For similar approaches, see Coates and Sowerby, *J. Am. Chem. Soc.* **93,** 1027 (1971); Näf and Decorzant, *Helv. Chim. Acta* **57,** 1317 (1974).

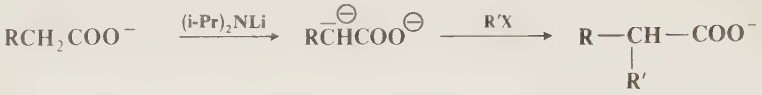
[913] For examples, see Truce, Hollister, Lindy, and Parr, *J. Org. Chem.* **33,** 43 (1968); Truce and Vrencur, *Can. J. Chem.* **47,** 860 (1969), *J. Org. Chem.* **35,** 1226 (1970); Julia and Arnould, *Bull. Soc. Chim. Fr.* 743, 746 (1973); Bird and Stirling, Ref. 898.

[914] Evans, Andrews, Fujimoto, and Wells, *Tetrahedron Lett.* 1385, 1389 (1973).

In most cases the alkylation takes place regiospecifically at the α-position, with little or no γ alkylation (see vinylology, p. 423) taking place. The reaction has been applied to primary and allylic R^5X.

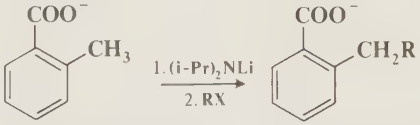
OS **III,** 44, 219, 221, 223, 397; **IV,** 278, 597, 641, 962; **V,** 187, 514, 559, 848; **52,** 33, 39; **54,** 93, 97; **55,** 91.

0-98 Alkylation of Carboxylic Acid Salts



$$RCH_2COO^- \xrightarrow{(i\text{-}Pr)_2NLi} R\overset{\ominus}{C}HCOO^{\ominus} \xrightarrow{R'X} R{-}\underset{R'}{CH}{-}COO^-$$

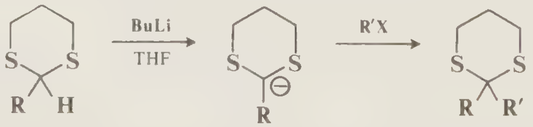
Carboxylic acids can be alkylated in the α-position by conversion of their salts to dianions by treatment with a strong base such as lithium diisopropylamide.[915] The use of Li^+ as the counter-ion is important, because it increases the solubility of the dianionic salt. The reaction has been applied to primary alkyl, allylic, and benzylic halides, and to carboxylic acids of the form RCH_2COOH and RR″CHCOOH. This method, which is an example of the alkylation of a dianion at its more nucleophilic position (see pp. 337, 421), is an alternative to the malonic ester synthesis (**0-96**) as a means of preparing carboxylic acids and has the advantage that acids of the form RR′R″CCOOH can also be prepared. In a related reaction, methylated aromatic acids can be alkylated at the methyl group by a similar procedure.[916] Ortho methyl groups react best



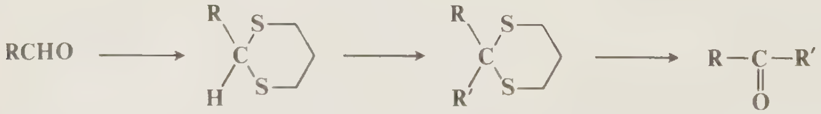
and meta groups most poorly, so it is possible to alkylate just one methyl group when two are present.

OS **V,** 526; **50,** 58.

0-99 Alkylation at a Position α to a Hetero Atom. Alkylation of 1,3-Dithianes



1,3-Dithianes can be alkylated if a proton is first removed by treatment with butyllithium in tetrahydrofuran.[917] Since 1,3-dithianes can be prepared by treatment of an aldehyde or its acetal (see OS **50,** 72) with 1,3-propanedithiol (reaction **6-12**) and can be hydrolyzed (reaction **0-7**), this is a method for the conversion of an aldehyde to a ketone (see also reactions **0-97, 8-10**):

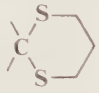


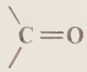
[915] Cregar, *J. Am. Chem. Soc.* **89,** 2500 (1967), **92,** 1397 (1970); Pfeffer and Silbert, *J. Org. Chem.* **35,** 262 (1970); Pfeffer, Silbert, and Chirinko, *J. Org. Chem.* **37,** 451 (1972).

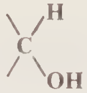
[916] Cregar, *J. Am. Chem. Soc.* **92,** 1396 (1970).

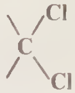
[917] Corey and Seebach, *Angew. Chem. Int. Ed., Engl.* **4,** 1075, 1077 (1965) [*Angew. Chem.* **77,** 1134, 1135]; Seebach, Corey, and Beck, *Chem. Ber.* **107,** 367 (1974); Seebach and Corey, *J. Org. Chem.* **40,** 231 (1975). For reviews, see Seebach, *Synthesis* 17–36 (1969), especially pp. 24–27; Olsen and Currie, in Patai, Ref. 525a, pt. 2, pp. 536–547.

Note that the normal mode of reaction of a carbonyl carbon is reversed. The carbon atom of an aldehyde molecule is normally electrophilic and is attacked by nucleophiles (Chapter 16), but by conversion to the dithiane, this carbon atom has been induced to perform as a nucleophile[918] (see also the similar reaction of cyanohydrin acetals, p. 423). The reaction can be applied to the unsubstituted dithiane (R = H), and one or two alkyl groups can be introduced, so that a wide variety of aldehydes and ketones can be made starting with formaldehyde.[919] R′ may be primary or secondary alkyl or benzylic. Iodides give the best results. The reaction has been used to close rings.[920] A similar synthesis of aldehydes can be performed starting with ethyl ethylthiomethyl sulfoxide $EtSOCH_2SEt$.[921]


A

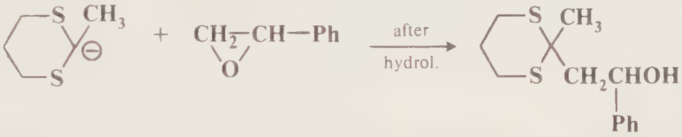

B


C

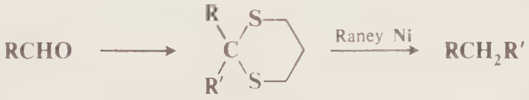

D

The group **A** may be regarded as a structural equivalent for the carbonyl group **B**, since introduction of **A** into a molecule is actually an indirect means of introducing **B**. It is convenient to have a word for units within molecules; such a word is *synthon*, introduced by Corey,[922] which is defined as a structural unit within a molecule which can be formed and/or assembled by known or conceivable synthetic operations. There are many other synthons equivalent to **A** and **B**, for example, **C** (by reactions **6-27** and **9-4**) and **D** (by reactions **0-2** and **6-26**).

Carbanions generated from 1,3-dithianes also react with epoxides[923] to give 1,3-dithiane derivatives of β-hydroxy aldehydes or ketones, e.g.,



Another useful application of this reaction stems from the fact that dithianes can be desulfurated with Raney nickel (reaction **4-37**). Aldehydes can therefore be converted to chain-extended hydrocarbons:[924]



Similar reactions have been carried out with other thioacetals, as well as with compounds containing three thioether groups on a carbon.[925]

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[918] For reviews of such reversals of carbonyl group reactivity, see Seebach and Kolb, *Chem. Ind.* (*London*) 687-692 (1974); Seebach, *Angew. Chem. Int. Ed. Engl.* **8,** 639-649 (1969) [*Angew. Chem.* **81,** 690-700].

[919] For a direct conversion of RX to RCHO, see reaction **0-104.**

[920] For example, see Seebach, Jones, and Corey, *J. Org. Chem.* **33,** 300 (1968); Hylton and Boekelheide, *J. Am. Chem. Soc.* **90,** 6887 (1968); Ogura, Yamashita, Suzuki, and Tsuchihashi, *Tetrahedron Lett.* 3653 (1974).

[921] Richman, Herrmann, and Schlessinger, *Tetrahedron Lett.* 3267 (1973). See also Ogura and Tsuchihashi, *Tetrahedron Lett.* 3151 (1971); Schill and Jones, *Synthesis* 117 (1974); Hori, Hayashi, and Midorikawa, *Synthesis* 705 (1974).

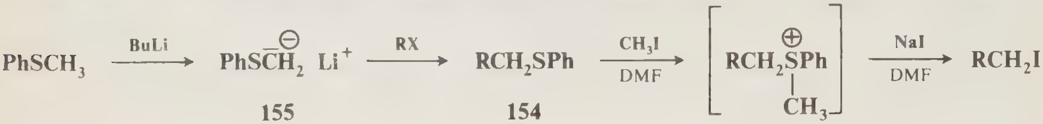
[922] Corey, *Pure Appl. Chem.* **14,** 19-37 (1967), pp. 20-23.

[923] For example, see Corey and Seebach, Ref. 917; Jones and Grayshan, *Chem. Commun.* 141, 741 (1970).

[924] For examples, see Hylton and Boekelheide, Ref. 920; Jones and Grayshan, Ref. 923.

[925] For example, see Seebach, *Angew. Chem. Int. Ed. Engl.* **6,** 442 (1967); [*Angew. Chem.* **79,** 468 (1967)]; Seebach and Steinmüller, *Angew. Chem. Int. Ed. Engl.* **7,** 619 (1968) [*Angew. Chem.* **80,** 617]; Olsson, *Acta Chem. Scand.* **22,** 2390 (1968); Mori, Hashimoto, Takenaka, and Takigawa, *Synthesis* 720 (1975).

The carbanion derived from a 1,3-dithiane is stabilized by two thioether groups. If a strong enough base is used, it is possible to alkylate at a position adjacent to only one such group. For example, benzylic and allylic thioethers ($\mathrm{RSCH_2Ar}$ and $\mathrm{RSCH_2CH{=}CH_2}$) have been successfully alkylated at the carbon adjacent to the sulfur atom.[926] Stabilization by one thioether group has also been used in a method for the homologization of primary halides.[927] Thioanisole is treated

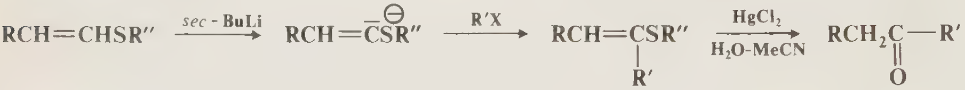


$$\mathrm{PhSCH_3} \xrightarrow{\mathrm{BuLi}} \mathrm{PhS}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{H_2}\ \mathrm{Li^+} \xrightarrow{\mathrm{RX}} \mathrm{RCH_2SPh} \xrightarrow[\mathrm{DMF}]{\mathrm{CH_3I}} \left[\mathrm{RCH_2}\underset{\mathrm{CH_3}}{\overset{\oplus}{\mathrm{S}}}\mathrm{Ph}\right] \xrightarrow[\mathrm{DMF}]{\mathrm{NaI}} \mathrm{RCH_2I}$$

155 **154**

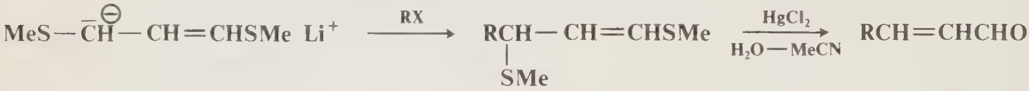
with BuLi to give the corresponding anion[928] which reacts with the halide to give the thioether **154. 154** is then refluxed with a mixture of methyl iodide and sodium iodide in dimethylformamide. By this sequence an alkyl halide RX is converted to its homolog $\mathrm{RCH_2X}$ by a pathway involving only two laboratory steps (the shortest pathway known for this conversion). RX may also be allylic, but here the use of the copper analog of **155** (prepared from **155** and CuI) gives higher yields.[927]

Vinyl sulfides containing an α-hydrogen can also be alkylated[929] by alkyl halides or epoxides. In this case the proton is removed by *sec*-butyllithium. The vinyl sulfide product can be hydrolyzed



$$\mathrm{RCH{=}CHSR''} \xrightarrow{sec\text{-}\mathrm{BuLi}} \mathrm{RCH{=}}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{SR''} \xrightarrow{\mathrm{R'X}} \mathrm{RCH{=}}\underset{\mathrm{R'}}{\mathrm{C}}\mathrm{SR''} \xrightarrow[\mathrm{H_2O\text{-}MeCN}]{\mathrm{HgCl_2}} \mathrm{RCH_2}\underset{\mathrm{O}}{\overset{}{\mathrm{C}}}\mathrm{{-}R'}$$

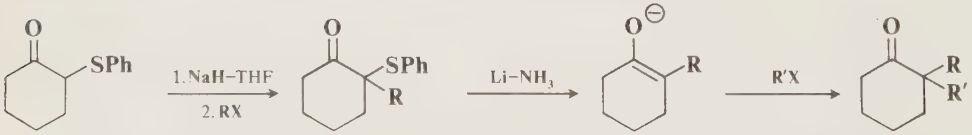
with mercuric chloride in aqueous acetonitrile[930] to give a ketone. In another application, the ion **156**, which can be prepared in three steps from epichlorohydrin, reacts with alkyl halides to



$$\mathrm{MeS{-}}\overset{\ominus}{\bar{\mathrm{C}}}\mathrm{H{-}CH{=}CHSMe\ Li^+} \xrightarrow{\mathrm{RX}} \mathrm{R}\underset{\mathrm{SMe}}{\mathrm{C}}\mathrm{H{-}CH{=}CHSMe} \xrightarrow[\mathrm{H_2O{-}MeCN}]{\mathrm{HgCl_2}} \mathrm{RCH{=}CHCHO}$$

156 **157** **158**

give the bis(methylthio) compound **157**[931] which is easily hydrolyzed. This is a method for converting an alkyl halide RX to an α,β-unsaturated aldehyde **158**, using **156**, which is the synthetic equivalent of the unknown $\overset{\ominus}{\mathrm{H}\bar{\mathrm{C}}}\mathrm{{=}CH{-}CHO}$ ion. α-Phenyl thioaldehydes and thioketones can be *gem*-dialkylated by the following procedure (shown for cyclohexanone):[932]



Alkylation can also be carried out, in certain compounds, at positions α to other hetero atoms. In one application of this, a secondary amine can be alkylated at an α-position if it is first converted to its N-nitroso derivative (reaction **2-50**).[933] The N-nitroso product is easily hydrolyzed

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[926] Biellmann and Ducep, *Tetrahedron Lett.* 5629 (1968), 3707 (1969), *Tetrahedron* **27**, 5861 (1971). See also Narasaka, Hayashi, and Mukaiyama, *Chem. Lett.* 259 (1972).

[927] Corey and Jautelat, *Tetrahedron Lett.* 5787 (1968).

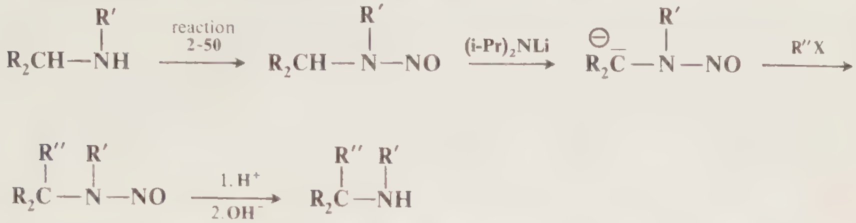
[928] Corey and Seebach, *J. Org. Chem.* **31**, 4097 (1966).

[929] Oshima, Shimoji, Takahashi, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **95**, 2694 (1973).

[930] Corey and Shulman, *J. Org. Chem.* **35**, 777 (1970).

[931] Corey, Erickson, and Noyori, *J. Am. Chem. Soc.* **93**, 1724 (1971).

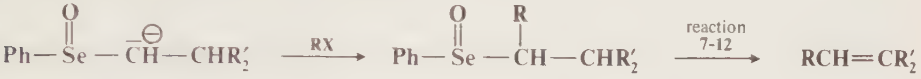
[932] Coates, Pigott, and Ollinger, *Tetrahedron Lett.* 3955 (1974).



$$R_2CH{-}\overset{\overset{R'}{|}}{N}H \xrightarrow{\text{reaction 2-50}} R_2CH{-}\overset{\overset{R'}{|}}{N}{-}NO \xrightarrow{(i\text{-}Pr)_2NLi} R_2\overset{\ominus}{C}{-}\overset{\overset{R'}{|}}{N}{-}NO \xrightarrow{R''X} R_2\overset{\overset{R''}{|}}{C}{-}\overset{\overset{R'}{|}}{N}{-}NO \xrightarrow[2.\ OH^-]{1.\ H^+} R_2\overset{\overset{R''}{|}}{C}{-}\overset{\overset{R'}{|}}{N}H$$

to the product amine.[934] Alkylation has also been reported at a position α to the nitrogen of tertiary amines[935] and α to a chlorine atom.[936]

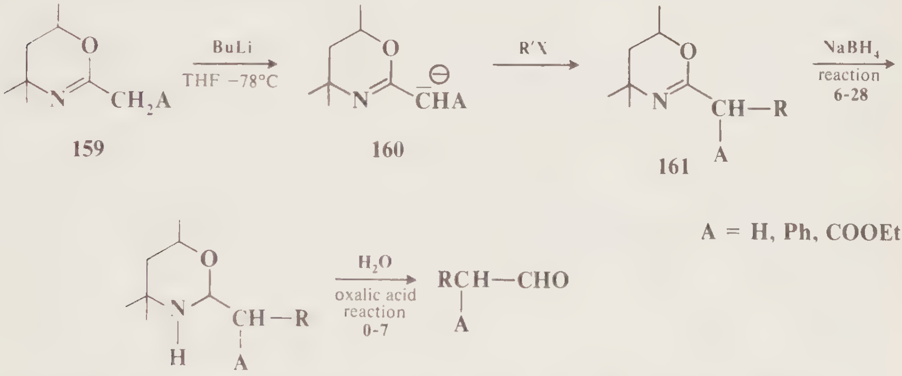
Alkylation at the α-position of selenoxides allows the formation of alkenes, since selenoxides easily undergo elimination (reaction **7-12**):[936a]



$$Ph{-}\overset{\overset{O}{\|}}{Se}{-}\overset{\ominus}{C}H{-}CHR'_2 \xrightarrow{RX} Ph{-}\overset{\overset{O}{\|}}{Se}{-}\overset{\overset{R}{|}}{C}H{-}CHR'_2 \xrightarrow{\text{reaction 7-12}} RCH{=}CR'_2$$

OS **51,** 39, 76; **54,** 27.

0-100 Alkylation of Dihydro-1,3-Oxazine The Meyers Synthesis of Aldehydes, Ketones, and Carboxylic Acids



159 **160** **161**

A = H, Ph, COOEt

A synthesis of aldehydes developed by Meyers[937] begins with the commercially available (or synthesized from 2-methyl-2,4-pentanediol and a nitrile ACH_2CN) dihydro-1,3-oxazine derivatives **159** (A = H, Ph, or COOEt).[938] Though the ions (**160**) prepared from **159** are ambident, they are regiospecifically alkylated at carbon by a wide variety of alkyl bromides and iodides. R may be primary or secondary alkyl, allylic, or benzylic and may carry another halogen or a CN group.[939]

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[933] Seebach and Enders, *Angew. Chem. Int. Ed. Engl.* **11,** 301, 1101 (1972) [*Angew. Chem.* **84,** 350, 1186], *Chem. Ber.* **108,** 1293 (1975).

[934] Fridman, Mukhametshin, and Novikov, *Russ. Chem. Rev.* **40,** 34–50 (1971), pp. 41–42.

[935] Lepley and Khan, *J. Org. Chem.* **31,** 2061, 2064 (1966), *Chem. Commun.* 1198 (1967); Lepley and Giumanini, *J. Org. Chem.* **31,** 2055 (1966).

[936] Hoeg and Lusk, *J. Organomet. Chem.* **5,** 1 (1966).

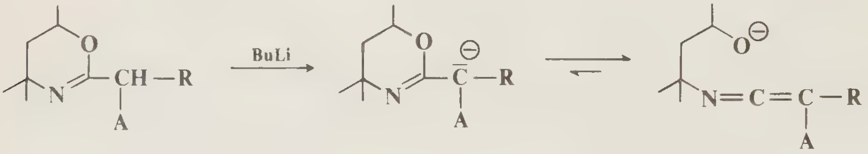
[936a] Reich and Shah, *J. Am. Chem. Soc.* **97,** 3250 (1975).

[937] Meyers, Nabeya, Adickes, Politzer, Malone, Kovelesky, Nolen, and Portnoy, *J. Org. Chem.* **38,** 36 (1973).

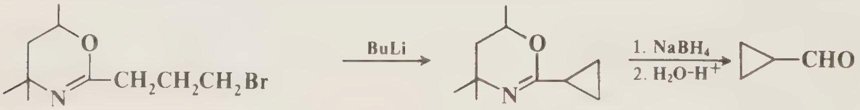
[938] For reviews of the preparation and reactions of **159,** see Schmidt, *Synthesis* 333–350 (1972); Collington, *Chem. Ind. (London)* 987–991 (1973).

[939] Meyers, Malone, and Adickes, *Tetrahedron Lett.* 3715 (1970).

The alkylated oxazine **161** is then reduced and hydrolyzed to give an aldehyde containing two more carbons than the starting RX. This method thus complements reaction **0-99** which converts RX to an aldehyde containing one more carbon. Since A may be H, mono- or disubstituted acetaldehydes can be produced by this method. Reduction with $NaBD_4$ leads to C-1-deuterated aldehydes. If desired, **161** can be alkylated again (provided A is Ph), with the same or a different alkyl halide, to give a trisubstituted aldehyde after reduction and hydrolysis. If A is H, however, **161** cannot be alkylated again, because the ion formed by BuLi treatment of **161** (which is **160** with an R group replacing the hydrogen) tautomerizes[940] to the ketenimine **162**.[941] An exception is found when a halogen is contained in R. In this case, cyclization can be accomplished to close three, four, and five-membered rings, e.g.,[942]



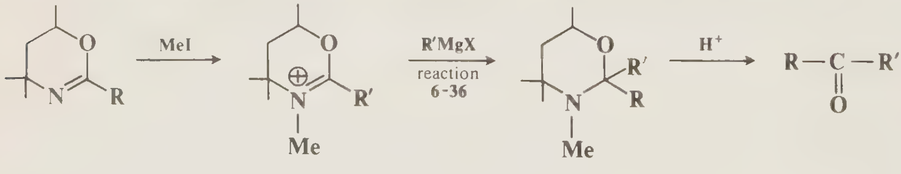
161 **162**



In an alternate procedure, **161** can be hydrolyzed instead of reduced (see reaction **6-2**), producing a carboxylic acid RCHA—COOH.[943]

The ion **160** also reacts with epoxides, to form γ-hydroxy aldehydes after reduction and hydrolysis,[944] and with aldehydes and ketones (reaction **6-42**). Similar aldehyde synthesis has also been carried out with thiazoles[945] and thiazolines[946] (five-membered rings containing N and S in the 1 and 3 positions).

The reaction has been extended to the preparation of ketones:[947] treatment of a dihydro-1,3-oxazine (**163**) with methyl iodide forms the iminium salt **164** (reaction **0-46**) which, when treated



163 **164** **165**

with a Grignard reagent or organolithium compound (reaction **6-36**) produces **165** which can be hydrolyzed to a ketone (for a similar preparation of aldehydes, see reaction **6-36**). R may be alkyl, cycloalkyl, aryl, benzylic, etc., and R′ may be alkyl, aryl, benzylic, or allylic. **159, 161,** and **163** themselves do not react with Grignard reagents.

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[940] Meyers and Smith, *Tetrahedron Lett.* 4355 (1970).

[941] However, this ketinimine can be alkylated, not with RX, but with RM (reaction **2-17**).

[942] Meyers, Adickes, Politzer, and Beverung, *J. Am. Chem. Soc.* **91,** 765 (1969).

[943] Meyers, Politzer, Bandlish, and Malone, *J. Am. Chem. Soc.* **91,** 5886 (1969).

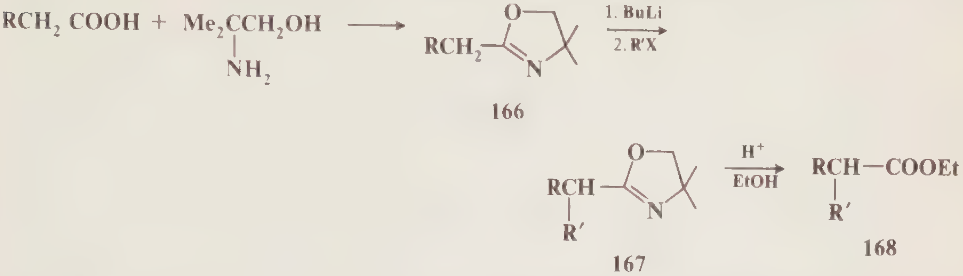
[944] Adickes, Politzer, and Meyers, *J. Am. Chem. Soc.* **91,** 2155 (1969).

[945] Altman and Richheimer, *Tetrahedron Lett.* 4709 (1971).

[946] Meyers and Durandetta, *J. Org. Chem.* **40,** 2021 (1975).

[947] Meyers and Smith, *J. Am. Chem. Soc.* **92,** 1084 (1970); *J. Org. Chem.* **37,** 4289 (1972).

The fact that dihydro-1,3-oxazines do not react with Grignard reagents gives rise to a useful method for the protection of carboxylic acids.[948] These could be converted to dihydro-1,3-oxazines, but in this case it is more convenient to use 2-oxazolines[948a] (**166**) which are readily formed by treatment of the acid with 2-amino-2-methyl-1-propanol [the simplest **166** (R = H) is commercially available].[949] Conversion of a carboxylic acid to a 2-oxazoline permits reaction of a functional group which may be present in R with a Grignard reagent[950] or with $LiAlH_4$[949] without disturbing the oxazoline ring. In a further application, **166** may be alkylated to give **167**[951] which are easily converted directly to the esters **168** by heating in 5 to 7% ethanolic sulfuric acid. **166** and **167** are thus synthons for carboxylic acids, and this is another indirect method for the α alkylation of a carboxylic acid,[952] representing an alternative to the malonic ester synthesis (**0-96**) and to reactions **0-98** and **0-101.** Note that, unlike **159, 166** can be alkylated even if R is alkyl. However, the C=N bond of **166** and **167** cannot be effectively reduced, so that aldehyde synthesis is not feasible here.[953]



166

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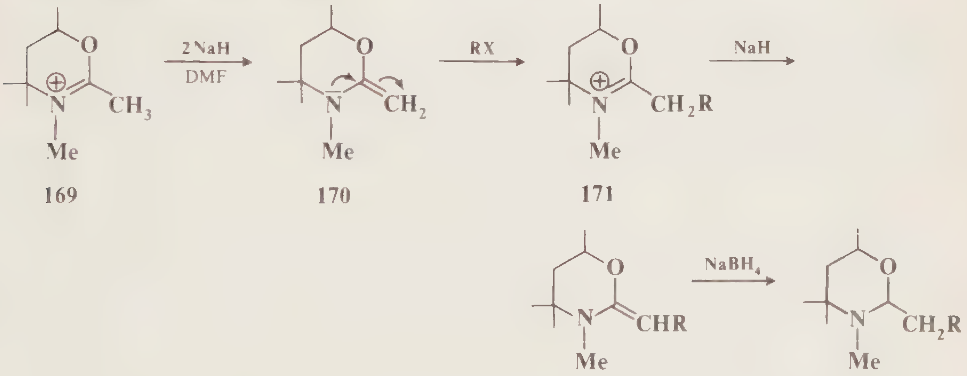
An alternate procedure[954] for aldehyde synthesis begins with **169** which is treated with 2 moles of NaH, the first of which removes a proton to give **170.** An alkyl halide is then added to give **171**



169 **170** **171**

172 **173**

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[948] Meyers, Temple, Haidukewych, and Mihelich, *J. Org. Chem.* **39,** 2787 (1974).

[948a] For a review, see Meyers and Mihelich, *Angew. Chem. Int. Ed. Engl.* **15,** 270–281 (1976) [*Angew. Chem.* **88,** 321–332].

[949] For an alternate method for the conversion of carboxylic acids to **166,** see Haidukewych and Meyers, *Tetrahedron Lett.* 3031 (1972).

[950] Meyers and Temple, *J. Am. Chem. Soc.* **92,** 6644, 6646 (1970).

[951] Meyers, Temple, Nolen, and Mihelich, *J. Org. Chem.* **39,** 2778 (1974); Meyers, Mihelich, and Nolen, *J. Org. Chem.* **39,** 2783 (1974); Meyers, Mihelich, and Kamata, *J. Chem. Soc., Chem. Commun.* 768 (1974).

[952] The method can be adapted to the preparation of optically active carboxylic acids by the use of a chiral reagent: Meyers, Knaus, and Kamata, *J. Am. Chem. Soc.* **96,** 268 (1974); Meyers and Knaus, *J. Am. Chem. Soc.* **96,** 6508 (1974); *Tetrahedron Lett.* 1333 (1974); Meyers, Knaus, and Kendall, *Tetrahedron Lett.* 3495 (1974).

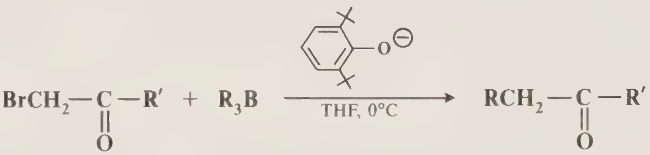
[953] Meyers and Temple, *J. Am. Chem. Soc.* **92,** 6644 (1970).

[954] Meyers and Nazarenko, *J. Am. Chem. Soc.* **94,** 3243 (1972).

which is immediately converted to **172** by the second mole of NaH. **172** is reduced to **173** by $NaBH_4$, and hydrolysis of **173** produces the aldehyde. This method is easier to carry out and requires a shorter reaction time than the original procedure.

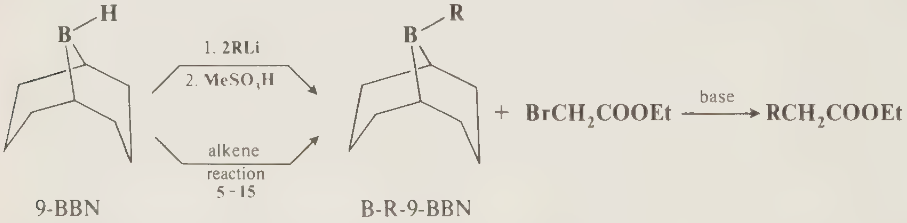
OS **51,** 24.

0-101 Alkylation with Trialkylboranes



$$BrCH_2-\underset{\underset{O}{\|}}{C}-R' + R_3B \xrightarrow[\text{THF, 0°C}]{} RCH_2-\underset{\underset{O}{\|}}{C}-R'$$

Trialkylboranes react rapidly and in high yields with α-halo ketones,[955] α-halo esters,[956] α-halo nitriles,[957] and α-halo sulfonyl derivatives (sulfones, sulfonic esters, sulfonamides)[958] in the presence of a base to give, respectively, alkylated ketones, esters, nitriles, and sulfonyl derivatives.[959] Potassium *t*-butoxide is often a suitable base, but potassium 2,6-di-*t*-butylphenoxide at 0°C in tetrahydrofuran gives better results in most cases, possibly because the large bulk of the two *t*-butyl groups prevents the base from coordinating with the R_3B.[960] The trialkylboranes are prepared by treatment of 3 mol of an alkene with 1 mol of BH_3 (reaction **5-15**). However, the use of R_3B prepared in this way has two disadvantages. With α-halo ketones, boranes containing branched R (e.g., isobutyl, *sec*-butyl) do not react; and with any substrate, 2 moles of R are lost. Both of these disadvantages are overcome by the use of a 9-alkyl-9-borabicyclo[3.3.1]nonane (B-R-9-BBN) in place of an ordinary R_3B.[961] These reagents, which can be prepared by addition of 9-borabicyclo[3.3.1]nonane (9-BBN) to an alkene (see p. 719) or by reaction of 9-BBN with an alkyl- or aryllithium followed by treatment with methanesulfonic acid,[962] react nicely with α-halo esters, α-halo ketones, and α-halo nitriles. When R_3B or B-R-9-BBN prepared from an alkene is used, the R must be an alkyl group containing at least two carbons, but the use of B-R-9-BBN prepared the other way allows R to be methyl or aryl. When the R of B-R-9-BBN contains a γ-halogen, treatment with a base gives a cyclopropane,[963] e.g.,



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[955] Brown, Rogić, and Rathke, *J. Am. Chem. Soc.* **90,** 6218 (1968).

[956] Brown, Rogić, Rathke, and Kabalka, *J. Am. Chem. Soc.* **90,** 818 (1968).

[957] Brown, Nambu, and Rogić, *J. Am. Chem. Soc.* **91,** 6854 (1969).

[958] Truce, Mura, Smith, and Young, *J. Org. Chem.* **39,** 1449 (1974).

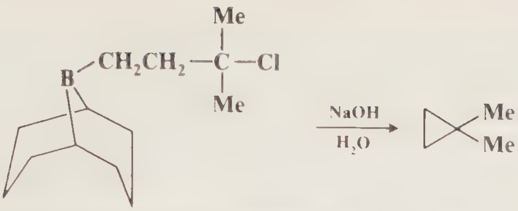
[959] For reviews, see Brown and Rogić, *Organomet. Chem. Synth.* **1,** 305–327 (1972); Rogić, *Intra-Sci. Chem. Rep.* **7**(2), 155–167 (1973); Brown, "Boranes in Organic Chemistry," Ref. 81, pp. 372–391, 404–409; Cragg, Ref. 749, pp. 275–278, 283–287.

[960] Brown, Nambu, and Rogić, *J. Am. Chem. Soc.* **91,** 6852, 6854, 6855 (1969).

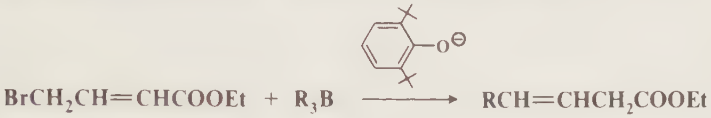
[961] Brown and Rogić, *J. Am. Chem. Soc.* **91,** 2146 (1969); Brown, Rogić, Nambu, and Rathke, *J. Am. Chem. Soc.* **91,** 2147 (1969).

[962] Brown and Rogić, *J. Am. Chem. Soc.* **91,** 4304 (1969).

[963] Brown and Rhodes, *J. Am. Chem. Soc.* **91,** 2149, 4306 (1969). For a review of this type of reaction, see Brown, Ref. 959, pp. 336–340.



The reaction (with R_3B or B-R-9-BBN) can be extended to α,α-dihalo esters[964] and α,α-dihalo nitriles.[965] It is possible to replace just one halogen or both. In the latter case the two alkyl groups can be the same or different. When dialkylation is applied to dihalo nitriles, the two alkyl groups can be primary or secondary, but with dihalo esters, dialkylation is limited to primary R. Another extension is the reaction of boranes with γ-halo-α,β-unsaturated esters.[966] Alkylation takes place in the γ-position, but the double bond migrates, e.g.,

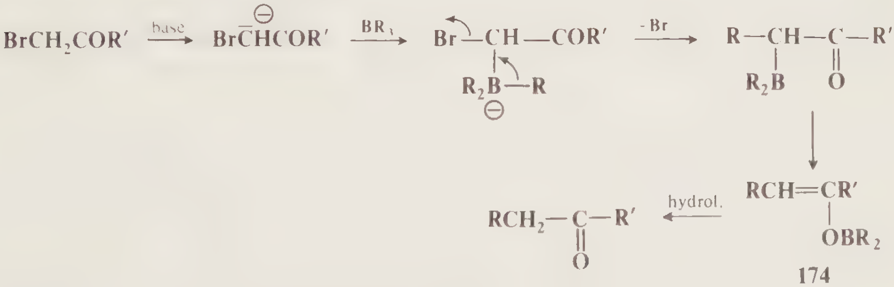


$$BrCH_2CH{=}CHCOOEt + R_3B \longrightarrow RCH{=}CHCH_2COOEt$$

In this case, however, double-bond migration is an advantage, because nonconjugated β,γ-unsaturated esters are usually much more difficult to prepare than their α,β-unsaturated isomers.

The alkylation of activated halogen compounds is one of several reactions of trialkylboranes developed by H. C. Brown[967] (see also reactions **5-15**, **5-21**, **8-27** to **8-31**, etc.). These compounds are extremely versatile and can be used for the preparation of many types of compounds. In this reaction, for example, an alkene (through the BR_3 or B-R-9-BBN prepared from it) can be coupled to a ketone, a nitrile, an ester, or a sulfonyl derivative. Note that this is still another indirect way to alkylate a ketone (see **0-97**) or a carboxylic acid (see **0-98**), and provides an additional alternative to the malonic ester and acetoacetic ester syntheses (**0-96**). In yet another alternative to these reactions, ethyl bromocyanoacetate EtOOCCHBrCN and bromomalononitrile $CHBr(CN)_2$ can be alkylated directly with trialkylboranes.[968]

Although superficially this reaction resembles reaction **0-87**, it is likely that the mechanism is quite different, involving migration of an R group from boron to carbon (see also reactions **8-27** to **8-31**). The mechanism is not known with certainty,[968a] but it may be tentatively shown as (illustrated for an α-halo ketone):



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[964] Brown, Rogić, Rathke, and Kabalka, *J. Am. Chem. Soc.* **90**, 1911 (1968).

[965] Nambu and Brown, *J. Am. Chem. Soc.* **92**, 5790 (1970).

[966] Brown and Nambu, *J. Am. Chem. Soc.* **92**, 1761 (1970).

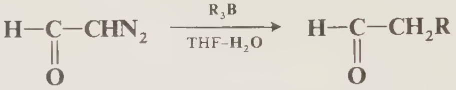
[967] Brown, "Organic Syntheses via Boranes," John Wiley & Sons, New York, 1975, "Hydroboration," W. A. Benjamin, Inc., New York, 1962, "Boranes in Organic Chemistry," Ref. 81.

[968] Nambu and Brown, *Organomet. Chem. Synth.* **1**, 95 (1970).

[968a] See Prager and Reece, *Aust. J. Chem.* **28**, 1775 (1975).

The first step is removal of the acidic proton by the base to give an enolate ion which combines with the borane (Lewis acid–base reaction). An R group then migrates, displacing the halogen leaving group. Another migration then follows, this time of BR_2 from carbon to oxygen to give the enol borinate **174**[969] which is hydrolyzed. Configuration at R is retained.[970]

The reaction has also been applied to compounds with other leaving groups. Diazo ketones, diazo esters, diazo nitriles, and diazo aldehydes[971] react with trialkylboranes in a similar manner, e.g.,



$$\underset{\displaystyle \overset{\|}{O}}{H-C}-CHN_2 \xrightarrow[THF-H_2O]{R_3B} \underset{\displaystyle \overset{\|}{O}}{H-C}-CH_2R$$

The mechanism is probably also similar. In this case a base is not needed, since the carbon already has an available pair of electrons. The reaction with diazo aldehydes[972] is especially notable, since successful reactions cannot be obtained with α-halo aldehydes. However, the reaction with diazo compounds suffers from the earlier noted disadvantage that two R groups are wasted. An attempt to use B-R-9-BBN here was not successful.[973] However, the use of alkyldichloroboranes $RBCl_2$ (prepared as on p. 720) overcomes this problem and also accommodates bulky groups which react slowly when R_3B is used.[974] Boranes have also been shown to react with

$$R_3B + \overset{\ominus}{\bar{C}}H_2-\overset{\oplus}{S}OMe_2 \longrightarrow RCH_2OH$$

Sulfur ylide

sulfur ylides[975] and with carbanions of the form $Ph\overset{\ominus}{\bar{C}}HSAr$.[976] The latter react with R_3B (R = primary) to give alkylbenzenes $PhCH_2R$.

OS **53,** 77.

0-102 Alkylation at an Alkynyl Carbon

$$RX + R'C{\equiv}C^- \longrightarrow RC{\equiv}CR'$$

The reaction between alkyl halides and acetylide ions is quite useful but is of limited scope.[977] Only primary halides unbranched in the β-position give good yields, though allylic halides can be used if CuI is present.[978] If acetylene is the reagent, two different groups can be successively attached. Sulfates, sulfonates, and epoxides[979] are sometimes used as substrates. The acetylide ion is often prepared by treatment of an alkyne with a strong base such as $NaNH_2$. Magnesium acetylides (ethynyl Grignard reagents; prepared as in reaction **2-19**) are also frequently used. Another convenient method for preparation of the acetylide ion is the addition of the alkyne to a solution of $CH_3SOCH_2^-$ in dimethyl sulfoxide.[980] This solution can be prepared by the addition of sodium hydride to dimethyl sulfoxide. Alternatively, the alkyl halide can be treated with a lithium acetylide ethylenediamine complex.[981] Tertiary alkyl halides can be coupled by treatment with an organoalkynylalane $(RC{\equiv}C)_3Al$.[981a]

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[969] Pasto and Wojtkowski, *Tetrahedron Lett.* 215 (1970), Ref. 911.

[970] Brown, Rogić, Rathke, and Kabalka, *J. Am. Chem. Soc.* **91,** 2150 (1969).

[971] Hooz and Linke, *J. Am. Chem. Soc.* **90,** 5936, 6891 (1968); Hooz and Gunn, *Chem. Commun.* 139 (1969), *J. Am. Chem. Soc.* **91,** 6195 (1969); Hooz and Morrison, *Can. J. Chem.* **48,** 868 (1970); Hooz, Gunn, and Kono, *Can. J. Chem.* **49,** 2371 (1971); Mikhailov and Gurskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **22,** 2588 (1973).

[972] Hooz and Morrison, Ref. 971.

[973] Hooz and Gunn, *Tetrahedron Lett.* 3455 (1969).

[974] Hooz, Bridson, Calzada, Brown, Midland, and Levy, *J. Org. Chem.* **38,** 2574 (1973). See also Brown, Midland, and Levy, *J. Am. Chem. Soc.* **94,** 3662 (1972).

[975] Tufariello and Lee, *J. Am. Chem. Soc.* **88,** 4757 (1966); Tufariello, Lee, and Wojtkowski, *J. Am. Chem. Soc.* **89,** 6804 (1967); Tufariello, Wojtkowski, and Lee, *Chem. Commun.* 505 (1967).

[976] Mukaiyama, Yamamoto, and Shiono, *Bull. Chem. Soc. Jpn.* **45,** 2244 (1972).

[977] For reviews, see Ziegenbein, in Viehe, "Acetylenes," pp. 185–206, 241–244, Marcel Dekker, Inc., New York, 1969; Jacobs, *Org. React.* **5,** 25 40 (1949).

[978] Bourgain and Normant, *Bull. Soc. Chim. Fr.* 1777 (1973).

[979] For example, see Fried, Lin, and Ford, *Tetrahedron Lett.* 1379 (1969).

Alkylation at an alkynyl carbon can also be done in the opposite way, with a triple-bond compound acting as an electrophile (see reaction **0-92**). For another method of alkylating at an alkynyl carbon, see reaction **8-31.**

OS **IV**, 117. Also see OS **IV**, 801; **50**, 97.

0-103 Preparation of Nitriles

$$\mathbf{RX + CN^- \longrightarrow RCN}$$

The reaction between cyanide ion (isoelectronic with $HC{\equiv}C^-$ and of similar geometry) and alkyl halides is a convenient method for the preparation of nitriles.[982] Primary, benzylic, and allylic halides give good yields of nitriles; secondary halides give moderate yields. The reaction fails for tertiary halides, which give elimination under these conditions. Many other groups on the molecule do not interfere. Though a number of solvents have been used, the high yields and short reaction times observed with dimethyl sulfoxide make it a very good solvent for this reaction.[983] Another way to obtain high yields under mild conditions is to use a crown ether (p. 324).[984] This is an important way of increasing the length of a carbon chain by one carbon, since nitriles are easily hydrolyzed to carboxylic acids (reaction **6-5**). The cyanide ion is an ambident nucleophile, and isonitriles may be side products. If the preparation of isonitriles is desired, they can be made the main products by the use of silver or copper(I) cyanide[985] (p. 338). Vinyl bromides can be converted to vinyl cyanides with CuCN,[986] or with the mixed cyanide "$NaCu(CN)_2$" prepared from NaCN and CuCN,[987] or with $K_4Ni_2(CN)_6$.[988]

The cyanide nucleophile also reacts with compounds containing other leaving groups. Esters of sulfuric and sulfonic acids behave like halides. Epoxides give β-hydroxy nitriles. Ortho esters give α-cyano acetals:

$$\mathbf{RC(OR')_3 + HCN \xrightarrow{ZnCl_2} NC{-}CR(OR')_2}$$

Primary and secondary alcohols are converted to nitriles on refluxing with Ph_3P, CCl_4, and NaCN in dimethyl sulfoxide.[989] NaCN in HMPT selectively cleaves methyl esters in the presence of ethyl esters: $RCOOMe + CN^- \rightarrow MeCN + RCOO^-$.[990] Lactones can be opened up with potassium cyanide:

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[980] Kříž, Beneš, and Peška, *Tetrahedron Lett.* 2881 (1965). See also Beckmann, Doerjer, Logemann, Merkel, Schill, and Zürcher, *Synthesis* 423 (1975).

[981] Smith and Beumel, *Synthesis* 441 (1974).

[981a] Negishi and Baba, *J. Am. Chem. Soc.* **97,** 7385 (1975).

[982] For reviews, see Friedrich and Wallenfels, in Rappoport, "The Chemistry of the Cyano Group," pp. 77–86, Interscience Publishers, New York, 1970; Mowry, *Chem. Rev.* **42,** 189–283 (1948), pp. 191–206, 244–246.

[983] Smiley and Arnold, *J. Org. Chem.* **25,** 257 (1960); Friedman and Shechter, *J. Org. Chem.* **25,** 877 (1960); Argabright and Hall, *Chem. Ind.* (*London*) 1365 (1964).

[984] Cook, Bowers, and Liotta, *J. Org. Chem.* **39,** 3416 (1974); Zubrick, Dunbar, and Durst, *Tetrahedron Lett.* 71 (1975).

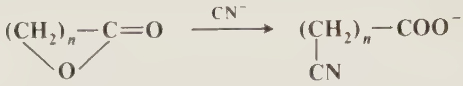
[985] For an example, see Jackson and McKusick, *Org. Synth.* **IV,** 438.

[986] For example, see Koelsch, *J. Am. Chem. Soc.* **58,** 1328 (1936); Newman and Boden, *J. Org. Chem.* **26,** 2525 (1961); Lapouyade, Daney, Lapenue, and Bouas-Laurent, *Bull. Soc. Chim. Fr.* 720 (1973).

[987] House and Fischer, *J. Org. Chem.* **34,** 3626 (1969).

[988] Corey and Hegedus, *J. Am. Chem. Soc.* **91,** 1233 (1969).

[989] Brett, Downie, and Lee, *J. Org. Chem.* **32,** 855 (1967).



OS **I,** 46, 107, 156, 181, 254, 256, 536; **II,** 292, 376; **III,** 174, 372, 557; **IV,** 438, 496, 576; **V,** 578, 614.

0-104 Direct Conversion of Alkyl Halides to Aldehydes and Ketones

$$RX + Na_2Fe(CO)_4 \xrightarrow{Ph_3P} \underset{\mathbf{175}}{RCOFe(CO)_3PPh_3^-} \xrightarrow{HOAc} RCHO$$

The direct conversion of alkyl bromides to aldehydes, with an increase in the chain length by one carbon, can be accomplished[991] by treatment with sodium tetracarbonylferrate(–II)[991a] in the presence of triphenylphosphine, and subsequent quenching of **175** with acetic acid. The reagent $Na_2Fe(CO)_4$ can be prepared by treatment of iron pentacarbonyl $Fe(CO)_5$ with sodium amalgam in tetrahydrofuran. Good yields are obtained from primary alkyl bromides; secondary bromides give lower yields. The reaction is not satisfactory for benzylic bromides. The initial species produced from RX and $Na_2Fe(CO)_4$ is the ion $RFe(CO)_4^-$ (**176**) (which can be isolated[992]); it then reacts with Ph_3P to give **175**.

The synthesis can be extended to the preparation of ketones in five distinct ways.[993]

1. Instead of quenching **175** with acetic acid, the addition of a second alkyl halide at this point gives a ketone: **175** + R′X → RCOR′.

2. Treatment of $Na_2Fe(CO)_4$ with an alkyl halide in the absence of Ph_3P gives rise to a solution of **176**. Addition of a second alkyl halide produces a ketone: **176** + R′X → RCOR′.

3. Treatment of $Na_2Fe(CO)_4$ with an alkyl halide in the presence of CO results in an acylated iron complex (**177**) which can be isolated.[992] Treatment of this with a second alkyl halide

$$RX + Na_2Fe(CO)_4 \xrightarrow{CO} \underset{\mathbf{177}}{RCOFe(CO)_4^-} \xrightarrow{R'X} RCOR'$$

gives a ketone.[994] R′X may also be a perfluorophenyl halide.

4. Treatment of $Na_2Fe(CO)_4$ with an acyl halide produces **177** which, when treated with an alkyl halide, gives a ketone.

5. Alkyl halides and tosylates react with $Na_2Fe(CO)_4$ in the presence of ethylene to give alkyl ethyl ketones.[994a] The reaction was not successful for higher alkenes.

In the first stage of methods 1, 2, and 3 primary bromides, iodides, and tosylates and secondary tosylates may be used. The second stage of the first four methods requires more active substrates, such as primary iodides or tosylates, or benzylic halides. Method 5 has been applied to primary and secondary substrates.

The conversion of alkyl halides to aldehydes can also be accomplished indirectly (reaction **0-99**). See also reaction **2-31.**

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[990] Müller and Siegfried, *Helv. Chim. Acta* **57,** 987 (1974).

[991] Cooke, *J. Am. Chem. Soc.* **92,** 6080 (1970).

[991a] For a review of this reagent, see Collman, *Acc. Chem. Res.* **8,** 342–347 (1975).

[992] Siegl and Collman, *J. Am. Chem. Soc.* **94,** 2516 (1972).

[993] For the first four of these methods, see Collman, Winter, and Clark, *J. Am. Chem. Soc.* **94,** 1788 (1972); Collman and Hoffman, *J. Am. Chem. Soc.* **95,** 2689 (1973).

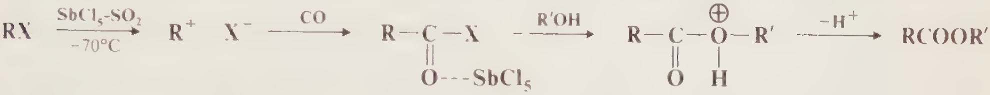
[994] See also Sawa, Ryang, and Tsutsumi, *Tetrahedron Lett.* 5189 (1969).

[994a] Cooke and Parlman, *J. Am. Chem. Soc.* **97,** 6863 (1975).

0-105 Conversion of Alkyl Halides, Alcohols, or Alkanes to Carboxylic Acids and Their Derivatives

$$\mathrm{RX + CO + R'OH \xrightarrow[-70\ ^\circ C]{SbCl_5,\ SO_2} RCOOR'}$$

Several methods, all based on carbon monoxide or metal carbonyls, have been developed for converting an alkyl halide to a carboxylic acid or an acid derivative with the chain extended by one carbon. When an alkyl halide is treated with $SbCl_5$-SO_2 at $-70^\circ C$, it dissociates into the corresponding carbonium ion (p. 152). If carbon monoxide and an alcohol are present, then a carboxylic ester is formed by the following route:[995]



$$\mathrm{RX \xrightarrow[-70^\circ C]{SbCl_5\text{-}SO_2} R^+ \quad X^- \xrightarrow{CO} \underset{\underset{O\text{---}SbCl_5}{\|}}{R{-}C{-}X} \xrightarrow{R'OH} R{-}\underset{\underset{O}{\|}}{C}{-}\overset{\oplus}{\underset{\underset{H}{|}}{O}}{-}R' \xrightarrow{-H^+} RCOOR'}$$

Not surprisingly, only tertiary halides perform satisfactorily; secondary halides give mostly rearrangement products. An analogous reaction takes place with alkanes possessing a tertiary hydrogen, e.g.,[996]

$$\mathrm{EtCHMe_2 \xrightarrow[2.\ H_2O]{1.\ HF\text{-}SbF_5\text{-}CO} 75\%\ EtCMe_2COOH}$$

Carboxylic acids or esters are the products, depending on whether the reaction mixture is solvolyzed with water or an alcohol. Similarly, alcohols react with H_2SO_4 and CO (which is often generated from HCOOH and the H_2SO_4 in the solution) to give trisubstituted acetic acids in a process called the *Koch-Haaf reaction* (see also reaction **5-25**).[997] If a primary or secondary alcohol is the substrate, the carbonium ion initially formed rearranges to a tertiary ion before reacting with the CO.

Another method[998] for the conversion of alkyl halides to esters is treatment with CO and an alcohol in the presence of cobalt carbonyl anion $Co(CO)_4^-$.[999] The reaction has been applied to

$$\mathrm{RX + CO \xrightarrow[R'OH]{Co(CO)_4^-} RCOOR' + HCo(CO)_4}$$

primary and secondary alkyl halides, sulfates, and sulfonates. Yields in general are low to moderate, though higher yields (80 to 82%) have been achieved in some cases. The reaction also takes place with epoxides,[1000] which give β-hydroxy esters. Treatment of a halide with nickel carbonyl $Ni(CO)_4$ (CO is not needed in this case) in the presence of an alcohol and its conjugate base also gives an ester.[1001] When R′ is primary, then RX may only be a vinyl or an aryl halide; retention of

$$\mathrm{RX + Ni(CO)_4 \xrightarrow[R'OH]{R'O^-} RCOOR'}$$

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[995] Nojima, Tatsumi, and Tokura, *Bull. Chem. Soc. Jpn.* **44,** 2001 (1971); Yoshimura, Nojima, and Tokura, *Bull. Chem. Soc. Jpn.* **46,** 2164 (1973); Nojima, Shiba, Yoshimura, and Tokura, *Chem. Lett.* 1133 (1972); Puzitskii, Pirozhkov, Ryabova, Myshenkova, and Éidus, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23,** 192 (1974).

[996] Paatz and Weisgerber, *Chem. Ber.* **100,** 984 (1967).

[997] For examples, see Éidus, Puzitskii, and Guseva, *J. Gen. Chem. USSR* **32,** 2934 (1962); Éidus, Puzitskii, and Gryabova, *J. Gen. Chem. USSR* **32,** 3143 (1962); Nojima, Shiba, and Tokura, *Chem. Lett.* 1137 (1972); Peters and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **92,** 379 (1973); Peters, Rog, and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **93,** 248 (1974).

[998] For a review of methods involving transition metals, see Cassar, Chiusoli, and Guerrieri, *Synthesis* 509–523 (1973).

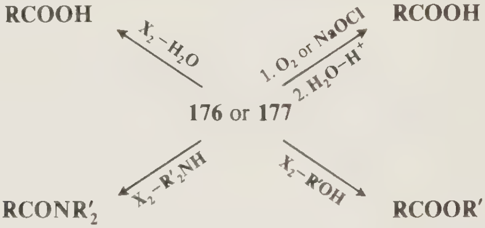
[999] For a review, see Heck, in Wender and Pino, "Organic Syntheses via Metal Carbonyls," vol. 1, pp. 379–388, Interscience Publishers, New York, 1968.

[1000] Heck, *J. Am. Chem. Soc.* **85,** 1460 (1963).

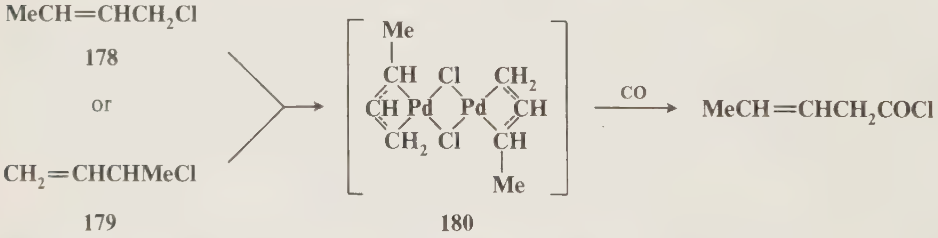
[1001] Corey and Hegedus, *J. Am. Chem. Soc.* **91,** 1233 (1969). See also Crandall and Michaely, *J. Organomet. Chem.* **51,** 375 (1973).

configuration is observed at a vinyl R. Consequently, a carbonium-ion intermediate is not involved here. When R′ is tertiary, then R may be primary alkyl as well as vinyl or aryl. This is thus one of the few methods for preparing esters of tertiary alcohols. Alkyl iodides give the best results, then bromides. In the presence of an amine, an amide can be isolated directly, at least in some instances.

Still another method for the conversion of halides to acid derivatives makes use of $Na_2Fe(CO)_4$. As described in reaction **0-104**, primary and secondary alkyl halides and tosylates react with this reagent to give the ion $RFe(CO)_4^-$ (**176**) or, if CO is present, the ion $RCOFe(CO)_4^-$ (**177**). Treatment of **176** or **177** with oxygen or sodium hypochlorite gives, after hydrolysis, a carboxylic acid.[1002] Alternatively, **176** or **177** react with a halogen (for example, I_2) in the presence of an alcohol to give an ester,[1003] or in the presence of a secondary amine or of water to give, respectively, the corresponding amide or free acid. **176** and **177** prepared from primary R give high yields. With secondary R, the best results are obtained in the solvent tetrahydrofuran by the use of **177** prepared from secondary tosylates. Ester and keto groups may be present in R without being affected. A similar reaction has been carried out with epoxides.[1004]



A final method involves treatment of an allylic chloride with CO under pressure in the presence of a π-allylic palladium complex or of $PdCl_2$; the product is a β,γ-unsaturated acyl chloride in high yield.[1005] Palladium metal, and Pt and Rh complexes, have also been found effective. The reaction probably proceeds through an allylic-Pd complex **180**, since both **178** and **179** give the same product. Saturated, vinyl, and benzylic halides fail to react, though benzylic and aryl halides can be converted to esters by treatment with CO, dichlorobis(triphenylphosphine)palladium(II), an alcohol, and NaOAc in an autoclave.[1006]



OS V, 20, 739.

[1002] Collman, Winter, and Komoto, *J. Am. Chem. Soc.* **95,** 249 (1973).

[1003] Ref. 1002; Masada, Mizuno, Suga, Watanabe, and Takegami, *Bull. Chem. Soc. Jpn.* **43,** 3824 (1970).

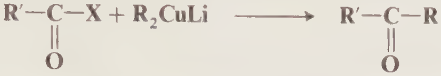
[1004] Takegami, Watanabe, Masada, and Kanaya, *Bull. Chem. Soc. Jpn.* **40,** 1456 (1967).

[1005] Tsuji, Kiji, and Morikawa, *Tetrahedron Lett.* 1811 (1963); Tsuji, Kiji, Imamura, and Morikawa, *J. Am. Chem. Soc.* **86,** 4350 (1964); Dent, Long, and Whitfield, *J. Chem. Soc.* 1588 (1964); Tsuji, *Acc. Chem. Res.* **2,** 144–152 (1969), *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 166–183.

[1006] Stille and Wong, *J. Org. Chem.* **40,** 532 (1975). See also Hidai, Hikita, Wada, Fujikura, and Uchida, *Bull. Chem. Soc. Jpn.* **48,** 2075 (1975).

B. Attack at an Acyl Carbon[1007]

0-106 The Conversion of Acyl Halides to Ketones with Organometallic Compounds[1008]



$$R'-\underset{\underset{O}{\|}}{C}-X + R_2CuLi \longrightarrow R'-\underset{\underset{O}{\|}}{C}-R$$

Acyl halides react cleanly and under mild conditions with lithium dialkylcopper reagents[805] (see reaction **0-87**) to give high yields of ketones.[1009] R′ may be primary, secondary, or tertiary alkyl or aryl and may contain iodo, keto, ester, nitro, or cyano groups. R groups which have been used successfully are methyl, primary alkyl, and vinylic. Secondary and tertiary alkyl groups can be introduced by the use of PhS(R)CuLi (p. 409) instead of R_2CuLi.[812] R may be alkynyl if a cuprous acetylide $R''C{\equiv}CCu$ is the reagent.[1010]

Another type of organometallic reagent which gives good yields of ketones when treated with acyl halides are organocadmiums R_2Cd (prepared from Grignard reagents, reaction **2-19**). In this case R may be aryl or primary alkyl. In general, secondary and tertiary alkylcadmium reagents are not stable enough to be useful in this reaction.[1011] An ester group may be present in either R′COX or R_2Cd. Organozinc compounds behave similarly, but are less often used. Organomercury compounds also give the reaction if an $AlBr_3$ catalyst is present.[1012] Still other reagents are lithium aryltrialkylborates[1013] $ArBR_3^-$ Li^+ (which transfer an aryl group) and the alkylrhodium(I) complexes bis(triphenylphosphine)carbonylalkylrhodium(I) $Rh^IR(CO)(Ph_3P)_2$. The latter, generated in situ from $Rh^ICl(CO)(Ph_3P)_2$ (**181**) and a Grignard reagent or organolithium compound, react with acyl halides in tetrahydrofuran at −78°C to give good yields of ketones.[1014] R may be primary alkyl or aryl. An advantage of the rhodium reagents is that they do not react with aldehydes, esters, or nitriles, so that these groups may be present in R′. Another advantage is that the complex **181** is regenerated in reusable form at the end of the reaction.

When the organometallic compound is a Grignard reagent,[1015] ketones are generally not obtained because the initially formed ketone reacts with a second molecule of RMgX to give the salt of a tertiary alcohol (reaction **6-34**). Ketones *have* been prepared in this manner by the use of low temperatures, inverse addition (i.e., addition of the acyl halide to the Grignard reagent, rather than the other way around), excess acyl halide, etc., but the yields are usually low. Some ketones are unreactive toward Grignard reagents for steric or other reasons, and these may be prepared in this way. Also, certain metallic halides, notably ferric and cuprous halides, are catalysts which improve the yields of ketone at the expense of tertiary alcohol.[1016] For these catalysts, both free-radical and ionic mechanisms have been proposed.[1017] The reactions with R_2CuLi, R_2Cd, and the rhodium complexes are successful because these compounds do not generally react with ketones.

[1007] For a discussion of many of the reactions in this section, see House, Ref. 873, pp. 691–694, 734–765.

[1008] For reviews, see Cais and Mandelbaum, in Patai, Ref. 349, vol. 1, pp. 303–330 (1966); Shirley, *Org. React.* **8**, 28–58 (1954).

[1009] Vig, Kapur, and Sharma, *J. Indian Chem. Soc.* **45**, 734 (1968); Vig, Sharma, and Kapur, *J. Indian Chem. Soc.* **46**, 167 (1969); Jukes, Dua, and Gilman, *J. Organomet. Chem.* **21**, 241 (1970); Posner and Whitten, *Tetrahedron Lett.* 4647 (1970); Posner, Whitten, and McFarland, *J. Am. Chem. Soc.* **94**, 5106 (1972); Jallabert, Luong-Thi, and Rivière, *Bull. Soc. Chim. Fr.* 797 (1970); Luong-Thi, Rivière, and Spassky, *Bull. Soc. Chim. Fr.* 2102 (1973); Luong-Thi and Rivière, *J. Organomet. Chem.* **77**, C52 (1974).

[1010] Castro, Havlin, Honwad, Malte, and Mojé, *J. Am. Chem. Soc.* **91**, 6464 (1969).

[1011] Cason and Fessenden, *J. Org. Chem.* **25**, 477 (1960).

[1012] Kurts, Beletskaya, Savchenko, and Reutov, *J. Organomet. Chem.* **17**, P21 (1969). See also Takagi, Okamoto, Sakakibara, Ohno, Oka, and Hayama, *Chem. Lett.* 951 (1975).

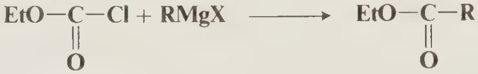
[1013] Negishi, Abramovitch, and Merrill, *J. Chem. Soc., Chem. Commun.* 138 (1975); Negishi, Chiu, and Yoshida, *J. Org. Chem.* **40**, 1676 (1975).

[1014] Hegedus, Lo, and Bloss, *J. Am. Chem. Soc.* **95**, 3040 (1973); Hegedus, Kendall, Lo, and Sheats, *J. Am. Chem. Soc.* **97**, 5448 (1975).

[1015] For a review, see Ref. 818, pp. 712–724.

[1016] For examples, see Cason and Kraus, *J. Org. Chem.* **26**, 1768, 1772 (1961); Dubois, Leheup, Hennequin, and Bauer, *Bull. Soc. Chim. Fr.* 1150 (1967); Dubois, Chastrette, and Schunk, *Bull. Soc. Chim. Fr.* 2011 (1967); Dubois, Boussu, and Lion, *Tetrahedron Lett.* 829 (1971); MacPhee and Dubois, *Tetrahedron Lett.* 467 (1972); Luong-Thi and Rivière, *Tetrahedron Lett.* 587 (1971); Luong-Thi, Rivière, Bégué, and Forestier, *Tetrahedron Lett.* 2113 (1971).

Grignard reagents react with ethyl chloroformate to give esters.

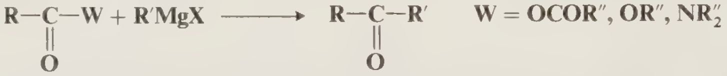


$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}Cl + RMgX \longrightarrow EtO{-}\underset{\underset{O}{\|}}{C}{-}R}$$

Acyl halides can also be converted to ketones by treatment with $Na_2Fe(CO)_4$ followed by R′X (reaction **0-104**, method 4).

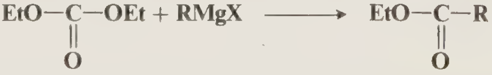
OS **II,** 198; **III,** 601; **IV,** 708; **54,** 97; **55,** 122.

0-107 The Conversion of Anhydrides, Esters, or Amides to Ketones with Organometallic Compounds[1018]



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}W + R'MgX \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}R'} \qquad \mathrm{W = OCOR'', OR'', NR''_2}$$

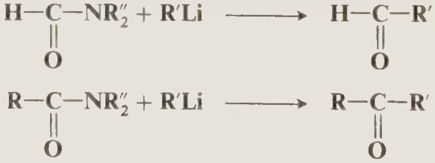
As is the case with acyl halides (reaction **0-106**), anhydrides and esters also give tertiary alcohols (reaction **6-34**) when treated with Grignard reagents. Low temperatures[1019] and inverse addition have been used to increase the yields of ketone. Amides give better yields of ketone at room temperature, but still only about 10 to 50%. 2-Pyridinethiol esters (p. 363) are one type of ester which gives high yields of ketones when added to Grignard reagents.[1020] Thioesters RCOSR′ give good yields of ketones when treated with lithium dialkylcopper reagents R″CuLi (R″ = primary or secondary alkyl or aryl).[1021] Organocadmium reagents are less successful with these substrates than with acyl halides (reaction **0-106**). Esters of formic acid, and dialkylformamides, give good yields of aldehydes, when treated with Grignard reagents. Ethyl carbonate has been used to prepare esters



$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}OEt + RMgX \longrightarrow EtO{-}\underset{\underset{O}{\|}}{C}{-}R}$$

but more often the reaction goes further to give the ketone or the tertiary alcohol.

Alkyllithium compounds have been used to give good yields of ketones from esters. The reaction must be carried out in a high-boiling solvent such as toluene, since reaction at lower temperatures gives tertiary alcohols.[1022] Alkyllithiums also give good yields of carbonyl compounds with N,N-disubstituted amides.[1023] Dialkylformamides give aldehydes, and other disubstituted amides give ketones.



$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}NR''_2 + R'Li \longrightarrow H{-}\underset{\underset{O}{\|}}{C}{-}R'}$$

$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NR''_2 + R'Li \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}R'}$$

[1017] For example, see Dubois and Boussu, *Tetrahedron Lett.* 2523 (1970), *Tetrahedron* **29,** 3943 (1973); MacPhee, Boussu, and Dubois, *J. Chem. Soc., Perkin Trans. 2* 1525 (1974).

[1018] For a review, see Ref. 818, pp. 561–562, 846–908.

[1019] See, for example, Newman and Booth, *J. Am. Chem. Soc.* **67,** 154 (1945); Newman and Smith, *J. Org. Chem.* **13,** 592 (1948); Edwards and Kammann, *J. Org. Chem.* **29,** 913 (1964); Araki and Mukaiyama, *Chem. Lett.* 663 (1974); Araki, Sakata, Takei, and Mukaiyama, *Chem. Lett.* 687 (1974).

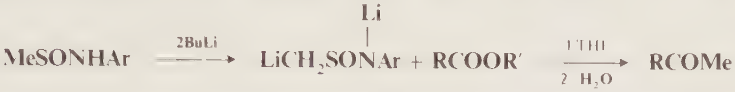
[1020] Araki, Sakata, Takei, and Mukaiyama, *Bull. Chem. Soc. Jpn.* **47,** 1777 (1974).

[1021] Anderson, Henrick, and Rosenblum, *J. Am. Chem. Soc.* **96,** 3654 (1974).

[1022] Petrov, Kaplan, and Tsir, *J. Gen. Chem. USSR* **32,** 691 (1962).

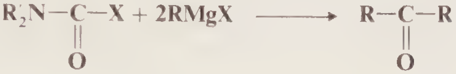
[1023] Evans, *J. Chem. Soc.* 4691 (1956); Izzo and Safir, *J. Org. Chem.* **24,** 701 (1959); Owsley, Nelke, and Bloomfield, *J. Org. Chem.* **38,** 901 (1973); Scilly, *Synthesis* 160 (1973).

Esters can be converted to methyl ketones by treatment with the dilithio salt of N-methanesulfinyl-*p*-toluidine in tetrahydrofuran followed by addition of water.[1024] N,N-Disubstituted car-



$$\mathrm{MeSONHAr} \xrightarrow{\mathrm{2BuLi}} \mathrm{LiCH_2SO\overset{Li}{\overset{|}{N}}Ar} + \mathrm{RCOOR'} \xrightarrow[\text{2 } H_2O]{\text{1 THF}} \mathrm{RCOMe}$$

bamates (X = OR″) and carbamoyl chlorides (X = Cl) react with 2 moles of an alkyl- or aryllithium or Grignard reagent to give symmetrical ketones, in which both R groups are derived from the organometallic compound.[1025]



$$\mathrm{R'_2N{-}\underset{\underset{O}{\|}}{C}{-}X} + \mathrm{2RMgX} \longrightarrow \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}R}$$

Ketones can also be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent (reaction **6-33**).

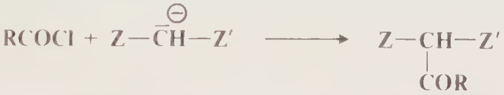
OS **II**, 282; **III**, 353; **IV**, 285; **52**, 75.

0-108 The Coupling of Acyl Halides

$$\mathrm{2RCOCl} \xrightarrow{\text{pyrophoric Pb}} \mathrm{RCOCOR}$$

Acyl halides can be coupled with pyrophoric lead to give symmetrical α-diketones in a Wurtz-type reaction.[1026] The reaction has been performed with R = Me and Ph.

0-109 Acylation by Acyl Halides or Anhydrides at a Carbon Bearing an Active Hydrogen



$$\mathrm{RCOCl} + \mathrm{Z{-}\overset{\ominus}{C}H{-}Z'} \longrightarrow \mathrm{Z{-}\underset{\underset{COR}{|}}{C}H{-}Z'}$$

This reaction is similar to reaction **0-96**, though many fewer examples have been reported. Z and Z′ may be any of the groups listed in **0-96**. Anhydrides react similarly but are less often used. The product contains three Z groups, since RCO is a Z group. One or two of these can then be cleaved (reactions **2-39**, **2-42**). In this way a compound ZCH_2Z' can be converted to ZCH_2Z'', or an acyl halide RCOCl to a methyl ketone $RCOCH_3$. O-Acylation is sometimes a side reaction. When thallium(I) salts of ZCH_2Z' are used, it is possible to achieve regiospecific acylation at either the C or the O position. For example, treatment of the thallium(I) salt of $MeCOCH_2COMe$ with acetyl chloride at −78°C gave >90% O-acylation, while acetyl fluoride at room temperature gave >95% C-acylation.[1027]

The application of this reaction to simple ketones (in parallel with reaction **0-97**) requires a strong base, such as $NaNH_2$, NaH, or Ph_3CNa, and is often complicated by O-acylation, which in many cases becomes the principal pathway because acylation at the oxygen is usually much faster. It is possible to increase the proportion of C-acylated product by employing an excess (2 to 3 equiv) of enolate ion (and adding the substrate to this, rather than vice versa), by the use of a relatively nonpolar solvent and a metal ion (such as Mg^{2+}) which is tightly associated with the enolate oxygen atom, and by the use of an acyl halide rather than an anhydride.[1028] In cases where the use of an excess of enolate ion results in C-acylation, it is because O-acylation takes place first, and the O-acylated product (an enol ester) is then C-acylated. (Note that C-acylation of ketones can be accomplished with BF_3; reaction **0-110.**) Simple esters RCH_2COOEt can be acylated at the α-carbon (at −78 C) if the strong base lithium N-isopropylcyclohexylamide is used to remove the proton.[1029]

[1024] Corey and Durst, *J. Am. Chem. Soc.* **90**, 5548 (1968).

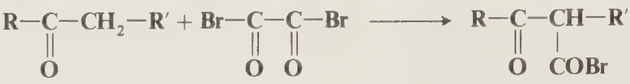
[1025] Michael and Hörnfeldt, *Tetrahedron Lett.* 5219 (1970); Scilly, Ref. 1023.

[1026] Mészáros, *Tetrahedron Lett.* 4951 (1967).

[1027] Taylor, Hawks, and McKillop, *J. Am. Chem. Soc.* **90**, 2421 (1968).

[1028] See House, Ref. 873, pp. 762–765; House, Auerbach, Gall, and Peet, *J. Org. Chem.* **38**, 514 (1973).

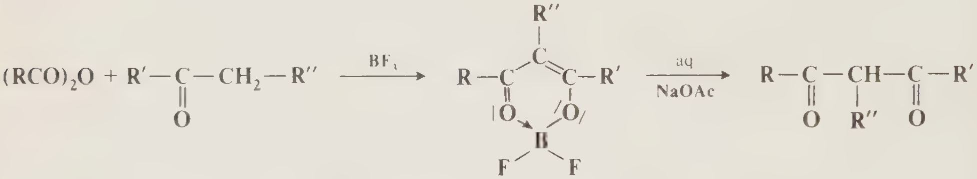
Ketones have been acylated by oxalyl bromide, with CO being lost in the process:[1030]



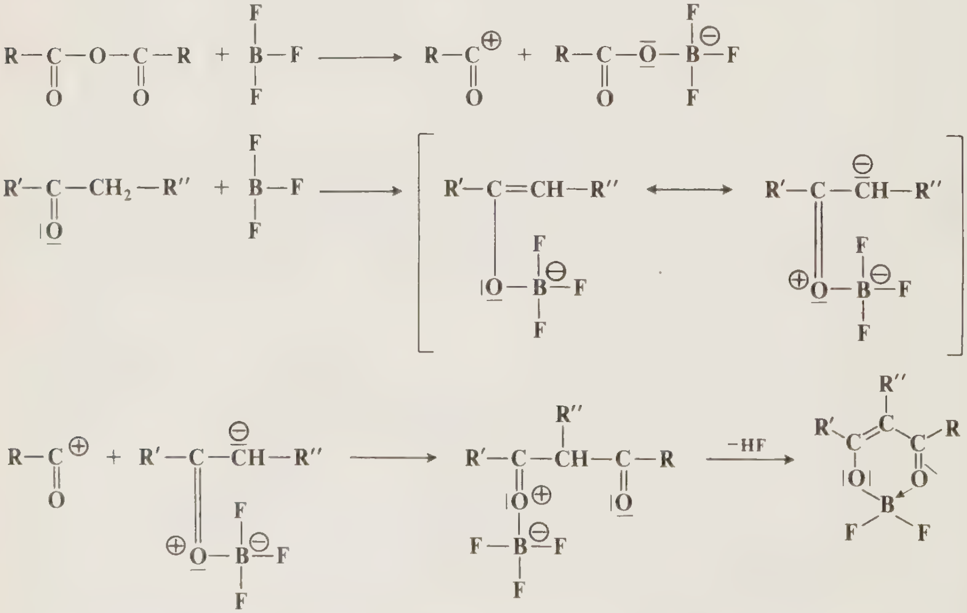
$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}CH_2{-}R' + Br{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}Br \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{COBr}{|}}{CH}{-}R'}$$

OS **II,** 266, 268, 594, 596; **III,** 390, 637; **IV,** 285, 415, 708; **V,** 384, 937.

0-110 Acylation of Ketones by Anhydrides



Ketones can by acylated by anhydrides, with BF_3 as catalyst,[1031] to give β-diketones. With unsymmetrical ketones, acylation occurs chiefly on the more highly substituted side. The actual product is a complex containing BF_2, which can be decomposed by aqueous sodium acetate to give the acylated ketone. Therefore 1 mole of boron trifluoride is required for each mole of ketone. The boron trifluoride plays a double role in the mechanism. It assists in ionization of the anhydride (an SN1 type of process) and converts the ketone into a boron derivative of the enolate:



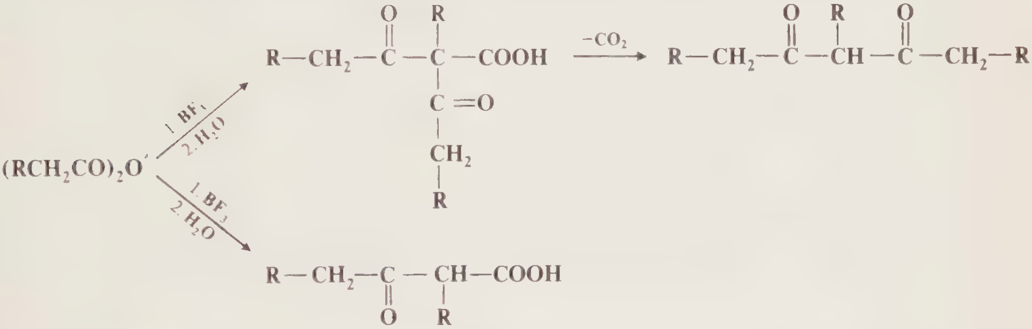
[1029] For example, see Rathke and Deitch, *Tetrahedron Lett.* 2953 (1971). See also Logue, *J. Org. Chem.* **39,** 3455 (1974).

[1030] Treibs, Riemer, and Orttmann, *Chem. Ber.* **93,** 551 (1960).

[1031] For a review, see Hauser, Swamer, and Adams, *Org. React.* **8,** 59–196 (1954), pp. 98–106.

With respect to the ketone, this is an electrophilic substitution with a mechanism similar to that of the bromination of ketones (reaction **2-4**). There is evidence that at least in some cases the enol is first O-acylated, and then the resulting enol ester is attacked by another acyl cation to give the β-diketone.[1032] Indeed, enol esters obtained in other ways can be converted to β-diketones in a similar manner.

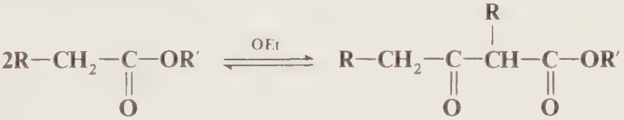
A side reaction is self-condensation of the anhydride, providing it has an α-hydrogen, to give either a β-diketone or a β-keto acid. In the former case, decarboxylation takes place (see reaction **2-39**). Of course, the β-keto acid can also be decarboxylated. These reactions are examples of acylation of anhydrides by anhydrides and are sometimes used as preparative methods. In the latter process, an anhydride is converted to a symmetrical ketone (after decarboxylation of the β-keto acid):[1033]



Another means of accomplishing essentially the same result is discussed in reaction **0-117.** Mixed carboxylic-carbonic anhydrides can react with magnesium enolates to give β-keto esters.[1034]

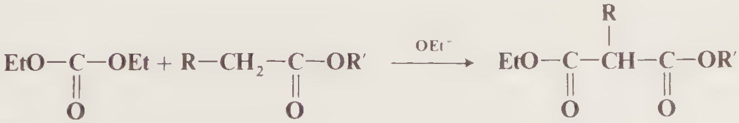
OS **III,** 16; **51,** 90.

0-111 Acylation of Esters by Esters. The Claisen and Dieckmann Condensations



$$2\mathrm{R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}OR'} \xrightleftharpoons{\mathrm{OEt}} \mathrm{R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R}{|}}{C}H{-}\underset{\underset{O}{\|}}{C}{-}OR'}$$

When esters containing an α-hydrogen are treated with a strong base such as sodium ethoxide, a condensation occurs to give a β-keto ester. This reaction is called the *Claisen condensation.*[1035] When the condensation is carried out with a mixture of two different esters, each of which possesses an α-hydrogen, a mixture of all four products is generally obtained and the reaction is seldom useful synthetically. However, if only one of the esters has an α-hydrogen, then the mixed reaction is frequently satisfactory. Among esters lacking α-hydrogens (hence acting as the substrate ester) which are commonly used in this way are esters of benzoic and other aromatic acids, and ethyl carbonate and ethyl oxalate. Ethyl carbonate gives malonic esters,



$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}OEt} + \mathrm{R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}OR'} \xrightarrow{\mathrm{OEt^-}} \mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R}{|}}{C}H{-}\underset{\underset{O}{\|}}{C}{-}OR'}$$

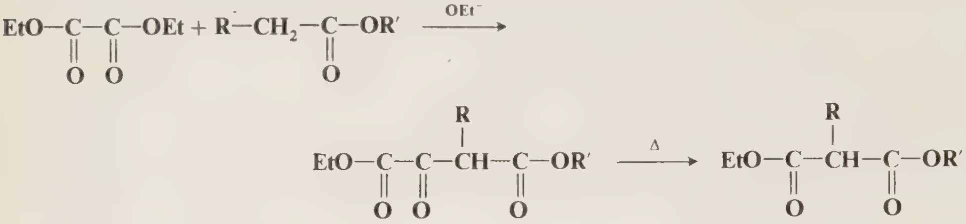
[1032] Mao, Frostick, Man, Manyik, Wells, and Hauser, *J. Org. Chem.* **34,** 1425 (1969).

[1033] See Musso and Figge, *Justus Liebigs Ann. Chem.* **668,** 1, 15 (1963).

[1034] Bram and Vilkas, *Bull. Soc. Chim. Fr.* 945 (1964).

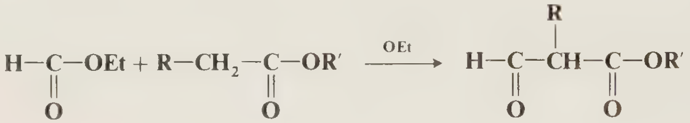
[1035] For a review, see Hauser and Hudson, *Org. React.* **1,** 266–302 (1942).

while ethyl oxalate gives α-keto esters, which may then be decarbonylated (reaction **0-13**) to the same malonic esters.



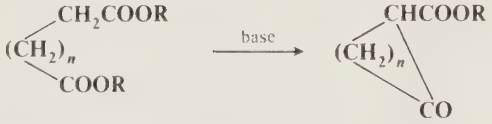
$$\text{EtO}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OEt}+\text{R}-\text{CH}_2-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OR}'\xrightarrow{\text{OEt}^-}\text{EtO}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\overset{\overset{\text{R}}{|}}{\text{C}}\text{H}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OR}'\xrightarrow{\Delta}\text{EtO}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\overset{\overset{\text{R}}{|}}{\text{C}}\text{H}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OR}'$$

Ethyl formate serves to introduce the formyl group:



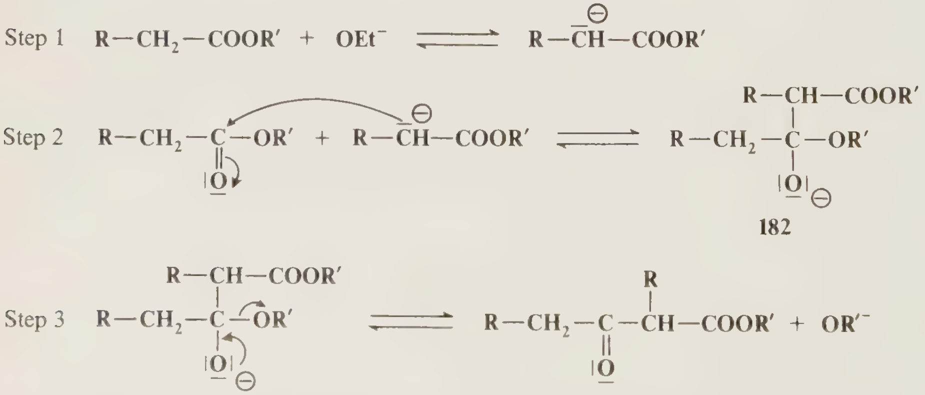
$$\text{H}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OEt}+\text{R}-\text{CH}_2-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OR}'\xrightarrow{\text{OEt}}\text{H}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\overset{\overset{\text{R}}{|}}{\text{C}}\text{H}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{OR}'$$

When the two ester groups involved in the condensation are in the same molecule, the product is a cyclic β-keto ester and the reaction is called the *Dieckmann condensation.*[1036]



The Dieckmann condensation is most successful for the formation of five-, six-, and seven-membered rings. Yields for rings of nine to twelve members are very low or nonexistent; larger rings can be closed with high-dilution techniques. Reactions in which large rings are to be closed are generally assisted by high dilution, since one end of the molecule has a better chance of finding the other end than of finding another molecule.

The mechanism of the Claisen and the Dieckmann reactions is the ordinary tetrahedral mechanism, with one molecule of ester being converted to a nucleophile by the base and the other serving as the substrate.



Step 1 $\text{R}-\text{CH}_2-\text{COOR}' + \text{OEt}^- \rightleftharpoons \text{R}-\overset{\ominus}{\underline{\text{C}}}\text{H}-\text{COOR}'$

Step 2 $\text{R}-\text{CH}_2-\underset{\underset{|\underline{\text{O}}}{\|}}{\text{C}}-\text{OR}' + \text{R}-\overset{\ominus}{\underline{\text{C}}}\text{H}-\text{COOR}' \rightleftharpoons \text{R}-\text{CH}_2-\overset{\overset{\text{R}-\text{CH}-\text{COOR}'}{|}}{\underset{\underset{|\underline{\text{O}}|^{\ominus}}{|}}{\text{C}}}-\text{OR}'$

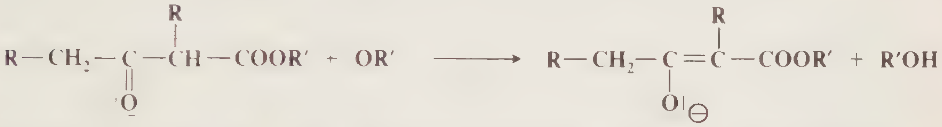
182

Step 3 $\text{R}-\text{CH}_2-\overset{\overset{\text{R}-\text{CH}-\text{COOR}'}{|}}{\underset{\underset{|\underline{\text{O}}|^{\ominus}}{|}}{\text{C}}}-\text{OR}' \rightleftharpoons \text{R}-\text{CH}_2-\underset{\underset{|\underline{\text{O}}}{\|}}{\text{C}}-\overset{\overset{\text{R}}{|}}{\text{C}}\text{H}-\text{COOR}' + \text{OR}'^-$

[1036] For a review, see Schaefer and Bloomfield, *Org. React.* **15**, 1–203 (1967).

This reaction illustrates the striking difference in behavior between esters on the one hand and aldehydes and ketones on the other. When a carbanion such as an enolate ion is added to the carbonyl group of an aldehyde or ketone (reaction **6-42**), the H or R is not lost, since these groups are much poorer leaving groups than OR. Instead the intermediate similar to **182** adds a proton at the oxygen to give a hydroxy compound.

In contrast to reaction **0-96** ordinary esters react quite well; that is, two Z groups are not needed. A lower degree of acidity is satisfactory because it is not necessary to convert the attacking ester entirely to its ion. Step 1, conversion of the ester to its ion, is an equilibrium reaction, and the equilibrium lies well over to the left. Nevertheless, the small amount of enolate ion formed is sufficient to attack the readily approachable ester substrate. All the steps in the reaction are equilibria. The reaction proceeds because the product is converted to its conjugate base by the base present (that is, a β-keto ester is a stronger acid than an alcohol):

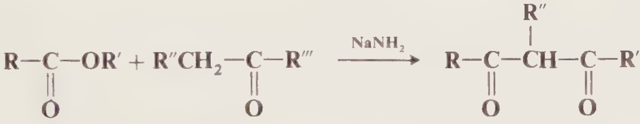


$$\mathrm{R{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R}{|}}{C}H{-}COOR' + OR'} \longrightarrow \mathrm{R{-}CH_2{-}\underset{\underset{O|^{\ominus}}{|}}{C}{=}\overset{\overset{R}{|}}{C}{-}COOR' + R'OH}$$

The use of a stronger base, such as sodium amide, sodium hydride, or potassium hydride,[1036a] often increases the yield. For some esters stronger bases *must* be used, since sodium ethoxide is ineffective. Among these are esters of the type $R_2CHCOOEt$, the products of which ($R_2CHCOCR_2$-COOEt) lack an acidic hydrogen, so that they cannot be converted to enolate ions by sodium ethoxide.

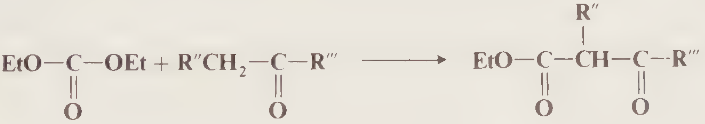
OS **I**, 235; **II**, 116, 194, 272, 288; **III**, 231, 300, 379, 510; **IV**, 141; **V**, 288, 687, 989.

0-112 Acylation of Ketones and Nitriles by Esters



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OR' + R''CH_2{-}\underset{\underset{O}{\|}}{C}{-}R'''} \xrightarrow{\mathrm{NaNH_2}} \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R''}{|}}{C}H{-}\underset{\underset{O}{\|}}{C}{-}R'''}$$

Esters can be treated with ketones to give β-diketones in a reaction which is essentially the same as reaction **0-111**.[1035] The reaction is so similar that it is sometimes also called the Claisen condensation, though this usage is unfortunate. A fairly strong base, such as sodium amide or sodium hydride, is required. Esters of formic acid R = H give β-keto aldehydes. Ethyl carbonate gives β-keto esters.



$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}OEt + R''CH_2{-}\underset{\underset{O}{\|}}{C}{-}R'''} \longrightarrow \mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}\overset{\overset{R''}{|}}{C}H{-}\underset{\underset{O}{\|}}{C}{-}R'''}$$

In the case of unsymmetrical ketones, the attack usually comes from the less highly substituted side, so that CH_3 is more reactive than RCH_2, and the R_2CH group rarely attacks. This is in sharp contrast to reaction **0-110**, and the two reactions are thus complementary. As in the case of reaction **0-111**, this reaction has been used to effect cyclization, especially to prepare five-

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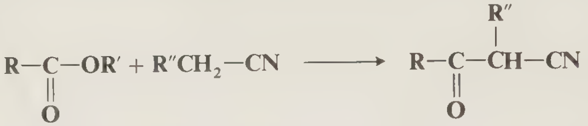
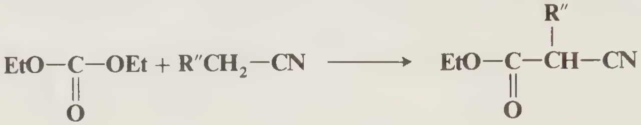
[1036a] Brown, *Synthesis* 326 (1975).

and six-membered rings. Nitriles are frequently used instead of ketones, the products being β-keto nitriles.



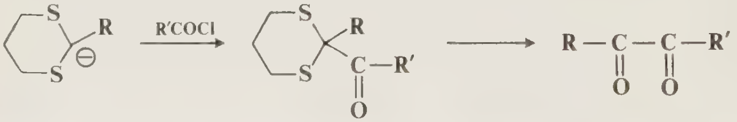
$$\mathrm{R{-}\underset{\underset{\textstyle O}{\|}}{C}{-}OR' + R''CH_2{-}CN \longrightarrow R{-}\underset{\underset{\textstyle O}{\|}}{C}{-}\overset{\overset{\textstyle R''}{|}}{C}H{-}CN}$$

Similarly, α-cyano esters can be obtained on treatment of ethyl carbonate with nitriles.

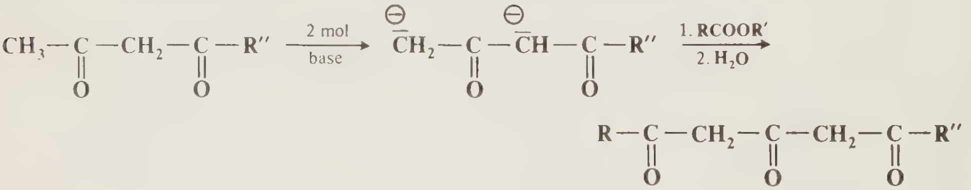


$$\mathrm{EtO{-}\underset{\underset{\textstyle O}{\|}}{C}{-}OEt + R''CH_2{-}CN \longrightarrow EtO{-}\underset{\underset{\textstyle O}{\|}}{C}{-}\overset{\overset{\textstyle R''}{|}}{C}H{-}CN}$$

Other carbanionic groups, such as acetylide ions, and ions derived from α-methylpyridines have also been used as nucleophiles. A particularly useful nucleophile is the methylsulfinyl carbanion $CH_3SOCH_2^-$,[1037] the conjugate base of dimethyl sulfoxide, since the β-keto sulfoxide produced can easily be reduced to a methyl ketone (p. 420). The methylsulfonyl carbanion $CH_3SO_2CH_2^-$, the conjugate base of dimethyl sulfone, behaves similarly,[1038] and the product can be similarly reduced. Certain esters, acyl halides, and dimethylformamide acylate 1,3-dithianes[1039] (see reaction **0-99**) to give, after oxidative hydrolysis with N-bromo- or N-chlorosuccinimide, α-keto aldehydes or α-diketones,[1040] e.g.,



As in reaction **0-96**, a ketone attacks with its second most acidic position if 2 moles of base are used. Thus, β-diketones have been converted to 1,3,5-triketones.[1041]



$$\mathrm{CH_3{-}\underset{\underset{\textstyle O}{\|}}{C}{-}CH_2{-}\underset{\underset{\textstyle O}{\|}}{C}{-}R'' \xrightarrow[\text{base}]{\text{2 mol}} \overset{\ominus}{\bar{C}}H_2{-}\underset{\underset{\textstyle O}{\|}}{C}{-}\overset{\ominus}{\bar{C}}H{-}\underset{\underset{\textstyle O}{\|}}{C}{-}R'' \xrightarrow[\text{2. }H_2O]{\text{1. RCOOR}'} R{-}\underset{\underset{\textstyle O}{\|}}{C}{-}CH_2{-}\underset{\underset{\textstyle O}{\|}}{C}{-}CH_2{-}\underset{\underset{\textstyle O}{\|}}{C}{-}R''}$$

Side reactions are condensation of the ketone with itself (reaction **6-40**), of the ester with itself (reaction **0-111**), and of the ketone with the ester but with the ester supplying the α-position (reaction **6-41**). The mechanism is the same as in reaction **0-111**.[1042]

OS **I,** 238; **II,** 126, 200, 287, 487, 531; **III,** 17, 251, 291, 387, 829; **IV,** 174, 210, 461, 536; **V,** 187, 198, 439, 567, 718, 747.

[1037] Becker, Mikol, and Russell, *J. Am. Chem. Soc.* **85,** 3410 (1963); Becker and Russell, *J. Org. Chem.* **28,** 1896 (1963); Corey and Chayovsky, *J. Am. Chem. Soc.* **86,** 1639 (1964); Russell and Mikol, *J. Am. Chem. Soc.* **88,** 5498 (1966); Russell, Sabourin, and Hamprecht, *J. Org. Chem.* **34,** 2339 (1969). For a review, see Durst, *Adv. Org. Chem.* **6,** 285–388 (1969), pp. 296–301.

[1038] Becker and Russell, Ref. 1037; Schank, Hasenfratz, and Weber, *Chem. Ber.* **106,** 1107 (1973); Ref. 878.

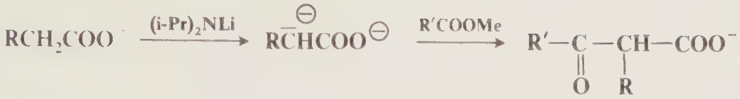
[1039] Corey and Seebach, Ref. 917.

[1040] Ref. 368. See also Herrman, Richman, Wepplo, and Schlessinger, *Tetrahedron Lett.* 4707 (1973); Ogura, Furukawa, and Tsuchihashi, *Chem. Lett.* 659 (1974).

[1041] Miles, Harris, and Hauser, *J. Org. Chem.* **30,** 1007 (1965).

[1042] Hill, Burkus, and Hauser, *J. Am. Chem. Soc.* **81,** 602 (1959).

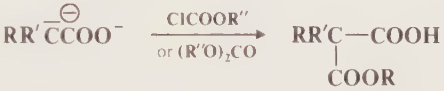
0-113 Acylation of Carboxylic Acid Salts



$$RCH_2COO^- \xrightarrow{(i\text{-}Pr)_2NLi} R\overset{\ominus}{C}HCOO^{\ominus} \xrightarrow{R'COOMe} R'-\underset{\substack{\| \\ O}}{C}-\underset{\substack{| \\ R}}{CH}-COO^-$$

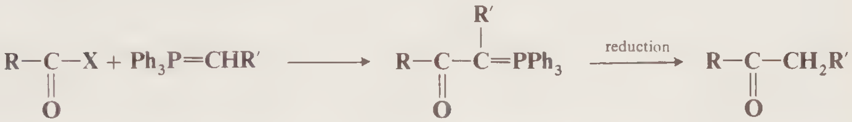
We have previously seen (reaction **0-98**) that dianions of carboxylic acids can be alkylated in the α-position. These ions can also be acylated on treatment with an ester[1043] to give salts of β-keto acids, which are isolated by conversion to trimethylsilyl esters which in turn are hydrolyzed to the free β-keto acids. As in reaction **0-98**, the carboxylic acid may be of the form RCH_2COOH or $RR''CHCOOH$. Since β-keto acids are so easily converted to ketones (reaction **2-39**), this is also a method for the preparation of ketones $R'COCH_2R$ and $R'COCHRR''$, where R′ can be primary, secondary, or tertiary alkyl, or aryl. If the ester is ethyl formate, an α-aldehydo carboxylate salt ($R' = H$) is formed, which on acidification spontaneously decarboxylates into an aldehyde.[1044] This is a method, therefore, for achieving the conversion $RCH_2COOH \rightarrow RCH_2CHO$, and as such is an alternative to the reduction methods discussed in reaction **0-83**.

When the substrate is an alkyl chloroformate or a dialkyl carbonate, mono esters of malonic acids are obtained.[1045]



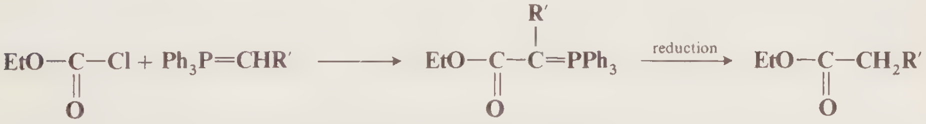
$$RR'\overset{\ominus}{C}COO^- \xrightarrow[\text{or }(R'O)_2CO]{ClCOOR''} RR'\underset{\substack{| \\ COOR}}{C}-COOH$$

0-114 Acylation of Phosphoranes



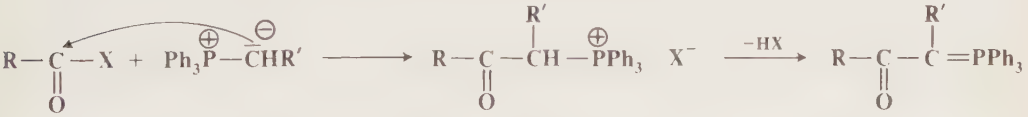
$$R-\underset{\substack{\| \\ O}}{C}-X + Ph_3P{=}CHR' \longrightarrow R-\underset{\substack{\| \\ O}}{C}-\overset{\substack{R' \\ |}}{C}{=}PPh_3 \xrightarrow{\text{reduction}} R-\underset{\substack{\| \\ O}}{C}-CH_2R'$$

Acyl halides, esters, and certain other acid derivatives react with phosphorus ylides (phosphoranes) containing an α-hydrogen to give stable β-keto alkylidene phosphoranes which can then be reduced to ketones.[1046] Ethyl chloroformate similarly gives esters:



$$EtO-\underset{\substack{\| \\ O}}{C}-Cl + Ph_3P{=}CHR' \longrightarrow EtO-\underset{\substack{\| \\ O}}{C}-\overset{\substack{R' \\ |}}{C}{=}PPh_3 \xrightarrow{\text{reduction}} EtO-\underset{\substack{\| \\ O}}{C}-CH_2R'$$

The initial reaction product is a phosphonium salt which loses HX:



$$R-\underset{\substack{\| \\ O}}{C}-X + Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}HR' \longrightarrow R-\underset{\substack{\| \\ O}}{C}-\overset{\substack{R' \\ |}}{C}H-\overset{\oplus}{P}Ph_3 \quad X^- \xrightarrow{-HX} R-\underset{\substack{\| \\ O}}{C}-\overset{\substack{R' \\ |}}{C}{=}PPh_3$$

When acyl halides are substrates, certain phosphoranes in which R′ = COR give O-acylated rather than C-acylated products.[1047]

[1043] Kuo, Yahner, and Ainsworth, *J. Am. Chem. Soc.* **93**, 6321 (1971).

[1044] Pfeffer and Silbert, *Tetrahedron Lett.* 699 (1970); Koch and Kop, *Tetrahedron Lett.* 603 (1974).

[1045] Krapčho, Jahngen, and Kashdan, *Tetrahedron Lett.* 2721 (1974).

[1046] For reviews, see Johnson, Ref. 870, pp. 45–48, 102–114; Bestmann, *Newer Methods Prep. Org. Chem.* **5**, 1–60 (1968), pp. 11–23, *Angew. Chem. Int. Ed. Engl.* **4**, 645–660 [*Angew. Chem.* **77**, 651–666]; Trippett, Ref. 870, pp. 424–426.

[1047] Chopard, Searle, and Devitt, *J. Org. Chem.* **30**, 1015 (1965).

0-115 Preparation of Acyl Cyanides

$$\mathrm{RCOX + CuCN \longrightarrow RCOCN}$$

Acyl cyanides can be prepared by treatment of acyl halides with copper cyanide.[1048] The mechanism is not known and might be free-radical or nucleophilic substitution. Sodium cyanide can also be employed if phase-transfer catalysts (p. 358) are used.[1049]

OS **III,** 119.

0-116 Preparation of Diazo Ketones

$$\mathrm{RCOX + CH_2N_2 \longrightarrow RCOCHN_2}$$

The reaction between acyl halides and diazomethane is of wide scope and is the best way to prepare diazo ketones.[1050] Diazomethane must be present in excess, or the HX produced will react with the diazo ketone (reaction **0-71**). This reaction is the first step of the Arndt-Eistert synthesis (reaction **8-9**). Diazo ketones can also be prepared directly from a carboxylic acid and diazomethane or diazoethane in the presence of dicyclohexylcarbodiimide.[1051]

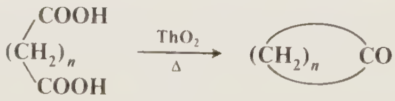
OS **III,** 119; **50,** 77; **53,** 35.

0-117 Ketonic Decarboxylation[1052]

$$\mathrm{2RCOOH \xrightarrow[ThO_2]{400\text{-}500^\circ C} RCOR + CO_2}$$

Carboxylic acids can be converted to symmetrical ketones by pyrolysis in the presence of thorium oxide. An alternative method involves heating of the ferrous salt of the acid.[1053] Although many books assert that ketones are prepared by heating calcium or barium salts of acids, in reality this reaction gives very low yields.[1054] However, methyl ketones have been prepared by heating barium acetate with barium salts of other acids in an example of a mixed process. In another mixed reaction, formic acid and another acid heated over thorium oxide give aldehydes. Mixed alkyl aryl ketones have been prepared by heating mixtures of ferrous salts.[1055] When the R group is large, the methyl ester rather than the acid can be decarbmethoxylated over thorium oxide to give the symmetrical ketone.

The reaction has been performed on dicarboxylic acids, whereupon cyclic ketones are obtained:



This process, called the *Ruzicka cyclization*, is good for the preparation of rings of six and seven members and, with lower yields, of eight members. In contrast to the lack of success with monocarboxylic acids, calcium and barium salts of dicarboxylic acids can be heated to give cyclic ketones of large rings (C_9 to C_{19}) as well as of five-, six-, and seven-membered rings. Cyclization can also be achieved by heating the dicarboxylic acid with $CdCO_3$.[1056]

[1048] For a review, see Thesing, Witzel, and Brehm, *Angew. Chem.* **68**, 425–435 (1956).

[1049] Koenig and Weber, *Tetrahedron Lett.* 2275 (1974).

[1050] For reviews, see Fridman, Ismagilova, Zalesov, and Novikov, *Russ. Chem. Rev.* **41**, 371–389 (1972); Ried and Mengler, *Fortschr. Chem. Forsch.* **5**, 1–88 (1965); Eistert, *Newer Methods Prep. Org. Chem.* **1**, 513–570 (1948).

[1051] Hodson, Holt, and Wall, *J. Chem. Soc. C* 971 (1970).

[1052] For a review, see Kwart and King, in Patai, Ref. 188, pp. 362–370.

[1053] Davis and Schultz, *J. Org. Chem.* **27**, 854 (1962).

[1054] Schultz and Sichels, *J. Chem. Educ.* **38**, 300 (1961).

[1055] Granito and Schultz, *J. Org. Chem.* **28**, 879 (1963).

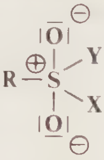
[1056] Liberman and Vasina, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 609 (1968); Liberman, Vasina, and Aleksandrova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **21**, 1942 (1972).

Not much work has been done on the mechanism of this reaction. However, a free-radical mechanism has been suggested on the basis of a thorough study (by means of a combined chromatograph mass spectrometer computer system) of all the side products.[1057]

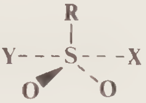
OS **I,** 192; **II,** 389; **IV,** 854; **V,** 589. Also see OS **IV,** 555, 560.

Nucleophilic Substitution at a Sulfonyl Sulfur Atom[1058]

Nucleophilic substitution at RSO_2X is similar to attack at RCOX. Many of the reactions are essentially the same, though sulfonyl halides are not as active as halides of carboxylic acids. Less work has been done on these reactions than on those at an acyl carbon. The actual mechanisms are not identical, because a "tetrahedral" intermediate in this case (**183**) would have five groups on the central atom.[1059] Though this is possible, since sulfur can accommodate up to 12 electrons in its valence shell, it seems more likely that these mechanisms more closely resemble the SN2 mechanism, with a trigonal pyramidal transition state (**184**). There are two major experimental results leading to this conclusion.



183



184

1. The stereospecificity of this reaction is more difficult to determine than that of nucleophilic substitution at a saturated carbon, where chiral compounds are relatively easy to prepare, but it may be recalled (p. 89) that optical activity is possible in a compound of the form RSO_2X if one oxygen is ^{16}O and the other ^{18}O. When a sulfonate ester possessing this type of chirality was converted to a sulfone with a Grignard reagent (reaction **0-123**), inversion of configuration was found.[1060] This is not incompatible with an intermediate such as **183,** but it is also in good accord with an SN2-like mechanism with backside attack.

2. More direct evidence against **183** (though still not conclusive) was found in an experiment involving acid and basic hydrolysis of aryl arenesulfonates, where it has been shown by the use of ^{18}O that an intermediate like **183** is not reversibly formed, since ester recovered when the reaction was stopped before completion contained no ^{18}O when the hydrolysis was carried out in the presence of labeled water.[1061]

Other evidence favoring the SN2-like mechanism comes from kinetics and substituent effects.[1062] However, evidence for the mechanism involving **183** is that the rates did not change much with changes in the leaving group[1063] and that ρ values were large, indicating that a negative charge builds up in the transition state.[1064]

[1057] Hites and Biemann, *J. Am. Chem. Soc.* **94,** 5772 (1972). See also Bouchoule, Blanchard, and Thomassin, *Bull. Soc. Chim. Fr.* 1773 (1973).

[1058] For a review of mechanisms of nucleophilic substitutions at di-, tri-, and tetracoordinated sulfur atoms, see Ciuffarin and Fava, *Prog. Phys. Org. Chem.* **6,** 81–109 (1968).

[1059] For a review, see Vizgert, *Russ. Chem. Rev.* **32,** 1–20 (1963).

[1060] Sabol and Andersen, *J. Am. Chem. Soc.* **91,** 3603 (1969). See also Williams, Nudelman, Booms, and Cram, *J. Am. Chem. Soc.* **94,** 4684 (1972); Jones and Cram, *J. Am. Chem. Soc.* **96,** 2183 (1974).

[1061] Christman and Oae, *Chem. Ind.* (*London*) 1251 (1959); Oae, Fukumoto, and Kiritani, *Bull. Chem. Soc. Jpn.* **36,** 346 (1963); Kaiser and Zaborsky, *J. Am. Chem. Soc.* **90,** 4626 (1968).

[1062] See for example, Robertson and Rossall, *Can. J. Chem.* **49,** 1441 (1971); Rogne, *J. Chem. Soc. B* 1855 (1971), *J. Chem. Soc., Perkin Trans. 2* 489 (1972).

[1063] Ciuffarin, Senatore, and Isola, *J. Chem. Soc., Perkin Trans. 2* 468 (1972).

[1064] Ciuffarin and Senatore, *Tetrahedron Lett.* 1635 (1974).

In certain cases in which the substrate carries an α-hydrogen, there is strong evidence[1065] that at least some of the reaction takes place by an elimination-addition mechanism (similar to the one shown on p. 352), going through a *sulfene* intermediate, e.g., the reaction between methanesulfonyl chloride and aniline.

$$CH_3{-}SO_2Cl \xrightarrow{\text{base}} \underset{\text{A sulfene}}{CH_2{=}SO_2} \xrightarrow{PhNH_2} CH_3{-}SO_2{-}NHPh$$

In the special case of nucleophilic substitution at a sulfonic ester, RSO_2OR', where R′ is alkyl, R′—O cleavage is much more likely than S—O cleavage, because the OSO_2R group is such a good leaving group (p. 326). Many of these reactions have been considered previously (e.g., reactions **0-4**, **0-16**, etc.), because they are nucleophilic substitutions at an alkyl carbon atom and not at a sulfur atom. However, when R′ is aryl, then the S—O bond is much more likely to cleave because of the very low tendency aryl substrates have for nucleophilic substitution.[1066]

The order of nucleophilicity toward a sulfonyl sulfur has been reported as $OH^- > RNH_2 > N_3^- > F^- > AcO^- > Cl^- > H_2O > I^-$.[1067] This order is similar to that at a carbonyl carbon (p. 324). Both these substrates can be regarded as relatively hard acids, in comparison with a saturated carbon which is considerably softer and which has a different order of nucleophilicity (p. 324).

0-118 Attack by OH. Hydrolysis of Sulfonic Acid Derivatives

$$RSO_2Cl \xrightarrow{H_2O} RSO_2OH$$

$$RSO_2OR' \xrightarrow[H^+]{H_2O} RSO_2OH$$

$$RSO_2NR'_2 \xrightarrow[H^+]{H_2O} RSO_2OH$$

Sulfonyl chlorides, and esters and amides of sulfonic acids, can be hydrolyzed to the corresponding acids. Sulfonyl chlorides can be hydrolyzed with water or with an alcohol in the absence of acid or base. Basic catalysis is also used, though the salt of course is the product obtained. Esters are readily hydrolyzed, many with water or dilute alkali. This is actually the same reaction as **0-4**, and usually involves R′—O cleavage, except when R′ is aryl. However, in some cases retention of configuration has been shown at alkyl R′, indicating S—O cleavage in these cases.[1068] Sulfonamides are generally not hydrolyzed by alkaline treatment, not even with hot concentrated alkali,[1069] but acids hydrolyze them, though less readily than they do sulfonyl halides or sulfonic esters. Of course, ammonia or the amine appears as the salt. However, sulfonamides can be hydrolyzed with base if the solvent is HMPT.[1070] Sulfonamides of the form RSO_2NH_2 can also be hydrolyzed with HNO_2 in a reaction similar to **0-5**. Primary and secondary amines can be obtained from N-substituted and N,N-disubstituted sulfonamides, respectively,[1071] and alcohols from sulfonic esters,[1072] by treatment with sodium naphthalene radical ion in 1,2-dimethoxyethane or tetrahydrofuran.

[1065] For a review, see Opitz, *Angew. Chem. Int. Ed. Engl.* **6,** 107–123 (1967) [*Angew. Chem.* **79,** 161–177]. See also King and Lee, *J. Am. Chem. Soc.* **91,** 6524 (1969); Douglas and Williams, *J. Chem. Soc., Chem. Commun.* 356 (1973); Williams, Douglas, and Loran, *J. Chem. Soc., Chem. Commun.* 689 (1974).

[1066] See, for example, Oae, Fukumoto, and Kiritani, *Bull. Chem. Soc. Jpn.* **36,** 346 (1963); Oae and Kiritani, *Bull. Chem. Soc. Jpn.* **38,** 765 (1965); Tagaki, Kurusu, and Oae, *Bull. Chem. Soc. Jpn.* **42,** 2894 (1969).

[1067] Kice, Kasperek, and Patterson, *J. Am. Chem. Soc.* **91,** 5516 (1969); Rogne, *J. Chem. Soc. B* 1056 (1970); Ref. 276.

[1068] Chang, *Tetrahedron Lett.* 305 (1964).

[1069] For a review, see Searles and Nukina, *Chem. Rev.* **59,** 1077–1103 (1959).

[1070] Cuvigny and Larchevêque, *J. Organmet. Chem.* **64,** 315 (1974).

[1071] Ji, Gortler, Waring, Battisti, Bank, Closson, and Wriede, *J. Am. Chem. Soc.* **89,** 5311 (1967); Closson, Ji, and Schulenberg, *J. Am. Chem. Soc.* **92,** 650 (1970).

OS **I,** 14; **II,** 471; **III,** 262; **IV,** 34; **V,** 406. Also see OS **V,** 673; **54,** 33.

0-119 Attack by OR. Formation of Sulfonic Esters

$$\mathbf{RSO_2Cl + R'OH \xrightarrow{\text{base}} RSO_2OR'}$$

$$\mathbf{RSO_2NR''_2 + R'OH \xrightarrow{\text{base}} RSO_2OR' + NHR''_2}$$

Sulfonic esters are most frequently prepared by treatment of the corresponding halides with alcohols in the presence of a base. The method is much used for the conversion of alcohols to tosylates,[1073] brosylates, and similar sulfonic esters (p. 326). Both R and R′ may be alkyl or aryl. The base is often pyridine, which functions as a nucleophilic catalyst,[1074] as in the similar alcoholysis of carboxylic acyl halides (**0-22**). Primary alcohols react the most rapidly, and it is often possible to sulfonate selectively a primary OH group in a molecule which also contains secondary or tertiary OH groups. The reaction with sulfonamides has been much less often used and is limited to N,N-disubstituted sulfonamides; that is, R″ may not be hydrogen. However, within these limits it is a useful reaction.[1069] The nucleophile in this case is actually $R'O^-$. However, R″ may be hydrogen (as well as alkyl) if the nucleophile is a phenol, so that the product is RSO_2OAr. Acidic catalysts are used in this case.[1075]

OS **I,** 145; **III,** 366; **IV,** 753; **55,** 57, 114. Also see OS **IV,** 529; **54,** 79, 84.

0-120 Attack by Nitrogen. Formation of Sulfonamides

$$\mathbf{RSO_2Cl + NH_3 \longrightarrow RSO_2NH_2}$$

The treatment of sulfonyl chlorides with ammonia or amines is the usual way of preparing sulfonamides. Primary amines give N-alkyl sulfonamides, and secondary amines give N,N-dialkyl sulfonamides. The reaction is the basis of the *Hinsberg test* for distinguishing between primary, secondary, and tertiary amines. N-Alkyl sulfonamides, having an acidic hydrogen, are soluble in alkali, while N,N-dialkyl sulfonamides are not. Since tertiary amines are usually recovered unchanged, primary, secondary, and tertiary amines can be told apart. However, the test is limited for at least two reasons.[1076] (1) Many N-alkyl sulfonamides in which the alkyl group has six or more carbons are insoluble in alkali, despite their acidic hydrogen,[1077] so that a primary amine may appear to be a secondary amine. (2) If the reaction conditions are not carefully controlled, tertiary amines may not be recovered unchanged.[1076] In fact, the reason the test often does succeed with aliphatic tertiary amines is not that they do not react with RSO_2Cl, but that (when the reagents are mixed in a 1 : 1 ratio) the reaction gives quaternary sulfonamide salts $RSO_2NR_3^+\ \ X^-$ which are hydrolyzed to RSO_2O^- under the usual aqueous basic conditions. When other proportions are used, or when aryl tertiary amines ($ArNR_2$) are involved, other reactions may take place and, if so, the test is negated.

A primary or a secondary amine can be protected by reaction with phenacylsulfonyl chloride ($PhCOCH_2SO_2Cl$) to give a sulfonamide $RNHSO_2CH_2COPh$ or $R_2NSO_2CH_2COPh$.[1078] The protecting group can be removed when desired with zinc and acetic acid. Sulfonamides can also be prepared from other sulfonamides in a transamination reaction.[1069] Sulfonyl chlorides react with azide ion to give sulfonyl azides RSO_2N_3.[1079]

[1072] Closson, Wriede, and Bank, *J. Am. Chem. Soc.* **88,** 1581 (1966).

[1073] For a procedure, see Fieser and Fieser, Ref. 376, vol. 1, p. 1180 (1967).

[1074] Rogne, *J. Chem. Soc. B* 1334 (1971).

[1075] Klamann and Fabienke, *Chem. Ber.* **93,** 252 (1960).

[1076] For directions for performing and interpreting the Hinsberg test, see Gambill, Roberts, and Shechter, *J. Chem. Educ.* **49,** 287 (1972).

[1077] Fanta and Wang, *J. Chem. Educ.* **41,** 280 (1964).

[1078] Hendrickson and Bergeron, *Tetrahedron Lett.* 345 (1970).

OS **IV,** 34, 943; **V,** 39, 179, 1055; **52,** 11.

0-121 Attack by Halogen. Formation of Sulfonyl Halides

$$\mathbf{RSO_2OH + PCl_5 \longrightarrow RSO_2Cl}$$

This reaction, parallel with reaction **0-75,** is the standard method for the preparation of sulfonyl halides. Also used are PCl_3 and $SOCl_2$, and sulfonic acid salts can also serve as substrates. Sulfonyl bromides and iodides have been prepared from sulfonyl hydrazides ($ArSO_2NHNH_2$, themselves prepared by reaction **0-120**) by treatment with bromine or iodine.[1080]

OS **I,** 84; **IV,** 571, 693, 846, 937; **V,** 196.

0-122 Attack by Hydrogen. Reduction of Sulfonyl Chlorides

$$\mathbf{2RSO_2Cl + Zn \longrightarrow (RSO_2)_2Zn \xrightarrow{H^+} 2RSO_2H}$$

Sulfinic acids can be prepared by reduction of sulfonyl chlorides.[1081] Though mostly done on aromatic sulfonyl chlorides, the reaction has also been applied to alkyl compounds. Besides zinc, sodium sulfite, hydrazine, sodium sulfide, and other reducing agents have been used. For reduction of sulfonyl chlorides to mercaptans, see reaction **9-55.**

OS **I,** 7, 492; **IV,** 674.

0-123 Attack by Carbon. Preparation of Sulfones

$$\mathbf{ArSO_2Cl + Ar'MgX \longrightarrow ArSO_2Ar'}$$

Grignard reagents convert aromatic sulfonyl chlorides to sulfones. Esters of aromatic sulfonic acids can also serve as substrates.

[1079] For an example, see Regitz, Hocker, and Liedhegener, *Org. Synth.* **V,** 179.

[1080] Poshkus, Herweh, and Magnotta, *J. Org. Chem.* **28,** 2766 (1963); Litvinenko, Dadali, Savelova, and Krichevtsova, *J. Gen. Chem. USSR* **34,** 3780 (1964).

[1081] For a review, see Truce and Murphy, *Chem. Rev.* **48,** 69–124 (1951), pp. 69–83.

Eleven

Aromatic Electrophilic Substitution

Most substitutions at an aliphatic carbon are nucleophilic. In aromatic systems the situation is reversed, because the high electron density at the aromatic ring attracts positive species and not negative ones. In electrophilic substitutions the attacking species is a positive ion or the positive end of a dipole or induced dipole. The leaving group (the electrofuge) must necessarily depart without its electron pair. In nucleophilic substitutions, the chief leaving groups are those best able to carry the unshared pair: Br^-, H_2O, OTs^-, etc., that is, the weakest bases. In electrophilic substitutions, the most important leaving groups are those which can best exist without the pair of electrons necessary to fill the outer shell, that is, the weakest Lewis acids. The most common leaving group in electrophilic aromatic substitutions is the proton.

MECHANISMS

Electrophilic aromatic substitutions are unlike nucleophilic substitutions in that the large majority proceed by just one mechanism with respect to the substrate.[1] In this mechanism, which we call the *arenium-ion mechanism*, the electrophilic attacks in the first step, giving rise to a positively charged intermediate (the arenium ion), and the leaving group departs in the second step, so that there is a resemblance to the tetrahedral mechanism of Chapter 10, but with the charges reversed. Another mechanism, much less common, consists of the opposite behavior: the leaving group departs *before* the electrophile arrives. This mechanism, the SE1 mechanism, corresponds to the SN1 mechanism of nucleophilic substitution. Simultaneous attack and departure mechanisms (corresponding to SN2) are not found at all. An addition-elimination mechanism has been postulated in one case (see reaction **1-6**).

The Arenium-ion Mechanism[2]

In the arenium-ion mechanism, the attacking species may be produced in various ways, often in several different ways even for the same reaction, and the same reaction may have different attacking species under different conditions, but what happens to the aromatic ring is basically the same in all cases. For this reason most attention in the study of this mechanism centers around the identity of the attacking entity and how it is produced.[3]

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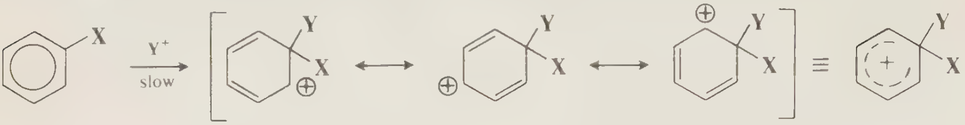
[1] For monographs, see Norman and Taylor, "Electrophilic Substitution in Benzenoid Compounds," American Elsevier Publishing Company, New York, 1965; de la Mare and Ridd, "Aromatic Substitution—Nitration and Halogenation," Academic Press, Inc., New York, 1959; for a review, see Taylor, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 13, pp. 1-406, American Elsevier Publishing Company, New York, 1972.

[2] This mechanism is sometimes called the SE2 mechanism, because it is bimolecular, but in this book we reserve that name for aliphatic substrates (see Chapter 12).

[3] For a review of the mechanism of the substitution process itself, see Berliner, *Prog. Phys. Org. Chem.* **2**, 253-321 (1964).

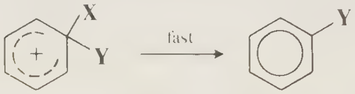
The electrophile may be a positive ion or a dipole. If it is a positive ion, it attacks the ring, removing a pair of electrons from the sextet, to give a carbonium ion:



1 2

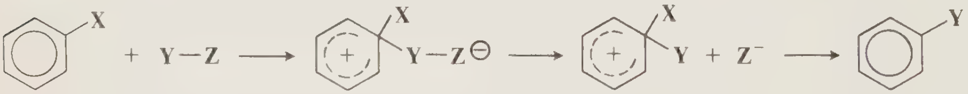
which is a resonance hybrid, as shown in **1**, and is frequently represented as in **2**. Ions of this type are called[4] *Wheland intermediates*, *σ complexes*, or *arenium ions*.[5] In the case of benzenoid systems they are cyclohexadienyl cations. It may easily be seen that the great stability associated with an aromatic sextet is no longer present in **1**, although the ion is stabilized by resonance of its own. The arenium ion is generally a highly reactive intermediate and must stabilize itself by a further reaction, though it has been isolated (see p. 456).

Carbonium ions may stabilize themselves in various ways (see p. 159), but for an ion of this type the most likely way[6] is by loss of either X^+ or Y^+, since the aromatic sextet will then be restored, and in fact this is the second step of the mechanism:



The second step is nearly always faster than the first, so that the first is rate-determining and the reaction is second order (unless the *formation* of the attacking species is slower still, in which case the aromatic compound does not take part in the rate expression at all). If Y^+ is lost, then there is no net reaction, but if X^+ is lost, an aromatic substitution has taken place. If X^+ is a proton, then a base is necessary to help remove it.

If the attacking species is not an ion but a dipole, then the product must have a negative charge unless part of the dipole, with its pair of electrons, is broken off somewhere in the process, e.g.,



The questions as to what the attacking entity is in each case, and how it is formed, are discussed for each reaction in the reactions section of this chapter.

The evidence for the arenium-ion mechanism is mainly of two kinds:

1. *Isotope effects.*[7] If the hydrogen ion departed before the arrival of the electrophile (SE1 mechanism) or if the arrival and departure were simultaneous, then there should be a substantial isotope effect (that is, deuterated substrates should undergo substitution more slowly than nondeuterated compounds) because, in each case, the C—H bond is broken in the rate-determining step. However, in the arenium-ion mechanism, the C—H bond is not broken in the rate-determining step, and so no isotope effect should be found. Many such studies have been carried out and, in most cases, especially in the case of nitrations, there is no isotope effect.[8] This result is incompatible with either the SE1 or the simultaneous mechanism.

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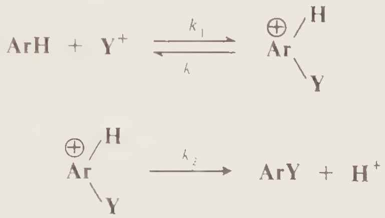
[4] Just what to call these ions has been a matter for debate. The term σ complex is a holdover from the time when much less was known about the structure of carbonium ions and it was thought they might be complexes of the type discussed in Chapter 3. Other names have also been used. Henceforth we will call them arenium ions, following the suggestion of Olah, *J. Am. Chem. Soc.* **94**, 808 (1972).

[5] For reviews of arenium ions formed by addition of a proton to an aromatic ring, see Brouwer, Mackor, and MacLean, in Olah and Schleyer, "Carbonium Ions," vol. 2, pp. 837–897, Interscience Publishers, New York, 1970; Perkampus and Baumgarten, *Angew. Chem. Int. Ed. Engl.* **3**, 776–783 (1964) [*Angew. Chem.* **76**, 965–972]; Perkampus, *Adv. Phys. Org. Chem.* **4**, 195–304 (1966).

[6] For a discussion of cases in which **1** stabilizes itself in other ways, see de la Mare, *Acc. Chem. Res.* **7**, 361–368 (1974).

[7] For reviews of hydrogen isotope effects in aromatic substitutions, see Zollinger, *Adv. Phys. Org. Chem.* **2**, 163–200 (1964); Ref. 3, pp. 281–294.

However, in many instances isotope effects have been found. Since the values are generally much lower than we would expect for either the SE1 or the simultaneous mechanisms (for example, 1 to 3 for k_{H} k_{D} instead of 6 to 7), we must look elsewhere for the explanation. For the case where hydrogen is the leaving group, the arenium-ion mechanism may be summarized:



Step 1 $$\mathrm{ArH} + \mathrm{Y}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overset{\oplus}{\mathrm{Ar}}(\mathrm{H})(\mathrm{Y})$$

Step 2 $$\overset{\oplus}{\mathrm{Ar}}(\mathrm{H})(\mathrm{Y}) \xrightarrow{k_2} \mathrm{ArY} + \mathrm{H}^+$$

Isotope effects can arise from this mechanism in at least two ways.[9] If the second step has a rate comparable to or less than the first ($k_2[\mathrm{ArHY}^+] \lesseqgtr k_1[\mathrm{ArH}][\mathrm{Y}^+]$), then there will obviously be an isotope effect. However, it is probable that most isotope effects in aromatic substitutions are not caused by this circumstance and that the first step is generally much slower than the second. It is likely that most isotope effects arise from the reversibility of step 1 by a *partitioning effect*. The rate at which ArHY^+ reverts to ArH should be essentially the same as that at which ArDY^+ (or ArTY^+) reverts to ArD (or ArT), since the Ar—H bond is not cleaving. However, ArHY^+ should go to ArY faster than either ArDY^+ or ArTY^+, since the Ar—H bond is broken in this step. If $k_2 \gg k_{-1}$, this does not matter: since a large majority of the intermediates go to product, the rate is determined only by the slow step ($k_1[\mathrm{ArH}][\mathrm{Y}^+]$), and no isotope effect is predicted. However, if $k_2 \lesseqgtr k_{-1}$, then reversion to starting materials is important. If k_2 for ArDY^+ (or ArTY^+) is less than k_2 for ArHY^+, but k_{-1} is the same, then a larger proportion of ArDY^+ reverts to starting compounds. That is, k_2 k_{-1} (the *partition factor*) for ArDY^+ is less than that for ArHY^+. Consequently, the reaction is slower for ArD than for ArH, and an isotope effect is observed.

One circumstance which could affect the k_2/k_{-1} ratio is steric hindrance. Thus, diazonium coupling of **3** gave no isotope effect, while coupling of **5** gave a $k_{\mathrm{H}}/k_{\mathrm{D}}$ ratio of 6.55.[10] For steric reasons it is much more difficult for **6** to lose a proton (it is harder for a base to approach) than it is for **4**, so k_2 is greater for the latter. Since no base is necessary to remove $\mathrm{ArN_2}^+$, k_{-1} does not depend on steric factors[11] and is about the same for each. Thus the partition factor k_2 k_{-1} is sufficiently different for **4** and **6** that **5** exhibits a large isotope effect and **3** exhibits none.[12] Base

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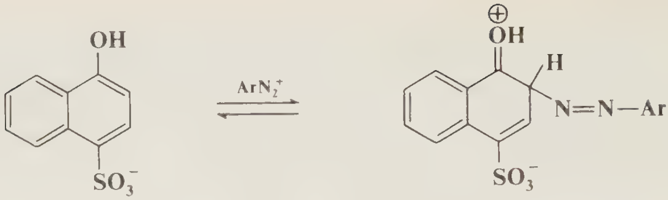
[8] The pioneering studies were by Melander: Melander, *Ark. Kemi* **2,** 211 (1950); Berglund-Larsson and Melander, *Ark. Kemi* **6,** 219 (1953). Zollinger, in Ref. 7, presents a table of isotope-effect results.

[9] For a discussion, see Hammett, "Physical Organic Chemistry," 2d ed., pp. 172–182, McGraw-Hill Book Company, New York, 1970.

[10] Zollinger, *Helv. Chim. Acta* **38,** 1597, 1617, 1623 (1955).

[11] Snyckers and Zollinger, *Helv. Chim. Acta* **53,** 1294 (1970).

[12] For some other examples of isotope effects caused by steric factors, see Helgstrand, *Acta Chem. Scand.* **19,** 1583 (1965); Helgstrand and Nilsson, *Acta Chem. Scand.* **20,** 1463 (1966); Nilsson, *Acta Chem. Scand.* **21,** 2423 (1967); Baciocchi, Illuminati, Sleiter, and Stegel, *J. Am. Chem. Soc.* **89,** 125 (1967); Myhre, Beug, and James, *J. Am. Chem. Soc.* **90,** 2105 (1968); Dubois and Uzan, *Bull. Soc. Chim. Fr.* 3534 (1968); Márton, *Acta Chem. Scand.* **23,** 3321, 3329 (1969).



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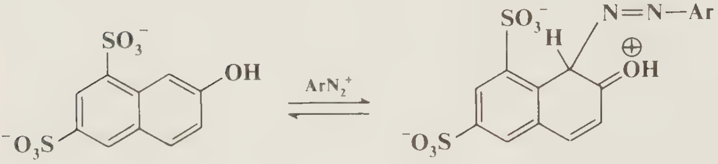


5 6

catalysis can also affect the partition factor, since an increase in base concentration increases the rate at which the intermediate goes to product without affecting the rate at which it reverts to starting materials. In some cases, isotope effects can be diminished or eliminated by a sufficiently high concentration of base.

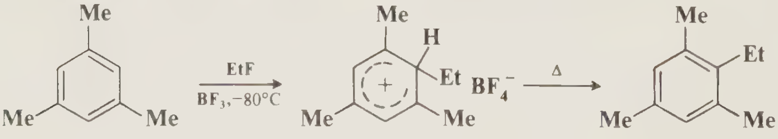
Small isotope effects can also arise in other ways (for example, in the step $ArXH^+ \rightarrow ArH$ there may be a *secondary* isotope effect), and not all the results are fully understood.

Evidence for the arenium-ion mechanism has also been obtained from another kind of isotope-effect experiment, involving substitutions of the type

$$ArMR_3 + H_3O^+ \longrightarrow ArH + R_3MOH_2^+$$

where M was Si, Ge, Sn, or Pb, and R was methyl or ethyl. In these reactions the proton is the electrophile. If the arenium-ion mechanism is operating, then the use of D_3O^+ should give rise to an isotope effect, since the D—O bond would be broken in the rate-determining step. Isotope effects of 1.55 to 3.05 were obtained,[13] in accord with the arenium-ion mechanism.

2. *Isolation of arenium ion intermediates.* Very strong evidence for the arenium-ion mechanism comes from the isolation of arenium ions in a number of instances.[14] For example, **7** was isolated as a solid with melting point −15°C from treatment of mesitylene with ethyl fluoride and the catalyst BF_3 at −80 C. When **7** was heated, the normal substitution product **8** was obtained.[15]



7 8

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[13] Bott, Eaborn, and Greasley, *J. Chem. Soc.* 4803 (1964).

[14] For a review, see Koptyug, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23,** 1031–1045 (1974).

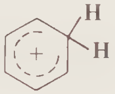
[15] Olah and Kuhn, *J. Am. Chem. Soc.* **80,** 6541 (1958). For other examples see Ershov and Volod'kin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 680 (1962); Farrell, Newton, and White, *J. Chem. Soc. B* 637 (1967); Niess, Nagel, and Effenberger, *Tetrahedron Lett.* 4265 (1968); Menzel and Effenberger, *Angew. Chem. Int. Ed. Engl.* **11,** 922 (1972); **14,** 62 (1975) [*Angew. Chem.* **84,** 954; **87,** 71]; Detsina and Koptyug, *J. Org. Chem. USSR* **8,** 2202 (1972); Kamshii and Koptyug, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23,** 232 (1974); Olah, Lin, and Mo, *J. Am. Chem. Soc.* **94,** 3667 (1972); Olah, Lin, and Forsyth, *J. Am. Chem. Soc.* **96,** 6908 (1974); Olah, Spear, Messina, and Westerman, *J. Am. Chem. Soc.* **97,** 4051 (1975).

TABLE 1 Relative stabilities of arenium ions and π complexes and relative rates of chlorination and nitration

In each case, p-xylene = 1.00

Substituents	Relative arenium-ion stability[18]	Relative π-complex stability[18]	Rate of chlorination[19]	Rate of nitration[24]
None (benzene)	0.09	0.61	0.0005	0.51
Me	0.63	0.92	0.157	0.85
p-Me$_2$	1.00	1.00	1.00	1.00
o-Me$_2$	1.1	1.13	2.1	0.89
m-Me$_2$	26	1.26	200	0.84
1,2,4-Me$_3$	63	1.36	340	
1,2,3-Me$_3$	69	1.46	400	
1,2,3,4-Me$_4$	400	1.63	2000	
1,2,3,5-Me$_4$	16,000	1.67	240,000	
Me$_5$	29,000		360,000	

Even the simplest such ion, the benzenium ion (**9**) has been prepared in $HF–SbF_5–SO_2ClF–SO_2F_2$ at −134°C, where it could be studied spectrally.[16]



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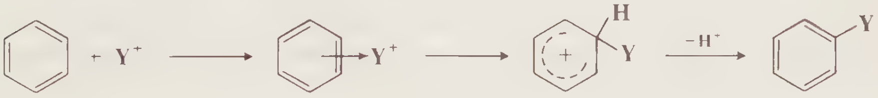
In Chapter 3 it was mentioned that positive ions can form addition complexes with π systems. Since the initial step of electrophilic substitution involves attack by a positive ion on an aromatic ring, it has been suggested[17] that such a complex, called a *π complex* (represented as **10**), is formed first and then is converted to the arenium ion **11.** Stable solutions of arenium ions or π complexes (e.g., with Br_2, I_2, picric acid, Ag^+, or HCl) can be formed at will. For example, π complexes are formed when aromatic hydrocarbons are treated with HCl alone, but the use of HCl plus a Lewis acid (e.g., $AlCl_3$) gives arenium ions. The two types of solution have very different properties. For example, a solution of an arenium ion is colored and conducts electricity (showing positive and negative ions are present), while a π complex formed from HCl and benzene is colorless and does not conduct a current. Furthermore, when DCl is used to form a π complex, no deuterium exchange takes place (because there is no covalent bond between the electrophile and the ring), while formation of an arenium ion with DCl and $AlCl_3$ gives deuterium exchange. The relative stabilities of some methylated arenium ions and π complexes are shown in Table 1.



10 **11**

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[16] Olah, Schlosberg, Porter, Mo, Kelly, and Mateescu, *J. Am. Chem. Soc.* **94,** 2034 (1972).

[17] Dewar, "Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, 1949.

The arenium ion stabilities listed here were determined by the relative basicity of the substrate toward HF.[18] The π-complex stabilities are relative equilibrium constants for the reaction[19] between the aromatic hydrocarbon and HCl. As shown in Table 1, the relative stabilities of the two types of species are very different, the π-complex stability changing very little with methyl substitution, but the arenium-ion stability changing a great deal. There are at least two reasons for this difference. (1) A methyl group stabilizes an adjacent positive charge (p. 153). In an arenium ion a full unit of positive charge is present on the ring, but in a π complex very little charge has been transferred to the ring. (2) In a π complex, the small amount of charge is spread over the entire ring, so that a methyl group can stabilize it more or less equally from any position, but an arenium ion is a hybrid of three canonical forms (**1**), and the charge is localized on three of the six carbons. A methyl group located on one of these three is particularly effective in stabilizing a positive charge.

How can we tell if **10** is present on the reaction path? If it is present, then there are two possibilities: (1) The formation of **10** is rate-determining (the conversion of **10** to **11** is much faster), or (2) the formation of **10** is rapid, and the conversion **10** to **11** is rate-determining. One way to ascertain which species is formed in the rate-determining step in a given reaction is to use the stability information given in Table 1. We measure the relative rates of reaction of a given electrophile with the series of compounds listed in Table 1. If the relative rates resemble the arenium-ion stabilities, then we conclude that the arenium ion is formed in the slow step; but if they resemble the stabilities of the π complexes, then the latter are formed in the slow step.[20] When such experiments are carried out, it is found in most cases that the relative rates are similar to the arenium-ion and not to the π-complex stabilities. For example, Table 1 lists chlorination rates.[19] Similar results have been obtained in room-temperature bromination with Br_2 in acetic acid[21] and in acetylation with $CH_3CO^+ \ SbF_6^-$.[22] It is clear that in these cases the π complex either does not form at all, or if it does, its formation is not rate-determining (unfortunately, it is very difficult to distinguish between these two possibilities).

On the other hand, in nitration with the powerful electrophile NO_2^+ (in the form of $NO_2^+ \ BF_4^-$) the relative rates resembled[23] π-complex stabilities much more than they did arenium-ion stabilities (Table 1),[24] and similar results were obtained for bromination with Br_2 and $FeCl_3$ in nitromethane.[25] These results were taken to mean[24,25] that in these cases π-complex formation is rate-determining (which means of course that they must be on the reaction path); and if so, it is likely that π complexes are also on the reaction path even where formation of arenium ions is rate-determining. However, the conclusion that π-complex formation is rate-determining has been challenged[26] on several grounds, especially for the nitration case. The current position seems to be that there is no conclusive evidence that π complexes are involved at all[27] (for further discussion of this question, see p. 472).

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[18] Kilpatrick and Luborsky, *J. Am. Chem. Soc.* **75,** 577 (1953).

[19] Brown and Brady, *J. Am. Chem. Soc.* **74,** 3570 (1952).

[20] Condon, *J. Am. Chem. Soc.* **74,** 2528 (1952).

[21] Brown and Stock, *J. Am. Chem. Soc.* **79,** 1421 (1957).

[22] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86,** 2203 (1964). See also Olah, Lukas, and Lukas, *J. Am. Chem. Soc.* **91,** 5319 (1969).

[23] It has been pointed out, nevertheless, that a straight line cannot be drawn when the nitration rate is plotted against π-complex stability: Rys, Skrabal, and Zollinger, *Angew. Chem. Int. Ed. Engl.* **11,** 874–883 (1972) [*Angew. Chem.* **84,** 921–930].

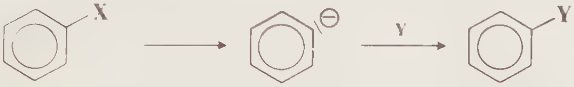
[24] Olah, Kuhn, and Flood, *J. Am. Chem. Soc.* **83,** 4571, 4581 (1961).

[25] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86,** 1039, 1044 (1964).

[26] For some of these challenges, see Tolgyesi, *Can. J. Chem.* **43,** 343 (1965); Caille and Corriu, *Chem. Commun.* 1251 (1967), *Tetrahedron* **25,** 2005 (1969); Coombes, Moodie, and Schofield, *J. Chem. Soc. B* 800 (1968); Hoggett, Moodie, and Schofield, *J. Chem. Soc. B* 1 (1969); Christy, Ridd, and Stears, *J. Chem. Soc. B* 797 (1970); Ridd, *Acc. Chem. Res.* **4,** 248–253 (1971); Taylor and Tewson, *J. Chem. Soc., Chem. Commun.* 836 (1973); Ref. 23. For replies to some of these challenges and further support for π complexes, see Olah and Overchuk, *Can. J. Chem.* **43,** 3279 (1965); Olah, Tashiro, and Kobayashi, *J. Am. Chem. Soc.* **92,** 6369 (1970); Olah, Kobayashi, and Tashiro, *J. Am. Chem. Soc.* **94,** 7448 (1972); Olah, *Acc. Chem. Res.* **4,** 240–248 (1971); Olah and Kobayashi, *J. Am. Chem. Soc.* **93,** 6964 (1971); Olah and Lin, *J. Am. Chem. Soc.* **96,** 2892 (1974).

The SE1 Mechanism

The SE1 mechanism (*substitution electrophilic unimolecular*) is rare, being found only in certain cases in which carbon is the leaving atom (see reactions **1-42, 1-43**), or when a very strong base is present (see reactions **1-1, 1-12, 1-48**).[28] It consists of two steps with an intermediate carbanion.



Reactions **2-40, 2-44,** and **2-45** also take place by this mechanism when applied to aryl substrates.

ORIENTATION AND REACTIVITY

Orientation and Reactivity in Monosubstituted Benzene Rings[29]

When an electrophilic substitution reaction is performed on a monosubstituted benzene, the new group may be directed primarily to the ortho, meta, or para position, and the substitution may be slower or faster than with benzene itself. The group already on the ring determines which position the new group will take and whether the reaction will be slower or faster than with benzene. Groups which increase the reaction rate are called *activating*, and those which slow it, *deactivating*. Some groups are predominantly meta-directing; all of these are deactivating. Others are mostly ortho-para-directing; some of these are deactivating too, but most are activating. Groups direct *predominantly*, but usually not *exclusively*. For example, nitration of nitrobenzene gave 93% *m*-dinitrobenzene, 6% of the ortho, and 1% of the isomer.

The orientation and reactivity effects of each group are explained on the basis of resonance and field effects on the stability of the intermediate arenium ion. In order to understand why we can use this approach, it is necessary to know that in these reactions the product is usually kinetically and not thermodynamically controlled (see p. 194). Some of the reactions are irreversible, and the others are usually stopped well before equilibrium is reached. Therefore, which of the three possible intermediates is formed is dependent not on the thermodynamic stability of the products, but on the activation energy necessary to form each of the three intermediates. It is not easy to predict which of the three activation energies is lowest, but we make the assumption that the free-energy profile resembles either Figure 2 or 3 in Chapter 6 (p. 193). In either case, the transition state is closer in energy to the arenium-ion intermediate than it is to the starting compounds. Invoking the Hammond postulate (p. 194), we can then assume that the geometry of the transition state also resembles that of the intermediate and that anything which will increase the stability of the intermediate will also lower the activation energy necessary to attain it. Since the intermediate, once formed, is rapidly converted to products, we can use the relative stabilities of the three intermediates as guides to predict which products will predominantly form. Of course, if reversible reactions are allowed to proceed to equilibrium, we may get product ratios which are quite different. For example, the sulfonation of naphthalene at 80°C, where the reaction does not reach equilibrium, gives mostly α-naphthalenesulfonic acid,[30] while at 160°C, where equilibrium is obtained, the β-isomer predominates[31] (the α-isomer is thermodynamically less stable, because of steric interaction between the SO_3H group and the hydrogen at the 8 position). An example from the benzene series is as follows: when ethylbenzene is ethylated under the usual Friedel-Crafts conditions (reaction **1-13**), the products are chiefly the *o*- and *p*-diethylbenzenes, but treatment of either *o*-, *m*-, or *p*-diethylbenzene with $AlCl_3$ eventually gives an equilibrium mixture which contains 3% *o*-, 69% *m*-, and 28% *p*-diethylbenzenes.[32] This result is in accord with the thermodynamic stabilities of the products.[33]

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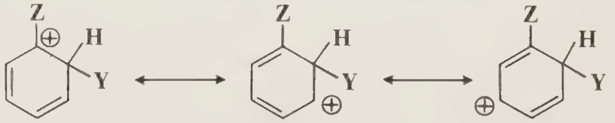
[27] For an excellent discussion of the whole question, see Banthorpe, *Chem. Rev.* **70,** 295–322 (1970), especially sections VI and IX.

[28] It has also been found with a metal ($SnMe_3$) as electrofuge: Eaborn, Hornfeld, and Walton, *J. Chem. Soc. B* 1036 (1967).

[29] For reviews of orientation and reactivity in benzene and other aromatic rings, see Hoggett, Moodie, Penton, and Schofield, "Nitration and Aromatic Reactivity," pp. 122–145, 163–220, Cambridge University Press, London, 1971; Ferguson, *Chem. Rev.* **50,** 47–67 (1952).

Now that we see why we can use the relative stabilities of the arenium ions to predict orientation effects, let us examine the three possible ions:

Ortho



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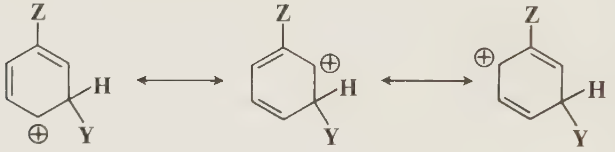
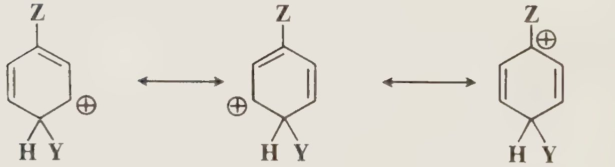
Meta



Para



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For each ion we see that the ring has a positive charge. We can therefore predict that any group Z which has an electron-donating field effect should stabilize all three ions (relative to **1**), but that electron-withdrawing groups, which increase the positive charge on the ring, should destabilize them. But we can make a further prediction concerning field effects. These taper off with distance and are thus strongest at the carbon connected to the group Z. But of the three arenium ions, only the ortho and para have any positive charge at this carbon. None of the canonical forms of the meta ion has a positive charge there, and so the hybrid has none either. Therefore, $+I$ groups should stabilize all three ions but mostly the ortho and para, so they should be not only activating but ortho-para-directing as well. On the other hand, $-I$ groups, by removing electron density, should destabilize all three ions but mostly the ortho and para, and should be not only deactivating but also meta-directing.

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[30] Fierz and Weissenbach, *Helv. Chim. Acta* **3**, 312 (1920).

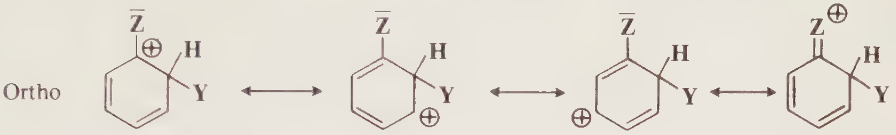
[31] Witt, *Ber.* **48**, 743 (1915).

[32] Olah, Meyer, and Overchuk, *J. Org. Chem.* **29**, 2313 (1964).

[33] Stull, in Olah, "Friedel-Crafts and Related Reactions," vol. 1, pp. 980–982, Interscience Publishers, New York, 1963. Actually, the values in this reference are for the three xylenes, but the order of stability is undoubtedly the same for the diethylbenzenes.

These conclusions are correct as far as they go, but they do not lead to the proper results in all cases. In many cases there is *resonance interaction* between Z and the ring, and this also affects the relative stability, in some cases in the same direction as the field effect, but in others differently.

Some Z groups have a pair of electrons (usually unshared) which may be contributed *toward* the ring. The three arenium ions would then look like this:



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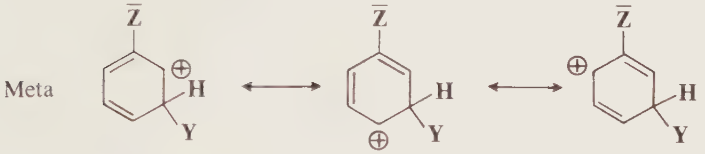

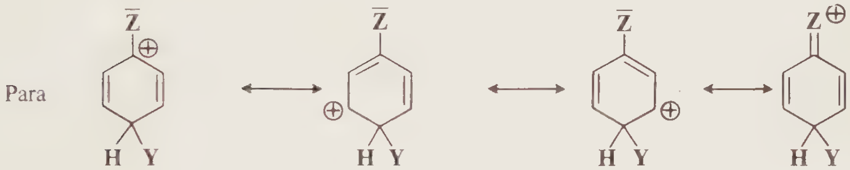

15

For each ion the same three canonical forms may be drawn as before, but now we may draw an extra form for the ortho and the para ions. The stability of these two is increased by the extra form not only because it is another canonical form, but because it is more stable than the others and makes a greater contribution to the hybrid. Every atom (except of course hydrogen) in these forms (**14** and **15**) has a complete octet, while all the other forms have one carbon atom with a sextet. No corresponding form can be drawn for the meta isomer. The inclusion of this form in the hybrid lowers the energy not only because of rule 6 (p. 37), but also because it spreads the positive charge over a larger area—out onto the group Z. Groups with a pair of electrons to contribute would be expected then, in the absence of field effects, not only to direct ortho and para, but also to activate the reaction for these positions.

On the basis of these discussions, we may distinguish three types of groups.

1. Groups which contain an unshared pair of electrons on the atom connected to the ring. In this category are O^-, NR_2, NHR, NH_2,[34] OH, OR, NHCOR, OCOR, SR, and the four halogens.[35] The SH group would probably belong here too, except that in the case of thiophenols electrophiles usually attack the sulfur rather than the ring, and ring substitution is not feasible with these substrates.[36] The resonance explanation predicts that all these groups should be ortho-para-directing, and they are, though all except O are electron-withdrawing by the field effect (p. 21). Therefore, for these groups, resonance is more important than the field effect. This is especially true for NR_2, NHR, NH_2, and OH, which are *strongly* activating, as is O^-. The other groups are mildly activating, except for the halogens, which are deactivating. Fluorine is the least deactivating, and fluorobenzenes usually show a reactivity approximating that of benzene itself. The other three halogens deactivate about equally. In order to explain why chlorine, bromine, and iodine deactivate the ring even though they direct ortho-para, we must assume that the canonical forms **14** and **15** make such great contributions to the respective hybrids that they make the ortho and para arenium ions more stable than the meta even though the $-I$ effect of the halogen is withdrawing sufficient electron density from the ring to deactivate it. The three halogens make the ortho and para ions more stable than the meta, but less stable than the unsubstituted **1**. For the other groups which contain an unshared pair, the ortho and para ions are more stable than either the meta ion or the unsubstituted ion. For most of the groups in this category, the meta ion is more stable than **1**, so that groups such as NH_2, OH, etc., activate the meta positions too, but not so much as the ortho and para positions (see also the discussion on pp. 468–470).

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[34] It must be remembered that in acid solution amines are converted to their conjugate acids, which for the most part are meta-directing (type 2). Therefore in acid (which is the most common medium for electrophilic substitutions) amino groups may direct meta. However, unless the solution is highly acidic, there will be a small amount of free amine present, and since amino groups are activating and the conjugate acids deactivating, ortho-para direction is often found even under acidic conditions.

2. Groups which lack an unshared pair on the atom connected to the ring and which are $-I$. In this category we may list, in approximate order of decreasing deactivating ability, NR_3^+, NO_2, CN, SO_3H, CHO, COR, COOH, COOR, $CONH_2$, CCl_3, and NH_3^+. Also in this category are all other groups with a positive charge on the atom directly connected to the ring[37] (for example, SR_2^+, PR_3^+, etc.), and many groups with positive charges on atoms farther away, since often these are still powerful $-I$ groups. The field-effect explanation predicts that these should all be meta-directing and deactivating, and (except for NH_3^+) this is the case. This is especially true for groups with a positive charge on the atom directly connected to the ring (this includes nitro) since, for these, canonical forms **12** and **13** have two positive charges on adjacent atoms, which destabilize the ortho and para arenium ions even more than otherwise. The NH_3^+ group is an anomaly, since this group directs para about as much as or a little more than it directs meta.[38] The NH_2Me^+, $NHMe_2^+$, and NMe_3^+ groups all give more meta than para substitution, the percentage of para product decreasing with the increasing number of methyl groups.[39]

3. Groups which lack an unshared pair on the atom connected to the ring and which are ortho-para-directing. In this category are alkyl groups, aryl groups, and the COO^- group,[40] all of which activate the ring. We shall discuss them separately. Since aryl groups are $-I$ groups, they might seem to belong to category 2. They are nevertheless ortho-para-directing and activating. This can be explained in a similar manner as in category 1, with a pair of electrons from the aromatic sextet playing the part played by the unshared pair, so that we have forms like **16**. The effect of

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[35] For a review of the directing and orienting effects of amino groups, see Chuchani, in Patai, "The Chemistry of the Amino Group," pp. 250 265, Interscience Publishers, New York, 1968; for ether groups, see Kohnstam and Williams, in Patai, "The Chemistry of the Ether Linkage," pp. 132–150, Interscience Publishers, New York, 1967.

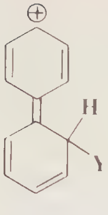
[36] Tarbell and Herz, *J. Am. Chem. Soc.* **75,** 4657 (1953). Ring substitution *is* possible if the SH group is protected. For a method of doing this, see Walker and Lieb, *J. Org. Chem.* **27,** 4455 (1962); and Walker, *J. Org. Chem.* **31,** 835 (1966).

[37] For discussions, see Gastaminza, Modro, Ridd, and Utley, *J. Chem. Soc. B* 534 (1968); Gastaminza, Ridd, and Roy, *J. Chem. Soc. B* 684 (1969); Gilow, De Shazo, and Van Cleave, *J. Org. Chem.* **36,** 1745 (1971); Hoggett, Moodie, Penton, and Schofield, Ref. 29, pp. 167–176.

[38] Brickman and Ridd, *J. Chem. Soc.* 6845 (1965); Hartshorn and Ridd, *J. Chem. Soc. B* 1063 (1968). For a discussion, see Ridd, in "Aromaticity," *Chem. Soc. Spec. Publ.* no. 21, 149–162 (1967).

[39] Brickman, Utley, and Ridd, *J. Chem. Soc.* 6851 (1965).

[40] Spryskov and Golubkin, *J. Gen. Chem. USSR* **31,** 833 (1961). Since the COO^- group is present only in alkaline solution, where electrophilic substitution is not often done, it is seldom met with.



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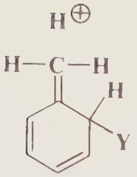

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negatively charged groups like COO is easily explained by the field effect (negatively charged groups are of course electron-donating), since there is no resonance interaction between the group and the ring. The effect of alkyl groups can be explained in the same way, but in addition, we can also draw canonical forms even though there is no unshared pair. These of course are hyperconjugation forms like **17**. This effect, like the field effect, predicts activation and ortho-para direction, so that it is not possible to say how much each effect contributes to the result. Another way of looking at the effect of alkyl groups (which sums up both field and hyperconjugation effects) is that (for $Z = R$) the ortho and para arenium ions are more stable because each contains a form (**12** and **13**) which is a tertiary carbonium ion, while all the canonical forms for the meta ion and for **1** are secondary carbonium ions. In activating ability, alkyl groups usually follow the Baker-Nathan order (p. 70), but not always.[41] The cyclopropyl group is highly activating, since cyclopropylbenzene could be brominated at −75 C and nitrated at −50 C.[42]

The Ortho/Para Ratio[43]

When an ortho-para-directing group is on a ring, it is usually difficult to predict how much of the product will be the ortho isomer and how much the para isomer. Indeed, these proportions may depend greatly on the reaction conditions. For example, chlorination of toluene gives anywhere from 62% *o*-chlorotoluene and 38% of the para isomer to 34% of the ortho and 66% of the para compound.[44] Nevertheless, certain points can be made. On a purely statistical basis there would be 67% ortho and 33% para, since there are two ortho positions and only one para. However, the arenium ion **9**, arising from protonation of benzene, has the approximate charge distribution shown.[45] If we accept this as a model for the arenium ion in aromatic substitution, then a para substituent would have a greater stabilizing effect on the adjacent carbon than an ortho substituent. If other effects are absent, this would mean that more than 33% para and less than 67% ortho substitution would be found. In hydrogen exchange (reaction **1-1**), where other effects are absent, it has been found for a number of substituents that the average ratio of the logarithms of the partial rate factors for these positions (see p. 468 for a definition of partial rate factor) was close to 0.865,[46] which is not far from the value predicted from the ratio of charge densities in **9**, as shown on p. 464. This picture is further supported by the fact that meta-directing groups, which destabilize a positive charge, give ortho para ratios greater than 67 : 33[47] (of course the total amount

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[41] For examples of situations where the Baker-Nathan order is not followed, see Eaborn and Taylor, *J. Chem. Soc.* 247 (1961); Stock, *J. Org. Chem.* **26**, 4120 (1961); Utley and Vaughan, *J. Chem. Soc. B* 196 (1968); Schubert and Gurka, *J. Am. Chem. Soc.* **91**, 1443 (1971); Himoe and Stock, *J. Am. Chem. Soc.* **91**, 1452 (1971).

[42] Levina and Gembitskii, *J. Gen. Chem. USSR* **31**, 3242 (1961).

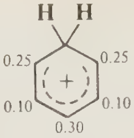
[43] For discussions see Pearson and Buehler, *Synthesis* 455–477 (1971), pp. 455–464; Norman and Taylor, Ref. 1, pp. 301–310.

[44] Stock and Himoe, *J. Am. Chem. Soc.* **83**, 4605 (1961).

[45] Olah, *Acc. Chem. Res.* **4**, 240 (1970); p. 248.

[46] Bailey and Taylor, *J. Chem. Soc. B* 1446 (1971); Ansell, Le Guen, and Taylor, *Tetrahedron Lett.* 13 (1973).

[47] Hoggett, Moodie, Penton, and Schofield, Ref. 29, pp. 176–180.



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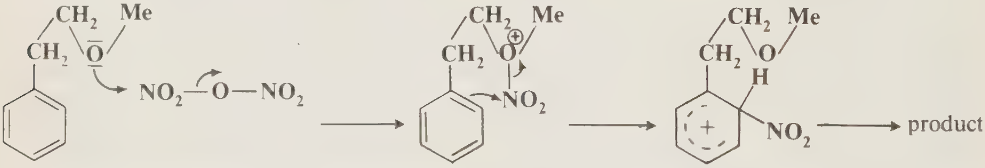
of ortho and para substitution with these groups is small, but the *ratios* are generally greater than 67 : 33). Another important factor which affects the ortho/para ratio is the steric effect. If either the group on the ring or the attacking group is large, then steric hindrance inhibits formation of the ortho product and thus increases the amount of the para isomer. An example of this may be seen in the nitration, under the same conditions, of toluene and *t*-butylbenzene. The former gave 58% of the ortho compound and 37% of the para, while the more bulky *t*-butyl group gave 16% of the ortho product and 73% of the para.[48] A few groups are so large that they direct almost entirely para.

When the ortho-para-directing group is one with an unshared pair (this of course applies to most of them), there is another effect which increases the amount of para product at the expense of the ortho. A comparison of the intermediates involved (p. 461) shows that **14** is a canonical form with an ortho-quinonoid structure, while **15** has a para-quinonoid structure. Since we know that *para*-quinones are more stable than the ortho isomers, it seems reasonable to assume that **15** is more stable than **14** and therefore contributes more to the hybrid and increases its stability in comparison with the ortho intermediate.

In some cases a high ortho/para ratio is observed because of interaction between the electrophile and the directing group. For example, methyl phenethyl ether gives a higher ortho/para ratio when nitrated with N_2O_5 than it does with the more usual mixture of nitric and sulfuric acids, where the attacking entity is NO_2^+ (reaction **1-2**). This behavior has been ascribed to the following mechanism:[49]



One further point can be made: with groups where the field effect is important, we should look for a greater effect at the ortho position than at the para, since field effects decrease with distance. Fluorine, which has the strongest $-I$ effect of the four halogens, should therefore have a greater relative deactivating effect at the ortho position compared to the para than chlorine, and the effect of chlorine should be greater than that of bromine, etc. Consequently, in electrophilic substitution on the halobenzenes, iodobenzene should give the largest amount of ortho product and fluorobenzene the smallest. Nitration of the halobenzenes gave ortho products as follows: PhF, 12%; PhCl, 30%; PhBr, 38%; PhI, 41%.[50] Note that this is opposite to what would be predicted on the basis of steric effects alone.

It has been shown that it is possible to compel regiospecific para substitution by enclosing the substrate molecules in a cavity from which only the para position projects. Anisole was chlorinated in solutions containing cyclohexaamylose, a molecule in which the anisole is almost entirely enclosed (similar to the inclusion compounds discussed at p. 83). With a high enough concentration of cyclohexaamylose, it was possible to achieve an ortho para ratio of 21.6[51] (in the absence of cyclohexaamylose the ratio was only 1.48). This behavior is a model for the regiospecificity found in the action of enzymes.

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[48] Nelson and Brown, *J. Am. Chem. Soc.* **73**, 5605 (1951). For product ratios in the nitration of many monoalkylbenzenes, see Baas and Wepster, *Recl. Trav. Chim. Pays-Bas* **90**, 1081, 1089 (1971), **91**, 285, 517, 831 (1972).

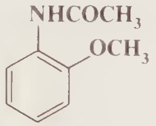
[49] Norman and Radda, *Proc. Chem. Soc.* 423 (1960), *J. Chem. Soc.* 3030 (1961). See also Hartshorn, Moodie, and Schofield, *J. Chem. Soc. B* 2454 (1971). For another example, see Kovacic and Hiller, *J. Org. Chem.* **30**, 1581 (1965).

[50] Holleman, *Chem. Rev.* **1**, 218 (1925).

Orientation in Benzene Rings with More than One Substituent[52]

It is often possible in these cases to predict the correct isomer. In many cases the groups already on the ring reinforce each other. Thus, 1,3-dimethylbenzene is substituted at the 4 position, since this is ortho to one group and para to the other, but not at the 5 position, which is meta to both. Likewise the incoming group in *p*-chlorobenzoic acid goes to the position ortho to the chloro and meta to the carboxyl group.

When the groups oppose each other, predictions may be more difficult. In a case such as **18**, where two groups of about equal directing ability are in competing positions, all four products may be expected, and it is not easy to predict the proportions, except that steric hindrance should probably reduce the yield of substitution ortho to the acetamido group, especially for large electrophiles. Mixtures of about equal proportions are frequent in such cases. Results are often hard to explain. Nevertheless, even when groups on a ring oppose each other, there are some regularities.



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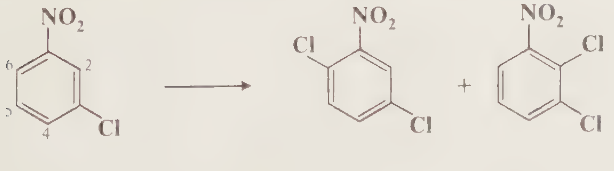
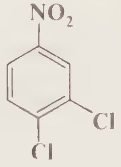
1. If a strongly activating group competes with a weaker one or with a deactivating group, the former controls. Thus *o*-cresol gives substitution mainly ortho and para to the *hydroxy* group and not to the methyl. For this purpose we can arrange the groups thusly: NH_2, OH, NR_2, O^- > OR, OCOR, NHCOR > R, Ar > halogen > meta-directing groups.

2. All other things being equal, a third group is least likely to enter between two groups in the meta relationship. This effect is the result of steric hindrance and increases in importance with the size of the groups on the ring and with the size of the attacking species.

3. When a meta-directing group is meta to an ortho-para-directing group, the incoming group primarily goes ortho to the meta-directing group, rather than para. For example, chlorination of **19** gives mostly **20**. The importance of this effect is underscored by the fact that **21**, which is in



19 **20** **21**



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[51] Breslow and Campbell, *J. Am. Chem. Soc.* **91**, 3085 (1969).

[52] For a quantitative discussion, see pp. 468–470.

violation of the preceding rule, is formed in smaller amounts, but **22** is not formed at all. This is called the *ortho effect*,[53] and many such examples are known.[54] Another is the nitration of *p*-bromotoluene, which gives 2,3-dinitro-4-bromotoluene. In this case, once the first nitro group came in, the second was directed ortho to it, rather than para, even though this means that the group has to come in between two groups in the meta position. There is no good explanation yet for the ortho effect, though possibly there is intramolecular assistance from the meta-directing group.

It is interesting that chlorination of **19** illustrates all three rules. Of the four positions open to the electrophile, the 5 position violates rule 1, the 2 position rule 2, and the 4 position rule 3. The principal attack is therefore at position 6.

Orientation in Other Ring Systems[55]

In fused ring systems the positions are not equivalent, and there is usually a preferred orientation even in the unsubstituted hydrocarbon. The preferred positions may often be predicted as for benzene rings. Thus it is possible to draw more canonical forms for the arenium ion when naphthalene is attacked at the α-position than when it is attacked at the β-position, and the α-position is the preferred site of attack,[56] though, as previously mentioned (p. 460), the isomer formed by substitution at the β-position is thermodynamically more stable and is the product if the reaction is reversible and equilibrium is reached. Because of the more extensive delocalization of charges in the corresponding arenium ions, naphthalene is more reactive than benzene, and substitution is faster at both positions. Similarly, anthracene, phenanthrene, and other fused polycyclic aromatic hydrocarbons are also substituted faster than benzene.

Heterocyclic compounds, too, have nonequivalent positions, and the principles are similar. Furan, thiophene, and pyrrole are chiefly substituted at the 2 position, and all are substituted faster than benzene.[57] Pyrrole is particularly reactive, with a reactivity approximating that of aniline or the phenoxide ion. For pyridine[58] it is not the free base which is attacked, but the conjugate acid, pyridinium ion.[59] The 3 position is most reactive, but the reactivity in this case is much less than that of benzene, being similar to that of nitrobenzene. However, groups can be introduced into the 4 position of a pyridine ring indirectly, by performing the reaction on the corresponding pyridine N-oxide.[60]

When fused ring systems contain substituents, successful predictions can often be made by using a combination of the above principles. Thus, ring A of 2-methylnaphthalene (**23**) is activated by the methyl group; ring B is not (though the presence of a substituent in a fused ring system affects all the rings, the effect is generally greatest on the ring to which it is attached). We therefore expect substitution in ring A. The methyl group activates the positions ortho to itself

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[53] This is not the same as the ortho effect discussed on p. 258.

[54] For a review, see Hammond and Hawthorne, in Newman, "Steric Effects in Organic Chemistry," pp. 164–200, 178–182, John Wiley & Sons, Inc., New York, 1956.

[55] For a review of substitution on nonbenzenoid aromatic systems, see Hafner and Moritz, in Olah, Ref. 33, vol. 4, pp. 127–183 (1965). For a review of aromatic substitution on ferrocenes, see Bublitz and Rinehart, *Org. React.* **17,** 1–154 (1969).

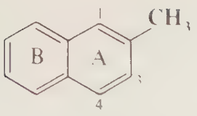
[56] For a discussion on the preferred site of attack for many ring systems, see de la Mare and Ridd, Ref. 1, pp. 169–209.

[57] For a review of electrophilic substitution on five-membered aromatic heterocycles, see Marino, *Adv. Heterocycl. Chem.* **13,** 235–314 (1971). For a review of electrophilic substitution on thiophenes, see Gronowitz, *Adv. Heterocycl. Chem.* **1,** 1–124 (1963), pp. 43–68.

[58] For a review of substitution on pyridines and other six-membered nitrogen-containing aromatic rings, see Aksel'rod and Berezovskii, *Russ. Chem. Rev.* **39,** 627–643 (1970); Katritzky and Johnson, *Angew. Chem. Int. Ed. Engl.* **6,** 608–615 (1967) [*Angew. Chem.* **79,** 629–636]; Abramovitch and Saha, *Adv. Heterocycl. Chem.* **6,** 229–345 (1966).

[59] Olah, Olah, and Overchuk, *J. Org. Chem.* **30,** 3373 (1965); Katritzky and Kingsland, *J. Chem. Soc. B* 862 (1968).

[60] Jaffé, *J. Am. Chem. Soc.* **76,** 3527 (1954).



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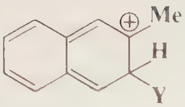

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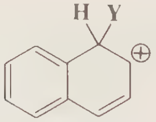

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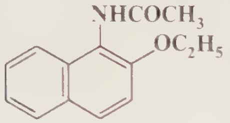
(1 and 3) but not position 4, which is meta to it. However, substitution at the 3 position gives rise to an arenium ion for which it is impossible to write a low-energy canonical form in which ring B has a complete sextet. All we can write are forms like **24**, in which the sextet is no longer intact. In contrast, substitution at the 1 position gives rise to a more stable arenium ion, for which two canonical forms (one of them is **25**) can be written in which ring B is benzenoid. We thus predict predominant substitution at C-1, and that is what is generally found.[61] However, in some cases predictions are much harder to make. For example, chlorination or nitration of **26** gives mainly the 4 derivative, but bromination yields chiefly the 6 compound.[62]

For fused heterocyclic systems too, we can often make predictions based on the above principles, though many exceptions are known. Thus, indole (**27**) is chiefly substituted in the pyrrole ring (at position 3), and reacts faster than benzene, while quinoline (**28**) generally reacts in the benzene ring (not the pyridine ring) at the 5 and 8 positions and slower than benzene, though faster than pyridine.



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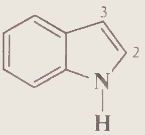

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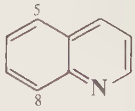

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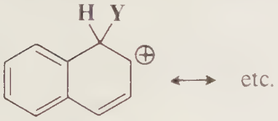
In alternant hydrocarbons (p. 51) the reactivity at a given position is proportional to its free valence (p. 69), not only for electrophilic substitution, but also for nucleophilic and free-radical substitution, because the same kind of resonance can be shown in all three types of intermediate (compare **25**, **29**, and **30**). Attack at the position which will best delocalize a positive charge will also best delocalize a negative charge or an unpaired electron. Since free valence is a measure of the ability of the system to spread the charge in the intermediate, it is proportional to the reactivity.[63] Most results are in accord with these predictions. For example, naphthalene is attacked primarily at the 1 position by NO_2^+, NH_2^-, and Ph•, and always more readily than benzene.



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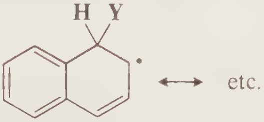

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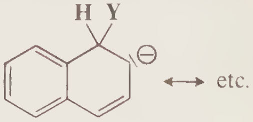

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[61] For example, see Alcorn and Wells, *Aust. J. Chem.* **18**, 1377, 1391 (1965); Eaborn, Golborn, Spillett, and Taylor, *J. Chem. Soc. B* 1112 (1968); Kim, Chen, Krieger, Judd, Simpson, and Berliner, *J. Am. Chem. Soc.* **92**, 910 (1970). For discussions, see Taylor, *Chimia* **22**, 1–8 (1968); Gore, Siddiquei, and Thorburn, *J. Chem. Soc., Perkin Trans. 1* 1781 (1972).

[62] Bell, *J. Chem. Soc.* 519 (1959).

[63] There are some exceptions. In biphenylene (p. 58) the highest free valence is at the 1 position, but substitution occurs at the 2 position [Pullman and Pullman, *Prog. Org. Chem.* **4**, 50 (1958)].

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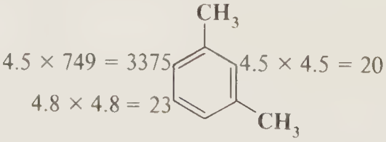
TABLE 2 Calculated and experimental isomer distributions in the acetylation of *m*-xylene[65]

	Isomer distribution, %	
Position	**Calculated**	**Observed**
2	0.30	0
4	99.36	97.5
5	0.34	2.5

Quantitative Treatments of Reactivity in the Substrate

Quantitative rate studies of aromatic substitutions are complicated by the fact that there are usually several hydrogens which can leave, so that measurements of overall rate ratios do not give a complete picture as they do in nucleophilic substitutions, where it is easy to compare substrates which have only one possible leaving group in a molecule. What is needed is not, say, the overall rate ratio for acetylation of toluene versus that for benzene, but the *rate ratio at each position.* These can be calculated from the overall rates and a careful determination of the proportion of isomers formed. We may thus define the *partial rate factor* for a given group and a given reaction as the rate of substitution at a single position relative to a single position in benzene. For example, for acetylation of toluene the partial rate factors are: for the ortho position $o_f^{Me} = 4.5$, for the meta $m_f^{Me} = 4.8$, and for the para $p_f^{Me} = 749$.[64] This means that toluene is acetylated at the ortho position 4.5 times as fast as a single position in benzene, or 0.75 times as fast as the overall rate of acetylation of benzene. A partial rate factor greater than 1 for a given position indicates that the group in question activates that position for the given reaction. Partial rate factors differ from one reaction to another and are even different, though less so, for the same reaction under different conditions.

Once we know the partial rate factors, we can predict the proportions of isomers to be obtained when two or more groups are present on a ring, *if we make the assumption that the effect of substituents is additive.* For example, if the two methyl groups in *m*-xylene have the same effect as the methyl group in toluene, we can calculate the theoretical partial rate factors at each position by multiplying those from toluene, so that they should be as indicated:



From this it is possible to calculate the overall theoretical rate ratio for acetylation of *m*-xylene relative to benzene, since this is one-sixth of the sum of the partial rate factors (in this case 1130), and the isomer distribution if the reaction is kinetically controlled. The overall rate ratio actually is 347,[65] and the calculated and observed isomer distributions are listed in Table 2. In this case, and in many others, agreement is fairly good, but many cases are known where the effects are

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[64] Brown, Marino, and Stock, *J. Am. Chem. Soc.* **81**, 3310 (1959).

[65] Marino and Brown, *J. Am. Chem. Soc.* **81**, 5929 (1959).

TABLE 3 Relative rates for two reactions with leaving groups other than hydrogen

Reaction a is cleavage of $ArSiMe_3$ *in* H_2SO_4-HOAc-H_2O *at* 50.18°C.[68] *Reaction b is cleavage of* $ArGePh_3$ *by aqueous* $HClO_4$-MeOH[69]

	Relative rates	
Group	**Reaction *a*[68]**	**Reaction *b*[69]**
p-NO_2	1.22×10^{-4}	
p-NMe_3^+	3.84×10^{-4}	
p-COOH	1.48×10^{-3}	
m-Cl	0.012	0.0165
p-Br	0.104	0.13
p-I	0.101	0.131
p-Cl	0.190	0.167
m-Ph	0.33	
m-OMe	0.38	0.58
p-F	0.95	0.9
H	1	1
m-Me		2.1
p-Ph	2.83	2.69
o-Ph	5.85	3.22
o-Me		12.4
p-Me	18.0	14.1
o-OMe		207
p-OMe	1010	540
p-OH		2730
p-NMe_2		3×10^6

not additive.[66] For example, the treatment predicts that for 1,2,3-trimethylbenzene there should be 35% 5 substitution and 65% 4 substitution, but acetylation gave 79% 5 substitution and 21% of the 4 isomer.[67] The treatment is thrown off by steric effects such as those mentioned earlier (p. 465), and by resonance interaction *between* groups (for example, **31**), which must make the results deviate from simple additivity of the effects of the groups.

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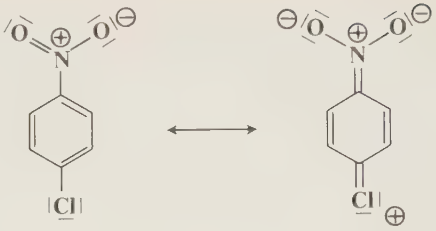
[66] For some examples where additivity fails, see Fischer, Vaughan and Wright, *J. Chem. Soc. B* 368 (1967); Coombes, Crout, Hoggett, Moodie, and Schofield, *J. Chem. Soc. B* 347 (1970); Richards, Wilkinson, and Wright, *Aust. J. Chem.* **25,** 2369 (1972); Cook, Phillips, and Ridd, *J. Chem. Soc., Perkin Trans. 2* 1166 (1974). For a theoretical treatment of why additivity fails, see Godfrey, *J. Chem. Soc. B* 1545 (1971).

[67] Obviously, the additivity treatment can only be valid if all of the cases being compared are run under exactly the same conditions. The importance of conditions in this example is emphasized by the work of Friedman and Honour, *J. Am. Chem. Soc.* **91,** 6344 (1969), which showed that acylation of 1,2,3-trimethylbenzene can give either the 4 or 5 isomer in more than 95% purity, depending on the reaction conditions.

[68] Deans and Eaborn, *J. Chem. Soc.* 2299 (1959).

[69] Eaborn and Pande, *J. Chem. Soc.* 297 (1961). For additional values, see Eaborn, Walton, and Young, *J. Chem. Soc. B* 15 (1969); Eaborn and Jackson, *J. Chem. Soc. B* 21 (1969).



31

Another approach which avoids the problem created by having competing leaving groups present in the same substrate is the use of substrates which contain only one leaving group. This is most easily accomplished by use of a leaving group other than hydrogen. By this means overall rate ratio can be measured for specific positions. Table 3 contains the results of two such studies.[69a] The results are in good agreement with each other and give a reactivity order quite consistent with that given before for hydrogen as leaving group.

A Quantitative Treatment of Reactivity of the Electrophile. The Selectivity Relationship

Not all electrophiles are equally powerful. The nitronium ion attacks not only benzene, but also aromatic rings which contain a strongly deactivating group. On the other hand, diazonium ions couple only with rings containing a powerful activating group. Attempts have been made to correlate the influence of substituents with the power of the attacking group. The most obvious way to do this is with the Hammett equation (p. 252):

$$\log \frac{k}{k_0} = \rho\sigma$$

For aromatic substitution, k_0 is divided by 6, and for meta substitution, k is divided by 2, so that comparisons are made for only one position (consequently, k/k_0 for say the methyl group at a para position is identical to the partial rate factor p_f^{Me}). It was soon found that, while this approach worked fairly well for electron-withdrawing groups, it failed for those which are electron-donating. However, if the equation is modified by the insertion of the Brown σ^+ values instead of the Hammett σ values (because a positive charge develops during the transition state), more satisfactory correlations can be made even for electron-donating groups (see p. 253 for a list of σ^+ values). Groups with a negative value of σ_p^+ or σ_m^+ are activating for that position; groups with a positive value are deactivating. The ρ values correspond to the susceptibility of the reaction to stabilization or destabilization by the Z group and to the reactivity of the electrophile. The ρ values vary not only with the electrophile but also with conditions. A large negative value of ρ means an electrophile of relatively low reactivity. Of course, this approach is completely useless for ortho substitution, since the Hammett equation does not apply there.

A modification of the Hammett approach, suggested by Brown, is called the *selectivity relationship*,[70] and is based on the principle that reactivity of a species varies inversely with selectivity. Table 4 shows how electrophiles can be arranged in order of selectivity as measured by two

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[69a] For a review of aryl-silicon and related cleavages, see Eaborn, *J. Organomet. Chem.* **100,** 43–57 (1975).

[70] For a comprehensive review, see Stock and Brown, *Adv. Phys. Org. Chem.* **1,** 35–154 (1963). Shorter reviews are by Olah, in Olah, Ref. 33, vol. 1, pp. 905–927 (1963); by Leffler and Grunwald, "Rates and Equilibria of Organic Reactions," pp. 196–210, John Wiley & Sons, Inc., New York, 1963; and by Brown and Stock, *J. Am. Chem. Soc.* **84,** 3298 (1962).

TABLE 4 Relative rates and product distributions in some electrophilic substitutions on toluene and benzene[71]

Reaction	Relative rate $k_{\text{toluene}}/k_{\text{benzene}}$	Product distribution, % m	p
Bromination	605	0.3	66.8
Chlorination	350	0.5	39.7
Benzoylation	110	1.5	89.3
Nitration	23	2.8	33.9
Mercuration	7.9	9.5	69.5
Isopropylation	1.8	25.9	46.2

indexes: (1) their selectivity in attacking toluene rather than benzene, and (2) their selectivity between the meta and para positions in toluene.[71] As the table shows, an electrophile more selective in one respect is also more selective in the other. In many cases, electrophiles known to be more stable and hence less reactive than others show a higher selectivity, as would be expected. For example, the *t*-butyl cation is more stable than the isopropyl (p. 152) and more selective, and Br_2 is more selective than Br^+. However, deviations from the relationship are known. Selectivity depends not only on the nature of the electrophile, but also on the temperature. As expected, it normally decreases with increasing temperature.

Brown assumed that a good measurement of selectivity was the ratio of the para and meta partial rate factors in toluene, and he defined the selectivity S_f of a reaction as

$$S_f = \log \frac{p_f^{\text{Me}}}{m_f^{\text{Me}}}$$

That is, the more reactive an attacking species, the less preference it has for the para position as against the meta. If we combine the Hammett-Brown $\sigma^+\rho$ relationship with the linearity between $\log S_f$ and $\log p_f^{\text{Me}}$ and between $\log S_f$ and $\log m_f^{\text{Me}}$, it is possible to derive the following expressions:

$$\log p_f^{\text{Me}} = \frac{\sigma_p^+}{\sigma_p^+ - \sigma_m^+} S_f$$

$$\log m_f^{\text{Me}} = \frac{\sigma_m^+}{\sigma_p^+ - \sigma_m^+} S_f$$

S_f is related to ρ by:

$$S_f = \rho(\sigma_p^+ - \sigma_m^+)$$

The general validity of these equations is supported by a great deal of experimental data on aromatic substitution reactions of toluene. Examples of values for some reactions obtained from these equations are given in Table 5.[72] It is obvious that this type of treatment can be extended

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[71] Stock and Brown, Ref. 70, p. 45.

[72] Stock and Brown, *J. Am. Chem. Soc.* **81**, 3323 (1959). Stock and Brown, Ref. 70, present many tables of these kinds of data.

TABLE 5 Values of m_f^{Me}, p_f^{Me}, S_f, and ρ for three reactions of toluene[72]

Reaction	m_f^{Me}	p_f^{Me}	S_f	ρ
$\mathrm{PhMe + EtBr} \xrightarrow[\text{benzene, 25°C}]{\mathrm{GaBr_3}}$	1.56	6.02	0.587	−2.66
$\mathrm{PhMe + HNO_3} \xrightarrow[\text{45°C}]{\text{90\% HOAc}}$	2.5	58	1.366	−6.04
$\mathrm{PhMe + Br_2} \xrightarrow[\text{25°C}]{\text{85\% HOAc}}$	5.5	2420	2.644	−11.40

to substituents other than methyl and for other aromatic rings. For other substituents, the treatment works well with groups which, like methyl, are not very polarizable. For more polarizable groups the correlations are sometimes satisfactory and sometimes not, probably because each electrophile in the transition state makes a different demand on the electrons of the substituent group.

Not only are there substrates for which the treatment is poor, but it also fails with very powerful electrophiles. Failure in these cases has been attributed[73] to rate-determining formation of a π complex (p. 457), which would mean that the *position* of attack is not determined in the slow step, so that the p/m ratio would not be related to the rate of the reaction, and it is possible to have high positional but low substrate selectivity.[74] However, we have seen (p. 458) that the evidence for rate-determining formation of π complexes is not very strong, and an alternate explanation for the failure of the selectivity relationship with strong electrophiles is that with these powerful electrophiles the reaction rate is so rapid (reaction taking place at virtually every encounter between the electrophile and the substrate) that the presence of additional activating groups can no longer increase the rate.[75] This explanation too is compatible with the observed high positional but low substrate selectivity. More complex treatments have been devised.[76]

The Effect of the Leaving Group

In the vast majority of aromatic electrophilic substitutions, the leaving group is $\mathrm{H^+}$ (it is certainly one of the best), and very little work has been done on the relative electrofugal ability of other leaving groups. However, the following orders of leaving-group ability have been suggested:[77] (1) for leaving groups which depart without assistance (SN1 process with respect to the leaving group), $\mathrm{NO_2^+} < \text{iso-Pr}^+ \sim \mathrm{SO_3} < t\text{-Bu}^+ \sim \mathrm{ArN_2^+} < \mathrm{ArCHOH^+} < \mathrm{NO^+} < \mathrm{CO_2}$; (2) for leaving groups which depart with assistance from an outside nucleophile (SN2 process), $\mathrm{Me^+ < Cl^+ < Br^+ < D^+ \sim RCO^+ < H^+ \sim I^+ < Me_3Si^+}$. We can use this kind of list to help predict which group, X or Y, will cleave from an arenium ion **1** once it has been formed, and so obtain an idea of which electrophile substitutions are feasible. However, a potential leaving group can also affect a reaction in another way: by influencing the rate at which the original electrophile attacks directly at that position. Partial rate factors for electrophilic attack at a position substituted by a group other than hydrogen are called *ipso partial rate factors* ($i_f{}^X$).[78] Such factors for the nitration of *p*-haloanisoles are 0.18, 0.08, and 0.06, for *p*-iodo, *p*-bromo-, and *p*-chloroanisole, respectively.[79] This means, for example, that the electrophile in this case attacks the 4 position (called the *ipso* position) of 4-iodoanisole 0.18 times as fast as a single position of benzene. Note that this is far slower than it attacks the 4 position of anisole itself, so that the presence of the iodo group greatly slows the reaction at that position. Thus halogens deactivate the ipso position just as they do the other positions (p. 462).[80]

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[73] Olah, Ref. 26.

[74] See for example, Olah, Ref. 26; Olah, Kobayashi, and Nishimura, *J. Am. Chem. Soc.* **95**, 564 (1973); Olah and Lin, *J. Am. Chem. Soc.* **96**, 549 (1974). See also Moodie, Schofield, and Weston, *J. Chem. Soc., Chem. Commun.* 382 (1974); Barnett, Moodie, Schofield, and Weston, *J. Chem. Soc., Perkin Trans. 2* 648 (1975).

[75] Coombes, Moodie, and Schofield, Ref. 26; Hoggett, Moodie, and Schofield, Ref. 26; Hartshorn, Moodie, Schofield, and Thompson, *J. Chem. Soc. B* 2447 (1971).

[76] For example, see Yukawa and Tsuno, *Bull. Chem. Soc. Jpn.* **32**, 971 (1959); Knowles, Norman, and Radda, *J. Chem. Soc.* 4885 (1960); Norman and Radda, *Tetrahedron Lett.* 125 (1962).

[77] Perrin, *J. Org. Chem.* **36**, 420 (1971).

REACTIONS

The reactions in this chapter are classified according to leaving group, hydrogen replacements being treated first, then rearrangements in which the attacking entity is first cleaved from another part of the molecule (hydrogen is also the leaving group in these cases), and finally replacements of other leaving groups.

Hydrogen as the Leaving Group in Simple Substitution Reactions

A. Hydrogen as the Electrophile

1-1 Hydrogen Exchange

$$\mathrm{ArH + D^+ \rightleftharpoons ArD + H^+}$$

Aromatic compounds can exchange hydrogens when treated with acids. The reaction is used chiefly to study mechanistic questions[81] (including substituent effects), but can also be useful to deuterate or tritiate aromatic rings selectively. The usual directive effects apply and, for example, phenol, treated with D_2O, gives slow exchange on heating, with only ortho and para hydrogens being exchanged.[82] Strong acids, of course, exchange faster with aromatic substrates, and this exchange must be taken into account when studying the mechanism of any aromatic substitution catalyzed by acids. There is a great deal of evidence that exchange takes place by the ordinary arenium-ion mechanism. Among the evidence are the orientation effects noted above, and the finding that the reaction is general-acid-catalyzed, which means that a proton is being transferred in the slow step[83] (p. 236). Furthermore, many examples have been reported of stable solutions of arenium ions formed by attack of a proton on an aromatic ring.[5] Simple aromatic compounds can be extensively deuterated in a convenient fashion by heating at 200 to 300°C with a dilute solution of HCl in D_2O.[84]

Hydrogen exchange may also be effected with strong bases,[84a] such as $NH_2{}^-$. In these cases the slow step is the proton transfer:

$$\mathrm{ArH + B \longrightarrow Ar^- + BH^+}$$

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[78] Perrin and Skinner, *J. Am. Chem. Soc.* **93,** 3389 (1971).

[79] Ref. 78. See also Fischer and Zollinger, *Hevl. Chim. Acta* **55,** 2139 (1972).

[80] For other work on ipso reactivity, see Baciocchi and Illuminati, *J. Am. Chem. Soc.* **89,** 4017 (1967); Berwin, *J. Chem. Soc., Chem. Commun.* 237 (1972); Hahn and Strack, *J. Am. Chem. Soc.* **96,** 4335 (1974); Galley and Hahn, *J. Am. Chem. Soc.* **96,** 4337 (1974); Fischer and Wright, *Aust. J. Chem.* **27,** 217 (1974).

[81] For a review, see Taylor, Ref. 1, pp. 194–277.

[82] Small and Wolfenden, *J. Chem. Soc.* 1811 (1936).

[83] For example, see Challis and Long, *J. Am. Chem. Soc.* **85,** 2524 (1963); Batts and Gold, *J. Chem. Soc.* 4284 (1964); Kresge, Chiang, and Sato, *J. Am. Chem. Soc.* **89,** 4418 (1967); Gruen and Long, *J. Am. Chem. Soc.* **89,** 1287 (1967); Butler and Hendry, *J. Chem. Soc. B* 852 (1970).

[84] Werstiuk and Kadai, *Can. J. Chem.* **51,** 1485 (1973), **52,** 2169 (1974).

[84a] For a review of base-catalyzed hydrogen exchange on heterocycles, see Elvidge, Jones, O'Brien, Evans, and Sheppard, *Adv. Heterocycl. Chem.* **16,** 1–31 (1974).

so that the SE1 mechanism and not the usual arenium-ion mechanism is operating.[85] As would be expected from the SE1 mechanism, only field and not resonance effects of substituents affect the rates, $-I$ groups causing increases, and $+I$ groups causing decreases.[86] The effect is most strongly felt at the ortho position. Aromatic rings can also be deuterated by treatment with D_2O and a platinum catalyst,[87] or with C_6D_6 and an alkylaluminum dichloride catalyst,[88] though rearrangements may take place during the latter procedure. Tritium can be introduced by treatment with T_2O and an alkylaluminum dichloride catalyst.[88]

B. Nitrogen Electrophiles

1-2 Nitration

$$\mathrm{ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2}$$

Most aromatic compounds, whether of high or low reactivity, can be nitrated, because a wide variety of nitrating agents is available.[89] For benzene and the simple alkylbenzenes, and less reactive compounds, the most common reagent is a mixture of concentrated nitric and sulfuric acids, but for active substrates, the reaction can be carried out with nitric acid alone, or in water, acetic acid, or acetic anhydride. In fact, these milder conditions are necessary for active compounds, like amines and phenols, since reaction with mixed nitric and sulfuric acids would be too violent. If anhydrous conditions are required, nitration can be effected with N_2O_5 in CCl_4 in the presence of P_2O_5, which removes the water formed in the reaction. Nitration in alkaline media can be accomplished with esters of nitric acid such as ethyl nitrate ($EtONO_2$). These reagents can also be used with proton or Lewis acid catalysts. Other nitrating agents are mixed anhydrides such as acetyl nitrate CH_3COONO_2 (see reaction **0-34** for their preparation), nitryl halides with a Friedel-Crafts catalyst such as $FeCl_3$,[90] methyl nitrate and BF_3,[91] and nitronium salts[92] such as $NO_2^+\ BF_4^-$, $NO_2^+\ PF_6^-$, and $NO_2^+\ CF_3SO_3^-$. The last-mentioned salt gives a very high yield of products at low temperatures.[93] With active substrates such as amines and phenols, nitration may be accomplished by nitrosation under oxidizing conditions with a mixture of dilute nitrous and nitric acids, so that what actually happens is nitrosation (reaction **1-3**) followed by oxidation:

$$\mathrm{ArH + HONO \longrightarrow ArNO + N_2O_4 \longrightarrow ArNO_2}$$

The N_2O_4 is formed by reaction between HNO_3 and HONO.[94]

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[85] Shatenshtein, *Tetrahedron* **18,** 95 (1962).

[86] Hall, Libby, and James, *J. Org. Chem.* **28,** 311 (1963); Streitwieser, Lawler, and Perrin, *J. Am. Chem. Soc.* **87,** 5383 (1965); Streitwieser and Lawler, *J. Am. Chem. Soc.* **87,** 5388 (1965); Streitwieser and Mares, *J. Am. Chem. Soc.* **90,** 644 (1968); Streitwieser, Hudson, and Mares, *J. Am. Chem. Soc.* **90,** 648 (1968).

[87] See for example, Leitch, *Can. J. Chem.* **32,** 813 (1954); Fraser and Renaud, *J. Am. Chem. Soc.* **88,** 4365 (1966); Fischer and Puza, *Synthesis* 218 (1973); Blake, Garnett, Gregor, Hannan, Hoa, and Long, *J. Chem. Soc., Chem. Commun.* 930 (1975). See also Parshall, *Acc. Chem. Res.* **8,** 113–117 (1975).

[88] Garnett, Long, Vining, and Mole, *J. Am. Chem. Soc.* **94,** 5913, 8632, (1972), *J. Chem. Soc., Chem. Commun.* 1172 (1972), *Tetrahedron Lett.* 4075 (1973).

[89] For a monograph, see Hoggett, Moodie, Penton, and Schofield, Ref. 29. For reviews, see Taylor, Ref. 1, pp. 10–47; Weaver, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 2, pp. 1–48, Interscience Publishers, New York, 1970; de la Mare and Ridd, Ref. 1, pp. 48–93; Olah and Kuhn, in Olah, Ref. 33, vol. 3, pp. 1393–1491 (1964).

[90] Kuhn and Olah, *J. Am. Chem. Soc.* **83,** 4564 (1961).

[91] Olah and Lin, *Synthesis* 488 (1973).

[92] Olah and Kuhn, *J. Am. Chem. Soc.* **84,** 3684 (1962).

[93] Coon, Blucher, and Hill, *J. Org. Chem.* **38,** 4243 (1973); Effenberger and Geke, *Synthesis* 40 (1975).

[94] Bonner and Hancock, *Chem. Commun.* 780 (1967); Bonner, Hancock, Yousif, and Rolle, *J. Chem. Soc. B* 1237 (1969).

When amines are nitrated under strong-acid conditions, meta orientation is generally observed, since the species undergoing nitration is actually the conjugate acid of the amine. If the conditions are less acidic, the free amine is nitrated and the orientation is ortho-para. Although the free base may be present in much smaller amounts than the conjugate acid, it is far more susceptible to aromatic substitution (see also p. 462). Because of these factors, and because they are vulnerable to oxidation by nitric acid, primary aromatic amines are often protected before nitration by treatment with acetyl chloride (reaction **0-54**) or acetic anhydride (reaction **0-55**). Nitration of the resulting acetanilide derivative avoids all these problems. There is evidence that when the reaction takes place on the free amine, it is the nitrogen which is attacked to give an N-nitro compound Ar—NH—NO_2 which rapidly undergoes rearrangement (see reaction **1-36**) to give the product.[95]

Since the nitro group is deactivating, it is usually easy to stop the reaction after one group has entered the ring, but a second and a third group can be introduced if desired, especially when an activating group is also present. Even *m*-dinitrobenzene itself can be nitrated if vigorous conditions are applied. This has been accomplished with $NO_2^+ \ BF_4^-$ in FSO_3H at 150°C.[96]

With most of the reagents mentioned (except for oxidative nitrosation) the attacking species is the nitronium ion NO_2^+. Among the ways in which this ion is formed are the following:

1. In concentrated sulfuric acid, by an acid-base reaction in which nitric acid is the base:

$$\mathbf{HNO_3 + 2H_2SO_4 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-}$$

This ionization is essentially complete.

2. In concentrated nitric acid alone, by a similar acid-base reaction in which one molecule of nitric acid is the acid and another the base:

$$\mathbf{2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O}$$

This equilibrium lies to the left (about 4% ionization), but enough NO_2^+ is formed for nitration to occur.

3. The equilibrium just mentioned occurs to a small extent even in organic solvents.

4. With N_2O_5 in CCl_4 there is spontaneous dissociation:

$$\mathbf{N_2O_5 \rightleftharpoons NO_2^+ + NO_3^-}$$

but in this case there is evidence that some nitration also takes place with undissociated N_2O_5 as the electrophile.

5. When nitronium salts are used, NO_2^+ is of course present to begin with. Esters, anhydrides, and acyl halides of nitric acid all ionize to form NO_2^+.

There is a great deal of evidence for the fact that the nitronium ion is present in most nitrations and that it is the attacking entity.[97] Some of this evidence is as follows:

1. Nitric acid has a peak in the Raman spectrum. When nitric acid is dissolved in concentrated sulfuric acid, the peak disappears and two new peaks appear, one at 1400 cm^{-1} attributable to NO_2^+ and one at 1050 cm^{-1} due to HSO_4^-.[98]

2. On addition of nitric acid, the freezing point of sulfuric acid is lowered about four times the amount expected if no ionization had taken place.[99] This means that the addition of one molecule of nitric acid results in the production of four particles, which is strong evidence for the ionization reaction between nitric and sulfuric acids given above.

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[95] Ridd and Scriven, *J. Chem. Soc., Chem. Commun.* 641 (1972).

[96] Olah and Lin, *Synthesis* 444 (1974).

[97] For an exhaustive study of this reaction, see Hughes, Ingold, and coworkers, *J. Chem. Soc.* 2400-2684 (1950).

[98] Ingold, Millen, and Poole, *J. Chem. Soc.* 2576 (1950).

[99] Gillespie, Graham, Hughes, Ingold, and Peeling, *J. Chem. Soc.* 2504 (1950).

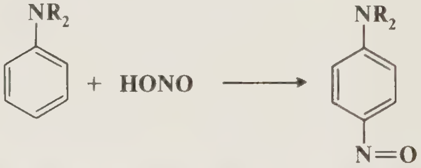
3. The fact that nitronium salts in which nitronium ion is known to be present (by x-ray studies) nitrate aromatic compounds shows that this ion does attack the ring.

4. The rate of the reaction with most reagents is proportional to the concentration of NO_2^+ and not to that of other species. When the reagent produces this ion in small amounts, the attack is slow, and only active substrates can be nitrated. In concentrated and aqueous mineral acids the kinetics are second order: first order each in aromatic substrate and in nitric acid (unless pure nitric acid is used in which case there are pseudo-first-order kinetics). But in organic solvents like nitromethane, acetic acid, and CCl_4, the kinetics are first order in nitric acid alone, and zero order in aromatic substrate, because the rate-determining step is formation of NO_2^+ and the substrate does not take part in this.

In a few cases (mostly when organic solvents are used) the attacking entity may not be nitronium ion, but a species such as $NO_2\text{–}OH_2^+$ or NO_2OAcH^+. It is obvious that in species like these another molecule (in these cases water and acetic acid, respectively) acts as a "carrier" of nitronium ions. In such cases the mechanism is essentially the same, but the carrier drops off somewhere in the process (p. 454).

OS **I,** 372, 396, 408 (see also OS **53,** 129); **II,** 254, 434, 438, 447, 449, 459, 466; **III,** 337, 644, 653, 658, 661, 837; **IV,** 42, 364, 654, 711, 722, 735; **V,** 346, 480, 829, 1029, 1067.

1-3 Nitrosation



Ring nitrosation with nitrous acid is normally carried out only with active substrates such as amines and phenols. However, primary aromatic amines give diazonium ions (reaction **2-48**) when treated with nitrous acid, and secondary amines tend to give N-nitroso rather than C-nitroso compounds (reaction **2-50**); hence this reaction is normally limited to phenols and tertiary aromatic amines. Nevertheless secondary aromatic amines can be C-nitrosated in two ways. The N-nitroso compound first obtained may be isomerized to a C-nitroso compound (the Fischer-Hepp rearrangement, **1-37**), or it may be treated with another mole of nitrous acid to give an N,C-dinitroso compound. Certain primary and secondary aromatic amines not containing electron-withdrawing groups (e.g., *m*-toluidine, α-naphthylamine) can be directly C-nitrosated in the para position by nitrosylsulfuric acid in concentrated H_2SO_4.[100] Nitroso groups can be introduced into less active aromatic rings by increasing the electrofugal ability of the leaving group: substituted trimethylphenylstannanes $ArSnMe_3$ treated with nitrosyl chloride in CH_2Cl_2 at -25 to 0°C give the nitroso compounds ArNO.[101] Ar-containing methyl and methoxy groups, as well as unsubstituted Ar, give good yields, but Ar-containing halogens give low yields (25 to 30%).

Much less work has been done on the mechanism of this reaction than on the preceding one. In some cases the attacking entity is NO^+, but in others it is apparently NOCl, NOBr, N_2O_3, etc., in each of which there is a carrier of NO^+. Evidence is that in many nitrosations NO^+ cannot be detected. NOCl and NOBr are formed during the normal process of making nitrous acid: the treatment of sodium nitrite with HCl or HBr. Nitrosation requires active substrates because NO^+ is much more stable than NO_2^+ and hence much less reactive. Kinetic studies have shown that NO^+ is at least 10^{14} times less reactive than NO_2^+.[102] A consequence of the relatively high stability of NO^+ is that this species is easily cleaved from the arenium ion, so that k_{-1} competes with k_2 (p. 455) and isotope effects are found.[103] Tertiary aromatic amines substituted in the ortho position generally do not react with HONO, probably because the ortho substituent prevents planarity of the dialkylamino group, without which the ring is no longer activated. This is an example of steric inhibition of resonance (p. 38).

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[100] Blangey, *Helv. Chim. Acta* **21,** 1579 (1938).

[101] Bartlett, Eaborn, and Walton, *J. Chem. Soc. C* 1717 (1970).

OS **I,** 214, 411, 511; **II,** 223; **IV,** 247.

1-4 Diazonium Coupling

$$ArH + Ar'N_2^+ \longrightarrow Ar{-}N{=}N{-}Ar'$$

Aromatic diazonium ions normally couple only with active substrates such as amines and phenols.[104] Presumably because of the size of the attacking species, substitution is mostly para to the activating group, unless that position is already occupied, in which case ortho substitution takes place. The pH of the solution is important both for phenols and amines. For amines, the solutions may be mildly acidic or neutral. The fact that amines give ortho and para products shows that even in mildly acidic solution they react in their un-ionized form. If the acidity is too high, the reaction does not occur, because the concentration of free amine becomes too small. Phenols must be coupled in slightly alkaline solution where they are converted to the more reactive phenoxide ions, because phenols themselves are not active enough for the reaction. However, neither phenols nor amines react in strongly alkaline solution, because the diazonium ion is converted to a diazo hydroxide Ar—N=N—OH. Primary and secondary amines face competition from attack at the nitrogen. However, the resulting N-azo compounds (aryl triazenes) may be isomerized to C-azo compounds (reaction **1-38**). Acylated amines and phenolic ethers and esters are ordinarily not active enough for this reaction, though it is sometimes possible to couple them (as well as such polyalkylated benzenes as mesitylene and pentamethylbenzene) to diazonium ions containing electron-withdrawing groups in the para position, since such groups increase the concentration of the positive charge and thus the electrophilicity of the ArN_2^+. Some coupling reactions which are otherwise very slow (in cases where the coupling site is crowded) are catalyzed by pyridine for reasons discussed on p. 456. Coupling of an aliphatic diazo compound to an aromatic ring has been reported.[105]

OS **I,** 49, 374; **II,** 35, 39, 145.

1-5 Direct Introduction of the Diazonium Group

$$ArH \xrightarrow[HX]{2HONO} ArN_2^+ \quad X^-$$

Diazonium salts can be prepared directly, by replacement of an aromatic hydrogen, without the necessity of going through the amino group.[106] The reaction is essentially limited to active substrates (amines and phenols), since otherwise poor yields are obtained. As in reaction **1-3,** and for the same reason, tertiary amines containing an ortho substituent react extremely slowly.[107] Since the reagents and the substrate are the same as in reaction **1-3**, the first species formed is the nitroso compound. In the presence of excess nitrous acid, this is converted to the diazonium ion.[108]

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[102] Challis, Higgins, and Lawson, *J. Chem. Soc., Perkin Trans. 2* 1831 (1972); Challis and Higgins, *J. Chem. Soc., Perkin Trans. 2* 2365 (1972).

[103] Challis and Lawson, *J. Chem. Soc. B* 770 (1971); Challis and Osborne, *J. Chem. Soc., Perkin Trans. 2* 1526 (1973); Challis and Higgins, *J. Chem. Soc., Perkin Trans. 2* 1597 (1973).

[104] For a review, see Zollinger, "Azo and Diazo Chemistry," pp. 210–265, Interscience Publishers, Inc., New York, 1961.

[105] St. Pyrek and Achmatowicz, *Tetrahedron Lett.* 2651 (1970).

[106] Tedder, *J. Chem. Soc.* 4003 (1957). For a review, see Belov and Kozlov, *Russ. Chem. Rev.* **32,** 59–75 (1963), pp. 61–62.

[107] Patel and Tedder, *J. Chem. Soc.* 4889 (1963).

This reaction can also be performed on inactive substrates, even those containing a meta-directing group, if $HgSO_4$ is introduced as a catalyst, but the yields are lower.[109] The reaction pathway is entirely different in this case. The mercury salt attacks the ring to give $ArHg^+$, so that the NO^+ replaces Hg^{2+} and not H^+.

1-6 Direct Amination[110]

$$\mathrm{ArH + NH_2{-}O{-}SO_2{-}OH \xrightarrow{AlCl_3} ArNH_2}$$

Aromatic compounds can be aminated by hydroxylamine-O-sulfonic acid,[111] but yields are fairly low, and the reaction is not often carried out. The mechanism has not been studied, but our knowledge of aromatic substitutions in general leads us to suspect that the attacking entity is NH_2^+ or a carrier of it. Other reagents which might give rise to this kind of attacking entity have also been tried, e.g., salts of hydroxylamine,[112] but yields are no better. However, hydrazoic acid in the presence of $AlCl_3$ or sulfuric acid gave direct amination in yields of 10 to 65%.[113] N-Substituted hydroxylamine ethers (RNHOMe and R_2NOMe) have been employed with Friedel-Crafts catalysts in attempts to introduce directly the NHR and NR_2 groups.[114] Secondary amines *were* formed in about 25% yield, but the method was not very practical for tertiary amines. However, tertiary amines have been prepared in fairly good yields (about 50 to 90%) by treatment of aromatic hydrocarbons with N-chlorodialkylamines, by heating in 96% sulfuric acid; or with $AlCl_3$ or $FeCl_3$ in nitroalkane solvents; or by irradiation.[115]

Tertiary (and to a lesser extent, secondary) aromatic amines can also be prepared in moderate to high yields by amination with an N-chlorodialkylamine (or an N-chloroalkylamine) and a metallic ion catalyst (e.g., Fe^{2+}, Ti^{3+}, Cu^+, Cr^{2+}) in the presence of sulfuric acid.[116] The attacking species in this case is the radical ion $R_2\overset{+}{N}H\cdot$ formed by

$$\mathrm{R_2\overset{\oplus}{N}HCl + M^+ \longrightarrow R_2\overset{\oplus}{N}H\cdot + M^{2+} + Cl^-}$$

Because attack is by a positive species (even though it is a free radical), orientation is similar to that in other electrophilic substitutions (e.g., phenol and acetanilide give ortho and para substitution, mostly para). When an alkyl group is present, attack at the benzylic position competes with ring substitution. Aromatic rings containing only meta-directing groups do not give the reaction at all. Fused ring systems react well.

Unusual orientation has been reported for amination with haloamines and with NCl_3 in the presence of $AlCl_3$. For example, toluene gave predominantly meta amination.[117] It has been suggested that initial attack in this case is by Cl^+ and that a nitrogen nucleophile (whose structure is not known but is represented here as NH_2^- for simplicity) adds to the resulting arenium ion, so that the initial reaction is addition to a carbon-carbon double bond, and that elimination of HCl follows:[118]

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[108] Tedder and Theaker, *Tetrahedron* **5,** 288 (1959).

[109] Tedder and Theaker, *J. Chem. Soc.* 4008 (1957).

[110] For a review, see Kovacic, in Olah, Ref. 33, vol. 3, pp. 1493–1506 (1964).

[111] Keller and Smith, *J. Am. Chem. Soc.* **66,** 1122 (1944).

[112] Kovacic, Bennett, and Foote, *J. Org. Chem.* **26,** 3013 (1961); *J. Am. Chem. Soc.* **84,** 759 (1962).

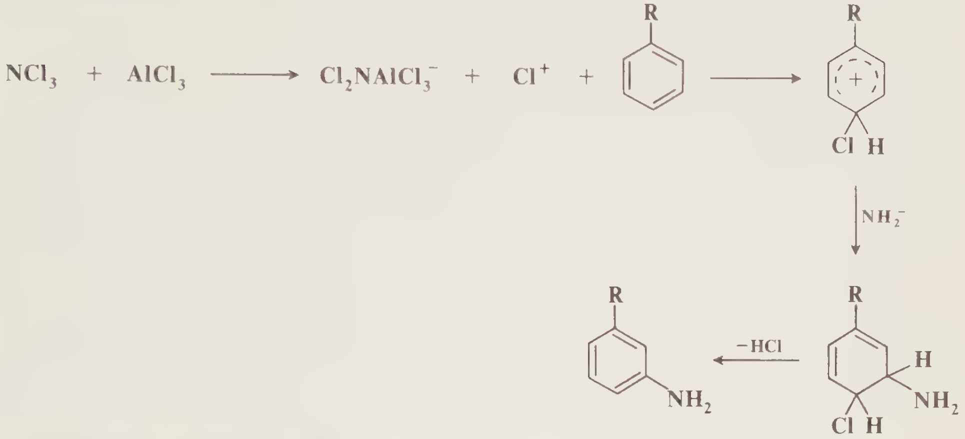
[113] Kovacic, Russell, and Bennett, *J. Am. Chem. Soc.* **86,** 1588 (1964).

[114] Kovacic and Foote, *J. Am. Chem. Soc.* **83,** 743 (1961).

[115] Bock and Kompa, *Angew. Chem. Int. Ed. Engl.* **4,** 783 (1965) [*Angew. Chem.* **77,** 807], *Chem. Ber.* **99,** 1347, 1357, 1361 (1966).

[116] For reviews, see Minisci, *Synthesis* 1–24 (1973), pp. 2–12; Sosnovsky and Rawlinson, *Adv. Free-Radical Chem.* **4,** 203–284 (1972), pp. 213–238.

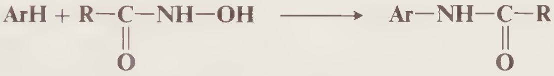
[117] Kovacic, Lange, Foote, Goralski, Hiller, and Levisky, *J. Am. Chem. Soc.* **86,** 1650 (1964); Kovacic, Goralski, Hiller, Levisky, and Lange, *J. Am. Chem. Soc.* **87,** 1262 (1965); Kovacic, Levisky, and Goralski, *J. Am. Chem. Soc.* **88,** 100 (1966); Kovacic and Gormisch, *J. Am. Chem. Soc.* **88,** 3819 (1966); Kovacic and Harrison, *J. Org. Chem.* **32,** 207 (1967); Kovacic, Field, Roskos, and Scalzi, *J. Org. Chem.* **32,** 585 (1967); Strand and Kovacic, *J. Am. Chem. Soc.* **95,** 2977 (1973).



Thus the actual electrophilic attack, according to this suggestion, is at the para position (or the ortho, which leads to the same product), and the meta orientation of the amino group arises indirectly. This mechanism is called the *σ-substitution mechanism.*

Aromatic compounds which do not contain meta-directing groups can be converted to diarylamines by treatment with aryl azides in the presence of phenol at −60°C: $ArH + Ar'N_3 \rightarrow ArNHAr'$.[119]

Direct *amidation* can be carried out in moderate yields if an aromatic compound is heated with an excess of a hydroxamic acid in polyphosphoric acid.[120] The mechanism is not known, but it is



$$ArH + R\text{—}\underset{\underset{O}{\|}}{C}\text{—}NH\text{—}OH \longrightarrow Ar\text{—}NH\text{—}\underset{\underset{O}{\|}}{C}\text{—}R$$

possible that an oxime (ArCR=NOH) is first formed, which in polyphosphoric acid rapidly isomerizes to the amide (Beckmann rearrangement, **8-21**).

Also see reactions **3-18** and **3-19.**

C. Sulfur Electrophiles

1-7 Sulfonation

$$ArH + H_2SO_4 \longrightarrow ArSO_2OH$$

The sulfonation reaction is very broad in scope, and many aromatic hydrocarbons (including fused ring systems), aryl halides, ethers, carboxylic acids, acylated amines, ketones, nitro compounds, and sulfonic acids have been sulfonated.[121] Phenols can also be successfully sulfonated, but attack at oxygen may compete. Sulfonation is often accomplished with concentrated sulfuric acid, but it may be done with fuming sulfuric acid, SO_3, $ClSO_2OH$, or other reagents. As with nitration (**1-2**), reagents of a wide variety of activity are available to suit both highly active and highly inactive substrates. Since this is a reversible reaction (see reaction **1-47**), it may be necessary to drive the reaction to completion. However, at low temperatures the reverse reaction is very slow, and the forward reaction is then practically irreversible.[122] SO_3 reacts much more rapidly than sulfuric acid—with benzene it is nearly instantaneous. Sulfones are often side products. When sulfonation is carried out on a benzene ring containing four or five alkyl and/or halogen groups, rearrangements usually occur (see reaction **1-44**).

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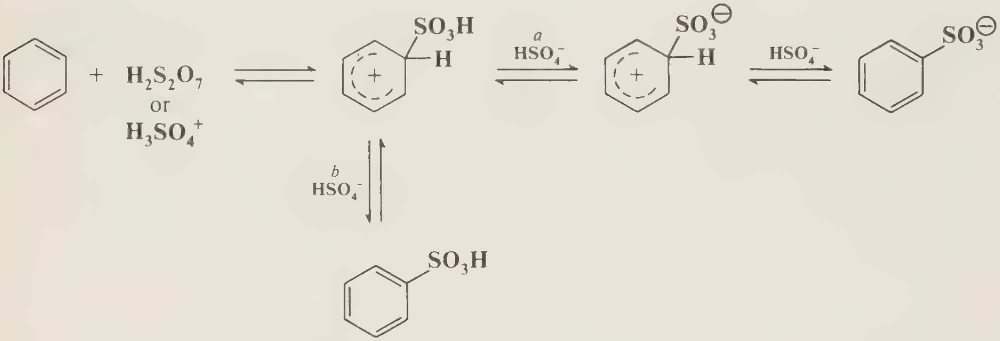
[118] Kovacic and Levisky, *J. Am. Chem. Soc.* **88,** 1000 (1966).

[119] Nakamura, Ohno, and Oka, *Synthesis* 882 (1974).

[120] Wassmundt and Padegimas, *J. Am. Chem. Soc.* **89,** 7131 (1967). For another direct amidation, see So, Becker, and Miller, *J. Chem. Soc., Chem. Commun.* 262 (1975).

[121] For reviews, see Suter and Weston, *Org. React.* **3,** 141–197 (1946); Nelson, in Olah, Ref. 33, vol. 3, pp. 1355–1392 (1964); Gilbert, "Sulfonation and Related Reactions," pp. 62–83, 87–124, Interscience Publishers, New York, 1965.

Although a great deal of work has been done on the mechanism,[123] the identity of the attacking species has proven difficult to establish with certainty, largely because of the complicated nature of the solutions under study. However, largely from the work of Cerfontain and coworkers, indications are that the electrophile varies with the reagent, though in all cases SO_3 is involved, either free or combined with a carrier. In aqueous H_2SO_4 solutions the electrophile is thought to be $H_3SO_4^+$ (or a combination of H_2SO_4 and H_3O^+) at concentrations below about 80 to 85% H_2SO_4, and $H_2S_2O_7$ (or a combination of H_2SO_4 and SO_3) at concentrations higher than this[124] (the changeover point varies with the substrate[125]). Evidence for a change in electrophile is that in the dilute and in the concentrated solutions the rate of the reaction was proportional to the activity of $H_3SO_4^+$ and $H_2S_2O_7$, respectively. Further evidence is that with toluene as substrate the two types of solution gave very different ortho/para ratios. The mechanism is essentially the same for both electrophiles and may be shown as:[124]



The other product of the first step is HSO_4^- or H_2O, from $H_2S_2O_7$ or $H_3SO_4^+$, respectively. Path *a* is the principal route, except at very high H_2SO_4 concentrations, when path *b* becomes important. With $H_3SO_4^+$ the first step is rate-determining under all conditions, but with $H_2S_2O_7$ the first step is the slow step only up to about 96% H_2SO_4, when a subsequent proton transfer becomes partially rate-determining.[126] $H_2S_2O_7$ is more reactive than $H_3SO_4^+$. Values of ρ for $H_2S_2O_7$ and $H_3SO_4^+$ attack were calculated as −6.1 and −9.3, respectively.[124] In fuming sulfuric acid (H_2SO_4 containing excess SO_3), the electrophile is thought to be $H_3S_2O_7^+$ (protonated $H_2S_2O_7$) up to about 104% H_2SO_4, and $H_2S_4O_{13}$ ($H_2SO_4 + 3SO_3$) beyond this concentration.[127] Again, these conclusions were reached from the fact that the rates of sulfonation were proportional to the

[122] Spryskov, *J. Gen. Chem. USSR* **30,** 2433 (1960).

[123] For a monograph, see Cerfontain, "Mechanistic Aspects in Aromatic Sulfonation and Desulfonation," Interscience Publishers, New York, 1968. For reviews, see Cerfontain and Kort, *Int. J. Sulfur Chem. C* **6,** 123–136 (1971); Taylor, Ref. 1, pp. 56–77.

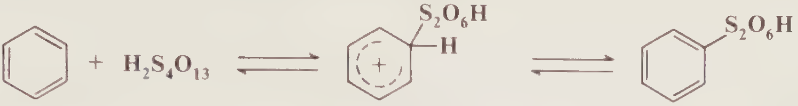
[124] Kort and Cerfontain, *Recl. Trav. Chim. Pays-Bas* **87,** 24 (1968), **88,** 860 (1969).

[125] See for example, Kaandorp and Cerfontain, *Recl. Trav. Chim. Pays-Bas* **88,** 725 (1969).

[126] Kort and Cerfontain, *Recl. Trav. Chim. Pays-Bas* **86,** 865 (1967).

[127] Kort and Cerfontain, *Recl. Trav. Chim. Pays-Bas* **88,** 1298 (1969); Koeberg-Telder and Cerfontain, *J. Chem. Soc., Perkin Trans. 2* 633 (1973).

concentrations of these species. For $H_3S_2O_7^+$ the mechanism shown above (with path *b*) seems to hold, while with $H_2S_4O_{13}$ the following mechanism has been proposed:



Finally, when pure SO_3 is the reagent in aprotic solvents, SO_3 itself is the actual electrophile.[128] Free SO_3 is the most reactive of all these species, so that attack here is generally fast, and a subsequent step is usually rate-determining.

OS **II,** 42, 97, 482, 539; **III,** 288, 824; **IV,** 364; **52,** 135.

1-8 Halosulfonation

$$\mathbf{ArH + ClSO_2OH \longrightarrow ArSO_2Cl}$$

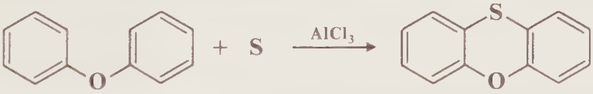
Aromatic sulfonyl chlorides can be prepared directly, by treatment of aromatic rings with chlorosulfuric acid.[129] Since sulfonic acids can also be prepared by the same reagent (reaction **1-7**), it is likely that they are intermediates, being converted to the halides by excess chlorosulfuric acid. The reaction has also been effected with bormo- and fluorosulfuric acids.

OS **I,** 8, 85.

1-9 Sulfurization

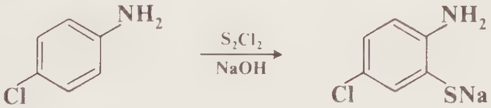
$$\mathbf{ArH + SCl_2 \xrightarrow{AlCl_3} ArSAr}$$

Diaryl sulfides can be prepared by treating aromatic compounds with SCl_2 and a Friedel-Crafts catalyst. Other reagents which can bring about the same result are S_2Cl_2, thionyl chloride, and even sulfur itself. A catalyst is not always necessary. The reaction has been used for ring closure:



When thionyl chloride is used, it is possible to obtain diaryl sulfoxides as the main products.[130] Unsymmetrical diaryl sulfides may be obtained by treatment of an aromatic compound with an aryl sulfenyl chloride (ArSCl) in the presence of a trace amount of iron powder.[131]

With certain substrates (primary amines with a chloro group, or a group not replaceable by chloro, in the para position), treatment with S_2Cl_2 and NaOH gives thiophenolate salts:



This is called the *Herz reaction.*[132]

OS **II,** 242, 485. Also see OS **I,** 574; **III,** 76.

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[128] Koeberg-Telder and Cerfontain, *Recl. Trav. Chim. Pays-Bas* **90,** 193 (1971), **91,** 22 (1972).

[129] For a review, see Gilbert, Ref. 121, pp. 84–87.

[130] Ňikolenko and Krizhechkovskaya, *J. Gen. Chem. USSR* **33,** 3664 (1963); Oae and Zalut, *J. Am. Chem. Soc.* **82,** 5359 (1960).

[131] Fujisawa, Kobori, Ohtsuka, and Tsuchihashi, *Tetrahedron Lètt.* 5071 (1968).

[132] For a review, see Warburton, *Chem. Rev.* **57,** 1011–1020 (1957).

1-10 Sulfonylation

$$ArH + RSO_2Cl \xrightarrow{AlCl_3} ArSO_2R$$

Aryl sulfones can be formed by treatment of aromatic compounds with sulfonyl halides and a Friedel-Crafts catalyst.[133] R may also be aryl. This reaction is analogous to Friedel-Crafts acylation with carboxylic acid halides (reaction **1-15**). Alternatively, the aromatic compound may be treated with a sulfonic acid with polyphosphoric acid as catalyst.[134]

1-11 Thiocyanation

$$ArH + (SCN)_2 \longrightarrow ArSCN$$

Phenols and aromatic amines can be converted to thiocyanates by treatment with thiocyanogen.[135] Substitution generally takes place in the para position if available, otherwise in the ortho position. Phenolic ethers and acylated aromatic amines do not react with $(SCN)_2$ but can be thiocyanated with thiocyanogen chloride (ClSCN).

D. Halogen Electrophiles

1-12 Halogenation[136]

1. *Chlorine and bromine.*

$$ArH + Br_2 \xrightarrow{Fe} ArBr$$

Aromatic compounds can be brominated or chlorinated by treatment with bromine or chlorine in the presence of a catalyst, most often iron. However, the real catalyst is not the iron itself, but the ferric bromide or ferric chloride formed in small amounts from the reaction between iron and the reagent. Ferric chloride and other Lewis acids are often directly used as catalysts, as is iodine. When thallium(III) acetate is the catalyst, many substrates are brominated with high regiospecificity para to an ortho-para-directing group.[137] For active substrates, including amines, phenols, naphthalene, and polyalkylbenzenes[138] such as mesitylene and isodurene, no catalyst is needed. Indeed, for amines and phenols the reaction is so rapid that it is carried out with a dilute solution of Br_2 or Cl_2 in water at room temperature. Even so, with amines it is not possible to stop the reaction before all the available ortho and para positions are substituted, because the initially formed haloamines are weaker bases than the original amines and are less likely to be protonated by the liberated HX. For this reason, primary amines are often converted to the corresponding anilides if monosubstitution is desired. Another method of obtaining monosubstitution (para) of amines is to use the reagent 2,4,4,6-tetrabromocyclohexa-2,5-dienone in CH_2Cl_2 or $CHCl_3$.[139] With phenols it is possible to stop after one group has entered. The rapid room-temperature reaction with amines and phenols is often used as a test for these compounds. Chlorine is a more active reagent than bromine. Phenols can be brominated exclusively in the ortho position (disubstitution of phenol gives 2,6-dibromophenol) by treatment at about −70°C with Br_2 in the presence of *t*-butylamine or triethylenediamine, which precipitates out the liberated HBr.[140]

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[133] For reviews, see Taylor, Ref. 1, pp. 77–83; Jensen and Goldman, in Olah, Ref. 33, vol. 3, pp. 1517–1593 (1964).

[134] Graybill, *J. Org. Chem.* **32,** 2931 (1967).

[135] Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, pp. 1152–1153, John Wiley & Sons, Inc., New York, 1967.

[136] For reviews, see Buehler and Pearson, "Survey of Organic Synthesis," pp. 392–404, Interscience Publishers, New York, 1970; de la Mare and Ridd, Ref. 1, pp. 105–148; Norman and Taylor, Ref. 1, pp. 119–155; Braendlin and McBee, in Olah, Ref. 33, vol. 3, pp. 1517–1593 (1964). For a review of the halogenation of heterocyclic compounds, see Eisch, *Adv. Heterocycl. Chem.* **7,** 1–37 (1966).

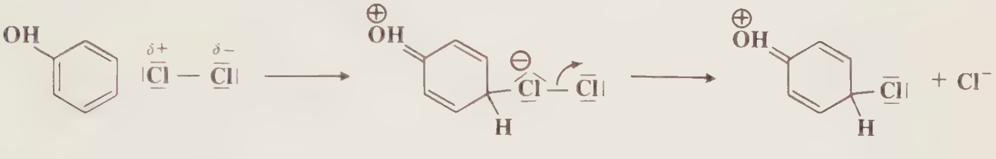
[137] McKillop, Bromley, and Taylor, *J. Org. Chem.* **37,** 88 (1972).

[138] For a review of aromatic substitution on polyalkylbenzenes, see Baciocchi and Illuminati, *Prog. Phys. Org. Chem.* **5,** 1–79 (1967).

[139] Caló, Ciminale, Lopez, and Todesco, *J. Chem. Soc. C* 3652 (1971).

Other reagents have also been used, among them HOCl, HOBr, and N-chloro and N-bromo amides (especially N-bromosuccinimide). In all these cases the reaction is catalyzed by the addition of acids. Dibromoisocyanuric acid in H_2SO_4 is a very good brominating agent[141] for substrates with strongly deactivating substituents.[142] A particularly powerful reagent consists of S_2Cl_2 and $AlCl_3$ in sulfuryl chloride (SO_2Cl_2).[143] Halogenation has also been accomplished with benzoyl peroxide and lithium halide.[144] If the substrate contains alkyl groups, then side-chain halogenation (reaction **4-1**) is possible with most of the reagents mentioned, including chlorine and bromine. Since side-chain halogenation is catalyzed by light, the reactions should be run in the absence of light wherever possible.

For reactions in the absence of a catalyst, the attacking entity is simply Br_2 or Cl_2 which has been polarized by the ring:[145]



32 **33**

Although the equation as written shows an intermediate which has two chlorines, the Cl—Cl bond may also be broken in the course of the attack, so that the only intermediate is **33.**

If **32** *is* present (note that the central chlorine has 10 electrons in its outer shell), then its stability may be such that an outside entity, such as the solvent, may be required to remove Cl^-. If this is the rate-determining step in these cases, then the rate should be different in different solvents. This has been shown to be the case.[146] Evidence for molecular chlorine or bromine as the attacking species in these cases is that acids, bases, and other ions, including especially chloride ion, accelerate the rate about equally, though if chlorine dissociated into Cl^+ and Cl^-, the addition of chloride should decrease the rate and acids should increase it.

When a Lewis acid catalyst is used along with chlorine or bromine, then the attacking entity is probably Cl^+ or Br^+, formed in this manner:

$$AlCl_3 + Br_2 \longrightarrow AlCl_3Br^- + Br^+$$

With other reagents, the attacking entity in brominations may be Br^+, or it may be a species such as H_2OBr^+ (the conjugate acid of HOBr), in which H_2O is a carrier of Br^+.[147] With HOCl in water the electrophile may be Cl_2O, Cl_2, or H_2OCl^+; in acetic acid it is generally AcOCl. All these species are more reactive than HOCl itself. It is extremely doubtful that Cl^+ is a significant electrophile in chlorinations by HOCl.[148] It has been demonstrated in the reaction between N-methylaniline and calcium hypochlorite that the chlorine attacking entity attacks the *nitrogen* to give N-chloro-N-methylaniline, which rearranges (as in reaction **1-39**) to give a mixture of ring-chlorinated N-methylanilines in which the ortho isomer predominates.[149] Ir spectra of the reaction mixture showed a continuous disappearance of the N—H peak.

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[140] Pearson, Wysong, and Breder, *J. Org. Chem.* **32,** 2358 (1967).

[141] Nitrobenzene is pentabrominated in 1 min with this reagent in 15% oleum at room temperature.

[142] Gottardi, *Monatsh. Chem.* **99,** 815 (1968), **100,** 42 (1969).

[143] Ballester, Molinet, and Castaner, *J. Am. Chem. Soc.* **82,** 4254 (1960).

[144] Kochi, Graybill, and Kurz, *J. Am. Chem. Soc.* **86,** 5257 (1964).

[145] For reviews of the mechanism of halogenation, see de la Mare and Swedlund, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 1, pp. 490–536, John Wiley & Sons, Inc., New York, 1973; Taylor, Ref. 1, pp. 83–139; Berliner, *J. Chem. Educ.* **43,** 124–232 (1966).

[146] Andrews and Keefer, *J. Am. Chem. Soc.* **81,** 1063 (1959).

[147] For example, see Gilow and Ridd, *J. Chem. Soc., Perkin Trans. 2* 1321 (1973).

[148] Swain and Crist, *J. Am. Chem. Soc.* **94,** 3195 (1972).

$FeCl_3$ itself,[150] and also $CuCl_2$, $SbCl_5$, etc.,[151] can give moderate yields of aryl chlorides.[152] The electrophile here might be a species such as $FeCl_2^+$, but the reactions can also take place by a free-radical mechanism.[153]

When chlorination or bromination is carried out at high temperatures (e.g., 300 to 400°C), ortho-para-directing groups direct meta, and vice versa.[154] A different mechanism operates here, which is not completely understood. It is also possible for bromination to take place by the SE1 mechanism, e.g., in the *t*-BuOK-catalyzed bromination of 1,3,5-tribromobenzene.[155]

2. *Iodine.* Iodine is the least reactive of the halogens in aromatic substitution. Except for active substrates, an oxidizing agent must normally be present to oxidize I_2 to a better electrophile.[156] Examples of such oxidizing agents are HNO_3, HIO_3, SO_3, and H_2O_2. ICl is a better iodinating agent than iodine itself. Iodination can also be accomplished by treatment of the substrate with I_2 (or virtually any group I–VIII metallic iodide) in the presence of copper salts,[157] or with I_2 and $SbCl_5$.[158]

The actual attacking species is less clear in this case than with bromine or chlorine. Iodine itself is too unreactive, except for active species such as phenols, where there is good evidence that I_2 is the attacking entity.[159] There is evidence that AcOI may be the attacking entity when peroxyacetic acid is the catalyst,[160] and I_3^+ when SO_3 or HIO_3 is the catalyst.[161] Another possibility in some situations is I^+. For an indirect method for accomplishing aromatic iodination, see reaction **2-28.**

3. *Fluorine.* Direct fluorination of aromatic rings with F_2 is not feasible at room temperature, because of the extreme reactivity of F_2. It has been accomplished at low temperatures (e.g., -70 to -20°C, depending on the substrate),[162] but the reaction is not yet of preparative significance.[163] Fluorination has also been reported with XeF_2[164] and with fluoroxytrifluoromethane CF_3OF[165] under various conditions and with various yields, in some cases by electrophilic and in other cases by free-radical mechanisms. However, none of these methods seems likely to displace the Schiemann reaction (**3-25**) as the most common method for introducing fluorine into aromatic rings.

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[149] Haberfield and Paul, *J. Am. Chem. Soc.* **87,** 5502 (1965); Gassman and Campbell, *J. Am. Chem. Soc.* **94,** 3891 (1972).

[150] Kovacic, Wu, and Stewart, *J. Am. Chem. Soc.* **82,** 1917 (1960).

[151] Ware and Borchert, *J. Org. Chem.* **26,** 2263, 2267 (1961).

[152] For a review of halogenations with metal halides, see Kovacic, in Olah, Ref. 33, vol. 4, pp. 111–126 (1965).

[153] Nonhebel, *J. Chem. Soc.* 1216 (1963); Mosnaim and Nonhebel, *Tetrahedron* **25,** 1591 (1969); Mosnaim, Nonhebel, and Russell, *Tetrahedron* **25,** 3458 (1969); Nonhebel and Russell, *Tetrahedron* **25,** 3493 (1969).

[154] For a review of this type of reaction, see Kooyman, *Pure. Appl. Chem.* **7,** 193–202 (1963).

[155] Mach and Bunnett, *J. Am. Chem. Soc.* **96,** 936 (1974).

[156] It is often stated that the function of the oxidizing agent is to oxidize the liberated HI which would otherwise reduce the aryl iodide. However, this statement is incorrect. See Butler, *J. Chem. Educ.* **48,** 508 (1971).

[157] Baird and Surridge, *J. Org. Chem.* **35,** 3436 (1970).

[158] Uemura, Onoe, and Okano, *Bull. Chem. Soc. Jpn.* **47,** 147 (1974).

[159] Grovenstein and Aprahamian, *J. Am. Chem. Soc.* **84,** 212 (1962); Grovenstein, Aprahamian, Bryan, Gnanapragasam, Kilby, McKelvey, and Sullivan, *J. Am. Chem. Soc.* **95,** 4261 (1973).

[160] Ogata and Nakajima, *Tetrahedron* **20,** 43, 2751 (1964); Ogata and Aoki, *J. Am. Chem. Soc.* **90,** 6187 (1968); Ogata and Urasaki, *J. Chem. Soc. C* 1689 (1970).

[161] Arotsky, Butler, and Darby, *J. Chem. Soc. C* 1480 (1970).

[162] Grakauskas, *J. Org. Chem.* **35,** 723 (1970).

[163] For a review of direct liquid-phase fluorination of organic compounds, aliphatic as well as aromatic, see Grakauskas, *Intra-Sci. Chem. Rep.* **5,** 85–104 (1971).

[164] Shaw, Hyman, and Filler, *J. Am. Chem. Soc.* **91,** 1563 (1969), **92,** 6498 (1970), *J. Org. Chem.* **36,** 2917 (1971); Mackenzie and Fajer, *J. Am. Chem. Soc.* **92,** 4994 (1970); Anand, Quarterman, Hyman, Migliorese, and Filler, *J. Org. Chem.* **40,** 807 (1975).

[165] Barton, Ganguly, Hesse, Loo, and Pechet, *Chem. Commun.* 806 (1968); Kollonitsch, Barash, and Doldouras, *J. Am. Chem. Soc.* **92,** 7494 (1970).

The overall effectiveness of reagents in aromatic substitution is $Cl_2 > BrCl > Br_2 > ICl > I_2$.
OS **I,** 111, 121, 123, 128, 207, 323; **II,** 95, 97, 100, 173, 196, 343, 347, 349, 357, 592; **III,** 132, 134, 138, 262, 267, 575, 796; **IV,** 114, 166, 256, 545, 547, 872, 947; **V,** 117, 147, 206, 346; **51,** 94; **55,** 20. Also see OS **II,** 128.

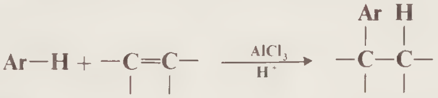
E. Carbon Electrophiles In the reactions in this section, a new carbon-carbon bond is formed. With respect to the aromatic ring they are electrophilic substitutions, since a positive species attacks the ring, and we treat them in this manner because it is customary. However, with respect to the electrophile most of these reactions are nucleophilic substitutions, and what was said in Chapter 10 is pertinent to them. Some are not substitutions with respect to the reagent. For example, reaction **1-13,** when performed with an olefin as reagent, is addition to a C=C double bond, and reaction **1-25** is addition to a C=O double bond.

1-13 Friedel-Crafts Alkylation

$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} ArR}$$

The alkylation of aromatic rings, called *Friedel-Crafts alkylation,* is a reaction of very broad scope.[166] The most important reagents are alkyl halides, olefins, and alcohols, but many other types of reagent have also been employed.[166] When alkyl halides are used, the reactivity is in the order F > Cl > Br > I[167] and, for example, $FCH_2CH_2CH_2Cl$ reacts with benzene to give $PhCH_2CH_2CH_2Cl$[168] when the catalyst is BCl_3. By the use of this catalyst it is therefore possible to place a halo alkyl group on a ring (see also reaction **1-27**).[169] Di- and trihalides, when all the halogens are the same, usually react with more than one molecule of aromatic compound, and it is usually not possible to stop the reaction earlier. Thus, benzene with CH_2Cl_2 gives not $PhCH_2Cl$, but Ph_2CH_2; and benzene with $CHCl_3$ gives Ph_3CH. With CCl_4, however, the reaction stops when only three rings have been substituted, and the product is Ph_3CCl.

Olefins are especially good alkylating agents. With respect to them the reaction is addition of ArH to a C=C double bond:



$$\mathrm{Ar{-}H + {-}\underset{|}{C}{=}\underset{|}{C}{-} \xrightarrow[H^+]{AlCl_3} {-}\overset{Ar}{\underset{|}{\overset{|}{C}}}{-}\overset{H}{\underset{|}{\overset{|}{C}}}{-}}$$

Acetylene reacts with 2 moles of aromatic compound to give 1,1-diarylethanes, but other alkynes react poorly if at all. Alcohols are more active than alkyl halides, though if a Lewis acid catalyst is used, more catalyst is required, since the catalyst complexes with the OH group. However, proton acids, especially H_2SO_4, are often used to catalyze alkylation with alcohols. When esters are the reagents, there is competition between alkylation and acylation (reaction **1-15**). Though this competition may often be controlled by choice of catalyst, and alkylation is usually favored, esters are not often employed in Friedel-Crafts reactions. Other alkylating agents are ethers, mercaptans, sulfides, thiocyanates, sulfates, sulfonates, and even alkanes and cycloalkanes, under conditions where these are converted to carbonium ions. Notable here are ethylene oxide, which puts the CH_2CH_2OH group onto the ring, and cyclopropane. For all types of reagent the reactivity order is allyl, benzyl type > tertiary > secondary > primary.

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[166] For a treatise on Friedel-Crafts reactions in general, see Olah, "Friedel-Crafts and Related Reactions," Interscience Publishers, New York, 1963–1965. Volume 1 covers general aspects, such as catalyst activity, intermediate complexes, etc. Volume 2 covers alkylation and related reactions. In this volume the various reagents are treated by the indicated authors as follows: alkenes and alkanes, Patinkin and Friedman, pp. 1–288; dienes and substituted alkenes, Koncos and Friedman, pp. 289–412; alkynes, Franzen, pp. 413–416; alkyl halides, Drahowzal, pp. 417–475; alcohols and ethers, Schriesheim, pp. 477–595; sulfonates and inorganic esters, Drahowzal, pp. 641–658. For a monograph in which five chapters of the above treatise are reprinted and more recent material added, see Olah, "Friedel-Crafts Chemistry," John Wiley & Sons, Inc., New York, 1973. Review articles are by Price, *Org. React.* **3,** 1–82 (1946); Baddeley, *Q. Rev., Chem. Soc.* **8,** 355–379 (1954); Roberts, *Chem. Eng. News* **43**(4) 96–112 (Jan. 25, 1965); and Norman and Taylor, Ref. 1, pp. 156–173.

[167] For example, see Calloway, *J. Am. Chem. Soc.* **59,** 1474 (1937); Brown and Jungk, *J. Am. Chem. Soc.* **77,** 5584 (1955).

[168] Olah and Kuhn, *J. Org. Chem.* **29,** 2317 (1964).

[169] For a review of selectivity in this reaction, i.e., which group preferentially attacks when the reagent contains two or more, see Olah, in Olah, Ref. 166, vol. 1, pp. 881–905. This review also covers the case of alkylation versus acylation.

Regardless of which reagent is used, a catalyst is always required. Aluminum chloride is the most common, but many other Lewis acids have been used, and also proton acids such as HF and H_2SO_4.[170] For active halides a trace of a less active catalyst, for example, $ZnCl_2$, may be enough. For an unreactive halide, such as methyl chloride, a more powerful catalyst is needed, for example, $AlCl_3$, and in larger amounts. In some cases, especially with olefins, a Lewis acid catalyst causes reaction only if a small amount of proton-donating cocatalyst is present. Catalysts have been arranged in the following order of overall reactivity: $AlBr_3 > AlCl_3 > GaCl_3 > FeCl_3 > SbCl_5 > ZrCl_4$, $SnCl_4 > BCl_3$, BF_3, $SbCl_3$;[171] but the reactivity order in each case depends on the substrate, reagent, and conditions. A survey of the field has shown that "in all probability in Friedel-Crafts type reactions no simple monotonic series of catalytic activity of Lewis acid and related proton acid catalysis is possible."[172] The most common solvent for Friedel-Crafts alkylation is carbon disulfide.

Friedel-Crafts alkylation is unusual among the principal aromatic substitutions in that the entering group is activating, so that di- and polyalkylation are frequently observed. However, the activating effect of simple alkyl groups (e.g., ethyl, isopropyl) is such that compounds with these groups as substituents are attacked in Friedel-Crafts alkylations only about 1.5 to 3 times as fast as benzene,[173] and so it is often possible to obtain high yields of monoalkyl product. Actually, the fact that di- and polyalkyl derivatives are frequently obtained is not due to the small difference in reactivity but to the circumstance that alkylbenzenes are preferentially soluble in the catalyst layer, where the reaction actually takes place.[174] This factor may be removed by the use of a suitable solvent, by high temperatures, or by high-speed stirring.

Also unusual is the fact that the OH, OR, NH_2, etc., groups do not facilitate the reaction, since the catalyst coordinates with these basic groups. Although phenols give the usual Friedel-Crafts reactions, orienting ortho and para,[175] the reaction is very poor for amines. However, amines can undergo the reaction if olefins are used as reagents and aluminum anilides as catalysts.[176] In this method the catalyst is prepared by treating the amine to be alkylated with $\frac{1}{3}$ mole of $AlCl_3$. A similar reaction may be performed with phenols, though here the catalyst is $Al(OAr)_3$.[177] Primary aromatic amines (and phenols) can be methylated regiospecifically in the ortho position by an indirect method (see reaction **1-29**).

Naphthalene and other fused ring compounds generally give poor yields in Friedel-Crafts alkylation, because they are so reactive that they react with the catalyst. Heterocyclic rings are usually also poor substrates for the reaction. Furan, thiophene, and pyridine cannot usually be alkylated. Although some furans and thiophenes have been alkylated, a true alkylation of a pyridine or a quinoline has never been described.[178] However, alkylation of pyridine and other nitrogen heterocycles can be accomplished by a free-radical (reaction **4-21**) and by a nucleophilic method (reaction **3-17**).

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[170] For a review of catalysts and solvents in Friedel-Crafts reactions, see Olah, in Olah, Ref. 166, vol. 1, pp. 201–366, 853–81.

[171] Russell, *J. Am. Chem. Soc.* **81**, 4834 (1959).

[172] Ref. 170, p. 859.

[173] Condon, *J. Am. Chem. Soc.* **70**, 2265 (1948); Olah, Kuhn, and Flood, *J. Am. Chem. Soc.* **84**, 1688 (1962).

[174] Francis, *Chem. Rev.* **43**, 257 (1948).

[175] For a review of alkylations of phenols, see Shuikin and Viktorova, *Russ. Chem. Rev.* **29**, 560–576 (1960).

[176] For a review, see Stroh, Ebersberger, Haberland, and Hahn, *Newer Methods Prep. Org. Chem.* **2**, 227–252 (1963). This article also appeared in *Angew. Chem.* **69**, 124–131 (1957).

[177] For a review, see Stroh, Seydel, and Hahn, *Newer Methods Prep. Org. Chem.* **2**, 337–359 (1963). This article also appeared in *Angew. Chem.* **69**, 669–706 (1957).

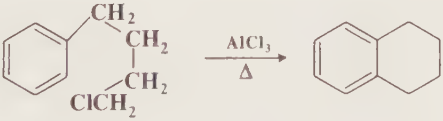
[178] Drahowzal, in Olah, Ref. 166, vol. 2, p. 433.

In most cases, meta-directing groups make the ring too inactive for alkylation. Nitrobenzene cannot be alkylated, and there are only a few reports of successful Friedel-Crafts alkylations when electron-withdrawing groups are present.[179] This is not because the attacking species is not powerful enough; indeed we have seen (p. 471) that alkyl carbonium ions are among the most powerful of electrophiles. The difficulty is caused by the fact that, with inactive substrates, degradation and polymerization of the electrophile occurs before it can attack the ring. However, if an activating and a deactivating group are both present on a ring, Friedel-Crafts alkylation can be accomplished.[180] Aromatic nitro compounds can be methylated by a nucleophilic mechanism (reaction **3-17**).

An important synthetic limitation of Friedel-Crafts alkylation is that rearrangement frequently takes place in the reagent. For example, benzene treated with *n*-propyl bromide gives mostly isopropylbenzene (cumene) and much less *n*-propylbenzene. Rearrangement is usually in the order primary → secondary → tertiary and occurs mostly by migration of H^-, but also of R^- (see discussion of rearrangement mechanisms in Chapter 18). However, it is sometimes possible to choose conditions which yield unrearranged products. For example, when treated with *n*-propyl chloride at room temperature, benzene gives mostly *n*-propylbenzene; and straight-chain alcohols usually do not rearrange when the catalyst is $AlCl_3$, though they do with BF_3[181] or H_2SO_4.[182] When unrearranged products are obtained, it is frequently the result of thermodynamic rather than kinetic control of the products. The order of thermodynamic stability of alkylbenzenes is primary > secondary > tertiary.[183] For example, the lack of rearrangement in the case of primary alcohols and $AlCl_3$ is only apparent: the products are actually the result of *two* rearrangements.[184] The initially formed product is the secondary alkylbenzene, which then rearranges to the thermodynamically more stable primary product.

Because of the rearrangements which usually accompany alkylation with primary reagents, *n*-alkylbenzenes are often prepared by *acylation* (reaction **1-15**) followed by Clemmensen or Wolff-Kishner reduction (reaction **9-39**). However, rearrangements are not the only reason for using this alternate approach. Alkylation is more active than acylation, and therefore less selective. For example, toluene with ethyl bromide and $GaBr_3$ gave 38.4% *o*-ethyltoluene, 40.6% of the para isomer, and 21.0% of the meta isomer, while acylation gave 97.6% *p*-methylacetophenone.[185] Hence, even in this case, where isomerization is not a factor, it is profitable to acylate and reduce, rather than to separate the mixture of isomers.

An important use of the Friedel-Crafts alkylation reaction is to effect ring closure.[186] The most common method is to heat with aluminum chloride an aromatic compound having a halogen, hydroxy, or olefinic group in the proper position, as, for example, in the preparation of tetralin:



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[179] Campbell and Spaeth, *J. Am. Chem. Soc.* **81**, 5933 (1959).

[180] Olah, in Olah, Ref. 166, vol. 1, p. 34.

[181] Streitwieser, Stevenson, and Shaeffer, *J. Am. Chem. Soc.* **81**, 1110 (1959); Streitwieser, Shaeffer, and Andreades, *J. Am. Chem. Soc.* **81**, 1113 (1959).

[182] Ioffe and Yan, *J. Gen. Chem. USSR* **33**, 2141 (1963).

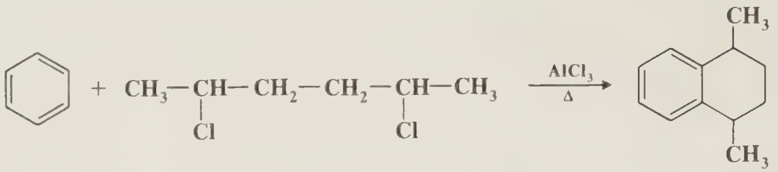
[183] Olah, in Olah, Ref. 166, vol. 1, p. 70.

[184] Roberts, Lin, and Anderson, *Tetrahedron* **25**, 4173 (1969).

[185] Stock and Brown, *Adv. Phys. Org. Chem.* **1**, 46–47 (1963).

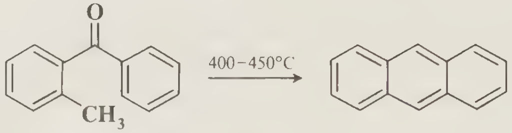
[186] For a review, see Barclay, in Olah, Ref. 166, vol. 2, pp. 785–977.

Another way of effecting ring closure through Friedel-Crafts alkylation is to use a reagent containing two groups, for example:



These reactions are most successful for the preparation of six-membered rings,[187] though five- and seven-membered rings have also been closed in this manner.

A ring-closure reaction which is somewhat similar is called the *Elbs reaction*.[188] Diaryl ketones containing an ortho methyl group can by cyclized by heating, although the yields are usually quite low:



Since water is lost, this is a cyclodehydration. Since the reaction requires no catalyst, it is probably not a true Friedel-Crafts reaction. The value of the reaction is that it can be used to prepare compounds, even in low yields, that are very difficult to prepare any other way.

For other Friedel-Crafts ring-closure reactions see reactions **1-14**, **1-15**, and **1-26**.

From what has been said thus far it is evident that the electrophile in Friedel-Crafts alkylation is a carbonium ion, at least in most cases.[189] This is in accord with the knowledge that carbonium ions rearrange in the direction primary → secondary → tertiary (see Chapter 18). In each case the carbonium ion is formed from the attacking reagent and the catalyst. For the three most important types of reagent these reactions are:

From alkyl halides: $\mathrm{RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-}$

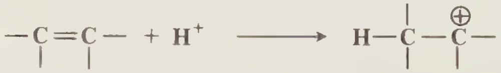
From alcohols and Lewis acids:

$$\mathrm{ROH + AlCl_3 \longrightarrow ROAlCl_2 \longrightarrow R^+ + {}^-OAlCl_2}$$

From alcohols and proton acids:

$$\mathrm{ROH + H^+ \longrightarrow ROH_2^+ \longrightarrow R^+ + H_2O}$$

From olefins (a supply of protons is always required):



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- \;+\; \mathrm{H^+} \longrightarrow \mathrm{H}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{\oplus}{\mathrm{C}}}-$$

In the case of olefins, Markovnikov's rule (p. 687) is followed. Alkylation has also been effected by carbonium ions generated by the diazotization of primary amines (see p. 328).[190] Carbonium-ion formation is particularly easy from some reagents, because of the stability of the cations. Triphenylmethyl chloride[191] and 1-chloroadamantane[192] alkylate activated aromatic rings (e.g., phenols, amines) with no catalyst or solvent. When the triphenylmethyl cation is generated from triphenylcarbinol and acid, the reaction is called the *Baeyer-Villiger condensation*, not to be confused with the Baeyer-Villiger rearrangement (reaction **8-23**). Ions as stable as this are less reactive than other carbonium ions and often attack only active substrates. The tropylium ion, for example, alkylates anisole but not benzene.[193]

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[187] See Khalaf and Roberts, *J. Org. Chem.* **31,** 89 (1966).

[188] For a review, see Fieser, *Org. React.* **1,** 129–154 (1942).

[189] For a discussion of the mechanism, see Taylor, Ref. 1, pp. 139–158.

[190] Pearson, Breder, and Craig, *J. Am. Chem. Soc.* **86,** 5054 (1964); Olah, Overchuk, and Lapierre, *J. Am. Chem. Soc.* **87,** 5785 (1965); Jurewicz, Bayless, and Friedman, *J. Am. Chem. Soc.* **87,** 5788 (1965); Friedman and Jurewicz, *J. Am. Chem. Soc.* **91,** 1808 (1969).

However, there is much evidence that many Friedel-Crafts alkylations, especially with primary reagents, do not go through a completely free carbonium ion. The ion may exist as a tight ion pair, with say $AlCl_4^-$ as the counterion, or as a complex. Among the evidence is that methylation of toluene by methyl bromide and methyl iodide gave different ortho/para/meta ratios,[194] though if the same species attacked in each case we would expect the same ratios. Other evidence is that, in some cases, the reaction kinetics are third order; first order each in aromatic substrate, attacking reagent, and catalyst.[195] In these instances a mechanism in which the carbonium ion is slowly formed and then rapidly attacks the ring is ruled out since, in such a mechanism, the substrate would not appear in the rate expression. Since it is known that free carbonium ions, once formed, rapidly attack the ring, there are no free carbonium ions here. Another possibility (with alkyl halides) is that some alkylations take place by an SN2 mechanism (with respect to the halide), in which case no carbonium ions would be involved at all. However, a completely SN2 mechanism requires inversion of configuration, and most investigations of Friedel-Crafts stereochemistry, even where an SN2 mechanism might most be expected, have resulted in total racemization, or at best a few percent inversion. A few exceptions have been found,[196] most notably where the reagent was optically active propylene oxide, in which case 100% inversion was reported.[197]

Rearrangement is possible even with a non-carbonium-ion mechanism. The rearrangement could occur *before* the attack on the ring takes place at all. It has been shown that treatment of $CH_3{}^{14}CH_2Br$ with $AlBr_3$ *in the absence of any aromatic compound* gave a mixture of the starting material and $^{14}CH_2CH_2Br$.[198] Similar results were obtained with $PhCH_2{}^{14}CH_2Br$, in which case the rearrangement was so fast that the rate could be measured only below −70°C. Rearrangement could also occur *after* formation of the product, since alkylation is reversible (see reaction **1-41**).[199] If there are ion pairs present, rearrangement may take place by hydride-ion shift without disturbing the ion-pair relationship.[200]

See reactions **4-19** and **4-21** for *free-radical* alkylation.

OS **I,** 95, 548; **II,** 151, 229, 232, 236, 248; **III,** 343, 347, 504, 842; **IV,** 47, 520, 620, 665, 702, 898, 960; **V,** 130, 654; **51,** 109.

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[191] See, for example, Chuchani, *J. Chem. Soc.* 325 (1960); Hart and Cassis, *J. Am. Chem. Soc.* **76,** 1634 (1954); Hickinbottom, *J. Chem. Soc.* 1700 (1934); Chuchani and Zabicky, *J. Chem. Soc. C* 297 (1966).

[192] Takaku, Taniguchi, and Inamoto, *Synth. Commun.* **1,** 141 (1971).

[193] Bryce-Smith and Perkins, *J. Chem. Soc.* 5295 (1962).

[194] Brown and Jungk, *J. Am. Chem. Soc.* **78,** 2182 (1956).

[195] For examples, see Brown and Grayson, *J. Am. Chem. Soc.* **75,** 6285 (1953); Jungk, Smoot, and Brown, *J. Am. Chem. Soc.* **78,** 2185 (1956); Choi and Brown, *J. Am. Chem. Soc.* **85,** 2596 (1963).

[196] One instance of retention of configuration has been reported; a neighboring group mechanism is likely in this case: Masuda, Nakajima, and Suga, *J. Chem. Soc., Chem. Commun.* 954 (1974).

[197] Nakajima, Suga, Sugita, and Ichikawa, *Tetrahedron* **25,** 1807 (1969). Partial inversion (up to about 40%) has been reported in several other instances: Brauman and Pandell, *J. Am. Chem. Soc.* **89,** 5421 (1967); Brauman and Solladié-Cavallo, *Chem. Commun.* 1124 (1968); Suga, Nakajima, Nakamoto, and Matsumoto, *Tetrahedron Lett.* 3283 (1969).

[198] Sixma and Hendriks, *Recl. Trav. Chim. Pays-Bas* **75,** 169 (1956); Adema and Sixma, *Recl. Trav. Chim. Pays-Bas* **81,** 323, 336 (1962).

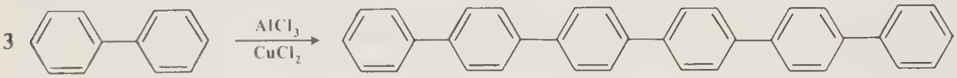
[199] For an example, see Lee, Hamblin, and Uthe, *Can. J. Chem.* **42,** 1771 (1964).

[200] For an example, see Douwes and Kooyman, *Recl. Trav. Chim. Pays-Bas* **83,** 276 (1964).

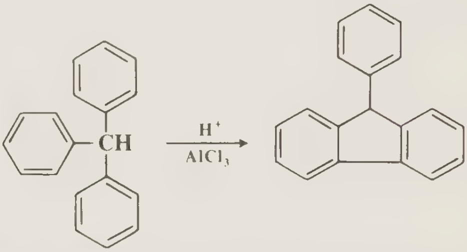
1-14 Friedel-Crafts Arylation. The Scholl Reaction

$$2\text{ArH} \xrightarrow[\text{H}^+]{\text{AlCl}_3} \text{Ar—Ar} + \text{H}_2$$

The coupling of two aromatic molecules by treatment with a Lewis acid and a proton acid is called the *Scholl reaction.*[201] Yields are low, and the synthesis is seldom useful. High temperatures and strong-acid catalysts are required, and the reaction fails for substrates which are destroyed by these conditions. Because the reaction becomes important with large fused ring systems, ordinary Friedel-Crafts reactions (**1-13**) on these systems are rare. For example, naphthalene gives binaphthyl under Friedel-Crafts conditions. Yields may be increased by the addition of a salt such as $CuCl_2$ or $FeCl_3$, which acts as an oxidant.[202] Thus biphenyl gave more than 50% *p*-sexiphenyl on treatment at 80°C with $AlCl_3$ and $CuCl_2$:[203]



Intramolecular Scholl reactions, e.g.,



are much more successful than the intermolecular kind. There are some who apply the term Scholl reaction only to the intramolecular type.

The mechanism is not clear, but it may involve attack by a proton to give an arenium ion of the type **9** (p. 457), which would then be the electrophile which attacks the other ring.[204] Sometimes arylations have been accomplished by treating aromatic substrates with particularly active aryl halides, especially fluorides. For free-radical arylations, see reactions **4-16** to **4-20.**

OS **IV,** 482. Also see OS **V,** 102, 952.

1-15 Friedel-Crafts Acylation

$$\text{ArH} + \text{RCOCl} \xrightarrow{\text{AlCl}_3} \text{ArCOR}$$

The most important method for the preparation of aryl ketones is known as *Friedel-Crafts acylation.*[205] The reaction is of wide scope. Reagents used are not only acyl halides but also carboxylic acids, anhydrides, and ketenes. Esters usually give predominant alkylation (see reaction **1-13**). R may be aryl as well as alkyl. Rearrangement of R is never found, whether R is straight-chain or branched. Because the RCO group is deactivating, the reaction stops cleanly after one group is introduced. All four acyl halides may be used, though chlorides are most commonly employed. The order of activity is usually, but not always, I > Br > Cl > F.[206] Catalysts are Lewis acids, similar to those in reaction **1-13**, but in acylation a little more than 1 mole of catalyst is required per mole of reagent, since the first mole coordinates with the oxygen of the reagent:[207]

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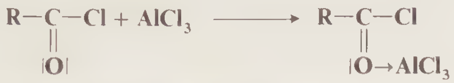
[201] For a review, see Balaban and Nenitzescu, in Olah, Ref. 166, vol. 2, pp. 979–1047.

[202] Kovacic and Koch, *J. Org. Chem.* **28,** 1864 (1963), **30,** 3176 (1965); Kovacic and Kyriakis, *J. Am. Chem. Soc.* **85,** 454 (1963); Kovacic and Wu, *J. Org. Chem.* **26,** 759, 762 (1961).

[203] Kovacic and Lange, *J. Org. Chem.* **29,** 2416 (1964).

[204] For a discussion, see Clowes, *J. Chem. Soc. C* 2519 (1968).

[205] For reviews of Friedel-Crafts acylation, see Olah, "Friedel-Crafts and Related Reactions," Interscience Publishers, New York, 1963-1964, as follows: vol. 1, Olah, pp. 91–115; vol. 3, Gore, pp. 1–381; Peto, pp. 535–910; Sethna, pp. 911–1002; Jensen and Goldman, pp. 1003–1032. Other reviews are by Baddeley, *Q. Rev., Chem. Soc.* **8,** 355–379 (1954); Gore, *Chem. Rev.* **55,** 229–281 (1955); *Chem. Ind.* (*London*) 727–731 (1974); Norman and Taylor, Ref. 1, pp. 174–182.



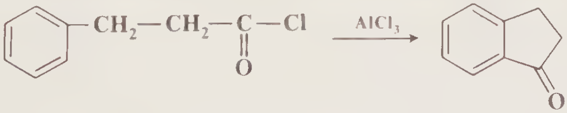
$$\underset{\underset{|\mathrm{O}|}{\|}}{\mathrm{R{-}C{-}Cl}} + \mathrm{AlCl_3} \longrightarrow \underset{\underset{|\mathrm{O}\rightarrow \mathrm{AlCl_3}}{\|}}{\mathrm{R{-}C{-}Cl}}$$

Frequently this 1 : 1 complex is separately prepared, and then the aromatic compound added. Proton acids may be used as catalysts when the reagent is a carboxylic acid. The mixed carboxylic sulfonic anhydrides $RCOOSO_2CF_3$ are extremely reactive acylating agents and can smoothly acylate benzene without a catalyst.[208] With active substrates (e.g., aryl ethers, fused ring systems, thiophenes) Friedel-Crafts acylation can be carried out with very small amounts of catalyst, often just a trace, or even sometimes with no catalyst at all. Ferric chloride, iodine, zinc chloride, and iron are the most common catalysts when the reaction is carried out in this manner.[209]

The reaction is quite successful for many types of substrate, including fused ring systems, which give poor results in reaction **1-13**. Compounds containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated and give mainly or exclusively the para products, because of the relatively large size of the acyl group. However, aromatic amines give poor results. With amines and phenols there may be competition from N- or O-acylation; however, O-acylated phenols can be converted to C-acylated phenols by the Fries rearrangement (reaction **1-34**). Friedel-Crafts acylation is usually prevented by meta-directing groups. Indeed, nitrobenzene is often used as a solvent for the reaction. Many heterocyclic systems, including furans, thiophenes, pyrans, and pyrroles but not pyridines or quinolines, may be acylated in good yield (however, pyridines and quinolines can be acylated by a free-radical mechanism, reaction **4-21**). Gore, in Ref. 205 (pp. 36–100; with tables, pp. 105–321), presents an exhaustive summary of the substrates to which this reaction has been applied.

When a mixed anhydride RCOOCOR′ is the reagent, it is possible to get two products, ArCOR and ArCOR′. Which product predominates depends on two factors. If R contains electron-withdrawing groups, then ArCOR′ is chiefly formed, but if this factor is approximately constant in R and R′, then the ketone with the larger R group predominantly forms.[210] This means that *formylations* of the ring do not occur with mixed anhydrides of formic acid HCOOCOR.

An important use of the Friedel-Crafts acylation is to effect ring closure.[211] This may be done if an acyl halide, anhydride, or acid group is in the proper position. An example is



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[206] Yamase, *Bull. Chem. Soc. Jpn.* **34,** 480 (1961); Corriu, *Bull. Soc. Chim. Fr.* 821 (1965).

[207] The crystal structures of several of these complexes have been reported: Rasmussen and Broch, *Acta Chem. Scand.* **20,** 1351 (1966); Weiss and Chevrier, *Chem. Commun.* 145 (1967); Le Carpentier and Weiss, *Acta Crystallogr., Sect. B* **28,** 1437, 1442 (1972); Chevrier, Le Carpentier, and Weiss, *J. Am. Chem. Soc.* **94,** 5718 (1972). For a review of these complexes, see Chevrier and Weiss, *Angew. Chem. Int. Ed. Engl.* **13,** 1–10 (1974) [*Angew. Chem.* **86,** 12–21].

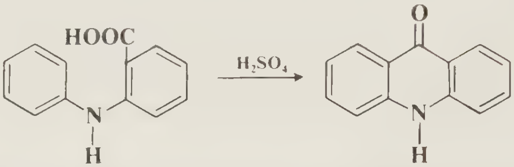
[208] Effenberger and Epple, *Angew. Chem. Int. Ed. Engl.* **11,** 299, 300 (1972) [*Angew. Chem.* **84,** 294, 295].

[209] For a review, see Pearson and Buehler, *Synthesis* 533–542 (1972).

[210] Edwards and Sibelle, *J. Org. Chem.* **28,** 674 (1963).

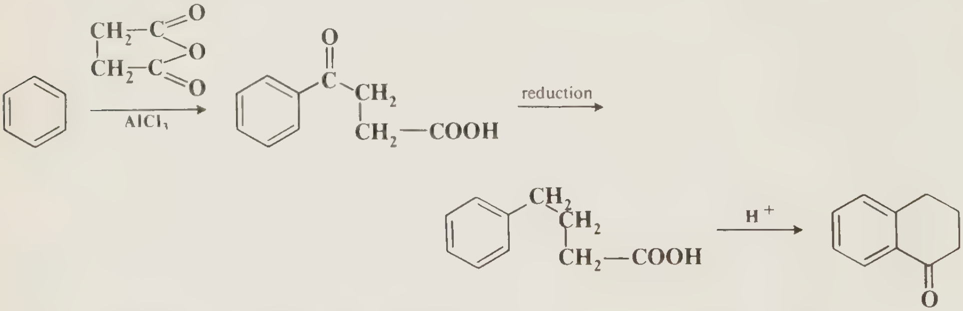
[211] For reviews, see Johnson, *Org. React.* **2,** 114–177 (1944); Sethna, Ref. 205.

The reaction is mostly used to close six-membered rings but has also been done for five- and seven-membered rings, which close less readily. Even larger rings may be closed by high-dilution techniques.[212] Tricyclic and larger systems are often made by using substrates containing one of the acyl groups on a ring, an example being the formation of acridone:



Many fused ring systems are made in this manner. If the bridging group is CO, then the product is a quinone.[213] One of the most common catalysts for intramolecular Friedel-Crafts acylation is polyphosphoric acid[214] (because of its high potency), but $AlCl_3$, H_2SO_4, and other Lewis and proton acids are also used, though acylations with acyl halides are not generally catalyzed by proton acids.

Friedel-Crafts acylation is often carried out with cyclic anhydrides,[215] in which case the product contains a carboxyl group in the side chain. When succinic anhydride is used, the product is $ArCOCH_2CH_2COOH$. This can be reduced (reaction **9-39**) to $ArCH_2CH_2CH_2COOH$, which can then be cyclized by an internal Friedel-Crafts acylation. The total process is called the *Haworth reaction:*



The mechanism of Friedel-Crafts acylation is not completely understood, but at least two mechanisms probably operate, depending on conditions.[216] In most cases the attacking species is the acyl cation, either free or as an ion pair, formed by[217]

$$RCOCl + AlCl_3 \longrightarrow RCO^+ + AlCl_4^-$$

If R is tertiary, then RCO^+ may lose CO to give R^+, so that in such cases the alkylarene ArH is often a side product or even the main product. This kind of cleavage is much more likely with relatively unreactive substrates, where the acylium ion has time to break down. For example, pivaloyl chloride Me_3CCOCl gives the normal acyl product with anisole, but the alkyl product Me_3CPh with benzene. In the other mechanism an acyl cation is not involved, but the 1 : 1 complex attacks directly:[218]

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[212] For example, see Schubert, Sweeney, and Latourette, *J. Am. Chem. Soc.* **76**, 5462 (1954).

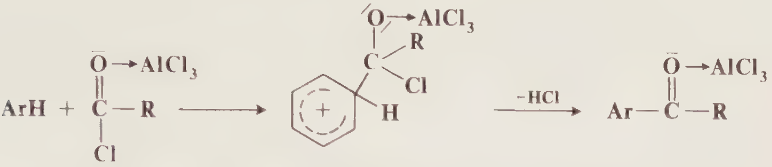
[213] For a discussion, see Thomson, in Patai, "The Chemistry of the Quinonoid Compounds," pt. 1, pp. 136–139, John Wiley & Sons, Inc., New York, 1974.

[214] For reviews of this catalyst, see Uhlig and Snyder, *Adv. Org. Chem.* **1**, 35–81 (1960); Popp and McEwen, *Chem. Rev.* **58**, 321–401 (1958).

[215] For reviews, see Berliner, *Org. React.* **5**, 229–289 (1949); Peto, Ref. 205.

[216] For a review of the mechanism, see Taylor, Ref. 1, pp. 166–185.

[217] After 2 min, exchange between PhCOCl and $Al(^{36}Cl)_3$ is complete: Oulevey and Susz, *Helv. Chim. Acta* **47**, 1828 (1964).

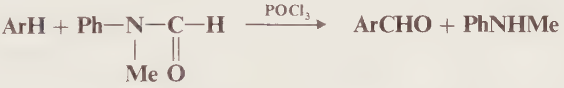


Free-ion attack is more likely for sterically hindered R.[219] The ion CH_3CO^+ has been detected (by ir spectroscopy) in the liquid complex between acetyl chloride and aluminum chloride, and in polar solvents such as nitrobenzene; but in nonpolar solvents such as chloroform only the complex and not the free ion is present.[220] In any event, 1 mole of catalyst certainly remains complexed to the product at the end of the reaction. When the reaction is performed with $RCO^+ \quad SbF_6^-$, no catalyst is required, and the free ion[221] (or ion pair) is undoubtedly the attacking entity.[222]

OS **I**, 109, 353, 476, 517; **II**, 3, 8, 15, 81, 156, 169, 304, 520, 569; **III**, 6, 14, 23, 53, 109, 183, 248, 272, 593, 637, 761, 798; **IV**, 8, 34, 88, 898, 900; **V**, 111; **51**, 100; **53**, 5.

Reactions **1-16** through **1-21** are direct formylations of the ring.[223] Reaction **1-13** has not been used for formylation, since neither formic anhydride nor formyl chloride is stable at ordinary temperatures. Formyl chloride has been shown to be stable in chloroform solution for 1 hr at −60 C[224] but it is not useful for formylating aromatic rings under these conditions. Formic anhydride has been prepared in impure form, but it slowly decomposes at room temperature.[225] It has not yet been used for aromatic formylations. Mixed anhydrides of formic and other acids are known[226] and can be used to formylate amines (see reaction **0-55**) and alcohols but, when they are applied to aromatic rings, no formylation takes place (p. 491).

1-16 Formylation with Disubstituted Formamides



$$\mathrm{ArH} + \mathrm{Ph{-}\underset{Me}{N}{-}\underset{O}{\overset{}{C}}{-}H} \xrightarrow{\mathrm{POCl_3}} \mathrm{ArCHO} + \mathrm{PhNHMe}$$

The reaction with disubstituted formamides and phosphorus oxychloride, which is called the *Vilsmeier* or the *Vilsmeier-Haack reaction*, is today the most common method for the formylation of aromatic rings.[227] However, it is applicable only to active substrates, such as amines and phenols. Aromatic hydrocarbons and heterocycles can also be formylated, but only if they are much more active than benzene (e.g., azulenes, ferrocenes). Though N-phenyl-N-methylformamide is a common reagent, other arylalkyl amides and dialkyl amides are also used. $COCl_2$ has been used in place of $POCl_3$. The reaction has also been carried out with other amides to give ketones (actually an example of reaction **1-15**), but not often. The attacking species is **34**,[228] and the mechanism is probably as follows.

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[218] For example, see Corriu and Coste, *Bull. Soc. Chim. Fr.* 2562, 2568, 2574 (1967), 3272 (1969); Corriu, Dore, and Thomassin, *Tetrahedron* **27**, 5601, 5819 (1971).

[219] Yamase, *Bull. Chem. Soc. Jpn.* **34**, 484 (1961); Gore, *Bull. Chem. Soc. Jpn.* **35**, 1627 (1962); Satchell, *J. Chem. Soc.* 5404 (1961).

[220] Cook, *Can. J. Chem.* **37**, 48 (1959); Cassimatis, Bonnin, and Theophanides, *Can. J. Chem.* **48**, 3860 (1970).

[221] Crystal structures of solid $RCO^+ \quad SbF_6^-$ salts have been reported: Boer, *J. Am. Chem. Soc.* **90**, 6706 (1968); Le Carpentier and Weiss, *Acta Crystallogr., Sect. B* **28**, 1430 (1972); Chevrier, Le Carpentier, and Weiss, *Acta Crystallogr., Sect. B* **28**, 2673 (1972); *J. Am. Chem. Soc.* **94**, 5718 (1972).

[222] Olah, Kuhn, Flood, and Hardie, *J. Am. Chem. Soc.* **86**, 2203 (1964); Olah, Lin, and Germain, *Synthesis* 895 (1974); Olah, Lukas, and Lukas, Ref. 22.

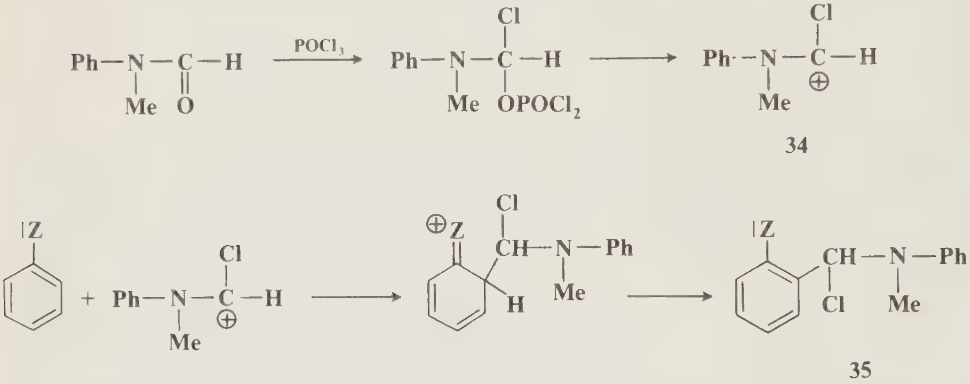
[223] For a review, see Olah and Kuhn, in Olah, Ref. 205, vol. 3, pp. 1153–1256 (1964).

[224] Staab and Datta, *Angew. Chem. Int. Ed. Engl.* **3**, 132 (1964) [*Angew. Chem.* **75**, 1203 (1963)].

[225] Schijf, Scheeren, van Es, and Stevens, *Recl. Trav. Chim. Pays-Bas* **84**, 594 (1965).

[226] Stevens and Van Es, *Recl. Trav. Chim. Pays-Bas* **83**, 863 (1964).

[227] For reviews, see de Meheas, *Bull. Soc. Chim. Fr.* 1989–1999 (1962); Minkin and Dorofeenko, *Russ. Chem. Rev.* **29**, 599 (1960).



35 is unstable and easily hydrolyzes to the product. Either formation of **34** or the reaction of **34** with the substrate may be rate-determining, depending on the reactivity of the substrate.[229]

OS **I,** 217; **III,** 98; **IV,** 331, 539, 831, 915.

1-17 Formylation with Carbon Monoxide and HCl. The Gatterman-Koch Reaction

$$\mathrm{ArH + CO + HCl \xrightarrow[CuCl]{AlCl_3} ArCHO}$$

Certain aromatic compounds can be formylated with a mixture of CO and HCl in the presence of $AlCl_3$. The method is known as the *Gatterman-Koch reaction*.[230] The mixture of CO and HCl apparently behaves as if it were formyl chloride. The reaction has been largely limited to benzene and alkylbenzenes. It fails for phenols, phenolic ethers, and rings which contain meta-directing substituents. Substitution is largely para. An easy way to prepare the reagent mixture is to drop chlorosulfuric acid HSO_3Cl on formic acid, which generates CO, HCl, and H_2SO_4. Cuprous chloride is necessary if the reaction is to be carried out at atmospheric pressure. Without it, pressures of 100 to 250 atm are required. The mechanism has not been extensively investigated, but it is probable that the attacking species is the ion pair $HCO^+ \ AlCl_4^-$, formed by transfer of a proton from the initially formed $H^+AlCl_4^-$ (itself formed by reaction between HCl and $AlCl_3$) to the carbon monoxide.[223] The function of the cuprous chloride is to coordinate with the CO, providing a higher local concentration of it. At high pressures the concentration is high enough to make the CuCl unnecessary.

OS **II,** 583.

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[228] Arnold and Holý, *Collect. Czech. Chem. Commun.* **27,** 2886 (1962); Martin and Martin, *Bull. Soc. Chim. Fr.* 1637 (1963); Filleux-Blanchard, Quemeneur, and Martin, *Chem. Commun.* 836 (1968); Martin, Poignant, Filleux, and Quemeneur, *Tetrahedron Lett.* 5061 (1970); Martin and Poignant, *J. Chem. Soc., Perkin Trans. 2* 1964 (1972); Fritz and Oehl, *Justus Liebigs Ann. Chem.* **749,** 159 (1971); Jugie, Smith, and Martin, *J. Chem. Soc., Perkin Trans. 2* 925 (1975).

[229] Alunni, Linda, Marino, Santini, and Savelli, *J. Chem. Soc., Perkin Trans. 2* 2070 (1972).

[230] For a review, see Crounse, *Org. React.* **5,** 290–300 (1949).

1-18 Formylation with Zinc Cyanide and HCl. The Gatterman Reaction

$$\mathrm{ArH + Zn(CN)_2 \xrightarrow{HCl} ArCH{=}NH_2^+\ \ Cl^- \xrightarrow{H_2O} ArCHO}$$

Formylation with $Zn(CN)_2$ and HCl is called the *Gatterman reaction.*[231] In contrast to reaction **1-17** this method may be successfully applied to phenols and their ethers and to many heterocyclic compounds. However, it cannot be applied to aromatic amines. In the original version of this reaction the substrate was treated with HCN, HCl, and $ZnCl_2$, but the use of $Zn(CN)_2$ and HCl (HCN and $ZnCl_2$ are thus generated in situ) makes the reaction more convenient to carry out and does not reduce yields. The reaction also takes place when an activated substrate is treated with *s*-triazine and HCl.[232] The mechanism of the Gatterman reaction has not been investigated very much, but there is an initial nitrogen-containing product which is normally not isolated but is hydrolyzed to aldehyde. The above structure is presumed for this product. The Gatterman reaction may be regarded as a special case of reaction **1-30.**

OS **III,** 549.

1-19 Formylation with Formyl Fluoride

$$\mathrm{ArH + FCHO \xrightarrow{BF_3} ArCHO}$$

In contrast to formyl chloride, formyl fluoride is stable enough to be used to formylate aromatic rings, with BF_3 as catalyst.[233] The scope of the reaction has not been extensively investigated. It has been successful for benzene, alkylbenzenes, chloro- and fluorobenzene, and naphthalene. The mechanism is presumably the same as that of reaction **1-15.**

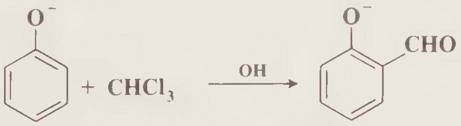
1-20 Formylation with Dichloromethyl Methyl Ether

$$\mathrm{ArH + Cl_2CHOMe \xrightarrow{AlCl_3} ArCHO}$$

Dichloromethyl methyl ether can formylate aromatic rings with Friedel-Crafts catalysts.[234] ArCHClOMe is probably an intermediate. Orthoformates have also been used in a similar reaction.[235] When phenoxymagnesium halides (ArOMgX) are formylated with orthoformates, only ortho products are obtained, in yields of 10 to 50%.[236]

OS **V,** 49.

1-21 Formylation with Chloroform. The Reimer-Tiemann Reaction



In the *Reimer-Tiemann reaction* chloroform and hydroxide ion are used to formylate aromatic rings.[237] The method is useful only for phenols and certain heterocyclic compounds such as pyrroles and indoles. Among the formylation methods (reactions **1-16** to **1-21**) it is the only method conducted in basic solution. Yields are generally low, seldom rising above 50%. The incoming group is directed ortho, unless both ortho positions are filled, in which case the attack is para. Certain substrates have been shown to give abnormal products instead of or in addition to the normal ones. For example, **36** and **38** gave, respectively, **37** and **39** as well as the normal aldehyde products. From the nature of the reagents and from the kind of abnormal products

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[231] For a review, see Truce, *Org. React.* **9,** 37–72 (1957).

[232] Kreutzberger, *Angew. Chem. Int. Ed. Engl.* **6,** 940 (1967) [*Angew. Chem.* **79,** 978].

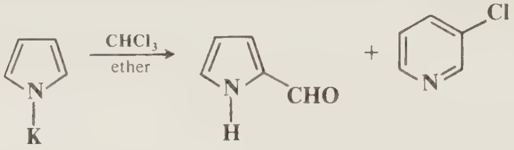
[233] Olah and Kuhn, *J. Am. Chem. Soc.* **82,** 2380 (1960).

[234] Rieche, Gross, and Höft, *Chem. Ber.* **93,** 88 (1960).

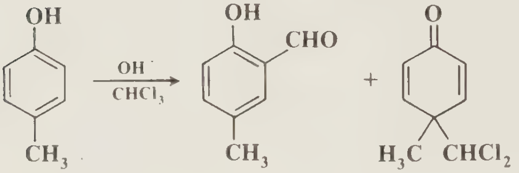
[235] Gross, Rieche, and Matthey, *Chem. Ber.* **96,** 308 (1963).

[236] Casnati, Crisafulli, and Ricca, *Tetrahedron Lett.* 243 (1965).

[237] For a review, see Wynberg, *Chem. Rev.* **60,** 169–184 (1960).

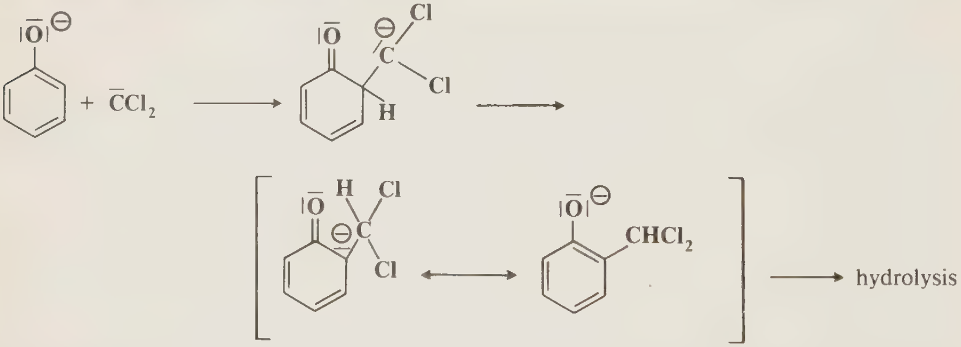


36 **37**



38 **39**

obtained, it is clear that the attacking entity in this reaction is dichlorocarbene CCl_2. This is known to be produced by treatment of chloroform with bases (p. 342); it is an electrophilic reagent, and it is known to give ring expansion of aromatic rings (see reaction **5-53**), accounting for products like **37**. The mechanism of the normal reaction is thus something like this:[238]



The proton transfer shown above probably does not occur by a single 1,2 proton shift, but by two intermolecular proton transfers;[239] that is, first the CCl_2^- group acquires a proton from the solvent, and then the ring proton is lost to the solvent. The formation of **39** in the case of **38** may be explained by attack of some of the CCl_2 para to the OH group. Since this position does not contain a hydrogen, normal proton loss cannot take place, and the reaction ends when the CCl_2^- moiety acquires a proton.

A method closely related to the Reimer-Tiemann reaction is the *Duff reaction*, in which hexamethylenetetramine $(CH_2)_6N_4$ is used instead of chloroform. This reaction can be applied only to phenols and amines; ortho substitution is generally observed, and the yields are low.

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[238] Robinson, *J. Chem. Soc.* 1663 (1961); Hine and van der Veen, *J. Am. Chem. Soc.* **81**, 6446 (1959).

[239] Kemp, *J. Org. Chem.* **36**, 202 (1971).

A mechanism[240] has been proposed which involves initial aminoalkylation (reaction **1-28**) to give $ArCH_2NH_2$, followed by dehydrogenation to ArCH=NH and hydrolysis of this to the aldehyde product. When $(CH_2)_6N_4$ is used in conjunction with F_3CCOOH, the reaction can be applied to simple alkylbenzenes; yields are much higher, and a high degree of regiospecifically para substitution is found.[241] In this case too an imine seems to be an intermediate.

OS **III**, 463; **IV**, 866.

Reactions **1-22** and **1-23** are direct carboxylations of aromatic rings.[242]

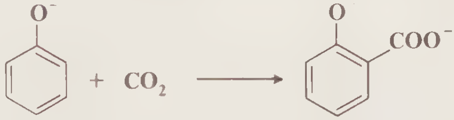
1-22 Carboxylation with Carbonyl Halides

$$\mathrm{ArH + COCl_2 \xrightarrow{AlCl_3} ArCOOH}$$

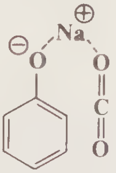
Phosgene, in the presence of Friedel-Crafts catalysts, can carboxylate the ring. This process is analogous to reaction **1-15**, but the ArCOCl initially produced hydrolyzes to the carboxylic acid. However, in most cases the reaction does not take this course, but instead the ArCOCl attacks another ring to give a ketone ArCOAr. A number of other reagents have been used to get around this difficulty, among them oxalyl chloride, urea hydrochloride, alkyl thiolchloroformates RSCOCl,[243] carbamoyl chloride H_2NCOCl, and N,N-diphenylcarbamoyl chloride.[244] With carbamoyl chloride the reaction is called the *Gatterman amide synthesis* and the product is an amide. With RSCOCl the product is a thiol ester ArCOSR; but of course these compounds can be hydrolyzed to the corresponding carboxylic acids. Among compounds carboxylated by one or another of these reagents are benzene, alkylbenzenes, and fused ring systems.

OS **V**, 706.

1-23 Carboxylation with Carbon Dioxide. The Kolbe-Schmitt Reaction



Sodium phenoxides can be carboxylated, mostly in the ortho position, by carbon dioxide. The process is called the *Kolbe-Schmitt reaction.*[245] The mechanism is not clearly understood, but apparently some kind of a complex is formed between the reactants[246] making the carbon of the CO_2 more positive and putting it in a good position to attack the ring. Potassium phenoxide,



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[240] Ogata, Kawasaki, and Sugiura, *Tetrahedron* **24**, 5001 (1968).

[241] Smith, *J. Org. Chem.* **37**, 3972 (1972).

[242] For a review, see Olah and Olah, in Olah, Ref. 205, vol. 3, pp. 1257–1273 (1964).

[243] Olah and Schilling, *Justus Liebigs Ann. Chem.* **761**, 77 (1972).

[244] Wilshire, *Aust. J. Chem.* **20**, 575 (1967).

[245] For a review, see Lindsey and Jeskey, *Chem. Rev.* **57**, 583–620 (1957).

[246] Hales, Jones, and Lindsey, *J. Chem. Soc.* 3145 (1954).

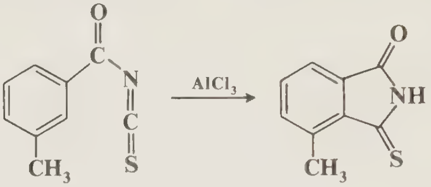
which is less likely to form such a complex,[247] is chiefly attacked in the para position.[248] Carbon tetrachloride may be used instead of CO_2, under Reimer-Tiemann (reaction **1-21**) conditions. Sodium or potassium phenoxide may be carboxylated regiospecifically in the para position in high yield by treatment with sodium or potassium carbonate and carbon monoxide.[249] ^{14}C labeling showed that it is the carbonate carbon which appears in the *p*-hydroxybenzoic acid product.[250] The CO is converted to sodium or potassium formate.

OS **II**, 557.

1-24 Amidation with Isocyanates

$$\mathrm{ArH + RNCO \xrightarrow{AlCl_3} ArCONHR}$$

N-Substituted amides can be prepared by direct attack of isocyanates on aromatic rings.[251] R may be alkyl or aryl, but if the latter, dimers and trimers are also obtained. Isothiocyanates similarly give thioamides. The reaction has been carried out intramolecularly both with aralkyl isothiocyanates and acyl isothiocyanates.[252] In the latter case, the product is easily hydrolyzable to a dicarboxylic acid; therefore this represents a way of putting a carboxyl group on a ring ortho to one which is already there (**40** is prepared by treatment of the acyl halide with lead thiocyanate). The reaction gives better yields with substrates of the type $ArCH_2CONCS$, where six-membered rings are formed.

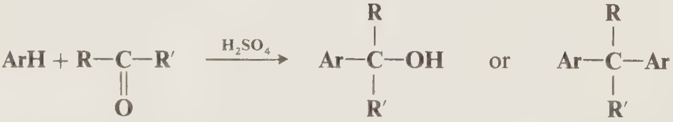


40

OS **V**, 1051; **50**, 52.

Reactions **1-25** to **1-29** involve the introduction of a CH_2Z group, where Z is halogen, hydroxy, amino, or alkylthio. They are all Friedel-Crafts reactions of aldehydes and ketones and, with respect to the carbonyl compound, additions to the C=O double bond. They follow mechanisms discussed in Chapter 16.

1-25 Hydroxyalkylation



$$\mathrm{ArH + R{-}\underset{\underset{O}{\|}}{C}{-}R' \xrightarrow{H_2SO_4} Ar{-}\overset{\overset{R}{|}}{\underset{\underset{R'}{|}}{C}}{-}OH \quad or \quad Ar{-}\overset{\overset{R}{|}}{\underset{\underset{R'}{|}}{C}}{-}Ar}$$

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[247] There is evidence that, in the complex formed from potassium salts, the bonding is between the aromatic compound and the carbon atom of CO_2: Hirao and Kito, *Bull. Chem. Soc. Jpn.* **46,** 3470 (1973).

[248] Actually, the reaction seems to be more complicated than this. At least part of the potassium *p*-hydroxybenzoate which forms comes from a rearrangement of initially formed potassium salicylate. Sodium salicylate does not rearrange. See Shine, "Aromatic Rearrangements," Ref. 289, pp. 344–348. See also Ota, *Bull. Chem. Soc. Jpn.* **47,** 2343 (1974).

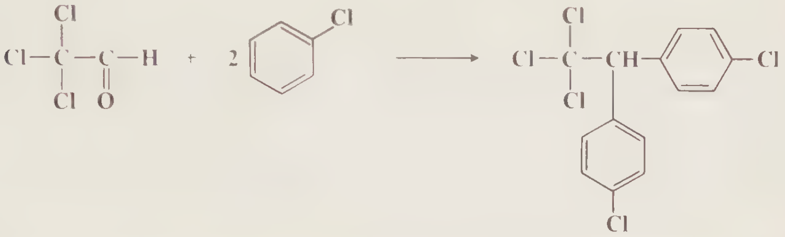
[249] Yasuhara and Nogi, *J. Org. Chem.* **33,** 4512 (1968); *Chem. Ind.* (*London*) 229 (1967), 77 (1969).

[250] Yasuhara, Nogi, and Saishō, *Bull. Chem. Soc. Jpn.* **42,** 2070 (1969).

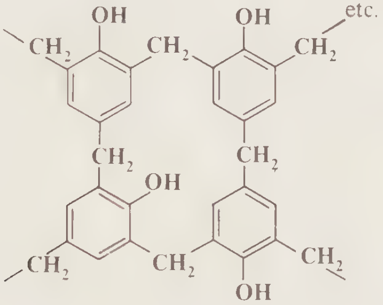
[251] Effenberger and Gleiter, *Chem. Ber.* **97,** 472 (1964); Effenberger, Gleiter, Heider, and Niess, *Chem. Ber.* **101,** 502 (1968).

[252] Smith and Kan, *J. Am. Chem. Soc.* **82,** 4753 (1960), *J. Org. Chem.* **29,** 2261 (1964).

The condensation of aromatic rings with aldehydes or ketones is called *hydroxyalkylation*.[253] The reaction is not generally useful as a method for the preparation of alcohols, though it has been used for that purpose, largely with ketones as reagents. More often, the alcohol initially produced reacts with another molecule of aromatic compound (reaction **1-13**) to give diarylation. For this the reaction is quite useful, an example being the preparation of DDT:

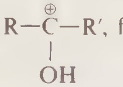


The diarylation reaction is especially common with phenols (the diaryl product here is called a *bisphenol*). The reaction is normally carried out in alkaline solution, on the phenolate ion.[254] The hydroxymethylation of phenols with formaldehyde is called the *Lederer-Manasse reaction.* This reaction must be carefully controlled, since it is possible for the para and both ortho positions to be substituted and then for each of these to be rearylated, so that a polymeric structure (**41**) is produced.



41

However, such polymers, which are of the Bakelite type (phenol-formaldehyde resins), are of considerable commerical importance.

The attacking species is the carbonium ion,  $\mathrm{R{-}\overset{\oplus}{\underset{OH}{C}}{-}R'}$, formed from the aldehyde or ketone and the acid catalyst, except when the reaction is carried out in basic solution. The reaction of benzophenones with phenols to give triarylcarbinols and/or tetraarylmethanebisphenols can also in some cases be performed photochemically.[255]

OS **III,** 326; **V,** 422; **55,** 45. Also see OS **I,** 214.

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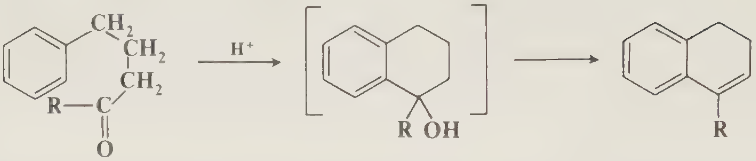
[253] For a review, see Hofmann and Schriesheim, in Olah, Ref. 205, vol. 2, pp. 597–640.

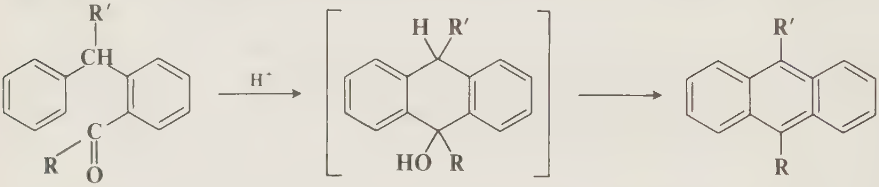
[254] For a review, see Schnell and Krimm, *Angew. Chem. Int. Ed. Engl.* **2,** 373–379 (1963) [*Angew. Chem.* **75,** 662–668].

[255] Becker, *J. Org. Chem.* **32,** 2115, 2124, 2131 (1967).

1-26 Cyclodehydration of Aldehydes and Ketones



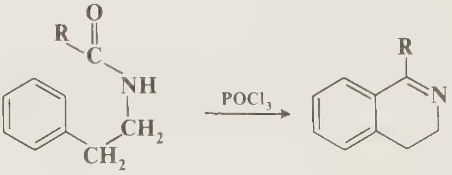
When an aromatic compound contains an aldehyde or ketone function which is in a position suitable for closing a six-membered ring, then treatment with acid results in cyclodehydration. The reaction is a special case of **1-25**, but in this case dehydration almost always takes place to give a double bond conjugated with the aromatic ring. The method is very general and is widely used to close both carbocyclic and heterocyclic rings. Polyphosphoric acid is a common reagent, but other acids have also been used. In a variation known as the *Bradsher reaction*,[256] diaryl-



methanes containing a carbonyl group in the ortho position can be cyclized to anthracene derivatives. In this case 1,4-dehydration takes place, at least formally.

Among the applications of cyclodehydration to the formation of heterocyclic systems are the following:

1. *The Bischler-Napieralski reaction.*[257] In this reaction amides of the type **42** are cyclized with phosphorus oxychloride:



42

If the starting compound contains a hydroxyl group in the α-position, then an additional dehydration takes place and the product is an isoquinoline. Higher yields can be obtained if the amide is treated with PCl_5 to give an imidoyl chloride $ArCH_2CH_2N{=}CR{-}Cl$, which is isolated and then cyclized by heating.[258] The nitrilium ion $ArCH_2CH_2\overset{\oplus}{N}{\equiv}CR$ is an intermediate here.

2. *The third step of the Skraup synthesis.*[259] In the Skraup synthesis a primary aromatic amine

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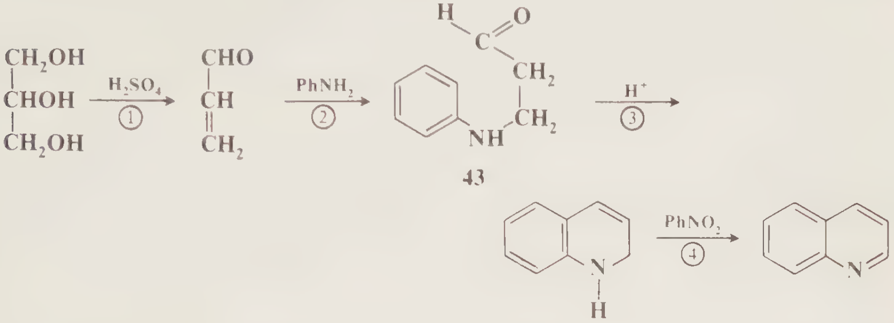
[256] For examples, see Bradsher, *J. Am. Chem. Soc.* **62**, 486 (1940); Vingiello and Henson, *J. Org. Chem.* **31**, 1357 (1966); Saraf and Vingiello, *Synthesis* 655 (1970); Ahmed, Ashby, Ayad, and Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1* 1099 (1973); Ashby, Ayad, and Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1* 1104 (1973).

[257] For a review, see Whaley and Govindachari, *Org. React.* **6**, 74–150 (1951).

[258] Fodor, Gal, and Phillips, *Angew. Chem. Int. Ed. Engl.* **11**, 919 (1972) [*Angew. Chem.* **84**, 947].

[259] For a review, see Manske and Kulka, *Org. React.* **7**, 59–98 (1953).

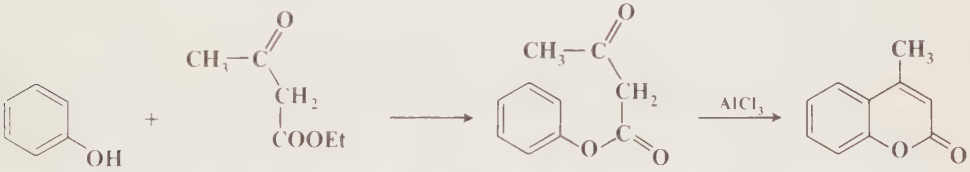
is treated with glycerol, sulfuric acid, and an aromatic nitro compound (usually nitrobenzene) to give a quinoline. The reaction has four steps, as shown:



43

The third step is the Friedel-Crafts ring closure. The first step is a dehydration (reaction **7-1**), the second a Michael-type reaction (**5-9**), and the fourth an oxidative aromatization (reaction **9-1**) in which, presumably, nitrobenzene is the oxidizing agent. Other oxidizing agents have also been used. Intermediates of the type **43** have been isolated from the reaction mixture[260] and have been shown to give quinolines under these conditions.[261] It has been shown that the oxidation step can take place before the cyclization step.[262] Since in the first step glycerol is dehydrated to acrolein, it might be expected that other α,β-unsaturated aldehydes and ketones also give the reaction. This is true, the reaction being called the *Doebner-Miller reaction.*

3. *The Pechmann* (*or von Pechmann*) *reaction.*[263] In this reaction phenols are condensed with β-keto esters to give coumarins. The first step is a transesterification (reaction **0-25**), and the second a Friedel-Crafts ring closure:



OS **I**, 360, 478; **II**, 62, 194; **III**, 281, 300, 329, 568, 580, 581; **IV**, 590; **V**, 550. Also see OS **I**, 54.

1-27 Haloalkylation

$$ArH + HCHO + HCl \xrightarrow{ZnCl_2} ArCH_2Cl$$

When certain aromatic compounds are treated with formaldehyde and HCl, the CH_2Cl group is introduced into the ring in a reaction called *chloromethylation.* The reaction has also been carried out with other aldehydes and with HBr and HI. The more general term *haloalkylation* covers these cases.[264] The reaction is successful for benzene, and alkyl-, alkoxy-, and halobenzenes. It is greatly hindered by meta-directing groups, which reduce yields or completely prevent the reaction.

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[260] Badger, Crocker, Ennis, Gayler, Matthews, Raper, Samuel, and Spotswood, *Aust. J. Chem.* **16**, 814 (1963); Badger, Crocker, and Ennis, *Aust. J. Chem.* **16**, 840 (1963).

[261] Badger, Ennis, and Matthews, *Aust. J. Chem.* **16**, 828 (1963).

[262] Ogata, Kawasaki, and Suyama, *J. Chem. Soc. B* 805 (1969), *Tetrahedron* **25**, 1361 (1969).

[263] For a review, see Sethna and Phadke, *Org. React.* **7**, 1–58 (1953).

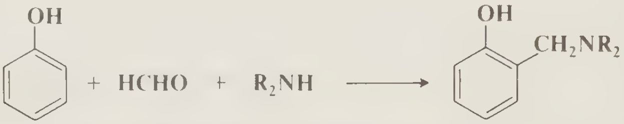
[264] For reviews, see Olah and Tolgyesi, in Olah, Ref. 205, vol. 2, pp. 659–784; and Fuson and McKeever, *Org. React.* **1**, 63–90 (1942).

Amines and phenols are too reactive and usually give polymers unless deactivating groups are also present, but phenolic ethers and esters successfully undergo the reaction. Compounds of lesser reactivity can often be chloromethylated with chloromethyl methyl ether $ClCH_2OMe$, bis-(chloromethyl) ether $(ClCH_2)_2O$,[265] or 1-chloro-4-(chloromethoxy)butane.[266] Zinc chloride is the most common catalyst, but other Friedel-Crafts catalysts are also employed. As with reaction **1-25**, and for the same reason, an important side product is the diaryl compound Ar_2CH_2 (from formaldehyde).

Apparently, the initial step involves reaction of the aromatic compound with the aldehyde to form the hydroxyalkyl compound, exactly as in reaction **1-25**, and then the HCl converts this to the chloroalkyl compound.[267] The acceleration of the reaction by $ZnCl_2$ has been attributed[268] to the raising of the acidity of the medium, causing a consequent increase in the concentration of $HOCH_2^+$ ions.

OS **III**, 195, 197, 468, 557; **IV**, 980.

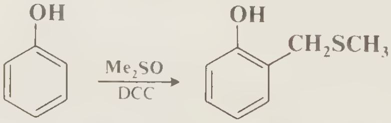
1-28 Aminoalkylation



Phenols, secondary and tertiary aromatic amines,[269] pyrroles, and indoles can be aminomethylated by treatment with formaldehyde and a secondary amine. Other aldehydes have sometimes been employed. Aminomethylation is a special case of the Mannich reaction (**6-17**).

OS **I**, 381; **IV**, 626; **V**, 434; **51**, 136.

1-29 Thioalkylation



A methylthiomethyl group can be inserted into the ortho position of phenols by heating with dimethyl sulfoxide and dicyclohexylcarbodiimide (DCC).[270] Other reagents can be used instead of DCC, among them pyridine-SO_3[271] and acetic anhydride.[272] Alternatively, the phenol can be treated with dimethyl sulfide and N-chlorosuccinimide, followed by triethylamine.[273] The reaction can be applied to amines (to give *o*-$NH_2C_6H_4CH_2SMe$) by treatment with *t*-BuOCl, Me_2S, and NaOMe in CH_2Cl_2.[274] It is possible to convert the CH_2SMe group to the CHO group,[275] so that this becomes an indirect method for the preparation of ortho-amino and ortho-hydroxy aromatic aldehydes; or to the CH_3 group (with Raney nickel reaction **4-37**), making this an indirect method for the introduction of a CH_3 group ortho to an OH or NH_2 group.[274]

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[265] Suzuki, *Bull. Chem. Soc. Jpn.* **43**, 3299 (1970); Kuimova and Mikhailov, *J. Org. Chem. USSR* **7**, 1485 (1971).

[266] Olah, Beal, Yu, and Olah, *Synthesis* 560 (1974).

[267] Ziegler, Hontschik, and Milowiz, *Monatsh. Chem.* **78**, 334 (1947); Ziegler, *Monatsh. Chem.* **79**, 142 (1948); Ogata and Okano, *J. Am. Chem. Soc.* **78**, 5423 (1956). See also Olah and Yu, *J. Am. Chem. Soc.* **97**, 2293 (1975).

[268] Lyushin, Mekhtiev, and Guseinova, *J. Org. Chem. USSR* **6**, 1445 (1970).

[269] Miocque and Vierfond, *Bull. Soc. Chim. Fr.* 1896, 1901, 1907 (1970).

[270] Burdon and Moffatt, *J. Am. Chem. Soc.* **88**, 5855 (1966), **89**, 4725 (1967); Marino, Pfitzner, and Olofson, *Tetrahedron* **27**, 4181 (1971); Olofson and Marino, *Tetrahedron* **27**, 4195 (1971).

[271] Claus, *Monatsh. Chem.* **102**, 913 (1971).

[272] Hayashi and Oda, *J. Org. Chem.* **32**, 457 (1967); Pettit and Brown, *Can. J. Chem.* **45**, 1306 (1967); Claus, *Monatsh. Chem.* **99**, 1034 (1968). See also Claus, Vavra, and Schilling, *Monatsh. Chem.* **102**, 1072 (1972).

[273] Gassman and Amick, *Tetrahedron Lett.* 889 (1974).

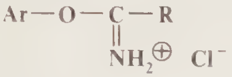
[274] Gassman and Gruetzmacher, *J. Am. Chem. Soc.* **95**, 588 (1973); Gassman and van Bergen, *J. Am. Chem. Soc.* **95**, 590, 591 (1973).

[275] Gassman and Amick, *Tetrahedron Lett.* 3463 (1974); Gassman and Drewes, *J. Am. Chem. Soc.* **96**, 3002 (1974).

1-30 Acylation with Nitriles. The Hoesch Reaction

$$\mathrm{ArH + RCN \xrightarrow[ZnCl_2]{HCl} ArCOR}$$

Friedel-Crafts acylation with nitriles and HCl is called the *Hoesch* or the *Houben-Hoesch reaction*.[276] In most cases, a Lewis acid is necessary, zinc chloride being the most common. The reaction is useful only with phenols, phenolic ethers, and some reactive heterocyclic compounds, e.g., pyrrole. Monohydric phenols, however, generally do not give ketones, but are attacked at the oxygen to produce imino esters (**44**). Many nitriles have been used. Even aryl nitriles give good

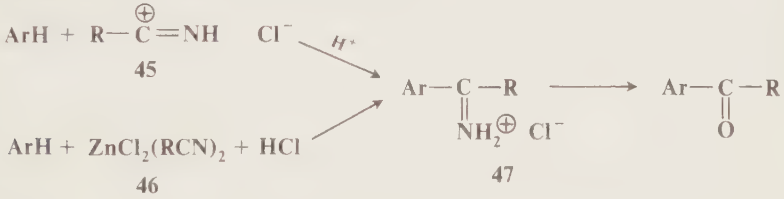


$$\mathrm{Ar{-}O{-}\underset{NH_2^{\oplus}}{\overset{}{C}}{-}R \quad Cl^-}$$

44

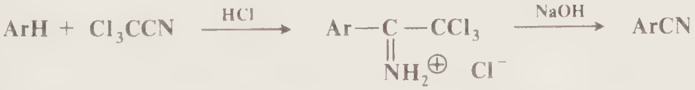
yields if they are first treated with HCl and $ZnCl_2$, and then the substate added at 0 C.[277] In fact, this procedure increases yields with any nitrile. If thiocyanates RSCN are used, thiol esters ArCOSR can be obtained. The Gatterman reaction (**1-18**) is a special case of the Hoesch synthesis.

The reaction mechanism is complex and not completely settled.[278] The first stage consists of an attack on the substrate by a species containing the nitrile and HCl (and the Lewis acid, if present) to give an imine salt (**47**). Among the possible attacking species are **45** and **46**. In the second stage, the salts are hydrolyzed to the products:



OS **II**, 522.

1-31 Direct Cyanogenation



$$\mathrm{ArH + Cl_3CCN \xrightarrow{HCl} Ar{-}\underset{NH_2^{\oplus}\ Cl^-}{\overset{}{C}}{-}CCl_3 \xrightarrow{NaOH} ArCN}$$

Aromatic hydrocarbons (including benzene), phenols, and phenolic ethers can be cyanogenated with trichloroacetonitrile, BrCN, or mercury fulminate $Hg(ONC)_2$.[279] In the case of Cl_3CCN, the actual attacking entity is probably $Cl_3C{-}\overset{\oplus}{C}{=}NH$, formed by addition of a proton to the cyano nitrogen. The cyano group has also been introduced electrolytically, by applying a potential to a mixture of the aromatic compound, HCN, and NaCN in methanol,[280] as well as photochemically.[280a]

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[276] For reviews, see Spoerri and DuBois, *Org. React.* **5**, 387–412 (1949); Zil'berman, *Russ. Chem. Rev.* **31**, 615–633 (1962); and Ruske, in Olah, Ref. 205, vol. 3, pp. 383–497 (1964).

[277] Zil'berman and Rybakova, *J. Gen. Chem. USSR* **30**, 1972 (1960).

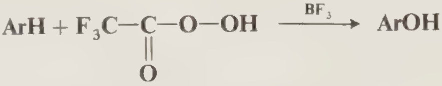
[278] For discussions, see Ref. 276 and Jeffery and Satchell, *J. Chem. Soc. B* 579 (1966).

[279] Olah, in Olah, Ref. 166, vol. 1, pp. 119–120 (1963).

OS **III**, 293.

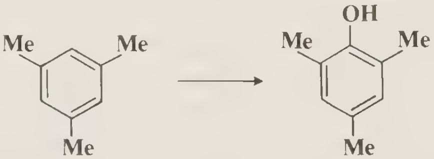
F. Oxygen Electrophiles Oxygen electrophiles are very uncommon, since oxygen does not bear a positive charge very well. However, there are two reactions which may be mentioned.

1-32 Direct Hydroxylation



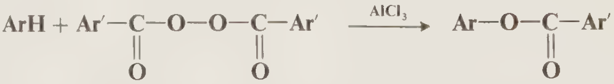
$$\mathrm{ArH} + \mathrm{F_3C{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}OH} \xrightarrow{\mathrm{BF_3}} \mathrm{ArOH}$$

There have been only a few reports of direct hydroxylation by an electrophilic process (see, however, reactions **2-23**, **3-20**, and **4-5**).[281] In general, poor results are obtained, in part because the introduction of an OH group activates the ring to further attack. Quinone formation is common. However, alkyl-substituted benzenes such as mesitylene or durene may be hydroxylated in good yield with trifluoroperacetic acid and boron trifluoride.[282] In the case of mesitylene, the product is not subject to further attack:



Low to moderate yields of phenols can be obtained by treatment of simple alkylbenzenes with H_2O_2 catalyzed by $AlCl_3$[283] or by liquid HF, in some cases under CO_2 pressure.[284] With the latter procedure even benzene could be converted to phenol in 37% yield (though 37% hydroquinone and 16% catechol were also obtained).

1-33 Direct Introduction of an Acyloxy Group



$$\mathrm{ArH} + \mathrm{Ar'{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}Ar'} \xrightarrow{\mathrm{AlCl_3}} \mathrm{Ar{-}O{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}Ar'}$$

An acyloxy group can be introduced into reactive nuclei (e.g., mesitylene, anisole) in low yields by treatment with a diacyl peroxide containing electron-withdrawing groups (e.g., *p,p'*-dinitrobenzoyl peroxide) and $AlCl_3$.[285] It had been reported[286] that benzene underwent this reaction when treated with benzoyl peroxide, but it has been shown[285] that the phenyl benzoate formed in this case does not arise from attack of benzoyl peroxide on benzene, but from a rearrangement

[280] Koyama, Susuki, and Tsutsumi, *Tetrahedron Lett.* 627 (1965); Parker and Burgert, *Tetrahedron Lett.* 4065 (1965), 2415 (1968). See also Andreades and Zahnow, *J. Am. Chem. Soc.* **91**, 4181 (1969); Eberson and Helgée, *Chem. Scr.* **5**, 47 (1974).

[280a] Mizuno, Pac, and Sakurai, *J. Chem. Soc., Chem. Commun.* 553 (1975).

[281] For a review of electrophilic hydroxylation, see Norman and Taylor, Ref. 1, pp. 110–116.

[282] Hart and Buehler, *J. Org. Chem.* **29**, 2397 (1964). See also Hart, *Acc. Chem. Res.* **4**, 337–343 (1971).

[283] Kurz and Johnson, *J. Org. Chem.* **36**, 3184 (1971).

[284] Vesely and Schmerling, *J. Org. Chem.* **35**, 4028 (1970). For other hydroxylations, see Chambers, Goggin, and Musgrave, *J. Chem. Soc.* 1804 (1959); Hamilton and Friedman, *J. Am. Chem. Soc.* **85**, 1008 (1963); Kovacic and Morneweck, *J. Am. Chem. Soc.* **87**, 1566 (1965); Kovacic and Kurz, *J. Am. Chem. Soc.* **87**, 4811 (1965), *J. Org. Chem.* **31**, 2011, 2549 (1966); Walling and Camaioni, *J. Am. Chem. Soc.* **97**, 1603 (1975); So, Becker, and Miller, Ref. 120.

[285] Edward, Chang, and Samad, *Can. J. Chem.* **40**, 804 (1962).

[286] Reynhart, *Recl. Trav. Chim. Pays-Bas* **46**, 54 (1927).

of the peroxide, catalyzed by $AlCl_3$; that is, both phenyl groups in the phenyl benzoate came from the benzoyl peroxide, and neither from the benzene. *p,p'*-Dinitrobenzoyl peroxide is less prone to rearrange than benzoyl peroxide and can thus attack an active substrate.

Aryl sulfonyl peroxides react with aromatic compounds to give sulfonic acids in a manner analogous to *p,p'*-dinitrobenzoyl peroxide.[287] Acyloxylation has also been accomplished by treatment with potassium peroxydisulfate in glacial acetic acid, catalyzed by Pd(II) amine complexes.[288]

$$\mathrm{ArH + Ar'{-}SO_2{-}O{-}O{-}SO_2{-}Ar' \longrightarrow Ar{-}O{-}SO_2{-}Ar'}$$

See also reaction **4-10.**

G. Metal Electrophiles Reactions in which a metal replaces the hydrogen of an aromatic ring are considered along with their aliphatic counterparts in Chapter 12 (reactions **2-19** and **2-20**).

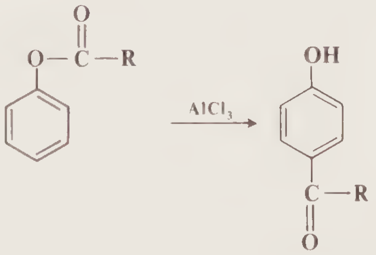
Hydrogen as the Leaving Group in Rearrangement Reactions

In these reactions a group is first detached from a *side chain* and then attacks the ring, but in other aspects they resemble the reactions already treated in this chapter.[289] Since a group moves from one position to another in a molecule, these are rearrangements. In all these reactions the question arises as to whether the group which cleaves from a given molecule attacks the same molecule or another one, that is, is the reaction intramolecular or intermolecular? For those that are intermolecular the mechanism is the same as ordinary aromatic substitution, but for intramolecular cases the migrating group could never be completely free, or else it would be able to attack another molecule. Since the migrating species in intramolecular rearrangements is thus likely to remain near the atom from which it cleaved, intramolecular reactions are more likely to lead to ortho products than are the intermolecular type; and this characteristic has been used, among others, to help decide whether a given rearrangement is inter- or intramolecular.

The Claisen (**8-38**) and benzidine (**8-44**) rearrangements, which superficially resemble those in this section, have different mechanisms and are treated in Chapter 18.

A. Groups Cleaving from Oxygen

1-34 The Fries Rearrangement



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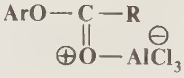
[287] Crovatt and McKee, *J. Org. Chem.* **24,** 2031 (1959); Haszeldine, Heslop, and Lethbridge, *J. Chem. Soc.* 4901 (1964); Dannley and Corbett, *J. Org. Chem.* **31,** 153 (1966); Dannley, Gagen, and Stewart, *J. Org. Chem.* **35,** 3076 (1970); Levi, Kovacic, and Gormish, *Tetrahedron* **26,** 4537 (1970).

[288] Eberson and Jönsson, *J. Chem. Soc., Chem. Commun.* 885 (1974).

[289] For a monograph, see Shine, "Aromatic Rearrangements," American Elsevier Publishing Company, New York, 1967. For reviews, see Shine, *MTP Int. Rev. Sci.: Org. Chem., Ser. One,* **3,** 66–103 (1973); Williams, in Bamford and Tipper, Ref. 1, pp. 433–486; Dewar, in Mayo, "Molecular Rearrangements," vol. 1, pp. 295–299, 306–323, Interscience Publishers, New York, 1963.

Phenolic esters may be rearranged by heating with Friedel-Crafts catalysts in a synthetically useful reaction known as the *Fries rearrangement*.[290] Both *o*- and *p*-acylphenols may be produced, and it is often possible to select conditions so that either one predominates. The ortho/para ratio is dependent on the temperature, solvent, and amount of catalyst used. Though exceptions are known, low temperatures generally favor the para product, and high temperatures the ortho product. R may be aliphatic or aromatic. Any meta-directing substituent on the ring interferes with the reaction, as might be expected for a Friedel-Crafts process.

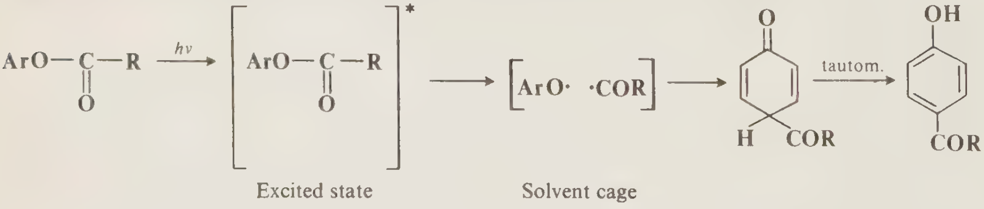
The exact mechanism has still not been completely worked out. Opinions have been expressed that it is completely intermolecular,[291] completely intramolecular,[292] and partially inter- and intramolecular.[293] One way to decide between inter- and intramolecular processes is to run the reaction of the phenolic ester in the presence of another aromatic compound, say, toluene. If some of the toluene is acylated, then the reaction must be, at least in part, intermolecular. If the toluene is not acylated, the presumption is that the reaction is intramolecular, though this is not certain, for it may be that the toluene is not attacked because it is less active than the other. A number of such experiments (called *crossover experiments*) have been carried out; and sometimes crossover products have been found and sometimes not. As in reaction **1-15**, an initial complex (**48**) is formed between the substrate and the catalyst, so that a catalyst/substrate molar ratio of at least 1 : 1 is required. There is evidence that both a mono- (**48**) and a di-$AlCl_3$ catalyst can be formed.[294]



$$\mathrm{ArO{-}\underset{\overset{\|}{\oplus O}}{C}{-}R}\quad \mathrm{O{-}\overset{\ominus}{A}lCl_3}$$

48

The Fries rearrangement can also be carried out with uv light, in the absence of a catalyst.[295] This reaction, called the *photo-Fries rearrangement*,[296] is predominantly an intramolecular free-radical process. Both ortho and para migration are observed. Unlike the Lewis-acid-catalyzed Fries rearrangement, the photo-Fries reaction can be accomplished, though often in low yields, when meta-directing groups are on the ring. The available evidence strongly suggests the following mechanism[297] for the photo-Fries rearrangement[298] (illustrated for para attack):



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[290] For reviews, see Shine, "Aromatic Rearrangements," Ref. 289, pp. 72–82, 365–368; Gerecs, in Olah, Ref. 205, vol. 3, pp. 499–533 (1964); Blatt, *Org. React.* **1**, 342–369 (1942).

[291] Krausz and Martin, *Bull. Soc. Chim. Fr.* 2192 (1965); Martin, *Bull. Soc. Chim. Fr.* 983 (1974).

[292] Ogata and Tabuchi, *Tetrahedron* **20**, 1661 (1964).

[293] Munavilli, *Chem. Ind.* (*London*) 293 (1972).

[294] Cullinane, Woolhouse, and Edwards, *J. Chem. Soc.* 3842 (1961); Cullinane and Bailey-Wood, *Recl. Trav. Chim. Pays-Bas* **78**, 440 (1959).

[295] Kobsa, *J. Org. Chem.* **27**, 2293 (1962); Anderson and Reese, *J. Chem. Soc.* 1781 (1963); Finnegan and Matice, *Tetrahedron* **21**, 1015 (1965).

[296] For reviews, see Belluš, *Adv. Photochem.* **8**, 109–159 (1971); Belluš and Hrdlovič, *Chem. Rev.* **67**, 599–609 (1967); Stenberg, *Org. Photochem.* **1**, 127–153 (1967).

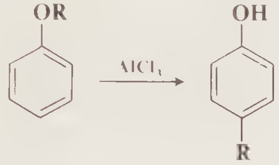
[297] Proposed by Kobsa, Ref. 295.

[298] It has been suggested that a second mechanism, involving a four-center transition state, is also possible: Belluš, Schaffner, and Hoigné, *Helv. Chim. Acta* **51**, 1980 (1968); Sander, Hedaya, and Trecker, *J. Am. Chem. Soc.* **90**, 7249 (1968); Belluš, Ref. 296.

The phenol ArOH is always a side product, resulting from some ArO• which leaks from the solvent cage and abstracts a hydrogen atom from a neighboring molecule. When the reaction was performed on phenyl acetate in the gas phase, where there are no solvent molecules to form a cage (but in the presence of isobutane as a source of abstractable hydrogens), phenol was the chief product, and virtually no *o*- or *p*-hydroxyacetophenone was found.[299] Other evidence for the mechanism is that CIDNP (p. 171) has been observed during the course of the reaction,[300] and that the ArO• radical has been detected by flash photolysis.[301]

OS **II,** 543; **III,** 280, 282.

1-35 Rearrangement of Phenolic Ethers



This reaction bears the same relationship to reaction **1-34** that reaction **1-13** bears to **1-15.**[302] However, yields are generally low, and this reaction is much less useful synthetically. Isomerization of the R group is usually found when that is possible. Evidence has been found for both inter- and intramolecular processes. The fact that dialkylphenols can often be isolated shows that at least some intermolecular processes occur. Evidence for intramolecular reaction is that conversion of optically active *p*-tolyl *sec*-butyl ether to 2-*sec*-butyl-4-methylphenol proceeded with some retention of configuration,[303] and that rearrangement of benzyl phenyl ethers (with $AlBr_3$ or $AlCl_3$) takes place with virtually exclusive ortho migration.[304] The mechanism is probably similar to that of reaction **1-13.** The fact that isomerization is generally found in the migrating group and the finding[305] that *sec*-butyl phenyl ether containing deuterium in the 2 position of the *sec*-butyl group gives *sec*-butylphenols in which the deuterium has been scrambled between the 2 and the 3 positions (arising from hydride shifts in the carbonium ion) indicate that carbonium ions are often involved, but the demonstration of partial inversion of configuration in the conversion of optically active *sec*-butyl phenyl ether to *o*- and *p*-*sec*-butylphenols[306] shows that an SN2 mechanism can also operate, probably featuring attack by a complex between the catalyst and one molecule of the ether on the ortho or para position of another molecule of the ether, to give an *o*- or *p*-*sec*-butylphenyl *sec*-butyl ether which is then cleaved. In substantiation of this hypothesis, both *o*- and *p*-*sec*-butylphenyl *sec*-butyl ethers were detected in the reaction mixture.[306] In at least some cases the reaction can proceed without a catalyst. For example, simple heating at 250 C of phenyl benzyl ether gave *o*- and *p*-benzylphenol.[307] The fact that phenol and toluene are also obtained shows that the thermal reaction is intermolecular. It is probably a free-radical reaction. The rearrangement can also be induced photochemically.[308]

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[299] Meyer and Hammond, *J. Am. Chem. Soc.* **92,** 2187 (1970); **94,** 2219 (1972).

[300] Adam, Arce de Sanabia, and Fischer, *J. Org. Chem.* **38,** 2571 (1973); Adam, *J. Chem. Soc., Chem. Commun.* 289 (1974).

[301] Kalmus and Hercules, *J. Am. Chem. Soc.* **96,** 449 (1974).

[302] For reviews, see Dalrymple, Kruger, and White, in Patai, "The Chemistry of the Ether Linkage," Ref. 35, pp. 628 635; Shine, "Aromatic Rearrangements," Ref. 289, pp. 82 89, 368–370.

[303] Sprung and Wallis, *J. Am. Chem. Soc.* **56,** 1715 (1934). See also Hart and Elia, *J. Am. Chem. Soc.* **76,** 3031 (1954).

[304] Tarbell and Petropoulos, *J. Am. Chem. Soc.* **74,** 244 (1952); Palmer and McVie, *J. Chem. Soc. B* 742 (1968).

[305] Dewar and Spanninger, *J. Chem. Soc., Perkin Trans. 2* 1204 (1972). In this paper the *sec*-butyl group is erroneously referred to as the isobutyl group.

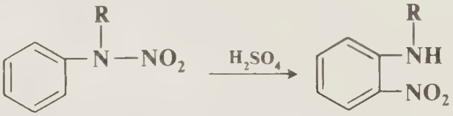
[306] Spanninger and von Rosenberg, *J. Am. Chem. Soc.* **94,** 1970, 1973 (1972).

[307] Elkobaisi and Hickinbottom, *J. Chem. Soc.* 1873 (1959), 1286 (1960).

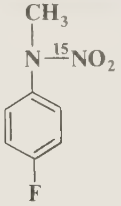
[308] For example, see Kelly, Pinhey, and Rigby, *Aust. J. Chem.* **22,** 977 (1969).

B. Groups Cleaving from Nitrogen[309] It has been shown that $Ph\overset{\oplus}{N}H_2D$ rearranges to *o*- and *p*-deuterioaniline.[310] The migration of OH, formally similar to reactions **1-36** to **1-40**, is a nucleophilic substitution and is treated in Chapter 13 (reaction **3-28**).

1-36 Migration of the Nitro Group



N-Nitro aromatic amines rearrange on treatment with acids to give *o*- and *p*-nitroamines, with the ortho compounds predominating.[311] Aside from this indication of an intramolecular process, there is also the fact that virtually no meta isomer is produced in this reaction,[312] though direct nitration of an aromatic amine generally gives a fair amount of meta product. Thus a mechanism in which NO_2^+ is dissociated from the ring and then attacks another molecule must be ruled out. Further results indicating an intramolecular process are that rearrangement of N-nitroaniline, N-nitro-1-naphthylamine, and N-nitro-N-methyl-1-naphthylamine in the presence of $K^{15}NO_3$ gave products containing no ^{15}N,[313] and that rearrangement of a mixture of $PhNH^{15}NO_2$ and unlabeled *p*-$MeC_6H_4NHNO_2$ gave 2-nitro-4-methylaniline containing no ^{15}N.[314] On the other hand, rearrangement of **49** in the presence of unlabeled $PhNMeNO_2$ gave labeled **50** which did not arise by displacement of F.[315] As indicated by the examples given, R may be hydrogen or alkyl.



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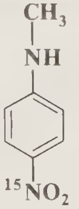

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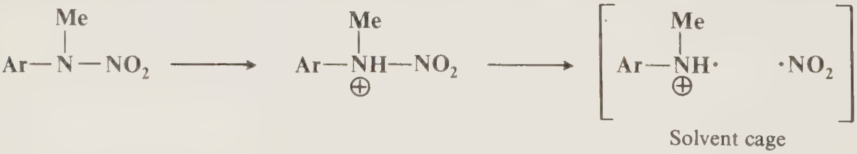
Two principal mechanisms have been suggested, one involving cyclic attack by the oxygen of the nitro group at the ortho position before the group cleaves,[316] and the other involving a cleavage into a radical and a radical ion held together in a solvent cage.[317] Among the evidence for the



$$Ar-\overset{Me}{\overset{|}{N}}-NO_2 \longrightarrow Ar-\underset{\oplus}{\overset{Me}{\overset{|}{N}H}}-NO_2 \longrightarrow \left[Ar-\underset{\oplus}{\overset{Me}{\overset{|}{N}H}}\cdot \quad \cdot NO_2\right]$$

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[309] For reviews, see Stevens and Watts, "Selected Molecular Rearrangements," pp. 192–199, Van Nostrand Reinhold Company, London, 1973; Hughes and Ingold, *Q. Rev., Chem. Soc.* **6**, 34–62 (1952).

[310] Okazaki and Okumura, *Bull. Chem. Soc. Jpn.* **34**, 989 (1961).

[311] For reviews, see White, *Mech. Mol. Migr.* **3**, 109–143 (1971); Shine, "Aromatic Rearrangements," Ref. 289, pp. 235–249.

[312] Hughes and Jones, *J. Chem. Soc.* 2678 (1950).

[313] Brownstein, Bunton, and Hughes, *J. Chem. Soc.* 4354 (1958); Banthorpe, Thomas, and Williams, *J. Chem. Soc.* 6135 (1965).

[314] Geller and Dubrova, *J. Gen. Chem. USSR* **30**, 2627 (1960).

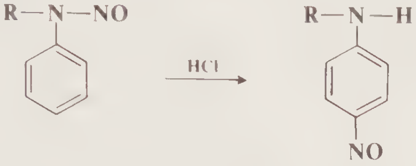
[315] White and Golden, *Chem. Ind. (London)* 138 (1962); *J. Org. Chem.* **35**, 2759 (1970).

[316] Banthorpe, Hughes, and Williams, *J. Chem. Soc.* 5349 (1964); Banthorpe and Thomas, *J. Chem. Soc.* 7149, 7158 (1965). Also see Ref. 313.

[317] White, Lazdins, and White, *J. Am. Chem. Soc.* **86**, 1517 (1964).

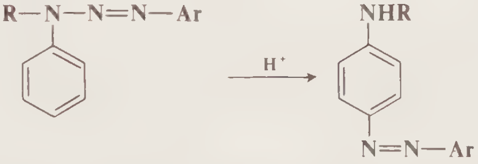
latter view[318] are the effects of substituents on the rate of the reaction,[319] and the fact that both N-methylaniline and nitrous acid are produced in sizable and comparable amounts in addition to the normal products *o*- and *p*-nitro-N-methylaniline.[320] These side products are formed when the radicals escape from the solvent cage.

1-37 Migration of the Nitroso Group. The Fischer-Hepp Rearrangement



The migation of a nitroso group, formally similar to reaction **1-36**, is important because *p*-nitroso secondary aromatic amines cannot generally be prepared by direct C-nitrosation of secondary aromatic amines (see reaction **2-50**). The reaction is known as the *Fischer-Hepp rearrangement*,[321] and is brought about by treatment of N-nitroso secondary aromatic amines with HCl. Other acids give poor or no results. In benzene systems the para product is exclusively formed. The mechanism of the rearrangement is not completely understood. It had been earlier believed that the rearrangement was intermolecular, in part because the amine ArNHR was a side product, but the fact that the reaction takes place in a large excess of urea[322] shows that it is intramolecular[323] since, if NO^+, NOCl, or some similar species were free in the solution, it would be captured by the urea, preventing the rearrangement. The ArNHR is formed by an independent process[324] not leading to rearrangement. It is because they promote this side process that acids other than HCl give poor yields of rearrangement product. The exclusive formation of para product is puzzling, since this is not what we would expect from an intramolecular rearrangement.

1-38 Migration of an Arylazo Group



Rearrangement of aryl triazenes is used to prepare azo derivatives of primary and secondary aromatic amines.[325] These are first diazotized at the amino group (see reaction **1-4**) to give triazenes, which are then rearranged by treatment with acid. The rearrangement always gives the para isomer, unless that position is occupied. The reaction is intermolecular, the migrating species probably being ArN_2^+.[326]

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[318] For additional evidence, see White, White, and Fentiman, *J. Am. Chem. Soc.* **92,** 4477 (1970); White, Hathaway, and Huston, *J. Org. Chem.* **35,** 737 (1970); White, Golden, and Lazdins, *J. Org. Chem.* **35,** 2048 (1970).

[319] White and Klink, *J. Org. Chem.* **35,** 965 (1970).

[320] White and White, *J. Org. Chem.* **35,** 1803 (1970).

[321] For a review, see Shine, "Aromatic Rearrangements," Ref. 289, pp. 231–235.

[322] Aslapovskaya, Belyaev, Kumarev, and Porai-Koshits, *Org. React. USSR* **5,** 189 (1968); Morgan and Williams, *J. Chem. Soc., Perkins Trans. 2* 74 (1972).

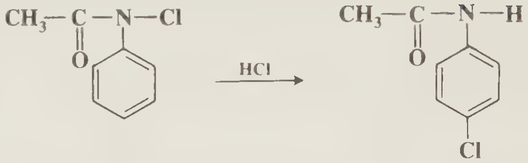
[323] See also Belyaev and Nikulicheva, *Org. React. USSR* **7,** 165 (1971); Williams and Wilson, *J. Chem. Soc., Perkin Trans. 2* 13 (1974); Biggs and Williams, *J. Chem. Soc., Perkin Trans. 2* 107 (1975), 601 (1976); Williams, *Int. J. Chem. Kinet.* **7,** 215 (1975); *Tetrahedron* **31,** 1343 (1975); *J. Chem. Soc., Perkin Trans. 2* 655 (1975).

[324] Morgan, Williams, and Wilson, *J. Chem. Soc., Perkin Trans. 2* 473 (1973).

[325] For reviews, see Shine, "Aromatic Rearrangements," Ref. 289, pp. 212–221; Zollinger, Ref. 104, pp. 182–187.

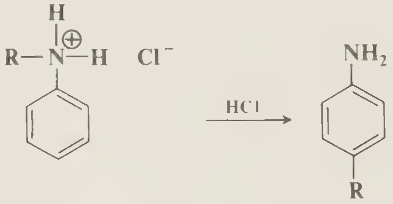
[326] Yamada, *Bull. Chem. Soc. Jpn.* **42,** 3565 (1969).

1-39 Migration of Halogen. The Orton Rearrangement



Migration of a halogen from a nitrogen side chain to the ring by treatment with HCl is called the *Orton rearrangement.*[327] The main product is the para isomer, though some ortho product may also be formed. The reaction has been carried out with N-chloro- and N-bromoamines, and less often with N-iodo compounds. The amine must be acylated, except that $PhNCl_2$ gives 2,4-dichloroaniline. The reaction is usually performed in water or acetic acid. There is much evidence (cross-halogenation, labeling, etc.) that this is an intermolecular process. First the HCl reacts with the starting material to give $ArNHCOCH_3$ and Cl_2, and then the chlorine halogenates the ring as in reaction **1-12.** Among the evidence for this is that chlorine has been isolated from the reaction mixture. The Orton rearrangement can also be brought about photochemically[328] and by heating in the presence of benzoyl peroxide.[329] These are free-radical processes.

1-40 Migration of an Alkyl Group[330]



When HCl salts of arylalkylamines are heated at about 200 to 300°C, migration occurs. This is called the *Hofmann-Martius reaction.* It is an intermolecular reaction, since crossing is found. For example, methylanilinium bromide gave not only the normal products *o*- and *p*-toluidine, but also aniline and di- and trimethylanilines.[331] As would be expected for an intermolecular process, there is isomerization when R is primary.

With primary R, the reaction probably goes through the alkyl halide formed initially in an S_N2 reaction:

$$\overset{\oplus}{RNH_2Ar} + Cl^- \longrightarrow RCl + ArNH_2$$

Evidence for this view is that alkyl halides have been isolated from the reaction mixture, and that Br^-, Cl^-, and I^- gave different ortho/para ratios, indicating that the halogen is involved in the reaction.[331] Further evidence is that the alkyl halides isolated are unrearranged (as would be expected if they are formed by an S_N2 mechanism), even though the alkyl groups in the ring are rearranged. Once the alkyl halide is formed, it reacts with the substrate by a normal Friedel-Crafts alkylation process (reaction **1-13**), accounting for the rearrangement. When R is secondary or tertiary, carbonium ions may be directly formed so that the reaction does not go through the alkyl halides.[332]

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[327] For reviews, see Shine, "Aromatic Rearrangements," Ref. 289, pp. 221–230, 362–364; Bieron and Dinan, in Zabicky, "The Chemistry of Amides," pp. 263–269, Interscience Publishers, New York, 1970.

[328] For example, see Hodges, *J. Chem. Soc.* 240 (1933).

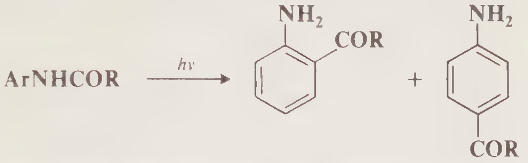
[329] For example, see Ayad, Beard, Garwood, and Hickinbottom, *J. Chem. Soc.* 2981 (1957); Coulson, Williams, and Johnston, *J. Chem. Soc. B* 174 (1967).

[330] For reviews, see Grillot, *Mech. Mol. Migr.* **3**, 237–270 (1971); Shine, "Aromatic Rearrangements," Ref. 289, pp. 249–257.

[331] Ogata, Tabuchi, and Yoshida, *Tetrahedron* **20**, 2717 (1964).

It is also possible to carry out the reaction by heating the amine (not the salt) at a temperature between 200 and 350°C with a metal halide such as $CoCl_2$, $CdCl_2$, or $ZnCl_2$. When this is done, the reaction is called the *Reilly-Hickinbottom rearrangement*. Primary R groups larger than ethyl give both rearranged and unrearranged products.[333] The reaction is not generally useful for secondary and tertiary R groups, which are usually cleaved to olefins under these conditions. The mechanism of the Reilly-Hickinbottom rearrangement is probably similar to that of the Hofman-Martius rearrangement.

When acylated arylamines are photolyzed, migration of an acyl group takes place[334] in a process which resembles the photo-Fries reaction (**1-34**). N,N-disubstituted amides ArNR′COR also give the reaction.



Other Leaving Groups

Three types of reactions are considered in this section.

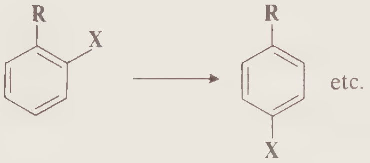
1. Reactions in which hydrogen replaces another leaving group:

$$ArX + H^+ \longrightarrow ArH$$

2. Reactions in which an electrophile other than hydrogen replaces another leaving group:

$$ArX + Y^+ \longrightarrow ArY$$

3. Reactions in which a group (other than hydrogen) migrates from one position in a ring to another:



Such migrations may be either inter- or intramolecular.

The three types are not treated separately, but reactions are classified on the basis of the nature of the leaving group.

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[332] Hart and Kosak, *J. Org. Chem.* **27,** 116 (1962).

[333] For example, see Birchall, Clark, Goldwhite, and Thorpe, *J. Chem. Soc., Perkin Trans. 1* 2579 (1972).

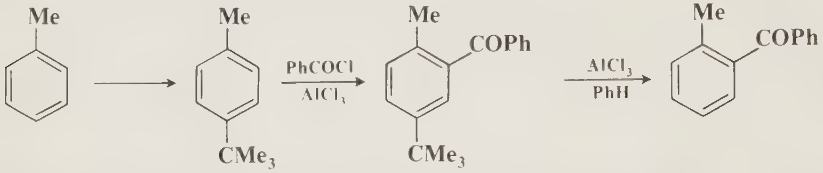
[334] For examples, see Elad, Rao, and Stenberg, *J. Org. Chem.* **30,** 3252 (1965); Shizuka and Tanaka, *Bull. Chem. Soc. Jpn.* **41,** 2343 (1968), **42,** 909 (1969); Fischer, *Tetrahedron Lett.* 4295 (1968); Hageman, *Recl. Trav. Chim. Pays-Bas* **91,** 1447 (1972).

A. Carbon Leaving Groups

1-41 Reversal of Friedel-Crafts Alkylation

$$\text{ArR} + \text{H}^+ \xrightarrow{\text{AlCl}_3} \text{ArH}$$

Alkyl groups may be cleaved from aromatic rings by treatment with proton and/or Lewis acids. Tertiary R groups are the most easily cleaved; because this is true, the *t*-butyl group is occasionally introduced into a ring, used to direct another group, and then removed. For example,[335]



Secondary R groups are harder to cleave, and primary R harder still. Because of this reaction, care must be taken when using Friedel-Crafts catalysts (Lewis or proton acids) on aromatic compounds containing alkyl groups. True cleavage, in which the R becomes an olefin, occurs only at high temperatures: above 400°C.[336] At ordinary temperatures, the R group attacks another ring, so that the bulk of the product may be dealkylated, but there is a residue of heavily alkylated material. The isomerization reaction, in which a group migrates from one position in a ring to another, or to a different ring, is therefore more important than true cleavage. In these reactions, the meta isomer is generally the most favored product among the dialkylbenzenes; and the 1,3,5 product the most favored among the trialkylbenzenes, because these have the highest thermodynamic stabilities (p. 460). Alkyl migrations may be inter- or intramolecular, depending on the conditions and on the R group. The following experiments can be cited: ethylbenzene treated with HF and BF_3 gave, almost completely, benzene and diethylbenzenes[337] (entirely intermolecular); propylbenzene labeled in the β-position gave benzene, propylbenzene, and di- and tripropylbenzenes, but the propylbenzene recovered was partly labeled in the α position and not at all in the γ-position[338] (both intra- and intermolecular); *o*-xylene treated with HBr and $AlBr_3$ gave a mixture of *o*- and *m*- but no *p-xylene*, while *p*-xylene gave *p*- and *m*- but no *o-xylene*, and no trimethyl compounds could be isolated in these experiments[339] (exclusively intramolecular rearrangement). Apparently, methyl groups migrate only intramolecularly, while other groups may follow either path.[340]

The mechanism[341] of intermolecular rearrangement may involve free carbonium ions, but there is much evidence to show that this is not necessarily the case. For example, many of them occur without rearrangement within the alkyl group. When rearrangement does occur, it may be of the type that could not arise from a free carbonium ion. For example, *t*-pentylbenzene when heated with $AlCl_3$ gave 65% neopentylbenzene, while the latter was almost unchanged.[342] A free carbonium ion would almost certainly rearrange the other way. The following mechanism has been proposed for intermolecular rearrangement without the involvement of carbonium ions which are separated from the ring.[343]

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[335] Hofman, Reiding, and Nauta, *Recl. Trav. Chim. Pays-Bas* **79**, 790 (1960).

[336] Olah, in Olah, Ref. 205, vol. 1, pp. 36–38 (1963).

[337] McCaulay and Lien, *J. Am. Chem. Soc.* **75**, 2407 (1953).

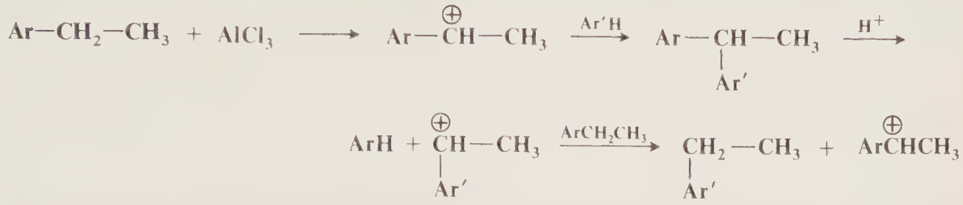
[338] Roberts and Brandenberger, *J. Am. Chem. Soc.* **79**, 5484 (1957); Roberts and Douglass, *J. Org. Chem.* **28**, 1225 (1963).

[339] Brown and Jungk, *J. Am. Chem. Soc.* **77**, 5579 (1955); Allen and Yats, *J. Am. Chem. Soc.* **81**, 5289 (1959).

[340] Allen, Alfrey, and Yats, *J. Am. Chem. Soc.* **81**, 42 (1959); Allen, Yats, and Erley, *J. Am. Chem. Soc.* **82**, 4853 (1960); Allen, *J. Am. Chem. Soc.* **82**, 4856 (1960).

[341] For a review of the mechanism of this and closely related reactions, see Shine, "Aromatic Rearrangements," Ref. 289, pp. 1–55.

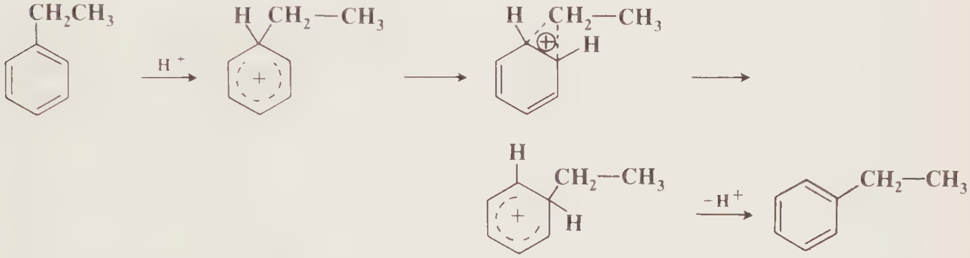
[342] Roberts and Han, *Tetrahedron Lett.* no. 6, 5 (1959).



$$\mathrm{Ar{-}CH_2{-}CH_3 + AlCl_3 \longrightarrow Ar{-}\overset{\oplus}{C}H{-}CH_3 \xrightarrow{Ar'H} Ar{-}\underset{Ar'}{CH}{-}CH_3 \xrightarrow{H^+}}$$

$$\mathrm{ArH + \underset{Ar'}{\overset{\oplus}{C}H}{-}CH_3 \xrightarrow{ArCH_2CH_3} \underset{Ar'}{CH_2}{-}CH_3 + Ar\overset{\oplus}{C}HCH_3}$$

Evidence for this mechanism was that optically active $PhCHDCH_3$ labeled in the ring with ^{14}C and treated with $GaBr_3$ in the presence of benzene gave ethylbenzene containing no deuterium and two deuteriums, and that the rate of loss of radioactivity was about equal to the rate of loss of optical activity.[343] The mechanism of intramolecular rearrangement is not very clear. 1,2 shifts of this kind have been proposed:[344]



There is evidence from ^{14}C labeling that intramolecular migration occurs only though 1,2 shifts.[345] Any 1,3 or 1,4 migration takes place by a series of two or more 1,2 shifts. The mechanism of the conversion of *t*-pentylbenzene to neopentylbenzene, mentioned above, does not involve migration of an alkyl group from one position to another in the same or a different ring, but migration of the benzene ring from one position to another in the alkyl group[346] (reaction **8-1**).

Phenyl groups have also been found to migrate. Thus *o*-terphenyl, heated with $AlCl_3$ H_2O, gave a mixture containing 7% *o*-, 70% *m*-, and 23% *p*-terphenyl.[347] Alkyl groups have also been replaced by groups other than hydrogen, for example, nitro groups.[348]

OS **V**, 332. Also see OS **III**, 282, 653; **V**, 598.

1-42 Decarbonylation of Aromatic Aldehydes

$$\mathrm{ArCHO \xrightarrow{H_2SO_4} ArH + CO}$$

The decarbonylation of aromatic aldehydes with H_2SO_4[349] is the reverse of reaction **1-17.** It has been carried out with trialkyl- and trialkoxybenzaldehydes. The reaction takes place by the ordinary arenium-ion mechanism: the attacking species is H^+, and the leaving group is HCO^+, which can lose a proton to give CO or combine with OH^- from the water solvent to give formic acid.[350] Aromatic aldehydes have also been decarbonylated over Pd,[351] and with basic catalysts.[352] When basic catalysts are used, the mechanism is probably similar to the SE1 process of reaction **1-43.** See also reaction **4-27.**

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[343] Streitwieser and Reif, *J. Am. Chem. Soc.* **86,** 1988 (1964).

[344] Olah, Meyer, and Overchuk, *J. Org. Chem.* **29,** 2313 (1964).

[345] See for example, Steinberg and Sixma, *Recl. Trav. Chim. Pays-Bas* **81,** 185 (1962); Koptyug, Isaev, and Vorozhtsov, *Doklad. Akad. Nauk SSSR* **149,** 100 (1963).

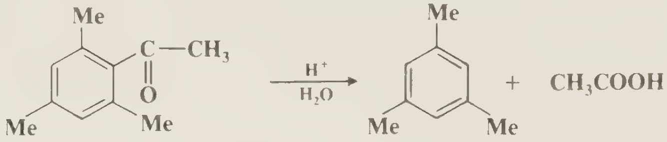
[346] Roberts, Khalaf, and Greene, *J. Am. Chem. Soc.* **86,** 2846 (1964); Roberts and Gibson, *J. Am. Chem. Soc.* **93,** 7340 (1971); Roberts, *Intra-Sci. Chem. Rep.* **6**(2), 89 (1972).

[347] Olah and Meyer, *J. Org. Chem.* **27,** 3682 (1962).

[348] For a review, see Nightingale, *Chem. Rev.* **40,** 117 (1947).

[349] For reviews of the mechanism, see Schubert and Kintner, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 695 760, Interscience Publishers, New York, 1966; Taylor, Ref. 1, pp. 316-323.

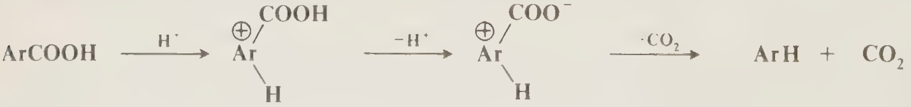
Aromatic ketones can also be cleaved, but only when sterically hindered, e.g.,



1-43 Decarboxylation of Aromatic Acids

$$\mathrm{ArCOOH} \xrightarrow[\text{quinoline}]{\text{Cu}} \mathrm{ArH} + \mathrm{CO_2}$$

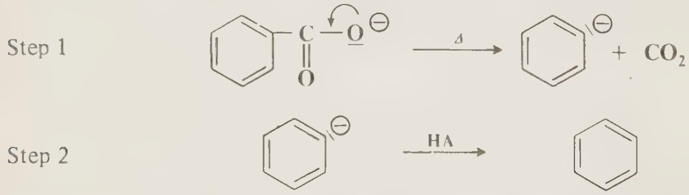
The decarboxylation of aromatic acids is most often carried out by heating with copper and quinoline. However, two other methods can be used with certain substrates. In one method the salt of the acid ($ArCOO^-$) is heated, and in the other the carboxylic acid is heated with a strong acid, often sulfuric. The latter method is accelerated by the presence of electron-donating groups in the ortho and para positions, and by the steric effect of groups in the ortho positions; in benzene systems it is generally limited to substrates which contain such groups. In this method decarboxylation takes place by the arenium-ion mechanism,[353] with H^+ as the electrophile and CO_2 as the leaving group.[354] Evidently, the order of electrofugal ability is $CO_2 > H^+ > COOH^+$, so



$$\mathrm{ArCOOH} \xrightarrow{H^+} \overset{+}{\mathrm{Ar}}(\mathrm{COOH})(\mathrm{H}) \xrightarrow{-H^+} \overset{+}{\mathrm{Ar}}(\mathrm{COO^-})(\mathrm{H}) \xrightarrow{-CO_2} \mathrm{ArH} + \mathrm{CO_2}$$

that it is necessary, at least in most cases, for the COOH to lose a proton before it can cleave.

When carboxylate *ions* are decarboxylated, the mechanism is entirely different, being essentially of the SE1 type. Evidence for this mechanism is that the reaction is first order, and that electron-withdrawing groups, which would stabilize a carbanion, facilitate the reaction.



Despite its synthetic importance, the mechanism of the copper-quinoline method has been studied very little, but it has been shown that the actual catalyst is cuprous ion.[355] In fact, the reaction proceeds much faster if the acid is heated in quinoline with cuprous oxide instead of copper, provided that atmospheric oxygen is rigorously excluded. A mechanism has been suggested in which it is the cuprous salt of the acid which actually undergoes the decarboxylation.[355] According to this suggestion the aryl group of ArCOO$^-$ is coordinated with Cu$^+$ which helps to stabilize the negative charge which develops on the ring as the CO_2 cleaves. The resulting Ar$^-$ (coordinated with Cu$^+$) rearranges to give ArCu which then reacts with some molecule in the solution (reaction **1-50**) to give the product. It has been shown that cuprous salts of aromatic acids are easily decarboxylated by heating in quinoline,[356] and that arylcopper compounds are intermediates which can be isolated in some cases.[356]

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[350] Burkett, Schubert, Schultz, Murphy, and Talbott, *J. Am. Chem. Soc.* **81,** 3923 (1959).

[351] Hawthorne and Wilt, *J. Org. Chem.* **25,** 2215 (1960).

[352] Bunnett, Miles, and Nahabedian, *J. Am. Chem. Soc.* **83,** 2512 (1961); Forbes and Gregory, *J. Chem. Soc. B* 205 (1968).

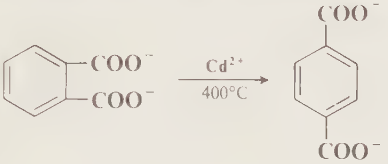
[353] For reviews, see Taylor, Ref. 1, pp. 303-316; Brown, *Q. Rev., Chem. Soc.* **5,** 131-146 (1951).

[354] See for example, Los, Rekker, and Tonsbeek, *Recl. Trav. Chim. Pays-Bas* **86,** 622 (1967); Longridge and Long, *J. Am. Chem. Soc.* **90,** 3092 (1968); Huang and Long, *J. Am. Chem. Soc.* **91,** 2872 (1969); Willi, Cho, and Won, *Helv. Chim. Acta* **53,** 663 (1970).

[355] Cohen and Schambach, *J. Am. Chem. Soc.* **92,** 3189 (1970). See also Chodowska-Palicka and Nilsson, *Acta Chem. Scand.* **24,** 3353 (1970).

In certain cases the carboxyl group can be replaced by electrophiles other than hydrogen, e.g., NO[357] or Br.[358]

Rearrangements are also known to take place. For example, when the phthalate ion (**51**) is heated with a catalytic amount of cadmium ion, the terphthalate ion (**52**) is produced:[359]



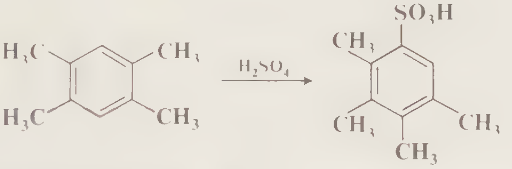
51 **52**

In a similar process, potassium benzoate heated with cadmium salts disproportionates to benzene and **52**. The term *Henkel reaction* is used for these rearrangements. An SE1 mechanism has been suggested.[360] The terphthalate is the main product, because it crystallizes from the reaction mixture, driving the equilibrium in that direction.[361]

For aliphatic decarboxylation, see reaction **2-39.**

OS **I**, 274, 455, 541; **II**, 100, 214, 217, 341; **III**, 267, 272, 471, 637; **IV**, 590, 628; **V**, 635, 813, 982, 985. Also see OS **I**, 56.

1-44 The Jacobsen Reaction



When polyalkyl- or polyhalobenzenes are treated with sulfuric acid, the ring is sulfonated, but in addition, rearrangement takes place.[362] The reaction, known as the *Jacobsen reaction*, is limited to benzene rings which have at least four substituents, which may be any combination of alkyl and halogen groups, where the alkyl groups may be ethyl or methyl and the halogen iodo, chloro, or bromo. When isopropyl or *t*-butyl groups are on the ring, these groups are cleaved to give olefins. Since a sulfo group can later be removed (reaction **1-46**), the Jacobsen reaction can be used as a means of rearranging polyalkylbenzenes. The rearrangement always brings the alkyl or halo groups closer together than they were originally. Side products in the case illustrated above are pentamethylbenzenesulfonic acid, 2,4,5-trimethylbenzenesulfonic acid, etc., indicating an intermolecular process, at least partially. Similar rearrangements take place when polyalkylbenzenes are trichloromethylated, with CCl_4 and $AlCl_3$.[363]

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[356] Cairncross, Roland, Henderson, and Sheppard, *J. Am. Chem. Soc.* **92,** 3187 (1970).

[357] For example, see Ibne-Rasa, *J. Am. Chem. Soc.* **84,** 4962 (1962); Tedder and Theaker, *J. Chem. Soc.* 257 (1959).

[358] For example, see Grovenstein and Henderson, *J. Am. Chem. Soc.* **78,** 569 (1956); Grovenstein and Ropp, *J. Am. Chem. Soc.* **78,** 2560 (1956).

[359] Raecke, *Angew. Chem.* **70,** 1 (1958); Riedel and Kienitz, *Angew. Chem.* **72,** 738 (1960); Ogata, Hojo, and Morikawa, *J. Org. Chem.* **25,** 2082 (1960); McNelis, *J. Org. Chem.* **30,** 1209 (1965); Ogata and Nakajima, *Tetrahedron* **21,** 2393 (1965); Ratuský and Šorm, *Chem. Ind.* (*London*) 1798 (1966).

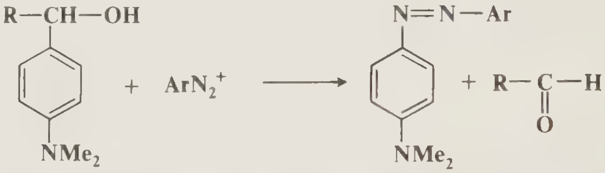
[360] See, for example, Ratuský, Tykva, and Šorm, *Collect. Czech. Chem. Commun.* **32,** 1719 (1967); Ratuský, *Collect. Czech. Chem. Commun.* **32,** 2504 (1967), **37,** 2436 (1972), **38,** 74, 87 (1973).

[361] Ratuský, *Chem. Ind.* (*London*) 1093 (1967), *Collect. Czech. Chem. Commun.* **33,** 2346 (1968).

[362] For a review, see Smith, *Org. React.* **1,** 370–384 (1942).

The mechanism of the Jacobsen reaction is not established,[364] but a likely possibility is attack by a sulfonating species (see reaction **1-7**) at a position occupied by an alkyl group, with the alkyl group thus freed migrating inter- or intramolecularly to another position. However, other mechanisms have also been suggested, including one which involves a radical cation intermediate.[365] It has been shown by labeling that ethyl groups migrate without internal rearrangement.[366]

1-45 The Stiles-Sisti Reaction



α-Hydroxyalkyl groups are replaced by azo groups when there is a dialkylamino group in the para position. The reaction is similar to reaction **1-4**, except that the leaving group is not hydrogen. The reaction is used to prepare aldehydes[367] and ketones.[368]

α-Hydroxyalkyl groups have also been replaced by halogen.[369] In this case too, best results are obtained when there is an activating group in the para position.

OS V, 46.

B. Oxygen Leaving Groups

1-46 Reduction of Aromatic Ethers

$$\mathrm{ArOR} \xrightarrow{\text{Raney Ni}} \mathrm{ArH} + \mathrm{RH}$$

Aromatic ethers may be reductively cleaved by heating with Raney nickel.[370] The hydrogen comes from that normally contained in this material, and from the solvent. R may also be aromatic, but if it is, it is usually reduced to a cyclohexane ring, unless degassed Raney nickel is used. The mechanism proposed is that, on the surface of the catalyst,

$$\mathrm{Ar{-}O{-}R} + \mathrm{H^-}\ \text{(from the catalyst)} \longrightarrow \mathrm{Ar^-} + \mathrm{ROH}$$

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[363] See for example, Hart and Janssen, *J. Org. Chem.* **35**, 3637 (1970).

[364] For discussions, see Suzuki, *Bull. Chem. Soc. Jpn.* **36**, 1642 (1963); Taylor, Ref. 1, pp. 22–32, 48–55; Cerfontain, Ref. 123, pp. 214–226.

[365] Bohlmann and Riemann, *Chem. Ber.* **97**, 1515 (1964).

[366] Marvell and Webb, *J. Org. Chem.* **27**, 4408 (1962).

[367] Stiles and Sisti, *J. Org. Chem.* **25**, 1691 (1960); Sisti, Burgmaster, and Fudim, *J. Org. Chem.* **27**, 279 (1962).

[368] Sisti, Sawinski, and Stout, *J. Chem. Eng. Data* **9**, 108 (1964).

[369] Clarke and Esselen, *J. Am. Chem. Soc.* **33**, 1135 (1911); Sarkanen and Dence, *J. Org. Chem.* **25**, 715 (1960); Arnett and Klingensmith, *J. Am. Chem. Soc.* **87**, 1023, 1032, 1038 (1965).

[370] Chandler and Sasse, *Aust. J. Chem.* **16**, 20 (1963).

The Ar^- takes a proton from the solvent. The ROH is then reduced as in reaction **0-79.** This mechanism is similar to the carboxylate ion mechanism in reaction **1-43.** With diaryl ethers, cleavage takes place so that the more stable carbanion is formed. See also reaction **3-9.**

C. Sulfur Leaving Groups

1-47 Desulfonation

$$ArSO_3H \xrightarrow[\text{dil. } H_2SO_4]{135\text{–}200^\circ C} ArH + H_2SO_4$$

The cleavage of sulfo groups from aromatic rings is the reverse of reaction **1-7.**[371] By the principle of microsopic reversibility, the mechanism is also the reverse. Dilute H_2SO_4 is generally used, as the reversibility of sulfonation decreases with increasing H_2SO_4 concentration. The reaction permits the sulfo group to be used as a blocking group to direct meta and then to be removed. Migration has also been found, so that *o*-methylbenzenesulfonic acid has been converted to *p*-methylbenzenesulfonic acid.[372] The sulfo group has also been replaced by nitro and halogen groups. Sulfo groups have also been removed from the ring by heating with an alkaline solution of Raney nickel.[373] In another catalytic process, aromatic sulfonyl bromides or chlorides are converted to aryl bromides or chlorides, respectively, on heating with chlorotris(triphenylphosphine)rhodium(I).[374] This reaction is similar to the decarbonylation of aromatic acyl halides mentioned in reaction **4-41.**

$$ArSO_2Br \xrightarrow{RhCl(PPh_3)_3} ArBr$$

OS **I,** 388; **II,** 97; **III,** 262; **IV,** 364. Also see OS **I,** 519; **II,** 128; **V,** 1070.

D. Halogen Leaving Groups

1-48 Dehalogenation

$$ArX \xrightarrow{AlCl_3} ArH$$

Aryl halides can be dehalogenated by Friedel-Crafts catalysts. Iodine is the most easily cleaved. Dechlorination is seldom performed, and defluorination apparently never. The reaction is most successful when a reducing agent, say Br^- or I^-, is present to combine with the I^+ or Br^+ coming off.[375] Except for deiodination, the reaction is seldom used for preparative purposes. Migration of halogen is also found, both intramolecular and intermolecular.[376] An example of the latter was conversion of *p*-dibromobenzene to a mixture containing 6% *o*-, 59% *m*-, and 35% *p*-dibromobenzene, as well as bromobenzene and some tribromobenzenes, by heating at 200°C with $AlBr_3$.[377] On the other hand, radioactive labeling showed that the $AlCl_3$-catalyzed isomerization of *o*-dichlorobenzene to a mixture consisting mostly of *m*-dichlorobenzene was largely intramolecular.[378] *p*-Bromophenols undergo isomerization and debromination under mild conditions: treatment with HBr at 25°C.[379]

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[371] For reviews, see Cerfontain, Ref. 123, pp. 185–214; Taylor, Ref. 1, pp. 349–355; Gilbert, Ref. 121, pp. 427–442.

[372] Syrkin, Yakerson, and Shnol, *J. Gen. Chem. USSR* **29,** 189 (1960); Wanders and Cerfontain, *Proc. Chem. Soc.* 174 (1963).

[373] Feigl, *Angew. Chem.* **73,** 113 (1961).

[374] Blum and Scharf, *J. Org. Chem.* **35,** 1895 (1970).

[375] Pettit and Piatak, *J. Org. Chem.* **25,** 721 (1960).

[376] Olah, Tolgyesi, and Dear, *J. Org. Chem.* **27,** 3441, 3449, 3455 (1962); Olah and Meyer, *J. Org. Chem.* **27,** 3464 (1962); de Valois, van Albada, and Veenland, *Tetrahedron* **24,** 1835 (1968).

[377] Kooyman and Louw, *Recl. Trav. Chim. Pays-Bas* **81,** 365 (1962); Augustijn, Kooyman, and Louw, *Recl. Trav. Chim. Pays-Bas* **82,** 965 (1963).

[378] Koptyug, Isaev, Gershtein, and Berezovskii, *J. Gen. Chem. USSR* **34,** 3830 (1964); Erykalov, Becker, and Belokurova, *J. Org. Chem. USSR* **4,** 2054 (1968).

[379] O'Bara, Balsley, and Starer, *J. Org. Chem.* **35,** 16 (1970).

The reaction is useful for preparing polyiodo aromatic compounds. Thus 2,4,5,6-tetraiodo-1,3,-dimethylbenzene was prepared by treatment of 4,6-diiodo-1,3-dimethylbenzene with sulfuric acid.[380] The mechanism is probably the reverse of that of reaction **1-12.**[381] Rearrangement of polyhalobenzenes can also be catalyzed by very strong bases; e.g., 1,2,4-tribromobenzene is converted to 1,3,5-tribromobenzene by treatment with PhNHK.[382] This reaction, which involves aryl carbanion intermediates (S_E1 mechanism) has been called the *halogen dance*.[383]

Removal of halogen from aromatic rings can also be accomplished by various reducing agents, among them Ph_3SnH,[384] HI, Sn and HBr, Ph_3P,[385] Cu and H_2O,[386] hydrazine and Pd–C,[387] catalytic hydrogenation, $LiAlH_4$,[388] $NaAlH_4$,[389] *t*-BuOK in 1 : 1 *t*-BuOH–Me_2SO,[390] $NaBH_4$ in the presence of Pd–C,[391] NaH,[392] and Raney nickel in alkaline solution,[393] the latter method being effective for fluorine as well as for the other halogens. Not all these reagents operate by electrophilic substitution mechanisms. Some are nucleophilic substitutions and some are free-radical processes. Photochemical reduction is also known.[394] Halogen can also be removed from aromatic rings indirectly, by conversion to Grignard reagents (**2-37**) followed by hydrolysis (**2-21**).

OS **III,** 132, 475, 519; **V,** 149, 346, 998; **52,** 62.

1-49 Formation of Organometallic Compounds

$$\mathrm{ArBr + M \longrightarrow ArM}$$

$$\mathrm{ArBr + RM \longrightarrow ArM + RBr}$$

These reactions are considered along with their aliphatic counterparts (reactions **2-37** and **2-38**).

E. Metal Leaving Groups

1-50 Hydrolysis of Organometallic Compounds

$$\mathrm{ArM + H^+ \longrightarrow ArH + M^+}$$

Organometallic compounds can be hydrolyzed by acid treatment. For active metals such as Mg, Li, etc., water is sufficiently acidic. The most important example of this reaction is hydrolysis of Grignard reagents, but M may be many other metals or metalloids. Examples are SiR_3, HgR,

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[380] Suzuki and Goto, *Bull. Chem. Soc. Jpn.* **36,** 389 (1963).

[381] Choguill and Ridd, *J. Chem. Soc.* 822 (1961); Ref. 341; Ref. 376.

[382] Moyer and Bunnett, *J. Am. Chem. Soc.* **85,** 1891 (1963).

[383] Bunnett and McLennan, *J. Am. Chem. Soc.* **90,** 2190 (1968); Bunnett and Moyer, *J. Am. Chem. Soc.* **93,** 1183 (1971); Bunnett and Scorrano, *J. Am. Chem. Soc.* **93,** 1190 (1971); McLennan and Bunnett, *J. Am. Chem. Soc.* **93,** 1198 (1971); Bunnett and Feit, *J. Am. Chem. Soc.* **93,** 1201 (1971); Bunnett, *Acc. Chem. Res.* **5,** 139–147 (1972).

[384] Rothman and Becker, *J. Org. Chem.* **24,** 294 (1959); Lorenz, Shapiro, Stern, and Becker, *J. Org. Chem.* **28,** 2332 (1963); Neumann and Hillgärtner, *Synthesis* 537 (1971).

[385] Hoffmann, Horner, Wippel, and Michael, *Chem. Ber.* **95,** 523 (1962); Hoffmann and Michael, *Chem. Ber.* **95,** 528 (1962).

[386] Sokolenko, L'vova, Tyurin, Platonov, and Yakobson, *J. Org. Chem. USSR* **6,** 2508 (1970).

[387] Mosby, *Chem. Ind.* (*London*) 1348 (1959), *J. Org. Chem.* **24,** 421 (1959).

[388] Karabatsos and Shone, *J. Org. Chem.* **33,** 619 (1968); Brown and Krishnamurthy, *J. Org. Chem.* **34,** 3918 (1969); Virtanen and Jaakkola, *Tetrahedron Lett.* 1223 (1969); Ricci, Danieli, and Pirazzini, *Gazz. Chim. Ital.* **105,** 37 (1975).

[389] Zakharkin, Gavrilenko, and Rukasov, *Dokl. Chem.* **205,** 551 (1972).

[390] Bunnett and Victor, *J. Am. Chem. Soc.* **90,** 810 (1968).

[391] Egli, *Helv. Chim. Acta* **51,** 2090 (1968); Bosin, Raymond, and Buckpitt, *Tetrahedron Lett.* 4699 (1974).

[392] Nelson and Gribble, *J. Org. Chem.* **39,** 1425 (1974).

[393] Buu-Hoï, Xuong, and van Bac, *Bull. Soc. Chim. Fr.* 2442 (1963); de Koning, *Org. Prep. Proced. Int.* **7,** 31 (1975).

[394] See for example, Pinhey and Rigby, *Tetrahedron Lett.* 1267, 1271 (1969); Barltrop and Bradbury, *J. Am. Chem Soc.* **95,** 5085 (1973).

Na, $B(OH)_2$. Since aryl Grignard and aryllithium compounds are fairly easy to prepare, they are often used to prepare salts of weak acids, e.g.,

$$\mathrm{PhMgBr} + \mathrm{H{-}C{\equiv}C{-}H} \longrightarrow \mathrm{H{-}C{\equiv}C^-}\quad \mathrm{MgBr^+} + \mathrm{PhH}$$

Where the bond between the metal and the ring is covalent, the usual arenium-ion mechanism operates.[395] Where the bonding is essentially ionic, this is a simple acid-base reaction. Other electrophiles can replace metals. For example, azo compounds can be prepared by attack of diazonium ions on arylzinc or arylmercury compounds[396] or on Grignard reagents,[397] and aryltrimethylsilanes $ArSiMe_3$ react with acyl chlorides in the presence of $AlCl_3$ to give ketones ArCOR.[398] For the aliphatic counterpart of this reaction, see reaction **2-21.**

Other reactions of aryl organometallic compounds are treated with their aliphatic analogs: reactions **2-22** through **2-35.**

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[395] For a discussion of the mechanism, see Taylor, Ref. 1, pp. 278–303, 324–349.

[396] Curtin and Tveten, *J. Org. Chem.* **26,** 1764 (1961).

[397] Nomura, Anzai, Tarao, and Shiomi, *Bull. Chem. Soc. Jpn.* **37,** 967 (1964); Nomura, *Bull. Chem. Soc. Jpn.* **34,** 1648 (1961).

[398] Dey, Eaborn, and Walton, *Organomet. Chem. Synth.* **1,** 151–160 (1971).

Twelve
Aliphatic Electrophilic Substitution

In Chapter 11 it was pointed out that the most important leaving groups in electrophilic substitution are those which can best exist with an outer shell which is deficient in a pair of electrons. For aromatic systems the most common leaving group is the proton. The proton is also a leaving group in aliphatic systems, but the reactivity depends on the acidity. Protons in saturated alkanes are very unreactive, but electrophilic substitutions are often easily carried out at more acidic positions, for example, α to a carbonyl group, or at an alkynyl position ($RC{\equiv}CH$). Since metallic ions are easily able to bear positive charges, we might expect that organometallic compounds would be especially susceptible to electrophilic substitution, and this is indeed the case.[1] Another important type of electrophile substitution, known as *anionic cleavage*, involves the breaking of C—C bonds: in these reactions there are carbon leaving groups (reactions **2-39** to **2-45**). A number of electrophilic substitutions at a nitrogen atom are treated at the end of the chapter.

Since a carbanion is what remains when a positive species is removed from a carbon atom, the subject of carbanion structure and stability (Chapter 5) is inevitably related to the material in this chapter. So is the subject of very weak acids and very strong bases (Chapter 8), since the weakest acids are those in which the hydrogen is bound to carbon.

MECHANISMS

The mechanistic picture for aliphatic electrophilic substitution is less clear than it is for aliphatic nucleophilic substitution (Chapter 10) or aromatic electrophilic substitution (Chapter 11). However, we can distinguish at least four possible major mechanisms,[2] which we call SE1, SE2 (front), SE2 (back), and SEi. The SE1 is unimolecular; the other three are bimolecular.

Bimolecular Mechanisms. SE2 and SEi

The bimolecular mechanisms for electrophilic aliphatic substitution are analogous to the SN2 mechanism (p. 266) in that the new bond forms as the old one breaks. However, in the SN2 mechanism the incoming group brings with it a pair of electrons, and this orbital can overlap with the central carbon only to the extent that the leaving group takes away *its* electrons; otherwise the carbon would have more than eight electrons at once in its outer shell. Since electron clouds repel, this means also that the incoming group attacks backside, at a position 180° from the leaving group, so that inversion of configuration is found. When the attacking species is an electrophile, which brings to the substrate only a vacant orbital, it is obvious that this consideration does not apply, and we cannot a priori predict from which direction the attack must come. We can therefore imagine two main possibilities: attack from the front, which we call SE2 (front), and attack from the rear, which we call SE2 (back). These possibilities can be pictured thus (charges not shown):

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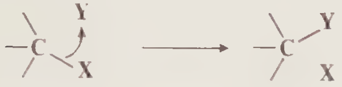
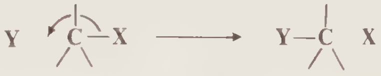
[1] For books on the preparation and reactions of organometallic compounds, see Coates, Green, and Wade, "Organometallic Compounds," 3d ed., 2 vols., Methuen & Co., London, 1967–1968; Eisch, "The Chemistry of Organometallic Compounds," The Macmillan Company, New York, 1967. For reviews, see, in Tsutsui, "Characterization of Organometallic Compounds," Interscience Publishers, New York, 1969–1971, the articles by Cartledge and Gilman, pt. 1, pp. 1–33, and by Reichle, pt. 2, pp. 653–826.

[2] For monographs, see Abraham, "Comprehensive Chemical Kinetics" (edited by Bamford and Tipper), vol. 12, American Elsevier Publishing Company, Inc., New York, 1973; Jensen and Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill Book Company, New York, 1968; Reutov and Beletskaya, "Reaction Mechanisms of Organometallic Compounds," North-Holland Publishing Company, Amsterdam, 1968. For reviews, see Reutov, *J. Organomet. Chem.* **100,** 219–235 (1975), *Pure Appl. Chem.* **17,** 79–94 (1968), *Russ. Chem. Rev.* **36,** 163–174 (1967), *Fortschr. Chem. Forsch.* **8,** 61–90 (1967), *Angew. Chem.* **72,** 198–208 (1960); Matteson, *Organomet. Chem. Rev., Sect. A* **4,** 263–305 (1969); Dessy and Kitching, *Adv. Organomet. Chem.* **4,** 267–351 (1966); Ingold, *Helv. Chim. Acta* **47,** 1191–1203 (1964) [reprinted in *Rec. Chem. Prog.* **25,** 145–158 (1964)]; Köbrich, *Angew. Chem. Int. Ed. Engl.* **1,** 382–393 (1962) [*Angew. Chem.* **74,** 453–465]; Dessy and Paulik, *J. Chem. Educ.* **40,** 185–194 (1963).

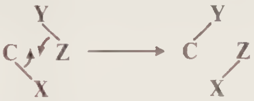


SE2 (front)



SE2 (back)

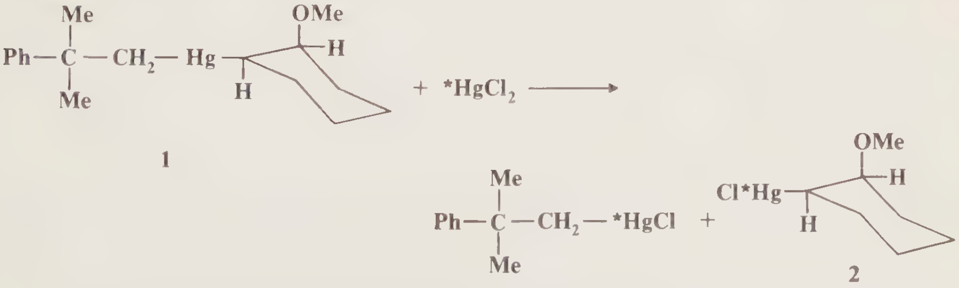
With substrates in which we can distinguish the possibility, the former mechanism should result in retention of configuration and the latter in inversion. When the electrophile attacks from the front, there is a third possibility. A portion of the electrophile may assist in removal of the leaving group, forming a bond with it at the same time that the new C—Y bond is formed:



SEi

This mechanism, which we call the SEi mechanism,[3] also results in retention of configuration. Plainly, where a second-order mechanism involves this kind of internal assistance, backside attack is impossible.

It is evident that these three mechanisms are not easy to distinguish. All three give second-order kinetics, and two result in retention of configuration. In fact, although much work has been done on this question, there are few cases in which we can unequivocally say that one of these three and not another is actually taking place. Clearly, a study of the stereochemistry can distinguish between SE2 (back) on the one hand and SE2 (front) or SEi on the other. Many such investigations have been made, and in the overwhelming majority of second-order electrophilic substitutions, the result has been retention of configuration or some other indication of frontside attack, indicating an SE2 (front) or SEi mechanism. For example, when *cis*-**1** was treated with labeled mercuric



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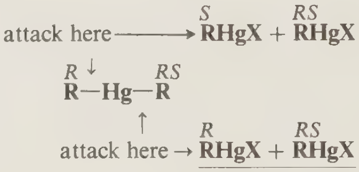
[3] The names for these mechanisms vary throughout the literature. For example, the SEi mechanism has also been called the SF2 and the SE2 (cyclic) mechanism. The original designations, SE1, SE2, etc., were devised by the Hughes-Ingold school.

chloride, the **2** produced was 100% cis. The bond between the mercury and the ring must have been broken (as well as the other Hg—C bond), since each of the products contained about half of the labeled mercury.[4] Another indication of frontside attack is that second-order electrophilic substitutions proceed very easily at *bridgehead* carbons (see p. 268).[5] Still another indication is the behavior of neopentyl as a substrate. SN2 reactions at neopentyl are extremely slow (p. 315), because attack from the rear is sterically blocked. The fact that neopentyl systems undergo electrophilic substitution only slightly more slowly than ethyl[6] is further evidence for frontside attack. One final elegant experiment may be noted. The compound di-*sec*-butylmercury was prepared with one *sec*-butyl group optically active and the other racemic.[7] This was accomplished by treatment of optically active *sec*-butylmercuric bromide with racemic *sec*-butylmagnesium bromide. The di-*sec*-butyl compound was then treated with mercuric bromide to give 2 moles of *sec*-butylmercuric bromide. The steric course of the reaction could then be predicted by the following analysis, assuming that the bonds between the mercury and each carbon have a 50% chance of breaking:

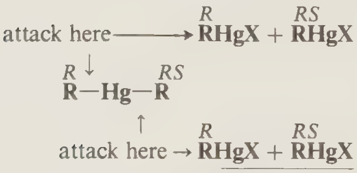
If inversion,



$$\text{attack here} \longrightarrow \overset{S}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$
$$\overset{R\downarrow}{\mathbf{R}}\mathbf{-Hg-}\overset{RS}{\mathbf{R}}$$
$$\uparrow$$
$$\text{attack here} \rightarrow \overset{R}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$

The sum is a
racemic mixture

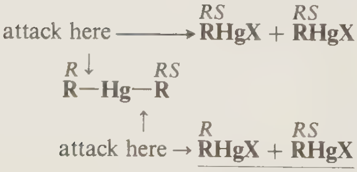
If retention,



$$\text{attack here} \longrightarrow \overset{R}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$
$$\overset{R\downarrow}{\mathbf{R}}\mathbf{-Hg-}\overset{RS}{\mathbf{R}}$$
$$\uparrow$$
$$\text{attack here} \rightarrow \overset{R}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$

The sum has
one-half of the
original activity

If racemization,



$$\text{attack here} \longrightarrow \overset{RS}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$
$$\overset{R\downarrow}{\mathbf{R}}\mathbf{-Hg-}\overset{RS}{\mathbf{R}}$$
$$\uparrow$$
$$\text{attack here} \rightarrow \overset{R}{\mathbf{RHgX}} + \overset{RS}{\mathbf{RHgX}}$$

The sum has
one-quarter of
the original
activity

The original activity referred to is the activity of the optically active *sec*-butylmercuric bromide used to make the dialkyl compound. The actual result was that, under several different sets of conditions, the product had one-half of the original activity, demonstrating retention of configuration.

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[4] Winstein, Traylor, and Garner, *J. Am. Chem. Soc.* **77,** 3741 (1955).

[5] Winstein and Traylor, *J. Am. Chem. Soc.* **78,** 2597 (1956); Schöllkopf, *Angew. Chem.* **72,** 147–159 (1960). For a discussion, see Fort and Schleyer, *Adv. Alicyclic Chem.* **1,** 283–370 (1966), pp. 353–370.

[6] Hughes and Volger, *J. Chem. Soc.* 2359 (1961).

[7] Jensen, *J. Am. Chem. Soc.* **82,** 2469 (1960); Ingold, Ref. 2.

On the other hand, inversion of configuration has been found in certain cases, demonstrating that the SE2 (back) mechanism can take place. For example, the reaction of optically active *sec*-butyltrineopentyltin with bromine (reaction **2-28**) gives inverted *sec*-butyl bromide.[8] A number of

$$sec\text{-}\mathbf{BuSnR_3} + \mathbf{Br_2} \longrightarrow sec\text{-}\mathbf{BuBr} \qquad \mathbf{R} = \text{neopentyl}$$

other organometallic compounds have also been shown to give inversion when treated with halogens.[9] It may be that still other examples of backside attack exist[10] but have escaped detection because of the difficulty in preparing compounds which contain a configurationally stable carbon-metal bond. Compounds which are chiral because of an asymmetric carbon at which a carbon-metal bond is located are often difficult to resolve and once resolved are often easily racemized. The resolution has been accomplished most often with organomercury compounds,[11] and most stereochemical investigations have therefore been made with these substrates. It is only comparatively recently that an optically active Grignard reagent has been prepared[12] (that is, one in which the only asymmetric center is the carbon bonded to the magnesium). Because of this, the steric course of electrophilic substitutions at the C—Mg bond has not often been determined. However, in one such case, the reaction of both the exo and endo isomers of the 2-norbornyl Grignard reagent with $HgBr_2$ (to give 2-norbornylmercuric bromide) has been shown to proceed with retention of configuration.[13]

The SE2 (back) mechanism can therefore be identified in certain cases (if inversion of configuration is found), but it is plain that stereochemical investigations cannot distinguish between the SE2 (front) and the SEi mechanisms and that, in the many cases where configurationally stable substrates cannot be prepared, such investigations are of no help at all in distinguishing among all three of the second-order mechanisms. Unfortunately, there are not many other methods which lead to unequivocal conclusions. One method which has been used in an attempt to distinguish between the SEi mechanism on the one hand and the SE2 pathways on the other involves the study of salt effects on the rate. It may be recalled (p. 333) that reactions in which neutral starting molecules acquire charges in the transition state are aided by an increasing concentration of added ions. Thus the SEi mechanism would be less influenced by salt effects than would either of the SE2 mechanisms. On this basis Abraham and coworkers[14] concluded that the reactions $R_4Sn + HgX_2 \rightarrow RHgX + R_3SnX$ ($X = Cl$ or I) take place by SE2 and not by SEi mechanisms. Similar investigations involve changes in solvent polarity[15] (see also p. 530). Information from salt-effect studies can be put on a quantitative basis: the extent of charge separation in the transition state (Z) can be calculated from the kinetic values.[16] A high value of Z means an "open" transition state (SE2), while a low value indicates a "closed" transition state (SEi).

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[8] Jensen and Davis, *J. Am. Chem. Soc.* **93,** 4048 (1971).

[9] For example, see Applequist and Chmurny, *J. Am. Chem. Soc.* **89,** 875 (1967); Glaze, Selman, Ball, and Bray, *J. Org. Chem.* **34,** 641 (1969); Brown and Lane, *Chem. Commun.* 521 (1971); Whitesides and Boschetto, *J. Am. Chem. Soc.* **93,** 1529 (1971); Jensen, Madan, and Buchanan, *J. Am. Chem. Soc.* **93,** 5283 (1971); Casey, Whitesides, and Kurth, *J. Org. Chem.* **38,** 3406 (1973); Espenson and Williams, *J. Am. Chem. Soc.* **96,** 1008 (1974); Bock, Boschetto, Rasmussen, Demers, and Whitesides, *J. Am. Chem. Soc.* **96,** 2814 (1974).

[10] Cases of inversion involving replacement of a metal by a metal have been reported. See Tada and Ogawa, *Tetrahedron Lett.* 2639 (1973); Fritz, Espenson, Williams, and Molander, *J. Am. Chem. Soc.* **96,** 2378 (1974); Gielen and Fosty, *Bull. Soc. Chim. Belg.* **83,** 333 (1974).

[11] Organomercury compounds were first resolved by three groups: Jensen, Whipple, Wedegaertner, and Landgrebe, *J. Am. Chem. Soc.* **81,** 1262 (1959); Charman, Hughes, and Ingold, *J. Chem. Soc.* 2523, 2530 (1959); Reutov and Uglova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 735 (1959).

[12] Walborsky and Young, *J. Am. Chem. Soc.* **86,** 3288 (1964).

[13] Jensen and Nakamaye, *J. Am. Chem. Soc.* **88,** 3437 (1966).

[14] Abraham and Spalding, *J. Chem. Soc. A* 784 (1969); Abraham and Johnston, *J. Chem. Soc. A* 188 (1970).

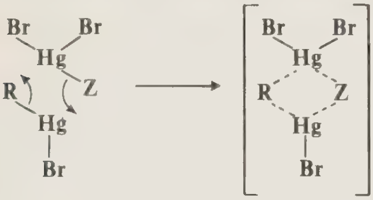
[15] See for example, Abraham and Dorrell, *J. Chem. Soc., Perkin Trans. 2* 444 (1973).

[16] Abraham and Behbahany, *J. Chem. Soc. A* 1469 (1971).

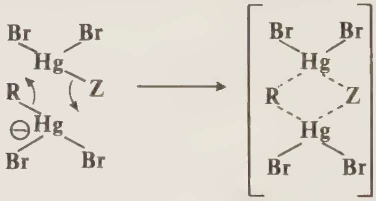
The effect of added salts has also been investigated in a different way. The reaction between *sec*-butylmercuric bromide and labeled mercuric bromide:

$$sec\text{-}\mathbf{Bu{-}HgBr} + {}^{*}\mathbf{HgBr_2} \rightleftharpoons sec\text{-}\mathbf{Bu{-}{}^{*}HgBr} + \mathbf{HgBr_2}$$

is second order and involves retention of configuration (which rules out the backside SE2 mechanism). It is catalyzed by I^-, Br^-, Cl^-, and acetate ion, in that order,[17] but interestingly, there are *two* catalytic processes at work, since the rate rises linearly with the addition of catalyst until a concentration of catalyst is reached which is equal to the concentration of $HgBr_2$, after which it again rises linearly but with a different slope. The catalysis is evidence for the SEi mechanism, since these ions are known to coordinate with mercury, and the strength of the coordination is in the same order. On the other hand, acetic acid and nitrate ion, neither of which coordinate with mercury, do not catalyze the reaction. The catalyst changes the attacking species from $HgBr_2$ to, say, $HgBr_2I^-$. It is hardly likely that such a change would increase the rate of an SE2 mechanism, since $HgBr_2I^-$ is a poorer electrophile than $HgBr_2$, but it would increase the rate of an SEi mechanism because the added nucleophile would assist in the removal of the leaving group. The transition state for the catalysis at the lower concentration of added ions (the one-ion catalysis) may thus be shown as in **A**.[18] The second anion catalyzes the reaction by coordinating with the other mercury atom; the transition state for the two-ion catalysis is shown in **B**.



A

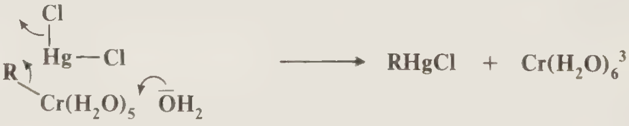


B

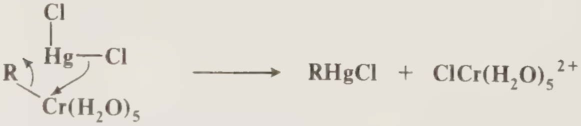
Another method for distinguishing the SE2 from the SEi mechanisms, which can be used in certain cases but unfortunately is not generally applicable, may be illustrated for the reaction of alkylchromium ions with mercuric chloride.[19] In this case we examine the chromium-containing products. If the mechanism is SE2 then the product can be $Cr(H_2O)_6{}^{3+}$ as shown, or $ClCr(H_2O)_5{}^{2+}$

$$\mathbf{RCr(H_2O)_5{}^{2+} + HgCl_2 \xrightarrow{H_2O} RHgCl + Cr(H_2O)_6{}^{3+} + X^-}$$

SE2



SEi



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[17] Charman, Hughes, Ingold, and Volger, *J. Chem. Soc.* 1142 (1961).

[18] It has been contended that the transition state **A** cannot be accurate, since it apparently violates the law of microscopic reversibility (Jensen and Rickborn, Ref. 2, p. 171; Matteson, Ref. 2, p. 278). However, a careful study has shown that there are several possible pathways available for this reaction which do not violate the law: Abraham, Dodd, Johnson, Lewis, and More O'Ferrall, *J. Chem. Soc. B* 762 (1971).

[19] Coombes and Johnson, *J. Chem. Soc. A* 1805 (1966). See also Coombes, Johnson, and Vamplew, *J. Chem. Soc. A* 2297 (1968).

if Cl^- takes the place of H_2O as shown in the equation, or a mixture of both. On the other hand, an SEi mechanism can give *only* $ClCr(H_2O)_5^{2+}$ (it is important to note that $ClCr(H_2O)_5^{2+}$ and $Cr(H_2O)_6^{3+}$ are not interconvertible under the reaction conditions). The finding that only $Cr(H_2O)_6^{3+}$ was produced thus indicates that one of the SE2 mechanisms operates here.[19] Another method for distinguishing the SE2 (back) mechanism from the others is discussed on p. 530.

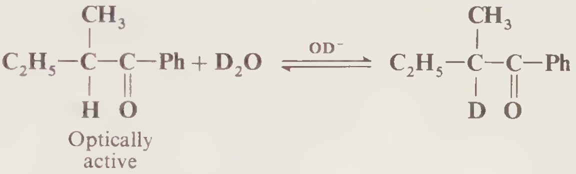
The SE1 Mechanism

The SE1 mechanism is analogous to the SN1 (p. 270). It involves two steps: a slow ionization and a fast combination.

Step 1 $\quad \mathrm{R{-}X} \xrightarrow{\text{slow}} \overline{\mathrm{R}}^- + \mathrm{X}^+$

Step 2 $\quad \overline{\mathrm{R}}^- + \mathrm{Y}^+ \longrightarrow \mathrm{R{-}Y}$

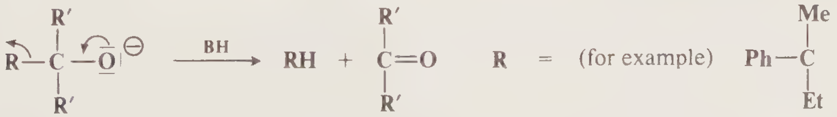
First-order kinetics are predicted, and many such examples have been found. Other evidence for the SE1 mechanism was obtained in a study of base-catalyzed tautomerism. In the reaction



the rate of deuterium exchange was the same as the rate of racemization,[20] and there *was* an isotope effect.[21] SN1 reactions do not proceed at bridgehead carbons in small bicyclic systems (p. 272) because at these carbons planar carbonium ions cannot form. However, carbanions not stabilized by resonance are probably not planar, and SE1 reactions should readily occur with this type of substrate. This is the case.

Indeed, the question of carbanion structure is intimately tied into the problem of the stereochemistry of the SE1 reaction. If a carbanion is planar (as are carbonium ions), then racemization should occur. If it is pyramidal and *can hold its structure*, then the result should be retention of configuration. On the other hand, even a pyramidal carbanion will give racemization if it cannot hold its structure, that is, if there is an umbrella effect as with amines (p. 90). Unfortunately, the only carbanions that can be easily studied are those stabilized by resonance, which makes them planar, as expected (p. 165). For simple alkyl carbanions, the main approach to determining structure has been to study the stereochemistry of SE1 reactions, rather than the other way around. What is found is almost always racemization. Whether this is caused by planar carbanions or by oscillating pyramidal carbanions is not known. In either case racemization occurs whenever a carbanion is completely free or is symmetrically solvated.

However, even planar carbanions need not give racemization. Cram found that retention and even inversion may occur in the alkoxide cleavage reaction (**2-40**):



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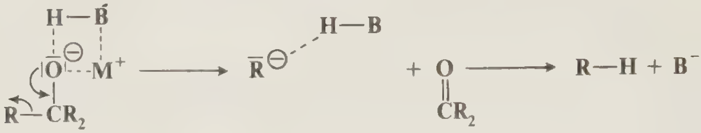
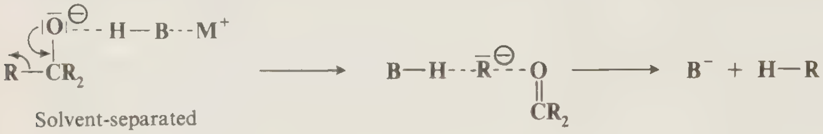
[20] Hsu, Ingold, and Wilson, *J. Chem. Soc.* 78 (1938).

[21] Wilson, *J. Chem. Soc.* 1550 (1936).

which is a first-order, SE1 reaction involving resonance-stabilized planar carbanions (here designated R^-).[22] By changing the solvent Cram was able to produce products ranging from 99% retention to 60% inversion and including complete racemization. These results are explained by a carbanion which is not completely free but is solvated. In nondissociating, nonpolar solvents, such as benzene or dioxane, the alkoxide ion exists as an ion pair, which is solvated by the solvent BH:

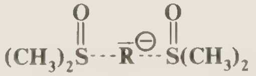


In the course of the cleavage, the proton of the solvent moves in to solvate the newly forming carbanion. As is easily seen, this solvation is asymmetrical since the solvent molecule is already on the front side of the carbanion. When the carbanion actually bonds with the proton, the result is retention of the original configuration. In protic solvents, such as diethylene glycol, a good deal of inversion is found. In these solvents, the *leaving group* solvates the carbanion, so that the solvent can solvate it only from the opposite side:



Solvent-separated
ion pair

When C—H bond formation occurs, the result is inversion. Racemization results in polar aprotic solvents like dimethyl sulfoxide. In these solvents the carbanions are relatively long-lived (because the solvent has no proton to donate) and symmetrically solvated:

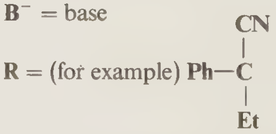


$$(CH_3)_2\overset{\overset{O}{\|}}{S}\cdots\overline{R}^{\ominus}\cdots\overset{\overset{O}{\|}}{S}(CH_3)_2$$

Similar behavior was found for carbanions generated by base-catalyzed hydrogen exchange (reaction **2-1**):[23]

$$R{-}H + B{-}D \xrightleftharpoons{B^-} R{-}D + B{-}H$$

B^- = base



R = (for example) $Ph{-}\overset{\overset{CN}{|}}{\underset{\underset{Et}{|}}{C}}$

In this case information was obtained from measurement of the ratio of k_e (rate constant for isotopic exchange) to k_α (rate constant for racemization). A k_e/k_α ratio substantially greater than 1 means retention of configuration, since many individual isotopic exchanges are not producing a change in configuration. A k_e/k_α ratio of about 1 indicates racemization, and a ratio of $\frac{1}{2}$ corresponds to inversion (see p. 269). All three types of steric behavior were found, depending on R, the base, and the solvent. As with the alkoxide cleavage reaction, retention was generally found in solvents of low dielectric constant, racemization in polar aprotic solvents, and inversion in protic solvents. However, in the proton exchange reactions, a fourth type of behavior was encountered. In aprotic solvents, with aprotic bases like tertiary amines, the k_e/k_α ratio was found to be *less* than 0.5, indicating that racemization took place *faster* than isotopic exchange (this process is known as *isoracemization*). Under these conditions, the conjugate acid of the amine remains associated with the carbanion as an ion pair. Occasionally, the ion pair dissociates long enough for the carbanion to turn over and recapture the proton:

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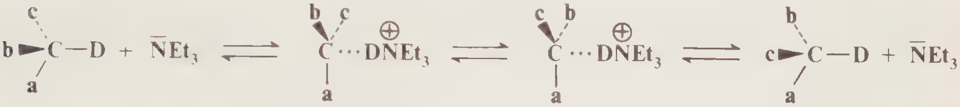
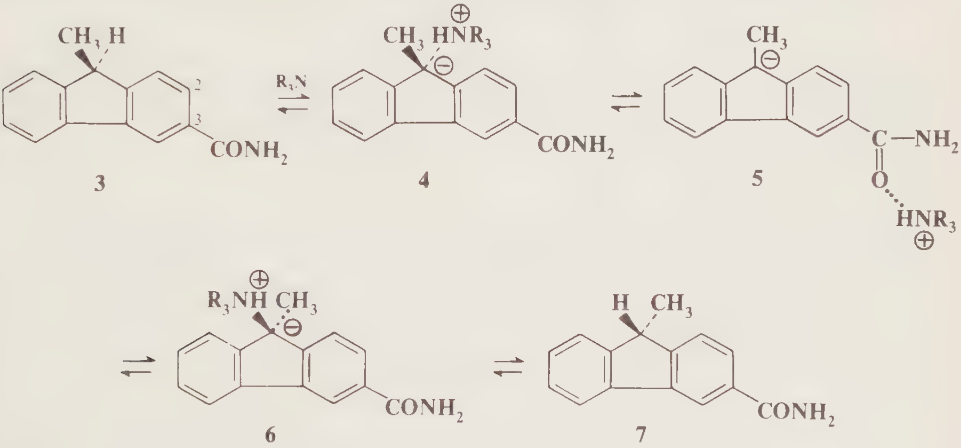
[22] Cram, Langemann, Allinger, and Kopecky, *J. Am. Chem. Soc.* **81,** 5740 (1959); Cram, Langemann, and Hauck, *J. Am. Chem. Soc.* **81,** 5750 (1959); Cram, Kopecky, Hauck, and Langemann, *J. Am. Chem. Soc.* **81,** 5754 (1959); Cram, Mateos, Hauck, Langemann, Kopecky, Nielsen, and Allinger, *J. Am. Chem. Soc.* **81,** 5774 (1959); Hoffman and Cram, *J. Am. Chem. Soc.* **91,** 1009 (1969). For a discussion, see Cram, "Fundamentals of Carbanion Chemistry," pp. 138–158, Academic Press, Inc., New York, 1965.

[23] Cram, Kingsbury, and Rickborn, *J. Am. Chem. Soc.* **83,** 3688 (1961); Cram, Rickborn, Kingsbury, and Haberfield, *J. Am. Chem. Soc.* **83,** 3678 (1961); Cram and Gosser, *J. Am. Chem. Soc.* **85,** 3890 (1963), **86,** 5445, 5457 (1964); Cram and Wingrove, *J. Am. Chem. Soc.* **86,** 5490 (1964); Kollmeyer and Cram, *J. Am. Chem. Soc.* **90,** 1779 (1968); Roitman and Cram, *J. Am. Chem. Soc.* **93,** 2225, 2231 (1971); Cram and Cram, *Intra-Sci. Chem. Rep.* **7**(3), 1–17 (1973). For a discussion, see Cram, Ref. 22, pp. 85–105.



Thus, inversion (and hence racemization, which is produced by repeated acts of inversion) occurs without exchange. A single act of inversion without exchange is called *isoinversion.*

The isoinversion process can take place by a pathway in which a positive species migrates in a stepwise fashion around a molecule from one nucleophilic position to another. For example, in the exchange reaction of 3-carboxamido-9-methylfluorene (**3**) with Pr_3N in *t*-BuOH, it has been proposed that the amine removes a proton from the 9 position of **3** and conducts the proton out



to the C=O oxygen (**5**), around the molecule, and back to C-9 on the opposite face of the anion. Collapse of **6** gives the inverted product **7**. Of course **5** could also go back to **3**, but a molecule which undergoes the total process **3** → **4** → **5** → **6** → **7** has experienced an inversion without an exchange. Evidence for this pathway, which is called the *conducted tour mechanism*,[24] is that the 2-carboxamido isomer of **3** does not give isoracemization. In this case the negative charge on the oxygen atom in the anion corresponding to **5** is less, because a canonical form in which oxygen acquires a full negative charge (**8**) results in disruption of the aromatic sextet in both benzene rings (compare **9** where one benzene ring is intact). Whether the isoracemization process takes place by

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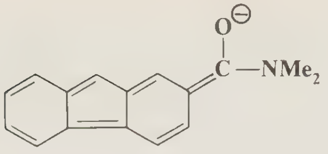
[24] Cram, Ford, and Gosser, *J. Am. Chem. Soc.* **90,** 2598 (1968); Ford and Cram, *J. Am. Chem. Soc.* **90,** 2606, 2612 (1968). See also Cram and Whitney, *J. Am. Chem. Soc.* **89,** 4651 (1967); Wong, Fischer, and Cram, *J. Am. Chem. Soc.* **93,** 2235 (1971).



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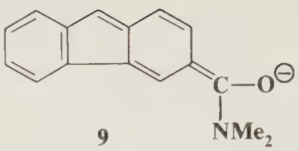
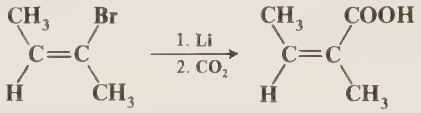


9

the conducted tour mechanism or by a simple nonstructured contact ion-pair mechanism depends on the nature of the substrate (e.g., a proper functional group is necessary for the conducted tour mechanism) and of the base.[25]

The four types of steric behavior, retention, inversion, racemization, and isoracemization, are not mutually exclusive, and two or more processes often operate simultaneously. The k_e/k_α ratios provide only a qualitative measure of the overall stereochemical course of the reaction. Two other methods have been devised[26] to dissect the overall outcome into its components, one being a purely kinetic method and the other (called the *reresolution method*) based on isotopic analysis.[26]

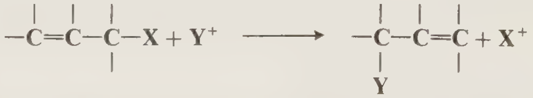
It is known that vinyl carbanions *can* maintain configuration, so that SE1 mechanisms should produce retention there. This has been found to be the case. For example, *trans*-2-bromo-2-butene was converted to 64–74% angelic acid:[27]



Only about 5% of the cis isomer, tiglic acid, was produced. In addition, certain carbanions in which the negative charge is stabilized by *d*-orbital overlap can maintain configuration (p. 166), and SE1 reactions involving them proceed with retention of configuration.

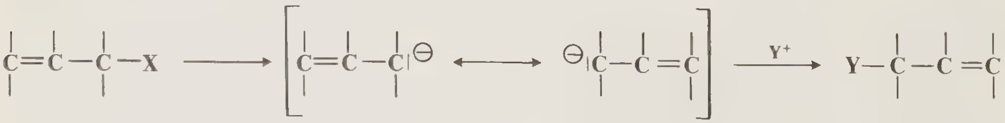
Electrophilic Substitution Accompanied by Double-Bond Shifts

When electrophilic substitution is carried out at an allylic substrate, the product may be rearranged:



$$-\overset{|}{C}=\overset{|}{C}-\underset{|}{\overset{|}{C}}-X + Y^+ \longrightarrow -\underset{\underset{Y}{|}}{\overset{|}{C}}-\overset{|}{C}=\underset{|}{\overset{|}{C}} + X^+$$

This type of process is analogous to the nucleophilic allylic shifts discussed in Chapter 10 (p. 303). There are two principal pathways. The first of these is analogous to the SE1 mechanism, in that the leaving group is first removed, giving a resonance-stabilized allyl type of carbanion, and then the electrophile attacks.



$$\underset{|}{\overset{|}{C}}=\overset{|}{C}-\underset{|}{\overset{|}{C}}-X \longrightarrow \left[\underset{|}{\overset{|}{C}}=\overset{|}{C}-\underset{|}{\overset{|}{C}}^{\ominus} \longleftrightarrow {}^{\ominus}\underset{|}{\overset{|}{C}}-\overset{|}{C}=\underset{|}{\overset{|}{C}}\right] \xrightarrow{Y^+} Y-\underset{|}{\overset{|}{C}}-\overset{|}{C}=\underset{|}{\overset{|}{C}}$$

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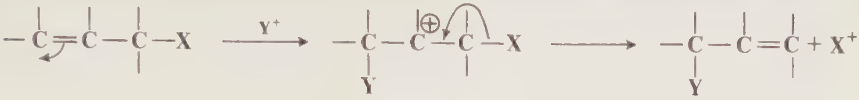
[25] Chu and Cram, *J. Am. Chem. Soc.* **94**, 3521 (1972); Almy, Hoffman, Chu, and Cram, *J. Am. Chem. Soc.* **95**, 1185 (1973).

[26] Ford, Graham, and Cram, *J. Am. Chem. Soc.* **89**, 4661 (1967).

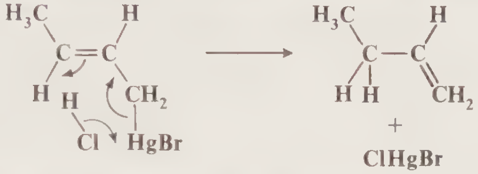
[27] Dreiding and Pratt, *J. Am. Chem. Soc.* **76**, 1902 (1954). See also Walborsky and Turner, *J. Am. Chem. Soc.* **94**, 2273 (1972).

In the other pathway the Y group first attacks, giving a carbonium ion, which then loses X.

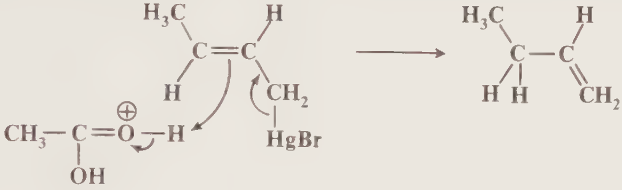


These mechanisms are more fully discussed under reaction **2-2.**

Most electrophilic allylic rearrangements involve hydrogen as the leaving group, but they have also been observed with metallic leaving groups.[28] Sleezer, Winstein, and Young found that crotylmercuric bromide reacted with HCl about 10^7 times faster than *n*-butylmercuric bromide, and the product was more than 99% 1-butene.[29] These facts point to an SEi′ mechanism:



The reaction of the same compound with acetic acid–perchloric acid seems to proceed by an SE2′ mechanism:[29]



Other Mechanisms

Elimination-addition (see reaction **2-1**), addition-elimination (reaction **2-15**), and cyclic mechanisms (reaction **2-39**) are also known.

Much less work has been done on electrophilic aliphatic substitution mechanisms than on nucleophilic substitutions, and the exact mechanisms of many of the reactions in this chapter are in doubt. For many of them, not enough work has been done to permit us to decide which of the mechanisms described in this chapter is operating, if indeed any is. There may be other electrophilic substitution mechanisms, and some of the reactions in this chapter may not even be electrophilic substitutions at all.

REACTIVITY

Only a small amount of work has been done in this area, in comparison to the vast amount done for aliphatic nucleophilic substitution and aromatic electrophilic substitution. Only a few conclusions, most of them sketchy or tentative, can be drawn.[30]

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[28] For a review of reactions of allylic organometallic compounds, see Courtois and Miginiac, *J. Organomet. Chem.* **69**, 1–44 (1974).

[29] Sleezer, Winstein, and Young, *J. Am. Chem. Soc.* **85**, 1890 (1963). See also Cunningham and Overton, *J. Chem. Soc., Perkin Trans. 1* 2140 (1975).

[30] For a discussion, see Abraham, Ref. 2, pp. 211–241.

1. *Effect of substrate.* For SE1 reactions electron-donating groups decrease rates and electron-withdrawing groups increase them. This is as would be expected from a reaction in which the rate-determining step is analogous to the cleavage of a proton from an acid. For the SE2 (back) mechanism, Jensen and Davis[8] showed that the reactivity of alkyl groups is similar to that for the SN2 mechanism (i.e., Me > Et > Pr > iso-Pr > neopentyl), as would be expected, since both involve backside attack and both are equally affected by steric hindrance. In fact, this pattern of reactivity can be regarded as evidence for the occurrence of the SE2 (back) mechanism in cases where stereochemical investigation is not feasible, since the other second-order mechanisms do not show this order. It has been proposed that the SE2 (front) mechanism also has a characteristic order: Me > Et > Pr > Bu > iso-Bu > neopentyl > iso-Pr.[31] Other rate orders reported for second-order mechanisms have shown great variability. For example, rate orders of vinyl > phenyl > Et > iso-Pr > Pr > Me,[32] of *t*-Bu > *sec*-Bu > Bu > vinyl > phenyl > Me,[33] and of *t*-Bu > Me > iso-Pr ~ Et > Pr ~ Bu[34] have been reported. Part of this variability may be caused by the presence of varying amounts of SE2 (front) and SEi processes, but it has been suggested that even where reactions are compared all of which have the SEi mechanism, no single reactivity series is possible.[35] Obviously, the SEi mechanism [and perhaps the SE2 (front) mechanism also] seems to be sensitive to relatively small changes in reaction conditions.

2. *Effect of leaving group.* For both SE1 and second-order mechanisms, the more polar the C—X bond, the easier it is for the electrofuge to cleave. For metallic leaving groups in which the metal has a valence greater than 1, the nature of the other group or groups attached to the metal thus has an effect on the reaction. For example, consider a series of organomercurials RHgW. Because a more electronegative W decreases the polarity of the C—Hg bond and furthermore results in a less stable HgW^+, the electrofugal ability of HgW decreases with increasing electronegativity of W. Thus, for example, HgR′ (from RHgR′) is a better leaving group than HgCl (from RHgCl). It might be expected that, when metals are the leaving groups, SE1 mechanisms would be favored, while with carbon leaving groups, second-order mechanisms would be found. However, the results so far reported have been just about the reverse of this. For carbon leaving groups the mechanism is usually SE1, while for metallic leaving groups the mechanism is almost always SE2 or SEi. A number of reports of SE1 reactions with metallic leaving groups have appeared,[36] but the mechanism is not easy to prove, and many of these reports have been challenged.[37] Reutov and coworkers[36] have expressed the view that in such reactions a nucleophile (which may be the solvent) must assist in the removal of the electrofuge and refer to such processes as SE1(*N*) reactions. For second-order mechanisms the leaving group may also help determine whether the SEi or one of the SE2 mechanisms takes place. The SEi mechanism is least likely in cases where the leaving group is unable to coordinate with the incoming group and where the leaving metal is not an exceedingly strong Lewis acid.[38]

3. *Effect of solvent.* In addition to the solvent effects on certain SE1 reactions, mentioned earlier (p. 526), solvents can influence the mechanism which is preferred. As with nucleophilic substitution (p. 331), an increase in solvent polarity increases the possibility of an ionizing mechanism, in this case SE1, in comparison with the second-order mechanisms, which do not involve ions. The solvent can also exert an influence as between the SE2 (front or back) and SEi mechanisms in at

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[31] Abraham and Grellier, *J. Chem. Soc., Perkin Trans. 2* 1132 (1973). See also Abraham, Grellier, and Hogarth, *J. Chem. Soc., Perkin Trans. 2* 1613 (1974).

[32] Dessy, Reynolds, and Kim, *J. Am. Chem. Soc.* **81,** 2683 (1959).

[33] Minato, Ware, and Traylor, *J. Am. Chem. Soc.* **85,** 3024 (1963).

[34] Boué, Gielen, and Nasielski, *J. Organomet. Chem.* **9,** 443 (1967).

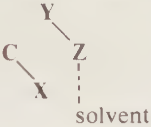
[35] Beletskaya, *Doklad. Chem.* **184,** 128 (1969); Beletskaya, Savinykh, and Reutov, *J. Organomet. Chem.* **26,** 13 (1971).

[36] For a review, see Beletskaya, Butin, and Reutov, *Organomet. Chem. Rev., Sect. A* **7,** 51–79 (1971).

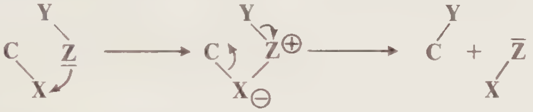
[37] For a discussion, see Kitching, *Rev. Pure Appl. Chem.* **19,** 1–16 (1969).

[38] Dodd, Johnson, and Winterton, *J. Chem. Soc. A* 910 (1971); Dodd, Johnson, and Vamplew, *J. Chem. Soc. B* 1841 (1971); Jensen, Madan, and Buchanan, Ref. 9.

least two ways. (1) As previously mentioned (p. 523), the rates of SE2 mechanisms should be increased by an increase in solvent polarity, while SEi mechanisms are much less affected. (2) We would predict that in polar solvents SE2 mechanisms should be further favored at the expense of SEi, since in these solvents Z would be solvated, leaving it less free to attack X:[39]



Results have been found in accord with this prediction, but since the conclusions are based on reactivity order in second-order reactions, we have seen (p. 530) that they must be taken with great caution. These results are as follows. It has been found that in polar solvents, such as methanol, acetic acid, or dimethylformamide, where SE2 mechanisms would be favored (as against SEi), the second-order rate constants for the reaction $R_4Sn + X_2 \rightarrow R_3SnX + RX$ were in the order Me > Et > Pr > iso-Pr.[40] As we have seen (p. 530), this sequence is compatible with the SE2 (back) mechanism. In less polar solvents, such as chlorobenzene or carbon tetrachloride, the order was Me < Et > Pr < iso-Pr. This order is ascribed to a combination of steric and field effects. Some reactions have been found which do not follow either sequence, but rather a strict polarity sequence: Me < Et, Pr < iso-Pr < *t*-Bu.[41] It has been suggested that in such cases the mechanism involves initial bond formation between the leaving group (before it becomes detached) and the electrophile, and a subsequent bond-breaking step



This process has been called the SEC[41] or SE2 (co-ord)[42] mechanism.

REACTIONS

The reactions in this chapter are arranged in order of leaving group: hydrogen, metals, halogen, and carbon. Electrophilic substitutions at a nitrogen atom are treated last. The following reactions, treated in other chapters, are also electrophilic substitutions with respect to the attacking molecule: **0-86** to **0-117**, **0-123**, **3-11** to **3-16**, **5-17** to **5-21**, and **6-31** to **6-56**.

Hydrogen as Leaving Group

A. Hydrogen as the Electrophile

2-1 Hydrogen Exchange

$$R{-}H + D^+ \rightleftharpoons R{-}D + H^+$$

Hydrogen exchange can be accomplished by treatment with acids or bases. As with reaction **1-1**, the exchange reaction is mostly used to study mechanistic questions such as relative acidities, but it can be used synthetically to prepare deuterated or tritiated molecules. When ordinary strong acids such as H_2SO_4 are used, only fairly acidic protons exchange, e.g., acetylenic, allylic, etc. However, primary, secondary, and tertiary hydrogens of alkanes can be exchanged by treatment with super-acids (p. 226).[43] The order of hydrogen reactivity is tertiary > secondary > primary. Where C—C bonds are present, these may be cleaved also (reaction **2-46**). The mechanism of the exchange (illustrated for methane) has been formulated as involving attack of H^+ on the

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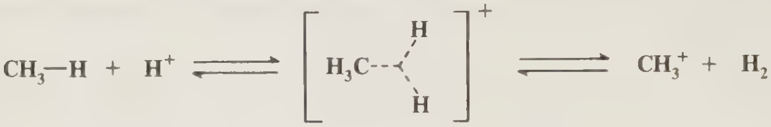
[39] Gielen and Nasielski, *Recl. Trav. Chim. Pays-Bas* **82**, 228 (1963).
[40] Gielen and Nasielski, *J. Organomet. Chem.* **1**, 173 (1963).
[41] Abraham and Hill, *J. Organomet. Chem.* **7**, 11 (1967).
[42] Abraham, Ref. 2, p. 15.



Methanonium ion

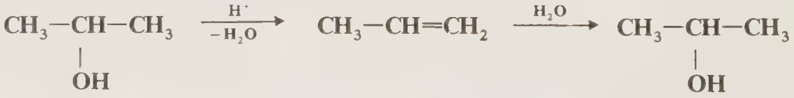
C—H bond to give the pentavalent methanonium ion which loses H_2 to give a carbonium ion. The three-center, two-electron bond is similar to that encountered in the 2-norbornyl cation (p. 297). It is not known whether the methanonium ion $CH_5{}^+$ is a transition state or a true intermediate, but an ion $CH_5{}^+$ has been detected in mass spectra.[44] Note that the two electrons in the three-center, two-electron bond can move in three directions, in accord with the threefold symmetry of such a structure. The electrons can move to unite the two hydrogens, leaving the $CH_3{}^+$ free (the forward reaction), or they can unite the CH_3 with either of the two hydrogens, leaving the other hydrogen as a free H^+ ion (the reverse reaction). Actually, the methyl cation is not stable under these conditions. It can go back to CH_4 by the route shown (leading to H^+ exchange), or it can react with additional CH_4 molecules (reaction **2-16**) to yield, eventually, the *t*-butyl cation, which is stable in these super-acid solutions. Hydride ion can also be removed from alkanes (producing carbonium ions) by treatment with pure SbF_5 in the absence of any source of H^+.[45] It has been proposed[45] that SbF_5 directly abstracts the hydride ion to give $R^+ \quad SbF_5H^-$.

Exchange with bases involves an SE1 mechanism (see p. 526).

Step 1 $\qquad RH + B^- \longrightarrow R^- + BH$

Step 2 $\qquad R^- + BD \longrightarrow RD + B^-$

Of course, such exchange is most successful for relatively acidic protons, such as those α to a carbonyl group,[46] but even weakly acidic protons can exchange with bases if the bases are strong enough (see p. 161). Still another mechanism has been found for the slow acid exchange of hydrogens β to an OH group (such as the methyl protons in 2-propanol). This is an elimination-addition mechanism in which the alcohol is first dehydrated (reaction **7-1**) and then water re-adds (reaction **5-2**).[47]



$$\underset{\displaystyle OH}{CH_3-\underset{|}{CH}-CH_3} \xrightarrow[-H_2O]{H^+} CH_3-CH{=}CH_2 \xrightarrow{H_2O} \underset{\displaystyle OH}{CH_3-\underset{|}{CH}-CH_3}$$

Alkanes and cycloalkanes, of both low and high molecular weight, can be fully perdeuterated by treatment with D_2 gas and a catalyst such as Rh, Pt, or Pd.[48]

OS **53**, 38.

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[43] Hogeveen and Bickel, *Chem. Commun.* 635 (1967), *Recl. Trav. Chim. Pays-Bas* **88**, 371 (1969); Hogeveen and Gaasbeek, *Recl. Trav. Chim. Pays-Bas* **87**, 319 (1968); Olah, Klopman, and Schlosberg, *J. Am. Chem. Soc.* **91**, 3261 (1969); Olah, Halpern, Shen, and Mo, *J. Am. Chem. Soc.* **95**, 4960 (1973). For reviews, see Olah, *Angew. Chem. Int. Ed. Engl.* **12**, 173–212 (1973) [*Angew. Chem.* **85**, 183–225]; *Chem. Technol.* **1**, 566–573 (1971); Brouwer and Hogeveen, *Prog. Phys. Org. Chem.* **9**, 179–240 (1972), pp. 180–203.

[44] See for example, Sefcik, Henis, and Gaspar, *J. Chem. Phys.* **61**, 4321 (1974).

[45] Lukas, Kramer, and Kouwenhoven, *Recl. Trav. Chim. Pays-Bas* **92**, 44 (1973).

[46] For example, see Caspar, Greff, and Wolff, *Bull. Soc. Chim. Fr.* 3033 (1968); Atkinson, Csakvary, Herbert, and Stuart, *J. Am. Chem. Soc.* **90**, 498 (1968).

[47] Gold and Satchell, *J. Chem. Soc.* 1930, 1937 (1963).

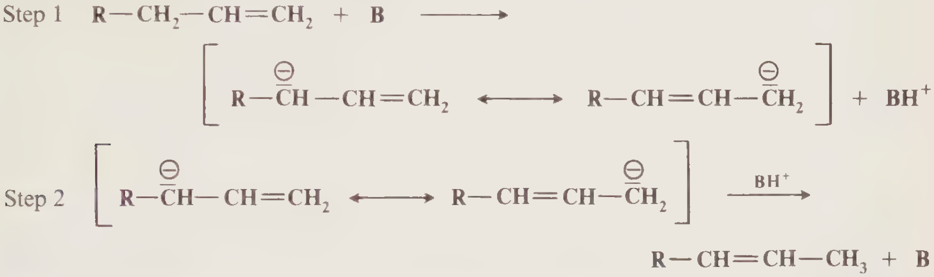
[48] See for example, Atkinson, Luke, and Stuart, *Can. J. Chem.* **45**, 1511 (1967).

2-2 Migration of Double Bonds

$$C_5H_{11}{-}CH_2{-}CH{=}CH_2 \xrightarrow[Me_2SO]{KNH_2} C_5H_{11}{-}CH{=}CH{-}CH_3$$

The double bonds of many unsaturated compounds are shifted on treatment with strong bases.[49] In many cases equilibrium mixtures are obtained, and the most thermodynamically stable isomer predominates. Thus, if the new double bond can be in conjugation with one already present or with an aromatic ring, it goes that way. If the choice is between an exocyclic and an endocyclic double bond (in a six-membered ring), it chooses the latter. In the absence of considerations like these, Zaitsev's rule (p. 910) applies, and the double bond goes to the carbon with the fewest hydrogens. All these considerations lead us to predict that terminal olefins can be isomerized to internal ones, nonconjugated olefins to conjugated, exo six-membered-ring olefins to endo, etc., and not the other way around. This is indeed usually the case.

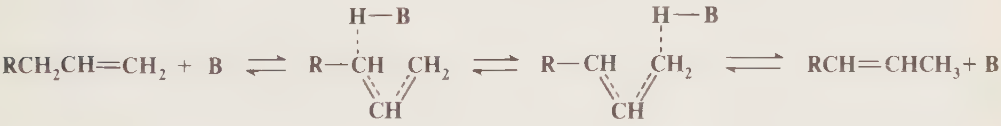
This reaction, for which the term *prototropic rearrangement* is often used, is an example of electrophilic substitution with an accompanying allylic rearrangement. The mechanism involves abstraction by the base to give a resonance-stabilized carbanion, which then combines with a proton at the position which will give the more stable olefin:



$$\text{Step 1}\quad R{-}CH_2{-}CH{=}CH_2 + B \longrightarrow \left[R{-}\overset{\ominus}{C}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{C}H_2\right] + BH^+$$

$$\text{Step 2}\quad \left[R{-}\overset{\ominus}{C}H{-}CH{=}CH_2 \longleftrightarrow R{-}CH{=}CH{-}\overset{\ominus}{C}H_2\right] \xrightarrow{BH^+} R{-}CH{=}CH{-}CH_3 + B$$

This mechanism is exactly analogous to the allylic-shift mechanism for nucleophilic substitution, discussed in Chapter 10 (p. 303). Uv spectra of allylbenzene and 1-propenylbenzene in solutions containing NH_2^- are identical, showing that the same carbanion is present in both cases, as required by this mechanism.[50] It has been shown that base-catalyzed double-bond shifts are partially intramolecular, at least in some cases.[51] The intramolecularity has been ascribed to a conducted tour mechanism (p. 527) in which the base leads the proton from one carbanionic site to the other:[52]



10 11 12 13

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[49] For reviews of double-bond migrations, see DeWolfe, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 437–449, American Elsevier Publishing Company, New York, 1973; Yanovskaya and Shakhidayatov, *Russ. Chem. Rev.* **39,** 859–874 (1970); Hubert and Reimlinger, *Synthesis* 97–112 (1969), 405–430 (1970); Mackenzie, in "The Chemistry of Alkenes," vol. 1, [Patai (ed.)], pp. 416–436, vol. 2 [Zabicky (ed.)], pp. 132–148, Interscience Publishers, New York, 1964, 1970; Broaddus, *Acc. Chem. Res.* **1,** 231–238 (1968); Cram, Ref. 22, pp. 175–210.

[50] Rabinovich, Astaf'ev, and Shatenshtein, *J. Gen. Chem. USSR* **32,** 746 (1962).

[51] See, for example, Cram and Uyeda, *J. Am. Chem. Soc.* **86,** 5466 (1964); Bank, Rowe, and Schriesheim, *J. Am. Chem. Soc.* **85,** 2115 (1963); Doering and Gaspar, *J. Am. Chem. Soc.* **85,** 3043 (1963); Bergson, *Acta Chem. Scand.* **17,** 2691 (1963); Bergson and Ohlsson, *Acta Chem. Scand.* **21,** 1393 (1967); Ohlsson, Wold, and Bergson, *Ark. Kemi* **29,** 351 (1968).

[52] Almy and Cram, *J. Am. Chem. Soc.* **91,** 4459 (1969).

The complete process shown (**10** → **11** → **12** → **13**) leads to isomerization without the introduction of external hydrogen. However, with certain substrates and under certain conditions, **11** or **12** may exchange BH^+ with a molecule from the environment, in which case the rearrangement is intermolecular. It has been suggested that the more stable the carbanion, the greater the intramolecular character of the reaction.[53]

Triple bonds may also migrate in the presence of bases, but through the allene intermediate:[54]

$$R{-}CH_2{-}C{\equiv}CH \rightleftharpoons R{-}CH{=}C{=}CH_2 \rightleftharpoons R{-}C{\equiv}C{-}CH_3$$

In general, strong bases such as $NaNH_2$ convert internal alkynes to terminal alkynes (a particularly good base for this purpose is potassium 3-aminopropylamide $NH_2CH_2CH_2CH_2NHK$[55]), because the equilibrium is shifted by formation of the acetylide ion; while with weaker bases such as NaOH (which are not strong enough to remove the acetylenic proton), the internal alkynes are favored because of their greater thermodynamic stability. In some cases the reaction can be stopped at the allene stage, and the reaction then becomes a method for the preparation of allenes.[56]

Double-bond rearrangements can also take place on treatment with acids. Both proton and Lewis acids can be used. The mechanism in the case of proton acids is the reverse of the previous one; first a proton is gained, giving a carbonium ion; and then another is lost:

$$\text{Step 1} \quad CH_3{-}CH_2{-}CH{=}CH_2 + H^+ \longrightarrow CH_3{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3$$

$$\text{Step 2} \quad CH_3{-}CH_2{-}\overset{\oplus}{C}H{-}CH_3 \longrightarrow CH_3{-}CH{=}CH{-}CH_3 + H^+$$

As in the case of the base-catalyzed reaction, the thermodynamically most stable olefin is the one predominantly formed. However, the acid-catalyzed reaction is much less synthetically useful because carbonium ions give rise to many side products. If the substrate has several possible locations for a double bond, mixtures of all possible isomers are usually obtained. Isomerization of 1-decene, for example, gives a mixture which contains not only 1-decene and *cis-* and *trans-*2-decene, but also the cis and trans isomers of 3-, 4-, and 5-decene, as well as branched alkenes resulting from rearrangement of carbonium ions. It is true that the most stable olefins predominate, but many of them have stabilities which are close together. Acid-catalyzed migration of triple bonds (with allene intermediates) can be accomplished if very strong acids (e.g., $HF{-}PF_5$) are used.[57] If the mechanism is the same as that for double bonds, then vinyl cations are intermediates.

Double-bond isomerization may also take place in other ways. Nucleophilic allylic rearrangements were discussed in Chapter 10 (p. 303). Electrocyclic and sigmatropic rearrangements are treated at reactions **8-32** to **8-40.** Isomerization of double bonds with HBr or I_2 and uv light is a free-radical process:[58]

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[53] Figuera, Gamboa, and Santos, *J. Chem. Soc., Perkin Trans. 2* 1434 (1972).

[54] For reviews, see Bushby, *Q. Rev., Chem. Soc.* **24,** 585–600 (1970); Iwai, *Mech. Mol. Migr.* **2,** 73–116 (1969); Wotiz, in Viehe, "Acetylenes," pp. 365–424, Marcel Dekker, Inc., New York, 1969; Vartanyan and Babanyan, *Russ. Chem. Rev.* **36,** 670 (1967). See also Carr, Gan, and Reid, *J. Chem. Soc., Perkin Trans. 2* 668, 672 (1973).

[55] Brown and Yamashita, *J. Am. Chem. Soc.* **97,** 891 (1975).

[56] For a review of allenes, see Mavrov and Kucherov, *Russ. Chem. Rev.* **36,** 233–249 (1967).

[57] Barry, Beale, Carr, Hei, and Reid, *J. Chem. Soc., Chem. Commun.* 177 (1973).

[58] Golden, Egger, and Benson, *J. Am. Chem. Soc.* **86,** 5416 (1964); Egger, Golden, and Benson, *J. Am. Chem. Soc.* **86,** 5420 (1964); Maccoll and Ross, *J. Am. Chem. Soc.* **87,** 1169 (1965); Abell, *Trans. Faraday Soc.* **60,** 2214 (1964), *J. Am. Chem. Soc.* **88,** 1346 (1966); Gale, *J. Am. Chem. Soc.* **88,** 4661 (1966).

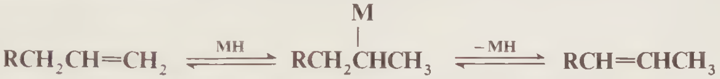
$$HBr \xrightarrow{h\nu} Br\cdot + H\cdot$$

$$CH_3CH_2CH{=}CH_2 + Br\cdot \longrightarrow$$

$$[CH_3{-}\dot{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3{-}CH{=}CH{-}\dot{C}H_2] + HBr$$

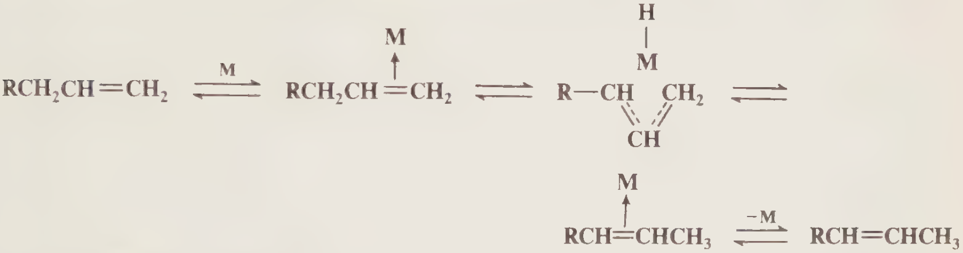
$$CH_3CH{=}CH\dot{C}H_2 + HBr \longrightarrow CH_3CH{=}CHCH_3 + Br\cdot$$

Olefins may also be isomerized on pyrolysis at, say, 400 to 500°C. Carbonium ions are presumably involved. Double-bond migrations have also been accomplished photochemically,[59] and by means of metallic ion or metal carbonyl catalysts.[60] In the latter case there are at least two possible mechanisms. One of these, which requires external hydrogen, is called the *metal hydride addition-elimination mechanism*:



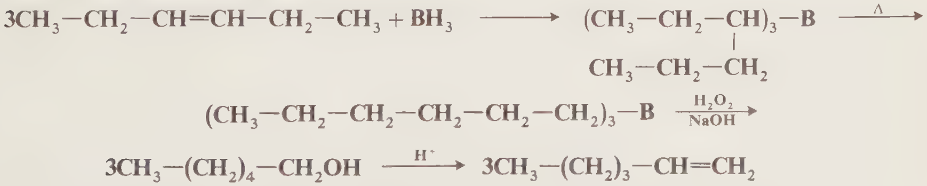
$$RCH_2CH{=}CH_2 \xrightleftharpoons{MH} RCH_2\overset{\displaystyle M}{\overset{|}{C}}HCH_3 \xrightleftharpoons{-MH} RCH{=}CHCH_3$$

The other mechanism, called the *π-allyl complex mechanism*, does not require external hydrogen:



Another difference between the two mechanisms is that the former involves 1,2 and the latter 1,3 shifts. The isomerization of 1-butene by rhodium(I) is an example of a reaction which takes place by the metal hydride mechanism,[61] while an example of the π-allyl complex mechanism is found in the $Fe_3(CO)_{12}$-catalyzed isomerization of 3-ethyl-1-pentene.[62]

No matter which of the electrophilic methods of double-bond shifting is employed, the thermodynamically most stable olefin is usually formed in the largest amount in most cases, though a few anomalies are known. However, there is another, indirect, method of double-bond isomerization, by means of which migration in the other direction can often be carried out. This involves conversion of the olefin to a borane (reaction **5-15**), rearrangement of the borane (reaction **8-14**), oxidation and hydrolysis of the newly formed borane to the alcohol (reaction **2-26**), and dehydration of the alcohol (reaction **7-1**):



$$3CH_3{-}CH_2{-}CH{=}CH{-}CH_2{-}CH_3 + BH_3 \longrightarrow (CH_3{-}CH_2{-}\underset{\displaystyle CH_3{-}CH_2{-}CH_2}{\underset{|}{C}H})_3{-}B \xrightarrow{\Delta}$$

$$(CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2)_3{-}B \xrightarrow[NaOH]{H_2O_2}$$

$$3CH_3{-}(CH_2)_4{-}CH_2OH \xrightarrow{H^+} 3CH_3{-}(CH_2)_3{-}CH{=}CH_2$$

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[59] Schönberg, "Preparative Organic Photochemistry," pp. 22–24, Springer-Verlag, New York, 1968.

[60] For reviews, see Khan and Martell, "Homogeneous Catalysis by Metal Complexes," pp. 9–37, Academic Press, Inc., New York, 1974; Heck, "Organotransition Metal Chemistry," pp. 76–82, Academic Press, Inc., New York, 1974; Jira and Freiesleben, *Organomet. React.* **3**, 1–190 (1972), pp. 133–149; Biellmann, Hemmer, and Levisalles, in Zabicky, Ref. 49, vol. 2, pp. 224–230; Bird, "Transition Metal Intermediates in Organic Synthesis," pp. 69–87, Academic Press, Inc., New York, 1967; Davies, *Rev. Pure Appl. Chem.* **17**, 83–93 (1967); Orchin, *Adv. Catal.* **16**, 1–47 (1966).

[61] Cramer, *J. Am. Chem. Soc.* **88**, 2272 (1966).

[62] Casey and Cyr, *J. Am. Chem. Soc.* **95**, 2248 (1973).

Since the migration reaction is always toward the end of a chain, terminal olefins may be produced from internal ones, so that the migration is often opposite to that with the other methods. Alternatively, the rearranged borane may be converted directly to the olefin by heating with an alkene of molecular weight higher than that of the product (reaction **7-15**). Photochemical isomerization can also lead to the thermodynamically less stable isomer.[63]

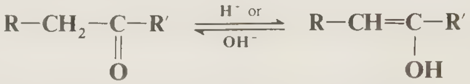
If a hydroxy group is present in the chain, *it* may lose a proton, so that a ketone is the product. For example,[64]

$$R_2C{=}CHCH_2CH_2CHOHCH_3 \xrightarrow[\text{acid}]{\text{polyphosphoric}} R_2CHCH_2CH_2CH_2COCH_3$$

Similarly, α-hydroxy triple-bond compounds have given α,β-unsaturated ketones.

OS **II,** 140; **III,** 207; **IV,** 189, 192, 195, 234, 398, 683; **50,** 97; **51,** 17; **54,** 1; **55,** 12.

2-3 Keto-Enol Tautomerization

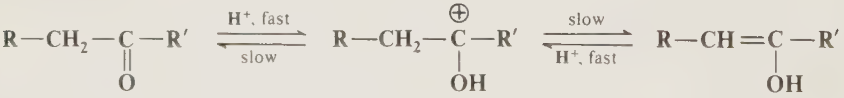


$$R-CH_2-\underset{\underset{O}{\|}}{C}-R' \underset{OH^-}{\overset{H^+\text{ or}}{\rightleftharpoons}} R-CH=\underset{\underset{OH}{|}}{C}-R'$$

The tautomeric equilibrium between enols and ketones or aldehydes is not normally a preparative reaction, though for some ketones both forms can be prepared (see p. 71 for a discussion of this and other aspects of tautomerism). For most ketones and aldehydes, only the keto form is detectable, though the equilibrium must occur, since aldehydes and ketones often react through their enol forms.

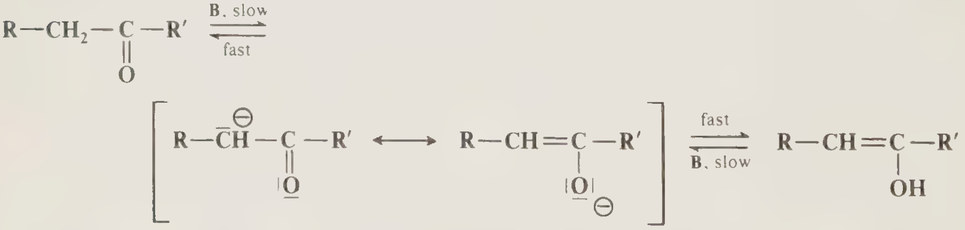
Neither the forward nor the reverse reaction can take place without at least a trace of acid or base, ruling out a direct shift of a hydrogen from carbon to oxygen, or vice versa. The mechanisms are identical to those in reaction **2-2**:[65]

Acid-catalyzed



$$R-CH_2-\underset{\underset{O}{\|}}{C}-R' \underset{\text{slow}}{\overset{H^+\text{, fast}}{\rightleftharpoons}} R-CH_2-\overset{\oplus}{\underset{\underset{OH}{|}}{C}}-R' \underset{H^+\text{, fast}}{\overset{\text{slow}}{\rightleftharpoons}} R-CH=\underset{\underset{OH}{|}}{C}-R'$$

Base-catalyzed



$$R-CH_2-\underset{\underset{O}{\|}}{C}-R' \underset{\text{fast}}{\overset{B\text{, slow}}{\rightleftharpoons}} \left[R-\overset{\ominus}{\overline{C}H}-\underset{\underset{|\underline{O}}{\|}}{C}-R' \longleftrightarrow R-CH=\underset{\underset{|\underline{O}|^{\ominus}}{|}}{C}-R'\right] \underset{B\text{, slow}}{\overset{\text{fast}}{\rightleftharpoons}} R-CH=\underset{\underset{OH}{|}}{C}-R'$$

14

For each catalyst, the mechanism for one direction is the exact reverse of the other, by the principle of microscopic reversibility. As expected from mechanisms in which the C—H bond is broken in the rate-determining step, substrates of the type RCD_2COR show deuterium isotope effects (of about 5) in both the basic-[66] and the acid[67]-catalyzed processes.

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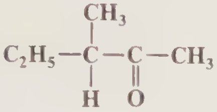
[63] For example, see Kropp and Krauss, *J. Am. Chem. Soc.* **89,** 5199 (1967); Rando and Doering, *J. Org. Chem.* **33,** 1671 (1968); Barltrop and Wills, *Tetrahedron Lett.* 4987 (1968); Jorgenson and Gundel, *Tetrahedron Lett.* 4991 (1968); Reardon and Krauss, *J. Am. Chem. Soc.* **93,** 5593 (1971).

[64] Colonge and Brunie, *Bull. Soc. Chim. Fr.* 1799 (1963).

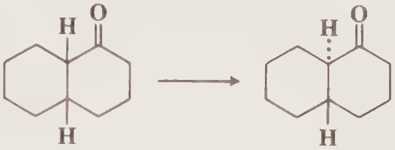
[65] For discussions of the mechanism, see Ingold, "Structure and Mechanism in Organic Chemistry," 2d ed., pp. 794–837, Cornell University Press, Ithaca, N.Y., 1969; Bell, "The Proton in Chemistry," 2d ed., pp. 171–181, Cornell University Press, Ithaca, N.Y., 1973; Bruice and Bruice, *J. Am. Chem. Soc.* **98,** 844 (1976).

Although the conversion of an aldehyde or a ketone to its enol tautomer is not generally a preparative procedure, the reactions do have their preparative aspects. If a full mole of base per mole of ketone is used, then the enolate ion (**14**) is formed and can be isolated. When enol ethers or esters are hydrolyzed, the enols initially formed immediately tautomerize to the aldehydes or ketones. In addition, the overall processes (forward plus reverse reactions) are often used for equilibration purposes. When an optically active compound in which the chirality is due to an asymmetric carbon α to a carbonyl group (as in **15**) is treated with acid or base, racemization results. If there is another asymmetric center in the molecule, the less stable epimer may be converted to the more stable one in this manner, and this is often done. For example, *cis*-decalone (**16**) may be equilibrated to the trans isomer. Isotopic exchange may also be accomplished at the α-position of an aldehyde or ketone in a similar manner. For the acid-catalyzed process, exchange or equilibration is accomplished only if the carbonyl compound is completely converted to the enol and then back, but in the base-catalyzed process exchange or equilibration can take place if only the first step (conversion to the enolate ion) takes place. The difference is usually academic.



$$C_2H_5-\underset{H}{\overset{CH_3}{C}}-\underset{O}{\underset{\|}{C}}-CH_3$$

15



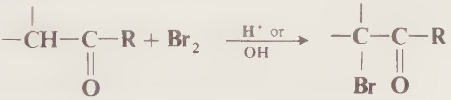
16

Enolizable hydrogens may be replaced by deuterium (and ^{16}O by ^{18}O) by passage of a sample through a deuterated (or ^{18}O-containing) gas-chromatography column.[68]

There are many enol-keto interconversions and acidifications of enolate ions to the keto forms listed in *Organic Syntheses*. No attempt is made to list them here.

B. Halogen Electrophiles

2-4 Halogenation of Aldehydes and Ketones



$$-\overset{|}{CH}-\underset{O}{\underset{\|}{C}}-R + Br_2 \xrightarrow[OH]{H^+\text{ or}} -\underset{Br}{\underset{|}{\overset{|}{C}}}-\underset{O}{\underset{\|}{C}}-R$$

Aldehydes and ketones may be halogenated in the α-position with bromine, chlorine, or iodine.[69] The reaction cannot be performed with fluorine, but active compounds, such as β-keto esters, have been fluorinated by treating the enolate ion with perchloryl fluoride ($FClO_3$).[70] However, if the

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[66] Riley and Long, *J. Am. Chem. Soc.* **84**, 522 (1962).

[67] Swain, Stivers, Reuwer, and Schaad, *J. Am. Chem. Soc.* **80**, 5885 (1958); Lienhard and Wang, *J. Am. Chem. Soc.* **91**, 1146 (1969). See also Toullec and Dubois, *J. Am. Chem. Soc.* **96**, 3524 (1974).

[68] Senn, Richter, and Burlingame, *J. Am. Chem. Soc.* **87**, 680 (1965); Richter, Senn, and Burlingame, *Tetrahedron Lett.* 1235 (1965).

[69] For a review, see House, "Modern Synthetic Reactions," 2d ed., pp. 459–478, W. A. Benjamin, Inc., New York, 1972.

[70] Inman, Oesterling, and Tyczkowski, *J. Am. Chem. Soc.* **80**, 6533 (1958); Machleidt, *Justus Liebigs Ann. Chem.* **667**, 24 (1963); Machleidt and Hartmann, *Justus Liebigs Ann. Chem.* **679**, 9 (1964); Kamlet and Adolph, *J. Org. Chem.* **33**, 3073 (1968); Sheppard, *Tetrahedron Lett.* 83 (1969). For reviews of perchloryl fluoride, see Sharts and Sheppard, *Org. React.* **21**, 125–406 (1974), pp. 225–236; Sheppard and Sharts, "Organic Fluorine Chemistry," pp. 136–148, W. A. Benjamin, Inc., New York, 1969; Khutoretskii, Okhlobystina, and Fainzil'berg, *Russ. Chem. Rev.* **36**, 145–155 (1967).

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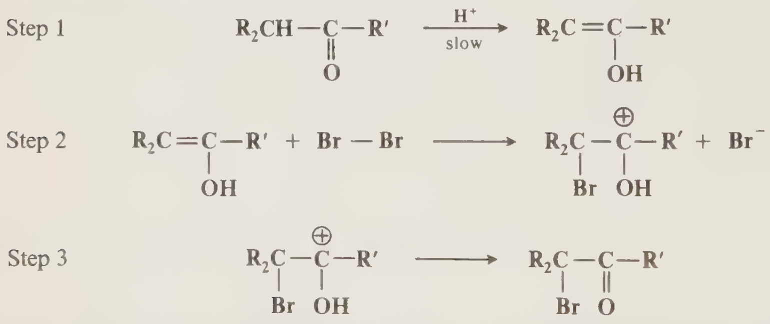
carbon attacked with $FClO_3$ has two hydrogens, then the reaction cannot be stopped until two fluorines have entered. Monofluorination can be accomplished indirectly, by treating an enamine, enol ether, or similar ketone derivative with $FClO_3$.[71] Trifluoromethyl hypofluorite CF_3OF and similar compounds behave similarly.[72] Sulfuryl chloride[73] and cupric chloride[74] have been used as reagents for chlorination, and N-bromosuccinimide for bromination (see reaction **4-2**). Pyrrolidone hydrotribromide is a reagent which can α-brominate a ketone without affecting a double bond also present.[75]

For unsymmetrical ketones the preferred position of halogenation is usually a CH group, then a CH_2 group, and then CH_3; however, mixtures are frequent. With aldehydes the aldehydic hydrogen is sometimes replaced (see reaction **4-3**). It is also possible to prepare di- and polyhalides. When basic catalysts are used, one α-position of a ketone is completely halogenated before the other is attacked, and the reaction cannot be stopped until all the hydrogens of the first carbon have been replaced (see below). If one of the groups is methyl, then the haloform reaction (**2-43**) takes place. With acid catalysts, it is easy to stop the reaction after only one halogen has entered, though a second halogen can be introduced by the use of excess reagent. In chlorination the second halogen generally appears on the same side as the first,[76] while in bromination the α,α′-dibromo product is found.[77] Actually, with both halogens it is the α,α-dihalo ketone which is formed first, but in the case of bromination this compound isomerizes under the reaction conditions to the α,α′ isomer.[76] Sometimes acetals and ketals are brominated directly.

It is not the aldehyde or ketone itself which is halogenated, but the corresponding enol or enolate ion. The purpose of the catalyst is to provide a small amount of enol or enolate. The reaction is often done without addition of acid or base, and even in the vapor state,[78] but traces of acid or base are always present, and these are enough to catalyze formation of the enol or enolate. With acid catalysis the mechanism is



Step 1 $$R_2CH-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[\text{slow}]{H^+} R_2C{=}\underset{\underset{OH}{|}}{C}-R'$$

Step 2 $$R_2C{=}\underset{\underset{OH}{|}}{C}-R' + Br-Br \longrightarrow R_2\underset{\underset{Br}{|}}{C}-\overset{\oplus}{\underset{\underset{OH}{|}}{C}}-R' + Br^-$$

Step 3 $$R_2\underset{\underset{Br}{|}}{C}-\overset{\oplus}{\underset{\underset{OH}{|}}{C}}-R' \longrightarrow R_2\underset{\underset{Br}{|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

The first step, as we have already seen (reaction **2-3**), actually consists of two steps. The second step is very similar to the first step in electrophilic addition to double bonds (p. 672). There is a great deal of evidence for this mechanism: (1) the rate is first order in substrate; (2) the bromine does not appear in the rate expression at all, a fact consistent with a rate-determining first step,[79] (3) the rate of the reaction is the same for bromination, chlorination, and iodination under the same conditions;[80] and (4) the reaction shows an isotope effect. With basic catalysts the mechanism may be the same as that given above (since bases also catalyze formation of the enol), or the reaction may go directly through the enolate ion without formation of the enol:[81]

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[71] For example, see Gabbard and Jensen, *J. Org. Chem.* **23**, 1406 (1958); Nakanishi, Morita, and Jensen, *J. Am. Chem. Soc.* **81**, 5259 (1959); Nakanishi and Jensen, *J. Org. Chem.* **27**, 702 (1962).

[72] Barton, Godinho, Hesse, and Pechet, *Chem. Commun.* 804 (1968); Barton, *Pure Appl. Chem.* **21**, 285–293 (1970). See also Sharts and Sheppard, Ref. 70, pp. 243–256.

[73] Wyman and Kaufman, *J. Org. Chem.* **29**, 1956 (1964).

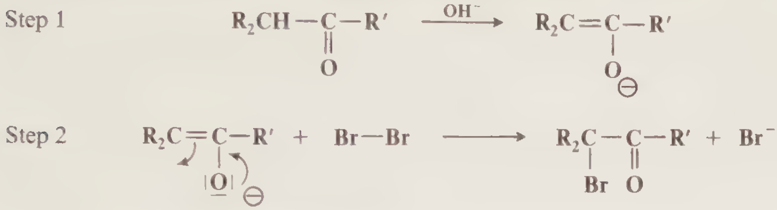
[74] For a review, see Nigh, in Trahanovsky, "Oxidation in Organic Chemistry," pt. B, pp. 67–81, Academic Press, Inc., New York, 1973. Cupric chloride has been used to chlorinate α,β-unsaturated aldehydes and ketones in the γ position: Dietl, Normark, Payne, Thweatt, and Young, *Tetrahedron Lett.* 1719 (1973).

[75] Awang and Wolfe, *Can. J. Chem.* **47**, 706 (1969).

[76] Rappe, *Ark. Kemi* **24**, 321 (1965). But see also Teo and Warnhoff, *J. Am. Chem. Soc.* **95**, 2728 (1973).

[77] Rappe and Schotte, *Acta Chem. Scand.* **16**, 2060 (1962); Rappe, *Acta Chem. Scand.* **16**, 2467 (1962), *Ark. Kemi* **21**, 503 (1964); Garbisch, *J. Org. Chem.* **30**, 2109 (1965).

[78] Dick, *J. Org. Chem.* **27**, 272 (1962).

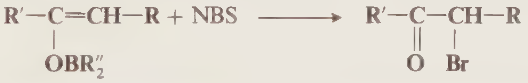


Step 1 $$R_2CH-\underset{\underset{\displaystyle O}{\|}}{C}-R' \xrightarrow{OH^-} R_2C=\underset{\underset{\displaystyle O^{\ominus}}{|}}{C}-R'$$

Step 2 $$R_2C=\underset{\underset{\displaystyle \overline{|O|}^{\ominus}}{|}}{C}-R' + Br-Br \longrightarrow R_2\underset{\underset{\displaystyle Br}{|}}{C}-\underset{\underset{\displaystyle O}{\|}}{C}-R' + Br^-$$

It is difficult to distinguish the two possibilities. It was mentioned above that in the base-catalyzed reaction, if the substrate has two or three α-halogens on the same side of the C=O group, then it is not possible to stop the reaction after just one halogen atom has entered. The reason for this is that the electron-withdrawing field effect of the first halogen increases the acidity of the remaining hydrogens: that is, a CHX group is more acidic than a CH_2 group, so that initially formed halo ketone is converted to enolate ion (and hence halogenated) more rapidly than the original substrate. It has been reported that the halogen atom also increases the acidity of hydrogens in the α′ position, but generally to a lesser degree,[82] though it can be to a greater degree in cases where the approach of the base is sterically hindered.[83]

Regiospecificity in the halogenation of unsymmetrical ketones can be attained by treatment of the appropriate enol borinate of the ketone with N-bromo- or N-chlorosuccinimide.[84]



$$R'-\underset{\underset{\displaystyle OBR''_2}{|}}{C}=CH-R + NBS \longrightarrow R'-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle Br}{|}}{CH}-R$$

The desired halo ketone is formed in high yield. In no case was the unwanted isomer found. Another method for achieving the same result involves bromination of the appropriate lithium enolate at a low temperature[85] (see p. 424 for the regiospecific formation of enolate ions). In a similar process, α-bromo and α-chloro aldehydes have been prepared in good yield by treatment of trimethylsilyl enol ethers $R_2C=CHOSiMe_3$ with Br_2 or Cl_2.[86]

OS **I,** 127; **II,** 87, 88, 244, 480; **III,** 188, 343, 538; **IV,** 110, 162, 590; **V,** 514; **52,** 33; **53,** 111, 123; **54,** 97; **55,** 24.

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[79] Under some conditions it is possible for step 2 to be rate-determining: Deno and Fishbein, *J. Am. Chem. Soc.* **95,** 7445 (1973).

[80] Bell and Yates, *J. Chem. Soc.* 1927 (1962).

[81] It has been suggested that base-catalyzed halogenation may also take place by a mechanism which does not go through either enol or enolate [Rappe, *Acta Chem. Scand.* **20,** 1721 (1966), **21,** 857, 1823 (1967), **22,** 219 (1968)], but evidence against this view has been presented: Swain and Dunlap, *J. Am. Chem. Soc.* **94,** 7204 (1972); Thorpe and Warkentin, *Can. J. Chem.* **50,** 3229 (1972); Cox and Warkentin, *Can. J. Chem.* **50,** 3233 (1972); Cox, Thorpe, and Warkentin, *Can. J. Chem.* **50,** 3239 (1972); Knipe and Cox, *J. Org. Chem.* **38,** 3429 (1973), *J. Chem. Soc., Perkin Trans. 2* 1391 (1973).

[82] Cox and Warkentin, *Can. J. Chem.* **50,** 3242 (1972).

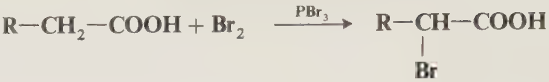
[83] Sachs, *Acta Chem. Scand.* **25,** 2643 (1971); Ref. 82.

[84] Hooz and Bridson, *Can. J. Chem.* **50,** 2387 (1972).

[85] Stotter and Hill, *J. Org. Chem.* **38,** 2576 (1973).

[86] Reuss and Hassner, *J. Org. Chem.* **39,** 1785 (1974).

2-5 Halogenation of Acids and Acyl Halides



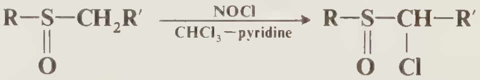
$$R{-}CH_2{-}COOH + Br_2 \xrightarrow{PBr_3} R{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}COOH$$

The α-hydrogens of carboxylic acids may be replaced by bromine or chlorine.[87] The reaction, known as the *Hell-Volhard-Zelinskii reaction*, is not applicable to iodine or fluorine. When there are two α-hydrogens, one or both may be replaced, although it is often hard to stop with just one. The reaction actually takes place on the acyl halide formed from the acid and the catalyst. Acids alone are inactive, except for those with relatively high enol content, such as malonic. Less than one full mole of catalyst (per mole of substrate) is required, because of the exchange reaction between acids and acyl halides (see reaction **0-75**). Each molecule of acid is α-halogenated while it is in the acyl halide stage. The halogen from the catalyst does not enter the α position. For example, the use of Cl_2 and PBr_3 results in α chlorination, not bromination. As expected from the foregoing, acyl halides undergo α halogenation without a catalyst. So do anhydrides and many compounds which enolize easily, e.g., malonic ester, aliphatic nitro compounds, etc. The mechanism is usually regarded as proceeding through the enol as in reaction **2-4.**[88]

A number of other methods exist for the α halogenation of acids or of their derivatives. Carboxylic acids or their chlorides or anhydrides can be α-chlorinated by treatment with $CuCl_2$ in polar inert solvents (e.g., sulfolane).[89] Acyl halides can be α-brominated or α-chlorinated by use of N-bromo- or N-chlorosuccinimide and HBr or HCl.[90] The latter is an ionic and not a free-radical halogenation (see reaction **4-2**). Acyl chlorides can be α-iodinated with I_2 and a trace of HI.[90] Esters can be α-iodinated by conversion to their enolate ions with lithium N-isopropylcyclohexylamide in tetrahyrofuran and addition of this solution at −78°C to a solution of I_2 in tetrahydrofuran.[91]

OS **I,** 115, 245; **II,** 74, 93; **III,** 347, 381, 495, 523, 623, 705, 848; **IV,** 254, 348, 398, 608, 616; **V,** 255; **50,** 31; **55,** 27. Also see OS **IV,** 877.

2-6 Halogenation of Sulfoxides and Sulfones



$$R{-}\underset{\displaystyle O}{\underset{\|}{S}}{-}CH_2R' \xrightarrow[CHCl_3-\text{pyridine}]{NOCl} R{-}\underset{\displaystyle O}{\underset{\|}{S}}{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}R'$$

Sulfoxides can be chlorinated in the α position[92] by treatment with NOCl,[93] Cl_2,[94] TsCl,[95] or $PhICl_2$,[96] all in the presence of pyridine, or with N-chlorosuccinimide and K_2CO_3,[97] or *t*-BuOCl and KOAc (or pyridine).[98] All these methods involve basic conditions. The reaction can also be accomplished in the absence of base with SO_2Cl_2 in CH_2Cl_2.[99] The bromination of sulfoxides with bromine[96] and with N-bromosuccinimide-bromine[100] have also been reported. Sulfones have been chlorinated by treatment of their conjugate bases $RSO_2\overset{\ominus}{\bar{C}}HR'$ with various reagents, among them SO_2Cl_2, N-chlorosuccinimide,[101] and hexachloroethane.[102]

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[87] For reviews, see Harwood, *Chem. Rev.* **62,** 99–154 (1962), pp. 102–103; Sonntag, *Chem. Rev.* **52,** 237–416 (1953), pp. 358–364.

[88] But see, however, Kwart and Scalzi, *J. Am. Chem. Soc.* **86,** 5496 (1964).

[89] Louw, *Chem. Commun.* 544 (1966).

[90] Gleason and Harpp, *Tetrahedron Lett.* 3431 (1970); Harpp, Bao, Black, Gleason, and Smith, *J. Org. Chem.* **40,** 3420 (1975).

[91] Rathke and Lindert, *Tetrahedron Lett.* 3995 (1971).

[92] For a review, see Venier and Barager, *Org. Prep. Proced. Int.* **6,** 77–102 (1974), pp. 81–84.

[93] Leoppky and Chang, *Tetrahedron Lett.* 5415 (1968).

[94] Tsuchihashi and Iriuchijima, *Bull. Chem. Soc. Jpn.* **43,** 2271 (1970).

[95] Hojo and Yoshida, *J. Am. Chem. Soc.* **90,** 4496 (1968).

[96] Cinquini and Colonna, *J. Chem. Soc., Perkin Trans. 1* 1883 (1972). See also Cinquini and Colonna, *Synthesis* 259 (1972).

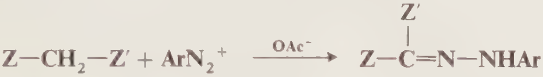
[97] Tsuchihashi and Ogura, *Bull. Chem. Soc. Jpn.* **44,** 1726 (1971).

[98] Iriuchijima and Tsuchihashi, *Tetrahedron Lett.* 5259 (1969).

[99] Tin and Durst, *Tetrahedron Lett.* 4643 (1970).

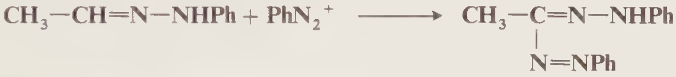
C. Nitrogen Electrophiles

2-7 Aliphatic Diazonium Coupling



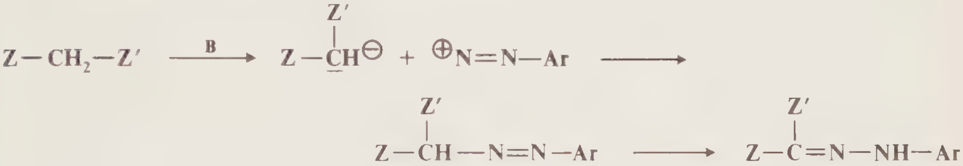
$$Z{-}CH_2{-}Z' + ArN_2^+ \xrightarrow{OAc^-} Z{-}\overset{\overset{\displaystyle Z'}{|}}{C}{=}N{-}NHAr$$

If a C—H bond is acidic enough, it couples with diazonium salts in the presence of a base, most often aqueous sodium acetate.[103] The reaction is commonly carried out on compounds of the form $Z{-}CH_2{-}Z'$, where Z and Z′ are as defined on p. 419, for example, β-keto esters, β-keto amides, malonic ester, nitroalkanes (in this case, only one Z is required), etc. However, certain compounds not of the form $Z{-}CH_2{-}Z'$ also give the reaction. Among these are conjugated dienes, where coupling takes place at the end of the conjugated system, and arylhydrazones, which give formazans:



$$CH_3{-}CH{=}N{-}NHPh + PhN_2^+ \longrightarrow CH_3{-}\underset{\underset{\displaystyle N{=}NPh}{|}}{C}{=}N{-}NHPh$$

The mechanism is probably of the simple SE1 type:



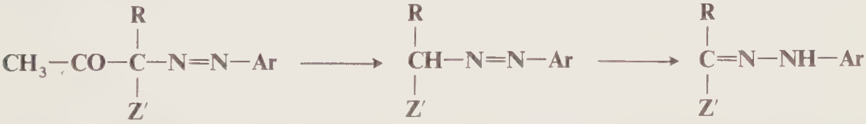
$$Z{-}CH_2{-}Z' \xrightarrow{B} Z{-}\overset{\overset{\displaystyle Z'}{|}}{\underline{C}}H^{\ominus} + {}^{\oplus}N{=}N{-}Ar \longrightarrow$$

$$Z{-}\overset{\overset{\displaystyle Z'}{|}}{C}H{-}N{=}N{-}Ar \longrightarrow Z{-}\overset{\overset{\displaystyle Z'}{|}}{C}{=}N{-}NH{-}Ar$$

17 **18**

Aliphatic azo compounds which contain a hydrogen at the carbon containing the azo group (**17**) are unstable and tautomerize to the isomeric hydrazones (**18**), which are therefore the products of the reaction.

When the reaction is carried out on a compound of the form $Z{-}CHR{-}Z'$, so that the azo compound does not have a tautomerizable hydrogen, if at least one Z is acyl or carboxyl, this group usually cleaves:



$$CH_3{-}CO{-}\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle Z'}{|}}{C}}{-}N{=}N{-}Ar \longrightarrow \overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle Z'}{|}}{C}}H{-}N{=}N{-}Ar \longrightarrow \overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle Z'}{|}}{C}}{=}N{-}NH{-}Ar$$

19

so that the product in this case too is the hydrazone, and not the azo compound. In fact, compounds of the type **19** are seldom isolable from the reaction, although this has been accomplished.[104] The cleavage step shown is actually an example of reaction **2-42** and, when a carboxyl group cleaves, of reaction **2-39.** The overall reaction in this case is called the *Japp-Klingemann reaction*[105] and involves conversion of a ketone (**20**) or an acid (**21**) to a hydrazone (**22**). When an acyl and a carboxyl group are both present, it is the carboxyl which preferentially cleaves. When

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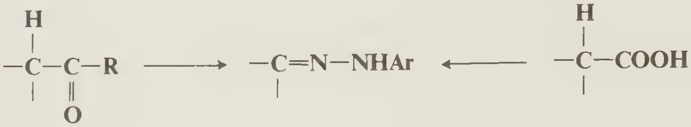
[100] Iriuchijima and Tsuchihashi, *Synthesis* 588 (1970).

[101] Paquette and Houser, *J. Am. Chem. Soc.* **91**, 3870 (1969), *J. Org. Chem.* **36**, 1015 (1971).

[102] Kattenberg, de Waard, and Huisman, *Tetrahedron* **29**, 4149 (1973), **30**, 463 (1974).

[103] For a review, see Parmerter, *Org. React.* **10**, 1–142 (1959).

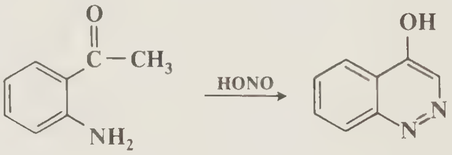


$$-\overset{H}{\underset{|}{\overset{|}{C}}}-\underset{\underset{O}{\|}}{C}-R \longrightarrow -\underset{|}{C}=N-NHAr \longleftarrow -\overset{H}{\underset{|}{\overset{|}{C}}}-COOH$$

20 **22** **21**

there is no acyl or carboxyl group present, then the aliphatic azo compound is stable (for example, the formazan shown above).

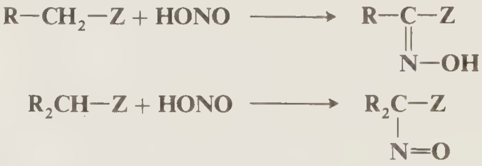
The reaction is occasionally used for ring closure:



In this case the ketone first formed tautomerizes to give the aromatic ring.

OS **III,** 660; **IV,** 633.

2-8 Nitrosation at a Carbon Bearing an Active Hydrogen



$$R-CH_2-Z + HONO \longrightarrow R-\underset{\underset{N-OH}{\|}}{C}-Z$$

$$R_2CH-Z + HONO \longrightarrow R_2\underset{\underset{N=O}{|}}{C}-Z$$

Carbons adjacent to a Z group (as defined on p. 419) may be nitrosated with nitrous acid or alkyl nitrites.[106] The initial product is always the C-nitroso compound, but these are stable only when there is no tautomerizable hydrogen. When there is, the product is the more stable oxime. The situation is analogous to that with azo compounds and hydrazones (reaction **2-7**). The mechanism is similar to that in reaction **2-7:**

$$R-H \rightarrow R^- + {}^+N=O \longrightarrow R-N=O$$

The attacking species is either NO^+ or a carrier of it. As in the Japp-Klingemann reaction, when Z is an acyl or carboxyl group (in the case of R_2CH-Z), it can be cleaved. Since oximes and nitroso compounds can be reduced to primary amines, this reaction often provides a route to amino acids. As in the case of reaction **2-4,** the trimethylsilyl enol ether of a ketone may be used instead of the ketone itself.[107]

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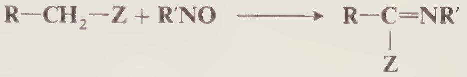
[104] See, for example, Yao and Resnick, *J. Am. Chem. Soc.* **84,** 3514 (1962).

[105] For a review, see Phillips, *Org. React.* **10,** 143–178 (1959).

[106] For a review, see Touster, *Org. React.* **7,** 327–377 (1953).

[107] Rasmussen and Hassner, *J. Org. Chem.* **39,** 2558 (1974).

Imines can be prepared in a similar manner by treatment of an active hydrogen compound with a nitroso compound:

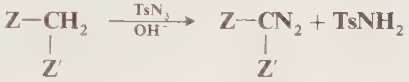


$$\mathrm{R{-}CH_2{-}Z + R'NO \longrightarrow R{-}\underset{\displaystyle Z}{\underset{|}{C}}{=}NR'}$$

Alkanes can be nitrosated photochemically, by treatment with NOCl and uv light.[108] For nitration at an activated carbon, see reaction **4-12.**

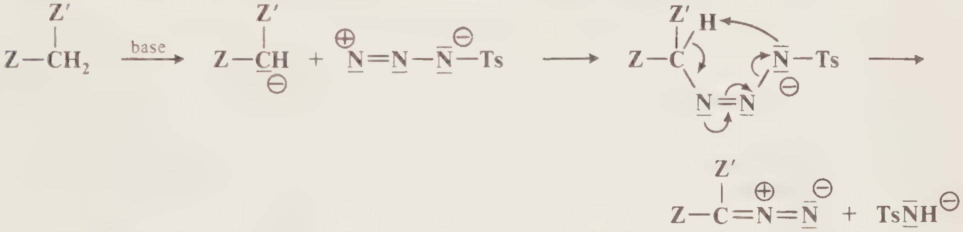
OS **II,** 202, 204, 223, 363; **III,** 191, 513; **V,** 32, 373; **52,** 53. Also see OS **V,** 650.

2-9 Direct Formation of Diazo Compounds

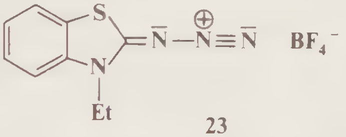


$$\mathrm{Z{-}\underset{\displaystyle Z'}{\underset{|}{C}}H_2 \xrightarrow[OH^-]{TsN_3} Z{-}\underset{\displaystyle Z'}{\underset{|}{C}}N_2 + TsNH_2}$$

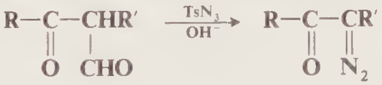
Compounds containing a CH_2 bonded to two Z groups (as defined on p. 419) may be converted to diazo compounds on treatment with tosyl azide in the presence of a base.[109] The use of phase-transfer catalysis (p. 358) increases the convenience of the method.[110] The reaction, which is called the *diazo transfer reaction*, can also be applied to other reactive positions, e.g., the 5 position of cyclopentadiene[110a] (to give **34** on p. 46). The mechanism is probably as follows:



Certain azidinium salts, e.g., 3-ethyl-2-azidobenzothiazolium fluoborate (**23**), may be used instead of tosyl azide. A diazo group can be introduced adjacent to a single carbonyl group indirectly by first converting the ketone to an α-formyl ketone (reaction **0-111**) and then treating with tosyl azide. As in the similar case of reactions **2-7** and **2-8,** the formyl group is cleaved during the reaction.



23



$$\mathrm{R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}\underset{\displaystyle CHO}{\underset{|}{C}}HR' \xrightarrow[OH^-]{TsN_3} R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}\underset{\displaystyle N_2}{\underset{\|}{C}}R'}$$

OS **V,** 179; **51,** 86.

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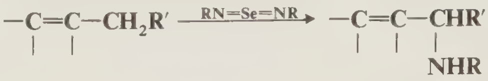
[108] For a review, see Pape, *Fortschr. Chem. Forsch.* **7,** 559–604 (1967).

[109] For reviews, see Regitz, *Synthesis* 351–373 (1972), *Angew. Chem. Int. Ed. Engl.* **6,** 733–749 (1967) [*Angew. Chem.* **79,** 786–801], *Newer Methods Prep. Org. Chem.* **6,** 81–126 (1971). See also Hendrickson and Wolf, *J. Org. Chem.* **33,** 3610 (1968); Hünig, *Angew. Chem. Int. Ed. Engl.* **7,** 335–344 (1968) [*Angew. Chem.* **80,** 343–352].

[110] Ledon, *Synthesis* 347 (1974).

[110a] Doering and DePuy, *J. Am. Chem. Soc.* **75,** 5955 (1953).

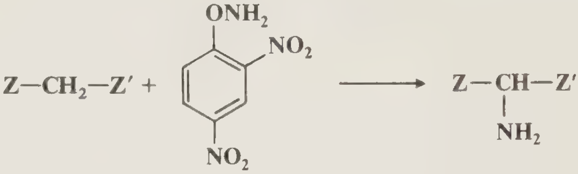
2-10 Direct Amination at an Activated Position



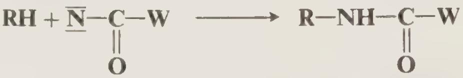
$$-\underset{|}{C}=\underset{|}{C}-CH_2R' \xrightarrow{RN=Se=NR} -\underset{|}{C}=\underset{|}{C}-\underset{\underset{NHR}{|}}{C}HR'$$

R = *t*-Bu, Ts

Alkenes can be aminated in the allylic position by treatment with solutions of imido selenium compounds R—N=Se=N—R.[111] The reaction, which is similar to the allylic oxidation of alkenes with SeO_2 (see reaction **4-4**), has been performed with R = *t*-Bu and R = Ts. The imido sulfur compound TsN=S=NTs has also been used.[111a] In another reaction, compounds containing an active hydrogen can be converted to primary amines, in moderate yields, by treatment with O-(2,4-dinitrophenyl)hydroxylamine.[112]

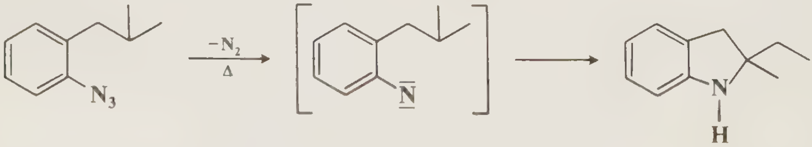


2-11 Insertion by Nitrenes



$$RH + \underline{N}-\underset{\underset{O}{\|}}{C}-W \longrightarrow R-NH-\underset{\underset{O}{\|}}{C}-W$$

Carbonylnitrenes NCOX (W = R', Ar, or OR') are very reactive species (see p. 184) and insert into the C—H bonds of alkanes to give amides (W = R' or Ar) or carbamates (W = OR').[113] The nitrenes are generated as discussed on p. 185. The order of reactivity among alkane C—H bonds is tertiary > secondary > primary.[114] In cyclohexyl systems, equatorial C—H bonds are preferred to axial C—H bonds.[115] Indications are that in general it is only singlet and not triplet nitrenes which insert.[116] Retention of configuration is found at a chiral carbon.[117] The mechanism is presumably similar to the simple one-step mechanism for insertion of carbenes (reaction **2-18**). Other nitrenes (e.g., cyanonitrene NCN[118] and arylnitrenes NAr) can also insert into C—H bonds, but alkylnitrenes usually undergo rearrangement before they can react with the alkane. The insertion reactions are not generally useful synthetically, since they usually lead to mixtures of products, but exceptions are known,[119] chiefly in cyclizations. For example, heating of 2-(2-methylbutyl)phenyl azide gave about 60% 2-ethyl-2-methylindoline.[117]



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[111] Sharpless, Hori, Truesdale, and Dietrich, *J. Am. Chem. Soc.* **98,** 269 (1976).

[111a] Sharpless and Hori, *J. Org. Chem.* **41,** 176 (1976).

[112] Sheradsky and Nir, *Tetrahedron Lett.* 77 (1969).

[113] For a review, see Lwowski, in Lwowski, "Nitrenes," pp. 199–207, Interscience Publishers, New York, 1970.

[114] Nitrenes are much more selective (and hence less reactive) in this reaction than are carbenes (reaction **2-18**). For a discussion, see Alewood, Kazmaier, and Rauk, *J. Am. Chem. Soc.* **95,** 5466 (1973).

[115] Shingaki, Inagaki, Torimoto, and Takebayashi, *Chem. Lett.* 155 (1972).

[116] For example, see Simson and Lwowski, *J. Am. Chem. Soc.* **91,** 5107 (1969).

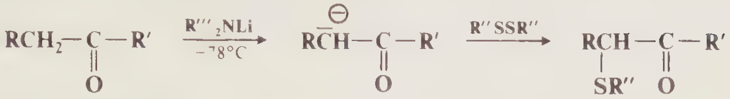
[117] Smolinsky and Feuer, *J. Am. Chem. Soc.* **86,** 3085 (1964).

[118] For a review of cyanonitrenes, see Anastassiou, Shepelavy, Simmons, and Marsh, in Lwowski, Ref. 113, pp. 305–344.

[119] For a synthetically useful noncyclization example, see Meinwald and Aue, *Tetrahedron Lett.* 2317 (1967).

D. Sulfur Electrophiles

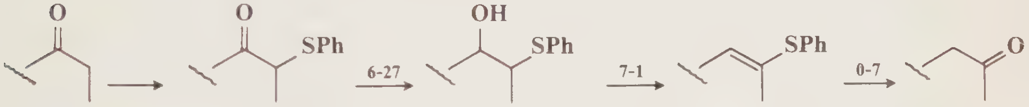
2-12 Sulfenylation and Selenylation of Ketones and Esters



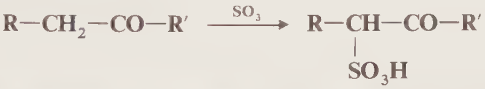
$$\mathrm{RCH_2{-}\underset{\overset{\|}{O}}{C}{-}R'} \xrightarrow[-78^\circ\mathrm{C}]{\mathrm{R'''_2NLi}} \mathrm{R\overset{\ominus}{\bar{C}}H{-}\underset{\overset{\|}{O}}{C}{-}R'} \xrightarrow{\mathrm{R''SSR''}} \mathrm{\underset{\overset{|}{SR''}}{RCH}{-}\underset{\overset{\|}{O}}{C}{-}R'}$$

Ketones and esters (including lactones) can be sulfenylated in the α position by conversion to the enolate ion with a base such as lithium N-isopropylcyclohexylamide and treatment of this with a disulfide.[120] The reaction, shown above for ketones, involves nucleophilic substitution at sulfur. Analogously, α-phenylseleno ketones RCH(SePh)COR′ and α-phenylseleno esters RCH(SePh)-COOR′ can be prepared by treatment of the corresponding enolates with PhSeBr[121] or PhSeSePh.[122] Another method for the introduction of a phenylseleno group into the α position of a ketone involves simple treatment of an ethyl acetate solution of the ketone with PhSeCl (but not PhSeBr) at room temperature.[123] This procedure is also successful for aldehydes but not for esters.

The α-seleno and α-sulfenyl carbonyl compounds prepared by this reaction can be converted to α,β-unsaturated carbonyl compounds (reaction **7-12**). The sulfenylation reaction has also been used as a key step in a sequence for moving the position of a carbonyl group to an adjacent carbon[124] (see also reaction **7-8**):



2-13 Sulfonation of Aldehydes, Ketones, and Acids

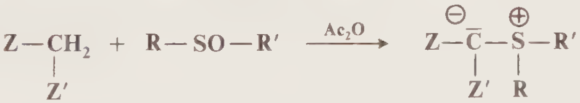


$$\mathrm{R{-}CH_2{-}CO{-}R'} \xrightarrow{\mathrm{SO_3}} \mathrm{R{-}\underset{\overset{|}{SO_3H}}{CH}{-}CO{-}R'}$$

Aldehydes, ketones, and carboxylic acids containing α hydrogens can be sulfonated with sulfur trioxide.[125] The mechanism is presumably similar to that of reaction **2-4**. Sulfonation has also been accomplished at vinylic hydrogen.

OS **IV**, 846, 862.

2-14 Formation of Sulfur Ylides from Sulfoxides and Active Methylene Compounds



$$\mathrm{Z{-}\underset{\overset{|}{Z'}}{CH_2}} + \mathrm{R{-}SO{-}R'} \xrightarrow{\mathrm{Ac_2O}} \mathrm{Z{-}\underset{\overset{|}{Z'}}{\overset{\ominus}{\bar{C}}}{-}\underset{\overset{|}{R}}{\overset{\oplus}{S}}{-}R'}$$

Compounds containing a CH_2 connected to two Z groups (as defined on p. 419) react with sulfoxides (most often dimethyl sulfoxide) in the presence of acetic anhydride,[126] or of dicyclohexylcarbodiimide in polyphosphoric acid,[127] thionyl chloride, P_2O_5, or protonic acids, to give stable sulfur ylides.[128]

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[120] Trost and Salzmann, *J. Am. Chem. Soc.* **95,** 6840 (1973); Seebach and Teschner, *Tetrahedron Lett.* 5113 (1973); Broçksom, Petragnani, and Rodrigues, *J. Org. Chem.* **39,** 2114 (1974).

[121] Reich, Reich, and Renga, *J. Am. Chem. Soc.* **95,** 5813 (1973); Clive, *J. Chem. Soc., Chem. Commun.* 695 (1973); Brocksom, Petragnani, and Rodrigues, Ref. 120.

[122] Grieco and Miyashita, *J. Org. Chem.* **39,** 120 (1974).

[123] Sharpless, Lauer, and Teranishi, *J. Am. Chem. Soc.* **95,** 6137 (1973).

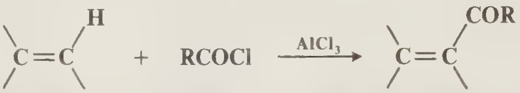
[124] Trost, Hiroi, and Kurozumi, *J. Am. Chem. Soc.* **97,** 438 (1975).

[125] For reviews, see Gilbert, *Chem. Rev.* **62,** 549–589 (1962), pp. 558–559; "Sulfonation and Related Reactions," pp. 33–61, Interscience Publishers, New York, 1965.

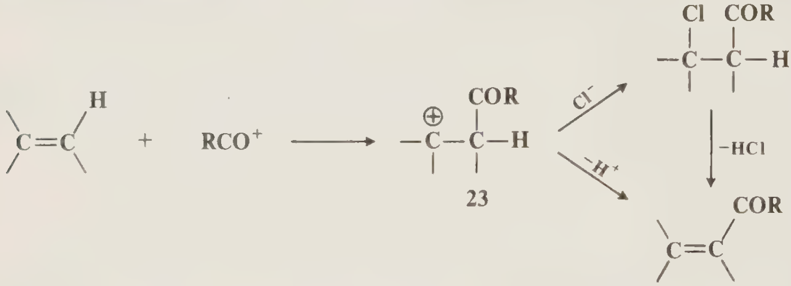
[126] For example, see Nozaki, Tunemoto, Morita, Nakamura, Watanabe, Takaku, and Kondô, *Tetrahedron* **23,** 4279 (1967).

E. Carbon Electrophiles With respect to the attacking molecule, these are nucleophilic substitutions.

2-15 Acylation at an Aliphatic Carbon



Olefins can be acylated with an acyl halide and a Lewis acid catalyst in what is essentially a Friedel-Crafts reaction at an aliphatic carbon.[129] The product can arise by two paths. The initial attack is by the acyl cation RCO^+ (or by the acyl halide free or complexed; see reaction **1-15**) on the olefin to give a carbonium ion:



The carbonium ion (**23**) may either lose a proton or combine with chloride ion. If it loses a proton, the product is an unsaturated ketone, and the mechanism is similar to the tetrahedral mechanism of Chapter 10, but with the charges reversed. If it combines with chloride, the product is a β-halo ketone, which can be isolated, so that the result is addition to the double bond (see reaction **5-38**). On the other hand, the β-halo ketone may, under the conditions of the reaction, lose HCl to give the unsaturated ketone, this time by an addition-elimination mechanism. In the case of unsymmetrical olefins, the attacking ion prefers the position at which there are more hydrogens, following Markovnikov's rule (p. 687). Anhydrides and carboxylic acids (the latter with a proton acid such as anhydrous HF, H_2SO_4, or polyphosphoric acid as a catalyst) are sometimes used instead of acyl halides. Even alkanes can be acylated with acyl halides and a Friedel-Crafts catalyst if there is present a trace of a compound, such as an olefin, which can give rise to carbonium ions. With some substrates and catalysts double-bond migrations are occasionally encountered so that, for example, when 1-methylcyclohexene was acylated with acetic anhydride and zinc chloride, the major product was 6-acetyl-1-methylcyclohexene.[130]

Conjugated dienes can be acylated by treatment with acyl- or alkylcobalt tetracarbonyls, followed by base-catalyzed cleavage of the resulting π-alkyl carbonyl derivatives.[131] The reaction is very general and seems to be applicable to all alkyl- and acylcobalt tetracarbonyls and all

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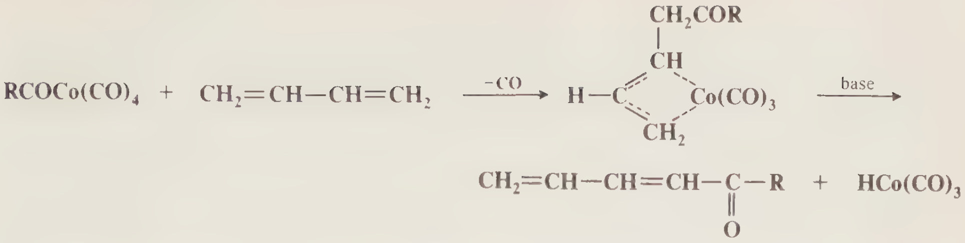
[127] For example, see Cook and Moffatt, *J. Am. Chem. Soc.* **90,** 740 (1968).

[128] For a review, see Durst, *Adv. Org. Chem.* **6,** 285–388 (1969), pp. 370–374.

[129] For reviews, see Groves, *Chem. Soc. Rev.* **1,** 73–97 (1972); House, Ref. 69, pp. 786–797; Satchell and Satchell, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 259–266, 270–273, Interscience Publishers, New York, 1966; Nenitzescu and Balaban, in Olah, "Friedel-Crafts and Related Reactions," vol. 3, pp. 1033–1152, Interscience Publishers, New York, 1964.

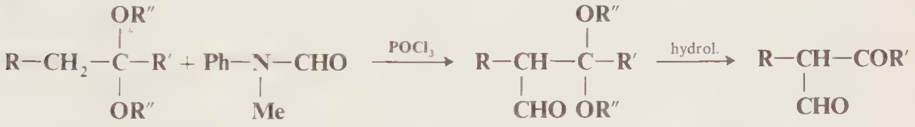
[130] Deno and Chafetz, *J. Am. Chem. Soc.* **74,** 3940 (1952); Groves and Jones, *J. Chem. Soc. C* 2215 (1968).

[131] For a review, see Heck, in Wender and Pino, "Organic Syntheses via Metal Carbonyls," vol. 1, pp. 388–397, Interscience Publishers, New York, 1968.



conjugated dienes and higher conjugated polyenes which have an appropriately situated hydrogen atom and which are not excessively hindered or constrained to unfavorable configurations. With unsymmetrical dienes, the acyl group generally substitutes most readily at a cis double bond, next at a terminal olefinic group, and least readily at a trans double bond. If both ends are trans, the acyl group prefers the less substituted side. The most useful bases are strongly basic, hindered amines such as dicyclohexylethylamine. The reaction may be performed by treating the diene with an acyl or alkyl halide and $Co(CO)_4^-$ (see p. 437) in the presence of CO and a base, in which case the entire process takes place in one synthetic step. Both an alkyl halide RX and an acyl halide RCOX lead to the same acylated olefin. In the case of an alkyl halide (or an alkylcobalt tetracarbonyl) the carbonyl group in the product arises from the carbon monoxide (or from a carbonyl group of the alkylcobalt tetracarbonyl).

Formylation of olefins can be accomplished with N-disubstituted formamides and $POCl_3$.[132] This is an aliphatic Vilsmeier reaction (see reaction **1-16**). Vilsmeier formylation may also be performed on the α position of acetals and ketals, so that hydrolysis of the products gives keto aldehydes or dialdehydes:[133]



$$R-CH_2-\underset{OR''}{\overset{OR''}{C}}-R' + Ph-\underset{Me}{N}-CHO \xrightarrow{POCl_3} R-\underset{CHO}{CH}-\underset{OR''}{\overset{OR''}{C}}-R' \xrightarrow{\text{hydrol.}} R-\underset{CHO}{CH}-COR'$$

Acetylation of acetals or ketals can be accomplished with acetic anhydride and BF_3-etherate.[134] The mechanism with acetals or ketals also involves attack at an olefinic carbon, since enol ethers are intermediates.[134] Ketones can be formylated in the α position by treatment with CO and a strong base.[135] A carbalkoxy group can be introduced by treatment of an olefin with a reagent prepared from ClHgCOOR or $Hg(COOR)_2$ and $LiPdCl_3$ (see reaction **4-18**).[136]

OS **IV**, 555, 560; **51**, 109. Also see OS **52**, 1.

2-16 Alkylation of Alkanes

$$RH + R'^+ \longrightarrow R-R' + H^+$$

Alkanes can be alkylated by treatment with solutions of stable carbonium ions[137] (p. 152), though the reaction has not been used for synthetic purposes. Mixtures are generally obtained.

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[132] For reviews, see Burn, *Chem. Ind.* (*London*) 870 (1973); Satchell and Satchell, Ref. 129, pp. 281–282; Minkin and Dorofeenko, *Russ. Chem. Rev.* **29**, 599–618 (1960), pp. 606–608; Olah and Kuhn, in Olah, Ref. 129, vol. 3, pp. 1214–1219 (1964).

[133] Youssefyeh, *Tetrahedron Lett.* 2161 (1964).

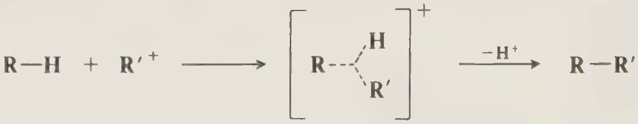
[134] Youssefyeh, *J. Am. Chem. Soc.* **85**, 3901 (1963).

[135] See, for example, van der Zeeuw and Gersmann, *Recl. Trav. Chim. Pays-Bas* **84**, 1535 (1965).

[136] Heck, *J. Am. Chem. Soc.* **90**, 5518 (1968).

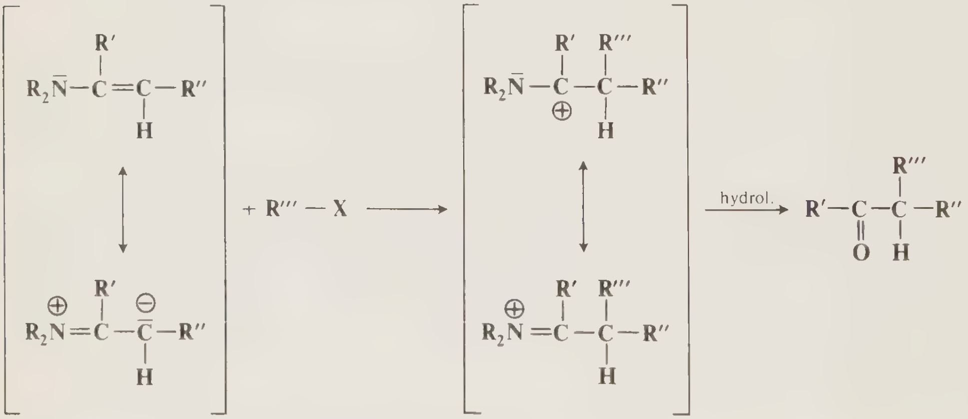
[137] Olah, Mo, and Olah, *J. Am. Chem. Soc.* **95**, 4939 (1973). For a review, see Baker, *Chem. Ind.* (*London*) 877 (1973).

For example, in a typical experiment, the treatment of propane with isopropyl fluoroantimonate (Me_2C^+ SbF_6^-) gave 26% 2,3-dimethylbutane, 28% 2-methylpentane, 14% 3-methylpentane, and 32% *n*-hexane, as well as some butanes, pentanes (formed by reaction **2-46**), and higher alkanes. Mixtures arise in part because intermolecular hydrogen exchange ($RH + R'^+ \rightleftharpoons R^+ + R'H$) is much faster than alkylation, so that alkylation products are also derived from the new alkanes and carbonium ions formed in the exchange reaction. Furthermore, the carbonium ions present are subject to rearrangement (Chapter 18), giving rise to new carbonium ions. Products result from all the hydrocarbons and carbonium ions present in the system, so that mixtures are to be expected. As expected from their relative stabilities, secondary alkyl cations alkylate alkanes more readily than tertiary alkyl cations (the *t*-butyl cation does not alkylate methane or ethane, though it does react with isobutane to give a small amount of 2,2,3,3-tetramethylbutane). Stable primary alkyl cations are not available, but alkylation has been achieved with complexes formed between CH_3F or C_2H_5F and SbF_5.[138] The mechanism of alkylation can be formulated (similar to that shown in hydrogen exchange with super acids, reaction **2-1**) as



It is by means of successive reactions of this sort that simple alkanes like methane and ethane give *t*-butyl cations in super-acid solutions (p. 154).[139]

2-17 The Stork Enamine Reaction



When enamines are treated with alkyl halides, an alkylation occurs which is analogous to the first step of reaction **2-15**. Hydrolysis of the imine salt gives a ketone. Since the enamine is normally formed from a ketone (reaction **6-15**), the net result is alkylation of the ketone at the α position. The method is known as the *Stork enamine reaction*[140] and represents an alternative to the ketone alkylation considered at reaction **0-97**. The Stork method has the advantage that it generally leads almost exclusively to monoalkylation of the ketone, while reaction **0-97,** when applied to ketones, is difficult to stop with the introduction of just one alkyl group. Alkylation usually takes place on the less substituted side of the original ketone. The most commonly used amines are the cyclic amines piperidine, morpholine, and pyrrolidine. There is evidence that at least in some cases the alkylation takes place on the nitrogen, and the quaternary salt thus formed rearranges to the C-alkylated product.[141]

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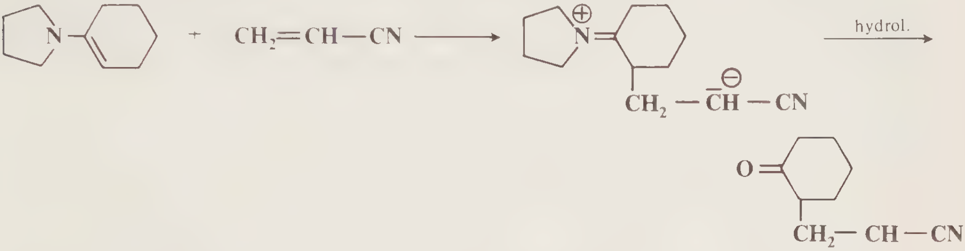
[138] Olah, DeMember, and Shen, *J. Am. Chem. Soc.* **95,** 4952 (1973).

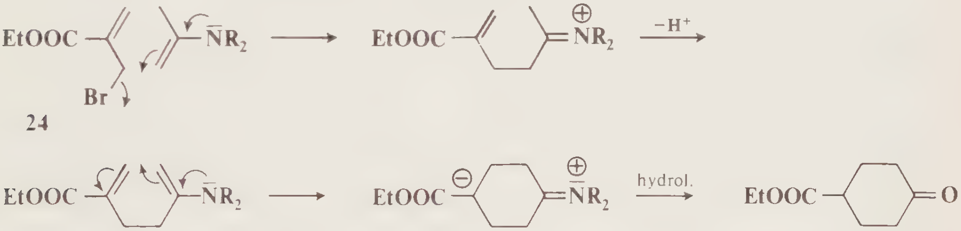
[139] For example, see Hogeveen and Roobeek, *Recl. Trav. Chim. Pays-Bas* **91,** 137 (1972).

[140] Stork, Brizzolara, Landesman, Szmuszkovicz, and Terrell, *J. Am. Chem. Soc.* **85,** 207 (1963). For reviews, see Kuehne, *Synthesis* 510-537 (1970); House, Ref. 69, pp. 570-582, 766-772; Bláha and Červinka, *Adv. Heterocycl. Chem.* **6,** 147-227 (1966), pp. 186-204; Szmuszkovicz, *Adv. Org. Chem.* **4,** 1-113 (1963), pp. 25-92; in Cook, "Enamines," Marcel Dekker, Inc., New York, 1969, the articles by Alt, pp. 115-168; and by Kuehne, pp. 313-468.

The method is quite useful for particularly active alkyl halides such as allyl, benzyl, and propargyl halides, and for α-halo ethers and esters, but is not very serviceable for ordinary primary and secondary halides. Tertiary halides do not give the reaction at all since, with respect to the halide, this is nucleophilic substitution and elimination predominates. The reaction may also be applied to activated aryl halides (such as 2,4-dinitrochlorobenzene; see Chapter 13), to epoxides,[142] and to activated olefins such as acrylonitrile, e.g.,

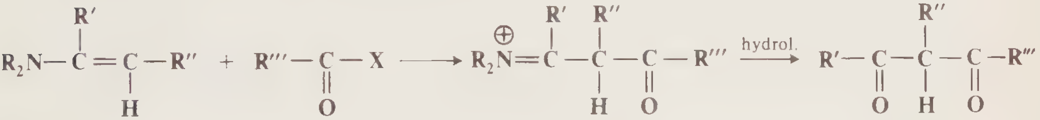


The latter is a Michael-type reaction (p. 679) with respect to the olefin. The compound ethyl α-(bromomethyl)acrylate (**24**), which is both an allylic halide and an activated olefin, reacts in a double fashion with enamines which have an α-hydrogen in the R′ group to give (after hydrolysis) a cyclohexanone:[143]


24

The application of this reaction to the enamine of cyclopentanone gives bicyclo[3.2.1]octanones.

Acylation[144] can be accomplished with acyl halides:



$$R_2N-\overset{R'}{\overset{|}{C}}=\underset{\underset{H}{|}}{C}-R'' + R'''-\underset{\underset{O}{\|}}{C}-X \longrightarrow R_2\overset{\oplus}{N}=\overset{R'}{\overset{|}{C}}-\overset{R''}{\overset{|}{\underset{\underset{H}{|}}{C}}}-\underset{\underset{O}{\|}}{C}-R''' \xrightarrow{\text{hydrol.}} R'-\underset{\underset{O}{\|}}{C}-\overset{R''}{\overset{|}{\underset{\underset{H}{|}}{C}}}-\underset{\underset{O}{\|}}{C}-R'''$$

25

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[141] For example, see Elkik, *Bull. Soc. Chim. Fr.* 903 (1969).

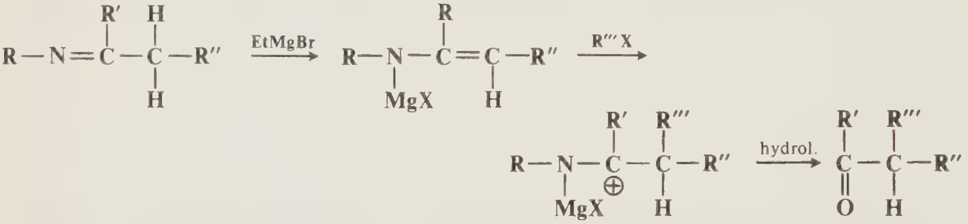
[142] Britten, Owen, and Went, *Tetrahedron* **25,** 3157 (1969).

[143] Nelson, McEuen, and Lawton, *J. Org. Chem.* **34,** 1225 (1969). For a similar reaction, see Hargreaves, Hickmott, and Hopkins, *J. Chem. Soc. C* 592 (1969); Hickmott, Hopkins, and Yoxall, *Tetrahedron Lett.* 2519 (1970).

[144] For reviews, see Hickmott, *Chem. Ind. (London)* 731 (1974); Hünig and Hoch, *Fortschr. Chem. Forsch.* **14,** 235 (1970).

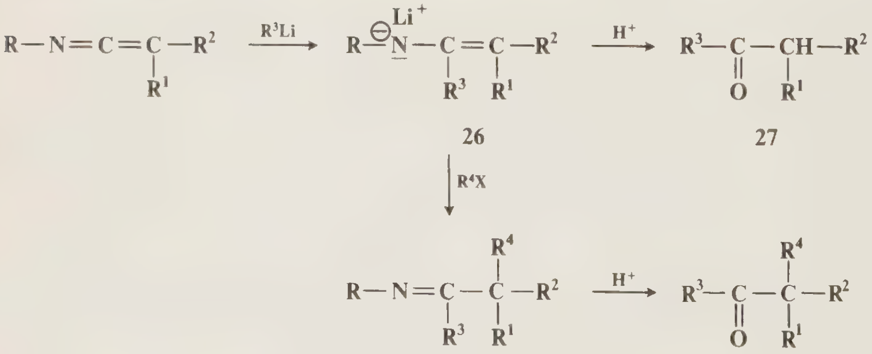
or with anhydrides. A COOEt group can be introduced by treatment of the enamine with ethyl chloroformate ClCOOEt,[145] a CN group with cyanogen chloride[146] (not cyanogen bromide or iodide, which leads to halogenation of the enamine), and a CHO group with the mixed anhydride of formic and acetic acids[145] or with dimethylformamide and phosgene.[147] The acylation of the enamine can take place by the same mechanism as alkylation, but in this case another mechanism is also possible, if the acyl halide has an α-hydrogen and if a tertiary amine is present, as it often is (it is added to neutralize the HX given off). In this mechanism, the acyl halide is dehydrohalogenated by the tertiary amine, producing a ketene (reaction **7-14**) which adds to the enamine to give a cyclobutanone (reaction **5-52**). This compound can be cleaved in the solution to form the same acylated imine salt (**25**) which would form by the more direct mechanism, or it can be isolated (in the case of enamines derived from aldehydes), or it may cleave in other ways.[148]

Primary and secondary halides do not perform well, mostly because N-alkylation becomes important, particularly with enamines derived from aldehydes. An alternative method, which does give good yields of alkylation with primary and secondary halides, is alkylation of enamine *salts*, which are prepared by treating an imine with ethylmagnesium bromide in tetrahydrofuran:[149]



The imines are prepared by reaction **6-15**. The enamine salt method has also been used to give good yields of mono α-alkylation of α,β-unsaturated ketones.[150] Enamines prepared from aldehydes and butylisobutylamine can be alkylated by simple primary alkyl halides in good yields.[151] N-alkylation in this case is presumably prevented by steric hindrance.

Ketenimines (these can be formed by the Meyers method, p. 430) react with alkyllithium



26 **27**

28 **29**

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[145] Stork, Brizzolara, Landesman, Szmuszkovicz, and Terrell, Ref. 140.

[146] Kuehne, *J. Am. Chem. Soc.* **81**, 5400 (1959).

[147] Ziegenbein, *Angew. Chem. Int. Ed. Engl.* **4**, 358 (1965) [*Angew. Chem.* **77**, 380].

[148] See Alt, Ref. 140, pp. 135–145.

[149] Stork and Dowd, *J. Am. Chem. Soc.* **85**, 2178 (1963).

[150] Stork and Benaim, *J. Am. Chem. Soc.* **93**, 5938 (1971).

[151] Curphey, Hung, and Chu, *J. Org. Chem.* **40**, 607 (1975). See also Ho and Wong, *Synth. Commun.* **4**, 147 (1974).

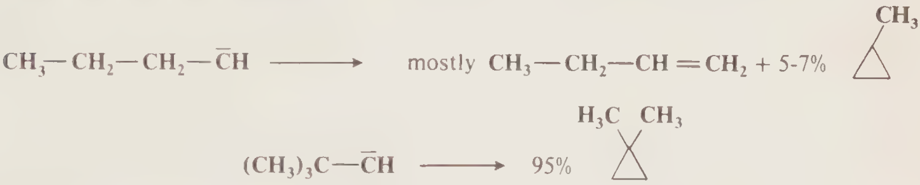
reagents[152] to give lithioenamines (**26**), which may be hydrolyzed to the ketones **27** or treated with an alkyl halide to give the Stork reaction product **28**, which on hydrolysis gives the α-alkylated ketones **29**. It is obvious that a large number of ketones of types **27** and **29** can be prepared starting from dihydro-1,3-oxazines (reaction **0-100**).

OS **V**, 533, 869; **53**, 48; **54**, 46.

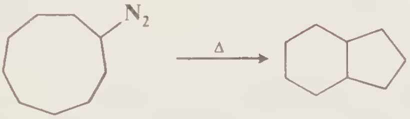
2-18 Insertion by Carbenes

$$RH + \bar{C}H_2 \longrightarrow RCH_3$$

The highly reactive species methylene inserts into C—H bonds,[153] both aliphatic and aromatic,[154] though with aromatic compounds ring expansion is also possible (see reaction **5-53**). The reaction is useless for synthetic purposes because of its nonselectivity (see p. 183). Alkylcarbenes usually rearrange rather than give insertion (p. 183), but, when this is impossible, *intramolecular* insertion is found rather than intermolecular:[155]



Transannular insertion is also known:[156]



CH_2 generated by photolysis of CH_2N_2 in the liquid phase is indiscriminate—totally nonselective—in its reactivity (p. 183). CH_2 generated in other ways, and other carbenes, are less reactive and insert in the order tertiary > secondary > primary.[157] Halocarbenes insert much less readily, though a number of instances have been reported[158] (an unusual example is that of adamantane, which gives a good yield of 1-dichloromethyladamantane with dichlorocarbene[159]).

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[152] Meyers, Smith, and Ao, *J. Org. Chem.* **38**, 2129 (1973); Lion and Dubois, *Tetrahedron* **29**, 3417 (1973), *Bull. Soc. Chim. Fr.* 2673 (1973).

[153] First reported by Meerwein, Rathjen, and Werner, *Ber.* **75**, 1610 (1942). For reviews, see Bethell, in McManus, "Organic Reactive Intermediates," pp. 92–101, Academic Press, Inc., New York, 1973; Kirmse, "Carbene Chemistry," 2d ed., pp. 209–266, Academic Press, Inc., New York, 1971; Hine, "Divalent Carbon," pp. 15–20, 110–116, The Ronald Press Company, New York, 1964; Bell, *Prog. Phys. Org. Chem.* **2**, 1–61 (1964), pp. 30–43.

[154] Terao and Shida, *Bull. Chem. Soc. Jpn.* **37**, 687 (1964).

[155] Kirmse and Doering, *Tetrahedron* **11**, 266 (1960); Friedman and Berger, *J. Am. Chem. Soc.* **83**, 492, 500 (1961). Also see Kirmse and Wächtershäuser, *Tetrahedron* **22**, 63, 73 (1966).

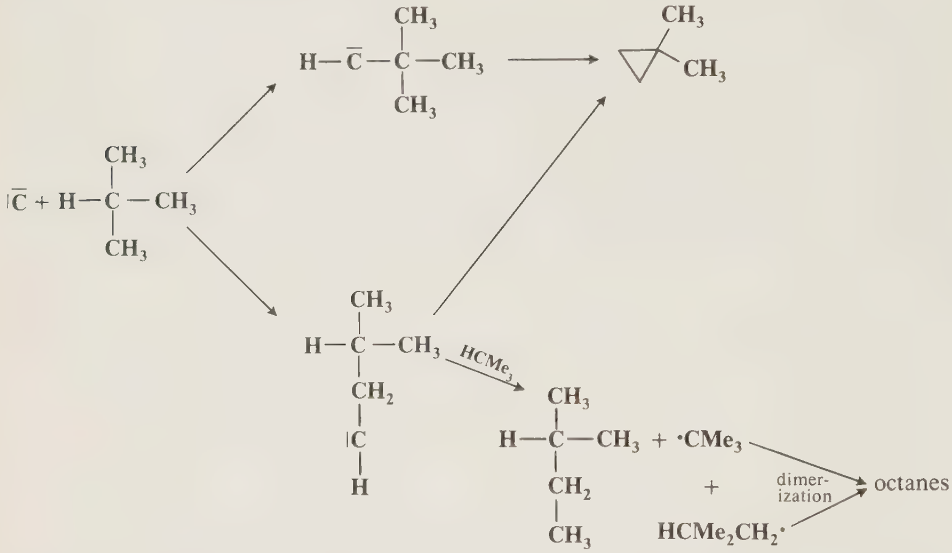
[156] Friedman and Shechter, *J. Am. Chem. Soc.* **83**, 3159 (1961).

[157] Doering and Knox, *J. Am. Chem. Soc.* **83**, 1989 (1961).

[158] For example, see Parham and Koncos, *J. Am. Chem. Soc.* **83**, 4034 (1961); Fields, *J. Am. Chem. Soc.* **84**, 1744 (1962); Anderson, Lindsay, and Reese, *J. Chem. Soc.* 4874 (1964); Seyferth and Burlitch, *J. Am. Chem. Soc.* **85**, 2667 (1963); Landgrebe and Thurman, *J. Am. Chem. Soc.* **91**, 1759 (1969); Franzen and Edens, *Justus Liebigs Ann. Chem.* **729**, 33 (1969); Seyferth, Washburne, Attridge, and Yamamoto, *J. Am. Chem. Soc.* **92**, 4405 (1970); Dehmlow, *Tetrahedron* **27**, 4071 (1971); Seyferth and Cheng, *J. Am. Chem. Soc.* **95**, 6763 (1973), *Synthesis* 114 (1974); Goh, Chan, Kam, and Chong, *Aust. J. Chem.* **28**, 381 (1975); Birchall, Haszeldine, and Tissington, *J. Chem. Soc., Perkin Trans. 1* 1638 (1975).

[159] Tabushi, Yoshida, and Takahashi, *J. Am. Chem. Soc.* **92**, 6670 (1970).

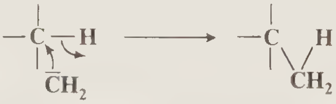
Nevertheless, even for less reactive carbenes, the insertion reaction has seldom been used for synthetic purposes. The carbenes can be generated in any of the ways mentioned in Chapter 5 (p. 181). Carbon atoms (which can be considered a type of carbene) also insert into C—H bonds. The reaction between carbon atoms and isobutane gave 1,1-dimethylcyclopropane, 2-methylbutane, and octanes, which were presumed to arise in this manner:[160]


CH₃
H—C̄—C—CH₃
CH₃
CH₃
CH₃
|C̄ + H—C—CH₃
CH₃
CH₃
CH₃
H—C—CH₃
CH₂
|C
H
HCMe₃
CH₃
H—C—CH₃ + ·CMe₃
CH₂
CH₃
+
HCMe₂CH₂·
dimer-ization
octanes

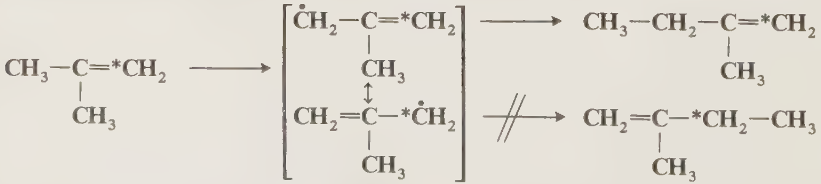
For the similar insertion of nitrenes, see reaction **2-11.**

The mechanism[161] of the insertion reaction is not known with certainty, but there seem to be at least two possible pathways.

1. A simple one-step process involving a three-center cyclic transition state:


—C—H
C̄H₂
—C H
CH₂

The most convincing evidence for this mechanism is that in the reaction between isobutylene-1-^{14}C and carbene the product 2-methyl-1-butene was labeled only in the 1 position.[162] This rules out a free radical or other free intermediate such as a carbonium ion or carbanion. If **30** (or a corresponding ion) were an intermediate, then resonance would ensure that some carbene attacked at the 1 position:


CH₃—C=*CH₂
CH₃
ĊH₂—C=*CH₂
CH₃
CH₂=C—*ĊH₂
CH₃
CH₃—CH₂—C=*CH₂
CH₃
CH₂=C—*CH₂—CH₃
CH₃

30

Not found

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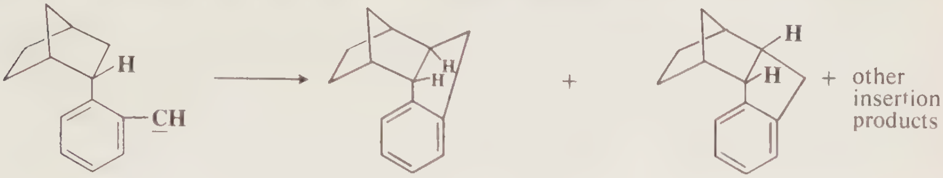
[160] Skell and Engel, *J. Am. Chem. Soc.* **88**, 4883 (1966). See also Skell, Villaume, Plonka, and Fagone, *J. Am. Chem. Soc.* **93**, 2699 (1971).

[161] For a discussion, see Bethell, *Adv. Phys. Org. Chem.* **7**, 153–209 (1969), pp. 190–194.

[162] Doering and Prinzbach, *Tetrahedron* **6**, 24 (1959).

Other evidence is that retention of configuration, which is predicted by this mechanism, has been found in a number of instances.[163] The fact that carbene **31** inserted intramolecularly to give primarily **32** (about 50%) and only 8% of the *less strained* isomer **33** (as well as other intramolecular insertion products) was interpreted to mean that there is a preferred pathway of attack of the carbene on the C—H bond: midway between the C and H atoms and perpendicular to the C—H bond,[164] though this is contrary to theoretical predictions.[165]



31 **32** **33**

2. A free-radical process in which the carbene directly abstracts a hydrogen from the substrate to generate a pair of free radicals:

$$\mathrm{RH + CH_2 \longrightarrow R\cdot + CH_3\cdot}$$
$$\mathrm{R\cdot + CH_3\cdot \longrightarrow RCH_3}$$

One fact supporting this mechanism is that among the products obtained (besides butane and isobutane) on treatment of propane with CH_2 (generated by photolysis of diazomethane and ketene) were propene and ethane,[166] which could arise, respectively, by

$$\mathrm{2CH_3CH_2CH_2\cdot \longrightarrow CH_3CH{=}CH_2 + CH_3CH_2CH_3} \qquad \text{(disproportionation)}$$

and

$$\mathrm{CH_3CH_2CH_3 + \overline{C}H_2 \longrightarrow CH_3CH_2CH_2\cdot + CH_3\cdot}$$
$$\mathrm{2CH_3\cdot \longrightarrow CH_3CH_3}$$

That this mechanism can take place under suitable conditions has been demonstrated by isotopic labeling[167] and by other means.[168] However, the obtention of disproportionation and dimerization products does not always mean that the free-radical abstraction process takes place. In some cases these products arise in a different manner.[169] We have seen that the product of the reaction between a carbene and a molecule may have excess energy (p. 180). Therefore it is possible for the substrate and the carbene to react by mechanism 1 (the direct-insertion process) and for the excess energy to cause the compound thus formed to cleave to free radicals. When this pathway is in operation, the free radicals are formed *after* the actual insertion reaction.

$$\underset{\text{Excited}}{\mathrm{CH_3CH_2CH_2CH_3}} \longrightarrow \underset{\text{disproportionation}}{\underset{\downarrow}{\mathrm{CH_3CH_2CH_2\cdot}}} + \underset{\text{dimerization}}{\underset{\downarrow}{\mathrm{CH_3\cdot}}}$$

It has been suggested[170] that singlet carbenes insert by the one-step direct-insertion process, and triplets (which, being free radicals, are more likely to abstract hydrogen) by the free-radical process. In support of this suggestion is that CIDNP signals (p. 171) were observed in the ethylbenzene produced from toluene and triplet CH_2, but not from the same reaction with singlet CH_2.[171]

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[163] See for example, Kirmse and Buschhoff, *Chem. Ber.* **102**, 1098 (1969); Seyferth and Cheng, *J. Am. Chem. Soc.* **93**, 4072 (1971); Landgrebe and Thurman, Ref. 158.

[164] Gutsche, Bachman, Udell, and Bäuerlein, *J. Am. Chem. Soc.* **93**, 5172 (1971); Baer and Gutsche, *J. Am. Chem. Soc.* **93**, 5180 (1971).

[165] Dobson, Hayes, and Hoffmann, *J. Am. Chem. Soc.* **93**, 6188 (1971).

[166] Frey, *Proc. Chem. Soc.* 318 (1959).

[167] Halberstadt and McNesby, *J. Chem. Phys.* **45**, 1666 (1966); McNesby and Kelly, *Int. J. Chem. Kinet.* **3**, 293 (1971).

[168] Ring and Rabinovitch, *J. Am. Chem. Soc.* **88**, 4285 (1966), *Can. J. Chem.* **46**, 2435 (1968).

[169] Bell, Ref. 153.

[170] Richardson, Simmons, and Dvoretzky, *J. Am. Chem. Soc.* **82**, 5001 (1961), **83**, 1934 (1961).

The reaction in which aldehydes are converted to methyl ketones, $RCHO + CH_2N_2 \rightarrow RCOCH_3$, while apparently similar, does not involve a free carbene intermediate. It is considered in Chapter 18 (reaction **8-10**).

F. Metal Electrophiles

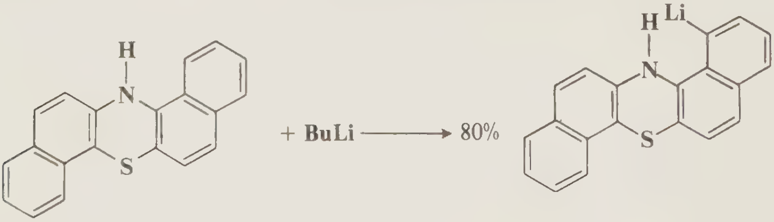
2-19 Metalation with Organometallic Compounds

$$RH + R'M \longrightarrow RM + R'H$$

Many organic compounds can be metalated by treatment with an organometallic compound.[172] Since the reaction involves a proton transfer, the equilibrium lies on the side of the weaker acid. For example, fluorene reacts with butyllithium to give butane and 9-fluoryllithium. Since aromatic hydrocarbons are usually stronger acids than aliphatic ones, R is most often aryl. The most common reagent is butyllithium. Normally, only active aromatic rings react with butyllithium. Benzene itself is not reactive enough, though benzene can be metalated by butyllithium in the presence of *t*-BuOK,[173] or by butyllithium coordinated with various diamines such as N,N,N′,N′-tetramethylethylenediamine.[174] Metalation of aliphatic RH is most successful when the carbanions are stabilized by resonance (allyl, benzyl, etc.) or when the negative charge is at an *sp* carbon (at triple bonds). In certain cases *gem*-dialkali metal compounds can be prepared. An example is the conversion of phenylacetonitrile to 1,1-dilithiophenylacetonitrile $PhCLi_2CN$ by treatment with excess butyllithium.[175]

In general, the reaction can be performed only with organometallics of active metals such as lithium, sodium, and potassium, but Grignard reagents abstract protons from a sufficiently acidic C—H bond, as in $R—C\equiv C—H \rightarrow R—C\equiv C—MgX$. This is the best method for the preparation of ethynyl Grignard reagents.[176]

The reaction may be used to determine relative acidities of very weak acids by allowing two R—H compounds to compete for the same R′M, and to determine which proton in a molecule is the most acidic. The reaction is often remarkably specific, for example,[177]



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[171] Roth, *J. Am. Chem. Soc.* **94,** 1761 (1972). See also Closs and Closs, *J. Am. Chem. Soc.* **91,** 4549 (1969).

[172] For reviews, see Mallan and Bebb, *Chem. Rev.* **69,** 693–755 (1969); Jones and Gilman, *Chem. Rev.* **54,** 835–890 (1954), pp. 865–867; Gilman and Morton, *Org. React.* **8,** 258–304 (1954) (for Li); Benkeser, Foster, Sauve, and Nobis, *Chem. Rev.* **57,** 867–894 (1957) (for Na).

[173] Schlosser, *J. Organomet. Chem.* **8,** 9 (1967).

[174] Eberhardt and Butte, *J. Org. Chem.* **29,** 2928 (1964); Langer, *Trans. N.Y. Acad. Sci.* **27,** 741 (1965); Eastham and Screttas, *J. Am. Chem. Soc.* **87,** 3276 (1965); Rausch and Ciappenelli, *J. Organomet. Chem.* **10,** 127 (1967).

[175] Kaiser, Solter, Schwarz, Beard, and Hauser, *J. Am. Chem. Soc.* **93,** 4237 (1971).

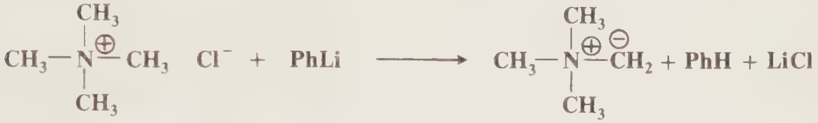
[176] For a review of the synthetic applications of metalation by Grignard reagents at positions other than at triple bonds, see Blagoev and Ivanov, *Synthesis* 615–628 (1970).

[177] Shirley and Gilmer, *J. Org. Chem.* **27,** 4421 (1962). For other uses of this reaction to determine position of maximum acidity, see Broaddus, Logan, and Flautt, *J. Org. Chem.* **28,** 1174 (1963); Finnegan and McNess, *J. Org. Chem.* **29,** 3234 (1964); Shirley, Johnson, and Hendrix, *J. Organomet. Chem.* **11,** 209 (1968); Shirley and Hendrix, *J. Organomet. Chem.* **11,** 217 (1968).

The mechanism involves a nucleophilic attack by R′ (or a polar R′) on the *hydrogen.*[178] Evidence for this is that mesomeric effects of substituents in R seem to make little difference. Only field effects are important. When R is aryl, OMe and CF_3 *both* direct ortho, while isopropyl directs meta and para (mostly meta).[179] These results are exactly what would be expected from pure field effects, with no contribution from resonance effects. All this implies that attack occurs at the hydrogen and not at R. Only the acidity seems to be important. Resonance factors would influence an intermediate or transition state. Since resonance factors in R are not important, R is involved very little in the transition state. Other evidence for the involvement of H in the rate-determining step is that there are large isotope effects.[180] The nature of R′ also has an effect on the rate. In the reaction between triphenylmethane and R′Li, the rate decreased in the order $R' = PhCH_2 > allyl > Bu > Ph > vinyl > Me$.[181]

With respect to the reagent, this reaction is a special case of reaction **2-21.**

A closely related reaction is formation of nitrogen ylides from quaternary ammonium salts (see reaction **7-7**):[182]



$$\mathrm{CH_3{-}\overset{CH_3}{\underset{CH_3}{\overset{\oplus}{N}}}{-}CH_3\quad Cl^- + PhLi \longrightarrow CH_3{-}\overset{CH_3}{\underset{CH_3}{\overset{\oplus}{N}}}{-}\overset{\ominus}{C}H_2 + PhH + LiCl}$$

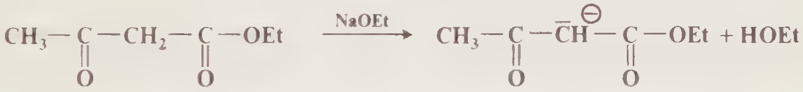
Phosphonium salts undergo a similar reaction (see reaction **6-47**).

OS **II,** 198; **III,** 413, 757; **IV,** 792; **V,** 751; **50,** 104; **52,** 90; **53,** 56.

2-20 Metalation with Metals and Strong Bases

$$2RH + M \longrightarrow 2RM + H_2$$

Organic compounds can be metalated at suitably acidic positions by active metals and by strong bases. The reaction has been used to study the acidities of very weak acids (see p. 161). Synthetically, the most important use of the method is to convert activated ketones, esters, and similar compounds to their enolate forms, e.g.,



$$\mathrm{CH_3{-}\underset{\overset{\|}{O}}{C}{-}CH_2{-}\underset{\overset{\|}{O}}{C}{-}OEt \xrightarrow{NaOEt} CH_3{-}\underset{\overset{\|}{O}}{C}{-}\overset{\ominus}{\bar{C}H}{-}\underset{\overset{\|}{O}}{C}{-}OEt + HOEt}$$

for use in nucleophilic substitutions (reactions **0-96** and **3-14**) and in additions to multiple bonds (reactions **5-19** and **6-42**). Another important use is the conversion of terminal alkynes to acetylide ions.[183] The mechanism for the reaction between $ArCR_2H$ and RNHLi has been shown to be SEi.[184] Ethyl acetate has been converted to ethyl lithioacetate $LiCH_2COOEt$ by treatment with lithium bis(trimethylsilyl)amide $LiN(SiMe_3)_2$ in tetrahydrofuran at −78 C.[185]

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[178] Benkeser, Trevillyan, and Hooz, *J. Am. Chem. Soc.* **84,** 4971 (1962).

[179] Bryce-Smith, *J. Chem. Soc.* 5983 (1963); Benkeser, Hooz, Liston, and Trevillyan, *J. Am. Chem. Soc.* **85,** 3984 (1963).

[180] Bryce-Smith, Gold, and Satchell, *J. Chem. Soc.* 2743 (1954); Pocker and Exner, *J. Am. Chem. Soc.* **90,** 6764 (1968).

[181] Waack and West, *J. Am. Chem. Soc.* **86,** 4494 (1964).

[182] For a review of the chemistry of nitrogen ylides, see Johnson, "Ylid Chemistry," pp. 251–283, Academic Press, Inc., New York, 1966.

[183] For a review, see Ziegenbein, in Viehe, "Acetylenes," pp. 170–185, Marcel Dekker, Inc., New York, 1969.

[184] Streitwieser, Van Sickle, and Langworthy, *J. Am. Chem. Soc.* **84,** 244 (1962); Streitwieser and Langworthy, *J. Am. Chem. Soc.* **84,** 249 (1962); Streitwieser, Langworthy, and Van Sickle, *J. Am. Chem. Soc.* **84,** 251 (1962); Streitwieser and Van Sickle, *J. Am. Chem. Soc.* **84,** 254 (1962); Streitwieser and Reif, *J. Am. Chem. Soc.* **84,** 258 (1962).

[185] Rathke, *J. Am. Chem. Soc.* **92,** 3222 (1970).

Mercuration of aromatic compounds can be accomplished with mercuric salts, most often $Hg(OAc)_2$ or $Hg(ClO_4)_2$ (to give ArHgOAc or $ArHgClO_4$, respectively). This is ordinary electrophilic aromatic substitution and takes place by the arenium-ion mechanism (p. 453).[186] Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $ArTl(OOCCF_3)_2$ by treatment with thallium(III) trifluoroacetate in trifluoroacetic acid.[187] These arylthallium compounds can be converted to phenols (reaction **2-23**), aryl iodides (reaction **2-28**), or aryl nitriles (reaction **2-32**).

OS **I,** 70, 161, 490; **IV,** 473; **52,** 75; **54,** 19; **55,** 70. We do not list conversions of ketones or esters to enolates.

Metals as Leaving Groups

A. Hydrogen as the Electrophile

2-21 Replacement of Metals by Hydrogen

$$\mathbf{RM + HA \longrightarrow RH + MA}$$

Organometallic compounds react with acids in reactions in which the metal is replaced by hydrogen.[188] R may be aryl (see reaction **1-50**). For Grignard reagents, water is usually a strong enough acid, but stronger acids are also used. Hydrogen (H_2) has been used as an acid to convert Grignard reagents and other organometallic compounds to hydrocarbons.[189] An important method for the reduction of alkyl halides consists of the process

$$\mathbf{RX \longrightarrow RMgX \longrightarrow RH}$$

Other organometallic compounds that are hydrolyzed by water are those of sodium, potassium, lithium, zinc, etc.: the ones high in the electromotive series. When the metal is farther down in the series, stronger acids are required. For example, R_2Zn compounds react explosively with water, R_2Cd slowly, and R_2Hg not at all, though the latter may be cleaved with concentrated HCl. However, this general statement has many exceptions, some hard to explain. For example, BR_3 compounds are completely inert to water, and GaR_3 at room temperature cleave just one R group, but AlR_3 react violently with water. However, BR_3 can be converted to RH with carboxylic acids.[190] For less active metals it is often possible to cleave just one R group from a multivalent metal. For example,

$$\mathbf{R_2Hg + HCl \longrightarrow RH + RHgCl}$$

Organometallic compounds of less active metals and metalloids, such as silicon, antimony, bismuth, etc., are quite inert to water. Organomercury compounds (RHgX or R_2Hg) can be reduced to RH by H_2, $NaBH_4$, or other reducing agents.[191] There is evidence that the reduction with $NaBH_4$ takes place by a free-radical mechanism.[192] Vinylsilanes $RR'C{=}CR''SiMe_3$ give alkenes $RR'C{=}CR''H$ with retention of configuration when treated with HI.[192a]

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[186] For a review, see Taylor, in Bamford and Tipper, Ref. 49, vol. 13, pp. 186–194 (1972).

[187] McKillop, Hunt, Zelesko, Fowler, Taylor, McGillivray, and Kienzle, *J. Am. Chem. Soc.* **93,** 4841 (1971); Taylor, Kienzle, Robey, McKillop, and Hunt, *J. Am. Chem. Soc.* **93,** 4845 (1971); Taylor, Kienzle, and McKillop, *Org. Synth.* **55,** 70 (1976).

[188] For reviews, see Abraham, Ref. 2, pp. 107–134; Jensen and Rickborn, Ref. 2, pp. 45–74; Schlosser, *Angew. Chem. Int. Ed. Engl.* **3,** 287–306, 362–373 (1964) [*Angew. Chem.* **76,** 124–143, 258–269], *Newer Methods Prep. Org. Chem.* **5,** 238–311 (1968).

[189] See for example, Becker and Ashby, *J. Org. Chem.* **29,** 954 (1964).

[190] Brown, "Hydroboration," pp. 64–65, W. A. Benjamin, Inc., New York, 1962, "Boranes in Organic Chemistry," pp. 313–317, Cornell University Press, Ithaca, N.Y., 1972.

[191] For a review, see Makarova, *Organomet. React.* **1,** 119–348 (1970), pp. 251–270, 275–300.

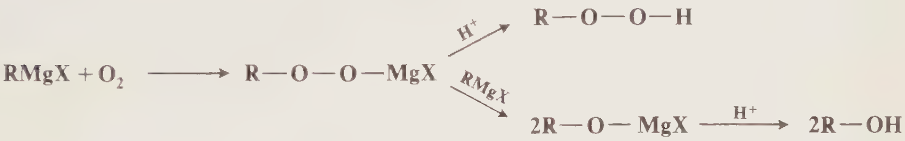
In the *Zerewittenoff process* the number of moles of active hydrogen in an unknown compound is determined by treatment of the compound with methylmagnesium bromide and measurement of the volume of methane evolved. An *active hydrogen* is defined as one which will react with this reagent. Usually it is a hydrogen connected to oxygen, nitrogen, sulfur, phosphorus, etc., but hydrogens attached to some carbons are acidic enough for the reaction.[193]

When the hydrogen of the HA is attached to carbon, this reaction is the same as reaction **2-19.**

We do not list the many hydrolyses of sodium or potassium enolates, etc., found in *Organic Syntheses*. The hydrolysis of a Grignard reagent to give an alkane is found in OS **II,** 478.

B. Oxygen Electrophiles

2-22 The Reaction between Organometallic Reagents and Oxygen



Oxygen reacts with Grignard reagents to give either hydroperoxides or alcohols.[194] The reaction is useful to convert alkyl halides to alcohols without side reactions. With aryl Grignard reagents yields are lower, and only phenols are obtained, not hydroperoxides. It is because of the possibility of this reaction that oxygen must be excluded when Grignard reagents are desired for other purposes. A better procedure for the conversion of aryl Grignard reagents to phenols involves the use of trimethyl borate followed by oxidation with H_2O_2 in acetic acid[195] (see reaction **2-26**).

$$\mathrm{ArMgX} \xrightarrow{\mathrm{B(OMe)_3}} \mathrm{ArB(OMe)_2} \xrightarrow[\mathrm{H_2O_2}]{\mathrm{H^+}} \mathrm{ArOH}$$

Most other organometallic compounds also react with oxygen. Trialkylboranes and alkyldichloroboranes $RBCl_2$ can be conveniently converted to hydroperoxides by treatment with oxygen followed by hydrolysis.[196] Dilithiated carboxylic acids (see reaction **0-98**) react with oxygen to give (after hydrolysis) α-hydroxy carboxylic acids.[197] There is evidence that the reaction between Grignard reagents and oxygen involves a free-radical mechanism.[198]

OS **V,** 918.

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[192] Pasto and Gontarz, *J. Am. Chem. Soc.* **91,** 719 (1969); Grey and Jackson, *J. Am. Chem. Soc.* **91,** 6205 (1969); Whitesides and San Filippo, *J. Am. Chem. Soc.* **92,** 6611 (1970); Chambers, Jackson, and Young, *J. Chem. Soc. C* 2075 (1971); Quirk and Lea, *Tetrahedron Lett.* 1925 (1974).

[192a] Utimoto, Kitai, and Nozaki, *Tetrahedron Lett.* 2825 (1975).

[193] For a review, see Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 1166–1198, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

[194] For a monograph, see Brilkina and Shushunov, "Reactions of Organometallic Compounds with Oxygen and Peroxides," Chemical Rubber Company Press, Cleveland, Ohio, 1969. For a review, see Ref. 193, pp. 1264–1274.

[195] Hawthorne, *J. Org. Chem.* **22,** 1001 (1957).

[196] Brown and Midland, *J. Am. Chem. Soc.* **93,** 4078 (1971); Midland and Brown, *J. Am. Chem. Soc.* **95,** 4069 (1973); Midland, *Intra-Sci. Chem. Rep.* 7(1), 65–71 (1973).

[197] Moersch and Zwiesler, *Synthesis* 647 (1971).

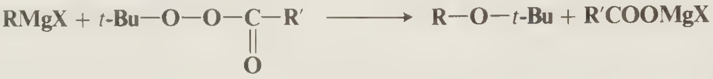
[198] Lamb, Ayers, Toney, and Garst, *J. Am. Chem. Soc.* **88,** 4261 (1966); Davies and Roberts, *J. Chem. Soc. B* 317 (1969); Walling and Cioffari, *J. Am. Chem. Soc.* **92,** 6609 (1970); Garst, Smith, and Farrar, *J. Am. Chem. Soc.* **94,** 7707 (1972).

2-23 Conversion of Arylthallium Compounds to Phenols

$$\mathrm{ArTl(OOCCF_3)_2} \xrightarrow[\text{2. PPh}_3\ \ \text{3. dil. NaOH}]{\text{1. Pb(OAc)}_4} \mathrm{ArOH}$$

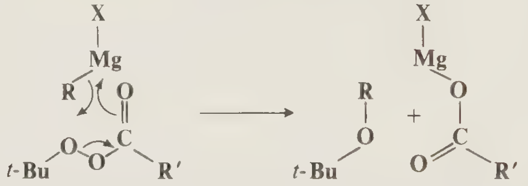
Arythallium bis(trifluoroacetates), which can be prepared by reaction **2-20**, can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine and then dilute NaOH.[199] The entire process, including the thallation reaction, can be carried out in a single reaction vessel without isolation of any of the intermediate products, so that this is a method of accomplishing the conversion ArH → ArOH. Diarylthallium trifluoroacetates undergo the same reaction.[199a]

2-24 Conversion of Grignard Reagents to *t*-Butyl Ethers



$$\mathrm{RMgX} + t\text{-Bu}{-}\mathrm{O}{-}\mathrm{O}{-}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}{-}\mathrm{R'} \longrightarrow \mathrm{R}{-}\mathrm{O}{-}t\text{-Bu} + \mathrm{R'COOMgX}$$

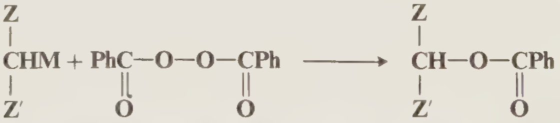
A convenient method of preparation of *t*-butyl ethers consists of treating Grignard reagents with *t*-butyl acyl peroxides.[200] Both alkyl and aryl Grignard reagents may be used. The mechanism is probably of the cyclic, six-center type:



The application of this reaction to Grignard reagents prepared from cyclopropyl halides permits cyclopropyl halides to be converted to *t*-butyl ethers of cyclopropanols,[201] which can then be easily hydrolyzed to the cyclopropanols. The direct conversion of cyclopropyl halides to cyclopropanols by reaction **0-1** is not generally feasible, because cyclopropyl halides do not generally undergo nucleophilic substitutions without ring opening.

OS V, 642, 924.

2-25 Esterification of Enolates



$$\underset{\mathrm{Z'}}{\overset{\mathrm{Z}}{\mathrm{CHM}}} + \mathrm{Ph}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}{-}\mathrm{O}{-}\mathrm{O}{-}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}\mathrm{Ph} \longrightarrow \underset{\mathrm{Z'}}{\overset{\mathrm{Z}}{\mathrm{CH}}}{-}\mathrm{O}{-}\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}\mathrm{Ph}$$

β-Keto esters and other compounds of the form Z—CHR—Z′ (see p. 419 for the definition of Z) can be esterified through their enolate salts by treatment with acyl peroxides.[202]

OS V, 379.

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[199] Taylor, Altland, Danforth, McGillivray, and McKillop, *J. Am. Chem. Soc.* **92,** 3520 (1970).

[199a] Taylor, Altland, and McKillop, *J. Org. Chem.* **40,** 2351 (1975).

[200] Lawesson and Yang, *J. Am. Chem. Soc.* **81,** 4230 (1959); Jakobsen, Larsen, and Lawesson, *Recl. Trav. Chim. Pays-Bas* **82,** 791 (1963); Lawesson and Frisell, *Ark. Kemi* **17,** 393 (1961); Lawesson, Frisell, Denney, and Denney, *Tetrahedron* **19,** 1229 (1963). For a monograph on the reactions of organometallic compounds with peroxides, see Ref. 194. For a review, see Razuveav, Shushunov, Dodonov, and Brilkina, in Swern, "Organic Peroxides," vol. 3, pp. 141-270, John Wiley & Sons, Inc., New York, 1972.

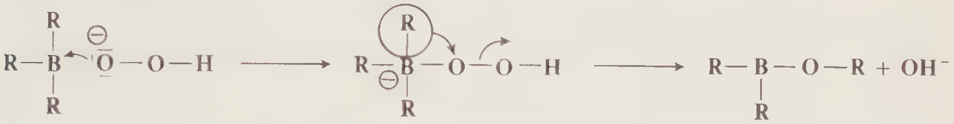
[201] Longone and Miller, *Tetrahedron Lett.* 4941 (1967).

[202] Lawesson and Frisell, *Ark. Kemi* **17,** 409 (1961); Lawesson, Andersson, and Berglund, *Ark. Kemi* **17,** 429 (1961); Lawesson, Jönsson, and Taipale, *Ark. Kemi* **17,** 441 (1961); Lawesson, Grönwall, and Andersson, *Ark. Kemi* **17,** 457 (1961).

2-26 Oxidation of Trialkylboranes to Borates

$$R_3B \xrightarrow[NaOH]{H_2O_2} (RO)_3B$$

Trialkylboranes can be oxidized to esters of boric acid by alkaline H_2O_2.[203] This reaction does not affect double or triple bonds, aldehydes, ketones, halides, or nitriles. The R group does not rearrange, and this reaction is a step in the hydroboration method of converting olefins to alcohols (reaction **5-13**). The mechanism has been formulated as involving a rearrangement from boron to oxygen:[203]



The other two R groups then similarly migrate. Retention of configuration in the R group has been observed in a similar reaction.[204] Boranes can also be oxidized to borates in good yields with oxygen[205] and with trimethylamine oxide, either anhydrous[206] or in the form of the dihydrate.[206a] The reaction with oxygen is free-radical in nature.[207]

OS V, 918; **50,** 88; **52,** 59; **53,** 77.

C. Sulfur Electrophiles

2-27 Conversion of Grignard Reagents to Sulfur Compounds

$$\begin{tikzcd} & & R\text{—}S\text{—}R \\ RMgX + S \arrow[r] & R\text{—}S\text{—}MgX \arrow[ur, "RMgX"] \arrow[dr, "H^+"'] & \\ & & R\text{—}SH \end{tikzcd}$$

Mercaptans and sulfides are occasionally prepared by treatment of Grignard reagents with sulfur. Analogous reactions are known for selenium and tellurium compounds. Grignard reagents also react with sulfuryl chloride to give sulfonyl chlorides,[208] with esters of sulfinic acids to give

$$\begin{tikzcd} RMgX + SO_2Cl_2 \arrow[r] & RSO_2Cl & \\ RMgX + R'SO\text{—}OR'' \arrow[r] & RSOR' & \\ RMgX + SO_2 \arrow[r] & RSO\text{—}OMgX \arrow[r, "H^+"] \arrow[d, "X_2"] & RSO_2H \\ & RSO_2X & \end{tikzcd}$$

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[203] For reviews, see Brown, "Hydroboration," Ref. 190, pp. 69–72, "Boranes in Organic Chemistry," Ref. 190, pp. 321–325.

[204] Davies and Roberts, *J. Chem. Soc. C* 1474 (1968).

[205] Brown, Midland, and Kabalka, *J. Am. Chem. Soc.* **93,** 1024 (1971).

[206] Köster and Morita, *Justus Liebigs Ann. Chem.* **704,** 70 (1967); Köster, Arora, and Binger, *Angew. Chem. Int. Ed. Engl.* **8,** 205 (1969) [*Angew. Chem.* **81,** 185].

[206a] Kabalka and Hedgecock, *J. Org. Chem.* **40,** 1776 (1975), *J. Chem. Educ.* **52,** 745 (1975).

[207] Mirviss, *J. Am. Chem. Soc.* **83,** 3051 (1961), *J. Org. Chem.* **32,** 1713 (1967); Davies and Roberts, *Chem. Commun.* 298 (1966); Midland and Brown, *J. Am. Chem. Soc.* **93,** 1506 (1971).

[207a] For a review, see Wardell, in Patai, "The Chemistry of the Thiol Group," pt. 1, pp. 211–215, John Wiley & Sons, Inc., New York, 1974.

[208] Bhattacharya, Eaborn, and Walton, *J. Chem. Soc. C* 1265 (1968). For a similar reaction with alkyllithiums, see Quast and Kees, *Synthesis* 489 (1974).

(stereospecifically) sulfoxides,[209] and with SO_2 to give sulfinic acid salts[210] which can be hydrolyzed to sulfinic acids or treated with halogens to give sulfonyl halides.[211]

OS **III,** 771; **IV,** 667; **50,** 104.

D. Halogen Electrophiles

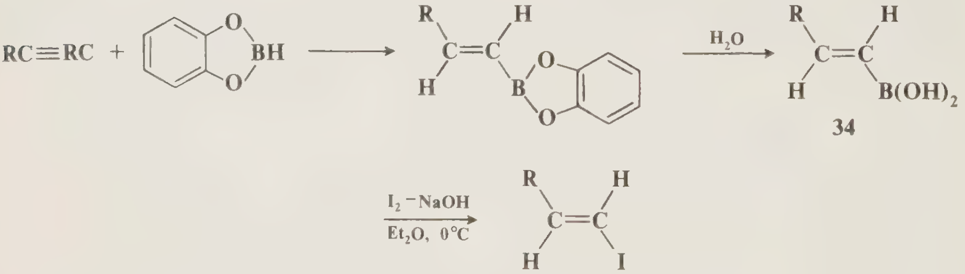
2-28 Halogenation of Organometallic Compounds

$$\mathrm{RMgX} + \mathrm{I_2} \longrightarrow \mathrm{RI} + \mathrm{MgIX}$$

Grignard reagents react with halogens to give alkyl halides. The reaction represents a useful method for the preparation of iodo compounds from the corresponding chloro or bromo compounds. The reaction is not useful for preparing chlorides, since the reagents RMgBr and RMgI react with Cl_2 to give mostly RBr and RI, respectively.[212] Alkyl, aryl, and vinyl Grignard reagents and lithium compounds can be converted to fluorides in moderate to high yields by treatment with perchloryl fluoride $FClO_3$.[213]

Most organometallic compounds, both alkyl and aryl, also react with halogens to give alkyl or aryl halides.[214] The reaction can be used to convert acetylide ions to 1-haloalkynes.[215] Since acetylide ions are easily prepared from alkynes (reaction **2-20**), this provides a means of making the conversion $RC{\equiv}CH \rightarrow RC{\equiv}CX$. Trialkylboranes react rapidly with I_2[216] or Br_2[217] in the presence of NaOMe in methanol to give alkyl iodides or bromides, respectively (see also reaction **4-32**). Combined with the hydroboration reaction (**5-15**), this is an indirect way of adding HBr or HI to a double bond to give products with an anti-Markovnikov orientation (see reaction **5-1**). An alternative procedure for achieving this result for HBr consists of treating the R_3B with $Hg(OAc)_2$ or HgO, which produces RHgOAc or R_2Hg, respectively, either of which, when treated with Br_2, gives RBr.[218]

trans-1-Alkenylboronic acids **34,** prepared by hydroboration of terminal alkynes with catecholborane (reaction **5-15**) followed by hydrolysis, react with I_2 in the presence of NaOH at 0°C in ethereal solvents to give trans vinyl iodides.[219] This is an indirect way of accomplishing the



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[209] Andersen, *Tetrahedron Lett.* 93 (1962).

[210] For a review of the reaction of organometallic compounds with SO_2, see Kitching and Fong, *Organomet. Chem. Rev., Sect. A* **5,** 281–321 (1970).

[211] Asinger, Laue, Fell, and Gubelt, *Chem. Ber.* **100,** 1696 (1967).

[212] Zakharkin, Gavrilenko, and Paley, *J. Organomet. Chem.* **21,** 269 (1970).

[213] Schlosser and Heinz, *Chem. Ber.* **102,** 1944 (1969).

[214] For a review with respect to organomercury compounds, see Makarova, Ref. 191, pp. 325–348.

[215] For a review, see Delavarenne and Viehe, Ref. 183, pp. 665–688.

[216] De Lue and Brown, *Synthesis* 114 (1976); Brown, De Lue, Kabalka, and Hedgecock, *J. Am. Chem. Soc.* **98,** 1290 (1976).

[217] Brown and Lane, *J. Am. Chem. Soc.* **92,** 6660 (1970). See also Lane and Brown, *J. Am. Chem. Soc.* **92,** 7212 (1970), *J. Organomet. Chem.* **26,** C51 (1971); Lane, *Intra-Sci. Chem. Rep.* **7**(2), 133–145 (1973).

[218] Tufariello and Hovey, *J. Am. Chem. Soc.* **92,** 3221 (1970), *Chem. Commun.* 372 (1970).

[219] Brown, Hamaoka, and Ravindran, *J. Am. Chem. Soc.* **95,** 5786 (1973).

anti-Markovnikov addition of HI to a terminal triple bond. The reaction cannot be applied to alkenylboronic acids prepared from internal alkynes. However, alkenylboronic acids prepared from both internal and terminal alkynes react with Br_2 (2 moles of Br_2 must be used) followed by base to give the corresponding vinyl bromide, but in this case with *inversion* of configuration; so the product is the cis vinyl bromide.[220] Vinylaluminum compounds react with Br_2 and I_2 to give vinyl bromides and iodides with retention of configuration.[221] Vinyl iodides can also be prepared by treatment of vinylcopper reagents with I_2.[222] This reaction is not applicable to bromides, but divinylmercury compounds (which can be prepared from vinylcopper compounds) give vinyl bromides when treated with Br_2.[222]

Aryl iodides can be prepared in high yield by the reaction of arylthallium bis(trifluoroacetates) (see reaction **2-20**) with KI.[223] This procedure affords an indirect method for achieving still another conversion, that of ArH → ArI. For the reaction of lithium enolates of esters with I_2, see reaction **2-5.**

It is unlikely that a single mechanism suffices to cover all conversions of organometallic compounds to alkyl halides.[224] In a number of cases the reaction has been shown to involve inversion of configuration (see p. 523), indicating an SE2 (back) mechanism, while in other cases retention of configuration has been shown,[225] implicating an SE2 (front) or SEi mechanism. In still other cases complete loss of configuration as well as other evidence have demonstrated the presence of a free-radical mechanism.[226]

OS **I,** 125, 325, 326; **III,** 774, 813; **55,** 70. Also see OS **II,** 150.

E. Nitrogen Electrophiles

2-29 The Conversion of Organometallic Compounds to Amines

$$R_3B \xrightarrow[NH_2OSO_2OH]{NH_2Cl\ \text{or}} 2RNH_2 + RB(OH)_2$$

Organoboranes react with chloramine or with hydroxylamine-O-sulfonic acid in diglyme to produce primary amines.[227] Only two of the three alkyl groups of the borane are converted to amine molecules. Since the boranes can be prepared by the hydroboration of alkenes (reaction **5-15**), this is an indirect method for the addition of NH_3 to a double bond with anti-Markovnikov orientation. Alkyl Grignard reagents also react with chloramine and with hydroxylamine derivatives to give moderate yields of primary amines.[228] Secondary amines can be prepared[229] by the treatment of alkyl- or aryldichloroboranes or dialkylchloroboranes (prepared as on p. 720) with alkyl or aryl azides. Trialkylboranes also give this reaction, but are less

$$RBCl_2 + R'N_3 \longrightarrow RR'NBCl_2 \xrightarrow[OH^-]{H_2O} RNHR'$$

$$R_2BCl + R'N_3 \xrightarrow[2.\ H_2O]{1.\ Et_2O} RNHR'$$

[220] Brown, Hamaoka, and Ravindran, *J. Am. Chem. Soc.* **95,** 6456 (1973); see also Hamaoka and Brown, *J. Org. Chem.* **40,** 1189 (1975).

[221] Zweifel and Whitney, *J. Am. Chem. Soc.* **89,** 2753 (1967).

[222] Normant, Cahiez, Chuit, and Villieras, *J. Organomet. Chem.* **77,** 269 (1974), *Synthesis* 803 (1974).

[223] Ref. 187. See also Ishikawa and Sekiya, *Bull. Chem. Soc. Jpn.* **47,** 1680 (1974); Ref. 199a.

[224] For reviews of the mechanisms, see Abraham, Ref. 2, pp. 135–177; Jensen and Rickborn, Ref. 2, pp. 75–97.

[225] For example, see Jensen and Gale, *J. Am. Chem. Soc.* **82,** 148 (1960).

[226] See for example, Ref. 225; Beletskaya, Reutov, and Gur'yanova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1483 (1961); Beletskaya, Reutov, and Azizyan, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 204 (1962); Beletskaya, Ermanson, and Reutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 218 (1965).

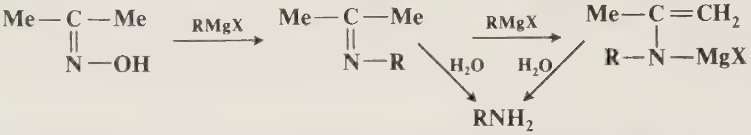
[227] Brown, Heydkamp, Breuer, and Murphy, *J. Am. Chem. Soc.* **86,** 3565 (1964); Rathke, Inoue, Varma, and Brown, *J. Am. Chem. Soc.* **88,** 2870 (1966). See also Tamura, Minamikawa, Fujii, and Ikeda, *Synthesis* 196 (1974).

[228] For example, see Coleman and Blomquist, *J. Am. Chem. Soc.* **63,** 1692 (1941).

[229] Brown, Midland and Levy, *J. Am. Chem. Soc.* **94,** 2114 (1972); **95,** 2394 (1973).

satisfactory because higher temperatures are required, and the reaction fails when R or R′ is bulky.[230]

It has been reported that alkyl or aryl Grignard reagents in toluene react with acetoxime to give (after hydrolysis) primary amines.[231] An imine intermediate is assumed.



Molecular nitrogen (N_2) reacts with aryllithium compounds in the presence of compounds of such transition metals as titanium, chromium, molybdenum, or vanadium (e.g., $TiCl_4$) to give (after hydrolysis) primary aromatic amines.[232]

$$\mathrm{ArLi} + \mathrm{N_2} \xrightarrow[\text{2. } \mathrm{H_2O}]{\text{1. } \mathrm{MX}_n} \mathrm{ArNH_2} + \mathrm{NH_3}$$

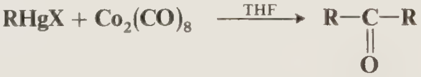
2-30 The Conversion of Grignard Reagents to Azides

$$\mathrm{ArMgX} + \mathrm{TsN_3} \longrightarrow \mathrm{(ArNNNTs)MgX} \xrightarrow[\text{pyrophosphate}]{\text{sodium}} \mathrm{ArN_3}$$

Aryl Grignard reagents react with tosyl azide to give triazene salts which can be fragmented by treatment with aqueous sodium pyrophosphate to give moderate to good yields of aryl azides.[233] Alkyl Grignard reagents also give the reaction, but yields are poor.

F. Carbon Electrophiles

2-31 The Conversion of Organometallic Compounds to Ketones or Aldehydes



$$\mathrm{RHgX} + \mathrm{Co_2(CO)_8} \xrightarrow{\text{THF}} \mathrm{R{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}R}$$

Symmetrical ketones can be prepared in good yields by the reaction of organomercuric halides with dicobalt octacarbonyl in tetrahydrofuran,[234] or with nickel carbonyl in dimethylformamide or certain other solvents.[235] R may be aryl or alkyl. However, when R is alkyl, rearrangements may intervene in the $Co_2(CO)_8$ reaction, though the $Ni(CO)_4$ reaction seems to be free from such rearrangements.[235] Diaryl ketones have also been prepared in low to moderate yields by treatment of the substrate with CO and Pd or Rh halide catalysts.[236] Diarylmercury compounds Ar_2Hg give Ar_2CO when treated with CO and a small amount of $Co_2(CO)_8$ acting as a catalyst, providing the reaction vessel is irradiated with uv light.[237] When arylmercury halides are treated with nickel carbonyl in the presence of Ar′I, unsymmetrical diaryl ketones can be obtained.[235] Aryllithium reagents react with iron pentacarbonyl to give aldehydes ArCHO,[238] while alkyllithium reagents react with CO to give symmetrical ketones.[239]

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[230] Suzuki, Sono, Itoh, Brown, and Midland, *J. Am. Chem. Soc.* **93,** 4329 (1971).

[231] Alvernhe and Laurent, *Tetrahedron Lett.* 1007 (1972).

[232] Vol'pin, *Pure Appl. Chem.* **30,** 607 (1972).

[233] Smith, Rowe, and Bruner, *J. Org. Chem.* **34,** 3430 (1969).

[234] Seyferth and Spohn, *J. Am. Chem. Soc.* **91,** 3037 (1969).

[235] Hirota, Ryang, and Tsutsumi, *Tetrahedron Lett.* 1531 (1971).

[236] Heck, *J. Am. Chem. Soc.* **90,** 5546 (1968).

[237] Seyferth and Spohn, *J. Am. Chem. Soc.* **91,** 6192 (1969).

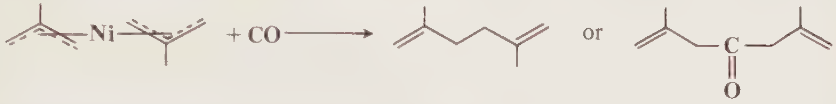
[238] Ryang, Rhee, and Tsutsumi, *Bull. Chem. Soc. Jpn.* **37,** 341 (1964).

[239] Ryang and Tsutsumi, *Bull. Chem. Soc. Jpn.* **35,** 1121 (1962); Ryang, Sawa, Hasimoto, and Tsutsumi, *Bull. Chem. Soc. Jpn.* **37,** 1704 (1964); Trzupek, Newirth, Kelly, Sbarbati, and Whitesides, *J. Am. Chem. Soc.* **95,** 8118 (1973).

Aryl and vinyl halides react with a 1 : 1 CO–H_2 mixture at about 80 atm pressure in the presence of a tertiary amine and a complex such as $(PPh_3)_2PdBr_2$ to give the corresponding aldehyde.[240] An organopalladium complex is an intermediate. When the reaction is carried out at atmospheric pressure and 100 C, without H_2, and with an alcohol R′OH or a primary or a secondary amine $R'NH_2$ or R'_2NH added, the product is, respectively, an ester RCOOR′ or an amide RCONHR′ or $RCONR'_2$.[241] Dibutyl ketone can be prepared in good yield by treatment of dibutylcopperlithium with CO.[242] Alkyl Grignard reagents react with CO under pressure to give alkenes which contain one more carbon atom than the doubled R group,[243] e.g.,

$$2CH_3CH_2CH_2MgBr + CO \longrightarrow CH_3CH_2CH_2CH{=}CHCH_2CH_3$$

Treatment of bis-π-allylnickel complexes [which can be prepared from an allyl Grignard reagent and $NiBr_2$ or from a π-allylnickel bromide (p. 413)] with CO gives either a 1,5-hexadiene or a diallyl ketone, depending on the structure of the ligand.[244]



See also reactions **0-104**, **5-22**, **6-76**, and **8-27** to **8-29**.

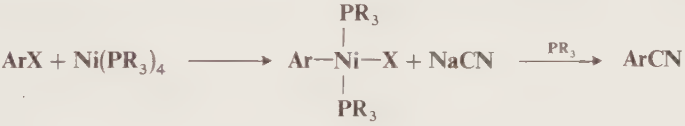
2-32 Cyanogenation of Organometallic Compounds

$$ArTl(OOCCF_3)_2 \xrightarrow[\text{aq. KCN}]{\text{excess}} ArTl(CN)_3^- \;\; K^+ \xrightarrow[\text{KCN}]{h\nu} ArCN$$

Arylthallium bis(trifluoroacetates) (reaction **2-20**) can be converted to aryl nitriles by treatment with excess aqueous KCN followed by photolysis of the resulting complex ion $ArTl(CN)_3^-$ in the presence of excess KCN.[199] Alternatively, arylthallium(III) salts react with $Cu(CN)_2$ or CuCN to give aryl nitriles without irradiation,[245] e.g.,

$$PhTl(OAc)(ClO_4) + Cu(CN)_2 \xrightarrow[\text{pyridine}]{\text{115 C, 5 hr}} 75\%\ PhCN$$

Yields from this procedure are variable, ranging from almost nothing to 90 or 100%. In another method, the arylnickel(0) complex **35** reacts with sodium cyanide to give aryl nitriles.[246] **35** are



$$ArX + Ni(PR_3)_4 \longrightarrow Ar{-}\underset{\underset{\displaystyle PR_3}{|}}{\overset{\overset{\displaystyle PR_3}{|}}{Ni}}{-}X + NaCN \xrightarrow{PR_3} ArCN$$

35

prepared by treatment of aryl halides with $Ni(PR_3)_4$ complexes.[247] In still another method, aryllithium reagents react with pentachlorobenzonitrile C_6Cl_5CN to give low to moderate yields of aryl nitriles.[248]

[240] Schoenberg and Heck, *J. Am. Chem. Soc.* **96,** 7761 (1974).

[241] Schoenberg, Bartoletti, and Heck, *J. Org. Chem.* **39,** 3318 (1974); Schoenberg and Heck, *J. Org. Chem.* **39,** 3327 (1974).

[242] Schwartz, *Tetrahedron Lett.* 2803 (1972).

[243] Puzitskii, Éidus, and Ryabova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1745 (1966). See also Sprangers, van Swieten, and Louw, *Tetrahedron Lett.* 3377 (1974).

[244] For a review, see Semmelhack, *Org. React.* **19,** 115–198 (1972), pp. 123–128.

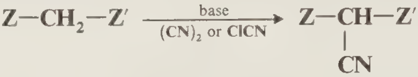
[245] Uemura, Ikeda, and Ichikawa, *Tetrahedron* **28,** 3025 (1972).

[246] Cassar, *J. Organomet. Chem.* **54,** C57 (1973).

[247] For example, see Gerlach, Kane, Parshall, Jesson, and Muetterties, *J. Am. Chem. Soc.* **93,** 3543 (1971).

[248] Foulger and Wakefield, *Tetrahedron Lett.* 4169 (1972).

In some cases nitriles can be prepared by treatment of Grignard reagents with chlorocyanogen ClCN or with cyanogen NCCN, but these methods are limited in scope. For example, the reaction of ClCN with RMgX where R is aryl, alkynyl, or primary alkyl, gives mostly nitriles, but when R is secondary or tertiary alkyl, the principal products are alkyl chlorides. Other organometallic compounds may also give nitriles when treated with these reagents. Important examples are enolates derived from malonic ester, acetoacetic ester, and similar compounds. Primary and secondary Grignard reagents and certain other organometallic compounds react



$$\text{Z—CH}_2\text{—Z}' \xrightarrow[(\text{CN})_2 \text{ or ClCN}]{\text{base}} \text{Z—}\underset{\displaystyle\text{CN}}{\underset{|}{\text{CH}}}\text{—Z}'$$

with triphenylmethyl isocyanide Ph_3CNC to give nitriles in variable yields.[249]

Olefinic cyanides can be prepared from alkenes and palladium cyanide in a polar aprotic solvent. Yields are not high.[250]

$$CH_2{=}CHR \xrightarrow{Pd(CN)_2} CH_2{=}CR{-}CN$$

For other electrophilic substitutions of the type RM → RC, see reactions **0-86** to **0-109**, which are discussed under nucleophilic substitutions in Chapter 10. See also reaction **6-76**.

G. Metal Electrophiles

2-33 Replacement of a Metal with a Metal

$$RM + M' \rightleftharpoons RM' + M$$

Many organometallic compounds are best prepared by this reaction, which involves replacement of a metal in an organometallic compound by another metal.[251] RM′ can be successfully prepared only when M′ is above M in the electromotive series, unless some other way is found to shift the equilibrium. That is, RM is usually an unreactive compound, and M′ a metal more active than M. Most often, RM is R_2Hg, since mercury alkyls are easy to prepare and mercury is far down in the electromotive series.[252] Alkyls of Li, Na, K, Be, Mg, Al, Ga, Zn, Cd, Te, Sn, etc., have been prepared in this way. An important advantage of this method over reaction **2-37** is that it ensures that the organometallic compound will be prepared free of any possible halide. This method can be used for the isolation of solid sodium and potassium alkyls. If the metals lie too close together in the series, it may not be possible to shift the equilibrium. For example, alkylbismuth compounds cannot be prepared in this way from alkylmercury compounds.

OS V, 1116.

2-34 Replacement of a Metal with a Metal Halide

$$RM + M'X \rightleftharpoons RM' + MX$$

In contrast to reaction **2-33** the reaction between an organometallic compound and a metal *halide* is successful only when M′ is *below* M in the electromotive series.[253] The two reactions considered together therefore constitute a powerful tool for preparing all kinds of organometallic compounds. In this reaction the most common substrates are Grignard reagents. Among others, alkyls of Be, Zn, Cd, Hg, Al, Sn, Pb, Co, Pt, and Au have been prepared by treatment of Grignard reagents with the appropriate halide.[254] The reaction has been used to prepare alkyls of almost all nontransition metals and even of some transition metals. Alkyls of metalloids and of nonmetals, including Si, B, Ge, P, As, Sb, and Bi, can also be prepared in this manner.[255] Except for alkali-metal alkyls and Grignard reagents, the reaction between RM and M′X is the most common method for the preparation of organometallic compounds.[256]

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[249] Walborsky, Niznik, and Periasamy, *Tetrahedron Lett.* 4965 (1971); Periasamy and Walborsky, *J. Org. Chem.* **39,** 611 (1974).

[250] Odaira, Oishi, Yukawa, and Tsutsumi, *J. Am. Chem. Soc.* **88,** 4105 (1966).

[251] For a review, see Jones and Gilman, *Chem. Rev.* **54,** 835–890 (1954), pp. 841–845.

[252] For a review of the reaction when M is mercury, see Makarova, Ref. 191, pp. 190–226.

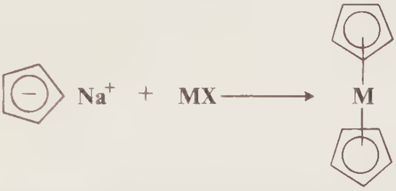
[253] For a review, see Ref. 251, pp. 847–856. Also see Schlosser, Ref. 188. For reviews of the mechanism, see Abraham, Ref. 2, pp. 39–106; Jensen and Rickborn, Ref. 2, pp. 100–192.

If M′ has a valence higher than 1, it is often possible to stop the reaction before all the halogens have been replaced, e.g.,

$$\mathrm{RMgX + SiCl_4 \longrightarrow RSiCl_3}$$

However, it is not always possible: RMgX + BF_3 gives only BR_3, although $BRCl_2$ can be prepared from R_2Zn and BCl_3.

Metallocenes (see p. 47) are usually made by this method:



Among others, metallocenes of Sc, Ti, V, Cr, Mn, Fe, Co, and Ni have been prepared in this manner.[257]

Metal nitrates are sometimes used instead of halides. For example, silver alkyls have been prepared from alkyllead compounds and silver nitrate.[258] Organosodium and organopotassium compounds can be prepared by the treatment of organolithium compounds with sodium and potassium alkoxides.[259]

OS **I,** 231, 550; **III,** 601; **IV,** 258, 473, 881; **V,** 211, 496, 727, 918, 1001; **55,** 127. Also see OS **IV,** 476.

2-35 Replacement of a Metal with an Organometallic Compound

$$\mathrm{RM + R'M' \rightleftharpoons RM' + R'M}$$

This type of metallic exchange is used much less often than reactions **2-33** and **2-34.** It is an equilibrium reaction and is useful only if the equilibrium lies in the desired direction. Usually the goal is to prepare a lithium compound which is not prepared easily in other ways, for example, vinyl- or allyllithium.[260] Examples are the preparation of vinyllithium from phenyllithium and tetravinyltin and the formation of α-dimethylamino organolithium compounds from the corresponding organotin compounds[261]

$$\mathrm{RR'NCH_2SnBu_3 + BuLi \xrightarrow{0^\circ C} RR'NCH_2Li + Bu_4Sn}$$

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[254] For a review, see Noltes, *Bull. Soc. Chim. Fr.* 2151 (1972).

[255] For a review as applied to Si, B, and P, see Ref. 193, pp. 1306–1345.

[256] For a review where M is aluminum, see Mole, *Organomet. React.* **1,** 1-54 (1970), pp. 31–43; where M is mercury, see Makarova, Ref. 191, pp. 129–178, 227–240.

[257] For reviews of the preparation of metallocenes, see Bublitz and Rinehart, *Org. React.* **17,** 1–154 (1969); Birmingham, *Adv. Organomet. Chem.* **2,** 365–413 (1965), pp. 375–382.

[258] Brown, Hérbert, and Snyder, *J. Am. Chem. Soc.* **83,** 1001 (1961).

[259] Lochmann, Pospíšil, and Lím. *Tetrahedron Lett.* 257 (1966); Lochmann and Lím, *J. Organomet. Chem.* **28,** 153 (1971).

[260] For reviews, see Seyferth, Vaughan, Raab, Welch, Cohen, and Alleston, *Bull. Soc. Chim. Fr.* 1364-1367 (1963); Ref. 251, pp. 863–865.

[261] Peterson, *J. Am. Chem. Soc.* **93,** 4027 (1971); Peterson and Ward, *J. Organomet. Chem.* **66,** 209 (1974).

In general, the equilibrium lies in the direction in which the more electropositive metal is bonded to that alkyl or aryl group which is the more stable carbanion (p. 161). The reaction proceeds with retention of configuration;[262] an SEi mechanism is likely.[263]

OS **V**, 452; **51,** 17.

Halogen as Leaving Group

A. Hydrogen as the Electrophile

2-36 Reduction of Alkyl Halides

Although this reaction can proceed by an electrophilic substitution mechanism, it is considered in Chapter 10 (reaction **0-77**).

B. Metal Electrophiles

2-37 Replacement of a Halogen with a Metal

$$\mathbf{RX + M \longrightarrow RM}$$

Alkyl halides react directly with certain metals to give organometallic compounds. The most common metal is magnesium, and of course this is by far the most common method for the preparation of Grignard reagents.[264] The order of halide activity is I > Br > Cl. The reaction may be applied to many alkyl halides—primary, secondary, and tertiary—and to aryl halides, though aryl *chlorides* require the use of tetrahydrofuran or another higher-boiling solvent instead of the usual ether, or the use of special entrainment methods.[265] Aryl iodides and bromides can be treated in the usual manner. Allyl Grignard reagents can also be prepared in the usual manner (or in tetrahydrofuran),[266] though in the presence of excess halide these may give Wurtz-type coupling products (see reaction **0-87**). Like aryl chlorides, vinyl halides require higher-boiling solvents (see OS **IV**, 258), and ethynyl Grignard reagents are not generally prepared by this method at all. For these, reaction **2-19** is used. Dihalides[267] can be converted to Grignard reagents if the halogens are different and are at least three carbons apart. If the halogens are the same, it is possible to obtain dimagnesium compounds, e.g., $BrMg(CH_2)_4MgBr$.[268] 1,2-Dihalides give elimination instead of Grignard reagent formation (reaction **7-27**), and the reaction is seldom successful with 1,1-dihalides, though the preparation of *gem*-disubstituted compounds, such as $CH_2(MgBr)_2$, has been accomplished with these substrates.[269] α-Halo Grignard reagents and α-halolithium reagents can be prepared by the method given in reaction **2-38.**[270] Alkylmagnesium fluorides can be prepared by refluxing alkyl fluorides with Mg in the presence of appropriate catalysts (e.g., I_2 or EtBr) in tetrahydrofuran for several days.[271]

The presence of other functional groups in the halide usually affects the preparation of the Grignard reagent. Groups which contain active hydrogen (as defined on p. 557), such as OH, NH_2, and COOH, may be present in the molecule, but only if they are converted to the salt form (O^-, NH^-, COO^-, respectively). Groups which react with Grignard reagents, such as

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[262] Seyferth and Vaughan, *J. Am. Chem. Soc.* **86,** 883 (1964).

[263] Dessy, Kaplan, Coe, and Salinger, *J. Am. Chem. Soc.* **85,** 1191 (1963).

[264] For reviews, see Ref. 193, pp. 5–91; Ref. 251, pp. 836–841.

[265] Pearson, Cowan, and Beckler, *J. Org. Chem.* **24,** 504 (1959).

[266] For a review of allyl and crotyl Grignard reagents, see Benkeser, *Synthesis* 347–358 (1971).

[267] For reviews of the preparation of Grignard reagents from dihalides, see Heaney, *Organomet. Chem. Rev.* **1,** 27–42 (1966); Millar and Heaney, *Q. Rev., Chem. Soc.* **11,** 109–120 (1957).

[268] For example, see Denise, Ducom, and Fauvarque, *Bull. Soc. Chim. Fr.* 990 (1972).

[269] For example, see Bertini, Grasselli, Zubiani, and Cainelli, *Tetrahedron* **26,** 1281 (1970).

[270] For a review of compounds containing both carbon-halogen and carbon-metal bonds, see Chivers, *Organomet. Chem. Rev., Sect. A* **6,** 1–64 (1970).

[271] Yu and Ashby, *J. Org. Chem.* **36,** 2123 (1971). See also Ashby and Nackashi, *J. Organomet. Chem.* **24,** C17 (1970).

C=O, C≡N, NO_2, COOR, etc., inhibit Grignard formation entirely. In general, the only functional groups which may be present in the halide molecule without any interference at all are double and triple bonds (except terminal triple bonds) and OR and NR_2 groups. However, β-halo ethers generally give β-elimination when treated with magnesium (see reaction **7-29**), and Grignard reagents from α-halo ethers[272] can only be formed in tetrahydrofuran or methylal at a low temperature, e.g.,[273]

$$\mathrm{EtOCH_2Cl + Mg \xrightarrow[-30^\circ C]{THF\ or\ CH_2(OMe)_2} EtOCH_2MgCl}$$

because such reagents immediately undergo α elimination (see reaction **2-38**) at room temperature in ether solution.

Because Grignard reagents react with water (reaction **2-21**) and with oxygen (reaction **2-22**), it is generally best to prepare them in an anhydrous nitrogen atmosphere. Grignard reagents are generally neither isolated nor stored; but solutions of Grignard reagents are used directly for the required synthesis. Grignard reagents can also be prepared in benzene or toluene, if a tertiary amine is added to complex with the RMgX.[274] This method eliminates the need for an ether solvent. With certain primary alkyl halides it is even possible to prepare alkylmagnesium compounds in hydrocarbon solvents in the absence of an organic base.[275]

Next to the formation of Grignard reagents, the most important application of this reaction is the conversion of alkyl and aryl halides to organolithium compounds, but it has also been carried out with many other metals, e.g., Na, Be, Zn, Hg, As, Sb, and Sn.[276] With sodium, the Wurtz reaction (**0-86**) is an important side reaction. The reaction is not successful for potassium, complex mixtures being obtained in which RK is an unimportant constituent.[277] In some cases where the reaction between a halide and a metal is too slow, an alloy of the metal with potassium or sodium can be used instead. The most important example is the preparation of tetraethyllead from ethyl bromide and a Pb–Na alloy. In another example it has been shown that in the treatment of an alkyl halide with lithium it is necessary that a small amount of sodium be alloyed with the lithium in order to obtain a good yield of alkyllithium.[278]

The mechanism of Grignard reagent formation is not well known, though much work has been done in the area.[279] There is evidence from CIDNP[280] (p. 171) and from stereochemical, rate, and product studies[281] that free radicals are intermediates, and the following mechanism has been proposed:[280]

$$\begin{aligned}
\mathrm{R{-}X} + \overline{\mathrm{Mg}} &\longrightarrow \mathrm{R{-}X}^{\dot{-}} + \mathrm{Mg}_s^{\dot{+}} \\
\mathrm{R{-}X}^{\dot{-}} &\longrightarrow \mathrm{R}\cdot + \mathrm{X}^- \\
\mathrm{X}^- + \mathrm{Mg}_s^{\dot{+}} &\longrightarrow \mathrm{XMg}_s^{\boldsymbol{\cdot}} \\
\mathrm{R}\cdot + \mathrm{XMg}_s^{\boldsymbol{\cdot}} &\longrightarrow \mathrm{RMgX}
\end{aligned}$$

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[272] For a review of organometallic compounds containing an α hetero atom (N, O, P, S, or Si), see Peterson, *Organomet. Chem. Rev., Sect. A* **7**, 295–358 (1972).

[273] For example, see Normant and Castro, *C. R. Acad. Sci.* **257**, 2115 (1963), **259**, 830 (1964); Castro, *Bull. Soc. Chim. Fr.* 1533, 1540, 1547 (1967); Taeger, Fiedler, Chiari, and Berndt, *J. Prakt. Chem.* [4] **28**, 1 (1965); Taeger, Kahlert, and Walter, *J. Prakt. Chem.* [4] **28**, 13 (1965).

[274] Ashby and Reed, *J. Org. Chem.* **31**, 971 (1966); Gitlitz and Considine, *J. Organomet. Chem.* **23**, 291 (1970).

[275] Smith, *J. Organomet. Chem.* **64**, 25 (1974).

[275a] For a monograph on organolithium compounds, see Wakefield, "The Chemistry of Organolithium Compounds," Pergamon Press, New York, 1974.

[276] For a review, see Rochow, *J. Chem. Educ.* **43**, 58–62 (1966).

[277] Finnegan, *Tetrahedron Lett.* 1303 (1962); 851 (1963).

[278] Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, pp. 618–619, John Wiley & Sons, Inc., New York, 1967.

[279] For a review, see Blomberg, *Bull. Soc. Chim. Fr.* 2143 (1972).

[280] Bodewitz, Blomberg, and Bickelhaupt, *Tetrahedron Lett.* 281 (1972), 2003 (1975), *Tetrahedron* **29**, 719 (1973), **31**, 1053 (1975).

[281] See for example, Walborsky and Aronoff, *J. Organomet. Chem.* **51**, 31 (1973); Czernecki, Georgoulis, Gross, and Prevost, *Bull. Soc. Chim. Fr.* 3720 (1968); Rogers, Mitchell, Fujiwara, and Whitesides, *J. Org. Chem.* **39**, 857 (1974).

The species $R{-}X^{\dot{-}}$ and $Mg^{\dot{+}}$ are radical ions. The subscript "s" is meant to indicate that the species so marked are bound to the surface of the magnesium.

There are too many preparations of Grignard reagents in *Organic Syntheses* for us to list here. Use of the reaction to prepare other organometallic compounds can be found in OS **I,** 228; **II,** 184, 517, 607; **III,** 413, 757; **52,** 19; **55,** 103. The preparation of unsolvated butylmagnesium bromide is described at OS **V,** 1141.

2-38 Replacement of a Halogen by a Metal from an Organometallic Compound

$$\mathbf{RX + R'M \longrightarrow RM + R'X}$$

The exchange reaction between alkyl halides and organometallic compounds is almost entirely limited to the cases where M is lithium and X is bromide or iodide,[282] though it has been shown to occur with magnesium.[283] R′ is usually, though not always, alkyl, and often butyl; R is usually aromatic. Of course, the R which becomes bonded to the halogen is the one for which RH is the weaker acid. The reaction can be used to prepare α-halo organolithium and α-halo organomagnesium compounds,[284] e.g.,[285]

$$\mathbf{CCl_4 + BuLi \xrightarrow[-105^\circ C]{THF} Cl_3C{-}Li}$$

Such compounds can also be prepared by hydrogen-metal exchange, e.g.,[286]

$$\mathbf{Br_3CH + iso\text{-}PrMgCl \xrightarrow[-95^\circ C]{THF-HMPT} Br_3C{-}MgCl + C_3H_8}$$

This is an example of reaction **2-19.** However, these α-halo organometallic compounds are stable only at low temperatures (~ −100°C) and only in tetrahydrofuran or mixtures of tetrahydrofuran and other solvents (e.g., HMPT). At ordinary temperatures they lose MX (α elimination) to give carbenes (which then react further) or carbenoid reactions. The α-chloro-α-magnesio sulfones $ArSO_2CH(Cl)MgBr$ are exceptions, being stable in solution at room temperature and even under reflux.[287]

When the substrate has a halogen and a hydrogen on the same carbon, halogen-metal exchange is usually more rapid than hydrogen-metal exchange (the reaction of bromoform under the conditions shown above is an exception).[288] α-Halo sodium and α-halo potassium compounds have also been prepared by a hydrogen-metal exchange reaction.[289]

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[282] For reviews, see Jones and Gilman, *Org. React.* **6,** 339–366 (1951); Ref. 251, pp. 867–868.

[283] See for example Zakharkin, Okhlobystin, and Bilevitch, *J. Organomet. Chem.* **2,** 309 (1964); Tamborski and Moore, *J. Organomet. Chem.* **26,** 153 (1971).

[284] For reviews of α-halo organolithium and α-halo organomagnesium compounds, see Köbrich, *Angew. Chem. Int. Ed. Engl.* **11,** 473–485 (1972), **6,** 41–52 (1967) [*Angew. Chem.* **84,** 557–570, **79,** 15–27], *Bull. Soc. Chim. Fr.* 2712–2720 (1969); Villiéras, *Organomet. Chem. Rev., Sect. A* **7,** 81–94 (1971). For a related review, see Normant, *J. Organomet. Chem.* **100,** 189–203 (1975).

[285] Hoeg, Lusk, and Crumbliss, *J. Am. Chem. Soc.* **87,** 4147 (1965). See also Fischer and Köbrich, *Chem. Ber.* **101,** 3230 (1968).

[286] Villiéras, *Bull. Soc. Chim. Fr.* 1520 (1967).

[287] Stetter and Steinbeck, *Justus Liebigs Ann. Chem.* **766,** 89 (1972).

[288] For a review of reactions of organometallic compounds with di- and polyhalomethanes, see Zhil'tsov and Druzhkov, *Russ. Chem. Rev.* **40,** 126–141 (1971).

[289] Martel and Hiriart, *Tetrahedron Lett.* 2737 (1971).

The mechanism in the reaction of alkyllithium compounds with alkyl and aryl iodides has been shown to involve free radicals:[290]

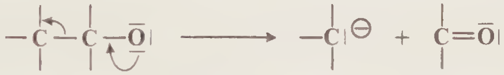
$$\mathbf{RX + R'M \rightleftharpoons \underset{\text{Solvent cage}}{[R\cdot, X, M, R'\cdot]} \rightleftharpoons RM + R'X}$$

Evidence for this mechanism is the obtention of coupling and disproportionation products from R• and R′•, and the observation of CIDNP (p. 171).[291]

Carbon Leaving Groups

In these reactions (**2-39** to **2-47**) a carbon-carbon bond cleaves.[292] We regard as the substrate that side which retains the electron pair; hence the reactions are considered electrophilic substitutions. The incoming group is hydrogen in all but one (reaction **2-41**) of the cases. The reactions in groups A and B are sometimes called *anionic cleavages*, though they do not always occur by mechanisms involving free carbanions (SE1). When they do, the reactions are facilitated by increasing stability of the carbanion.

A. Carbonyl-forming Cleavages These reactions follow the pattern



The leaving group is stabilized because the electron deficiency at its carbon is satisfied by a pair of electrons from the oxygen. With respect to the leaving group the reaction is elimination to form a C=O bond. Retrograde aldol condensations (reaction **6-40**) and cleavage of cyanohydrins (reaction **6-50**) belong to this classification but are treated in Chapter 16 under their more important reverse reactions. Other eliminations to form C=O bonds are discussed in Chapter 17 (reactions **7-44** to **7-46**).

2-39 Decarboxylation of Aliphatic Acids

$$\mathbf{RCOOH \longrightarrow RH + CO_2}$$

Many carboxylic acids can be successfully decarboxylated, either as the free acid or in the salt form, but not simple fatty acids.[293] An exception is acetic acid, which as the acetate, heated with base, gives good yields of methane. Aliphatic acids which do undergo successful decarboxylation have certain functional groups or double or triple bonds in the α or β position. Some of these are shown in Table 1. For decarboxylation of aromatic acids, see reaction **1-43.** Decarboxylation of an α-cyano acid may give a nitrile or a carboxylic acid, since the cyano group may or may not be hydrolyzed in the course of the reaction. In addition to the compounds listed in Table 1, decarboxylation can also be carried out on α,β-unsaturated and α,β-acetylenic acids, acids with a positive sulfur in the α position, for example, $Me_2\overset{+}{S}CH_2COOH\ Br^-$,[294] and certain acids with a

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[290] Ward, Lawler, and Cooper, *J. Am. Chem. Soc.* **91,** 746 (1969); Lepley and Landau, *J. Am. Chem. Soc.* **91,** 748 (1969).

[291] Ward, Lawler, and Loken, *J. Am. Chem. Soc.* **90,** 7359 (1968); Ref. 290.

[292] For a review, see Shemyakin and Shchukina, *Q. Rev., Chem. Soc.* **10,** 261–282 (1956).

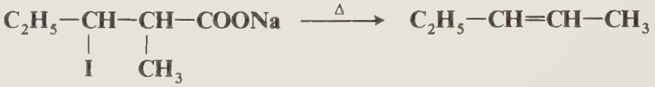
[293] March, *J. Chem. Educ.* **40,** 212 (1963).

[294] Burness, *J. Org. Chem.* **24,** 849 (1959).

TABLE 1 Some acids which undergo decarboxylation fairly readily
Others are described in the text

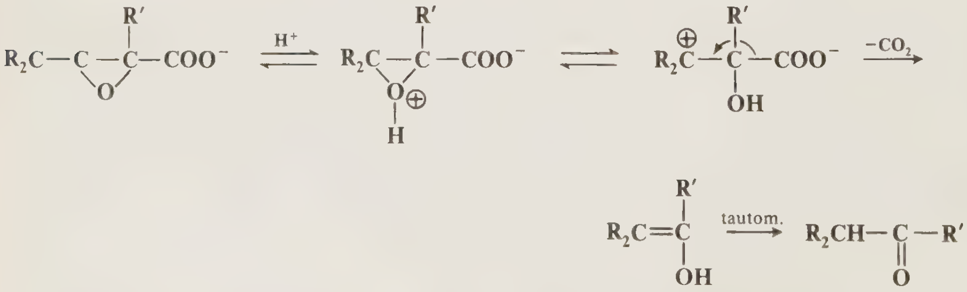
	Acid type	Decarboxylation product
Malonic	$HOOC-\overset{\mid}{\underset{\mid}{C}}-COOH$	$HOOC-\overset{\mid}{\underset{\mid}{C}}-H$
α-Cyano	$NC-\overset{\mid}{\underset{\mid}{C}}-COOH$	$NC-\overset{\mid}{\underset{\mid}{C}}-H$ or $HOOC-\overset{\mid}{\underset{\mid}{C}}-H$
α-Nitro	$O_2N-\overset{\mid}{\underset{\mid}{C}}-COOH$	$O_2N-\overset{\mid}{\underset{\mid}{C}}-H$
α-Aryl	$Ar-\overset{\mid}{\underset{\mid}{C}}-COOH$	$Ar-\overset{\mid}{\underset{\mid}{C}}-H$
α-Keto	$-\underset{\underset{O}{\Vert}}{C}-COOH$	$-\underset{\underset{O}{\Vert}}{C}-H$
α,α,α-Trihalo	$X_3C-COOH$	X_3CH
β-Keto	$-\underset{\underset{O}{\Vert}}{C}-\overset{\mid}{\underset{\mid}{C}}-COOH$	$-\underset{\underset{O}{\Vert}}{C}-\overset{\mid}{\underset{\mid}{C}}-H$
β,γ-Unsaturated	$-\underset{\mid}{C}=\underset{\mid}{C}-\overset{\mid}{\underset{\mid}{C}}-COOH$	$-\underset{\mid}{C}=\underset{\mid}{C}-\overset{\mid}{\underset{\mid}{C}}-H$

positive nitrogen in the α position.[295] β-Halo acids give decarboxylation accompanied by elimination:[296]



$$C_2H_5-\underset{I}{\underset{\mid}{CH}}-\underset{CH_3}{\underset{\mid}{CH}}-COONa \xrightarrow{\Delta} C_2H_5-CH=CH-CH_3$$

α,β-Unsaturated acids can also be decarboxylated with copper and quinoline in a manner similar to that discussed in reaction **1-43.** Glycidic acids give aldehydes on decarboxylation. The following mechanism has been suggested:[297]



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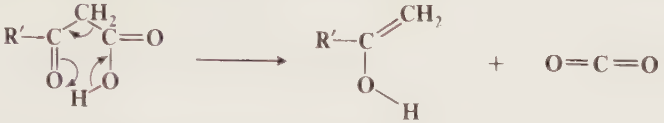
[295] Haake and Mantecon, *J. Am. Chem. Soc.* **86,** 5230 (1964).

[296] For a discussion of the mechanism of this elimination, see Vaughan, Cartwright, and Henzi, *J. Am. Chem. Soc.* **94,** 4978 (1972).

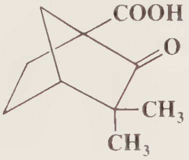
[297] Singh and Kagan, *J. Org. Chem.* **35,** 2203 (1970).

The direct product is an enol which tautomerizes to the aldehyde.[298] This is the usual last step in the Darzens reaction (reaction **6-45**).

Decarboxylations may be regarded as reversals of the addition of carbanions to carbon dioxide (reaction **6-34**), but free carbanions are not always involved.[299] When it is the carboxylate *ion* which is decarboxylated, the mechanism may be either SE1 or SE2. In the case of the SE1 mechanism, the reaction is of course aided by the presence of electron-withdrawing groups, which stabilize the carbanion.[300] Decarboxylations of carboxylate ions can be accelerated by the addition of a suitable crown ether, which in effect removes the metallic ion.[301] But some acids can also be decarboxylated directly, and in most of these cases there is a cyclic, six-center mechanism:



Here too there is an enol which tautomerizes to the product. The mechanism is illustrated for the case of β-keto acids,[302] but it is likely that malonic acids, α-cyano acids, α-nitro acids, and β,γ-unsaturated acids[303] behave similarly, since similar six-membered transition states can be written for them. Some α,β-unsaturated acids are also decarboxylated by this mechanism by isomerizing to the β,γ-isomers before they actually decarboxylate.[304] Evidence is that **36** and similar bicyclic β-keto acids resist decarboxylation.[305] In such compounds the six-membered cyclic transition state cannot form for steric reasons, and if it could, formation of the immediate enol product would violate Bredt's rule (p. 147). Some carboxylic acids which cannot form a six-membered transition state can still be decarboxylated, and these presumably react through an SE1 or SE2 mechanism.[306] Further evidence for the cyclic mechanism is that the reaction rate varies very little with a change from a nonpolar to a polar solvent (even from benzene to water[307]), and is not subject to acid catalysis.[308]



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[298] Shiner and Martin, *J. Am. Chem. Soc.* **84,** 4824 (1962).

[299] For reviews of the mechanism, see Richardson and O'Neal, in Bamford and Tipper, Ref. 49, vol. 5, pp. 447–482 (1972); Clark, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 589 622, Interscience Publishers, New York, 1969; Brown, *Q. Rev., Chem. Soc.* **5,** 131–146 (1951).

[300] See for example, Uneyama, Tagaki, Minamida, and Oae, *Tetrahedron* **24,** 5271 (1968); Oae, Tagaki, Uneyama, and Minamida, *Tetrahedron* **24,** 5283 (1968).

[301] Hunter, Lee, and Sim, *J. Chem. Soc., Chem. Commun.* 1018 (1974).

[302] For a review of the mechanism of the decarboxylation of β-keto acids, see Jencks, "Catalysis in Chemistry and Enzymology," pp. 116–120, McGraw-Hill Book Company, New York, 1969.

[303] See Bigley and Thurman, *J. Chem. Soc. B* 941 (1967). For a review, see Smith and Kelly, *Prog. Phys. Org. Chem.* **8,** 75–234 (1971), pp. 150–153.

[304] Bigley, *J. Chem. Soc.* 3897 (1964).

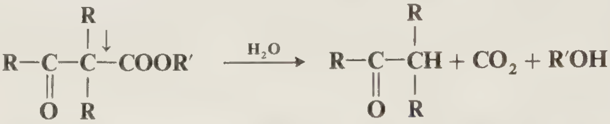
[305] Wasserman, in Newman, "Steric Effects in Organic Chemistry," p. 352, John Wiley & Sons, Inc., New York, 1956. See also Buchanan, Kean, and Taylor, *Tetrahedron* **31,** 1583 (1975).

[306] For example, see Ferris and Miller, *J. Am. Chem. Soc.* **88,** 3522 (1966).

[307] Westheimer and Jones, *J. Am. Chem. Soc.* **63,** 3283 (1941); Swain. Bader, Esteve, and Griffin, *J. Am. Chem. Soc.* **83,** 1951 (1961). See also Logue, Pollack, and Vitullo, *J. Am. Chem. Soc.* **97,** 6868 (1975).

[308] Pederson, *Acta Chem. Scand.* **15,** 1718 (1961); Noyce and Metesich, *J. Org. Chem.* **32,** 3243 (1967).

Although β-keto acids are easily decarboxylated, this reaction is seldom performed. The reason is that such acids are usually prepared from β-keto esters, and the esters are easily decarboxylated themselves on hydrolysis, without isolation of the acids. This decarboxylation of β-keto esters involving cleavage on the carboxyl side of the substituted methylene group (arrow) is carried out under acidic, neutral, or slightly basic conditions to yield a ketone. When strongly basic conditions are used, cleavage occurs on the other side of the CR_2 group (reaction **2-42**). β-Keto



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}\overset{R}{\underset{R}{C}}{\downarrow}{-}COOR'} \xrightarrow{H_2O} \mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}\overset{R}{\underset{R}{C}}H + CO_2 + R'OH}$$

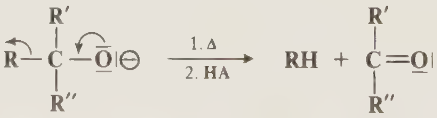
esters can be decarbalkoxylated without passing through the free-acid stage by treatment with boric anhydride B_2O_3 at 150°C.[309] The alkyl portion of the ester (R′) is converted to an alkene or, if it lacks a β-hydrogen, into an ether R′OR′. Another method for the decarbalkoxylation of β-keto esters, malonic esters, and α-cyano esters consists of heating the substrate in wet dimethyl sulfoxide containing NaCl, Na_3PO_4, or some other simple salt.[310] In this method too, the free acid is probably not an intermediate, but here the alkyl portion of the substrate is converted to the corresponding alcohol. Certain amides (e.g., Ph_3CCONH_2 and $Ph_2CHCONH_2$) can be decarboxaminated (to give, respectively, Ph_3CH and Ph_2CH_2) by treatment with butyllithium.[311] An SE1 mechanism is likely. Certain decarboxylations can also be accomplished photochemically.[312]

Some of the decarboxylations listed in *Organic Syntheses* are performed with concomitant ester or nitrile hydrolysis, and others are simple decarboxylations.

With ester or nitrile hydrolysis: OS **I,** 290, 451, 523; **II,** 200, 391; **III,** 281, 286, 317, 326, 510, 513, 591; **IV,** 55, 93, 176, 441, 664, 708, 790, 804; **V,** 76, 288, 572, 687, 989; **53,** 70, 98.

Simple decarboxylations: OS **I,** 351, 401, 440, 473, 475; **II,** 21, 61, 93, 229, 302, 333, 368, 416, 474, 512, 523; **III,** 213, 425, 495, 705, 733, 783; **IV,** 234, 254, 278, 337, 555, 560, 597, 630, 731, 857; **V,** 251, 585; **51,** 73, 136. Also see OS **IV,** 633.

2-40 Cleavage of Alkoxides



$$\mathrm{R{-}\overset{R'}{\underset{R''}{C}}{-}\overline{\underline{O}}|^{\ominus}} \xrightarrow[2.\ \mathrm{HA}]{1.\ \Delta} \mathrm{RH} + \mathrm{\overset{R'}{\underset{R''}{C}}{=}\underline{O}|}$$

Alkoxides of tertiary alcohols can be cleaved in a reaction which is essentially the reverse of addition of carbanions to ketones (reaction **6-31**).[313] The reaction is unsuccessful when the R groups are simple unbranched alkyl groups, e.g., the alkoxide of triethylcarbinol. Cleavage is accomplished with branched alkoxides such as the alkoxides of triisopropylcarbinol or diisopropylneopentylcarbinol. The reaction also takes place when R is aryl; for example, the alkoxide of triphenylcarbinol gives benzene and benzophenone. The reaction has been used for extensive mechanistic studies (see p. 525).

OS **51,** 70.

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[309] Lalancette and Lachance, *Tetrahedron Lett.* 3903 (1970).

[310] Krapcho and Lovey, *Tetrahedron Lett.* 957 (1973); Krapcho, Jahngen, Lovey, and Short, *Tetrahedron Lett.* 1091 (1974); Liotta and Cook, *Tetrahedron Lett.* 1095 (1974).

[311] Smith and Hauser, *J. Am. Chem. Soc.* **91,** 7774 (1969).

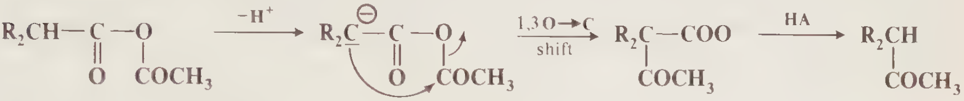
[312] For a short survey and discussion, see Davidson and Steiner, *J. Chem. Soc. C* 1682 (1971); *J. Chem. Soc., Perkin Trans. 2* 1357 (1972).

[313] Zook, March, and Smith, *J. Am. Chem. Soc.* **81,** 1617 (1959); Benkeser and Broxterman, *J. Am. Chem. Soc.* **91,** 5162 (1969).

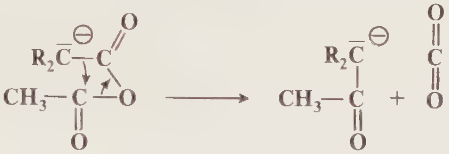
2-41 Replacement of a Carboxyl Group by an Acyl Group

$$R_2CHCOOH + (CH_3CO)_2O \longrightarrow R_2CHCOCH_3 + CO_2 + CH_3COOH$$

When a carboxylic acid containing at least one α-hydrogen is treated with an anhydride, it sometimes happens that decarboxylation occurs, accompanied by entrance of an acyl group. The reaction is aided by the presence of γ- and δ-NR_2 groups.[314] The first step is probably the formation of the mixed anhydride $R_2CHCOOCOCH_3$ by an acid-anhydride exchange (see reaction **0-30**). What happens next is not certain, but a 1,3 shift following loss of the α-proton has been proposed:[315]



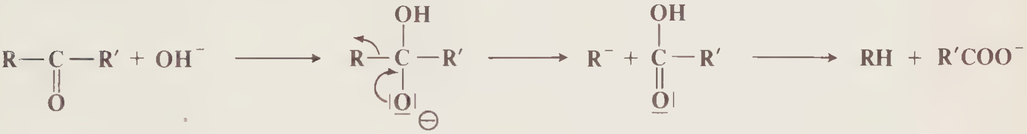
The 1,3 shift and the decarboxylation may occur in one step:[316]



This reaction was an important step in the total synthesis of strychnine.[317]

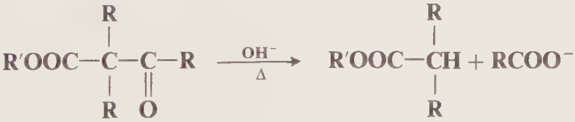
OS **IV**, 5; **V**, 27.

B. Acyl Cleavages In these reactions (**2-42** to **2-45**) a carbonyl group is attacked by a hydroxide ion (or amide ion), giving an intermediate which undergoes cleavage to a carboxylic acid (or a carboxylic acid amide). With respect to the leaving group, this is nucleophilic substitution at a carbonyl group, and the mechanism is the tetrahedral one discussed in Chapter 10 (p. 308).



With respect to R of course this is electrophilic substitution. Indications are that the mechanism is usually S_E1.

2-42 Basic Cleavage of β-Keto Esters and β-Diketones



$$R'OOC-\underset{R}{\overset{R}{C}}-\underset{O}{\overset{\|}{C}}-R \xrightarrow[\Delta]{OH^-} R'OOC-\underset{R}{\overset{R}{CH}} + RCOO^-$$

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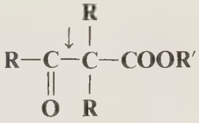
[314] Cruickshank and Sheehan, *J. Am. Chem. Soc.* **83**, 2891 (1961).

[315] Buchanan and McArole, *J. Chem. Soc.* 2944 (1952); Smith and Fahey, *J. Am. Chem. Soc.* **81**, 3391 (1959).

[316] Woodward, Cava, Ollis, Hunger, Daeniker, and Schenker, *Tetrahedron* **19**, 247 (1963).

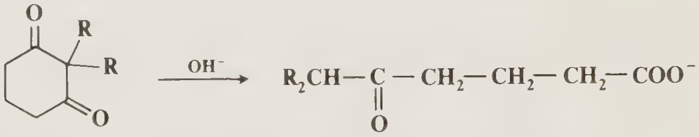
[317] Ref. 316, p. 260 (XXXIX → XL in that paper).

When β-keto esters are treated with concentrated base, cleavage occurs, but is on the keto side of the CR_2 group (arrow) in contrast to the acid cleavage mentioned on page 572. The products



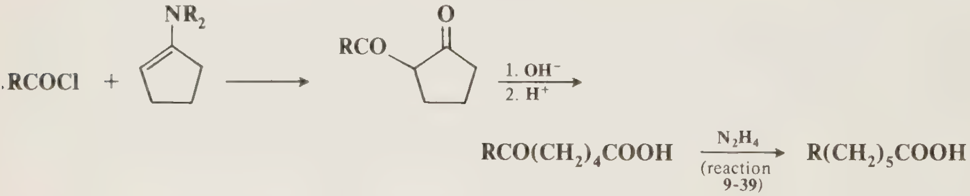
$$R-\underset{\underset{O}{\|}}{C}\overset{\downarrow}{-}\underset{\underset{R}{|}}{\overset{\overset{R}{|}}{C}}-COOR'$$

are an ester and the salt of an acid. However, the utility of the reaction is somewhat limited by the fact that decarboxylation is a side reaction, even under basic conditions. β-Diketones behave similarly to give a ketone and the salt of a carboxylic acid. The reaction has often been applied to cyclic β-diketones:[318]



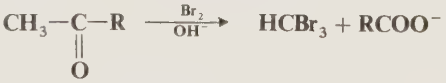
With both β-keto esters and β-diketones, OEt^- may be used instead of OH^-, in which case the ethyl esters of the corresponding acids are obtained instead of the salts. In the case of β-keto esters, this is the reverse of Claisen condensation (**0-111**).

A combination of reaction **2-17** and this reaction has been used as a method of extending a chain by 5, 6, or 12 carbons (illustrated for 5):[319]



OS **II**, 266, 531; **III**, 379; **IV**, 415, 957; **V**, 179, 187, 277, 533, 747, 767.

2-43 The Haloform Reaction



$$CH_3-\underset{\underset{O}{\|}}{C}-R \xrightarrow[OH^-]{Br_2} HCBr_3 + RCOO^-$$

In the *haloform reaction*, methyl ketones (and the only methyl aldehyde, acetaldehyde) are cleaved with halogen and a base. The halogen may be bromine, chlorine, or iodine. What takes place is actually a combination of two reactions. The first is an example of reaction **2-4**, in which, under the basic conditions employed, the methyl group is trihalogenated. Then the resulting trihalo ketone is attacked by hydroxide ion:

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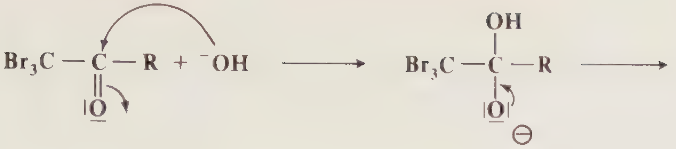
[318] For a review see Stetter, *Angew. Chem.* **67**, 769 (1955), *Newer Methods Prep. Org. Chem.* **2**, 51–99 (1963).

[319] Hünig and Lendle, *Chem. Ber.* **93**, 913 (1960); Hünig and Salzwedel, *Chem. Ber.* **99**, 823 (1966); Hünig and Buysch, *Chem. Ber.* **100**, 4010, 4017 (1967).

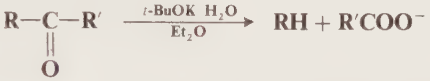


$$Br_3C^{\ominus} + RCOOH \longrightarrow Br_3CH + RCOO^-$$

Primary or secondary methylcarbinols also give the reaction, since they are oxidized to the carbonyl compounds under the conditions employed. As with reaction **2-4**, the rate-determining step is the preliminary enolization of the methyl ketone.[320] A side reaction is α halogenation of the nonmethyl R group. Sometimes these groups are also cleaved.[321] The reaction cannot be applied to F_2, but ketones of the form $RCOCF_3$ (R = alkyl or aryl) give fluoroform and $RCOO^-$ when treated with base.[322] The haloform reaction is often used as a test for methylcarbinols and methyl ketones. Iodine is most often used as the test reagent, since iodoform is an easily identifiable yellow solid. The reaction is also frequently used for synthetic purposes.

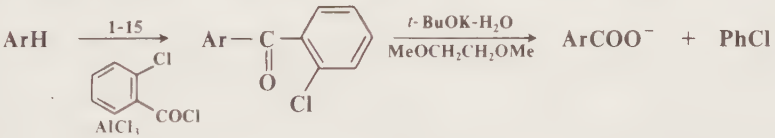
OS **I,** 526; **II,** 428; **III,** 302; **IV,** 345; **V,** 8. Also see OS **51,** 100.

2-44 Cleavage of Nonenolizable Ketones



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[Et_2O]{t\text{-BuOK}\ H_2O} RH + R'COO^-$$

Ordinary ketones are generally much more difficult to cleave than trihalo ketones or β-diketones, since the carbanion intermediates in these cases are more stable than simple carbanions. However, nonenolizable ketones can be cleaved by treatment with a 10 : 3 mixture of t-BuOK–H_2O in an aprotic solvent such as ether, dimethyl sulfoxide, 1,2-dimethoxyethane (glyme), etc.[323] When the reaction is applied to monosubstituted diaryl ketones, that aryl group preferentially cleaves which comes off as the more stable carbanion, except that aryl groups substituted in the ortho position are more readily cleaved than otherwise because of the steric effect (relief of strain).[324] Combined with the preparation of diaryl ketones by Friedel-Crafts acylation (reaction **1-15**), this reaction provides an indirect method for introducing a carboxyl group into an aromatic ring:[325]



2-Chlorobenzoyl chloride is the preferred reagent here, because a 2-chlorophenyl group cleaves much more readily than most other aryl groups. In certain cases, cyclic ketones may be cleaved by base treatment, even if they are enolizable.[326]

In another application of this reaction, cyclobutanones substituted with electron-withdrawing groups such as SR may be cleaved with OR^- to give esters.[327] Since the cyclobutanones can be

[320] Pocker, *Chem. Ind.* (*London*) 1383 (1959).

[321] Levine and Stephens, *J. Am. Chem. Soc.* **72,** 1642 (1950).

[322] See Hudlický, "Chemistry of Organic Fluorine Compounds," pp. 208–209, The Macmillan Company, New York, 1962.

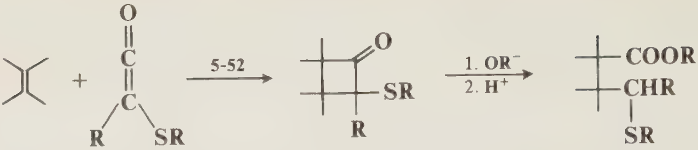
[323] Swan, *J. Chem. Soc.* 1408 (1948); Gassman, Lumb, and Zalar, *J. Am. Chem. Soc.* **89,** 946 (1967).

[324] Davies, Derenberg, and Hodge, *J. Chem. Soc. C* 455 (1971).

[325] Derenberg and Hodge, *Tetrahedron Lett.* 3825 (1971).

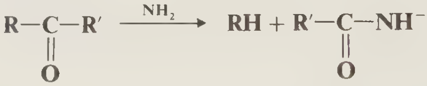
[326] For example, see Swaminathan and Newman, *Tetrahedron* **2,** 88 (1958); Hoffman and Cram, Ref. 22.

[327] Cossement, Binamé, and Ghosez, *Tetrahedron Lett.* 997 (1974).



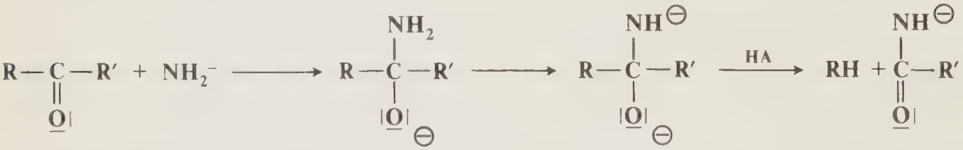
prepared by treatment of olefins with the appropriate ketenes (reaction **5-52**), this is an indirect method for the addition of two carbon moieties to a double bond (see also reactions **5-57, 5-58**).

2-45 The Haller-Bauer Reaction



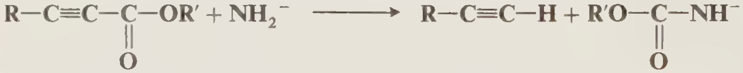
$$\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{R{-}C{-}R'}} \xrightarrow{\mathrm{NH_2}} \mathrm{RH} + \underset{\substack{\| \\ \mathrm{O}}}{\mathrm{R'{-}C{-}NH^-}}$$

Cleavage of ketones with sodium amide is called the *Haller-Bauer reaction.*[328] As with reaction **2-44**, which is exactly analogous, the reaction is usually applied only to nonenolizable ketones. It is most often applied to ketones of the form $ArCOCR_3$, where the products R_3CCONH_2 are not easily attainable by other methods. However, many other ketones have been used, though benzophenone is virtually unaffected. It has been shown that the configuration of optically active R is retained.[329] The NH_2 loses its proton *before* the R is cleaved:[330]



$$\underset{\substack{\| \\ \underline{\mathrm{O}}|}}{\mathrm{R{-}C{-}R'}} + \mathrm{NH_2^-} \longrightarrow \overset{\substack{\mathrm{NH_2} \\ |}}{\underset{\substack{| \\ |\underline{\mathrm{O}}|^{\ominus}}}{\mathrm{R{-}C{-}R'}}} \longrightarrow \overset{\substack{\mathrm{NH}^{\ominus} \\ |}}{\underset{\substack{| \\ |\underline{\mathrm{O}}|^{\ominus}}}{\mathrm{R{-}C{-}R'}}} \xrightarrow{\mathrm{HA}} \mathrm{RH} + \overset{\substack{\mathrm{NH}^{\ominus} \\ |}}{\underset{\substack{\| \\ \underline{\mathrm{O}}|}}{\mathrm{C{-}R'}}}$$

A very similar reaction may be applied to esters and amides of α,β-acetylenic acids with no γ-hydrogen:[331]



$$\mathrm{R{-}C{\equiv}C{-}}\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}\mathrm{{-}OR'} + \mathrm{NH_2^-} \longrightarrow \mathrm{R{-}C{\equiv}C{-}H} + \mathrm{R'O{-}}\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{C}}\mathrm{{-}NH^-}$$

Carbamates are obtained from esters, and ureas from amides.

OS V, 384, 1074.

C. Other Cleavages

2-46 The Cleavage of Alkanes in Super-acid Solutions

$$(CH_3)_4C \xrightarrow{FSO_3H\text{-}SbF_5} CH_4 + (CH_3)_3C^+$$

The C—C bonds of alkanes can be cleaved by treatment with super acids[43] (p. 226). The reaction may be called *alkylolysis*. For example, neopentane in FSO_3H–SbF_5 can cleave to give methane and the *t*-butyl cation. C—H cleavage (see reaction **2-1**) is a competing reaction, and, for example, neopentane can give H_2 and the *t*-pentyl cation (formed by rearrangement of the initially formed neopentyl cation) by this pathway. In general, the order of reactivity is tertiary C—H > C—C > secondary C—H ≫ primary C—H, though steric factors cause a shift in favor of C—C cleavage in such a hindered compound as tri-*t*-butylmethane. The mechanism is similar to that shown in reactions **2-1** and **2-16** and involves attack by H^+ on the C—C bond to give a pentavalent cation. The two major pathways for neopentane may therefore be shown as:

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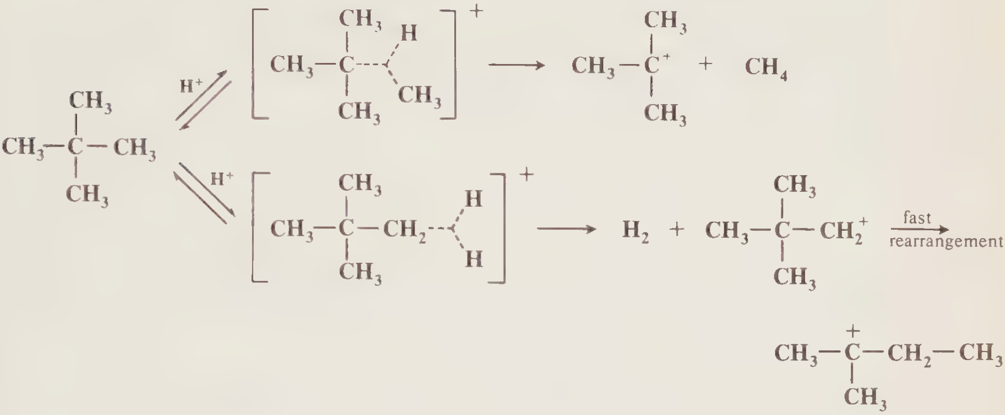
[328] For a review, see Hamlin and Weston, *Org. React.* **9**, 1–36 (1957). For an improved procedure, see Kaiser and Warner, *Synthesis* 395 (1975).

[329] Impastato and Walborsky, *J. Am. Chem. Soc.* **84**, 4838 (1962).

[330] Bunnett and Hrutfiord, *J. Org. Chem.* **27**, 4152 (1962).

[331] Craig and Moyle, *J. Chem. Soc.* 4402 (1963).



t-Pentyl cation

2-47 Decyanation of Alkyl Nitriles

$$\mathrm{RCN} \xrightarrow[\text{Na-Fe(acac)}_3]{\text{Na NH}_3 \text{ or}} \mathrm{RH}$$

The cyano group of alkyl nitriles can be removed by treatment with metallic sodium, either in liquid ammonia;[332] or together with tris(acetylacetonato)iron(III) $Fe(acac)_3$ [333] or, with lower yields, titanocene $C_{20}H_{20}Ti_2$. The two procedures are complementary. Although both can be used to decyanate many kinds of nitriles, the Na–NH_3 method gives high yields with R groups such as trityl, benzyl, phenyl, and tertiary alkyl, but lower yields (~35 to 50%) when R = primary or secondary alkyl. On the other hand, primary and secondary alkyl nitriles are decyanated in high yields by the Na–$Fe(acac)_3$ procedure. Sodium in liquid ammonia is known to be a source of solvated electrons, and the reaction may proceed through the free radical R• which would then be reduced to the carbanion R^-, which by abstraction of a proton from the solvent, would give RH. The mechanism with $Fe(acac)_3$ is presumably different. Another procedure, which is successful for R = primary, secondary, or tertiary, involves the use of Li, Na, or K in the solvent HMPT with or without an alcohol cosolvent at 0°C.[334] Best results were obtained with K, using *t*-BuOH as cosolvent. Nitriles can also be decyanated by solvated electrons produced electrochemically.[335]

α-Amino and α-amido nitriles $RCH(CN)NR'_2$ and $RCH(CN)NHCOR'$ can be decyanated in high yield by treatment with $NaBH_4$.[336]

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[332] Büchner and Dufaux, *Helv. Chim. Acta* **49,** 1145 (1966); Arapakos, *J. Am. Chem. Soc.* **89,** 6794 (1967); Arapakos, Scott, and Huber, *J. Am. Chem. Soc.* **91,** 2059 (1969); Birch and Hutchinson, *J. Chem. Soc., Perkin Trans. 1* 1546 (1972); Yamada, Tomioka, and Koga, *Tetrahedron Lett.* 61 (1976).

[333] van Tamelen, Rudler, and Bjorklund, *J. Am. Chem. Soc.* **93,** 7113 (1971).

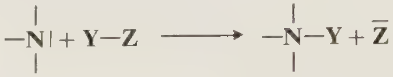
[334] Cuvigny, Larcheveque, and Normant, *Bull. Soc. Chim. Fr.* 1174 (1973).

[335] Arapakos and Scott, *Tetrahedron Lett.* 1975 (1968).

[336] Yamada and Akimoto, *Tetrahedron Lett.* 3105 (1969); Fabre, Hadj Ali Salem, and Welvart, *Bull. Soc. Chim. Fr.* 178 (1975).

Electrophilic Substitution at Nitrogen

In most of the reactions in this section, an electrophile bonds with the unshared pair of a nitrogen atom. The electrophile may be a free positive ion or a positive species attached to a carrier which breaks off in the course of the attack or shortly after:



$$-\overset{|}{\underset{|}{\mathrm{N}}}| + \mathrm{Y{-}Z} \longrightarrow -\overset{|}{\underset{|}{\mathrm{N}}}\mathrm{{-}Y} + \overline{\mathrm{Z}}$$

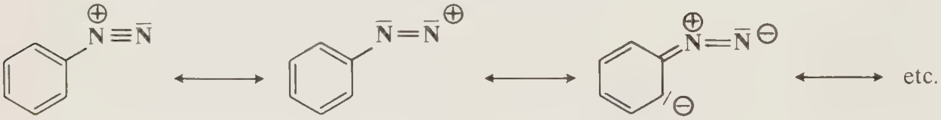
37

Further reaction of **37** depends on the nature of Y and of the other groups attached to the nitrogen.

2-48 Diazotization

$$\mathrm{Ar{-}NH_2} \quad + \quad \mathrm{HONO} \longrightarrow \mathrm{Ar{-}\overset{\oplus}{N}{\equiv}\overline{N}}$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[337] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see p. 327). Aromatic diazonium ions are more stable, because of resonance interaction between the nitrogens and the ring:



38 **39**

Incidentally, **38** contributes more to the hybrid than **39,** as shown by bond-distance measurements. In benzenediazonium chloride, the C—N distance is 1.42 Å, and the N—N distance 1.11 Å,[338] which values fit more closely to a single and a triple bond than to two double bonds (see p. 24). Even aromatic diazonium salts are stable only at low temperatures, usually only below 5°C, though more stable ones, such as the diazonium salt obtained from sulfanilic acid, are stable up to 10 or 15°C. Diazonium salts are usually prepared in aqueous solution and used without isolation, though it is possible to prepare solid diazonium salts if desired.[339]

For aromatic amines, the reaction is very general.[340] Halogen, nitro, alkyl, aldehyde, sulfonic acid, etc., groups do not interfere. Since aliphatic amines do not react with nitrous acid below a pH of about 3, it is even possible, by working at a pH of about 1, to diazotize an aromatic amine *without disturbing* an aliphatic amino group in the same molecule.[341]

If an aliphatic amino group is α to a COOR, CN, CHO, COR, etc., and has an α-hydrogen, then treatment with nitrous acid gives not a diazonium salt, but a *diazo compound.* Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with

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[337] For reviews, see Challis and Butler, in Patai, "The Chemistry of the Amino Group," pp. 305–320, Interscience Publishers, New York, 1968; Ridd, *Q. Rev., Chem. Soc.* **15,** 418–441 (1961); Belov and Kozlov, *Russ. Chem. Rev.* **32,** 59 75 (1963), pp. 59–63; Zollinger, "Azo and Diazo Chemistry," pp. 1–37, Interscience Publishers, Inc., New York, 1961.

[338] Rømming, *Acta Chem. Scand.* **13,** 1260 (1959).

[339] For example, see Hodgson and Mahadevan, *J. Chem. Soc.* 325 (1947); Piercey and Ward, *J. Chem. Soc.* 3841 (1962).

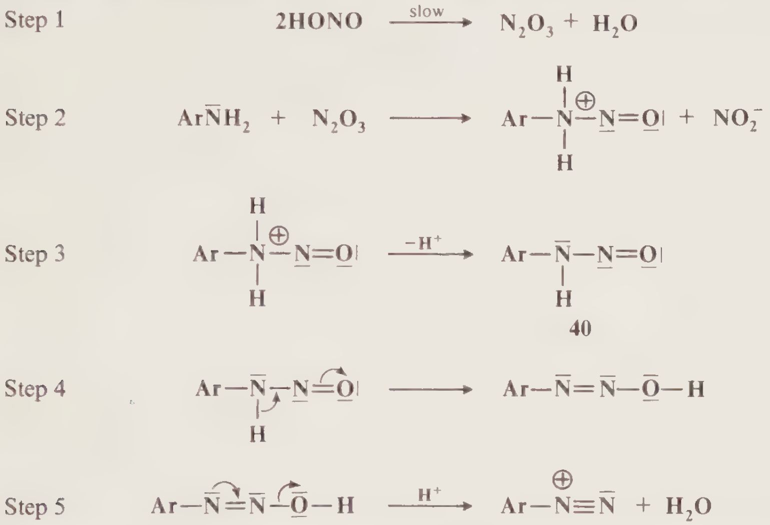
[340] For a review with respect to heterocyclic amines, see Butler, *Chem. Rev.* **75,** 241–257 (1975).

[341] Kornblum and Iffland, *J. Am. Chem. Soc.* **71,** 2137 (1949).

$$\mathrm{EtOOC{-}CH_2{-}NH_2 + HONO \longrightarrow EtOOC{-}CH{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{N}}}$$

isoamyl nitrite and a small amount of acid.[342] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[340]

Despite the fact that diazotization takes place in acid solution, the actual species attacked is not the salt of the amine, but the small amount of free amine present.[343] It is because aliphatic amines are stronger bases than aromatic ones that at pH values below 3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence for this is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[344] Under these conditions the mechanism is



40

There exists other evidence for this mechanism.[345] Other attacking species may be NOCl, $H_2NO_2^+$, and at high acidities even NO^+ itself.

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. We do not list them here, but under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also OS **52**, 53.

2-49 The Conversion of Hydrazines to Azides

$$\mathrm{RNHNH_2 + HONO \longrightarrow R{-}\overline{N}{=}\overset{\oplus}{N}{=}\overset{\ominus}{\underline{\overline{N}}}}$$

Monosubstituted hydrazines treated with nitrous acid give azides in a reaction which is exactly analogous to the formation of aliphatic diazo compounds mentioned in reaction **2-48**.

OS **III**, 710; **IV**, 819; **V**, 157.

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[342] Takamura, Mizoguchi, Koga, and Yamada, *Tetrahedron* **31**, 227 (1975).

[343] Challis and Ridd, *J. Chem. Soc.* 5197, 5208 (1962); Challis, Larkworthy, and Ridd, *J. Chem. Soc.* 5203 (1962).

[344] Hughes, Ingold, and Ridd, *J. Chem. Soc.* 58, 65, 77, 88 (1958); Hughes and Ridd, *J. Chem. Soc.* 70, 82 (1958).

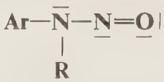
[345] For a discussion, see Ridd, Ref. 337, pp. 422–424.

2-50 N-Nitrosation

$$R_2NH + HONO \longrightarrow R_2N{-}NO$$

When secondary amines are treated with nitrous acid, N-nitroso compounds are formed.[346] The reaction may be accomplished with dialkyl-, diaryl-, or alkylarylamines, and even with mono-N-substituted amides: $RCONHR' + HONO \rightarrow RCON(NO)R'$. Tertiary amines have also been N-nitrosated, but in these cases one group cleaves, so that the product is the nitroso derivative of a secondary amine.[347] The group which cleaves appears as an aldehyde or ketone. Other reagents have also been used, for example NOCl, which is useful for amines or amides which are not soluble in an acidic aqueous solution, or in cases where the N-nitroso compounds are highly reactive.

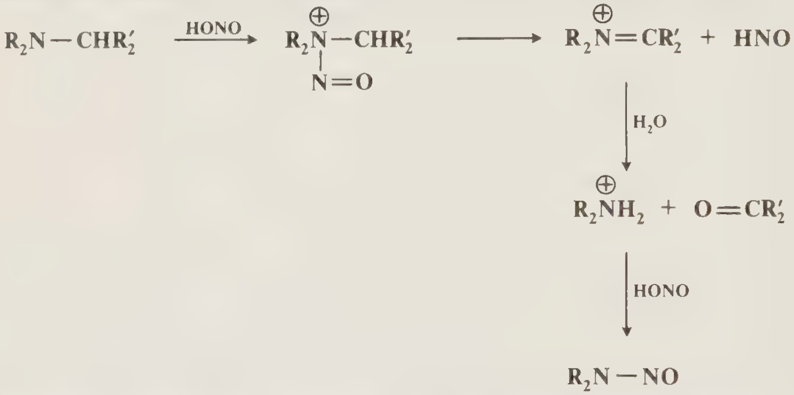
The mechanism of nitrosation is essentially the same as in reaction **2-48** up to the point where **41** (analogous to **40**) is formed. Since this species cannot lose a proton, it is stable and the



$$Ar{-}\underset{\displaystyle R}{\underset{|}{\bar{N}}}{-}\underline{N}{=}\underline{O}|$$

41

reaction ends there. The attacking entity may be any of those mentioned in reaction **2-48.** The following has been suggested as the mechanism for the reaction with tertiary amines:[348]


$R_2N{-}CHR'_2$
HONO
$R_2\overset{\oplus}{N}{-}CHR'_2$
$N{=}O$
$R_2\overset{\oplus}{N}{=}CR'_2$ + HNO
H_2O
$R_2\overset{\oplus}{N}H_2$ + $O{=}CR'_2$
HONO
$R_2N{-}NO$

The evidence for this mechanism includes the facts that nitrous oxide is a product (formed by $2HNO \rightarrow H_2O + N_2O$) and that quinuclidine, where the nitrogen is at a bridgehead and therefore cannot give elimination, does not react.[348]

Amines and amides can be N-*nitrated* with N_2O_5,[349] and aromatic amines can be converted to triazenes with diazonium salts. Aliphatic primary amines can also be converted to triazenes if the diazonium salts contain electron-withdrawing groups.[350] C-nitrosation is discussed in reactions **1-3** and **2-8.**

OS **I,** 177, 399, 417; **II,** 163, 211, 290, 460, 461, 462, 464 (also see **V,** 842); **III,** 106, 244; **IV,** 718, 780, 943; **V,** 336, 650, 797, 839, 962. Also see OS **III,** 711.

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[346] For reviews, see Sandler and Karo, "Organic Functional Group Preparations," vol. 2, pp. 424–450, Academic Press, Inc., New York, 1971; Turney and Wright, *Chem. Rev.* **59,** 497–513 (1959), pp. 498–504; Ridd, Ref. 337. For a review of the chemistry of aliphatic N-nitroso compounds, including methods of synthesis, see Fridman, Mukhametshin, and Novikov, *Russ. Chem. Rev.* **40,** 34–50 (1971).

[347] Hein, *J. Chem. Educ.* **40,** 181 (1963).

[348] Smith and Loeppky, *J. Am. Chem. Soc.* **89,** 1147 (1967); Smith and Pars, *J. Org. Chem.* **24,** 1324 (1959).

[349] Emmons, Pagano, and Stevens, *J. Org. Chem.* **23,** 311 (1958); Runge and Treibs, *J. Prakt. Chem.* [4] **15,** 223 (1962); Halevi, Ron, and Speiser, *J. Chem. Soc.* 2560 (1965).

[350] Ahern and Vaughan, *J. Chem. Soc., Chem. Commun.* 701 (1973).

2-51 Conversion of Amines to Azides

$$\mathrm{RNH^-} \xrightarrow[\text{base}]{\mathrm{TsN_3}} \mathrm{RN_3}$$

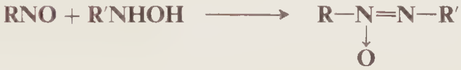
The treatment of the anion of a primary amine with tosyl azide produces the corresponding alkyl azide in low to moderate yields.[351] The reaction is analogous to the diazo transfer reaction (**2-9**) but takes place at a nitrogen rather than a carbon substrate. The conversion of amine anions to azides has also been effected with nitrous oxide N_2O.[352]

2-52 Conversion of Amines to Azo Compounds

$$\mathrm{ArNH_2 + Ar'NO} \xrightarrow{\mathrm{HOAc}} \mathrm{Ar{-}N{=}N{-}Ar'}$$

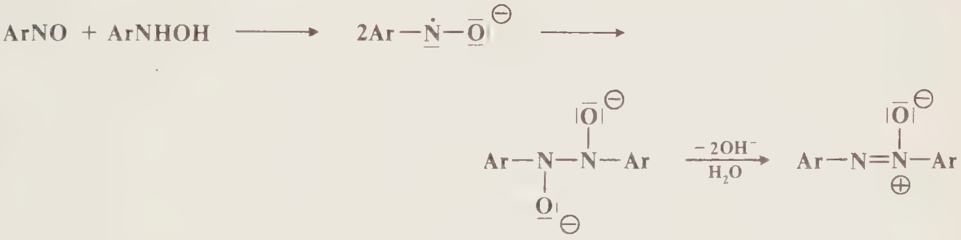
Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[353] A wide variety of substituents may be present in both aryl groups. The mechanism under acidic or neutral conditions probably involves rate-determining attack of $ArNH_2$ on the nitroso compound.[354]

2-53 Conversion of Nitroso Compounds to Azoxy Compounds



$$\mathrm{RNO + R'NHOH} \longrightarrow \mathrm{R{-}\underset{\substack{\downarrow\\ O}}{N}{=}N{-}R'}$$

In a reaction similar to **2-52**, azoxy compounds can be prepared by the condensation of a nitroso compound with a hydroxylamine.[355] The position of the oxygen in the final product is determined by the nature of the R groups, and not by which R group came from which starting compound. Both R and R′ may be alkyl or aryl, but when two different aryl groups are involved, mixtures of azoxy compounds (ArNONAr, ArNONAr′, and Ar′NONAr′) are obtained,[356] and the unsymmetrical product (ArNONAr′) is likely to be formed in the smallest amount. This behavior is probably caused by an equilibration between the starting compounds prior to the actual reaction ($\mathrm{ArNO + Ar'NHOH \rightleftharpoons Ar'NO + ArNHOH}$).[357] The mechanism has been investigated in the presence of base. Under these conditions both reactants are converted to radical anions, which couple:



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[351] Anselme and Fischer, *Tetrahedron* **25,** 855 (1969). Steinheimer, Wulfman, and McCullagh, *Synthesis* 325 (1971).

[352] Koga and Anselme, *Chem. Commun.* 446 (1968).

[353] For examples, see Faessinger and Brown, *J. Am. Chem. Soc.* **73,** 4606 (1950); Nutting, Jewell, and Rapoport, *J. Org. Chem.* **35,** 505 (1970). For a review, see Boyer, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 1, pp. 278–283, Interscience Publishers, New York, 1969.

[354] Yunes, Terenzani, and do Amaral, *J. Am. Chem. Soc.* **97,** 368 (1975). For an investigation of the mechanism in basic solution, see Brown and Kipp, *J. Org. Chem.* **36,** 170 (1971).

[355] Boyer, Ref. 353.

[356] See for example, Ogata, Tsuchida, and Takagi, *J. Am. Chem. Soc.* **79,** 3397 (1957).

[357] Knight and Saville, *J. Chem. Soc., Perkin Trans. 2* 1550 (1973).

These radical anions have been detected by esr.[358] This mechanism is consistent with the following result: when nitrosobenzene and phenylhydroxylamine are coupled, ^{18}O and ^{15}N labeling show that the two nitrogens and the two oxygens become equivalent.[359] Unsymmetrical azoxy compounds can be prepared[360] by combination of a nitroso compound with an N,N-dichloroamine in the presence of CuCl or certain other promoters.

2-54 N-Halogenation

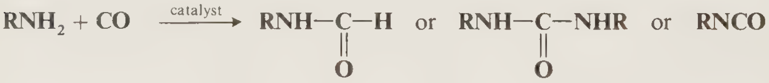
$$RNH_2 + NaOCl \longrightarrow RNHCl$$

Treatment with sodium hypochlorite or hypobromite converts primary amines into N-halo- or N,N-dihaloamines. Secondary amines may be converted to N-halo secondary amines. Similar reactions may be carried out on unsubstituted and N-substituted amides and on sulfonamides. With unsubstituted amides the N-halogen product is seldom isolated but usually rearranges (see reaction **8-17**); however, N-halo-N-alkyl amides and N-halo imides are quite stable. The important reagent N-bromosuccinimide is made in this manner. N-halogenation has also been accomplished with other reagents, for example, *t*-BuOCl.[361] Unsubstituted amides can be N-brominated or N,N-dibrominated by treatment with dibromoisocyanuric acid.[362] The mechanisms of these reactions involve attack by a positive halogen and are probably similar to those of reactions **2-48 and 2-50.**[363] N-Fluorination can be accomplished by direct treatment of amines[364] or amides[365] with F_2. Fluorination of N-alkyl-N-fluoro amides results in cleavage to N,N-difluoroamines.[366]

$$RNFCOR' \xrightarrow{F_2} RNF_2$$

OS **III,** 159; **IV,** 104, 157; **V,** 208, 663, 909.

2-55 The Reaction of Amines with Carbon Monoxide



$$RNH_2 + CO \xrightarrow{\text{catalyst}} RNH-\underset{\underset{O}{\|}}{C}-H \quad \text{or} \quad RNH-\underset{\underset{O}{\|}}{C}-NHR \quad \text{or} \quad RNCO$$

Three types of product can be obtained from the reaction of amines with carbon monoxide, depending on the catalyst. (1) Both primary and secondary amines react with CO in the presence of various catalysts [e.g., $Cu(CN)_2$, trimethylamine–hydrogen selenide, rhodium or ruthenium complexes] to give N-substituted and N,N-disubstituted formamides, respectively.[367] (2) Symmetrically substituted ureas can be prepared by treatment of a primary amine (or ammonia) with CO in the presence of selenium[368] or sulfur.[369] R may be alkyl or aryl. (3) When $PdCl_2$ is the catalyst, primary amines yield isocyanates.[370] Isocyanates can also be obtained by treatment of CO with azides: $RN_3 + CO \rightarrow RNCO$.[371] Thiocarbamates RNHCOSR′ are formed on treatment of primary aliphatic amines RNH_2 with CO and a disulfide R′SSR′ in the presence of selenium.[372]

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[358] Russell and Geels, *J. Am. Chem. Soc.* **87,** 122 (1965); Russell, Geels, Smentowski, Chang, Reynolds, and Kaupp, *J. Am. Chem. Soc.* **89,** 3821 (1967). See also Hutton and Waters, *J. Chem. Soc. B* 191 (1968).

[359] Shemyakin, Maimind, and Vaichunaite, *Izv. Akad. Nauk SSSR, Ser. Khim.* 1260 (1957); Oae, Fukumoto, and Yamagami, *Bull. Chem. Soc. Jpn.* **36,** 728 (1963).

[360] Sullivan, Luck, and Kovacic, *J. Chem. Soc., Chem. Commun.* 217 (1974); Nelson, Serianz, and Kovacic, *J. Org. Chem.* **41,** 1751 (1976).

[361] Altenkirk and Isrealstam, *J. Org. Chem.* **27,** 4532 (1962).

[362] Gottardi, *Monatsh. Chem.* **104,** 421 (1973), **106,** 611 (1975).

[363] For studies of reactivity in this reaction, see Thomm and Wayman, *Can. J. Chem.* **47,** 3289 (1969); Higuchi, Hussain, and Pitman, *J. Chem. Soc. B* 626 (1969).

[364] Sharts, *J. Org. Chem.* **33,** 1008 (1968).

[365] Grakauskas and Baum, *J. Org. Chem.* **34,** 2840 (1969); **35,** 1545 (1970).

[366] Ref. 365. See also Wiesboeck and Ruff, *Tetrahedron* **26,** 837 (1970).

[367] Tsuji and Iwamoto, *Chem. Commun.* 380 (1966); Durand and Lassau, *Tetrahedron Lett.* 2329 (1969); Saegusa, Kobayashi, Hirota, and Ito, *Bull. Chem. Soc. Jpn.* **42,** 2610 (1969); Byerley, Rempel, Takebe, and James, *Chem. Commun.* 1482 (1971); Nefedov, Sergeeva, and Éidus, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **22,** 784 (1973); Kondo, Sonoda, and Sakurai, *J. Chem. Soc., Chem. Commun.* 853 (1973).

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[368] Sonoda, Yasuhara, Kondo, Ikeda, and Tsutsumi, *J. Am. Chem. Soc.* **93,** 6344 (1971).

[369] Franz and Applegath, *J. Org. Chem.* **26,** 3304 (1961); Franz, Applegath, Morriss, and Baiocchi, *J. Org. Chem.* **26,** 3306 (1961); Franz, Applegath, Morriss, Baiocchi, and Bolze, *J. Org. Chem.* **26,** 3309 (1961).

[370] Stern and Spector, *J. Org. Chem.* **31,** 596 (1966).

[371] Bennett and Hardy, *J. Am. Chem. Soc.* **90,** 3295 (1968).

[372] Koch, *Tetrahedron Lett.* 2087 (1975).

Thirteen

Aromatic Nucleophilic Substitution

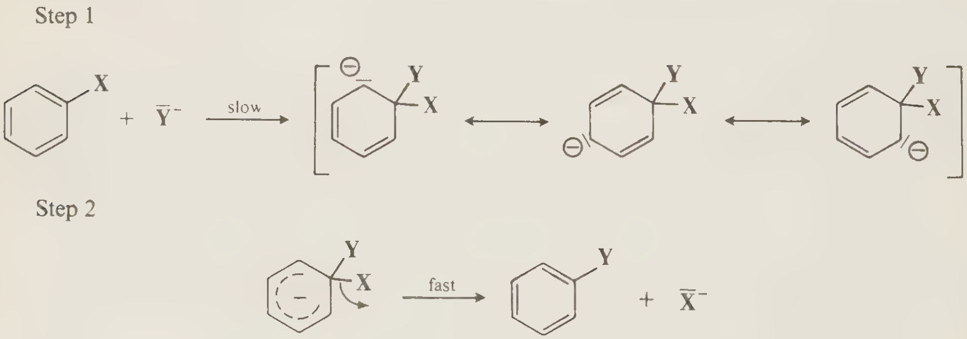
On p. 317 it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions which form the subject of this chapter.[1] Reactions which *are* successful at an aromatic substrate are largely of three kinds: (1) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (2) reactions catalyzed by very strong bases and proceeding through aryne intermediates; and (3) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. However, not all the reactions discussed in this chapter fit into these categories.

MECHANISMS

Each of the three principal mechanisms is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.[2]

The SNAr Mechanism

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps:



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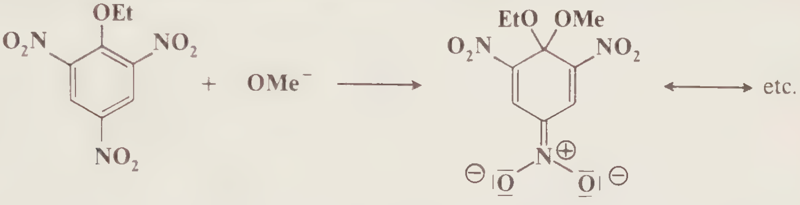
[1] For reviews of aromatic nucleophilic substitution, see Zoltewicz, *Top. Curr. Chem.* **59**, 33–64 (1975); Bunnett and Zahler, *Chem. Rev.* **49**, 273–412 (1951).

[2] For a monograph on aromatic-nucleophilic-substitution mechanisms, see Miller, "Aromatic Nucleophilic Substitution," American Elsevier Publishing Company, Inc., New York, 1968. For reviews, see Bunnett, *J. Chem. Educ.* **51**, 312–315 (1974), *Q. Rev., Chem. Soc.* **12**, 1–16 (1958); Bernasconi, *MTP Int. Rev. Sci.: Org. Chem. Ser. One*, **3** 33–63 (1973); Ross, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 13, pp. 407–431, American Elsevier Publishing Company, Inc., New York, 1972, *Prog. Phys. Org. Chem.* **1**, 31–74 (1963); Buck, *Angew. Chem. Int. Ed. Engl.* **8**, 120–131 (1969) [*Angew. Chem.* **81**, 136–148]; Buncel, Norris, and Russell, *Q. Rev., Chem. Soc.* **22**, 123–146 (1968); Sauer and Huisgen, *Angew. Chem.* **72**, 294–315 (1960); and Ref. 1.

The first step is usually, but not always, rate-determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 10 (p. 308) and, in another way, the arenium-ion mechanism of electrophilic aromatic substitution (p. 453). In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, and then the leaving group departs. This mechanism is sometimes called the SN2 mechanism because it is bimolecular, but in this book we reserve that name for nucleophilic substitutions in which attack and departure are simultaneous, so that there is no intermediate. We shall refer to this mechanism as the SNAr mechanism.[3]

There is a great deal of evidence for the mechanism, and we shall discuss only some of it.[2] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **1** in the reaction between ethyl picrate and methoxide ion.[4] Intermediates of this type are stable salts, called *Meisenheimer salts*, and many more of them have been isolated since 1902.[5] The structures of several of these intermediates have been proved by nmr[6] and by x-ray crystallography.[7] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the SN1 or SN2 mechanisms described in Chapter 10, the Ar—X bond would be broken in the rate-determining step. In the SNAr mechanism this bond is not broken until after the rate-determining step (that is, if step 1 is rate-determining). We would predict from this that if the SNAr mechanism is operating, a change in leaving group should not have much effect on the rate of the reaction. In the reaction



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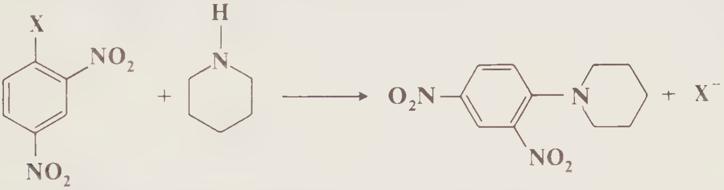

when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of about 5.[8] This behavior would not be expected in a reaction in which the Ar—X bond is broken in the rate-determining step. We do not expect the rates to be *identical*, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density around the substrate carbon, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the SN1 and the SN2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (p. 312).

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[3] The mechanism has also been called by other names, including the SN2Ar, the addition-elimination, and the intermediate complex mechanism.

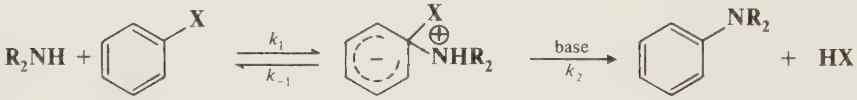
[4] Meisenheimer, *Justus Liebigs Ann. Chem.* **323,** 205 (1902).

[5] For reviews of structural and other studies on Meisenheimer salts, see Strauss, *Chem. Rev.* **70,** 667–712 (1970), *Acc. Chem. Res.* **7,** 181–188 (1974); Hall and Poranski, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 2, pp. 329–384, Interscience Publishers, New York, 1970; Crampton, *Adv. Phys. Org. Chem.* **7,** 211–257 (1969); Foster and Fyfe, *Rev. Pure Appl. Chem.* **16,** 61–82 (1966).

[6] See, for example, Crampton and Gold, *J. Chem. Soc.* 4293 (1964), *J. Chem. Soc. B* 893 (1966); Foster, Fyfe, and Morris, *Recl. Trav. Chim. Pays-Bas* **84,** 516 (1965); Foster and Fyfe, *Tetrahedron* **21,** 3372 (1965); Servis, *J. Am. Chem. Soc.* **87,** 5495 (1965); **89,** 1508 (1967); Caveng, Fischer, Heilbronner, Miller, and Zollinger, *Helv. Chim. Acta* **50,** 848 (1967); Byrne, Fendler, Fendler, and Griffin, *J. Org. Chem.* **32,** 2506 (1967); Fendler, Camaioni, and Fendler, *J. Org. Chem.* **36,** 1544 (1971).

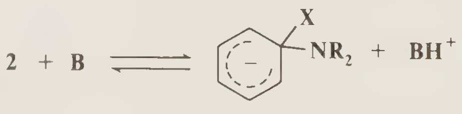
[7] Destro, Gramaccioli, and Simonetta, *Acta Crystallogr.* **24,** 1369 (1968); Ueda, Sakabe, Tanaka, and Furusaki, *Bull. Chem. Soc. Jpn.* **41,** 2866 (1968); Messmer and Palenik, *Chem. Commun.* 470 (1969).

[8] Bunnett, Garbisch, and Pruitt, *J. Am. Chem. Soc.* **79,** 385 (1957).



2

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (such as OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[9] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_{-1} is large and step 2 is rate-determining. This is evidence for the SNAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 455), is also evidence for the SNAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate which goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants, and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated, and there is evidence that the mechanism for this process is as follows:[10]



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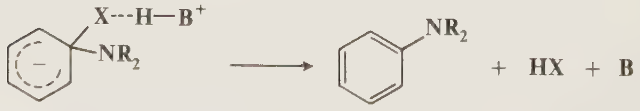

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[9] Kirby and Jencks, *J. Am. Chem. Soc.* **87**, 3217 (1965); Bunnett and Garst, *J. Am. Chem. Soc.* **87**, 3875, 3879 (1965), *J. Org. Chem.* **33**, 2320 (1968); Bunnett and Bernasconi, *J. Am. Chem. Soc.* **87**, 5209 (1965), *J. Org. Chem.* **35**, 70 (1970); Bernasconi, *J. Org. Chem.* **32**, 2947 (1967); Bernasconi and Schmid, *J. Org. Chem.* **32**, 2953 (1967); Bernasconi and Zollinger, *Helv. Chim. Acta* **49**, 103, 2570 (1966), **50**, 1 (1967); Pietra and Vitali, *J. Chem. Soc. B* 1595 (1968).

[10] Orvik and Bunnett, *J. Am. Chem. Soc.* **92**, 2417 (1970). See also Bernasconi and deRossi, *J. Org. Chem.* **38**, 500 (1973); Lee and Main, *Aust. J. Chem.* **28**, 2521 (1975).

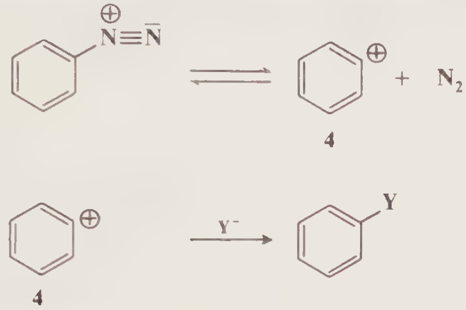
First, the base reversibly removes a proton from **2** to give its conjugate base **3** and BH$^+$. There follows rate-determining expulsion of X from **3** with general acid catalysis by BH$^+$. Further evidence for the SNAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[11]

The SN1 Mechanism

For aryl halides, even active ones, a unimolecular SN1 mechanism has never been observed with certainty. It is with diazonium salts that this mechanism is important:[12]

Step 1

Step 2



4

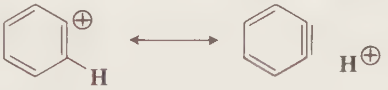
Among the evidence for the SN1 mechanism is the following:[13]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.

2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.

3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[14]

4. When reactions were run with substrate deuterated in the ortho position, isotope effects of about 1.22 were obtained.[15] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation, which is



reduced when hydrogen is replaced by deuterium.

5. That the first step is a reversible cleavage was demonstrated by the observation that when $Ar^{15}\overset{\oplus}{N}\equiv N$ was the reacting species, recovered starting material contained not only $Ar^{15}\overset{\oplus}{N}\equiv N$ but also $Ar\overset{\oplus}{N}\equiv {}^{15}N$.[16] This could arise only if the nitrogen breaks away from the ring and then returns. However, the rearrangement is very slow compared with the normal hydrolysis of the ArN_2^+.

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[11] Hart and Bourns, *Tetrahedron Lett.* 2995 (1966); Ayrey and Wylie, *J. Chem. Soc. B* 738 (1970).

[12] Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).

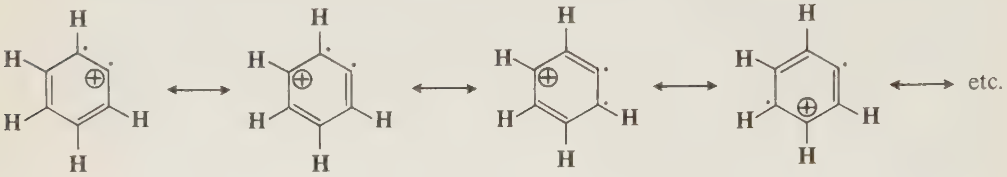
[13] For discussions, see Swain, Sheats, and Harbison, *J. Am. Chem. Soc.* **97**, 783, 796 (1975); Burri, Wahl, and Zollinger, *Helv. Chim. Acta* **57**, 2099 (1974); Richey and Richey, in Olah and Schleyer, "Carbonium Ions," vol. 2, pp. 922–931, Interscience Publishers, New York, 1970; Zollinger, "Azo and Diazo Chemistry," pp. 138 142, Interscience Publishers, Inc., New York, 1961; Miller, Ref. 2, pp. 29–40.

[14] Lewis and Miller, *J. Am. Chem. Soc.* **75,** 429 (1953).

[15] Swain, Sheats, Gorenstein, and Harbison, *J. Am. Chem. Soc.* **97**, 791 (1975).

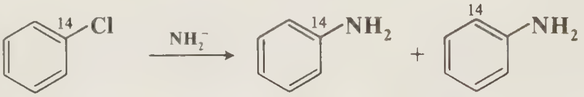
[16] Lewis and Insole, *J. Am. Chem. Soc.* **86,** 32 (1964); Lewis and Kotcher, *Tetrahedron* **25,** 4873 (1969); Lewis and Holliday, *J. Am. Chem. Soc.* **91,** 426 (1969); Bergstrom, Wahl, and Zollinger, *Tetrahedron Lett.* 2975 (1974).

It is possible that the aryl cations formed in these reactions do not have the simple structure represented as **4**. The fact that esr spectra are obtained from these solutions indicates that the carbonium ion has unpaired electrons.[17] The simplest way to explain this is to assume that the ion has a diradical structure or that the diradical is in equilibrium with **4**.[18]



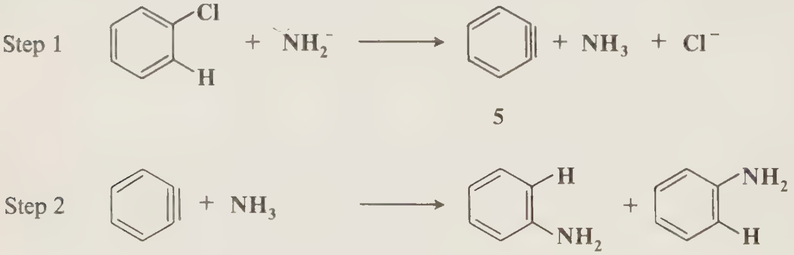
The Benzyne Mechanism[19]

Some aromatic nucleophilic substitutions are clearly different in character from those which occur by the SNAr mechanism (or the SN1 mechanism). These substitutions occur on aryl halides which have no activating groups; bases are required which are stronger than those normally used; and, most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.[20]

A mechanism which can explain all these observations involves elimination followed by addition:



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[17] Abramovitch, Hymers, Rajan, and Wilson, *Tetrahedron Lett.* 1507 (1963). See also Abramovitch and Saha, *Can. J. Chem.* **43**, 3269 (1965); Abramovitch and Gadallah, *J. Chem. Soc. B* 497 (1968); Kamigata, Kobayashi, and Minato, *Bull. Chem. Soc. Jpn.* **45**, 2047 (1972). See however, Swain, Sheats, and Harbison, *J. Am. Chem. Soc.* **97**, 783 (1975); Jaffé and Koser, *J. Org. Chem.* **40**, 3082 (1975).

[18] The idea that aryl carbonium ions might be diradicals was first suggested by Taft, *J. Am. Chem. Soc.* **83**, 3350 (1961).

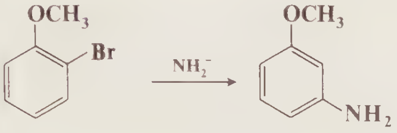
[19] For a monograph, see Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, Inc., New York, 1967. For reviews, see Fields, in McManus, "Organic Reactive Intermediates," pp. 449–508, Academic Press, Inc., New York, 1973; Heaney, *Fortschr. Chem. Forsch.* **16**, 35–74 (1970), *Essays Chem.* **1**, 95–115 (1970), *Chem. Rev.* **62**, 81–97 (1962); Hoffmann, in Viehe, "Acetylenes," pp. 1063–1148, Marcel Dekker, Inc., New York, 1969; Fields and Meyerson, *Adv. Phys. Org. Chem.* **6**, 1–61 (1968); Wittig, *Angew. Chem. Int. Ed. Engl.* **4**, 731–737 (1965) [*Angew. Chem.* **77**, 752–759], *Pure Appl. Chem.* **7**, 173–191 (1963); Bunnett, *J. Chem. Educ.* **38**, 278–285 (1961); Huisgen and Sauer, *Angew. Chem.* **72**, 91–108 (1960); Jenny, Caserio, and Roberts, *Experientia* **14**, 348 (1958).

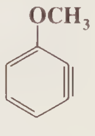
[20] Roberts, Semenow, Simmons, and Carlsmith, *J. Am. Chem. Soc.* **78**, 601 (1956).

The symmetrical intermediate **5** can be attacked by the nitrogen at either of two positions, explaining why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism is the following:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[20]

2. It had been known for many years before this mechanism was suggested that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*[21] and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[22] In this particular case, only the meta isomer is formed. The reason a 1 : 1 mixture is not formed is that the intermediate **6** is not symmetrical and the methoxy group directs the incoming group meta but not ortho (see p. 594). However, not all cine substitutions proceed by this kind of mechanism (see reaction **3-26**).[23]





6

3. The fact that the order of halide reactivity is $Br > I > Cl \gg F$ (when the reaction is performed with KNH_2 in liquid NH_3) shows that the SNAr mechanism is not operating here.[20]

In the conversion of the substrate to **6**, either proton removal or subsequent loss of halide ion may be rate-determining. In fact the unusual leaving-group order just mentioned ($Br > I > Cl$) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate-determining and the rate order for this step is $F > Cl > Br > I$. When Cl or F is the leaving group, cleavage of the C—X bond is rate-determining and the order for this step is $I > Br > Cl > F$. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with NH_2^-.[24] In such compounds, the most acidic hydrogen is the one between the two halogens, and when it leaves, the anion which remains can lose either halogen. Therefore a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be $I > Br > Cl$.[24]

Species such as **5** and **6** are called *benzynes* (sometimes *dehydrobenzenes*), or more generally *arynes*, and the mechanism is known as the *benzyne mechanism*. Benzynes differ from the species discussed in Chapter 5 in that each carbon has a valence of 4. However, they are very reactive, as are the species in that chapter. Neither benzyne nor any other aryne has yet been isolated under ordinary conditions, but stable benzyne has been isolated in an argon matrix at 8 K,[25] where its ir spectrum could be observed. In addition, spectra of transient benzynes have been detected,[26] and benzynes may be trapped; e.g., they undergo the Diels-Alder reaction (see reaction **5-51**). A stable solid complex of benzyne, π-benzyne diiodo-μ-carbonylnickel dimer (**7**)

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[21] For a review of cine substitution, see Dyall, *Rev. Pure Appl. Chem.* **8,** 33–52 (1958).

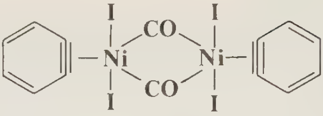
[22] This example is from Gilman and Avakian, *J. Am. Chem. Soc.* **67,** 349 (1945). For a table of many such examples, see Ref. 1, pp. 385–386.

[23] For another example, see Reinecke and Adickes, *J. Am. Chem. Soc.* **90,** 511 (1968).

[24] Bunnett and Kearley, *J. Org. Chem.* **36,** 184 (1971).

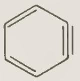
[25] Chapman, Mattes, McIntosh, Pacansky, Calder, and Orr, *J. Am. Chem. Soc.* **95,** 6134 (1973).

[26] Berry, Spokes, and Stiles, *J. Am. Chem. Soc.* **84,** 3570 (1962). Benzynes have also been detected by mass spectroscopy. Fisher and Lossing, *J. Am. Chem. Soc.* **85,** 1018 (1963); Berry, Clardy, and Schafer, *J. Am. Chem. Soc.* **86,** 2738 (1964).

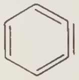


7

has been isolated.[27] That benzynes are highly reactive is indicated not only by the failure to isolate them (except in a matrix at 8 K) but also by their low selectivity. When bromobenzene is treated with amide ion in the presence of other nucleophiles, a considerable lack of selectivity is noted.[28] This reactivity is undoubtedly caused by the strain in a six-membered ring containing a triple bond. It should be noted that the extra pair of electrons does not affect the aromaticity. The original sextet still functions as a closed ring, and the two additional electrons are merely located in a π orbital which covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The infrared spectrum,



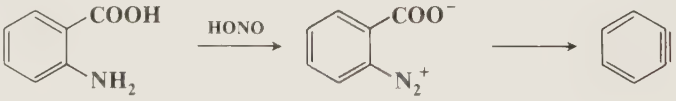
A



B

mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings but other aromatic rings[29] and even nonaromatic rings (p. 314) can react through this kind of intermediate. Of course the nonaromatic rings do have a formal triple bond.

There are other ways to prepare benzyne intermediates.[30] Probably the most convenient method involves thermal or photolytic decomposition of the product of diazotization of anthranilic acid or its derivatives:[31]



8

The zwitterion (**8**) decomposes to give the highly reactive benzyne.

Other Mechanisms

There is no clear-cut proof that a one-step SN2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. Such a mechanism has been suggested[32] in cases where fluoro is a very poor leaving group, since this would be consistent with an SN2 process, but not with the SNAr mechanism as shown on p. 584. On the other hand, an SNAr mechanism in which the *second* step is rate-determining would be quite compatible with reactions in which fluoro is a poor leaving group, and some of them have been shown to operate by such a process.[33] The hypothetical aromatic SN2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* SNAr mechanism.

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[27] Gowling, Kettle, and Sharples, *Chem. Commun.* 21 (1968).

[28] Scardiglia and Roberts, *Tetrahedron* **3**, 197 (1958).

[29] For reviews of *hetarynes* (benzyne intermediates in heterocyclic rings), see den Hertog and van der Plas, in Viehe, Ref. 19, pp. 1149–1197, *Adv. Heterocycl. Chem.* **4**, 121–144 (1971); Kauffmann and Wirthwein, *Angew. Chem. Int. Ed. Engl.* **10**, 20–33 (1971) [*Angew. Chem.* **83**, 21–34]; Kauffmann, *Angew. Chem. Int. Ed. Engl.* **4**, 543–557 (1965) [*Angew. Chem.* **77**, 557–571]; Hoffmann, "Dehydrobenzene and Cycloalkynes," Ref. 19, pp. 275–309.

[30] For a full discussion, see Hoffmann, "Dehydrobenzene and Cycloalkynes," Ref. 19, pp. 9–98.

[31] Stiles and Miller, *J. Am. Chem. Soc.* **82**, 3802 (1962); Stiles, Miller, and Burckhardt, *J. Am. Chem. Soc.* **85**, 1792 (1963); Friedman and Logullo, *J. Org. Chem.* **34**, 3089 (1969); Gompper, Seybold, and Schmolke, *Angew. Chem. Int. Ed. Engl.* **7**, 389 (1968) [*Angew. Chem.* **80**, 404]; Logullo, Seitz, and Friedman, *Org. Synth.* **V**, 54.

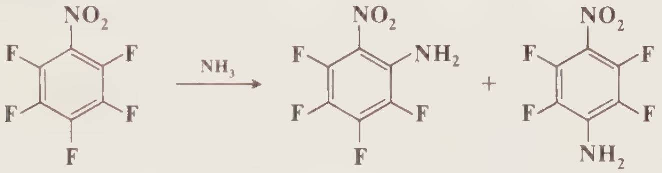
[32] Chapman and Russell-Hill, *J. Chem. Soc.* 1563 (1956); Parker and Read, *J. Chem. Soc.* 9, 3149 (1962).

Some of the reactions in this chapter operate by still other mechanisms, among them an addition-elimination mechanism (see reaction **3-17**).

REACTIVITY

The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens which could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule. However, there *have* been studies of the latter question.[34] For example, the nitro group has been shown to be ortho-para-directing by the observation that pentafluoronitrobenzene gave 95% of a mixture of 2-nitro-3,4,5,6-tetrafluoroaniline and 4-nitro-2,3,5,6-tetrafluoroaniline when treated with ammonia:[35]



Similarly, it was shown (for C_6F_5X) that the groups H, Me, CF_3, Cl, Br, I, SMe, and NMe_2 are mostly para-directing and NH_2 and O^- are largely meta-directing.[36]

Aromatic nucleophilic substitutions proceeding by the SNAr mechanism are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group, and are hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 459). Table 1 contains a list of groups arranged approximately in order of activating or deactivating ability. Hetero nitrogen atoms are also strongly activating (especially to the α and γ positions)

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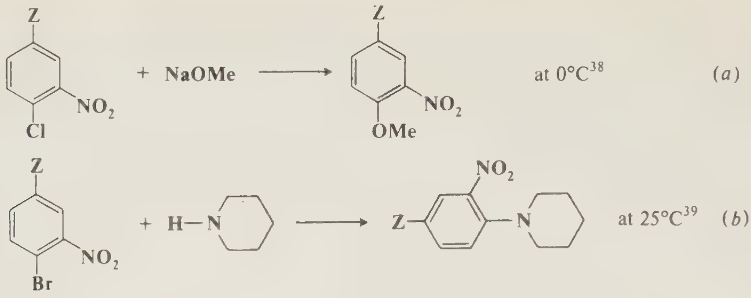
[33] Bunnett and Randall, *J. Am. Chem. Soc.* **80,** 6020 (1958). See also Lam and Miller, *Chem. Commun.* 642 (1966); Lamm and Lammert, *Acta Chem. Scand.* **27,** 191 (1973).

[34] See Burdon, Hollyhead, and Tatlow, *J. Chem. Soc.* 6336 (1965); Burdon and Westwood, *J. Chem. Soc. C* 1271 (1970); and other papers in this series.

[35] Brooke, Burdon, and Tatlow, *J. Chem. Soc.* 802 (1961); Allen, Burdon, and Tatlow, *J. Chem. Soc.* 1045 (1965).

[36] Burdon, *Tetrahedron* **21,** 3373 (1965); Burdon, Coe, Marsh, and Tatlow, *Tetrahedron* **22,** 1183 (1966). See also Ho and Miller, *Aust. J. Chem.* **19,** 423 (1966).

TABLE 1 Groups listed in approximate descending order of activating ability in the SNAr mechanism[37]



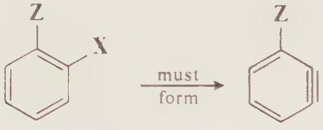
For reaction (a) the rates are relative to **H**, *but for reaction (b) they are relative to* **NH_2**

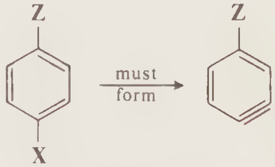
		Relative rate of reaction	
	Group Z	(*a*) **H** = 1[38]	(*b*) **NH_2** = 1[39]
Activates halide exchange at room temperature	**N_2^+**		
Activates reaction with strong nucleophiles at room temperature	$\overset{+}{\text{N}}$—R (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°C	**NO**	5.22×10^6	
	NO_2	6.73×10^5	Very fast
	N (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	**SO_2Me**		
	NMe_3^+		
	CF_3		
	CN	3.81×10^4	
	CHO	2.02×10^4	
With nitro also present, activate reactions with strong nucleophiles at 40–60°C	**COR**		
	COOH		
	SO_3^-		
	Br		6.31×10^4
	Cl		4.50×10^4
	I		4.36×10^4
	COO^-		2.02×10^4
	H	1	8.06×10^3
	F		2.10×10^3
	CMe_3		1.37×10^3
	Me		1.17×10^3
	OMe		145
	NMe_2		9.77
	OH		4.70
	NH_2		1

The comments on the left are from Bunnett and Zahler, Ref. 1, p. 308.

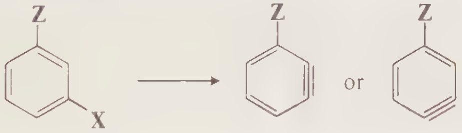
and are even more so when quaternized.[40] Thus 2- and 4-chloropyridine, for example, are often used as substrates. Heterocyclic N-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[41] The N_2^+ group is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound such as *p*-nitroaniline or *p*-chloroaniline the group para to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+\ \ X^-$, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group and to leave the para group untouched.[42] By far the most common activating group is the nitro group, and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[43] Polyfluorobenzenes, e.g., C_6F_6, also undergo aromatic nucleophilic substitution quite well.[44] Benzene rings which lack activating substituents are generally not useful substrates for the SNAr mechanism.[45]

In reactions involving aryne intermediates, two factors affect the position of the incoming group, the first being the direction in which the benzyne forms.[46] When there are groups ortho or para to the leaving group, there is no choice:





but when a meta group is present, the benzyne may form in two different ways:



In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the benzyne, once formed, may be attacked at two positions. The favored position for nucleophilic attack is the one which leads to the more stable carbanion intermediate, and this in turn also depends on the field effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative

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[37] For additional tables of this kind, see Miller, Ref. 2, pp. 61–136.

[38] Miller and Parker, *Aust. J. Chem.* **11,** 302 (1958).

[39] Berliner and Monack, *J. Am. Chem. Soc.* **74,** 1574 (1952).

[40] For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, *Adv. Heterocycl. Chem.* **3,** 285–371 (1964); Shepherd and Fedrick, *Adv. Heterocycl. Chem.* **4,** 145–423 (1965).

[41] For a review, see Katritzky and Lagowski, "Chemistry of the Heterocyclic N-Oxides," pp. 258–319, 550–553, Academic Press, Inc., New York, 1971.

[42] In some cases this can be turned to good effect: the replacement of a *p*-fluoro substituent has been used to detect the presence of the N_2^+ group (or other group which causes the fluorine to be labile) during the course of a reaction: Suschitzky, *Angew. Chem. Int. Ed. Engl.* **6,** 596–607 (1967) [*Angew. Chem.* **79,** 636–648].

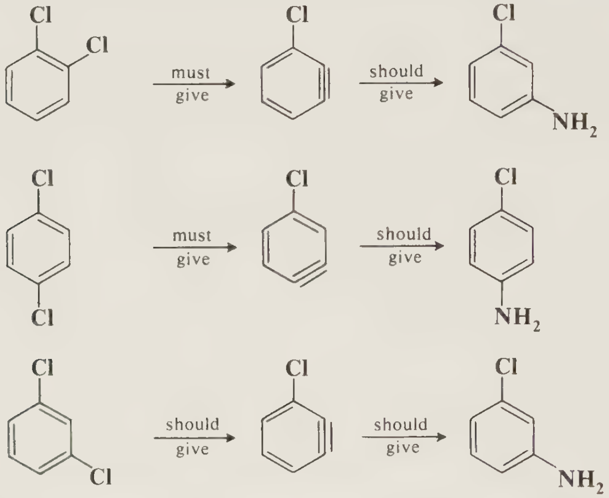
[43] For a review of the activating effect of nitro groups, see de Boer and Dirkx, in Feuer, Ref. 5, pt. 1, pp. 487–612.

[44] For a review, see Kobrina, *Fluorine Chem. Rev.* **7,** 1–114 (1974).

[45] It has been shown that such substrates can react by this mechanism but extremely slowly: Liotta and Pinholster, *Chem. Commun.* 1245 (1969).

[46] This analysis is from Roberts, Vaughan, Carlsmith, and Semenow, *J. Am. Chem. Soc.* **78,** 611 (1956). For a discussion, see Hoffmann, "Dehydrobenzene and Cycloalkynes," Ref. 19, pp. 134–150.

charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes with alkali-metal amides. The predicted products are



In each case the predicted product was the one chiefly formed,[47] though the para isomer also gave 19% *m*-chloroaniline.[48] The obtention of *m*-methoxyaniline, mentioned on p. 589, is also in accord with these predictions.

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ; see p. 470), so do nucleophilic substitutions follow it, with σ^- instead of σ for electron-withdrawing groups.[49]

As pointed out on p. 467, the position of attack at alternant hydrocarbons is the same for electrophiles, nucleophiles, and free radicals.

The Effect of the Leaving Group[50]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R, and SR, which are not generally lost in aliphatic systems,[51] *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[52] An approximate order of leaving-group ability is[53] $F > NO_2 > OTs > SOPh > Cl, Br, I > N_3 > NR_3^+ > OAr, OR, SR, SO_2R, NH_2$. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; i.e., one methoxy group is replaced in preference to five chlorines.[54] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually Cl > Br > I, but not always.[55] The leaving-group order is quite different from that for the SN1 or SN2 mechanisms. The most likely explanation is that the first step of the SNAr mechanism is usually rate-determining, and this step is promoted by groups with strong $-I$ effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. An alternate explanation has been proposed for the leaving ability of fluorine. According to this, fluorine, the only one of the halogens which can form hydrogen bonds, does form such a bond with the nucleophile.[56] Of course, this can be possible only when the nucleophile contains a hydrogen. Fluoro is the poorest leaving group of the halogens when the second step of the SNAr mechanism is rate-determining (p. 591) or when the benzyne mechanism is operating. Of course, the only important leaving group in the SN1 mechanism is N_2^+.

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[47] Wotiz and Huba, *J. Org. Chem.* **24,** 595 (1959). Eighteen other reactions also gave products predicted by these principles. See also Caubère and Lalloz, *Bull. Soc. Chim. Fr.* 1983, 1989, 1996 (1974).

[48] Zoltewicz and Bunnett, *J. Am. Chem. Soc.* **87,** 2640 (1965).

[49] Greizerstein, Bonelli, and Brieux, *J. Am. Chem. Soc.* **84,** 1026 (1962); Knowles, Norman, and Prosser, *Proc. Chem. Soc.* 341 (1961). For a list of σ^- values, see p. 253.

[50] For a review, see Miller, Ref. 2, pp. 137–179.

[51] For an example where NO_2 is a leaving group in an aliphatic system, see Fainzil'berg, Khisamutdinov, and Slovetskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 427 (1969).

[52] For a discussion, see Pietra and Vitali, *J. Chem. Soc., Perkin Trans. 2* 385 (1972).

[53] Loudon and Shulman, *J. Chem. Soc.* 722 (1941); Suhr, *Chem. Ber.* **97,** 3268 (1964).

[54] Kobrina and Yakobson, *J. Gen. Chem. USSR* **33,** 3238 (1963).

The Effect of the Attacking Nucleophile[57]

It is not possible to construct a nucleophilicity order which is invariant, since different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $NH_2^- > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^- > R_2NH > ArO^- > OH^- > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[58] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength, and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions; e.g., OH^-, a stronger base than ArO^-, is a poorer nucleophile. In a series of similar nucleophiles, such as substituted anilines,[59] nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts (reaction **3-12**) and in the von Richter (**3-26**) and Rosenmund–von Braun (**3-11**) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

All Leaving Groups except Hydrogen and N_2^+

A. Oxygen Nucleophiles

3-1 Replacement by OH

$$\mathbf{ArBr + OH^- \longrightarrow ArOH}$$

Aryl halides can be converted to phenols only if activating groups are present or if exceedingly strenuous conditions are employed.[60] Other leaving groups, including nitro,[61] azide, NR_3^+, etc., can also be replaced by OH groups. When the reaction is carried out at high temperatures, as in the commercial process for the preparation of phenol from chlorobenzene, cine substitution is observed, indicating a benzyne mechanism.[62] Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2.[63] Nitro and OR groups can also be replaced by OH groups in photochemical reactions.[64] In some of these photochemical processes, electron-withdrawing (at least in the ground state) substituents activate the meta more than the ortho or para positions.

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[55] Reinheimer, Taylor, and Rohrbaugh, *J. Am. Chem. Soc.* **83,** 835 (1961); Ross, *J. Am. Chem. Soc.* **81,** 2113 (1959); Bunnett, Garbisch, and Pruitt, *J. Am. Chem. Soc.* **79,** 385 (1957); Parker and Read, *J. Chem. Soc.* 9, 3149 (1962).

[56] Chapman and Parker, *J. Chem. Soc.* 3301 (1951); Bamkole, Bevan, and Hirst, *Chem. Ind.* (*London*) 119 (1963).

[57] For a review, see Miller, Ref. 2, pp. 180–233.

[58] This list is compiled from data in Bunnett and Zahler, Ref. 1, p. 340; Bunnett, Ref. 2, p. 13; Sauer and Huisgen, Ref. 2, p. 311; and Bunnett, *Annu. Rev. Phys. Chem.* **14,** 271–290 (1963).

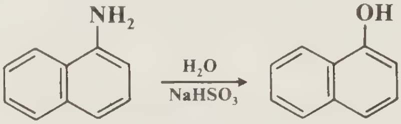
[59] Sauer and Huisgen, Ref. 2, p. 311. Also see Murto, *Acta Chem. Scand.* **18,** 1043 (1964).

[60] For a review of OH^- and OR^- as nucleophiles in aromatic substitution, see Fyfe, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, pp. 83–124, Interscience Publishers, Inc., New York, 1971.

[61] For a convenient way of achieving this conversion, see Knudsen and Snyder, *J. Org. Chem.* **39,** 3343 (1974).

OS **I**, 455; **II**, 451; **V**, 632. Also see OS **V**, 918.

3-2 Replacement of an Amino Group by a Hydroxyl Group



The amino group of naphthylamines can be replaced by a hydroxyl group by treatment with aqueous bisulfite.[65] The scope is greatly limited: the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see reaction **3-7**), and both the forward and reverse reactions are called the *Bucherer reaction.* The mechanism is completely different from any outlined in the first section of this chapter and is discussed at reaction **3-7.**

3-3 Alkali Fusion of Sulfonate Salts

$$ArSO_3^- \xrightarrow[300\text{–}320°C]{NaOH\ fus.} ArO^-$$

Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups which are attacked by alkali at the fusion temperatures. Milder conditions may be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[66]

OS **I**, 175; **III**, 288.

3-4 Replacement by OR or OAr

$$ArBr + OR^- \longrightarrow ArOR$$

This reaction is similar to reaction **3-1** and, like that one, generally requires activated substrates.[60] With unactivated substrates, side reactions predominate, though aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPT.[66a] This reaction gives better yields than reaction **3-1** and is used more often. In addition to halides, leaving groups may be nitro, NR_3^+, other OR, etc., even OH.[67] The substrates Ar_2Br^+ are converted to ArOR in very high yields.[68] Acid salts, $RCOO^-$, are sometimes used as nucleophiles. Good yields of aryl benzoates can be obtained by the treatment of aryl halides with cuprous benzoate in diglyme or xylene at 140 to 160°C.[69]

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[62] The benzyne mechanism for this reaction is also supported by ^{14}C labeling experiments: Bottini and Roberts, *J. Am. Chem. Soc.* **79,** 1458 (1957); Dalman and Neumann, *J. Am. Chem. Soc.* **90,** 1601 (1968).

[63] Pickles and Thorpe, *J. Organomet. Chem.* **76,** C23 (1974).

[64] For reviews of photochemical aromatic nucleophilic substitutions, see Cornelisse, de Gunst, and Havinga, *Adv. Phys. Org. Chem.* **11,** 225–266 (1975); Cornelisse, *Pure Appl. Chem.* **41,** 433–453 (1975); Pietra, *Q. Rev., Chem. Soc.* **23,** 504–521 (1969), pp. 519–521.

[65] For reviews, see Seeboth, *Angew. Chem. Int. Ed. Engl.* **6,** 307–317 (1967) [*Angew. Chem.* **79,** 329–340]; Drake, *Org. React.* **1,** 106–128 (1942); Gilbert, "Sulfonation and Related Reactions," pp. 166–169, Interscience Publishers, New York, 1965.

[66] Buzbee, *J. Org. Chem.* **31,** 3289 (1966); Oae, Furukawa, Kise, and Kawanishi, *Bull. Chem. Soc. Jpn.* **39,** 1212 (1966).

[66a] Shaw, Kunerth, and Swanson, *J. Org. Chem.* **41,** 732 (1976).

For aroxide nucleophiles, the reaction is promoted by copper salts, and when these are used, activating groups need not be present. This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*[69a] and should not be confused with the more important Ullmann coupling reaction (**3-16**). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.[70] The Ullmann ether synthesis is best performed in pyridine or in certain other solvents containing hetero atoms.[71] Because aryloxycopper(I) reagents ArOCu react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.[72] Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[73]

OS **I,** 219; **II,** 445; **III,** 293, 566; **V,** 926; **51,** 82.

B. Sulfur Nucleophiles

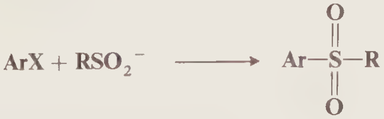
3-5 Replacement by SH or SR

$$\mathbf{ArBr + SH^- \longrightarrow ArSH}$$
$$\mathbf{ArBr + SR^- \longrightarrow ArSR}$$

Aryl thiols and thioethers can be prepared in reactions similar to **3-1** and **3-4**.[74] Activated aryl halides generally give good results, but side reactions are occasionally important. Diaryl sulfides can be prepared by the use of SAr^-. Sulfide salts, e.g., Na_2S, can also be used to prepare mercaptans, though yields are not high. Even unactivated aryl halides react with SAr^- if polar aprotic solvents, e.g., dimethylformamide[75] or dimethyl sulfoxide,[76] are used, though the mechanism is still nucleophilic substitution. Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^- in liquid ammonia under irradiation.[77] The mechanism in this case is probably SRN1 (see p. 599).

Other sulfur nucleophiles also react with activated aryl halides:

$$\mathbf{2ArX + S_2^{2-} \longrightarrow Ar{-}S{-}S{-}Ar}$$
$$\mathbf{ArX + SO_3^{2-} \longrightarrow Ar{-}SO_3^-}$$
$$\mathbf{ArX + SCN^- \longrightarrow ArSCN}$$



$$\mathbf{ArX + RSO_2^- \longrightarrow Ar{-}\overset{\overset{\textstyle O}{\|}}{\underset{\underset{\textstyle O}{\|}}{S}}{-}R}$$

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[67] Oae and Kiritani, *Bull. Chem. Soc. Jpn.* **37,** 770 (1964); **39,** 611 (1966).

[68] Lubinkowski and McEwen, *Tetrahedron Lett.* 4817 (1972).

[69] Cohen and Lewin, *J. Am. Chem. Soc.* **88,** 4521 (1966); Cohen, Wood, and Dietz, *Tetrahedron Lett.* 3555 (1974).

[69a] For a review of the Ullmann ether synthesis, see Moroz and Shvartsberg, *Russ. Chem. Rev.* **43,** 679–689 (1974).

[70] Weingarten, *J. Org. Chem.* **29,** 977, 3624 (1964).

[71] Williams, Kinney, and Bridger, *J. Org. Chem.* **32,** 2501 (1967).

[72] Kawaki and Hashimoto, *Bull. Chem. Soc. Jpn.* **45,** 1499 (1972).

[73] Whitesides, Sadowski, and Lilburn, *J. Am. Chem. Soc.* **96,** 2829 (1974).

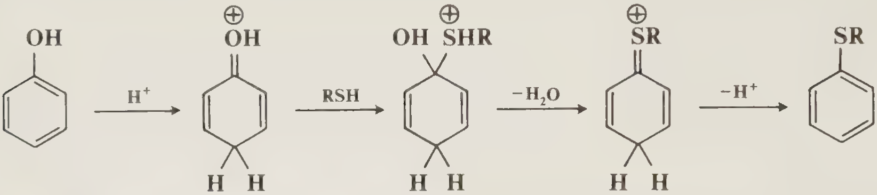
[74] For reviews of sulfur nucleophiles in aromatic substitution, see Peach, in Patai, "The Chemistry of the Thiol Group," pt. 2, pp. 735–744, John Wiley & Sons, Inc., New York, 1974; Parker, in Kharasch, "Organic Sulfur Compounds," vol. 1, pp. 103–111, Pergamon Press, New York, 1961.

[75] Campbell, *J. Org. Chem.* **29,** 1830 (1964).

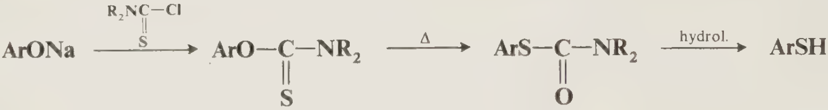
[76] Bradshaw, South, and Hales, *J. Org. Chem.* **37,** 2381 (1972).

[77] Bunnett and Creary, *J. Org. Chem.* **39,** 3173, 3611 (1974).

Hydroxyl groups can be replaced by SR groups in acid solution.[78] In this case the mechanism bears certain resemblances to that of the Bucherer reaction (**3-7**):



As with the Bucherer reaction, yields are highest with naphthols (50 to 60%), though in this case phenols also give the reaction (20 to 40% yields). Phenols can be converted to thiophenols by treatment of their salts with N,N-dimethylthiocarbamoyl chloride, pyrolysis of the resulting O-aryl dialkylthiocarbamate to the S-aryl dialkylthiocarbamate, and hydrolysis of this compound:[79]



$$\mathrm{ArONa} \xrightarrow{\mathrm{R_2N}\underset{\underset{\displaystyle \mathrm{S}}{\|}}{\mathrm{C}}\mathrm{-Cl}} \mathrm{ArO}-\underset{\underset{\displaystyle \mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{NR_2} \xrightarrow{\Delta} \mathrm{ArS}-\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{NR_2} \xrightarrow{\text{hydrol.}} \mathrm{ArSH}$$

OS **I,** 220; **III,** 86, 239, 667; **V,** 107, 474; **50,** 75; **51,** 139. Also see OS **V,** 977.

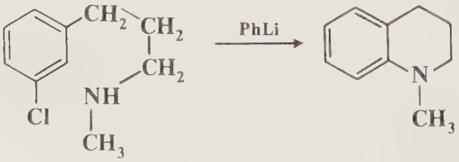
C. Nitrogen Nucleophiles

3-6 Replacement by NH_2, NHR, or NR_2

$$\mathrm{ArBr} + \mathrm{NH_3} \longrightarrow \mathrm{ArNH_2}$$
$$\mathrm{ArBr} + \mathrm{RNH_2} \longrightarrow \mathrm{ArNHR}$$
$$\mathrm{ArBr} + \mathrm{R_2NH} \longrightarrow \mathrm{ArNR_2}$$

Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine being especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO_2, N_3, OSO_2R, OR, and SR.

Nonactivated aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR,[80] or $NaNR_2$.[81] With these reagents, the benzyne mechanism operates, and so cine substitution is often found. Ring closure has been effected by this type of reaction,[82] e.g.,



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[78] Oae and Kiritani, *Bull. Chem. Soc. Jpn.* **38,** 1381 (1965).

[79] Newman and Karnes, *J. Org. Chem.* **31,** 3980 (1966).

[80] See Biehl, Smith, and Reeves, *J. Org. Chem.* **36,** 1841 (1971).

[81] For a review, see Heaney, *Chem. Rev.* **62,** 81–97 (1962), pp. 83–89.

[82] Huisgen, König, and Lepley, *Chem. Ber.* **93,** 1496 (1960); Bunnett and Hrutfiord, *J. Am. Chem. Soc.* **83,** 1691 (1961). For a review of ring closures by the benzyne mechanism, see Hoffmann, "Dehydrobenzene and Cycloalkynes," Ref. 19, pp. 150–164.

It has proved possible to close larger rings too in this manner: eight- and even twelve-membered. Triarylamines have been prepared in a similar manner, from ArI and Ar'_2NLi, even with unactivated ArI.[83] Sulfonic acid salts can be fused with alkali-metal amides to give aromatic amines, a process similar to reaction **3-3.** With some substrates, the SNAr and benzyne mechanisms can run concurrently.[84]

The reaction with ammonia or amines, which undoubtedly proceeds by the SNAr mechanism, is catalyzed by copper and nickel[84a] salts, though these are normally used only with rather unreactive halides. The manner of catalysis is poorly understood.[85] Copper-ion catalysts (especially cuprous iodide) also permit the Gabriel synthesis (reaction **0-60**) to be applied to aromatic substrates. Aryl bromides or iodides are refluxed with potassium phthalimide and CuI in dimethylacetamide to give N-aryl phthalimides, which can be hydrolyzed to primary aryl amines.[86]

In certain reactions in which a benzyne mechanism would seem obvious, an analysis of the products has shown that another mechanism must intervene. For example, 5- and 6-iodo-1,2,4-trimethylbenzenes, treated with KNH_2 in NH_3, each gave a different ratio of 5- and 6-amino-1,2,4-trimethylbenzenes, though if a benzyne mechanism were the only one operating, the same benzyne intermediate (and consequently the same product ratio) should be present in both cases.[87] It has been proposed[87] that besides the benzyne mechanism, a free-radical mechanism (called SRN1) is also operating in these cases:

$$\mathbf{ArI} \xrightarrow[\text{donor}]{\text{electron}} [\mathbf{ArI}]\cdot^- \longrightarrow \mathbf{Ar}\cdot + \mathbf{I}^-$$

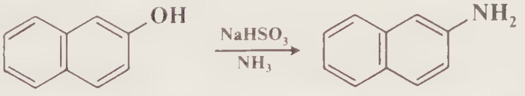
$$\mathbf{Ar}\cdot + \mathbf{NH_2} \longrightarrow \mathbf{ArNH_2}\cdot^- + \mathbf{ArI} \longrightarrow \mathbf{ArNH_2} + \mathbf{ArI}\cdot^-$$

Termination steps

The identity of the electron donor is not known, though if a known electron donor is added, e.g., K, the extent of the free-radical pathway is increased. For other examples of the SRN1 mechanism, see reactions **3-5, 3-7,** and **3-14.**[88]

OS **I,** 544; **II,** 15, 221, 228; **III,** 53, 307, 573; **IV,** 336, 364; **V,** 816, 1067.

3-7 Replacement of a Hydroxy Group by an Amino Group



The reaction of naphthols with ammonia and sodium bisulfite is the reverse of reaction **3-2** and has a similar scope.[65] It is also called the *Bucherer reaction.* Primary amines may be used instead of ammonia, in which case N-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary, by a transamination reaction:

$$\mathbf{ArNH_2} + \mathbf{RNH_2} \xrightarrow{\mathrm{NaHSO_3}} \mathbf{ArNHR}$$

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[83] Neunhoeffer and Heitmann, *Chem. Ber.* **94,** 2511 (1961).

[84] Kauffmann and Nürnberg, *Chem. Ber.* **100,** 3427 (1967); Kauffmann, Nürnberg, and Wirthwein, *Chem. Ber.* **102,** 1161 (1969); Kauffmann, Nürnberg, and Udluft, *Chem. Ber.* **102,** 1177 (1969).

[84a] See Cramer and Coulson, *J. Org. Chem.* **40,** 2267 (1975).

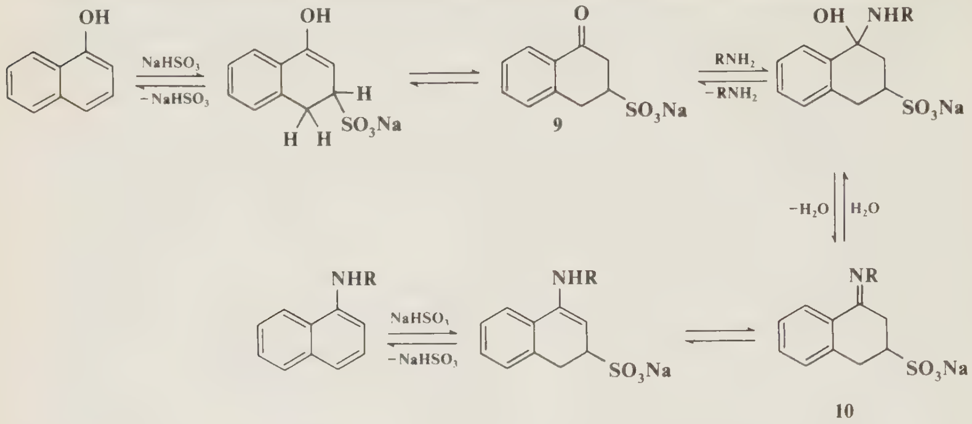
[85] For discussion, see Tuong and Hida, *Bull. Chem. Soc. Jpn.* **43,** 1763 (1970), **44,** 765 (1971), *J. Chem. Soc., Perkin Trans. 2* 676 (1974).

[86] Bacon and Karim, *Chem. Commun.* 578 (1969), *J. Chem. Soc., Perkin Trans. 1* 272, 278 (1973).

[87] Kim and Bunnett, *J. Am. Chem. Soc.* **92,** 7463, 7464 (1970).

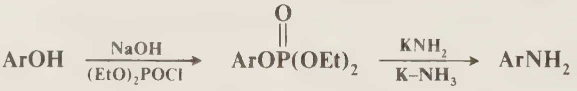
[88] For other examples, see Wolfe, Greene, and Hudlicky, *J. Org. Chem.* **37,** 3199 (1972).

The mechanism of the Bucherer reaction amounts to a kind of overall addition-elimination:[89]



The first step in either direction consists of addition of $NaHSO_3$ to one of the double bonds of the ring, giving an enol (or enamine), which tautomerizes to the keto (or imine) form. The conversion of **9** to **10** (or vice versa) is an example of reaction **6-15** (or **6-2**). Evidence for this mechanism was the isolation of **9**[90] and the demonstration that, for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[91] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so that the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[92]

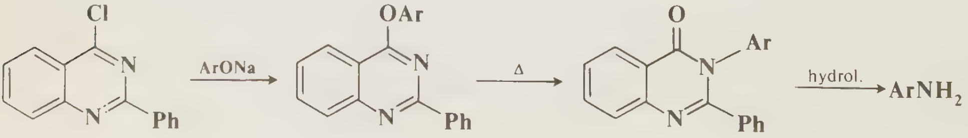
Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid ammonia



$$\mathrm{ArOH} \xrightarrow[(\mathrm{EtO})_2\mathrm{POCl}]{\mathrm{NaOH}} \mathrm{ArO}\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{P}}(\mathrm{OEt})_2 \xrightarrow[\mathrm{K\text{–}NH_3}]{\mathrm{KNH_2}} \mathrm{ArNH_2}$$

gives the corresponding primary aromatic amines.[93] The mechanism of the second step is SRN1 (see reaction **3-6**). Phenols can also be converted to amines by conversion to 4-aryloxy-2-phenylquinazolines; conversion of these (by heat) to 3-aryl-2-phenyl-4(3*H*)-quinazolinones; and hydrolysis of the latter.[94]

OS **III**, 78.



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[89] Rieche and Seeboth, *Justus Liebigs Ann. Chem.* **638**, 66 (1960).

[90] Rieche and Seeboth, *Justus Liebigs Ann. Chem.* **638**, 43, 57 (1960).

[91] Kozlov and Veselovskaia, *J. Gen. Chem. USSR* **28**, 3359 (1958).

[92] Rieche and Seeboth, *Justus Liebigs Ann. Chem.* **638**, 76 (1960).

[93] Rossi and Bunnett, *J. Org. Chem.* **37**, 3570 (1972).

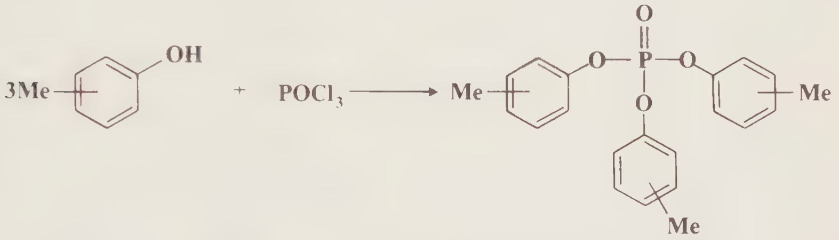
[94] Scherrer and Beatty, *J. Org. Chem.* **37**, 1681 (1972). See also Morrow and Butler, *J. Org. Chem.* **29**, 1893 (1964); Morrow and Hofer, *J. Med. Chem.* **9**, 249 (1966).

D. Halogen Nucleophiles

3-8 The Introduction of Halogens

$$\mathrm{Ar{-}X + X'^- \longrightarrow Ar{-}X' + X^-}$$

It is possible to replace a halogen on a ring by another halogen if the ring is activated. There is an equilibrium, but it is usually possible to shift this in the desired direction by the use of an excess of added halide ion.[95] Another common leaving group is nitro, which can be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures, and the mechanism is not always nucleophilic substitution. A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if activated. Unactivated phenols give phosphates when treated with $POCl_3$. An example is formation of tricresyl phosphate (TCP):



Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2[96] (see reaction **0-67**). However, when an ortho *t*-butyl group is present, this group may be cleaved.[97]

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens.[98] Activated aryl chlorides give fluorides when treated with KF in dimethylformamide, dimethyl sulfoxide, or dimethyl sulfone.[99] All six chlorines of hexachlorobenzene can be replaced by F by heating with KF at 450 to 500°C in the absence of a solvent.[100] Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $I > Br > Cl \gg F$, the SNAr mechanism is probably not operating.[101]

An indirect method for the replacement of OH or SH by F has been developed by Christie and Pavlath.[102] The method consists in the treatment of a phenol or thiophenol (or their salts) with COFCl to give a fluoroformate (or fluorothioformate), which is pyrolyzed to the product

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[95] Sauer and Huisgen, *Angew. Chem.* **72,** 294–315 (1960), p. 297.

[96] Wiley, Hershkowitz, Rein, and Chung, *J. Am. Chem. Soc.* **86,** 964 (1964); Wiley, Rein, and Hershkowitz, *Tetrahedron Lett.* 2509 (1964); Schaefer and Higgins, *J. Org. Chem.* **32,** 1607 (1967).

[97] Lee, *Chem. Commun.* 1554 (1968).

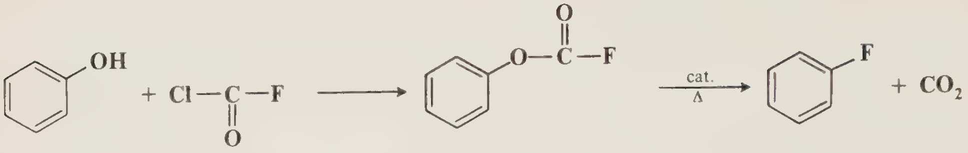
[98] For a review of the preparation of organic fluorides by halogen exchange, see Barbour, Belf, and Buxton, *Adv. Fluorine Chem.* **3,** 181–270 (1963).

[99] Starr and Finger, *Chem. Ind.* (*London*) 1328 (1962); Finger, Starr, Dickerson, Gutowsky, and Hamer, *J. Org. Chem.* **28,** 1666 (1963); Finger, Dickerson, and Shiley, *J. Fluorine Chem.* **1,** 415 (1972); Shiley, Dickerson, and Finger, *J. Fluorine Chem.* **2,** 19 (1972).

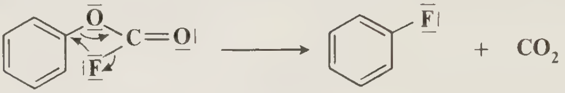
[100] Vorozhtsov, Platonov, and Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1389 (1963); Yakobson, Platonov, and Vorozhtsov, *J. Gen. Chem. USSR* **35,** 1161 (1965). See also Yakobson, Platonov, Kryukova, Gershtein, and Vorozhtsov, *J. Gen. Chem. USSR* **36,** 2124 (1966); Yakobson, Platonov, Petrov, Kryukova, Gershtein, and Vorozhtsov, *J. Gen. Chem. USSR* **36,** 2128 (1966).

[101] Bacon and Hill, *J. Chem. Soc.* 1097, 1108 (1964). See also van Koten, Jastrzebski, and Noltes, *Tetrahedron Lett.* 223 (1976).

[102] Christie and Pavlath, *J. Org. Chem.* **30,** 3170, 4104 (1965), **31,** 559 (1966).



Overall yields are high in most cases. An SNi mechanism has been proposed for the pyrolysis step:



OS **III,** 194, 272, 475; **V,** 142, 478.

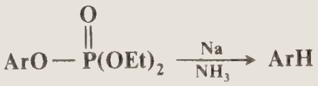
E. Hydrogen as Nucleophile

3-9 Reduction of Phenols and Phenolic Esters and Ethers

$$\mathrm{ArOH} \xrightarrow{\mathrm{Zn}} \mathrm{ArH}$$

Phenols can be reduced by distillation over zinc dust or with HI and red phosphorus, but these methods are quite poor and are seldom feasible. Catalytic hydrogenation has also been used, but the corresponding cyclohexanol (see reaction **5-13**) is a side product.[103]

Much better results have been obtained by conversion of phenols to certain esters or ethers, and reduction of the latter:

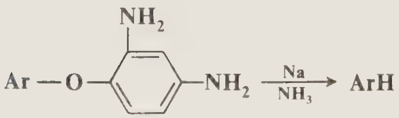


$$\mathrm{ArO{-}\overset{O}{\overset{\|}{P}}(OEt)_2} \xrightarrow[\mathrm{NH_3}]{\mathrm{Na}} \mathrm{ArH}$$

Ref. 104

$$\mathrm{ArOTs + NH_2NH_2} \xrightarrow{\mathrm{Pd}} \mathrm{ArH}$$

Ref. 105



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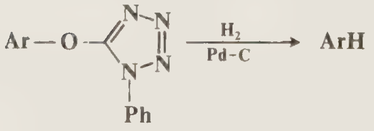
Ref. 106



12

Ref. 107

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[103] Shuikin and Erivanskaya, *Russ. Chem. Rev.* **29,** 309–320 (1960), pp. 313–315.

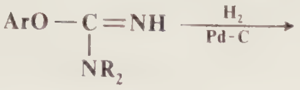
[104] Kenner and Williams, *J. Chem. Soc.* 522 (1955); Pelletier and Locke, *J. Org. Chem.* **23,** 131 (1958); Rossi and Bunnett, *J. Org. Chem.* **38,** 2314 (1973).

[105] Kenner and Murray, *J. Chem. Soc.* S178 (1949); Rottendorf and Sternhell, *Aust. J. Chem.* **16,** 647 (1963).

[106] Sawa, Tsuji, and Maeda, *Tetrahedron* **15,** 144, 154 (1961); Pirkle and Zabriskie, *J. Org. Chem.* **29,** 3124 (1964).

[107] Musliner and Gates, *J. Am. Chem. Soc.* **88,** 4271 (1966). For related methods, see Pailer and Gössinger, *Monatsh. Chem.* **100,** 1613 (1969); van Muijlwijk, Kieboom, and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **93,** 204 (1974).

$$ArOSO_3^- K^+ \xrightarrow[\text{aq. KOH}]{\text{Raney Ni}} ArH \qquad \text{Ref. 108}$$



$$ArO-C(NR_2)=NH \xrightarrow[\text{Pd-C}]{H_2} ArH \qquad \text{Ref. 108a}$$

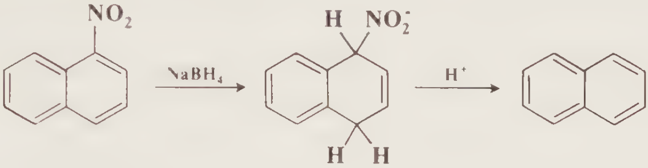
11 are prepared by treatment of phenols with 2,4-dinitrofluorobenzene (reaction **3-4**) and reduction of the dinitro product. **12** are prepared by treatment of phenols with 1-phenyl-5-chlorotetrazole in acetone containing K_2CO_3. See also reaction **1-46.**

OS **51,** 82.

3-10 Reduction of Halides and Nitro Compounds

The reaction ArX → ArH is treated in Chapter 11 (reaction **1-48**) though, depending on reagent and conditions, it may be nucleophilic[109] or free-radical[110] substitution, as well as electrophilic.

The nitro group of aromatic nitro compounds has been removed with sodium borohydride.[111] This reaction involves an addition-elimination mechanism, in which the addition is 1,4:



F. Carbon Nucleophiles

3-11 Replacement of Halides by Cyanide. The Rosenmund—von Braun reaction

$$ArBr + \text{anhyd. } CuCN \xrightarrow{200\text{ C}} ArCN$$

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund–von Braun reaction.*[112] The mechanism may involve conversion of the aryl halide to an arylcopper intermediate.[69] Other cyanides, e.g., KCN and NaCN, do not react with aryl halides, even activated ones. However, KCN does convert aryl halides to nitriles in dimethylformamide in the presence of Pd(II) salts.[113] Also, in aprotic solvents (e.g., $CHCl_3$, dimethylformamide), CN^- reacts with 1,3-dinitrobenzene or 1,3,5-trinitrobenzene (at the 2 or 4 positions) to form Meisenheimer salts.[114] Aromatic ethers have been photochemically converted to nitriles (ArOR → ArCN) by irradiation of a mixture of the ether and sodium cyanide.[115] A similar photochemical process has been reported for some aromatic nitro compounds ($ArNO_2$ → ArCN).[116]

OS **III,** 212, 631.

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[108] Lonsky, Traitler, and Kratzl, *J. Chem. Soc., Perkin Trans. 1* 169 (1975). For a related method, see Clauss and Jensen, *Angew. Chem. Int. Ed. Engl.* **12,** 918 (1973) [*Angew. Chem.* **85,** 981].

[108a] Vowinkel and Baese, *Chem. Ber.* **107,** 1213 (1974). See also Vowinkel and Wolff, *Chem. Ber.* **107,** 907, 1739 (1974).

[109] For example, see Corbett and Holt, *J. Chem. Soc.* 2385 (1963).

[110] Menapace and Kuivila, *J. Am. Chem. Soc.* **86,** 3047 (1964).

[111] Severin, Schmitz, and Temme, *Chem. Ber.* **96,** 2499 (1963); Kniel, *Helv. Chim. Acta* **51,** 371 (1968).

[112] For a review, see Mowry, *Chem. Rev.* **42,** 189–283 (1948), pp. 207–209.

[113] Takagi, Okamoto, Sakakibara, Ohno, Oka, and Hayama, *Bull. Chem. Soc. Jpn.* **48,** 3298 (1975). See also Sekiya and Ishikawa, *Chem. Lett.* 277 (1975).

[114] See for example, Vickery, *Chem. Ind. (London)* 1523 (1967); Norris, *J. Org. Chem.* **34,** 1486 (1969), *Can. J. Chem.* **45,** 2703 (1967), **47,** 2895 (1969); Buncel, Norris, Proudlock, and Russell, *Can. J. Chem.* **47,** 4129 (1969); Norris and Shurrell, *Can. J. Chem.* **47,** 4267 (1969).

[115] Letsinger and Colb, *J. Am. Chem. Soc.* **94,** 3665 (1972).

[116] See for example Vink, Verheijdt, Cornelisse and Havinga, *Tetrahedron* **28,** 5081 (1972).

3-12 Cyanide Fusion of Sulfonate Salts[117]

$$\mathrm{ArSO_3^-} \xrightarrow{\text{NaCN fus.}} \mathrm{ArCN}$$

This reaction is very similar to reaction **3-3.** Yields are usually low.

3-13 Coupling of Organometallic Compounds with Aryl Halides and Ethers

$$\mathrm{ArI + R_2CuLi} \longrightarrow \mathrm{ArR}$$

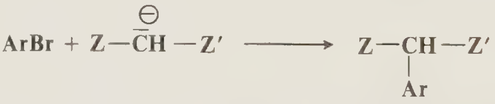
Aryl iodides, which need not be activated, couple with lithium dialkylcopper reagents. The reaction is discussed at reaction **0-87.** Aryl halides, even when activated, generally do not couple with Grignard reagents. The reaction proceeds better when OR can be the leaving group, providing that activating groups are present in the ring. Chloro-substituted nitrogen heterocycles can be alkylated indirectly by treatment with phosphorus ylides and subsequent hydrolysis:[118]

$$\mathrm{ArCl + RCH{=}PR'_3} \longrightarrow \mathrm{Ar{-}CR{=}PR'_3} \xrightarrow{\mathrm{OH^-}} \mathrm{ArCH_2R}$$

Unactivated aryl halides couple with alkyllithium reagents in tetrahydrofuran to give moderate to good yields of alkyl arenes.[119]

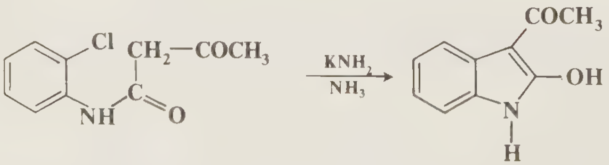
OS **52,** 128.

3-14 Arylation at a Carbon Containing an Active Hydrogen



$$\mathrm{ArBr} + \mathrm{Z{-}}\overset{\ominus}{\underline{\mathrm{C}}}\mathrm{H{-}Z'} \longrightarrow \mathrm{Z{-}}\underset{\substack{|\\ \mathrm{Ar}}}{\mathrm{CH}}\mathrm{{-}Z'}$$

The arylation of compounds of the form $\mathrm{ZCH_2Z'}$ is analogous to reaction **0-96,** and Z is as defined there. Activated aryl halides generally give good results. Even unactivated aryl halides can be employed if the reaction is carried out in the presence of excess sodium amide.[120] Compounds of the form $\mathrm{ZCH_2Z'}$ and even simple ketones[121] and esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from $\mathrm{ZCH_2Z'}$ and catalyzes the benzyne mechanism. The reaction has been used for ring closure:[122]



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[117] For a review, see Ref. 112, pp. 193–194.

[118] Taylor and Martin, *J. Am. Chem. Soc.* **96,** 8095 (1974).

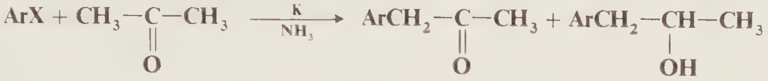
[119] Merrill and Negishi, *J. Org. Chem.* **39,** 3452 (1974).

[120] Leake and Levine, *J. Am. Chem. Soc.* **81,** 1169, 1627 (1959).

[121] For example, see Caubere and Guillaumet, *Bull. Soc. Chim. Fr.* 4643, 4649 (1972).

[122] Bunnett and Hrutfiord, *J. Am. Chem. Soc.* **83,** 1691 (1961); Bunnett, Kato, Flynn, and Skorcz, *J. Org. Chem.* **28,** 1 (1963). For a review, see Hoffmann, Ref. 82, pp. 150–164.

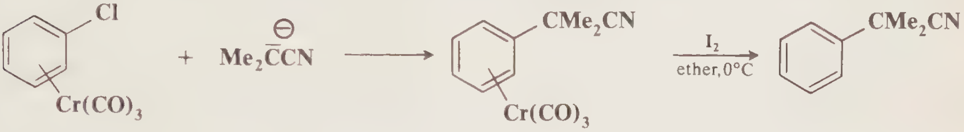
Compounds of the form CH_3Z can be arylated by treatment with an aryl halide in liquid ammonia containing Na or K, e.g.,[123]



$$ArX + CH_3-\underset{\underset{O}{\|}}{C}-CH_3 \xrightarrow[NH_3]{K} ArCH_2-\underset{\underset{O}{\|}}{C}-CH_3 + ArCH_2-\underset{\underset{OH}{|}}{CH}-CH_3$$

The same products are obtained (though in different proportions) when Na or K is omitted but the solution is irradiated with near-uv light.[124] In either case other leaving groups may be used instead of halogens (e.g. NR_3^+, SAr), and the mechanism is the SRN1 mechanism (see reaction **3-6**).

Another method for achieving the coupling of an aryl halide with certain carbanions involves the use of aryl halides activated by conversion to chromium carbonyl complexes.[125] For example,



13 **14**

13 couples with the anion of isobutyronitrile to give **14.** The chromium tricarbonyl group can be quantitatively removed from **14** by treatment with iodine and ether at 0°C.

Diaryliodonium salts have also been used to arylate ZCH_2Z', but the mechanism is apparently free-radical.[126]

Aryl iodides (even unactivated) react with copper acetylides to give arylacetylenes.[127] The mechanism in this case may also be free-radical.

OS V, 12, 263; **51,** 128.

3-15 Carbalkoxylation and Carboxylation

$$ArI \xrightarrow[Ni(CO)_4]{ROH} ArCOOR$$

Aryl iodides can be converted directly to esters by treatment with nickel carbonyl in ROH as solvent[128] (see reaction **0-105**). The yields are nearly quantitative. In aprotic solvents, such as tetrahydrofuran, the products are benzils, ArCOCOAr. The reaction is not successful for aryl chlorides, bromides, or fluorides. Aryl bromides can be carboxylated ($\text{ArBr} \rightarrow \text{ArCOOH}$) in high yields by treatment with CO in the presence of water and a catalytic amount of Ni(CO)_4 provided that a salt such as KOAc is present to neutralize the HBr formed.[129]

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[123] Rossi and Bunnett, *J. Am. Chem. Soc.* **94,** 683 (1972), *J. Org. Chem.* **38,** 3020 (1973); Bunnett and Gloor, *J. Org. Chem.* **38,** 4156 (1973), **39,** 382 (1974).

[124] Rossi and Bunnett, *J. Org. Chem.* **38,** 1407 (1973); Hay, Hudlicky, and Wolfe, *J. Am. Chem. Soc.* **97,** 374 (1975); Rossi, de Rossi, and López, *J. Am. Chem. Soc.* **98,** 1252 (1976); Bunnett and Sundberg, *J. Org. Chem.* **41,** 1702 (1976).

[125] Semmelhack and Hall, *J. Am. Chem. Soc.* **96,** 7091, 7092 (1974); Semmelhack, Hall, Yoshifuji, and Clark, *J. Am. Chem. Soc.* **97,** 1247 (1975).

[126] Hampton, Harris, and Hauser, *J. Org. Chem.* **29,** 3511 (1964).

[127] Castro and Stephens, *J. Org. Chem.* **28,** 2163 (1963); Stephens and Castro, *J. Org. Chem.* **28,** 3313 (1963); Sladkov, Ukhin, and Korshak, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2043 (1963); Shvartsberg, Kozhevnikova, and Kotlyarevskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 460 (1967); Castro, Gaughan, and Owsley, *J. Org. Chem.* **31,** 4071 (1966); Castro, Havlin, Honwad, Malte, and Mojé, *J. Am. Chem. Soc.* **91,** 6464 (1969); Atkinson, Curtis, Jones, and Taylor, *J. Chem. Soc. C* 2173 (1969). See also Wiles and Massey, *Tetrahedron Lett.* 5137 (1967); Shvartsberg, Moroz, and Kotlyarevskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **20,** 1209 (1971), **21,** 946 (1972); Oliver and Walton, *Tetrahedron Lett.* 5209 (1972).

[128] Bauld, *Tetrahedron Lett.* 1841 (1963). See also Corey and Hegedus, *J. Am. Chem. Soc.* **91,** 1233 (1969); Nakayama and Mizoroki, *Bull. Chem. Soc. Jpn.* **44,** 508 (1971).

3-16 The Ullmann Reaction

$$2\text{ArI} \xrightarrow[\Delta]{\text{Cu}} \text{Ar—Ar}$$

The coupling of aryl halides with copper is called the *Ullmann reaction*.[130] The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls. When a mixture of two different aryl halides is used, there are three possible products, but often only one of these is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.[131] The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used. The reaction rate can be increased by the use of copper which has been activated by a complexing agent, e.g., the sodium salt of ethylenediaminetetraacetic acid.[132]

The effects of other groups on the ring are unusual. The nitro group is strongly activating, but only in the ortho (not meta or para) position.[133] R and OR activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO_2NH_2, and similar groups, for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the Wurtz reaction (**0-86**):

Step 1 $\quad \text{ArI} + \text{Cu} \longrightarrow \text{ArCu}$

Step 2 $\quad \text{ArCu} + \text{ArI} \longrightarrow \text{ArAr}$

The species represented as ArCu may not actually have this structure, but some kind of a complex is formed. Organocopper compounds have been trapped by coordination with organic bases.[134] In addition, arylcopper compounds (ArCu) have been independently prepared and shown to give biaryls (ArAr′) when treated with aryl iodides Ar′I.[135] An alternate possible second step is $2\text{ArCu} \rightarrow \text{ArAr}$, and indeed arylcopper compounds are known to dimerize in this fashion.[136] The mechanisms of steps 1 and 2 are in doubt. It has been suggested[137] that step 1 is a free-radical reaction

$$\text{ArI} + \text{Cu} \longrightarrow \text{Ar}\bullet \xrightarrow{\text{Cu}} \text{ArCu}$$

and that step 2 is a nucleophilic attack by ArCu on ArI. Evidence for the latter is that a Meisenheimer salt could be isolated from treatment of 1,3,5-trinitrobenzene with an arylcopper compound[138] (in this case the leaving group is hydrogen).

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[129] Nakayama and Mizoroki, *Bull. Chem. Soc. Jpn.* **42,** 1124 (1969). See also Cassar and Foà, *J. Organomet. Chem.* **51,** 381 (1973).

[130] For reviews, see Fanta, *Synthesis* 9–21 (1974), *Chem. Rev.* **64,** 613–632 (1964), **38,** 139–196 (1946); Goshaev, Otroshchenko, and Sadykov, *Russ. Chem. Rev.* **41,** 1046 (1972); Bacon and Hill, *Q. Rev., Chem. Soc.* **19,** 95–125 (1965), pp. 101–107.

[131] Rule and Smith, *J. Chem. Soc.* 1096 (1937).

[132] Lewin, Zovko, Rosewater, and Cohen, *Chem. Commun.* 80 (1967).

[133] Forrest, *J. Chem. Soc.* 592 (1960).

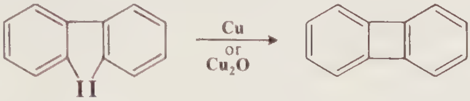
[134] Lewin and Cohen, *Tetrahedron Lett.* 4531 (1965).

[135] For examples, see Nilsson, *Tetrahedron Lett.* 675 (1966); Cairncross and Sheppard, *J. Am. Chem. Soc.* **90,** 2186 (1968); Nilsson and Ullenius, *Acta Chem. Scand.* **24,** 2379 (1970); Ullenius, *Acta Chem. Scand.* **26,** 3383 (1972).

[136] Nilsson and Wennerström, *Tetrahedron Lett.* 3307 (1968); *Acta Chem. Scand.* **24,** 482 (1970).

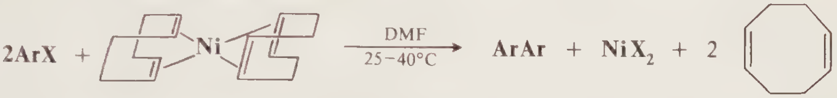
[137] For example, see Gragerov and Kasukhin, *J. Org. Chem. USSR* **5,** 2 (1969); Goshaev, Otroshchenko, and Sadykov, Ref. 130, p. 1054.

A similar reaction has been used for ring closure:



Either copper[139] or copper oxide[140] may be used in this ring-closure reaction, though the former gives better yields.[139]

Aryl halides can also be coupled by treatment with the complex bis(1,5-cyclooctadiene)-nickel(0) at 25 to 40°C in dimethylformamide.[141]

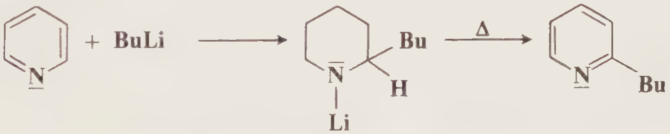


Ullmann-type coupling has also been carried out with ArNa and Ar′Cl. This proceeds by the benzyne mechanism.[142] For other methods of coupling of aromatic rings, see reactions **4-16, 4-19,** and **4-20.**

OS III, 339; 1120.

Hydrogen as Leaving Group

3-17 Alkylation and Arylation



The alkylation of heterocyclic nitrogen compounds with alkyllithiums is called *Ziegler alkylation.* Aryllithiums give arylation. The reaction occurs by an addition-elimination mechanism, and the adduct can be isolated.[143] Upon heating of the adduct, elimination of LiH occurs (see reaction **7-18**) and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the SNAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so that the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen.

The reaction has been applied to nonheterocyclic aromatic compounds: benzene, naphthalene, and phenanthrene have been alkylated with alkyllithiums, though the usual reaction with these reagents is **2-19,**[144] and Grignard reagents have been used to alkylate naphthalene.[145] The addition-elimination mechanism apparently applies in these cases also. Aryl azo compounds can also be arylated (in ortho positions) with aryl Grignard reagents.[146]

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[138] Björklund, Nilsson, and Wennerström, *Acta Chem. Scand.* **24,** 3599 (1970).

[139] Salfeld and Baume, *Tetrahedron Lett.* 3365 (1966).

[140] Lothrop, *J. Am. Chem. Soc.* **63,** 1187 (1941).

[141] Semmelhack, Helquist, and Jones, *J. Am. Chem. Soc.* **93,** 5908 (1971). See also Clark, Norman, and Thomas, *J. Chem. Soc., Perkin Trans. 1* 121 (1975); Kende, Liebeskind, and Braitsch, *Tetrahedron Lett.* 3375 (1975).

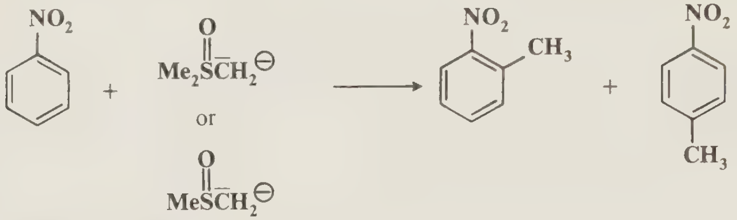
[142] Ehrhart, *Chem. Ber.* **96,** 2042 (1963). See also Friedman and Chlebowski, *J. Am. Chem. Soc.* **91,** 4864 (1969).

[143] Nmr spectra of these adducts have been reported: Fraenkel and Cooper, *Tetrahedron Lett.* 1825 (1968); Foster and Fyfe, *Tetrahedron* **25,** 1489 (1969). See also Abramovitch and Poulton, *Chem. Commun.* 274 (1967).

[144] Dixon and Fishman, *J. Am. Chem. Soc.* **85,** 1356 (1963); Eppley and Dixon, *J. Am. Chem. Soc.* **90,** 1606 (1968).

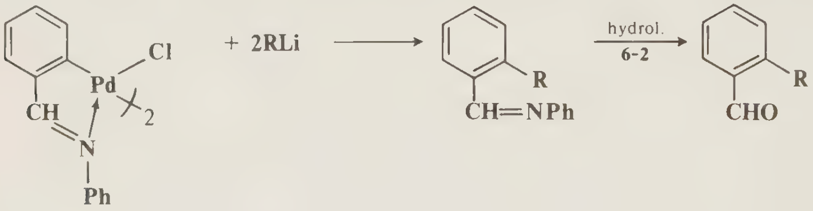
[145] Bryce-Smith and Wakefield, *Tetrahedron Lett.* 3295 (1964).

Aromatic nitro compounds can be methylated by treatment with dimethyloxosulfonium methylide[147] or the methylsulfinyl carbanion (obtained by treatment of dimethyl sulfoxide with a strong base):[148]



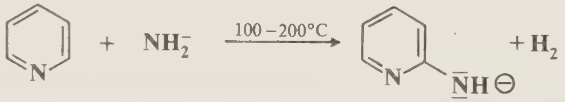
The latter reagent also methylates certain heterocyclic compounds, e.g., quinoline, and certain fused aromatic compounds, e.g., anthracene, phenanthrene.[149] The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel-Crafts procedure (reaction **1-13**). For the introduction of CH_2SR groups into phenols, see reaction **1-29.**

Alkyl and aryl groups can be introduced into the ortho positions of aromatic aldehydes indirectly by reaction of palladium complexes of the corresponding Schiff bases with alkyl- or aryllithiums.[150]



OS **II**, 517.

3-18 Amination of Heterocyclic Nitrogen Compounds



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides, in a process called the *Chichibabin reaction.*[151] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Nitro compounds do not give the reaction.[151a]

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[146] Risaliti, Bozzini and Stener, *Tetrahedron* **25,** 143 (1969).

[147] Traynelis and McSweeney, *J. Org. Chem.* **31,** 243 (1966).

[148] Russell and Weiner, *J. Org. Chem.* **31,** 248 (1966).

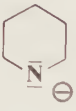
[149] Ref. 148; Argabright, Hofmann, and Schriesheim, *J. Org. Chem.* **30,** 3233 (1965); Nozaki, Yamamoto, and Noyori, *Tetrahedron Lett.* 1123 (1966); Trost, *Tetrahedron Lett.* 5761 (1966); Yamamoto, Nisimura, and Nozaki, *Bull. Chem. Soc. Jpn.* **44,** 541 (1971).

[150] Murahashi, Tanba, Yamamura, and Moritani, *Tetrahedron Lett.* 3749 (1974).

[151] For a review, see Leffler, *Org. React.* **1,** 91–104 (1942).

[151a] See for example, Levitt and Levitt, *Chem. Ind.* (*London*) 520 (1975).

Substituted alkali-metal amides, e.g., sodium piperidide (**15**), have also been used. Free amines may give the reaction, but only in the presence of bases like KOH.[152] Very likely the amide ion is the actual nucleophile in these cases. Apparently the hydride ion which is the leaving group combines with a proton from the initial $ArNH_2$ product to give H_2. At lower temperatures, in ammonia, potassium nitrate is sometimes necessary to oxidize the hydride ion. The mechanism is probably similar to that of reaction **3-17.** The existence of intermediate ions such as **16** (from quinoline) has been demonstrated by nmr spectra.[153] A pyridyne type of intermediate was ruled out by the observations that deuterium is not lost from pyridine-3-*d*[154] and that 3-ethylpyridine gave 2-amino-3-ethylpyridine.[155]



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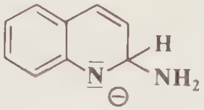
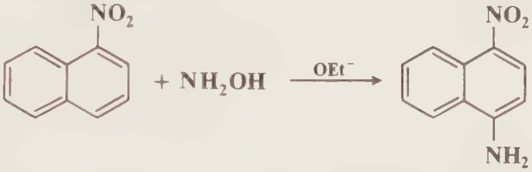


16

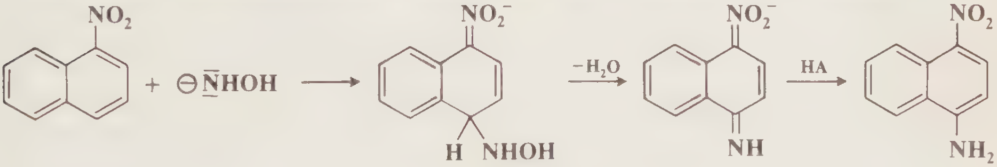
Analogous reactions have been carried out with hydrazide ions, $R_2N\bar{N}H^-$.[156] For other methods of aminating aromatic rings, see reactions **1-6, 3-19,** and **3-20.**

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

3-19 Amination by Hydroxylamine



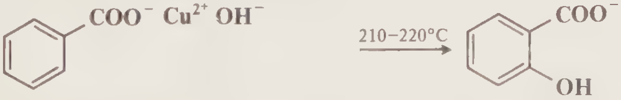
Activated aromatic compounds can be directly aminated with hydroxylamine in the presence of strong bases. Conditions are mild, and yields are high. Ions of the type **17** are intermediates:



17

OS **III**, 664.

3-20 Hydroxylation and Amination of Aromatic Acids



When basic copper salts of aromatic acids are heated, hydroxylation occurs in the ortho position.[157]

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[152] Bradley and Williams, *J. Chem. Soc.* 360 (1959).

[153] Zoltewicz, Helmick, Oestreich, King, and Kandetzki, *J. Org. Chem.* **38,** 1947 (1973).

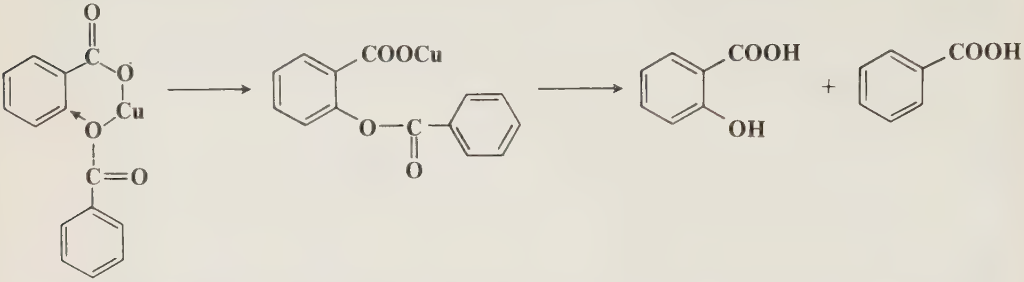
[154] Abramovitch, Helmer, and Saha, *Can. J. Chem.* **43,** 725 (1965).

[155] Ban and Wakamatsu, *Chem. Ind.* (*London*) 710 (1964).

[156] Kauffmann, Hansen, Kosel, and Schoeneck, *Justus Liebigs Ann. Chem.* **656,** 103 (1962).

[157] Kaeding and Shulgin, *J. Org. Chem.* **27,** 3551 (1962). For a review, see Nigh, in Trahanovsky, "Oxidation in Organic Chemistry," pt. B, pp. 91–94, Academic Press, Inc., New York, 1973.

Better results are obtained by heating cupric carboxylates in protic solvents.[158] In the latter case there is a cyclic process leading to an ester intermediate:



Phenols are also produced, by concomitant decarboxylation of the salicylic acids or their esters.[159] In an analogous reaction, aromatic amines are produced by heating copper salts of aromatic acids with ammonia at 220°C under pressure.[160] See also reactions **1-32, 4-5,** and **4-10.**

N_2^+ as Leaving Group

The diazonium group can be replaced by a number of groups. Most of these are nucleophilic substitutions, with SN1 mechanisms (p. 587), but some are free-radical reactions and are treated in Chapter 14. (For *formation* of diazonium ions, see reaction **2-48.**) The N_2^+ group can be replaced by Cl^-, Br^-, and CN^-, by a nucleophilic mechanism (see OS **IV,** 182), but the Sandmeyer reaction is much more useful (reactions **4-25** and **4-28**). As mentioned on p. 593, it must always be kept in mind that the N_2^+ group may activate the removal of another group on the ring.

3-21 Replacement by OH

$$ArN_2^+ + H_2O \longrightarrow ArOH$$

Water is usually present whenever diazonium salts are made, but at these temperatures (0 to 5°C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, e.g., boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.[161] The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-. Phenols can also be prepared by treatment of aryl diazonium fluoborates with water and copper salts.[162] In this case the attacking species is a free radical, probably the $H_2O\cdot^+$ radical ion.

OS **I,** 404; **III,** 130, 453, 564; **V,** 1130.

3-22 Replacement by Sulfur-containing Groups

$$ArN_2^+ + HS^- \longrightarrow ArSH$$
$$ArN_2^+ + S^{2-} \longrightarrow ArSAr$$
$$ArN_2^+ + RS^- \longrightarrow ArSR$$
$$ArN_2^+ + SCN^- \longrightarrow ArSCN + ArNCS$$

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[158] Kaeding and Collins, *J. Org. Chem.* **30,** 3750 (1965).
[159] See Oae, Watabe, and Furukawa, *Bull. Chem. Soc. Jpn.* **39,** 1329 (1966).
[160] Arzoumanidis and Rauch, *J. Chem. Soc., Chem. Commun.* 666 (1973).
[161] Horning, Ross, and Muchowski, *Can. J. Chem.* **51,** 2347 (1973).
[162] Lewin and Cohen, *J. Org. Chem.* **32,** 3844 (1967).

These reactions represent a convenient method of putting sulfur-containing groups onto an aromatic ring. With $Ar'S^-$ attack at the nitrogen takes precedence, so that the product is a diazosulfide ($Ar{-}N{=}N{-}S{-}Ar'$).[163] Thiophenols can be made as shown above, but more often the diazonium ion is treated with $EtO{-}CSS^-$ or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. See also reaction **4-27**.

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see OS **II**, 238.

3-23 Replacement by the Azido Group

$$ArN_2^+ + N_3^- \longrightarrow ArN_3$$

Diazonium salts can be converted to aryl azides by the addition of sodium azide to the acidic diazonium salt solution.[164]

OS **IV**, 75; **V**, 829.

3-24 Replacement by Iodine

$$ArN_2^+ + I^- \longrightarrow ArI$$

One of the best methods for the introduction of iodine into aromatic rings is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and reactions **4-25** and **3-25** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products.

The actual attacking species is probably not only I^-, if it is that at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent) to iodine, which in a solution containing iodide ions is converted to I_3^-, and this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+\ I_3^-$ salts, which, on standing, gave ArI.[165] From this, it can be inferred that the reason the other halide ions give poor results is not that they are poor nucleophiles but that they are poor reducing agents (compared with iodide). A free-radical mechanism has also been proposed.[166]

OS **II**, 351, 355, 604; **V**, 1120.

3-25 Replacement by Fluorine. The Schiemann Reaction

$$ArN_2^+\ BF_4^- \xrightarrow{\Delta} ArF + N_2 + BF_3$$

Heating of diazonium fluoborates (the *Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.[167] In the most common procedure, the fluoborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is then dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually quite successful. In general, any aromatic amine which can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoborates can be formed directly from primary aromatic amines and $NOBF_4$.[168] The reaction has also been carried out on $ArN_2^+\ PF_6^-$, $ArN_2^+\ SbF_6^-$, and $ArN_2^+\ AsF_6^-$ salts, in many cases with better yields.[169] The reaction has been extended to

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[163] Price and Tsunawaki, *J. Org. Chem.* **28,** 1867 (1963).

[164] Smith and Brown, *J. Am. Chem. Soc.* **73,** 2438 (1951). For a review, see Biffin, Miller, and Paul, in Patai, "The Chemistry of the Azido Group," pp. 147–176, Interscience Publishers, Inc., New York, 1971.

[165] Carey, Jones, and Millar, *Chem. Ind.* (*London*) 1018 (1959); Carey and Millar, *Chem. Ind.* (*London*) 97 (1960).

[166] Singh and Kumar, *Aust. J. Chem.* **25,** 2133 (1972); Kumar and Singh, *Tetrahedron Lett.* 613 (1972).

[167] For reviews, see Suschitzky, *Adv. Fluorine Chem.* **4,** 1–30 (1965); Roe, *Org. React.* **5,** 193–228 (1949).

[168] Wannegat and Hohlstein, *Chem. Ber.* **88,** 1839 (1955); Yakobson, D'yachenko, and Bel'chikova, *J. Gen. Chem. USSR* **32,** 842 (1962).

[169] Rutherford, Redmond, and Rigamonti, *J. Org. Chem.* **26,** 5149 (1961); Sellers and Suschitzky, *J. Chem. Soc. C* 2317 (1968).

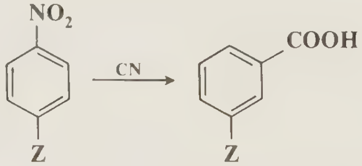
$ArN_2^+\ BCl_4^-$ and $ArN_2^+\ BBr_4^-$,[170] but aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (**4-25**).

The mechanism is of the S_N1 type. That phenyl cations are intermediates was shown by the following experiments:[171] aryl diazonium chlorides are known to arylate other aromatic rings by a free-radical mechanism (see reaction **4-16**). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If a phenyl free radical were an intermediate in the Schiemann reaction and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: mixtures of biaryls should be obtained in all cases. But if a phenyl cation is an intermediate in the Schiemann reaction, compounds containing meta-directing groups, i.e., meta-directing for *electrophilic* substitutions, should be meta-arylated and those containing ortho-para-directing groups should be ortho- and para-arylated, since a phenyl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[172] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[173]

OS **II**, 188, 295, 299; **V**, 133.

Rearrangements

3-26 The von Richter Rearrangement



When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters but does not take the place vacated by the nitro, as determined by analyses of products obtained from substituted nitrobenzenes. The carboxyl group always appears ortho to the displaced nitro group, never meta or para. This is thus a cine substitution (p. 589). The scope of this reaction, called the *von Richter rearrangement*, is variable.[174] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually less than 20% and never more than 50%.

For many years, it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (reaction **6-5**). However, a remarkable series of results have shown this belief to be in error. Bunnett and Rauhut demonstrated[175] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile cannot be an intermediate in this case and cast doubt on all other cases, since it is unlikely that different mechanisms would be operating. It was subsequently demonstrated that *elemental nitrogen* is a major product of the reaction.[176] It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen-nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:[176]

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[170] Olah and Tolgyesi, *J. Org. Chem.* **26**, 2053 (1961).

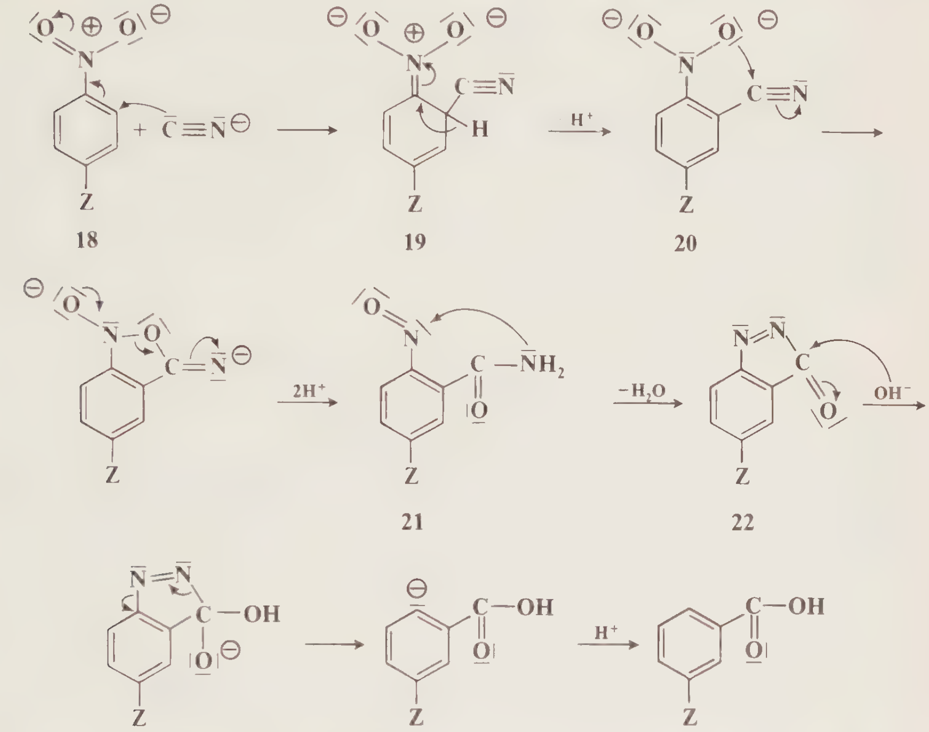
[171] See also Swain, Sheats, and Harbison, Ref. 13.

[172] Makarova and Matveeva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 548 (1958); Makarova and Gribchenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 672 (1958); Makarova, Matveeva, and Gribchenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1399 (1958).

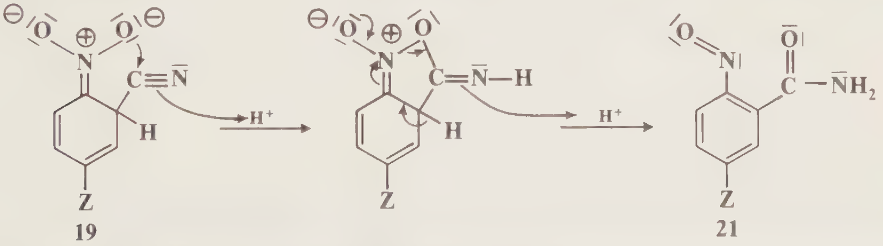
[173] Swain and Rogers, *J. Am. Chem. Soc.* **97**, 799 (1975).

[174] For a review, see Shine, "Aromatic Rearrangements," pp. 326–335, American Elsevier Publishing Company, Inc., New York, 1967.

[175] Bunnett and Rauhut, *J. Org. Chem.* **21**, 934, 944 (1956).



It may be remarked that this mechanism postulates as an intermediate at least one stable compound, **21**, and perhaps another (**22**). It also postulates the existence of **20**, which has the unusual functional group $-NO_2^{2-}$. It is possible that **21** could be formed without going through **20**[177]



if the attack of the oxygen at the cyano carbon occurs *before* the proton leaves the ring and if another proton attacks the nitrogen as the ring proton is leaving. Since **21** are stable compounds, it should be possible to prepare them independently and subject them to the conditions of the von Richter rearrangement. This has been done, and the correct products are obtained.[178] Further evidence for the mechanism is as follows: among the side products isolated from reaction of **18** (Z = Cl) was **23**, which could arise from reduction of **21**;[179] **22** (Z = H) was prepared, though

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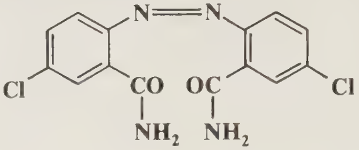
[176] Rosenblum, *J. Am. Chem. Soc.* **82,** 3796 (1960).

[177] Cullen and L'Écuyer, *Can. J. Chem.* **39,** 862 (1961).

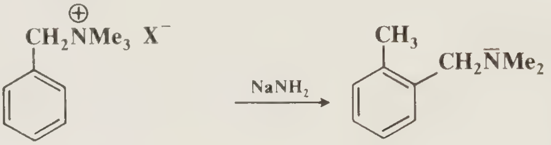


23

not isolated, and treatment with cyanide gave nitrogen and benzoic acid;[180] and when **18** (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, one-half of the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[181]

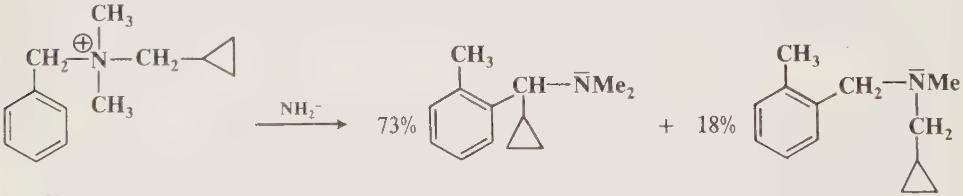
OS **IV**, 114.

3-27 The Sommelet-Hauser Rearrangement



Benzyl quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement which some call the *Sommelet rearrangement* and others the *Hauser rearrangement*.[182] Since both of these men were important in our present knowledge of this reaction, we shall use the joint name, adopted by Bumgardner.[183] Since the product is a benzyl tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.[184]

The rearrangement occurs with high yields and can be performed with various groups present in the ring.[185] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used, though if a β-hydrogen is present, Hofmann elimination (reaction **7-6**) can and often does compete. When the three groups are not the same, competing products may be obtained, e.g.,[183]



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[178] Ibne-Rasa and Koubek, *J. Org. Chem.* **28**, 3240 (1963).

[179] Cullen and L'Écuyer, *Can. J. Chem.* **39**, 144, 155, 382 (1961).

[180] Ullman and Bartkus, *Chem. Ind.* (*London*) 93 (1962).

[181] Samuel, *J. Chem. Soc.* 1318 (1960).

[182] For reviews, see Pine, *Org. React.* **18**, 403–464 (1970); Lepley and Giumanini, *Mech. Mol. Migr.* **3**, 297–440 (1971): Wittig, *Bull. Soc. Chim. Fr.* 1921–1924 (1971); Stevens and Watts, "Selected Molecular Rearrangements," pp. 81–88, Van Nostrand Reinhold Company, London, 1973; Shine, Ref. 174, pp. 316–326; Zimmerman, in Mayo, "Molecular Rearrangements," pp. 382–391, Interscience Publishers, New York, 1963.

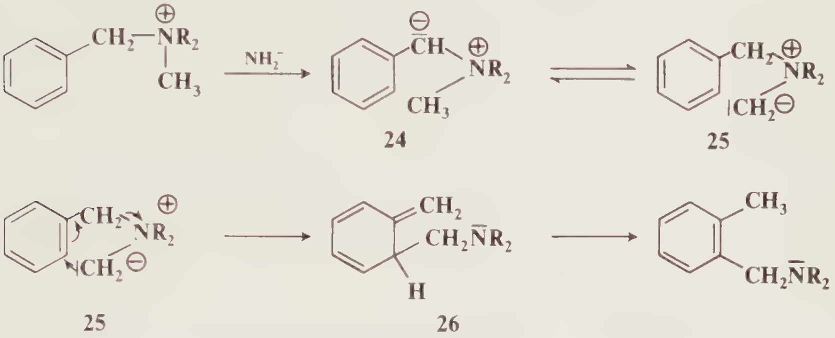
[183] Bumgardner, *J. Am. Chem. Soc.* **85**, 73 (1963).

[184] Beard and Hauser, *J. Org. Chem.* **25**, 334 (1960).

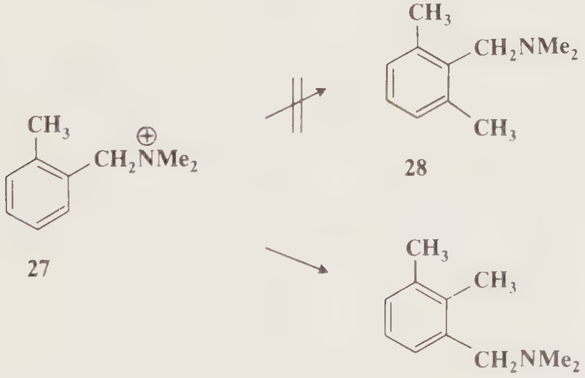
[185] Beard and Hauser, *J, Org. Chem.* **26**, 371 (1961); Vaulx, Jones, and Hauser, *J. Org. Chem.* **27**, 4385 (1962); Jones, Beard, and Hauser, *J. Org. Chem.* **28**, 199 (1963).

In any case, the Stevens rearrangement (reaction **8-25**) is a competing process. When both rearrangements are possible, the Stevens is favored at high temperatures and the Sommelet-Hauser at low temperatures.[186] When the migrating group carries an α-SR′ group, the Sommelet-Hauser product is an aromatic aldehyde, formed by hydrolysis during the workup of the $ArCH(SR')NR_2$ product.[187]

The mechanism is



The benzyl hydrogen is most acidic and is the one which first loses a proton to give the ylide **24.** However, **25,** which is present in smaller amount, is the species which undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3] sigmatropic rearrangement (see reaction **8-40**). Another mechanism which might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study and by labeling experiments. If the second mechanism were true, **27** should give **28,** but the former mechanism predicts the formation of **29,** which is what was actually obtained.[188] In the labeling experiments, benzyltrimethylamine, labeled with ^{14}C in the α position of the benzyl group, gave a product labeled in the ring methyl group, as predicted by the first mechanism, and not in the methylene, as required by



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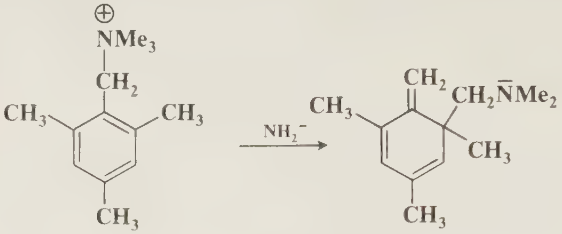
[186] Wittig and Streib, *Justus Liebigs Ann. Chem.* **584,** 1 (1953).

[187] Huynh, Julia, Lorne, and Michelot, *Bull. Soc. Chim. Fr.* 4057 (1972).

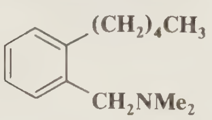
[188] Kantor and Hauser, *J. Am. Chem. Soc.* **73,** 4122 (1951).

the second.[189] Further evidence for the cyclic mechanism was the isolation of **31** from reaction of **30**.[190] Since **30** is substituted in both ortho positions, it could not give the normal rearrangement



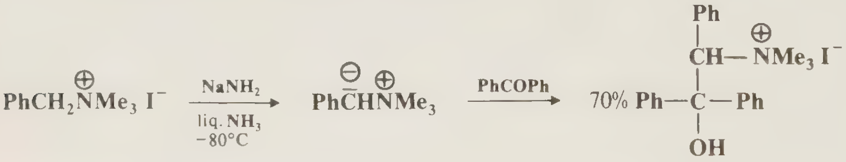
30 **31**

product, but the first step of the mechanism *has* occurred. The intermediate **26** has been shown to exist even when no ortho group is present by the obtention of **32** when the reaction was



32

carried out with BuLi as the base. **32** is formed by addition of BuLi to **26**.[191] The intermediate **24** has been trapped at −80°C by treatment with benzophenone:[192]

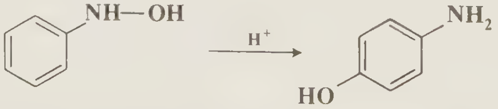


$$Ph\overset{\oplus}{CH_2NMe_3}\ I^- \xrightarrow[\substack{\text{liq. } NH_3\\ -80^\circ C}]{NaNH_2} Ph\overset{\ominus}{\underline{C}}H\overset{\oplus}{N}Me_3 \xrightarrow{PhCOPh} 70\%\ Ph-\underset{\substack{|\\ OH}}{\overset{\substack{Ph\\ |\\ CH-\overset{\oplus}{N}Me_3\,I^-\\ |}}{C}}-Ph$$

The mechanism as we have pictured it can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.[193] A mechanism[183] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the Stevens rearrangement, p. 1014) has been invoked to explain the obtention of the para products.

OS **IV**, 585.

3-28 Rearrangement of Aryl Hydroxylamines



Aryl hydroxylamines treated with acids rearrange to aminophenols.[194] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to reactions **1-36** to **1-40**, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:

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[189] Jones and Hauser, *J. Org. Chem.* **26**, 2979 (1961).

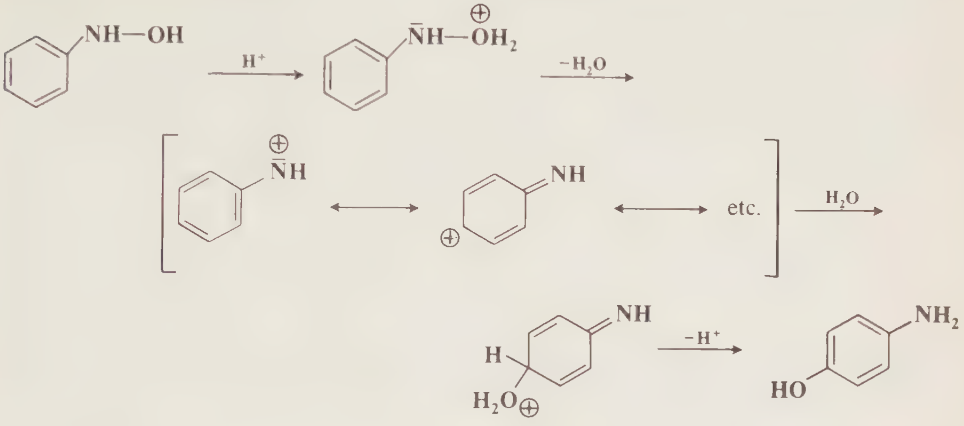
[190] Hauser and Van Eenam, *J. Am. Chem. Soc.* **79**, 5512 (1957).

[191] Pine and Sanchez, *Tetrahedron Lett.* 1319 (1969).

[192] Puterbaugh and Hauser, *J. Am. Chem. Soc.* **86**, 1105 (1964).

[193] Pine, *Tetrahedron Lett.* 3393 (1967); Pine, Ref. 182, p. 418.

[194] For reviews, see Ref. 174, pp. 182–190; Hughes and Ingold, *Q. Rev., Chem. Soc.* **6**, 34–62 (1952); pp. 45–48.

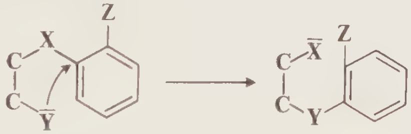


33

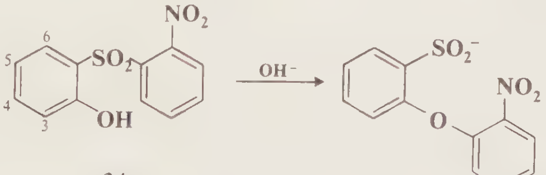
Among the evidence for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, e.g., *p*-ethoxyaniline when ethanol is present, and that when the para position is blocked, compounds similar to **33** are isolated.

OS **IV**, 148.

3-29 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements which follow the pattern given above.[195] A specific example is



34

Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its ortho position. The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. X is usually S, SO, SO_2,[196] O, or COO. Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with

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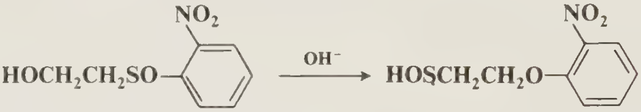
[195] For reviews, see Truce, Kreider, and Brand, *Org. React.* **18,** 99–215 (1971); Shine, Ref. 174, pp. 307–316; Stevens and Watts, Ref. 182, pp. 120–126; Bunnett and Zahler, Ref. 1, pp. 362–372.

[196] For a review for the case of $X = SO_2$, see Cerfontain, "Mechanistic Aspects in Aromatic Sulfonation and Desulfonation," pp. 262–274, Interscience Publishers, New York, 1968.

$Y = CH_2^-$ (phenyllithium was the base here).[197] The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **34** caused the rate to be about 10^5 times faster than when the same groups were in the 4 position,[198] though electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adopt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required. Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case; e.g.,[199]



35

In this case the sulfenic acid (**35**) is unstable, and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).

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[197] Truce and Ray, *J. Am. Chem. Soc.* **81**, 481 (1959); Truce, Robbins, and Kreider, *J. Am. Chem. Soc.* **88**, 4027 (1966); Drozd and Nikonova, *J. Org. Chem. USSR* **5**, 313 (1969).

[198] Bunnett and Okamoto, *J. Am. Chem. Soc.* **78**, 5363 (1956).

[199] Kent and Smiles, *J. Chem. Soc.* 422 (1934).

Fourteen
Free-Radical Substitution

MECHANISMS

Free-Radical Mechanisms in General[1]

Any free-radical process must consist of at least two steps. The first step involves the *formation* of free radicals, nearly always by homolytic cleavage of a bond, i.e., a cleavage in which each fragment retains one electron:

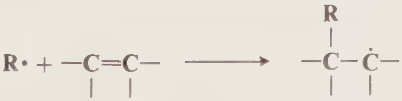
$$\mathbf{A{-}B} \longrightarrow \mathbf{A\cdot + B\cdot}$$

This is called an *initiation* step, and it may happen spontaneously or may have to be induced by heat or light (see the discussion on p. 176), depending on the type of bond. Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peracids are the most common source of free radicals induced spontaneously or by heat, but other organic compounds with low-energy bonds, such as azo compounds, are also used. Molecules which are cleaved by light are most often chlorine, bromine, and various ketones (see Chapter 7).

The second necessary step involves the *destruction* of free radicals, and this usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:

$$\mathbf{A\cdot + B\cdot} \longrightarrow \mathbf{A{-}B}$$

This type of step is called *termination*,[2] and it ends the reaction as far as these particular radicals are concerned unless the bond is broken once again and a new round begins.[3] However, it is not often that termination follows *directly* upon initiation. The reason for this is that most radicals are very reactive and will react with the first available species with which they come in contact, and in the usual situation, in which the concentration of radicals is low, this is much more likely to be a molecule than another radical. When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), the products must have a total number of electrons which is odd. The product in a particular step of this kind may be one particle, e.g.,



$$\mathbf{R\cdot + -\underset{|}{C}=\underset{|}{C}- \longrightarrow -\overset{\overset{R}{|}}{\underset{|}{C}}-\underset{|}{\dot{C}}-}$$

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[1] For books on free-radical mechanisms, see Nonhebel and Walton, "Free-Radical Chemistry," Cambridge University Press, London, 1974; Huyser, "Free-Radical Chain Reactions," Interscience Publishers, New York, 1970; *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **10** (1973); Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1966; Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, 1957. For reviews, see Huyser, in McManus, "Organic Reactive Intermediates," pp. 1–59, Academic Press, New York, 1973; Lloyd, *Chem. Technol.* 176–180, 371–381, 687–696 (1971), 182–188 (1972).

[2] Another type of termination is disproportionation (see p. 177).

[3] For a review of termination reactions, see Lapporte, *Angew. Chem.* **72,** 759–766 (1960).

in which case it must be another free radical; or it may consist of two particles, e.g.,

$$\mathrm{R\cdot + R'H \longrightarrow RH + R'\cdot}$$

in which case one must be a molecule and one a free radical, but in any case *a new radical is generated.* This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals do meet each other and terminate the process. The process just described is called a *chain reaction*, and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a molecule at all. These are (1) cleavage of a radical into, necessarily, a radical and a molecule and (2) rearrangement of one radical to another (see Chapter 18). When free radicals are highly reactive, e.g., alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, e.g., aryl radicals, the radical may be unable to react with anything until it meets another radical, so that chains are short, or the reaction may be a nonchain process. In any particular chain process there is usually a wide variety of propagation and termination steps. Because of this, these reactions lead to many products and are often difficult to treat kinetically.[4]

The following are some general characteristics of free-radical reactions:

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.[5]

2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.

3. They are initiated or accelerated by typical free-radical sources, such as the peroxides referred to, or by light. In the latter case the concept of quantum yield applies (p. 224). Quantum yields may be quite high, e.g., 1000%, if each quantum generates a long chain, or low, in the case of nonchain processes.

4. Their rates are decreased or the reactions are suppressed entirely by substances which scavenge free radicals, e.g., nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.

In this chapter are discussed free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. In addition, many of the oxidation-reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book. Among these are polymerizations and high-temperature pyrolyses.

Free-Radical Substitution Mechanisms

In a free-radical substitution reaction

$$\mathrm{R{-}X \longrightarrow R{-}Y} \tag{1}$$

there must first be a cleavage of the substrate RX so that R· radicals are produced. This may happen by a spontaneous cleavage

$$\mathrm{R{-}X \longrightarrow R\cdot + X\cdot} \tag{2}$$

---

[4] For a discussion of kinetic aspects of free-radical chain reactions, see Huyser, "Free-Radical Chain Reactions," Ref. 1, pp. 39–65.

[5] For a discussion, see Mayo, *J. Am. Chem. Soc.* **89**, 2654 (1967).

it may be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction*

$$\mathrm{R{-}X + W\cdot \longrightarrow R\cdot + W{-}X} \tag{3}$$

W• is produced by adding a compound, such as a peroxide, which spontaneously forms free radicals. Such a compound is called an *initiator*. Once R• is formed, it may go to product in two ways, by abstraction

$$\mathrm{R\cdot + Y{-}W \longrightarrow R{-}Y + W\cdot} \tag{4}$$

or by coupling with another radical

$$\mathrm{R\cdot + Y\cdot \longrightarrow R{-}Y} \tag{5}$$

In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called SH1 (H for homolytic), and abstraction steps like (3) and (4) have been called SH2; reactions can be classified as SH1 or SH2 on the basis of whether RX is converted to R by (2) or (3).[6] Most chain substitution mechanisms follow the pattern of (3), (4), (3), (4),.... Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse than slightly endothermic, see pp. 626, 635).

It would be interesting to know just how abstraction steps like (3) [and for that matter (4)] occur. Does the radical make a frontside attack, as in most SE2 reactions or a backside attack as in SN2 reactions? The details of these steps are not known, despite much work,[7] except for the special case where X is a carbon atom which is part of a cyclopropane ring (see p. 694).

It is known that with certain radicals the transition state in an abstraction reaction has some polar character. For example, consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. We can represent the transition state (assuming it is linear) as

$$\mathrm{PhCH_2\cdots\cdots H\cdots\cdots Br}$$

Since bromine is more electronegative than carbon, it is reasonable to assume that in the transition state there is a separation of charge, with a partial negative charge on the halogen and a partial positive charge on the carbon. Another way of representing this is to draw canonical forms for the transition state. Evidence for the polar character of the transition state is that

$$\mathrm{Ph\overset{\delta+}{C}H_2\overset{\cdot}{\vphantom{x}}\cdots\cdots H\cdots\cdots \overset{\delta-}{Br}} \qquad \text{or} \qquad \mathrm{PhCH_2{-}H\cdot Br \leftrightarrow PhCH_2\cdot H{-}Br \leftrightarrow Ph\overset{+}{C}H_2\quad \dot{H}\quad \bar{Br}}$$

electron-withdrawing groups in the para position of toluene (which would destabilize a positive charge) decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.[8] However, as we might expect, substituents have a smaller effect here ($\rho \approx 1.4$) than they do in reactions where a completely ionic intermediate is involved, e.g., the SN1 mechanism (see p. 320). Other evidence for polar transition states in radical abstraction reactions is mentioned on p. 627. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen abstraction from ring-substituted toluenes by the methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.[9] When the abstracting radical is *t*-butyl, the ρ value is positive ($\rho = +0.99$),[10] indicating that in this case the direction of the dipole is reversed:[11]

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[6] Eliel, in Newman, "Steric Effects in Organic Chemistry," pp. 142–143, John Wiley & Sons, Inc., New York, 1956.

[7] Pryor and Pickering, *J. Am. Chem. Soc.* **84**, 2705 (1962). For a discussion of the transition state of radical-abstraction steps, see Szwarc, in "The Transition State," *Chem. Soc. Spec. Publ.* no. 16, 91–117, 1962.

[8] For example, see Pearson and Martin, *J. Am. Chem. Soc.* **85**, 354, 3142 (1963).

$$\overset{\delta-}{\mathrm{PhCH_2}}\text{-----}\mathrm{H}\text{-----}\overset{\delta+}{\mathrm{CMe_3}}$$

When the reaction step $\mathrm{R{-}X \rightarrow R\cdot}$ takes place at a chiral carbon, racemization is almost always observed because free radicals do not retain configuration. Exceptions to this rule are found at cyclopropyl substrates, where both inversion[12] and retention[13] of configuration have been reported, and in the reactions mentioned on p. 624.

Mechanisms at an Aromatic Substrate[14]

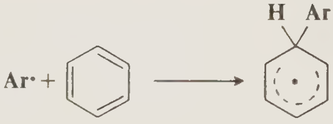
When the R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes such as the following (see reactions **4-16, 4-19,** and **4-20**):

$$\mathrm{Ar\cdot + ArH \longrightarrow Ar{-}Ar} \tag{6}$$

which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction

$$\mathrm{Ar\cdot + ArH \longrightarrow Ar{-}Ar + H\cdot} \tag{7}$$

since, as discussed on p. 625, abstraction of an entire group such as phenyl by a free radical is very unlikely. The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a nucleophile:



(8)

1

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[9] For example, see Kalatzis and Williams, *J. Chem. Soc. B* 1112 (1966); Pryor, Tonellato, Fuller, and Jumonville, *J. Org. Chem.* **34,** 2018 (1969).

[10] The undecyl and 3-heptyl radicals also have positive ρ values in this reaction: Henderson and Ward, *J. Am. Chem. Soc.* **96,** 7556 (1974); Pryor and Davis, *J. Am. Chem. Soc.* **96,** 7557 (1974); Henderson, *J. Am. Chem. Soc.* **97,** 213 (1975).

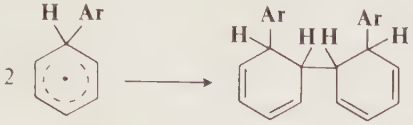
[11] Pryor, Davis, and Stanley, *J. Am. Chem. Soc.* **95,** 4754 (1973). A list of ρ values for abstraction of an α-hydrogen from ring-substituted toluenes by various radicals is given by Pryor, Lin, Stanley, and Henderson, *J. Am. Chem. Soc.* **95,** 6993 (1973).

[12] Altman and Nelson, *J. Am. Chem. Soc.* **91,** 5163 (1969).

[13] Jacobus and Pensak, *Chem. Commun.* 400 (1969).

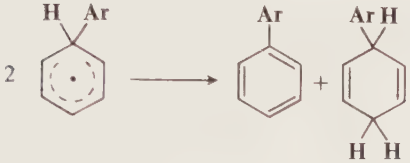
[14] For a treatise, see Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, 1960. For reviews, see Bolton and Williams, *Adv. Free-Radical Chem.* **5,** 1–25 (1975); Nonhebel and Walton, Ref. 1, pp. 417–469; Minisci and Porta, *Adv. Heterocycl. Chem.* **16,** 123–180 (1974); Bass and Nababsing, *Adv. Free-Radical Chem.* **4,** 1 47 (1972); Hey, *Bull. Soc. Chim. Fr.* 1591 (1968); Norman and Radda, *Adv. Heterocycl. Chem.* **2,** 131–177 (1963).

The intermediate is relatively stable because of the resonance. The reaction may terminate in three ways: by simple coupling, or by disproportionation



(9)

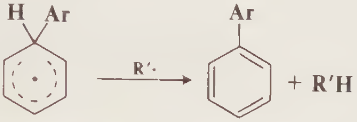
2



(10)

3

or, if a species (R′•) is present which abstracts hydrogen, by abstraction



(11)

2 is a partially hydrogenated quaterphenyl. Of course, the coupling need not be ortho-ortho, and other isomers may also be formed. Among the evidence for steps (9) and (10) was isolation of compounds of types **2** and **3**,[15] although normally under the reaction conditions dihydrobiphenyls like **3** are oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **1** by CIDNP[16] (see p. 171) and the absence of isotope effects, which would be expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. A similar mechanism has been shown where the attacking radical was HO• (reaction **4-5**).

Neighboring-Group Assistance in Free-Radical Reactions

In a few cases it has been shown that cleavage steps (2) and abstraction steps (3) have been accelerated by the presence of neighboring groups. Photolytic halogenation (reaction **4-1**) is a process which normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regiospecificity. Bromination of alkyl bromides gave 84 to 94% substitution at the carbon adjacent to the bromine already in the molecule.[17] This result is especially surprising because, as we shall see (p. 627), positions close to a polar group such as bromine should actually be *deactivated* by the electron-withdrawing field effect of the bromine. The unusual regiospecificity is explained by a mechanism in which abstraction (2) is assisted by a neighboring bromine atom:[18]

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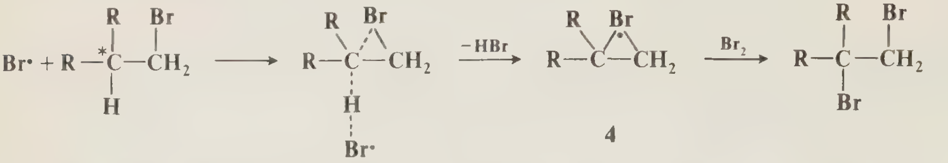
[15] De Tar and Long, *J. Am. Chem. Soc.* **80,** 4742 (1958). See also Ref. 235.

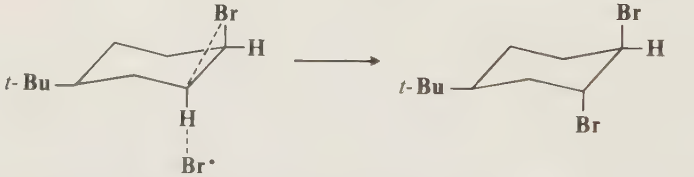
[16] Fahrenholtz and Trozzolo, *J. Am. Chem. Soc.* **94,** 282 (1972).

[17] Thaler, *J. Am. Chem. Soc.* **85,** 2607 (1963). See also Traynham and Hines, *J. Am. Chem. Soc.* **90,** 5208 (1968); Ucciani, Morot-Sir, and Naudet, *Bull. Soc. Chim. Fr.* 1913 (1967); Ucciani, Pierri, and Naudet, *Bull. Soc. Chim. Fr.* 791 (1970); Hargis, *J. Org. Chem.* **38,** 346 (1973).



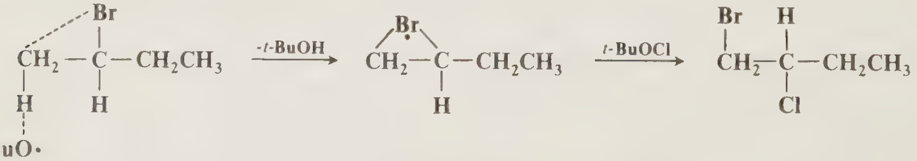
(12)

In the normal mechanism, Br• abstracts a hydrogen from RH, leaving R•. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **4**).[19] In the final step (very similar to R• + $Br_2 \rightarrow$ RBr + Br•) the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.[18] Furthermore, when this reaction was carried out in the presence of DBr, the "recovered" 1-bromo-2-methylbutane was found to be deuterated regiospecifically in the 2 position, and its configuration was retained.[20] This is just what would be predicted if some of the **4** present abstracted D from DBr. Additional evidence for this mechanism was shown in bromination of *cis*-4-bromo-*t*-butylcyclohexane. In this compound the bromo group is forced to be axial by the presence of the *t*-butyl group (see p. 131). Substitution occurred in the 3 position and was trans, as would be expected by the neighboring-group mechanism:[21]



(13)

The trans isomer, in which the bromine is equatorial and therefore in a much poorer position to be a neighboring group, was both less reactive and less selective than the cis. Low reactivity is normally associated with high selectivity, but in this case neighboring bromine (in the cis isomer) both accelerates the reaction and makes the attack both regiospecific and stereoselective. Other evidence is that chlorination with *t*-BuOCl (see p. 633 for the mechanism) of optically active *sec*-butyl bromide gave (along with other products) about 3% of 1-bromo-2-chlorobutane, *which was optically active.*[22] Such a product could have arisen only via a bridged intermediate:



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[18] Skell, Tuleen, and Readio, *J. Am. Chem. Soc.* **85,** 2849 (1963). For other stereochemical evidence, see Huyser and Feng, *J. Org. Chem.* **36,** 731 (1971).

[19] For a monograph, see Kaplan, "Bridged Free Radicals," Marcel Dekker, Inc., New York, 1972.

[20] Shea and Skell, *J. Am. Chem. Soc.* **95,** 283 (1973).

[21] Skell and Readio, *J. Am. Chem. Soc.* **86,** 3334 (1964).

[22] Skell, Pavlis, Lewis, and Shea, *J. Am. Chem. Soc.* **95,** 6735 (1973); for a similar result, see Juneja and Hodnett, *J. Am. Chem. Soc.* **89,** 5685 (1967).

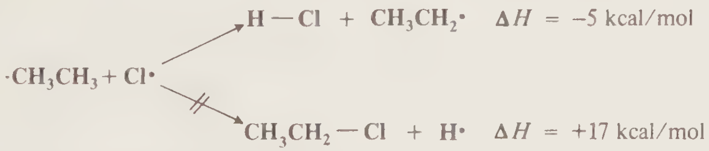
What took place here was a migration of Br arising from attack by *t*-BuOCl at C-2 rather than at C-1. We have previously seen similar behavior in the case of the neighboring-group mechanism for nucleophilic substitution (p. 281). Evidence that Cl can form bridged radicals comes from esr spectra, which show that the bridging is not necessarily symmetrical.[23] Still more evidence for bridging by Br has been found in isotope-effect and other kinetic studies.[24] However, evidence from CIDNP (p. 171) shows that the methylene protons of the β-bromoethyl radical are not equivalent, at least while the radical is present in the radical pair [$PhCOO\cdot \quad \cdot CH_2CH_2Br$] within a solvent cage.[25] This evidence indicates that under these conditions $BrCH_2CH_2\cdot$ is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the Hunsdiecker reaction[26] (**4-39**), and in abstraction of iodine atoms by the phenyl radical.[27] Neighboring-group participation in cleavage reactions (2) has also been shown, in the case of decomposition of *t*-butyl peresters.[28] The neighboring group in this case was SR.

The above facts support the neighboring-group mechanism for certain free-radical substitutions. However, the concept of anchimeric assistance in these reactions has been challenged by Tedder and coworkers[29] on the basis of results obtained in brominations in the gas phase. These workers distinguish between (1) interaction between a neighboring group and the half-filled orbital at the adjacent carbon (bridging) and (2) accelerated attack resulting from this bridging; they believe that bridging may be an important factor but that anchimeric assistance is not. However, anchimeric assistance approaching 10^3 in magnitude has been demonstrated in the bromination of alkyl bromides.[30] No such assistance was found in bromination of alkyl fluorides or chlorides.

REACTIVITY

Reactivity for Aliphatic Substrates

In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a free radical is almost never a tetra- or trivalent atom and not often a divalent one.[31] Nearly always it is univalent, and so, for organic compounds, it is hydrogen or halogen. For example, a reaction between a chlorine atom and ethane gives an ethyl radical and not a hydrogen atom:



$$CH_3CH_3 + Cl\cdot \longrightarrow H{-}Cl + CH_3CH_2\cdot \qquad \Delta H = -5 \text{ kcal/mol}$$

$$CH_3CH_3 + Cl\cdot \not\longrightarrow CH_3CH_2{-}Cl + H\cdot \qquad \Delta H = +17 \text{ kcal/mol}$$

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[23] Bowles, Hudson, and Jackson, *Chem. Phys. Lett.* **5**, 552 (1970); Cooper, Hudson, and Jackson, *Tetrahedron Lett.* 831 (1973); Chen, Elson, and Kochi, *J. Am. Chem. Soc.* **95**, 5341 (1973).

[24] Lewis and Kozuka, *J. Am. Chem. Soc.* **95**, 282 (1973); Cain and Solly, *J. Chem. Soc., Chem. Commun.* 148 (1974); Chenier, Tremblay, and Howard, *J. Am. Chem. Soc.* **97**, 1618 (1975).

[25] Hargis and Shevlin, *J. Chem. Soc., Chem. Commun.* 179 (1973).

[26] Applequist and Werner, *J. Org. Chem.* **28**, 48 (1963).

[27] Danen and Winter, *J. Am. Chem. Soc.* **93**, 716 (1971).

[28] Bentrude and Martin, *J. Am. Chem. Soc.* **84**, 1561 (1963); Tuleen, Bentrude, and Martin, *J. Am. Chem. Soc.* **85**, 1938 (1963); Fisher and Martin, *J. Am. Chem. Soc.* **88**, 3382 (1966).

[29] Ashton, Tedder, Walker, and Walton, *J. Chem. Soc., Perkin Trans. 2* 1346 (1973); Ashton, Tedder, Walton, Nechvatal, and Stoddart, *J. Chem. Soc., Perkin Trans. 1* 846 (1973); Ody, Nechvatal, and Tedder, *J. Chem. Soc., Perkin Trans. 2* 521 (1976).

[30] Shea, Lewis, and Skell, *J. Am. Chem. Soc.* **95**, 7768 (1973).

[31] For a monograph on abstractions of divalent and higher-valent atoms, see Ingold and Roberts, "Free-Radical Substitution Reactions," Interscience Publishers, New York, 1971.

TABLE 1 Relative susceptibility to attack by Cl• of primary, secondary, and tertiary positions at 100 and 600°C in the gas phase[36]

Temp., °C	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

The principal reason for this is *steric*. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Another reason is that in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a C_2H_5—H bond is broken ($D = 98$ kcal/mol, from Table 2, Chapter 5, p. 175) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103$ kcal/mol) while in the latter case it is a C_2H_5—Cl bond ($D = 81$ kcal/mol). Thus the first reaction is favored because it is exothermic by 5 kcal/mol (98 − 103), while the latter is endothermic by 17 kcal/mol (98 − 81).[32] However, the steric reason is clearly more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.

Most studies of aliphatic reactivity have been made with hydrogen as the atom which is replaced and chlorine atoms as the abstracting species.[33] In these reactions, every hydrogen in the substrate is potentially replaceable, and mixtures are usually obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. We discuss the position of attack under several headings:[34]

1. *Alkanes*. The tertiary hydrogens of an alkane are the ones that are preferentially abstracted by almost any radical, with secondary hydrogens being next preferred. This is in the same order as D values for these types of C—H bonds (Table 2 in Chapter 5) although this agreement is partly fortuitous, since D values are not always in agreement with position of abstraction.[35] The extent of the preference depends upon the reactivity (hence selectivity) of the abstracting radical and upon the temperature. Table 1 shows[36] that at high temperatures selectivity decreases, as might be expected. An example of the effect of radical reactivity may be noted in a comparison of the selectivity of fluorine atoms with that of bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1 : 1.4, while for the less reactive bromine atom this ratio is 1 : 1600.[34] With certain large radicals there is a steric factor which may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H_2SO_4 with N-chloro-di-*t*-butylamine and N-chloro-*t*-butyl-*t*-pentylamine, the primary hydrogens are abstracted 1.7 times *faster* than the tertiary hydrogen.[37] In this case the attacking radicals (the radical ions $R_2NH\cdot^+$, see p. 634) are bulky enough for steric hindrance to become a major factor.

2. *Olefins*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution. However, for other free radicals (and

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[32] ΔH for a free-radical abstraction reaction may be regarded simply as the difference in D values for the bond being broken and the one formed.

[33] For a review which lists many rate constants for abstraction of hydrogen at various positions of many molecules, see Hendry, Mill, Piszkiewicz, Howard, and Eigenmann, *J. Phys. Chem. Ref. Data* **3**, 937–978 (1974).

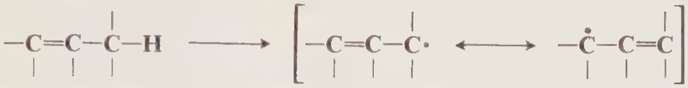
[34] For reviews, see Russell, in Kochi, "Free Radicals," vol. 1, pp. 275–331, John Wiley & Sons, Inc., New York, 1973; Rüchardt, *Angew. Chem. Int. Ed. Engl.* **9**, 830–843 (1970) [*Angew. Chem.* **82**, 845–858]; Poutsma, *Methods Free-Radical Chem.* **1**, 79–193 (1969); Davidson, *Q. Rev., Chem. Soc.* **21**, 249–258 (1967); Tedder, *Q. Rev., Chem. Soc.* **14**, 336–356 (1960); Pryor, Fuller, and Stanley, *J. Am. Chem. Soc.* **94**, 1632 (1972).

[35] Russell and Brown, *J. Am. Chem. Soc.* **77**, 4578 (1955).

[36] Hass, McBee, and Weber, *Ind. Eng. Chem.* **28**, 333 (1936).

[37] Deno, Fishbein, and Wyckoff, *J. Am. Chem. Soc.* **93**, 2065 (1971).

even for chlorine or bromine atoms when they do abstract a hydrogen) the position of attack is perfectly clear. Vinylic hydrogens are practically never abstracted, and allylic hydrogens are greatly preferred to other positions of the molecule. This is hardly surprising, since the resulting allylic radicals are stabilized by resonance:



$$-\underset{|}{C}=\underset{|}{C}-\overset{|}{\underset{|}{C}}-H \longrightarrow \left[-\underset{|}{C}=\underset{|}{C}-\overset{|}{\underset{|}{C}}\cdot \longleftrightarrow -\overset{\bullet}{\underset{|}{C}}-\underset{|}{C}=\overset{|}{\underset{|}{C}}\right]$$

Also unsurprising is the fact that allylic rearrangements (see p. 303) are common in these cases.[38]

3. *Alkyl side chains of aromatic rings.* The preferential position of attack on a side chain is usually the one α to the ring. Both for active radicals such as chlorine and phenyl and for less active ones like bromine such attack is faster than that at a primary carbon, but for the active radicals benzylic attack is slower than for tertiary positions, while for the inactive ones it is faster. Two or three aryl groups on a carbon activate its hydrogens even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:[39]

	$Me-H$	$MeCH_2-H$	Me_2CH-H	Me_3C-H	$PhCH_2-H$	Ph_2CH-H	Ph_3C-H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing which is certain is that *aromatic* hydrogens are seldom abstracted if there are aliphatic ones to compete (note from Table 2, Chapter 5, p. 175, that D for Ph—H is higher than that for any alkyl—H bond which might be present in the same molecule).

4. *Compounds containing electron-withdrawing substituents.* In halogenations electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type $Z-CH_2-CH_3$ are attacked predominantly or exclusively at the β position when Z is COOH, COCl, CN, COOR, SO_2Cl, or CX_3. Such compounds as acetic acid and acetyl chloride are not attacked at all. This is in sharp contrast to electrophilic halogenations (reactions **2-4** to **2-6**), where *only* the α position is substituted. This deactivation of α positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed on p. 621. Halogen atoms are *electrophilic radicals* and look for positions of high electron density. Positions next to electron-withdrawing groups have low electron densities (because of the field effect of Z) and are therefore shunned. Radicals which are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are:[40]

	CH_3-CH_2-COOH	
Me·	1	7.8
Cl·	1	0.03

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[38] For reviews, see Wilt, in Kochi, Ref. 34, pp. 458-466; Walling, in Mayo, "Molecular Rearrangements," pp. 431-438, Interscience Publishers, New York, 1963.

[39] Russell, Ref. 34, p. 289.

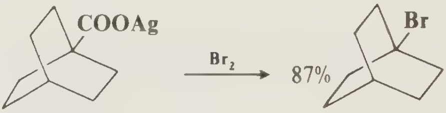
[40] Russell, Ref. 34, p. 311.

Some free radicals, e.g., *t*-butyl (see p. 622), benzyl,[41] 3-heptyl,[10] cyclopropyl,[42] and undecyl,[10] are *nucleophilic*. The phenyl radical appears to have a very small degree of nucleophilic character.[43] For longer chains, the field effect continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. We have already mentioned (p. 621) that abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the Hammett equation. A similar correlation with Taft σ_I values (p. 255) has been found for abstraction of hydrogen from substituted adamantanes by the electrophilic radical $\cdot CCl_3$.[44]

Abstraction of a halogen has been studied much less,[45] but the order of reactivity is $RI > RBr > RCl \gg RF$.

Reactivity at a Bridgehead[46]

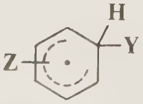
Many free-radical reactions have been observed to occur at bridgehead carbons, e.g. (see reaction **4-39**),[47]



demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl peroxide gave mostly 2-chloronorbornane, although the bridgehead position is tertiary.[48] So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.[49] It is interesting that the 2-substituted norbornanes formed by free-radical substitutions consist mostly of the exo isomers (see p. 295).

Reactivity in Aromatic Substrates

Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 12; i.e., we need to know which position on the ring will be attacked to give the intermediate



The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as is so often done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical

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[41] Clerici, Minisci, and Porta, *Tetrahedron* **29,** 2775 (1973).

[42] Stefani, Chuang, and Todd, *J. Am. Chem. Soc.* **92,** 4168 (1970).

[43] Clerici, Minisci and Porta, *Gazz. Chim. Ital.* **103,** 171 (1973).

[44] Owens, Gleicher, and Smith, *J. Am. Chem. Soc.* **90,** 4122 (1968).

[45] For a review, see Danen, *Methods Free-Radical Chem.* **5,** 1–99 (1974).

[46] For reviews, see Bingham and Schleyer, *Fortschr. Chem. Forsch.* **18,** 1 102 (1971), pp. 79 81; Fort and Schleyer, *Adv. Alicyclic Chem.* **1,** 283–370 (1966), pp. 337–352; Schöllkopf, *Angew. Chem.* **72,** 147–159 (1960).

[47] Grob, Ohta, Renk, and Weiss, *Helv. Chim. Acta* **41,** 1191 (1958).

[48] Roberts, Urbanek, and Armstrong, *J. Am. Chem. Soc.* **71,** 3049 (1949). See also Kooyman and Vegter, *Tetrahedron* **4,** 382 (1958); Walling and Mayahi, *J. Am. Chem. Soc.* **81,** 1485 (1959).

[49] See for example Koch and Gleicher, *J. Am. Chem. Soc.* **93,** 1657 (1971).

TABLE 2 Partial rate factors for attack of substituted benzenes by phenyl radicals generated from Bz_2O_2 (reaction **4-19**)[52]

	Partial rate factor		
Z	*o*	*m*	*p*
H	1	1	1
NO_2	5.50	0.86	4.90
CH_3	4.70	1.24	3.55
CMe_3	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para but the intermediate from the para attack may go on to product while that from ortho attack gives a side reaction. In such a case, analysis of the three products will not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, although there has been much controversy over just how meaningful such conclusions are:[50]

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.

2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho-para-directing; none are deactivating or (chiefly) meta-directing.

3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.

4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds XC_6H_4Y showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).[51] The increase could be correlated with the Hammett σ_p values for X.

5. Substituents have much less effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see p. 468) are not great. Partial rate factors for a few groups are given in Table 2.[52]

It should be remembered that in *alternant hydrocarbons*, the position of attack is the same for electrophilic, nucleophilic, and free-radical substitution (see p. 467).[53]

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[50] De Tar, *J. Am. Chem. Soc.* **83,** 1014 (1961) (book review); Dickerman and Vermont, *J. Am. Chem. Soc.* **84,** 4150 (1962); Morrison, Cazes, Samkoff, and Howe, *J. Am. Chem. Soc.* **84,** 4152 (1962); Ohta and Tokumaru, *Bull. Chem. Soc. Jpn.* **44,** 3218 (1971); Vidal, Court, and Bonnier, *J. Chem. Soc., Perkin Trans. 2* 2071 (1973).

[51] Davies, Hey, and Summers, *J. Chem. Soc. C* 2653 (1970).

[52] Davies, Hey, and Summers, *J. Chem. Soc. C* 2681 (1971).

[53] For a review as applied to free-radical substitution, see Dou, Vernin, and Metzger, *Bull. Soc. Chim. Fr.* 4189–4202 (1971). For partial rate factors for homolytic phenylation of some fused systems, see Dickerman, Feigenbaum, Fryd, Milstein, Vermont, Zimmerman, and McOmie, *J. Am. Chem. Soc.* **95,** 4624 (1973).

TABLE 3 Some common free radicals in decreasing order of activity

The E values represent activation energies for the reaction

$$X\cdot + C_2H_6 \rightarrow X{-}H + C_2H_5\cdot$$[56]

iso-Pr• *is less active than* Me•, *and t*-Bu• *still less so*[57]

Radical	*E*, kcal/mol	Radical	*E*, kcal/mol
F•	0.3	H•	9.0
Cl•	1.0	Me•	11.8
MeO•	7.1	Br•	13.2
$CF_3\cdot$	7.5		

Reactivity in the Attacking Radical[54]

We have already seen that less active radicals are much more selective than active radicals (p. 626). The bromine atom is so selective that when only primary hydrogens are available, as in neopentane or *t*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *t*-butyl bromide in high yields. However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, e.g., ethylbenzene and cumene, takes place exclusively at the α position,[55] emphasizing the selectivity of Br•. The dissociation energy *D* of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some free radicals, e.g., triphenylmethyl, are so unreactive that they abstract hydrogens very poorly if at all. Table 3 lists some common free radicals in approximate order of reactivity.[56]

It has been mentioned that some free radicals, e.g., chloro, are electrophilic and some, e.g., *t*-butyl, are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

The Effect of Solvent on Reactivity[58]

As has been noted earlier, the solvent usually has little effect on free-radical substitutions, in contrast to ionic ones: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. The chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% **5** and 40% **6**, while in aromatic solvents the ratio became about 10 : 90:[59]

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[54] For reviews, see Trotman-Dickenson, *Adv. Free-Radical Chem.* **1**, 1–38 (1965); Spirin, *Russ. Chem. Rev.* **38**, 529–539 (1969). For a review with respect to $CH_3\cdot$ and $CF_3\cdot$, see Gray, Herod, and Jones, *Chem. Rev.* **71**, 247–294 (1971).

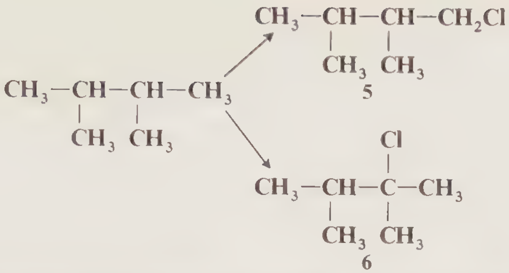
[55] Huyser, "Free-Radical Chain Reactions," Ref. 1, p. 97.

[56] Trotman-Dickenson, Ref. 54.

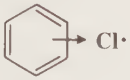
[57] Kharasch, Hambling, and Rudy, *J. Org. Chem.* **24**, 303 (1959).

[58] For a review, see Huyser, *Adv. Free-Radical Chem.* **1**, 77–135 (1965).

[59] Russell, *J. Am. Chem. Soc.* **80**, 4987, 4997, 5002 (1958), *J. Org. Chem.* **24**, 300 (1959).



This result is attributed to complex formation between the aromatic solvent and the chlorine atom



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which makes the chlorine less reactive and more selective.[60] This type of effect is not found in cases where the differences in abstractability are caused by field effects of electron-withdrawing groups (p. 627). In such cases aromatic solvents make little difference.[61] The complex **7** has been detected as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4.[62] Differences caused by solvents have also been reported in reactions of benzyloxy and *t*-butoxy radicals.[63] Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 627) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.[64]

REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion), and these are considered first.[65]

Hydrogen as Leaving Group

A. Substitution by Halogen

4-1 Halogenation at an Alkyl Carbon

$$\mathrm{R{-}H + Cl_2 \xrightarrow{h\nu} R{-}Cl}$$

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or uv light.[66] The reaction also can be applied to alkyl chains containing many functional

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[60] See also Soumillion and Bruylants, *Bull. Soc. Chim. Belg.* **78**, 425 (1969).

[61] Russell, *Tetrahedron* **8**, 101 (1960); Nagai, Horikawa, Ryang, and Tokura, *Bull. Chem. Soc. Jpn.* **44**, 2771 (1971).

[62] Bühler, *Helv. Chim. Acta* **51**, 1558 (1968).

[63] Walling and Azar, *J. Org. Chem.* **33**, 3885 (1968); Walling and Wagner, *J. Am. Chem. Soc.* **85**, 2333 (1963).

[64] Russell, Ito, and Hendry, *J. Am. Chem. Soc.* **85**, 2976 (1963); Corbiau and Bruylants, *Bull. Soc. Chim. Belg.* **79**, 203, 211 (1970); Newkirk and Gleicher, *J. Am. Chem. Soc.* **96**, 3543 (1974).

[65] For a review of *intramolecular* free-radical substitutions, see Heusler and Kalvoda, *Angew. Chem. Int. Ed. Engl.* **3**, 525–538 (1964) [*Angew. Chem.* **76**, 518–531].

[66] For reviews, see Huyser, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 1, pp. 549–607, John Wiley & Sons, Inc., New York, 1973; Poutsma, Ref. 34 (chlorination); Thaler, *Methods Free-Radical Chem.* **2**, 121–227 (1969) (bromination); Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," pp. 282–331, 355–382, 387–401, The Macmillan Company, New York, 1964.

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groups. The reaction is usually not useful for preparative purposes precisely because it is so general: not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polyhalogen substitution almost invariably occurs also, even if there is a large molar ratio of substrate to halogen. Thus methane always gives chloro-, dichloro-, trichloro-, and tetrachloromethane, in ratios which differ depending on the initial molar ratio of methane to chlorine, but all four products are always obtained. When functional groups are present, the principles are those outlined on p. 627: favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Tertiary carbons are most likely to be attacked and primary least. Positions α to an OR group are very readily attacked. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the specificity of electrophilic halogenation (reactions **2-4** to **2-6**), which always takes place α to a carbonyl group (except when the reaction is catalyzed by $AgSbF_6$; see following). Of course, if a *mixture* of halides is wanted, the reaction is usually quite satisfactory and indeed it is of considerable industrial importance. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates which have only one type of replaceable hydrogen, e.g., ethane, cyclohexane, neopentane. The most common of these are substrates which have methyl groups on aromatic rings, e.g., toluene and the xylenes, since few cases are known where halogen atoms substitute at an aromatic position.[67] Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (reaction **1-12**). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include hydrogen gas, olefins, higher alkanes, lower alkanes, and halogen derivatives of *them.*

Since the bromine atom is less reactive than the chlorine atom, it would be expected that greater specificity would be obtained in brominations, and this is true. As indicated on p. 630, it is often possible to brominate tertiary positions selectively.[68] High specificity may also be obtained where the neighboring-group mechanism (p. 623) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,[69] but seldom, because it is too reactive and hard to control.[70] It often breaks carbon chains down into smaller units, a side reaction which sometimes becomes troublesome in chlorinations too. Fluorination has been achieved by the use of fluoroxytrifluoromethane CF_3OF and uv light.[71] For example, cyclohexane gave 44% fluorocyclohexane ($CFCl_3$ solvent, $-78°C$). CF_3OF without uv light fluorinates tertiary positions of certain molecules in good yields with high regiospecificity.[71a] For example, adamantane gave 75% 1-fluoroadamantane. F_2 at $-78°C$, diluted with N_2, gives the same result. These reactions probably have electrophilic (see p. 635) and not free-radical mechanisms.

Iodine can be used if the activating light has a wavelength of 1849 Å,[72] but iodinations are seldom attempted, largely because the HI formed reduces the alkyl iodide. Iodinations have been accomplished in low to moderate yields with "*t*-BuOI," generated in situ from HgI_2 and *t*-BuOCl.[73]

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[67] Dermer and Edmison, *Chem. Rev.* **57,** 77–122 (1957), pp. 110–112. An example of free-radical ring halogenation can be found in Engelsma and Kooyman, *Recl. Trav. Chim. Pays-Bas* **80,** 526, 537 (1961). For a review of aromatic halogenation in the gas phase, see Kooyman, *Adv. Free-Radical Chem.* **1,** 137–153 (1965).

[68] For example, see Siegmann, Beers, and Huisman, *Recl. Trav. Chim. Pays-Bas* **83,** 67 (1964).

[69] Hudlický, "The Chemistry of Organic Fluorine Compounds," pp. 72–87, The Macmillan Company, New York, 1962; Tedder, *Adv. Fluorine Chem.* **2,** 104–137 (1961); Henne, *Org. React.* **2,** 49–93 (1944); pp. 69–93.

[70] However, there are several methods by means of which *all* the C—H bonds in a molecule can be converted to C—F bonds. For reviews, see Burdon and Tatlow, *Adv. Fluorine Chem.* **1,** 129–165 (1960); Stacey and Tatlow, *Adv. Fluorine Chem.* **1,** 166 198 (1960). See also Maraschin, Catsikis, Davis, Jarvinen, and Lagow, *J. Am. Chem. Soc.* **97,** 513 (1975).

[71] Kollonitsch, Barash, and Doldouras, *J. Am. Chem. Soc.* **92,** 7494 (1970).

[71a] Barton, Hesse, Markwell, Pechet, and Toh, *J. Am. Chem. Soc.* **98,** 3034 (1976); Barton, Hesse, Markwell, Pechet, and Rozen, *J. Am. Chem. Soc.* **98,** 3036 (1976).

[72] Gover and Willard, *J. Am. Chem. Soc.* **82,** 3816 (1960).

[73] Tanner and Gidley, *J. Am. Chem. Soc.* **90,** 808 (1968).

Many other halogenation agents have been employed, the most common of which is sulfuryl chloride SO_2Cl_2. The reaction in this case is more rapid and convenient than the one with chlorine itself. A mixture of Br_2 and HgO is a more active brominating agent than bromine alone.[74] The actual brominating agent in this case is believed to be bromine monoxide Br_2O. Other agents used have been N-bromosuccinimide (see reaction **4-2**), CCl_4, oxalyl chloride, $BrCCl_3$,[75] PCl_5,[76] phosgene, *t*-butyl hypobromite[77] and hypochlorite[78] (see also reaction **4-42**), N-haloamines and sulfuric acid,[79] and trichloromethanesulfonyl chloride and bromide.[80] In all these cases a chain-initiating catalyst is required, usually peroxides or uv light.

When chlorination is carried out with N-haloamines and sulfuric acid (catalyzed by either uv light or metal ions), selectivity is much greater than with other reagents.[79] In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the $\omega - 1$ position). Some typical selectivity values are[81]

$$\underset{1}{CH_3}-\underset{56}{CH_2}-\underset{29}{CH_2}-\underset{14}{CH_2}-CH_2-CH_2-CH_3 \qquad \text{Ref. 82}$$

$$\underset{1}{CH_3}-\underset{92}{CH_2}-\underset{3}{CH_2}-\underset{1}{CH_2}-\underset{1}{CH_2}-\underset{2}{CH_2}-\underset{0}{CH_2}-\underset{0}{CH_2}-OH \qquad \text{Ref. 83}$$

$$\underset{3}{CH_3}-\underset{72}{CH_2}-\underset{20}{CH_2}-\underset{4}{CH_2}-\underset{1}{CH_2}-\underset{0}{CH_2}-COOMe \qquad \text{Ref. 84}$$

Furthermore, di- and polychlorination are much less prevalent. Adamantane and bicyclo[2.2.2]-octane are predominantly chlorinated at the bridgeheads by this procedure.[85] The reasons for the high $\omega - 1$ specificity are not clearly understood.[81] Alkyl bromides can be regiospecifically chlorinated one carbon away from the bromine (to give *vic*-bromochlorides) by treatment with PCl_5.[86] Alkyl chlorides can be converted to *vic*-dichlorides by treatment with $MoCl_5$.[86a] For regiospecific chlorination at certain positions of the steroid nucleus, see reaction **9-3.**

In almost all cases, the mechanism involves a free-radical chain:[87]

$$\text{Initiation} \qquad X_2 \xrightarrow{h\nu} 2X\cdot$$

$$\text{Propagation} \qquad RH + X\cdot \longrightarrow R\cdot + XH$$

$$R\cdot + X_2 \longrightarrow RX + X\cdot$$

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[74] Bunce, *Can. J. Chem.* **50,** 3109 (1972).

[75] Huyser, *J. Am. Chem. Soc.* **82,** 391 (1960).

[76] Wyman, Wang, and Freeman, *J. Org. Chem.* **28,** 3173 (1963).

[77] Walling and Padwa, *J. Org. Chem.* **27,** 2976 (1962).

[78] Walling and Jacknow, *J. Am. Chem. Soc.* **82,** 6108, 6113 (1960); Anbar and Ginsburg, *Chem. Rev.* **54,** 925–958 (1954), pp. 933–937; Walling and Mintz, *J. Am. Chem. Soc.* **89,** 1515 (1967).

[79] For reviews, see Minisci, *Synthesis* 1–24 (1973); Deno, *Methods Free-Radical Chem.* **3,** 135–154 (1972); Sosnovsky and Rawlinson, *Adv. Free-Radical Chem.* **4,** 203–284 (1972).

[80] Huyser and Giddings, *J. Org. Chem.* **27,** 3391 (1962); Pinnell, Huyser, and Kleinberg, *J. Org. Chem.* **30,** 38 (1965).

[81] The $\omega - 1$ selectivity values shown here may actually be lower than the true values because of selective solvolysis of the $\omega - 1$ chlorides in concentrated H_2SO_4: see Deno and Pohl, *J. Org. Chem.* **40,** 380 (1975).

[82] Bernardi, Galli, and Minisci, *J. Chem. Soc. B* 324 (1968).

[83] Deno, Billups, Fishbein, Pierson, Whalen, and Wyckoff, *J. Am. Chem. Soc.* **93,** 438 (1971).

[84] Minisci, Galli, Galli, and Bernardi, *Tetrahedron Lett.* 2207 (1967); Minisci, Gardini, and Bertini, *Can. J. Chem.* **48,** 544 (1970).

[85] Smith and Billups, *J. Am. Chem. Soc.* **96,** 4307 (1974).

[86] Luche, Bertin, and Kagan, *Tetrahedron Lett.* 759 (1974).

[86a] San Filippo, Sowinski, and Romano, *J. Org. Chem.* **40,** 3463 (1975).

[87] For reviews, see Chiltz, Goldfinger, Huybrechts, Martens, and Verbeke, *Chem. Rev.* **63,** 355–372 (1963); Bratolyubov, *Russ. Chem. Rev.* **30,** 602–612 (1961).

$$\text{Termination} \qquad R\cdot + X\cdot \longrightarrow RX$$

When the reagent is halogen, initiation occurs as shown above. When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps which do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *t*-BuOCl are[88]

$$\begin{aligned} RH + t\text{-BuO}\cdot &\longrightarrow R\cdot + t\text{-BuOH} \\ R\cdot + t\text{-BuOCl} &\longrightarrow RCl + t\text{-BuO}\cdot \end{aligned}$$

and the abstracting radicals in the case of N-haloamines are the radical cations $R_2NH\cdot^+$, with the following mechanism (in the case of initiation by Fe^{2+}):[79]

$$\begin{aligned} &\text{Initiation} \qquad R_2NCl \xrightarrow{H^+} R_2\overset{\oplus}{N}HCl \xrightarrow{Fe^{2+}} R_2NH\cdot^+ + FeCl^{2+} \\ &\text{Propagation} \qquad R_2NH\cdot^+ + RH \longrightarrow R_2\overset{\oplus}{N}H_2 + R\cdot \\ &\qquad\qquad\qquad R\cdot + R_2\overset{\oplus}{N}HCl \longrightarrow RCl + R_2NH\cdot^+ \end{aligned}$$

This mechanism is similar to that of the Hofmann-Löffler reaction (**8-46**).

The two propagation steps shown above for X_2 are those which lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine. Thus, products like hydrogen, higher alkanes, and alkyl halides can be accounted for by steps like these (these are for chlorination of methane, but analogous steps can be written for other substrates):

$$\begin{aligned} Cl\cdot + HCl &\longrightarrow Cl{-}Cl + H\cdot \\ H\cdot + H\cdot &\longrightarrow H{-}H \\ CH_3\cdot + CH_3\cdot &\longrightarrow CH_3CH_3 \\ CH_3CH_3 + Cl\cdot &\longrightarrow CH_3CH_2\cdot + HCl \\ CH_3CH_2\cdot + Cl_2 &\longrightarrow CH_3CH_2Cl + Cl\cdot \\ CH_3CH_2\cdot + CH_3CH_2\cdot &\longrightarrow CH_3CH_3 + CH_2{=}CH_2 \\ CH_3CH_2\cdot + CH_3CH_2\cdot &\longrightarrow CH_3CH_2CH_2CH_3 \\ CH_3CH_2\cdot + HCl &\longrightarrow CH_3CH_3 + Cl\cdot \end{aligned}$$

etc.

At least when methane is the substrate, the rate-determining step is

$$CH_4 + Cl\cdot \longrightarrow CH_3\cdot + HCl$$

since an isotope effect of 12.1 was observed at 0°C.[89] For chlorinations, chains are very long, typically 10^4 to 10^6 propagations before a termination step takes place.

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[88] Carlsson and Ingold, *J. Am. Chem. Soc.* **89**, 4885, 4891 (1967); Walling and Kurkov, *J. Am. Chem. Soc.* **89**, 4895 (1967); Walling and McGuiness, *J. Am. Chem. Soc.* **91**, 2053 (1969).

[89] Wiberg and Motell, *Tetrahedron* **19**, 2009 (1963).

TABLE 4 Some *D* values[90]

Bond	*D*, kcal/mol	Bond	*D*, kcal/mol	Bond	*D*, kcal/mol
H—F	135	F—F	37	CH_3—F	108
H—Cl	103	Cl—Cl	58	CH_3—Cl	84
H—Br	87	Br—Br	46	CH_3—Br	70
H—I	71	I—I	37	CH_3—I	56

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps are:

	kcal/mol			
	F_2	Cl_2	Br_2	I_2
$CH_4 + X\cdot \rightarrow CH_3\cdot + HX$	−31	+1	+17	+33
$CH_3\cdot + X_2 \rightarrow CH_3X + X\cdot$	−71	−26	−24	−19

In each case *D* for CH_3—H is 104 kcal mol, while *D* values for the other bonds involved are given in Table 4.[90] F_2 is so reactive that neither uv light nor any other initiation is needed (total $\Delta H = -102$ kcal mol);[91] while Br_2 and I_2 essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step which is very unfavorable for Br_2 and I_2. It is apparent that the most important single factor causing the order of halogen reactivity to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in *D* values for R—H in the order primary > secondary > tertiary (Table 2 in Chapter 5, p. 175). (Note that for chlorination step 1 is exothermic for practically all substrates other than CH_4, since most other C—H bonds are weaker than those in CH_4.)

Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.[92] As with free-radical halogenation, mixtures of alkyl halides and other products are obtained. The most reactive positions are tertiary (e.g., *n*-alkanes give no reaction with Br_2 or Cl_2 and $AgSbF_6$), but the chief products are not necessarily the tertiary halides. For example, reaction of Br_2, $AgSbF_6$, and isobutane in a 5 : 1 : 10 ratio at −15°C gave 84% isobutyl bromide and 11% *t*-butyl bromide.[92] The isobutyl bromide is not the initial product but is probably formed by the pathway isobutane → *t*-butyl bromide → isobutene →

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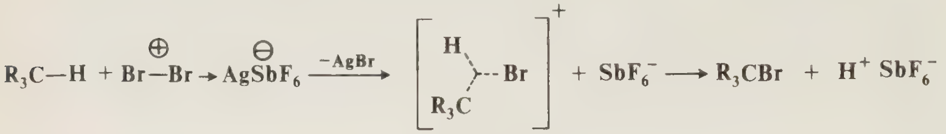
[90] Kerr, *Chem. Rev.* **66**, 465–500 (1966); Trotman-Dickenson and Kerr, in Weast, "Handbook of Chemistry and Physics," 51st ed., p. F158 (1970).

[91] For F_2 the following initiation step is possible: $F_2 + RH \rightarrow R\cdot + F\cdot + HF$ [first demonstrated by Miller, Koch, and McLafferty, *J. Am. Chem. Soc.* **78**, 4992 (1956)]. ΔH for this reaction is equal to the small positive value of 4 kcal/mol. The possibility of this reaction (which does not require an initiator) explains why fluorination can take place without uv light (which would otherwise be needed to furnish the 37 kcal/mol necessary to break the F—F bond). Once the reaction has been initiated, the large amount of energy given off by the propagation steps is ample to cleave additional F_2 molecules. Indeed, it is the magnitude of this energy which is responsible for the cleavage of carbon chains by F_2.

[92] Olah and Schilling, *J. Am. Chem. Soc.* **95**, 7680 (1973); Olah, Renner, Schilling, and Mo, *J. Am. Chem. Soc.* **95**, 7686 (1973); See also Olah, Schilling, Renner, and Kerekes, *J. Org. Chem.* **39**, 3472 (1974).

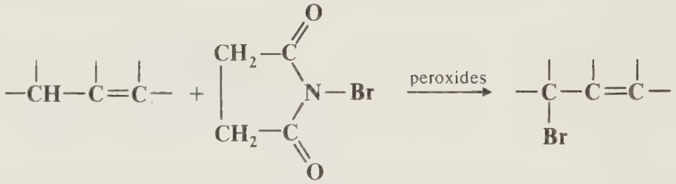
1,2-dibromo-2-methylpropane → isobutyl bromide. The following mechanism, similar to that of reaction **2-16,** has been proposed for the initial reaction:[92]



Electrophilic fluorination has already been mentioned (p. 632).

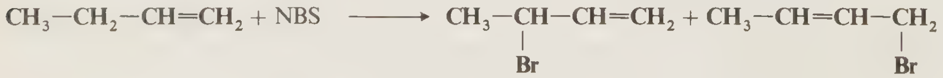
OS **II,** 89, 133, 443, 549; **III,** 737, 788; **IV,** 807, 921, 984; **V,** 145, 221, 328, 504, 635, 825; **50,** 33; **51,** 73. Also see OS **V,** 921.

4-2 Allylic Halogenation



This reaction is actually a special case of reaction **4-1,** but it is important enough to be treated separately.[93] Olefins can be halogenated in the allylic position by a number of reagents, of which N-bromosuccinimide (NBS) is by far the most common. When this reagent is used, the reaction is known as *Wohl-Ziegler bromination.* A nonpolar solvent is used, most often CCl_4. Other N-bromo amides, including various N-bromohydantoins and N-bromocaprolactam,[94] have also been used, as have N-bromo-*t*-butylamine,[95] 1,2-dibromo-1,2,3,4-tetrachloroethane[96] (the latter is a *brominating* agent), and 4-bromo-2,4,6-tri-*t*-butyl-2,5-cyclohexadienone.[97] To a much lesser extent, allylic chlorination has been carried out, with N-chlorosuccinimide, N-chloro-N-cyclohexylbenzenesulfonamide,[98] or *t*-butyl hypochlorite.[99] With any reagent an initiator is needed, and this is usually a peroxide or, less often, uv light. When the reagent is NBS and the solvent CCl_4, the progress of the reaction is easily monitored. Both NBS and the reaction by-product (succinimide) are insoluble in CCl_4, but the NBS is denser than the solvent, while succinimide is less dense. Thus the solid at the bottom of the reaction mixture disappears during the course of the reaction and is replaced by solid floating on the surface.

The reaction is usually quite specific at the allylic position, and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic shifts can take place, so that mixtures of both possible products are obtained, e.g.,



$$CH_3{-}CH_2{-}CH{=}CH_2 + NBS \longrightarrow CH_3{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}CH{=}CH_2 + CH_3{-}CH{=}CH{-}\underset{\displaystyle Br}{\underset{|}{CH_2}}$$

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[93] For reviews, see Nechvatal, *Adv. Free-Radical Chem.* **4,** 175–201 (1972); Novikov, Sevost'yanova, and Fainzil'berg, *Russ. Chem. Rev.* **31,** 671–681 (1962), pp. 674–677; Horner and Winkelmann, *Newer Methods Prep. Org. Chem.* **3,** 151–198 (1964), *Angew. Chem.* **71,** 349–365 (1959); Djerassi, *Chem. Rev.* **43,** 271–317 (1948).

[94] Taub and Hino, *J. Org. Chem.* **25,** 263 (1960).

[95] Boozer and Moncrief, *J. Org. Chem.* **27,** 623 (1962).

[96] Huyser and DeMott, *Chem. Ind.* (*London*) 1954 (1963).

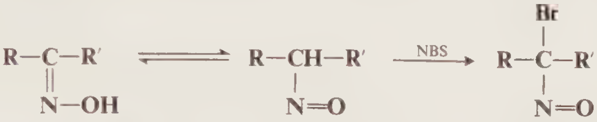
[97] Lee, *Tetrahedron* **25,** 4357 (1969).

[98] Theilacker and Wessel, *Justus Liebigs Ann. Chem.* **703,** 34 (1967).

[99] Walling and Thaler, *J. Am. Chem. Soc.* **83,** 3877 (1961).

When a double bond has two different α positions, e.g., $CH_3CH{=}CHCH_2CH_3$, a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[100] It is possible to brominate both sides of the double bond.[101] Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine.

NBS is also a highly specific brominating agent at other positions, including positions α to a carbonyl group, to a C≡C triple bond, to a boron atom[102] (see p. 1018), and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[103] Allylic bromination can also be carried out on oximes, in which case it is the tautomeric nitroso form which is brominated:



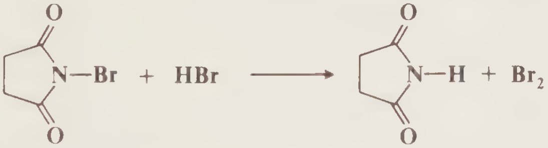
$$\underset{\displaystyle N{-}OH}{R{-}\overset{\|}{C}{-}R'} \rightleftharpoons \underset{\displaystyle N{=}O}{R{-}\overset{|}{CH}{-}R'} \xrightarrow{NBS} \overset{\displaystyle Br}{\underset{\displaystyle N{=}O}{R{-}C{-}R'}}$$

That the mechanism of allylic bromination is of the free-radical type was demonstrated by Dauben and McCoy,[104] who showed that the reaction is very sensitive to free-radical initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species which actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br•. Once it is formed, the main propagation steps are

Step 1 $Br\bullet + RH \longrightarrow R\bullet + HBr$

Step 2 $R\bullet + Br_2 \longrightarrow RBr + Br\bullet$

The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2, in a low, steady-state concentration, and to use up the HBr liberated in step 1.[105] The main evidence for this mechanism is that NBS and Br_2 show similar selectivity[106] and that the various N-bromo amides also show similar selectivity,[107] which is consistent with the hypothesis that the same species is abstracting in each case.[108]

[100] Dauben and McCoy, *J. Org. Chem.* **24,** 1577 (1959).

[101] Ucciani and Naudet, *Bull. Soc. Chim. Fr.* 871 (1962).

[102] Brown and Yamamoto, *Synthesis* 699 (1972).

[103] Peiffer, *Bull. Soc. Chim. Fr.* 537 (1963).

[104] Dauben and McCoy, *J. Am. Chem. Soc.* **81,** 4863 (1959).

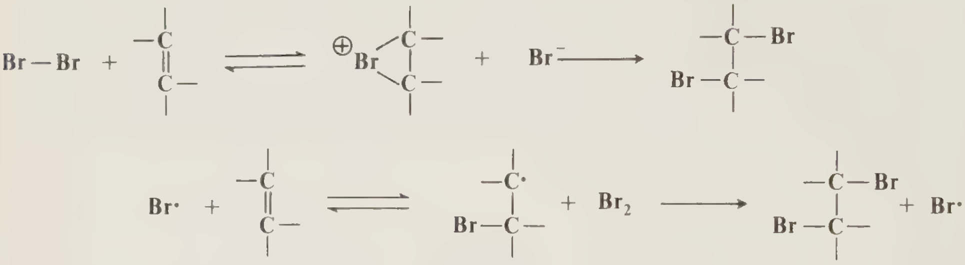
[105] This mechanism was originally suggested by Adam, Gosselain, and Goldfinger, *Nature* **171,** 704 (1953), *Bull. Soc. Chim. Belg.* **65,** 533 (1956), but did not win acceptance for a number of years.

[106] Walling, Rieger, and Tanner, *J. Am. Chem. Soc.* **85,** 3129 (1963); Russell and Desmond, *J. Am. Chem. Soc.* **85,** 3139 (1963); Russell, DeBoer, and Desmond, *J. Am. Chem. Soc.* **85,** 365 (1963); Pearson and Martin, *J. Am. Chem. Soc.* **85,** 3142 (1963); Skell, Tuleen, and Readio, *J. Am. Chem. Soc.* **85,** 2850 (1963).

[107] Walling and Rieger, *J. Am. Chem. Soc.* **85,** 3134 (1963); Pearson and Martin, Ref. 106; Incremona and Martin, *J. Am. Chem. Soc.* **92,** 627 (1970).

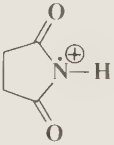
[108] For other evidence, see Day, Lindstrom, and Skell, *J. Am. Chem. Soc.* **96,** 5616 (1974).

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see reaction **5-30**). Apparently the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free-radical:



The other bromine comes from another bromine-containing molecule or ion. If the concentration is sufficiently low, there will not be a high probability that the proper species will be in the vicinity once the intermediate forms and the equilibrium will lie to the left. This slows the rate of addition so that allylic substitution can compete successfully. If this is true, it should be possible to brominate an olefin in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.[109]

In polar solvents, the mechanism may be entirely different, involving electrophilic attack by Br^+. In protonating solvents the protonated radical **8** may be the abstracting species:[110]



8

OS **IV**, 108; **V**, 825.

4-3 Halogenation of Aldehydes

$$\mathbf{RCHO + Cl_2 \longrightarrow RCOCl}$$

Aldehydes can be directly converted to acyl chlorides by treatment with chlorine; however, the reaction operates only when the aldehyde does not contain an α hydrogen and even then is not very useful. When there is an α hydrogen, α halogenation (reaction **2-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2 [111] and *t*-BuOCl.[112] The mechanisms are probably of the free-radical type.

OS **I**, 155.

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[109] McGrath and Tedder, *Proc. Chem. Soc.* 80 (1961).

[110] Tanner, *J. Am. Chem. Soc.* **86,** 4674 (1964).

[111] Arai, *Nippon Kagaku Zasshi* **81,** 1450 (1960) [*CA* **56,** 2370f (1962)], *Bull. Chem. Soc. Jpn.* **37,** 1280 (1964), **38,** 252 (1965).

[112] Anbar and Ginsburg, Ref. 78, pp. 937–939; Walling and Mintz, Ref. 78.

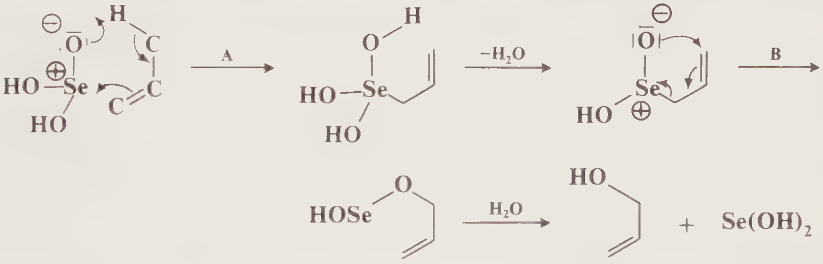
B. Substitution by Oxygen

4-4 Hydroxylation at an Aliphatic Carbon

$$R_3CH \xrightarrow[HOAc\text{-}H_2SO_4]{Na_2Cr_2O_7} R_3COH$$

Compounds containing susceptible C—H bonds can be oxidized to alcohols, though yields are often low.[113] Nearly always, the C—H bond involved is tertiary, so that the product is a tertiary alcohol. This is partly because tertiary C—H bonds are more susceptible to free-radical attack than primary and secondary bonds and partly because the reagents involved would oxidize primary and secondary alcohols further. The reagents may be chromic acid,[114] alkaline permanganate,[115] peracetic acid and uv light,[116] O_3, or H_2O_2 with nitrates or nitrites.[117] Best yields (as high as 99%) are obtained with O_3 when the substrate is adsorbed on silica gel.[117a] When chromic acid is the reagent, the mechanism is probably as follows: a Cr^{6+} species abstracts a hydrogen to give $R_3C\cdot$, which is held in a solvent cage near the resulting Cr^{5+} species. The two species then combine to give R_3COCr^{4+}, which is hydrolyzed to the alcohol. This mechanism predicts retention of configuration; this is largely observed.[118] The oxidation by permanganate also involves predominant retention of configuration, and a similar mechanism has been proposed.[119] The reaction is particularly useful for hydroxylation at bridgeheads, provided that the bridgehead system is large enough; e.g., bicyclo[3.3.1]nonane oxidized with chromic acid gave a 40 to 50% yield of 1-bicyclo[3.3.1]nonanol, but bridged bicyclooctanes gave no significant bridgehead substitution.[120]

Treatment of double-bond compounds with selenium dioxide introduces an OH group into the allylic position (see also reaction **9-16**).[121] Allylic rearrangements are common. There is evidence that the mechanism does not involve free radicals but includes two pericyclic steps (**A** and **B**):[122]



The step marked **A** is similar to the ene synthesis (reaction **5-18**). The step marked **B** is a [2,3]sigmatropic rearrangement (see reaction **8-40**).

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[113] For reviews, see Chinn, "Selection of Oxidants in Synthesis," pp. 7–11, Marcel Dekker, Inc., New York, 1971; Lee, in Augustine, "Oxidation," vol. 1, pp. 2–6, Marcel Dekker, Inc., New York, 1969.

[114] Sager and Bradley, *J. Am. Chem. Soc.* **78,** 1187 (1956).

[115] Eastman and Quinn, *J. Am. Chem. Soc.* **82,** 4249 (1960).

[116] Rotman and Mazur, *J. Am. Chem. Soc.* **94,** 6228 (1972); Mazur, *Pure Appl. Chem.* **41,** 145–166 (1975).

[117] Inoue, Sonoda, and Tsutsumi, *Bull. Chem. Soc. Jpn.* **36,** 1549 (1963).

[117a] Cohen, Keinan, Mazur, and Varkony, *J. Org. Chem.* **40,** 2141 (1975).

[118] Wiberg and Foster, *J. Am. Chem. Soc.* **83,** 423 (1961), *Chem. Ind. (London)* 108 (1961); Wiberg and Eisenthal, *Tetrahedron* **20,** 1151 (1964).

[119] Wiberg and Fox, *J. Am. Chem. Soc.* **85,** 3487 (1963); Brauman and Pandell, *J. Am. Chem. Soc.* **92,** 329 (1970). See however, Heckner, Dalchau, and Landsberg, *J. Prakt. Chem.* **313,** 153 (1971).

[120] Bingham and Schleyer, *J. Org. Chem.* **36,** 1198 (1971).

[121] For reviews, see Jerussi, *Sel. Org. Transform.* **1,** 301–326 (1970); Trachtenberg, in Augustine, Ref. 113, pp. 125–153.

[122] Sharpless and Lauer, *J. Am. Chem. Soc.* **94,** 7154 (1972); Arigoni, Vasella, Sharpless, and Jensen, *J. Am. Chem. Soc.* **95,** 7917 (1973). For other mechanistic proposals, see Schaefer, Horvath, and Klein, *J. Org. Chem.* **33,** 2647 (1968); Trachtenberg, Nelson, and Carver, *J. Org. Chem.* **35,** 1653 (1970); Bhalerao and Rapoport, *J. Am. Chem. Soc.* **93,** 4835 (1971).

Ketones and esters can be α-hydroxylated by treatment of their enolate forms (prepared by adding the ketone or ester to lithium diisopropylamide) with a molybdenum peroxide reagent (MoO_5–pyridine–HMPT) in tetrahydrofuran-hexane at −70°C[123] or by oxidation of their trimethylsilyl enol ethers with *m*-chloroperbenzoic acid.[123a] Yields in both methods are moderate to high. The enolate forms of amides and esters can similarly be converted to their α-hydroxy derivatives by reaction with molecular oxygen.[124] The MoO_5 method can also be applied to certain nitriles.[123]

OS **IV**, 23.

4-5 Hydroxylation at an Aromatic Carbon[124a]

$$\mathbf{ArH + H_2O_2 + FeSO_4 \longrightarrow ArOH}$$

A mixture of hydrogen peroxide and ferrous sulfate,[125] called *Fenton's reagent*,[126] can be used to hydroxylate aromatic rings, though yields are usually not high. Biaryls are usually side products. Among other reagents used have been H_2O_2 and titanous ion; a mixture of ferrous ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*);[127] and peracids such as pernitrous and trifluoroperacetic acids. Hydroxylation has also been accomplished by photochemical methods[128] and by exposure of aqueous solutions of aromatic substrates to ionizing radiation, e.g., γ-rays and x-rays, but these methods are seldom used for synthetic purposes.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process such as $HO\cdot + ArH \rightarrow Ar\cdot + H_2O$) are not intermediates. The mechanism is essentially that outlined on p. 622, with HO• as the attacking species,[129] formed by

$$\mathbf{Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + HO\cdot}$$

The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

Another hydroxylation reaction is the *Elbs reaction*.[130] In this method phenols can be oxidized to *para*-diphenols with $K_2S_2O_8$ in alkaline solution. Primary, secondary, or tertiary aromatic amines give predominant or exclusive ortho substitution unless both ortho positions are blocked, in which case para substitution is found. The reaction with amines is called the *Boyland-Sims oxidation*. Yields are low with either phenols or amines, generally under 50%. The mechanisms are not clear but may involve attack by $S_2O_8^{2-}$ at the oxygen or nitrogen, followed by rearrangement to the products.[131]

See also reactions **1-32** and **3-20.**

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[123] Vedejs, *J. Am. Chem. Soc.* **96,** 5944 (1974); Vedejs and Telschow, *J. Org. Chem.* **41,** 740 (1976).

[123a] Rubottom, Vazquez, and Pelegrina, *Tetrahedron Lett.* 4319 (1975).

[124] Wasserman and Lipshutz, *Tetrahedron Lett.* 1731 (1975).

[124a] For reviews, see Vysotskaya, *Russ. Chem. Rev.* **42,** 851–856 (1974); Sangster, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, pp. 133–191, Interscience Publishers, New York, 1971; Metelitsa, *Russ. Chem. Rev.* **40,** 563–580 (1971); Enisov and Metelitsa, *Russ. Chem. Rev.* 37, 656–665 (1969); Loudon, *Prog. Org. Chem.* **5,** 47–72 (1961); Williams, Ref. 14, pp. 110–116; Dermer and Edmison, *Chem. Rev.* **57,** 77–122 (1957); pp. 101–107.

[125] For a review of reactions of H_2O_2 and metal ions with all kinds of organic compounds, including aromatic rings, see Sosnovsky and Rawlinson, in Swern, "Organic Peroxides," vol. 2, pp. 269-336, Interscience Publishers, New York, 1970.

[126] For a discussion of Fenton's reagent, see Walling, *Acc. Chem. Res.* **8,** 125–131 (1975).

[127] Udenfriend, Clark, Axelrod, and Brodie, *J. Biol. Chem.* **208,** 731 (1954); Brodie, Shore, and Udenfriend, *J. Biol. Chem.* **208,** 741 (1954).

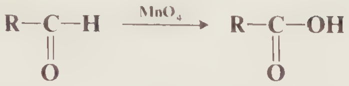
[128] For a review, see Matsuura and Omura, *Synthesis* 173–184 (1974).

[129] Dixon and Norman, *Proc. Chem. Soc.* 97 (1963); Lindsay-Smith and Norman, *J. Chem. Soc.* 2897 (1963); Jefcoate, Lindsay-Smith, and Norman, *J. Chem. Soc. B* 1013 (1969).

[130] For reviews, see Sosnovsky and Rawlinson, Ref. 125, pp. 319-323; Sethna, *Chem. Rev.* **49,** 91–101 (1951).

[131] Behrman, *J. Am. Chem. Soc.* **85,** 3478 (1963), **89,** 2424 (1967); Ogata and Akada, *Tetrahedron* **26,** 5945 (1970).

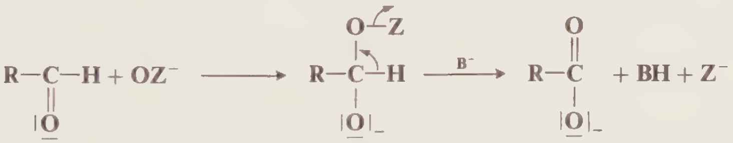
4-6 Oxidation of Aldehydes to Carboxylic Acids



$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H \xrightarrow{MnO_4} R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OH}$$

Oxidation of aldehydes to carboxylic acids is one of the most common oxidation reactions in organic chemistry[132] and has been carried out with many oxidizing agents, the most popular of which is permanganate in acid, basic, or neutral solution. Chromic acid and bromine are other reagents frequently employed. Silver oxide is a fairly specific oxidizing agent for aldehydes and does not readily attack other groups. Benedict's and Fehling's solutions oxidize aldehydes,[133] and a test for aldehydes depends on this reaction, but the method is seldom used for preparative purposes and in any case gives very poor results with aromatic aldehydes. Aldehydes are also oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peracid RCO_3H,[134] which with another molecule of aldehyde disproportionates to give two molecules of acid (see reaction **4-8**).[135] The disproportionation evidently takes place by formation of an adduct between the perester and the aldehyde, which then decomposes to the products.[136] The structure of the adduct, which can be isolated, has been shown by nmr to be RC(=O)—O—O—CH(OH)R.[137]

Mechanisms of aldehyde oxidation[138] are not firmly established, but there seem to be at least two main types, a free-radical mechanism and an ionic one. In the free-radical process, the aldehydic hydrogen is abstracted to leave an acyl radical, which obtains OH from the oxidizing agent. In the ionic process, the first step is addition of a species OZ^- to the carbonyl bond, to give **9** in alkaline solution and **10** in acid or neutral solution. The aldehydic hydrogen of **9** or **10** is then lost as a proton, to a base, while Z leaves with its electron pair.



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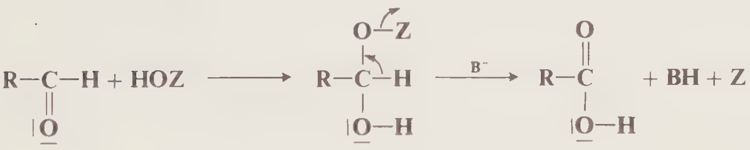

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[132] For reviews, see Chinn, Ref. 113, pp. 63-70; Lee, Ref. 113, pp. 81–86.

[133] For a review, see Nigh, in Trahanovsky, "Oxidation in Organic Chemistry," pp. 31–34, Academic Press, Inc., New York, 1973.

[134] For a review of the preparation of peroxy acids by this and other methods, see Swern, in Swern, Ref. 125, vol. 1, pp. 313–516.

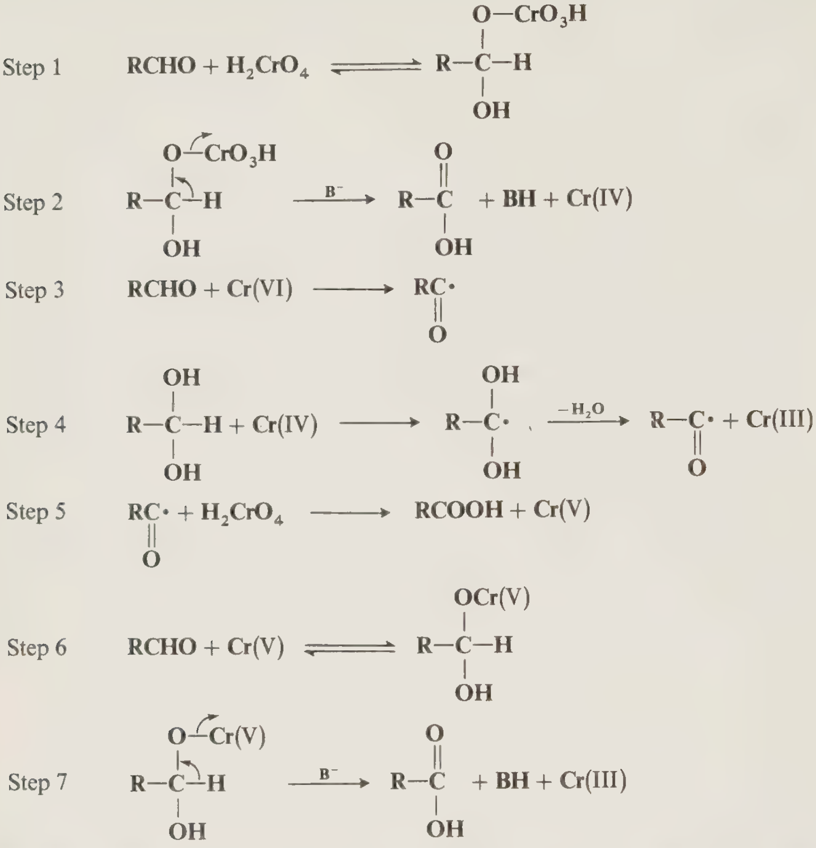
[135] For a review of the autoxidation of aldehydes, see McNesby and Heller, *Chem. Rev.* **54**, 325 (1954). For a review of photochemical oxidation of aldehydes by O_2, see Niclause, Lemaire, and Letort, *Adv. Photochem.* **4**, 25–48 (1966).

[136] Vinogradov, Kereselidze, and Nikishin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 998 (1970).

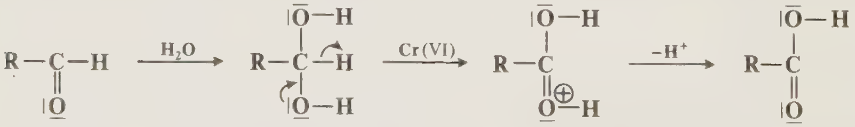
[137] Yablonskii, Vinogradov, Kereselidze, and Nikishin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 272 (1969).

[138] For a review, see Roček, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 461–505, Interscience Publishers, New York, 1966.

For oxidations with acid dichromate the picture seems to be quite complex, with several processes of both types going on:[139]



Steps 1 and 2 represent an oxidation by the ionic pathway by Cr(VI), and steps 6 and 7 a similar oxidation by Cr(V), which is produced in a free-radical process. Either Cr(VI) (step 3) or Cr(IV) (step 4) [Cr(IV) is produced in step 2] may abstract a hydrogen, and the resulting acyl radical is converted to carboxylic acid in step 5. Thus, chromium in three oxidation states is instrumental in oxidizing aldehydes. Still another possible process has been proposed in which the aldehydic hydrogen of a hydrated aldehyde molecule is removed by the dichromate as a *hydride ion:*[140]



This process is essentially nucleophilic substitution by the tetrahedral mechanism (see p. 308).

The mechanism with permanganate is less well known, but an ionic mechanism has been proposed for neutral and acid permanganate, similar to steps 1 and 2 for dichromate:

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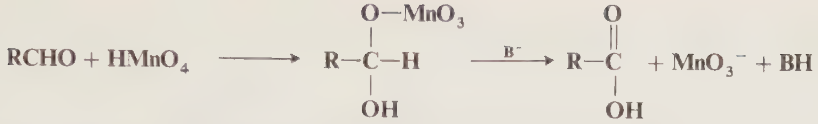
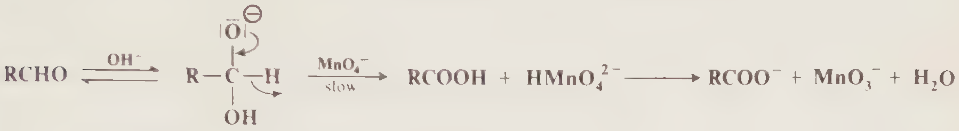
[139] Wiberg and Richardson, *J. Am. Chem. Soc.* **84,** 2800 (1962); Wiberg and Lepse, *J. Am. Chem. Soc.* **86,** 2612 (1964); Wiberg and Szeimies, *J. Am. Chem. Soc.* **96,** 1889 (1974). See also Roček and Ng, *J. Am. Chem. Soc.* **96,** 1522, 2840 (1974).

[140] Roček, *Tetrahedron Lett.* no. 5, 1 (1959); Roček and Ng, *J. Org. Chem.* **38,** 3348 (1973); Banerji and Goswami, *Tetrahedron Lett.* 5039 (1970); Goswami and Banerji, *Bull. Chem. Soc. Jpn.* **45,** 2925 (1972).



$$\mathrm{RCHO} + \mathrm{HMnO_4} \longrightarrow \mathrm{R{-}\overset{\overset{\large O-MnO_3}{|}}{\underset{\underset{\large OH}{|}}{C}}{-}H} \xrightarrow{B^-} \mathrm{R{-}\overset{\overset{\large O}{\|}}{\underset{\underset{\large OH}{|}}{C}}} + \mathrm{MnO_3^-} + \mathrm{BH}$$

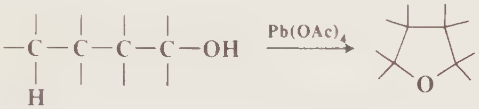
For alkaline permanganate, the following mechanism has been proposed:[141]



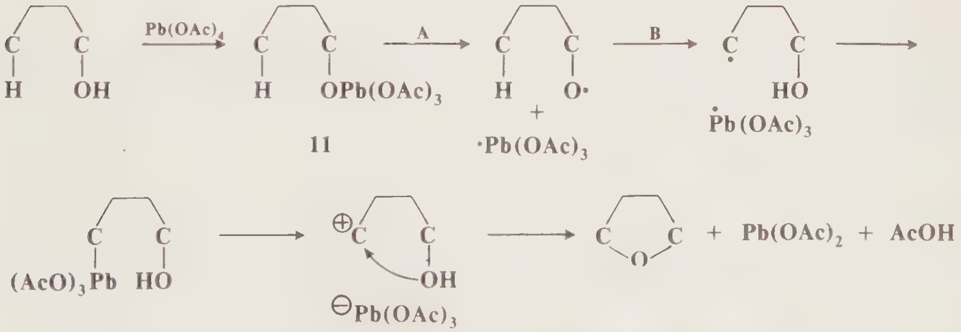
$$\mathrm{Mn(V)} + \mathrm{Mn(VII)} \longrightarrow \mathrm{2Mn(VI)}$$

OS **I**, 166; **II**, 302, 315, 538; **III**, 745; **IV**, 302, 493, 499, 919, 972, 974.

4-7 Formation of Cyclic Ethers



Alcohols which have a hydrogen in the δ position can be cyclized with lead tetraacetate.[142] The reaction is usually carried out at about 80 C (most often in refluxing benzene) but can also be done at room temperature if the reaction mixture is irradiated with uv light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε hydrogens are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),[143] and with ceric ammonium nitrate.[143a] The following mechanism is likely for the lead tetraacetate reaction:[144]



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[141] Freeman, Brant, Hester, Kamego, Kasner, McLaughlin, and Paull, *J. Org. Chem.* **35,** 982 (1970).

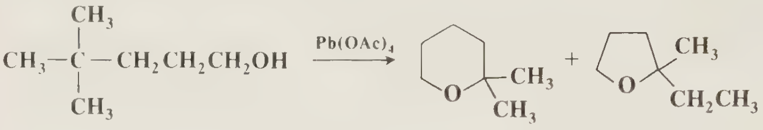
[142] For reviews, see Mihailović and Partch, *Sel. Org. Transform.* **2,** 97–182 (1972); Mihailović and Čeković, *Synthesis* 209–224 (1970).

[143] Akhtar and Barton, *J. Am. Chem. Soc.* **86,** 1528 (1964); Sneen and Matheny, *J. Am. Chem. Soc.* **86,** 3905, 5503 (1964); Akhtar, Hunt, and Dewhurst, *J. Am. Chem. Soc.* **87,** 1807 (1965); Smolinsky and Feuer, *J. Org. Chem.* **30,** 3216 (1965); Mihailović, Čeković, and Stanković, *Chem. Commun.* 981 (1969); Roscher, *Chem. Commun.* 474 (1971); Deluzarche, Maillard, Rimmelin, Schue, and Sommer, *Chem. Commun.* 976 (1970); Mihailović, Gojković, and Konstantinović, *Tetrahedron* **29,** 3675 (1973); Roscher and Jedziniak, *Tetrahedron Lett.* 1049 (1973). For a review, see Kalvoda and Heusler, *Synthesis* 501–526 (1971).

[143a] See for example, Trahanovsky, Young, and Nave, *Tetrahedron Lett.* 2501 (1969); Doyle, Zuidema, and Bade, *J. Org. Chem.* **40,** 1454 (1975).

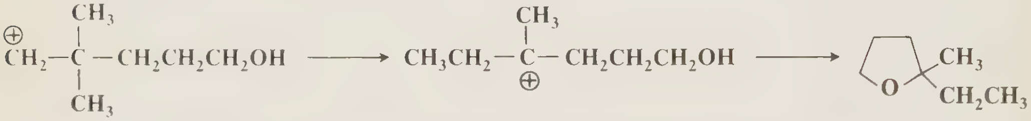
[144] Mihailović, Čeković, Maksimović, Jeremić, Lorenc, and Mamuzić, *Tetrahedron* **21,** 2799 (1965).

although **11** has never been isolated. The step marked **A** is a photochemical cleavage if irradiation is used; otherwise it is a thermal cleavage. The step marked **B** is a 1,5 internal hydrogen abstraction. Such abstractions are well known (see p. 1068) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions). Evidence for the intermediacy of a carbonium ion is that 4,4-dimethylpentanol, which cannot give a normal product since it has no δ hydrogen, gave 1% of the rearranged product 2-methyl-2-ethyltetrahydrofuran (**12**) in addition to 4 to 6% of the tetrahydropyran:[145]



4–6% **12** 1%

In this case the initial abstraction was 1,6, since a 1,5 abstraction was impossible. **12** was formed by a 1,2 shift of methyl:



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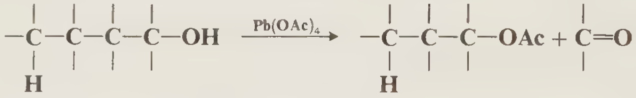
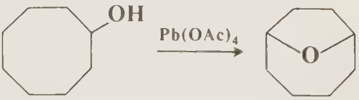
Carbonium ions, but not free radicals, commonly rearrange in this manner (see Chapter 18).

Reactions which sometimes compete are oxidation to the aldehyde or acid (reactions **9-4** and **9-22**) and fragmentation:



$$\underset{\mathrm{H}}{\overset{|}{\underset{|}{-\mathrm{C}}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{OH} \xrightarrow{\mathrm{Pb(OAc)_4}} \underset{\mathrm{H}}{\overset{|}{\underset{|}{-\mathrm{C}}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{OAc} + \overset{|}{\underset{|}{\mathrm{C}}}{=}\mathrm{O}$$

Tetrahydrofuran formation decreases and fragmentation increases in the order primary, secondary, tertiary alcohol, and in the order β-unsubstituted, β-monomethyl-substituted, β,β-dimethyl-substituted alcohol.[146] When the OH group is on a ring of at least seven members, a transannular product may be formed, e.g.,[147]



There are no references in *Organic Syntheses*, but see OS **V**, 692, for a related reaction.

4-8 Formation of Hydroperoxides

$$\mathrm{RH} + \mathrm{O_2} \longrightarrow \mathrm{R{-}O{-}O{-}H}$$

The slow atmospheric oxidation (*slow* meaning without combustion) of a C—H bond to a

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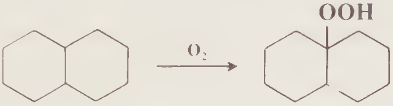
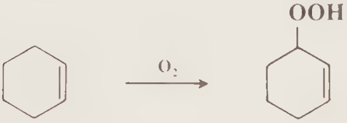
[145] Mihailović, Čeković, and Jeremić, *Tetrahedron* **21**, 2813 (1965).

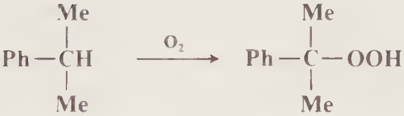
[146] Mihailović, Jakovljević, Trifunović, Vukov, and Čeković, *Tetrahedron* **24**, 6959 (1968).

[147] Cope, Gordon, Moon, and Park, *J. Am. Chem. Soc.* **87**, 3119 (1965); Moriarty and Walsh, *Tetrahedron Lett.* 465 (1965); Mihailović, Čeković, Andrejević, Matić, and Jeremić, *Tetrahedron* **24**, 4947 (1968).

C—O—O—H group is called *autoxidation.*[148] The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so that unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. The hydroperoxides produced often react further, to alcohols, ketones, and more complicated products, so that the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield. It is because of autoxidation that foods, rubber, paint, lubricating oils, etc., deteriorate on exposure to the atmosphere over periods of time. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes. As with other free-radical reactions of C—H bonds, some bonds are attacked more readily than others,[149] and these are the ones we have seen before (pp. 626–628), although the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), allylic (though allylic rearrangements are common), and benzylic R.[150] The following are actual examples:

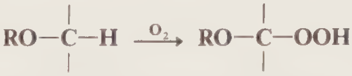






$$\mathrm{Ph{-}\overset{\displaystyle Me}{\underset{\displaystyle Me}{C}}H \xrightarrow{O_2} Ph{-}\overset{\displaystyle Me}{\underset{\displaystyle Me}{C}}{-}OOH}$$

Another susceptible position is aldehydic C—H, but the peracids so produced are not easily isolated[134] since they are converted to the corresponding carboxylic acids (reaction **4-6**). The α positions of ethers are also easily attacked by oxygen:



$$\mathrm{RO{-}\overset{|}{\underset{|}{C}}{-}H \xrightarrow{O_2} RO{-}\overset{|}{\underset{|}{C}}{-}OOH}$$

but the resulting hydroperoxides are almost never isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.[151]

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[148] The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. For reviews see Lloyd, *Methods Free-Radical Chem.* **4,** 1–131 (1973); Betts, *Q. Rev., Chem. Soc.* **25,** 265–288 (1971); Huyser, "Free-Radical Chain Reactions," Ref. 1, pp. 306–312; Chinn, Ref. 113, pp. 29–39, Ingold, *Acc. Chem. Res.* **2,** 1–9 (1969); Mayo, *Acc. Chem. Res.* **1,** 193–201 (1968); Waters, "Mechanisms of Oxidation of Organic Compounds," pp. 6–16, John Wiley & Sons, Inc., New York, 1964, *Prog. Org. Chem.* **5,** 1–46 (1961), pp. 17–26; Hock and Kropf, *Angew. Chem.* **69,** 313–321 (1957); Twigg, *Chem. Ind. (London)* 4–11 (1962); and Frank, *Chem. Rev.* **46,** 155–169 (1950).

[149] For a discussion, see Korcek, Chenier, Howard, and Ingold, *Can. J. Chem.* **50,** 2285 (1972); and previous papers in this series.

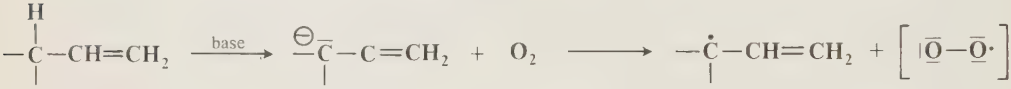
[150] For reviews of autoxidation at allylic and benzylic positions, see Voronenkov, Vinogradov, and Belyaev, *Russ. Chem. Rev.* **39,** 944–952 (1970); Bateman, *Q. Rev., Chem. Soc.* **8,** 147–167 (1954).

[151] For methods of detection and removal of peroxides from ether solvents, see Gordon and Ford, "The Chemist's Companion," p. 437, John Wiley & Sons, Inc., New York, 1972.

Oxygen itself (a diradical) is too unreactive to be the species which actually abstracts the hydrogen. But if a trace of free radical (say R′•) is produced by some initiating process, *it* reacts with oxygen to give R′—O—O•, and since this type of radical *does* abstract hydrogen, the chain is

$$\begin{aligned} R'OO\cdot + RH &\longrightarrow R\cdot + R'OOH \\ R\cdot + O_2 &\longrightarrow R\text{—}O\text{—}O\cdot \\ &\text{etc.} \end{aligned}$$

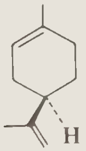
In at least some cases (in alkaline media)[152] the radical R• can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, e.g.,[153]



$$\text{H—}\underset{|}{\overset{|}{C}}\text{—CH=CH}_2 \xrightarrow{\text{base}} {}^{\ominus}\underset{|}{\bar{C}}\text{—C=CH}_2 + O_2 \longrightarrow \text{—}\underset{|}{\dot{C}}\text{—CH=CH}_2 + \left[\,|\bar{O}\text{—}\bar{O}\cdot\,\right]^-$$

Autoxidations in alkaline media may also proceed by a different mechanism: R—H + base → $R^- + O_2 \rightarrow ROO^-$.[154]

When alkenes are treated with oxygen which has been photosensitized (p. 218), they are substituted by OOH in the allylic position.[155] Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not the ground-state oxygen (a triplet) but an excited singlet state[156] (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means, e.g., by the reaction between H_2O_2 and NaOCl[157] or between ozone and triphenyl phosphite.[158] The oxygen generated by either photochemical or nonphotochemical methods reacts with olefins in the same way,[159] and this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free-radical mechanism, and further evidence that free radicals are not involved comes from the treatment of optically active limonene (**13**) with singlet oxygen. Among



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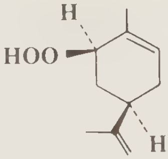
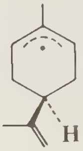


14



15

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[152] For a review of base-catalyzed autoxidations in general, see Sosnovsky and Zaret, in Swern, Ref. 125, vol. 1, pp. 517–560.

[153] Barton and Jones, *J. Chem. Soc.* 3563 (1965); Russell and Bemis, *J. Am. Chem. Soc.* **88,** 5491 (1966).

[154] Gersmann, Nieuwenhuis, and Bickel, *Tetrahedron Lett.* 1383 (1963); Gersmann and Bickel, *J. Chem. Soc. B* 2230 (1971).

[155] For reviews, see Denny and Nickon, *Org. React.* **20,** 133–336 (1973); Adams, in Augustine, Ref. 113, vol. 2, pp. 65–112.

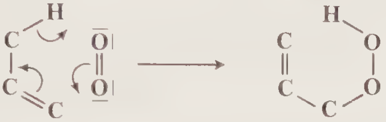
[156] For reviews of singlet oxygen, see Kearns, *Chem. Rev.* **71,** 395–427 (1971); Wayne, *Adv. Photochem.* **7,** 311–371 (1969); Kaplan, *Chem. Technol.* 621–626 (1971).

[157] Foote and Wexler, *J. Am. Chem. Soc.* **86,** 3879 (1964).

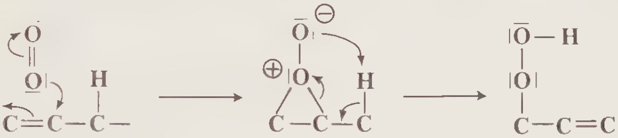
[158] Murray and Kaplan, *J. Am. Chem. Soc.* **91,** 5358 (1969). See also Schapp, Kees, and Thayer, *J. Org. Chem.* **40,** 1185 (1975).

[159] Foote, Wexler, Ando, and Higgins, *J. Am. Chem. Soc.* **90,** 975 (1968). See also McKeown and Waters, *J. Chem. Soc. B* 1040 (1966).

other products is the optically active hydroperoxide **14**, though if **15** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.[160] In contrast, autoxidation of **13** gave optically inactive **14** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more highly substituted than with less highly substituted alkenes (note that only the trisubstituted double bond of **13** was attacked). The order of alkene reactivity is tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the olefin.[161] Two mechanisms have been proposed for the reaction with singlet oxygen.[162] One of



these is a pericyclic mechanism, similar to that of the ene synthesis (**5-18**) and to the first step of the reaction between alkenes and SeO_2 (reaction **4-4**).[163] The other involves addition of singlet



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oxygen to the double bond to give a peroxirane (**16**), followed by internal proton transfer.[164]

OS **IV**, 895.

4-9 Formation of Peroxides

$$\mathrm{RH + R'OOH \xrightarrow{CuCl} ROOR'}$$

Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, e.g., cobalt and manganese salts.[165] Very high yields may be obtained. The type of hydrogen replaced is similar to that with N-bromosuccinimide (reaction **4-2**), i.e., mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO• formed from ROOH and the metal ion.

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[160] Schenck, Gollnick, Buchwald, Schroeter and Ohloff, *Justus Liebigs Ann. Chem.* **674,** 93 (1964); Schenck, Neumüller, Ohloff, and Schroeter, *Justus Liebigs Ann. Chem.* **687,** 26 (1965).

[161] For example, see Foote and Denny, *J. Am. Chem. Soc.* **93,** 5162 (1971).

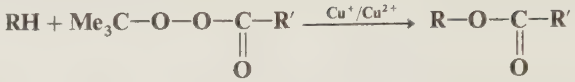
[162] For reviews of the mechanism, see Foote, *Acc. Chem. Res.* **1,** 104–110 (1968), *Pure Appl. Chem.* **27,** 635–645 (1971); Gollnick, *Adv. Photochem.* **6,** 1–122 (1968); Gollnick and Schenck, *Pure Appl. Chem.* **9,** 507–525 (1965); House, "Modern Synthetic Reactions," 2d ed., pp. 337–348, W. A. Benjamin, Inc., New York, 1972; Kearns, Ref. 156.

[163] For evidence and arguments in favor of this mechanism, see Nickon and Mendelson, *J. Am. Chem. Soc.* **87,** 3921 (1965); Nickon, Chuang, Daniels, Denny, DiGiorgio, Tsunetsugu, Vilhuber, and Werstiuk, *J. Am. Chem. Soc.* **94,** 5517 (1972); Nickon, DiGiorgio, and Daniels, *J. Org. Chem.* **38,** 533 (1973); Gollnick, Haisch, and Schade, *J. Am. Chem. Soc.* **94,** 1747 (1972); Foote, Fujimoto, and Chang, *Tetrahedron Lett.* 45 (1972); Kopecky and van de Sande, *Can. J. Chem.* **50,** 4034 (1972); Jefford, Laffer, and Boschung, *J. Am. Chem. Soc.* **94,** 8904 (1972); Jefford and Boschung, *Helv. Chim. Acta* **57,** 2242, 2257 (1974); Matsuura, Horinaka, and Nakashima, *Chem. Lett.* 887 (1973). See also Jefford, Boschung, Moriarty, Rimbault, and Laffer, *Helv. Chim. Acta* **56,** 2649 (1973).

[164] For evidence and arguments in favor of this mechanism, see Fenical, Kearns, and Radlick, *J. Am. Chem. Soc.* **91,** 3396, 7771 (1969); Hasty, Merkel, Radlick, and Kearns, *Tetrahedron Lett.* 49 (1972); Stephenson, McClure, and Sysak, *J. Am. Chem. Soc.* **95,** 7888 (1973). See also Kellogg and Kaiser, *J. Org. Chem.* **40,** 2575 (1975).

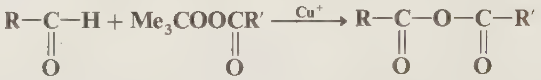
[165] For a review, see Sosnovsky and Rawlinson, Ref. 125, pp. 153–268.

4-10 Acyloxylation



$$\mathrm{RH} + \mathrm{Me_3C{-}O{-}O{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}R'} \xrightarrow{\mathrm{Cu^+/Cu^{2+}}} \mathrm{R{-}O{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}R'}$$

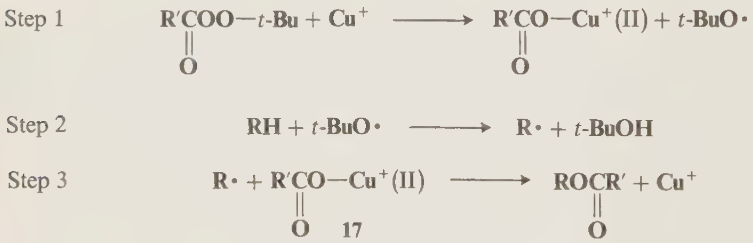
Susceptible positions of organic compounds can be directly acyloxylated by *t*-butyl peresters, the most frequently used being acetic and benzoic ($R' = Me$ or Ph).[166] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in reaction **4-8:** benzylic, allylic, and the α position of ethers (and sulfides). Terminal olefins are substituted almost entirely in the 3 position, i.e., with only a small amount of allylic rearrangement, but internal olefins generally give mixtures containing a large amount of allylic-shift product. If the reaction with olefins is carried out in an excess of another acid R″COOH, the ester produced is of *that* acid ROCOR″. Aldehydes give anhydrides:



$$\mathrm{R{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}H} + \mathrm{Me_3COO}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{R'} \xrightarrow{\mathrm{Cu^+}} \mathrm{R{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}O{-}}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{{-}R'}$$

Acyloxylation has also been achieved with metallic acetates such as lead tetraacetate and mercuric acetate.[167] In this case not only does the reaction take place at allylic and benzylic positions and at those α to an OR or SR group but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those α to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases the reaction takes place through the enol forms of these substrates. Ketones may be α-acetoxylated indirectly by conversion to the enamine (reaction **6-15**) and treatment of this with thallium triacetate.[168] Thallium triacetate also acyloxylates carboxylic acids in the α position.[169] Palladium acetate converts alkenes to vinyl and/or allylic acetates.[170]

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:[171]



Step 1 $$\mathrm{R'}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{OO{-}}t\text{-}\mathrm{Bu} + \mathrm{Cu^+} \longrightarrow \mathrm{R'}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{O{-}Cu^+(II)} + t\text{-}\mathrm{BuO}\cdot$$

Step 2 $$\mathrm{RH} + t\text{-}\mathrm{BuO}\cdot \longrightarrow \mathrm{R}\cdot + t\text{-}\mathrm{BuOH}$$

Step 3 $$\mathrm{R}\cdot + \underset{17}{\mathrm{R'}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{O{-}Cu^+(II)}} \longrightarrow \mathrm{RO}\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}\mathrm{R'} + \mathrm{Cu^+}$$

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[166] For reviews, see Rawlinson and Sosnovsky, *Synthesis* 1–28 (1972); Sosnovsky and Rawlinson, in Swern, Ref. 125, vol. 1, pp. 585–608; Doumaux, in Augustine, Ref. 113, vol. 2, pp. 141–185 (1971); Sosnovsky and Lawesson, *Angew. Chem. Int. Ed. Engl.* **3,** 269–276 (1964) [*Angew. Chem.* **76,** 218–225].

[167] For a review, see Rawlinson and Sosnovsky, *Synthesis* 567–602 (1973). For a discussion, see Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, pp. 539–545, 646–647; vol. 2, p. 234; vol. 3, p. 171, John Wiley & Sons, Inc., New York, 1967–1972.

[168] Kuehne and Giacobbe, *J. Org. Chem.* **33,** 3359 (1968).

[169] Taylor, Altland, McGillivray, and McKillop, *Tetrahedron Lett.* 5285 (1970).

[170] For reviews, see Rylander, "Organic Synthesis with Noble Metal Catalysts," pp. 80–87, Academic Press, Inc., New York, 1973; Jira and Freiesleben, *Organomet. React.* **3,** 1–190 (1972), pp. 44–84; Heck, *Fortschr. Chem. Forsch.* **16,** 221–242 (1971), pp. 231–237; Tsuji, *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 132–143.

[171] Kharasch, Sosnovsky, and Yang, *J. Am. Chem. Soc.* **81,** 5819 (1959); Kochi, *Tetrahedron* **18,** 483 (1962), *J. Am. Chem. Soc.* **84,** 774 (1962); Kochi and Mains, *J. Org. Chem.* **30,** 1862 (1965).

This mechanism, involving a free radical R•, is compatible with the allylic shifts found.[172] The finding that *t*-butyl peresters labeled with ^{18}O in the carbonyl oxygen gave ester with 50% of the label in each oxygen[173] is in accord with a combination of R• with the intermediate **17**, in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *t*-butoxy radicals have been trapped with dienes.[174]

Free-radical acyloxylation of aromatic substrates has been accomplished by heating with cupric benzoate[175] (see also reaction **3-20**), with benzoyl peroxide iodine,[176] and with cobalt(III) trifluoroacetate.[177] Aromatic substrates can be converted to carbonate esters by treatment with diisopropyl peroxydicarbonate and ceric ammonium nitrate (CAN):[178]

$$\mathrm{ArH + (ROCOO)_2 \xrightarrow{CAN} ArOCOOR + ROH + CO_2} \qquad \mathrm{R = iso\text{-}Pr}$$

Both aromatic and aliphatic substrates can be acyloxylated with lead tetra(trifluoroacetate) $Pb(OOCCF_3)_4$.[179]

OS **III**, 3; **V**, 70, 151.

C. Substitution by Sulfur

4-11 Chlorosulfonation

$$\mathrm{RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl}$$

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.[180] In scope and in range of products obtained, the reaction is similar to reaction **4-1**. The mechanism is also similar, except that there are two additional main propagation steps:

$$\mathrm{R\cdot + SO_2 \longrightarrow R{-}SO_2\cdot}$$
$$\mathrm{R{-}SO_2\cdot + Cl_2 \longrightarrow R{-}SO_2Cl + Cl\cdot}$$

Chlorosulfenation can be accomplished by treatment with SCl_2 and uv light:[181]

$$\mathrm{RH + SCl_2 \xrightarrow{h\nu} RSCl}$$

D. Substitution by Nitrogen

4-12 Nitration of Paraffins

$$\mathrm{RH + HNO_3 \xrightarrow{400^\circ C} RNO_2}$$

Nitration of paraffins can be carried out in the gas phase, at about 400°C, or in the liquid phase.[182] The reaction is not practical for the production of pure products for any alkane except methane. For other alkanes, not only does the reaction produce mixtures of the mono-, di-, and polynitrated alkanes at every combination of positions, but extensive chain cleavage occurs[183] and to some extent the nitro products are further oxidized. As with reaction **4-1**, the order of preference is tertiary > secondary > primary, and allylic and benzylic positions are especially susceptible. The mechanism of the reaction has been the subject of considerable study. Titov has demonstrated[184] that nitric acid has no effect on paraffins in the absence of nitrogen dioxide (which is, of course, a free radical, since it has a total number of electrons which is odd). This suggests that the abstracting species is NO_2. The principal product-forming steps are

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[172] Goering and Mayer, *J. Am. Chem. Soc.* **86**, 3753 (1964); Denney, Appelbaum, and Denney, *J. Am. Chem. Soc.* **84**, 4969 (1962).

[173] Denney, Denney, and Feig, *Tetrahedron Lett.* no. 15, p. 19 (1959).

[174] Kochi, *J. Am. Chem. Soc.* **84**, 2785, 3271 (1962); Story, *Tetrahedron Lett.* 401 (1962).

[175] Kaeding, Kerlinger, and Collins, *J. Org. Chem.* **30**, 3754 (1965).

[176] For example, see Kovacic, Reid, and Brittain, *J. Org. Chem.* **35**, 2152 (1970).

[177] Kochi, Tang, and Bernath, *J. Am. Chem. Soc.* **95**, 7114 (1973).

[178] Kurz, Steele, and Vecchio, *J. Org. Chem.* **39**, 3331 (1974). See also Kurz and Kovacic, *J. Am. Chem. Soc.* **89**, 4960 (1967); Kurz, Kovacic, Bose, and Kugajevsky, *J. Am. Chem. Soc.* **90**, 1818 (1968); Kovacic, Reid, and Kurz, *J. Org. Chem.* **34**, 3302 (1969).

[179] Partch, *J. Am. Chem. Soc.* **89**, 3662 (1967).

[180] For reviews, see Walling, Ref. 1, pp. 393-396; Gilbert, "Sulfonation and Related Reactions," pp. 126-131, Interscience Publishers, New York, 1965.

[181] Müller and Schmidt, *Chem. Ber.* **96**, 3050 (1963), **97**, 2614 (1964). For a review of the formation and reactions of sulfenyl halides, see Kühle, *Synthesis* 561-580 (1970), 563-586, 617-638 (1971).

[182] For a review, see Sosnovsky, Ref. 66, pp. 216-234.

$$\mathrm{RH} + \cdot\mathrm{NO_2} \longrightarrow \mathrm{R}\cdot + \mathrm{HNO_2}$$
$$\mathrm{R}\cdot + \cdot\mathrm{NO_2} \longrightarrow \mathrm{RNO_2}$$

The only purpose of the nitric acid is to furnish a supply of nitrogen dioxide, perhaps by the reaction

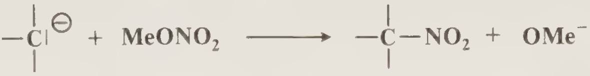
$$\mathrm{NO} + 2\mathrm{HNO_3} \longrightarrow 3\mathrm{NO_2} + \mathrm{H_2O}$$

The NO is presumed to arise by one of the following pathways:

$$\mathrm{N_2O_3} \longrightarrow \mathrm{NO_2} + \mathrm{NO}$$
$$\mathrm{HNO_2} \longrightarrow \mathrm{HO}\cdot + \mathrm{NO}$$

Other evidence for the radical character of the reaction (besides the conclusions drawn from the positions which are preferred) is the fact that racemization is found with optically active substrates.[185]

Activated positions (e.g., ZCH_2Z' compounds) can be nitrated by fuming nitric acid in acetic acid, by acetyl nitrate and an acid catalyst,[185a] or by alkyl nitrates under alkaline conditions.[186] In the latter case it is the carbanionic form of the substrate which is actually nitrated. What is



$$-\underset{|}{\overset{|}{\mathrm{C}}}|^{\ominus} + \mathrm{MeONO_2} \longrightarrow -\underset{|}{\overset{|}{\mathrm{C}}}-\mathrm{NO_2} + \mathrm{OMe^-}$$

isolated under these alkaline conditions is the conjugate base of the nitro compound. Yields are not high. Of course, the mechanism in this case is not of the free-radical type at all but is electrophilic substitution with respect to the carbon (similar to the mechanisms of reactions **2-7** and **2-8**). With respect to the nitrogen it is nucleophilic substitution. Positions activated by only one electron-withdrawing group, e.g., α positions of simple ketones, nitriles, sulfones, or N,N-dialkyl amides, can be nitrated with alkyl nitrates if a very strong base, e.g., *t*-BuOK or $NaNH_2$, is present to convert the substrate to the carbanionic form.[187] Electrophilic nitration of alkanes has been performed with nitronium salts, e.g., $NO_2^+ \; PF_6^-$, and with HNO_3-H_2SO_4 mixtures, but mixtures of nitration and cleavage products are obtained, and yields are generally low.[188]

OS **I,** 390; **II,** 440, 512.

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[183] For a discussion of the mechanism of this cleavage, see Matasa and Hass, *Can. J. Chem.* **49,** 1284 (1971).

[184] Titov, *Tetrahedron* **19,** 557–580 (1963). This paper is a review of Titov's considerable work in this field. See also Dubourg, Fischer, and Brini, *Bull. Soc. Chim. Fr.* 3665, 3669 (1971).

[185] Shechter and Brain, *J. Am. Chem. Soc.* **85,** 1806 (1963).

[185a] Sifniades, *J. Org. Chem.* **40,** 3562 (1975).

[186] For reviews, see Larson, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," vol. 1, pp. 310–316, Interscience Publishers, New York, 1969; Kornblum, *Org. React.* **12,** 101–156 (1962), 120–127.

[187] For examples, see Feuer, Shepherd, and Savides, *J. Am. Chem. Soc.* **78,** 4364 (1956); Feuer and Pivawer, *J. Org. Chem.* **31,** 3152 (1966); Feuer and Monter, *J. Org. Chem.* **34,** 991 (1969); Feuer and Lawrence, *J. Org. Chem.* **37,** 3662 (1972); Truce and Christensen, *Tetrahedron* **25,** 181 (1969). Pfeffer and Silbert, *Tetrahedron Lett.* 699 (1970).

[188] Olah and Lin, *J. Am. Chem. Soc.* **93,** 1259 (1973).

4-13 The Direct Conversion of Aldehydes to Amides

$$\mathrm{ArCHO} \xrightarrow[\text{nickel peroxide}\ -20^\circ\mathrm{C}]{\mathrm{NH_3}} \mathrm{ArCONH_2}$$

Aromatic and α,β-unsaturated aldehydes can be directly converted to the corresponding amides by treatment with dry ammonia gas and nickel peroxide.[189] Best yields (80 to 90%) are obtained at -25 to -20°C. The reaction has also been performed with MnO_2 and NaCN along with ammonia or an amine at 0°C in isopropyl alcohol.[190] In the nickel peroxide reaction the corresponding alcohols ($ArCH_2OH$) have also been used as substrates.

E. Attack by Carbon In these reactions a new carbon-carbon bond is formed, and they may be given the collective title *coupling reactions.* In each case an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or olefin to give the coupling product.

4-14 Simple Coupling at a Susceptible Position

$$2\mathrm{RH} \xrightarrow{\text{peroxides}} \mathrm{R{-}R}$$

In this reaction, the peroxide decomposes to give a radical which abstracts a hydrogen from RH to give R•, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 640). This reaction is far from general, although in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,[191] as well as those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[192] an ether group,[193] a carbonyl group,[194] a cyano group,[195] a dialkylamino group,[196] or a carboxylic ester group, either the acid or alcohol side.[197]

OS **IV,** 367; **V,** 1026.

4-15 Coupling of Alkynes

$$2\mathrm{R{-}C{\equiv}C{-}H} \xrightarrow[\text{pyridine}]{\mathrm{CuX_2}} \mathrm{R{-}C{\equiv}C{-}C{\equiv}C{-}R}$$

Alkynes which have a hydrogen on one of the triple-bond carbons can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction.*[198] The large-ring annulenes of Sondheimer et al. (see p. 64) were prepared by rearrangement and hydrogenation of cyclic polyynes, prepared by Eglinton coupling of terminal diynes, for example:[199]

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[189] Nakagawa, Onoue, and Minami, *Chem. Commun.* 17 (1966).

[190] Gilman, *Chem. Commun.* 733 (1971).

[191] Meshcheryakov and Érzyutova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 94 (1966).

[192] McBay, Tucker, and Groves, *J. Org. Chem.* **24,** 536 (1959); Johnston and Williams, *J. Chem. Soc.* 1168 (1960).

[193] Pfordte and Leuschner, *Justus Liebigs Ann. Chem.* **643,** 1 (1961).

[194] Kharasch, McBay, and Urry, *J. Am. Chem. Soc.* **70,** 1269 (1948); Leffingwell, *Chem. Commun.* 357 (1970); Hawkins and Large, *J. Chem. Soc., Perkin Trans. 1* 280 (1974).

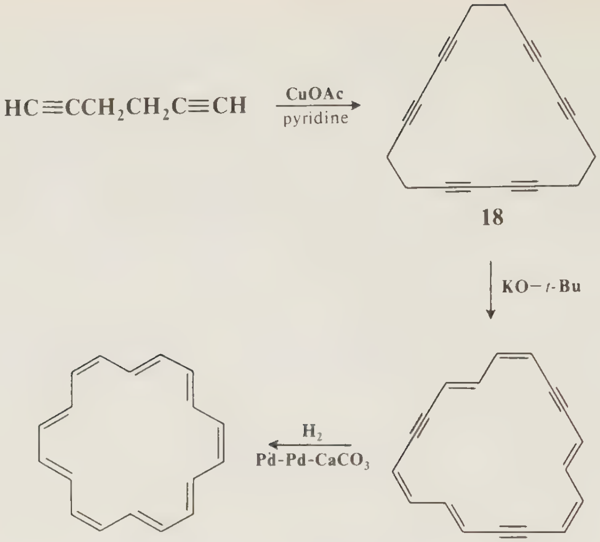
[195] Kharasch and Sosnovsky, *Tetrahedron* **3,** 97 (1958).

[196] Schwetlick, Jentzsch, Karl, and Wolter, *J. Prakt. Chem.* [4] **25,** 95 (1964).

[197] Boguslavskaya and Razuvaev, *J. Gen. Chem. USSR* **33,** 1967 (1963).

[198] For reviews, see Nigh, Ref. 133, pp. 11–31; Cadiot and Chodkiewicz, in Viehe, "Acetylenes," pp. 597 647, Marcel Dekker, Inc., New York, 1969; Eglinton and McCrae, *Adv. Org. Chem.* **4,** 225–328 (1963).

[199] Sondheimer and Wolovsky, *J. Am. Chem. Soc.* **84,** 260 (1962); Sondheimer, Wolovsky, and Amiel, *J. Am. Chem. Soc.* **84,** 274 (1962).



18 is a cyclic trimer of 1,5-hexadiyne. The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed.

The Eglinton reaction is of wide scope. Many functional groups may be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen. The cuprous ion is a necessary intermediate, but apparently there is always enough present in cupric salts to make the reaction possible. Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent such as permanganate or hydrogen peroxide is required in the latter procedure. This method is not satisfactory for cyclic coupling. Unsymmetrical diynes can be prepared by *Cadiot-Chodkiewicz* coupling:[200]

$$\mathrm{R{-}C{\equiv}C{-}H + R'{-}C{\equiv}C{-}Br \xrightarrow{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' + HBr}$$

This may be regarded as a variation of reaction **0-102** but must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not, and this is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. Propargyl halides also give the reaction.[201] A variation of the Cadiot-Chodkiewicz method consists of treating a haloalkyne ($R'C{\equiv}CX$) with a copper acetylide ($RC{\equiv}CCu$).[202] The Cadiot-Chodkiewicz procedure can be adapted to the preparation of diynes in which $R' = H$ by the use of $BrC{\equiv}CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.[203] This protecting group can also be used in the Eglinton or Glaser methods.[204]

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton

$$\mathrm{R{-}C{\equiv}C{-}H \xrightarrow[Cu^+]{base} R{-}C{\equiv}C^- + Cu^+}$$

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[200] Chodkiewicz, *Ann. Chim.* (*Paris*) [13] **2,** 819 (1957).

[201] Sevin, Chodkiewicz, and Cadiot, *Bull. Soc. Chim. Fr.* 913 (1974).

[202] Curtis and Taylor, *J. Chem. Soc. C* 186 (1971).

[203] Eastmond and Walton, *Tetrahedron* **28,** 4591 (1972); Ghose and Walton, *Synthesis* 890 (1974).

[204] Eastmond, Johnson, and Walton, *Tetrahedron* **28,** 4601 (1972); Johnson and Walton, *Tetrahedron* **28,** 5221 (1972).

since there is a base present and acetylenic protons are acidic. The last step is probably the coupling of two free radicals:

$$2\text{R—C}{\equiv}\text{C}\cdot \longrightarrow \text{R—C}{\equiv}\text{C—C}{\equiv}\text{C—R}$$

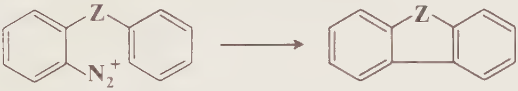
but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[205] and depend on the oxidizing agent. It is known, of course, that cuprous ion can form complexes with triple bonds.

OS **V,** 517; **50,** 97; **54,** 1.

4-16 Arylation of Aromatic Compounds by Diazonium Salts

$$\text{ArH} + \text{Ar}'\text{N}_2{}^+ \ \ \text{X}^- \xrightarrow{\text{OH}^-} \text{Ar—Ar}'$$

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg-Bachmann reaction*,[206] it has been performed on several types of aromatic ring, including ferrocenes,[207] and on quinones. Yields are not high (usually under 40%) because of the many side reactions undergone by diazonium salts. The conditions of the Meerwein reaction (**4-17**), treatment of the solution with a copper-ion catalyst, have also been used, as has the addition of sodium nitrite in dimethyl sulfoxide (to benzene diazonium fluoborate in dimethyl sulfoxide).[208] When the Gomberg-Bachmann reaction is performed intramolecularly, either by the alkaline solution or by the copper-ion procedure, it is called the *Pschorr ring closure*[209] and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the Pschorr reaction electrochemically.[210] The Pschorr reaction has been carried out for $\text{Z} = \text{CH}{=}\text{CH}$, CH_2CH_2, NH, $\text{C}{=}\text{O}$, CH_2, and quite a few others. A rapid and convenient way to carry out the Pschorr synthesis is to diazotize the amine substrate with isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.[211]



Other compounds with nitrogen-nitrogen bonds have been used instead of diazonium salts. Among these are N-nitroso amides [Ar—N(NO)—COR], triazenes, and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.[212]

In each case the mechanism involves generation of an aryl radical from a *covalent* azo compound. In acid solution diazonium salts are ionic, and their reactions are polar. When they cleave, the product is an aryl cation (see p. 587). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals:

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[205] See the discussions in Nigh, Ref. 133, pp. 27–31; Fedenok, Berdnikov, and Shvartsberg, *J. Org. Chem. USSR* **9,** 1908 (1973); Clifford and Waters, *J. Chem. Soc.* 3056 (1963).

[206] For reviews, see Hey, *Adv. Free-Radical Chem.* **2,** 47–86 (1966); Dermer and Edmison, *Chem. Rev.* **57,** 77-122 (1957); Bachmann and Hoffman, *Org. React.* **2,** 224–261 (1944); Williams, Ref. 14, pp. 27–34, 80–93. For a review applied to heterocyclic substrates, see Vernin, Dou, and Metzger, *Bull. Soc. Chim. Fr.* 1173–1203 (1972).

[207] Rosenblum, Howells, Banerjee, and Bennett, *J. Am. Chem. Soc.* **84,** 2726 (1962).

[208] Kobayashi, Minato, Kobori, and Yamada, *Bull. Chem. Soc. Jpn.* **43,** 1131 (1970); Kamigata, Kurihara, Minato, and Kobayashi, *Bull. Chem. Soc. Jpn.* **44,** 3152 (1971).

[209] For reviews, see Abramovitch, *Adv. Free-Radical Chem.* **2,** 87–138 (1966).

[210] Elofson and Gadallah, *J. Org. Chem.* **36,** 1769 (1971).

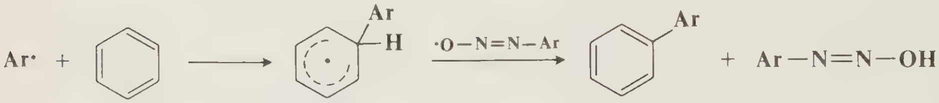
[211] Chauncy and Gellert, *Aust. J. Chem.* **22,** 993 (1969).

[212] Cadogan, *J. Chem. Soc.* 4257 (1962); Fillipi, Vernin, Dou, Metzger, and Perkins, *Bull. Soc. Chim. Fr.* 1075 (1974).

$$\mathrm{Ar{-}N{=}N{-}Z} \longrightarrow \mathrm{Ar{\cdot}} + \mathrm{N{\equiv}N} + \mathrm{Z{\cdot}}$$

Under Gomberg-Bachmann conditions, the species which cleaves is the anhydride Ar—N=N—O—N=N—Ar:[213]

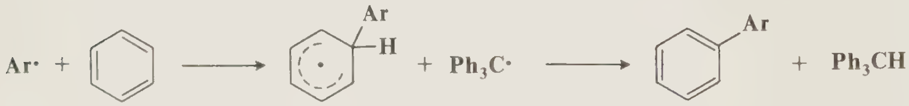
$$\mathrm{Ar{-}N{=}N{-}O{-}N{=}N{-}Ar} \longrightarrow \mathrm{Ar{\cdot}} + \mathrm{N_2} + \mathrm{{\cdot}O{-}N{=}N{-}Ar}$$



19

The aryl radical thus formed attacks the substrate to give the intermediate **19**, from which the radical Ar—N=N—O• abstracts hydrogen to give the product. When the reagent is phenylazotriphenylmethane ($\mathrm{Ph_3C{-}N{=}N{-}Ar}$), the latter cleaves directly and hydrogen is abstracted by the $\mathrm{Ph_3C{\cdot}}$ radical:[214]

$$\mathrm{Ar{-}N{=}N{-}CPh_3} \longrightarrow \mathrm{Ar{\cdot}} + \mathrm{N_2} + \mathrm{Ph_3C{\cdot}}$$



19

Although the triphenylmethyl radical is normally too unreactive to abstract hydrogens, it can do so in this case because of the favorable energy change in the conversion of the radical **19** to a fully aromatic compound. With N-nitroso amides the situation is much more complicated.[215] Here too a covalent azo compound decomposes to give aryl radicals, but several pathways seem to be involved. There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.[216]

The Pschorr reaction may take place by two different mechanisms, depending on conditions: (1) attack by an aryl radical (as in the Gomberg-Bachmann reaction) or (2) attack by an aryl cation (similar to the SN1 mechanism discussed on p. 587).[217] Under certain conditions the ordinary Gomberg-Bachmann reaction can also involve attack by aryl cations.[218]

OS **I**, 113; **IV**, 718.

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[213] Rüchardt and Merz, *Tetrahedron Lett.* 2431 (1964); Eliel, Saha, and Meyerson, *J. Org. Chem.* **30,** 2451 (1965).

[214] Hey, Perkins, and Williams, *J. Chem. Soc.* 110 (1965); Garst and Cole, *Tetrahedron Lett.* 679 (1963).

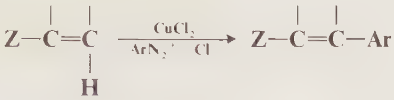
[215] For discussions, see Cadogan, *Acc. Chem. Res.* **4,** 186–192 (1971); Brydon, Cadogan, Cook, Harger, and Sharp, *J. Chem. Soc. B* 1996 (1971).

[216] Gragerov and Levit, *J. Org. Chem. USSR* **4,** 7 (1968).

[217] For an alternative to the second mechanism, see Gadallah, Cantu, and Elofson, *J. Org. Chem.* **38,** 2386 (1973).

[218] For examples, see Kobayashi, Minato, Yamada, and Kobori, *Bull. Chem. Soc. Jpn.* **43,** 215 (1970); Kobayashi, Minato, and Kobori, *Bull. Chem. Soc. Jpn.* **43,** 219 (1970); Kobori, Kobayashi, and Minato, *Bull. Chem. Soc. Jpn.* **43,** 223 (1970); Kamigata, Hisada, Minato, and Kobayashi, *Bull. Chem. Soc. Jpn.* **46,** 1016 (1973); Abramovitch and Gadallah, *J. Chem. Soc. B* 497 (1968); Cooper and Perkins, *Tetrahedron Lett.* 2477 (1969); Kaul and Zollinger, *Helv. Chim. Acta* **51,** 2132 (1968); Gloor, Kaul, and Zollinger, *Helv. Chim. Acta* **55,** 1596 (1972); Burri and Zollinger, *Helv. Chim. Acta* **56,** 2204 (1973); Eustathopoulos, Rinaudo, and Bonnier, *Bull. Soc. Chim. Fr.* 2911 (1974). For a discussion, see Zollinger, *Acc. Chem. Res.* **6,** 335–341 (1973), pp. 338–339.

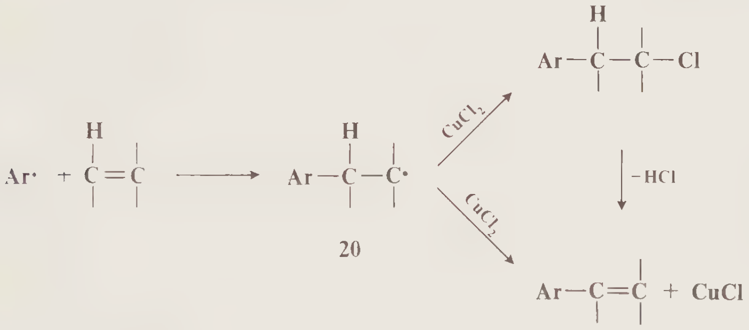
4-17 Arylation of Activated Olefins by Diazonium Salts. Meerwein Arylation



$$\mathrm{Z{-}\overset{|}{C}{=}\underset{H}{\overset{|}{\underset{|}{C}}}} \xrightarrow[\mathrm{ArN_2^+\ Cl^-}]{\mathrm{CuCl_2}} \mathrm{Z{-}\overset{|}{C}{=}\overset{|}{C}{-}Ar}$$

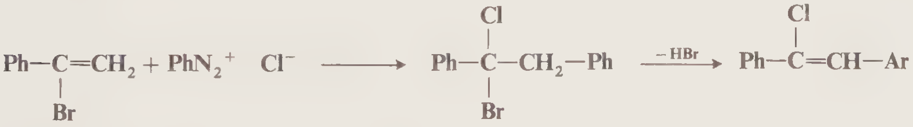
Olefins activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride catalyst.[219] This is called the *Meerwein arylation reaction.* Addition of ArCl to the double bond (to give $\mathrm{Z{-}\overset{|}{\underset{Cl}{C}}{-}\overset{|}{\underset{H}{C}}{-}Ar}$) is a side reaction (reaction **5-37**). The reaction gives best results on quinones, cinnamic acid derivatives, and other activated olefins, but it has been performed even on unactivated compounds such as ethylene and acetylene. The reaction can be carried out without the catalyst, but yields are lower.

The mechanism is probably of the free-radical type, with Ar• forming as in reaction **4-25** and then[220]



20

The radical **20** may react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl.[221] In the reaction between diazonium chlorides and α-bromostyrene the substitution product was definitely formed by addition-elimination, since the product was α-*chloro*stilbene:[222]



$$\mathrm{Ph{-}\underset{Br}{C}{=}CH_2 + PhN_2^+\ \ Cl^-} \longrightarrow \mathrm{Ph{-}\overset{Cl}{\underset{Br}{C}}{-}CH_2{-}Ph} \xrightarrow{-\mathrm{HBr}} \mathrm{Ph{-}\overset{Cl}{C}{=}CH{-}Ar}$$

OS IV, 15.

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[219] For a review, see Rondestvedt, *Org. React.* **11,** 189–260 (1960).

[220] Dickerman and Vermont, *J. Am. Chem. Soc.* **84,** 4150 (1962); Morrison, Cazes, Samkoff, and Howe, *J. Am. Chem. Soc.* **84,** 4152 (1962).

[221] For a discussion of the mechanism, see Zollinger, "Azo and Diazo Chemistry," pp. 162–165, Interscience Publishers, Inc., New York, 1961.

[222] Dombrovskii and Tashchuk, *J. Gen. Chem. USSR* **34,** 3393 (1964).

4-18 Arylation and Alkylation of Olefins by Organopalladium Compounds

$$R_2C{=}CH_2 + \text{“ArPdX”} \longrightarrow R_2C{=}CH{-}Ar$$

Arylation of olefins can also be achieved[223] by treatment with an “arylpalladium” reagent which can be generated in situ by three methods: (1) by treatment of an aryl iodide with palladium acetate in the presence of a base such as tributylamine or potassium acetate (ArI → “ArPdI”);[224] (2) by treatment of an arylmercury compound (either Ar_2Hg or ArHgX) with $LiPdCl_3$ (ArHgX → “ArPdX”)[225] (in some cases other group VIII metal salts have been used); or (3) by the reaction of an aromatic compound with palladium acetate or palladium metal and silver acetate in acetic acid; in this case an aryl *hydrogen* is replaced (ArH → “ArPdOAc”).[226]

Unlike reaction **4-17**, this reaction is not limited to activated substrates. The substrate may be a simple olefin, or it may contain a variety of functional groups, such as ester, keto, or cyano groups. Primary and secondary allylic alcohols give aldehydes or ketones which are products of double-bond migration,[226a] e.g.,

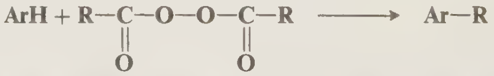
$$CH_2{=}CH{-}CH_2OH \xrightarrow{\text{“PhPdCl”}} PhCH_2CH_2CHO$$

Ethylene is the most reactive olefin. Increasing substitution lowers the reactivity. Substitution therefore takes place at the less highly substituted side of the double bond.[227] Alkylation can also be accomplished, but only if the alkyl group lacks a β-hydrogen; e.g., the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.[228] However, vinyl groups, even those possessing β-hydrogens, have been successfully introduced (to give 1,3-dienes) by the reaction of the olefin with a vinyl halide in the presence of a trialkylamine and a catalytic amount of $Pd(PPh_3)_2(OAc)_2$ at 100 to 150°C.[229]

The mechanisms are not completely known, but it is likely that in all three methods an addition-elimination reaction (addition of ArPdX followed by elimination of HPdX) is involved.[230] Methods 2 and 3 are stereospecific, yielding products expected from syn addition followed by syn elimination.[231]

OS **51,** 17.

4-19 Alkylation and Arylation of Aromatic Compounds by Peroxides



$$ArH + R{-}\underset{\underset{O}{\|}}{C}{-}O{-}O{-}\underset{\underset{O}{\|}}{C}{-}R \longrightarrow Ar{-}R$$

Arylation by peroxides is most often carried out with R = aryl, so that the net result is the same

[223] For reviews of this and related reactions, see Moritani and Fujiwara, *Synthesis* 524–533 (1973); Jira and Freiesleben, *Organomet. React.* 3, 1–190 (1972), pp. 84–105; Volkova, Levitin, and Vol'pin, *Russ. Chem. Rev.* **44,** 552 560 (1975).

[224] Mizoroki, Mori, and Ozaki, *Bull. Chem. Soc. Jpn.* **44,** 581 (1971); Mori, Mizoroki, and Ozaki, *Bull. Chem. Soc. Jpn.* **46,** 1505 (1973); Heck and Nolley, *J. Org. Chem.* **37,** 2320 (1972); Dieck and Heck, *J. Am. Chem. Soc.* **96,** 1133 (1974). See also Julia and Duteil, *Bull. Soc. Chim. Fr.* 2790 (1973); Julia, Duteil, Grard, and Kuntz, *Bull. Soc. Chim. Fr.* 2791 (1973).

[225] Heck, *J. Am. Chem. Soc.* **90,** 5518, 5526, 5535 (1968).

[226] See for example, Fujiwara, Moritani, Matsuda, and Teranishi, *Tetrahedron Lett.* 3863 (1968); Fujiwara, Moritani, and Matsuda, *Tetrahedron* **24,** 4819 (1968); Asano, Moritani, Sonoda, Fujiwara, and Teranishi, *J. Chem. Soc. C* 3691 (1971); Watanabe, Yamamura, Moritani, Fujiwara, and Sonoda, *Bull. Chem. Soc. Jpn.* **47,** 1035 (1974); Fujiwara, Asano, Moritani, and Teranishi, *J. Org. Chem.* **41,** 1681 (1976).

[226a] See for example Melpolder and Heck, *J. Org. Chem.* **41,** 265 (1976); Chalk and Magennis, *J. Org. Chem.* **41,** 273, 1206 (1976).

[227] Heck, *J. Am. Chem. Soc.* **91,** 6707 (1969), **93,** 6896 (1971).

[228] Heck, *J. Organomet. Chem.* **37,** 389 (1972); Heck and Nolley, Ref. 224.

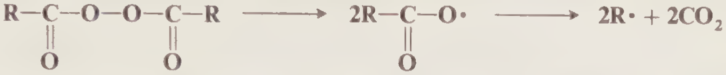
[229] Dieck and Heck, *J. Org. Chem.* **40,** 1083 (1975).

[230] Heck, *J. Am. Chem. Soc.* **91,** 6707 (1969); Shue, *J. Am. Chem. Soc.* **93,** 7116 (1971); Heck and Nolley, Ref. 224.

[231] Heck, Ref. 230; Moritani, Danno, Fujiwara, and Teranishi, *Bull. Chem. Soc. Jpn.* **44,** 578 (1971).

as in reaction **4-16**, though the reagent is different.[232] It is used less often than reaction **4-16**, but the scope is similar. When R = alkyl, the scope is more limited.[233] Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism involves attack on the substrate by free radicals formed by



$$\mathrm{R{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}O{-}O{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}R \longrightarrow 2R{-}\underset{\displaystyle \overset{\|}{O}}{C}{-}O\cdot \longrightarrow 2R\cdot + 2CO_2}$$

The attack is similar to that shown in reaction **4-16**, to give **19** (CIDNP has been observed[234]). However, in this case, there is no relatively stable free radical (such as Ph—N=N—O• or $Ph_3C\cdot$) present to abstract hydrogen from **19**, so that most of the product arises from dimerization and disproportionation, as shown on p. 623.[235] The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts the hydrogen from **19**, reducing the extent of side reactions.[236]

Aromatic compounds can also be arylated by aryllead tricarboxylates.[237] Best yields (~70 to 85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely.

$$\mathrm{ArH + Ar'Pb(OAc)_3 \longrightarrow ArAr'}$$

OS V, 51. See also OS V, 952.

4-20 Photochemical Arylation of Aromatic Compounds

$$\mathrm{ArI + Ar'H \xrightarrow{h\nu} ArAr'}$$

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.[238] Yields are generally higher than in reaction **4-16** or **4-19**. The aryl iodide may contain OH or COOH groups. The mechanism is similar to that of reaction **4-16**. Aryl radicals, generated by the photolytic cleavage ArI → Ar• + I•, attack the substrate to give **19**, from which hydrogen is abstracted by the I• atom. The reaction has been applied to intramolecular arylation (analogous to the Pschorr reaction).[239]

A similar reaction is photolysis of an arylthallium bis(trifluoroacetate) (reaction **2-20**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.[240] In this case

$$\mathrm{ArTl(OCOCF_3)_2 \xrightarrow[Ar'H]{h\nu} ArAr'}$$

it is the C—Tl bond which is cleaved to give aryl radicals.

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[232] For reviews, see Hey, Ref. 206; Vernin, Dou, and Metzger, Ref. 206.

[233] For a review of the free-radical alkylation of aromatic compounds, see Dou, Vernin, and Metzger, *Bull. Soc. Chim. Fr.* 4593 (1971).

[234] Kaptein, Freeman, Hill, and Bargon, *J. Chem. Soc., Chem. Commun.* 953 (1973).

[235] We have given the main steps which lead to biphenyls. The mechanism is actually more complicated than this and includes more than 100 elementary steps resulting in many side products, including those mentioned on p. 623: DeTar, Long, Rendleman, Bradley, and Duncan, *J. Am. Chem. Soc.* **89**, 4051 (1967); DeTar, *J. Am. Chem. Soc.* **89**, 4058 (1967).

[236] Hey, Liang, Perkins, and Williams, *J. Chem. Soc. C* 1153 (1967); Chalfont, Hey, Liang, and Perkins, *J. Chem. Soc. B* 233 (1971).

[237] Bell, Kalman, Pinhey, and Sternhell, *Tetrahedron Lett.* 857 (1974).

[238] Wolf and Kharasch, *J. Org. Chem.* **30**, 2493 (1965). For a review, see Sharma and Kharasch, *Angew. Chem. Int. Ed. Engl.* **7**, 36–44 (1968) [*Angew. Chem.* **80**, 69–77].

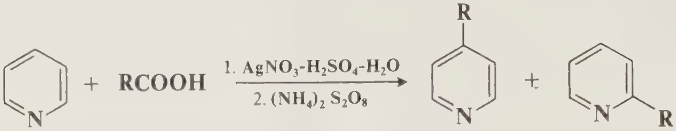
[239] See for example, Kupchan and Wormser, *J. Org. Chem.* **30**, 3792 (1965); Jeffs and Hansen, *J. Am. Chem. Soc.* **89**, 2798 (1967); Thyagarajan, Kharasch, Lewis, and Wolf, *Chem. Commun.* 614 (1967).

[240] Taylor, Kienzle, and McKillop, *J. Am. Chem. Soc.* **92**, 6088 (1970).

A PhC≡C group can be introduced into an aromatic ring by photolysis of 1-iodo-2-phenylacetylene in an aromatic solvent:[241]

$$\text{PhC}{\equiv}\text{CI} + \text{ArH} \xrightarrow{h\nu} \text{ArC}{\equiv}\text{CPh}$$

4-21 Alkylation and Acylation of Nitrogen Heterocycles[242]

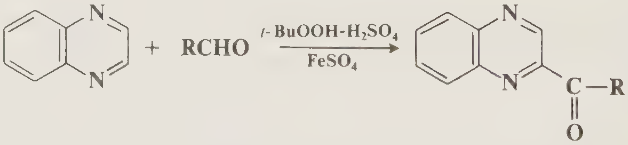


Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.[243] R may be primary, secondary, or tertiary. The attacking species is R•, formed by[244]

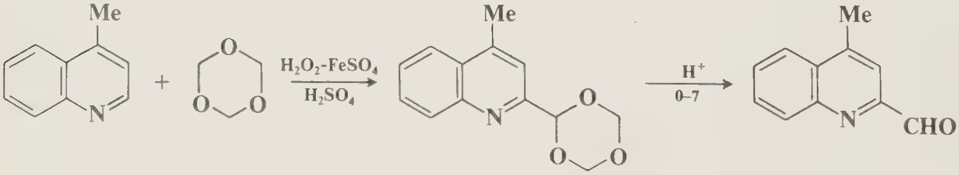
$$2\text{Ag}^+ + \text{S}_2\text{O}_8{}^{2-} \longrightarrow 2\text{Ag}^{2+} + 2\text{SO}_4{}^{2-}$$
$$\text{RCOOH} + \text{Ag}^{2+} \longrightarrow \text{RCOO}\cdot + \text{H}^+ + \text{Ag}^+$$
$$\text{RCOO}\cdot \longrightarrow \text{R}\cdot + \text{CO}_2$$

Similar alkylation can also be accomplished with other reagents, including hydroperoxides and FeSO_4;[245] and carboxylic acids and lead tetraacetate. Alcohols and ethers can be used instead of carboxylic acids to supply the free radicals, in this case α-hydroxy and α-alkoxy radicals.[246]

Protonated nitrogen heterocycles can be acylated by treatment with an aldehyde, *t*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, e.g.,[247]



A formyl group can be introduced indirectly (though yields are not high) by treating the substrate with trioxane, Fenton's reagent, and H_2SO_4 followed by hydrolysis; e.g.,[248]



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[241] Martelli, Spagnolo, and Tiecco, *J. Chem. Soc. B* 1413 (1970).

[242] For a review, see Minisci, *Synthesis* 1–24 (1973), pp. 12–19.

[243] Minisci, Bernardi, Bertini, Galli, and Perchinunno, *Tetrahedron* **27**, 3575 (1971); Minisci, Mondelli, Gardini, and Porta, *Tetrahedron* **28**, 2403 (1972).

[244] Anderson and Kochi, *J. Am. Chem. Soc.* **92**, 1651 (1970).

[245] Minisci, Galli, Malatesta, and Caronna, *Tetrahedron* **26**, 4083 (1970); Minisci, Selva, Porta, Barilli, and Gardini, *Tetrahedron* **28**, 2415 (1972).

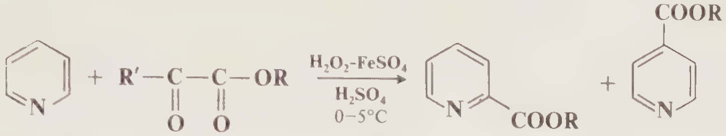
[246] Buratti, Gardini, Minisci, Bertini, Galli, and Perchinunno, *Tetrahedron* **27**, 3655 (1971).

[247] Caronna, Gardini, and Minisci, *Chem. Commun.* 201 (1969); Gardini and Minisci, *J. Chem. Soc. C* 929 (1970); Caronna, Galli, Malatesta, and Minisci, *J. Chem. Soc. C* 1747 (1971); Caronna, Fronza, Minisci, Porta, and Gardini, *J. Chem. Soc., Perkin Trans. 2* 1477 (1972).

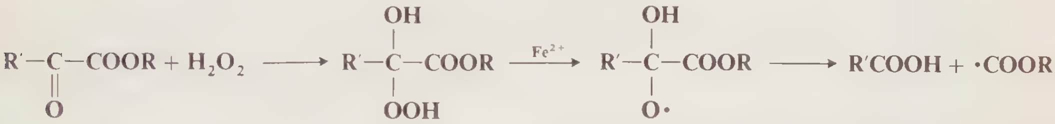
[248] Gardini, *Tetrahedron Lett.* 4113 (1972).

These alkylation and acylation reactions are important because Friedel-Crafts alkylation and acylation (reactions **1-13**, **1-15**) cannot be applied to most nitrogen heterocycles. See also reaction **3-17**.

4-22 Carbalkoxylation and Carboamidation of Nitrogen Heterocycles



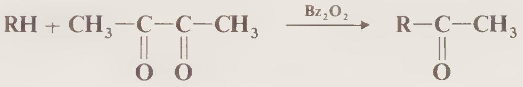
In a reaction related to **4-21**, protonated nitrogen heterocycles can be carbalkoxylated[249] by treatment with •COOR radicals generated from esters of α-keto acids:



$$R'\underset{\underset{O}{\|}}{C}{-}COOR + H_2O_2 \longrightarrow R'{-}\overset{\overset{OH}{|}}{\underset{\underset{OOH}{|}}{C}}{-}COOR \xrightarrow{Fe^{2+}} R'{-}\overset{\overset{OH}{|}}{\underset{\underset{O\cdot}{|}}{C}}{-}COOR \longrightarrow R'COOH + \cdot COOR$$

Similarly, a carbamoyl group can be introduced[250] by the use of the radicals $H_2N\underset{\underset{O}{\|}}{C}\cdot$ or $Me_2N\underset{\underset{O}{\|}}{C}\cdot$, generated from formamide or dimethylformamide and H_2SO_4, H_2O_2, and $FeSO_4$ or other oxidants.

4-23 Free-Radical Acylation and Chlorocarbonylation at an Aliphatic Carbon



$$RH + CH_3{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow{Bz_2O_2} R{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

Cyclohexane can be acylated by thermal decomposition of benzoyl peroxide in the presence of biacetyl.[251] The reaction has also been carried out with dioxane as substrate (to give 2-acetyldioxane), but the further scope of the reaction has not yet been established.

Chlorocarbonylation (RH →RCOCl) can be accomplished by treatment of the substrate (e.g., pentane, cyclohexane) with oxalyl chloride ClCOCOCl[252] or with CO and CCl_4.[253] using peroxides, uv light, or γ-radiation to initiate the chain.

N_2 as Leaving Group[254]

In these reactions diazonium salts are cleaved to aryl radicals,[255] in most cases with the assistance of copper salts. Reactions **4-16** and **4-17** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts, see reactions **3-21** to **3-25**.

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[249] Bernardi, Caronna, Galli, Minisci, and Perchinunno, *Tetrahedron Lett.* 645 (1973).

[250] Minisci, Gardini, Galli, and Bertini, *Tetrahedron Lett.* 15 (1970); Gardini, Minisci, Palla, Arnone, and Galli, *Tetrahedron Lett.* 59 (1971); Arnone, Cecere, Galli, Minisci, Perchinunno, Porta, and Gardini, *Gazz. Chim. Ital.* **103**, 13 (1973).

[251] Bentrude and Darnall, *J. Am. Chem. Soc.* **90**, 3588 (1968).

[252] Kharasch and Brown, *J. Am. Chem. Soc.* **64**, 329 (1942); Kharasch, Kane, and Brown, *J. Am. Chem. Soc.* **64**, 1621 (1942); Tabushi, Okada, and Oda, *Tetrahedron Lett.* 1605 (1969); Tabushi, Okada, Aoyama, and Oda, *Tetrahedron Lett.* 4069 (1969).

[253] Thaler, *J. Am. Chem. Soc.* **88**, 4278 (1966), **89**, 1902 (1967), **90**, 4370 (1968).

[254] For a review, see Cowdrey and Davies, *Q. Rev., Chem. Soc.* **6**, 358–379 (1952).

[255] For reviews, see Zollinger, *Acc. Chem. Res.* **6**, 335–341 (1973), pp. 339–341, Ref. 221, pp. 153–169; Belov and Kozlov, *Russ. Chem. Rev.* **32**, 59–75 (1963).

4-24 Replacement of the Diazonium Group by Hydrogen. Dediazonation

$$\mathbf{ArN_2{}^+ + H_3PO_2 \longrightarrow ArH}$$

Reduction of the diazonium group (*dediazonation*) provides an indirect method for the removal of an amino group from a ring. The best and most common way of accomplishing this is by use of H_3PO_2,[256] although many other reducing agents have also been used, among them ethanol, sodium methoxide in methanol, hydroquinone,[257] alkaline formaldehyde, and sodium stannite. Ethanol was the earliest reagent used, and it frequently gives good yields, but often ethers (ArOEt) are side products. When hypophosphorous acid (H_3PO_2) is used, 5 to 15 mol of this reagent is required per mole of substrate. Diazonium salts can be reduced in nonaqueous media either by treatment with Bu_3SnH or Et_3SiH in ethers or MeCN[258] or by isolation as the $BF_4{}^-$ salt, and reduction of this with $NaBH_4$ in dimethylformamide.[259] Aromatic amines can be deaminated ($ArNH_2 \rightarrow ArH$) in one laboratory step by treatment with pentyl nitrite in boiling tetrahydrofuran.[260] The corresponding diazonium salt is an intermediate, but it is not necessary to isolate a solution of it.

Not many investigations of the mechanism have been carried out. It is generally assumed that the reaction of diazonium salts with ethanol to produce ethers takes place by an ionic (SN1) mechanism while the reduction to ArH proceeds by a free-radical process.[261] The reduction with H_3PO_2 is also believed to have a free-radical mechanism.[262] The mechanism with NaOMe in MeOH is free-radical at low NaOMe concentrations, but at high concentrations aryl carbanions are involved.[263] In the reduction with $NaBH_4$, an aryldiazene intermediate (ArN=NH) has been demonstrated,[264] arising from nucleophilic attack by $BH_4{}^-$ on the β-nitrogen. Such diazenes can be obtained as moderately stable (half-life of several hours) species in solution by the decarboxylation of aryldiazenecarboxylate ions ($ArN{=}NCOO^-$).[265] It is not entirely clear how the aryldiazene decomposes, but there are indications that either the aryl radical Ar• or the corresponding anion Ar^- may be involved.[266]

An important use of the dediazonation reaction is to remove an amino group after it has been used to direct one or more other groups to ortho and para positions. For example, the compound 1,3,5-tribromobenzene cannot be prepared by direct bromination of benzene because the bromo group is ortho-para-directing; however, this compound is easily prepared by the following sequence:

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[256] For reviews, see Kornblum, *Org. React.* **2,** 262–340 (1944); Belov and Kozlov, Ref. 255, pp. 65–66.

[257] McDonald and Richmond, *J. Chem. Soc., Chem. Commun.* 605 (1973).

[258] Nakayama, Yoshida, and Simamura, *Tetrahedron* **26,** 4609 (1970).

[259] Hendrickson, *J. Am. Chem. Soc.* **83,** 1251 (1961).

[260] Cadogan and Molina, *J. Chem. Soc., Perkin Trans. 1* 541 (1973).

[261] For examples, see DeTar and Turetzky, *J. Am. Chem. Soc.* **77,** 1745 (1955), **78,** 3925, 3928 (1956); DeTar and Kosuge, *J. Am. Chem. Soc.* **80,** 6072 (1958); Broxton, Bunnett, and Paik, *Chem. Commun.* 1363 (1970); Lewis and Chambers, *J. Am. Chem. Soc.* **93,** 3267 (1971).

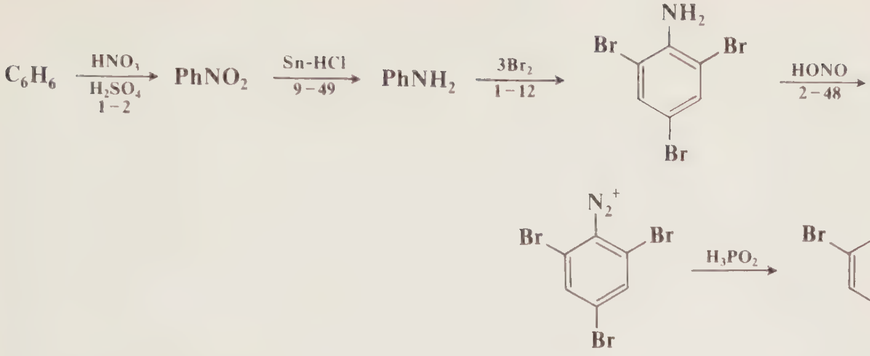
[262] See for example, Kornblum, Cooper, and Taylor, *J. Am. Chem. Soc.* **72,** 3013 (1950); Beckwith, *Aust. J. Chem.* **25,** 1887 (1972).

[263] Bunnett, Happer, and Takayama, *Chem. Commun.* 367 (1966); Bunnett and Takayama, *J. Am. Chem. Soc.* **90,** 5173 (1968), *J. Org. Chem.* **33,** 1924 (1968).

[264] Bloch, Musso, and Záhorszky, *Angew. Chem. Int. Ed. Engl.* **8,** 370 (1969) [*Angew. Chem.* **81,** 392]; König, Musso, and Záhorszky, *Angew. Chem. Int. Ed. Engl.* **11,** 45 (1972) [*Angew. Chem.* **84,** 33]; McKenna and Traylor, *J. Am. Chem. Soc.* **93,** 2313 (1971).

[265] Huang and Kosower, *J. Am. Chem. Soc.* **90,** 2354, 2362, 2367 (1968).

[266] Rieker, Niederer, and Leibfritz, *Tetrahedron Lett.* 4287 (1969); Kosower, Huang, and Tsuji, *J. Am. Chem. Soc.* **91,** 2325 (1969); König, Musso, and Záhorsky, Ref. 264.



Many other compounds which would otherwise be difficult to prepare are easily synthesized with the aid of the dediazonation reaction.

OS **I,** 133, 415; **II,** 353, 592; **III,** 295; **IV,** 947.

4-25 Replacement of the Diazonium Group by Chlorine or Bromine

$$\mathbf{ArN_2^+ + CuCl \longrightarrow ArCl}$$

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case the reaction is called the *Sandmeyer reaction.* The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with reaction **1-18**). The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is by no means known with certainty but is believed to take the following course:[267]

$$\mathbf{ArN_2^+\ X^- + CuX \longrightarrow Ar\cdot + N_2 + CuX_2}$$
$$\mathbf{Ar\cdot + CuX_2 \longrightarrow ArX + CuX}$$

The first step involves a reduction of the diazonium ion by the cuprous ion, resulting in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. CuX is regenerated and is thus a true catalyst.

Aryl bromides can be prepared from primary aromatic amines in one step by two procedures: (1) by treatment of the amine with a complex of $CuBr_2$ and NO:[268]

$$\mathbf{ArNH_2 + CuBr_2NO \longrightarrow ArBr + H_2O + N_2 + CuBr}$$

(2) by treatment of the amine with pentyl nitrite in the presence of bromoform.[269] Procedure 1 is also applicable to the formation of chlorides, but procedure 2 gives low yields of chlorides when chloroform or carbon tetrachloride is used. Both procedures are, in effect, a combination of reaction **2-48** and the Sandmeyer reaction. A further advantage is that cooling is not needed. Procedure 1 proceeds at room temperature, while procedure 2 is carried out at 100°C.

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[267] Dickerman, Weiss, and Ingberman, *J. Org. Chem.* **21,** 380 (1956), *J. Am. Chem. Soc.* **80,** 1904 (1958); Kochi, *J. Am. Chem. Soc.* **79,** 2942 (1957); Dickerman, DeSouza, and Jacobson, *J. Org. Chem.* **34,** 710 (1969).

[268] Brackman and Smit, *Recl. Trav. Chim. Pays-Bas* **85,** 857 (1966).

[269] Cadogan, Roy, and Smith, *J. Chem. Soc. C* 1249 (1966).

For the preparation of fluorides and iodides from diazonium salts, see reactions **3-25** and **3-24.**

OS **I,** 135, 136, 162, 170; **II,** 130; **III,** 185; **IV,** 160. Also see OS **III,** 136; **IV,** 182.

4-26 Replacement of the Diazonium Group by Nitro

$$\mathbf{ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2}$$

Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the Sandmeyer reaction, although, like reactions **4-25** and **4-28,** it was discovered by Sandmeyer. BF_4^- is often used as the negative ion, to avoid competition from the chloride ion. The mechanism is probably like that of reaction **4-25.**[270] If electron-donating groups are present, irradiation with uv light may be substituted for the cuprous ion catalyst.[271] If electron-withdrawing groups are present, neither the cuprous-ion catalyst nor irradiation is needed; $NaNO_2$ alone gives nitro compounds in high yields.[272]

OS **II,** 225; **III,** 341.

4-27 Replacement of the Diazonium Group by Sulfur-containing Groups

$$\mathbf{ArN_2^+ + SO_2 \xrightarrow[HCl]{CuCl_2} ArSO_2Cl}$$

Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.[273] The use of $FeSO_4$ and copper metal instead of $CuCl_2$ gives sulfinic acids $ArSO_2H$.[274] See also reaction **3-22.**

OS **V,** 60.

4-28 Replacement of the Diazonium Group by Cyano

$$\mathbf{ArN_2^+ + CuCN \longrightarrow ArCN}$$

This reaction, also called the *Sandmeyer reaction,* is similar to reaction **4-25** in scope and mechanism. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I,** 514.

4-29 Aryl Dimerization with Diazonium Salts

$$\mathbf{2ArN_2^+ \xrightarrow[\text{or } Cu + H^+]{Cu^+} Ar{-}Ar + 2N_2 \quad \text{or} \quad Ar{-}N{=}N{-}Ar + N_2}$$

When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from reaction **4-16** (and from reaction **1-4**) in that *both* aryl groups in the product originate from ArN_2^+; i.e., hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.[275]

OS **I,** 222; **IV,** 872. Also see OS **IV,** 273.

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[270] For a discussion, see Opgenorth and Rüchardt, *Justus Liebigs Ann. Chem.* 1333 (1974).

[271] El'tsov, Frolov, Smirnov, and Sof'ina, *J. Org. Chem. USSR* **8,** 1352 (1972).

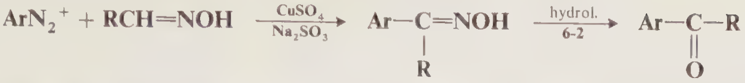
[272] Bagal, Pevzner, and Frolov, *J. Org. Chem. USSR* **5,** 1767 (1969).

[273] Gilbert, *Synthesis* 1–10 (1969), p. 6.

[274] Wittig and Hoffmann, *Org. Synth.* V, 60.

[275] See Cohen, Lewarchik, and Tarino, *J. Am. Chem. Soc.* **96,** 7753 (1974).

4-30 Conversion of Diazonium Salts to Aldehydes or Ketones



$$\mathrm{ArN_2^{\,+} + RCH{=}NOH \xrightarrow[\mathrm{Na_2SO_3}]{\mathrm{CuSO_4}} Ar{-}\underset{\displaystyle R}{\underset{|}{C}}{=}NOH \xrightarrow[6\text{-}2]{\text{hydrol.}} Ar{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}R}$$

Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.[276] A copper sulfate–sodium sulfite catalyst is essential. In most cases higher yields (40 to 60 %) are obtained when the reaction is used for aldehydes than for ketones.

OS **V**, 139.

4-31 Replacement of the Diazonium Group by a Metal

$$\mathrm{ArN_2^{\,+}\ \ BF_4^{\,-} + M \longrightarrow ArM}$$

Aromatic organometallic compounds can be prepared by the treatment of diazonium salts (most often fluoborates) with metals.[277] Among the metals used have been Hg, Tl, Sn, Pb, Sb, and Bi. Another method consists of treating the double salt of the diazonium salt and a metal chloride with a metallic powder, e.g.,

$$\mathrm{ArN_2Cl{\cdot}HgCl_2 \xrightarrow{Cu} ArHgCl + CuCl_2}$$

Organometallic compounds of Hg, Ge, Sn, and As have been among those prepared by this method. The mechanisms are not clear and may be either homolytic or heterolytic.

OS **II**, 381, 432, 494; **III**, 665.

Metals as Leaving Groups

4-32 The Conversion of Boranes to Iodides

$$\mathrm{R_3B + CH_2{=}CH{-}CH_2I \xrightarrow{air} RI + CH_2{=}CHCH_2CH_2CH{=}CH_2}$$

The reaction of trialkylboranes with allyl iodide in the presence of air converts the R group to an alkyl iodide,[278] in high yield. An equimolar amount of oxygen is required. The allyl group is dimerized to 1,5-hexadiene. If other iodides are used, dimerization products of these may be obtained; e.g., benzyl iodide gave bibenzyl. The reaction has a free-radical mechanism; the fact that an equimolar amount of oxygen is required indicates a nonchain process. See also reaction **2-28**.

4-33 The Conversion of Boranes to Sulfides

$$\mathrm{R_3B + R'SSR' \xrightarrow[\text{or } h\nu]{O_2} RSR' + R_2BSR'}$$

Unsymmetrical sulfides can be prepared in very high yields by treatment of a trialkylborane with a disulfide.[279] The reaction has been applied to R = primary or secondary alkyl and R′ = methyl or phenyl. The reaction rate is greatly accelerated by either light or air but totally inhibited by the addition of iodine, indicating a free-radical mechanism.

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[276] Beech, *J. Chem. Soc.* 1297 (1954).

[277] For a review, see Reutov and Ptitsyna, *Organomet. React.* **4**, 73–162 (1972).

[278] Suzuki, Nozawa, Harada, Itoh, Brown, and Midland, *J. Am. Chem. Soc* **93**, 1508 (1971). For reviews, see Brown and Midland, *Angew. Chem. Int. Ed. Engl.* **11**, 692–700 (1972), pp. 699–700 [*Angew. Chem.* **84**, 702–710]. Brown, "Boranes in Organic Chemistry," pp. 442–446, Cornell University Press, Ithaca, N.Y., 1972.

[279] Brown and Midland, *J. Am. Chem. Soc.* **93**, 3291 (1971).

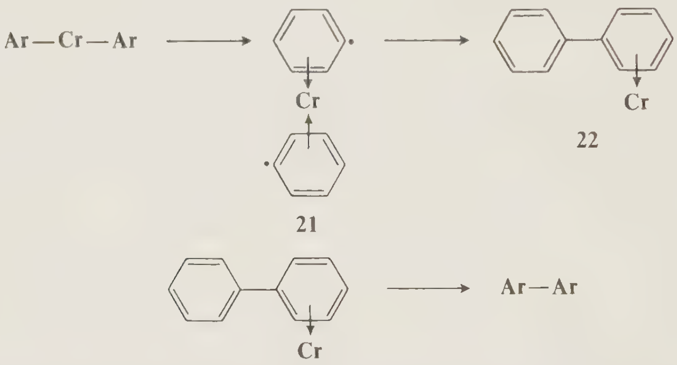
4-34 Coupling of Grignard Reagents

$$2RMgX \xrightarrow{TlBr} RR$$

Grignard reagents can be coupled, to give symmetrical dimers, by treatment with either thallium(I) bromide[280] or with a transition-metal halide such as $CrCl_2$, $CrCl_3$, $CoCl_2$, $CoBr_2$, or $CuCl_2$.[281] The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with ortho substituents. Vinyl and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively), by treatment with thionyl chloride.[282] Primary alkyl, vinyl, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield ($\sim 90\%$) when treated with a silver(I) salt, e.g., $AgNO_3$, AgBr, $AgClO_4$, in the presence of a nitrogen-containing oxidizing agent such as lithium nitrate, methyl nitrate, or NO_2.[283]

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (reaction **2-34**), followed by its decomposition to free radicals.[284] For aryl Grignard reagents the following mechanism has been proposed:[285]

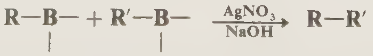
$$2ArMgBr + CrCl_2 \longrightarrow Ar{-}Cr{-}Ar$$



The first step of the reaction involves replacement of magnesium by the transition metal. The diaryl- transition-metal compound then rearranges to a sandwich diradical (**21**), which couples to give **22**, in which the chromium, now reduced to zero oxidation state, is still complexed to one ring. **22** is decomposed by boiling in benzene.

OS **55,** 48.

4-35 Coupling of Boranes



$$R{-}\underset{|}{B}{-} + R'{-}\underset{|}{B}{-} \xrightarrow[NaOH]{AgNO_3} R{-}R'$$

Alkylboranes can be coupled by treatment with silver nitrate and base.[286] Since alkylboranes are easily prepared from olefins (reaction **5-15**), this is essentially a way of coupling and reducing olefins; in fact, olefins can be hydroborated and coupled in the same flask. For symmetrical coupling ($R = R'$) yields range from 60 to 80% for terminal olefins and from 35 to 50% for those with the double bond not at the end of a chain. Unsymmetrical coupling has also been carried out,[286a] but with lower yields. Arylboranes react similarly, yielding biaryls.[287] Dienes have been coupled intramolecularly, to give cycloalkanes.[287a] The mechanism is probably of the free-radical type but has not yet been studied much.

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[280] McKillop, Elsom, and Taylor, *J. Am. Chem. Soc.* **90,** 2423 (1968), *Tetrahedron* **26,** 4041 (1970).

[281] For reviews, see Kauffmann, *Angew. Chem. Int. Ed. Engl.* **13,** 291–305 (1974) [*Angew. Chem.* **86,** 321–335]; Elsom, Hunt, and McKillop, *Organomet. Chem. Rev., Sect. A* **8,** 135 152 (1972); Nigh, Ref. 133, pp. 85–91.

[282] Uchida, Nakazawa, Kondo, Iwata, and Matsuda, *J. Org. Chem.* **37,** 3749 (1972).

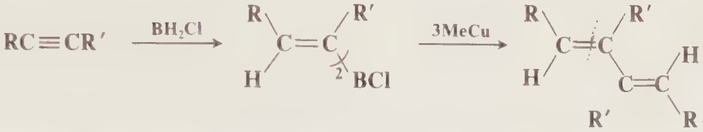
[283] Tamura and Kochi, *Bull. Chem. Soc. Jpn.* **45,** 1120 (1972).

[284] See for example, Aleksankin, Fileleeva, and Gragerov, *J. Org. Chem. USSR* **4,** 1384 (1968). For a different mechanism, see Tamura and Kochi, *Bull. Chem. Soc. Jpn.* **44,** 3063 (1971).

[285] Tsutsui, *Ann. N.Y. Acad. Sci.* **93,** 133–146 (1962); Tsutsui, Hancock, Ariyoshi, and Levy, *Angew. Chem. Int. Ed. Engl.* **8,** 410–420 (1969) [*Angew. Chem.* **81,** 453–463].

[286] Brown, Ref. 278, pp. 332–336; Snyder, *Intra-Sci. Chem. Rep.* **7** (2), 169–179 (1973).

Vinyl dimerization can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see reaction **5-15**) with methylcopper. (*E*,*E*)-1,3-Dienes are prepared in high yields:[288]



In a similar reaction, symmetrical conjugated diynes $RC{\equiv}C{-}C{\equiv}CR$ can be prepared by reaction of lithium dialkyldialkynylborates $Li^+ \quad [R'_2B(C{\equiv}CR)_2]^-$ with iodine.[288a]

4-36 Coupling of Other Organometallic Reagents

$$R_2CuLi \xrightarrow[-78^\circ C,\ THF]{O_2} RR$$

Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at $-78°C$ in tetrahydrofuran.[289] The reaction is successful for R = primary and secondary alkyl, vinyl, or aryl. Other oxidizing agents, e.g., nitrobenzene, can be used instead of O_2. Vinylcopper and vinylsilver reagents dimerize simply on standing at 0°C for several days or at 25°C for several hours, to yield 1,3-dienes.[290] The finding of retention of configuration for this reaction demonstrates that free-radical intermediates are not involved. Terminal vinylalanes (prepared by reaction **5-16**) can be dimerized to 1,3-dienes with cuprous chloride in tetrahydrofuran.[291] Diarylmercury compounds Ar_2Hg are converted to biaryls ArAr by heating with palladium or platinum metal.[292] Alkyl- and aryllithium compounds can be dimerized by transition-metal halides in a reaction similar to **4-34**.[293] Aryllithium compounds can also be converted to biaryls by uv irradiation.[294] Arylthallium(III) compounds (ArTlXY, where X and Y are such groups as Cl, OAc, ClO_4) give biaryls when treated with $PdCl_2$ in HOAc containing NaOAc.[295]

Halogen as Leaving Group

The conversion of RX to RH may occur by a free-radical mechanism but is treated at reaction **0-77**.

[286a] Brown, Verbrugge, and Snyder, *J. Am. Chem. Soc.* **83,** 1001 (1961).

[287] Breuer and Broster, *Tetrahedron Lett.* 2193 (1972).

[287a] Murphy and Prager, *Tetrahedron Lett.* 463 (1976).

[288] Yamamoto, Yatagai, and Moritani, *J. Am. Chem. Soc.* **97,** 5606 (1975).

[288a] Pelter, Smith, and Tabata, *J. Chem. Soc., Chem. Commun.* 857 (1975).

[289] Whitesides, SanFilippo, Casey, and Panek, *J. Am. Chem. Soc.* **89,** 5302 (1967). See also Kauffmann, Beissner, Köppelmann, Kuhlmann, Schott, and Schrecken, *Angew. Chem. Int. Ed. Engl.* **7,** 131 (1968) [*Angew. Chem.* **80,** 117]; Kauffmann, Beissner, Berg, Köppelmann, Legler, and Schönfelder, *Angew. Chem. Int. Ed. Engl.* **7,** 540 (1968) [*Angew. Chem.* **80,** 565]; Kauffmann, Kuhlmann, Sahm, and Schrecken, *Angew. Chem. Int. Ed. Engl.* **7,** 541 (1968) [*Angew. Chem.* **80,** 566].

[290] Whitesides, Casey, and Krieger, *J. Am. Chem. Soc.* **93,** 1379 (1971). See also Burkhardt and Kauffmann, *Angew. Chem. Int. Ed. Engl.* **6,** 84 (1967) [*Angew. Chem.* **79,** 57].

[291] Zweifel and Miller, *J. Am. Chem. Soc.* **92,** 6678 (1970).

[292] Makarova, *Organomet. React.* **1,** 119–348 (1970), pp. 271–274. See also Vedejs and Weeks, *Tetrahedron Lett.* 3207 (1974).

[293] Morizur, *Bull. Soc. Chim. Fr.* 1331 (1964).

[294] van Tamelen, Brauman, and Ellis, *J. Am. Chem. Soc.* **93,** 6141 (1971).

[295] Uemura, Ikeda, and Ichikawa, *Chem. Commun.* 390 (1971).

Sulfur as Leaving Group

4-37 Desulfurization with Raney Nickel

$$\mathrm{RSH} \xrightarrow[\mathrm{Ni}]{\mathrm{H_2}} \mathrm{RH}$$

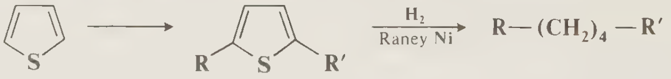
$$\mathrm{RSR'} \xrightarrow[\mathrm{Ni}]{\mathrm{H_2}} \mathrm{RH} + \mathrm{R'H}$$

Thiols and thioethers, both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[296] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them

Disulfides	$\mathrm{RSSR'}$	$\longrightarrow$	$\mathrm{RH} + \mathrm{R'H}$
Thioamides	$\mathrm{RCSNHR'}$	$\longrightarrow$	$\mathrm{RCH_2NHR'}$
Sulfoxides	$\mathrm{RSOR'}$	$\longrightarrow$	$\mathrm{RH} + \mathrm{R'H}$
Hemithioacetals	$\mathrm{RO}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{SR'}$	$\longrightarrow$	$\mathrm{RO}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H}$
Dithioacetals	$\mathrm{RS}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{SR'}$	$\longrightarrow$	$\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{H_2}$

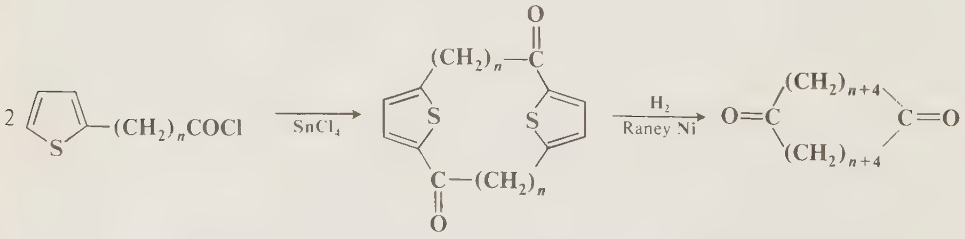
The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see reaction **9-39**), can also give the olefin if an α-hydrogen is present.[297] In most of the examples given, R may also be aryl. Other reagents have also been used.[298]

An important special case is desulfurization of thiophene derivatives (a special case of RSR reduction). This proceeds with concomitant reduction of the double bonds. Many otherwise difficultly accessible compounds have been made by alkylation of thiophene, followed by reduction:



23

An example is the following, which was accomplished for $n = 8$ and 9:[299]



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[296] For reviews, see Pettit and van Tamelen, *Org. React.* **12,** 356–529 (1962); Hauptmann and Walter, *Chem. Rev.* **62,** 347–404 (1962); Reid, "Organic Chemistry of Bivalent Sulfur," vol. 1, pp. 115–118, Chemical Publishing Company, New York, 1958.

[297] Fishman, Torigoe, and Guzik, *J. Org. Chem.* **28,** 1443 (1963).

[298] For example, triethyl phosphite, by Hoffmann, Ess, Simmons, and Hanzel, *J. Am. Chem. Soc.* **78,** 6414 (1956); sodium in liquid ammonia, by Truce, Tate, and Burdge, *J. Am. Chem. Soc.* **82,** 2872 (1960); the hydridotetracarbonylferrate ion $\mathrm{HFe(CO)_4^-}$, by Alper, *J. Org. Chem.* **40,** 2694 (1975).

[299] Gol'dfarb, Taits, and Belen'kii, *J. Gen. Chem. USSR* **29,** 3526 (1959).

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **23**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[300]

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free-radical type.[301] It has been shown that reduction of thiophene proceeds through butadiene and butene and not through butyl mercaptan or other sulfur compounds; i.e., the sulfur is removed before the double bonds are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.[302]

OS **IV**, 638; **V**, 419.

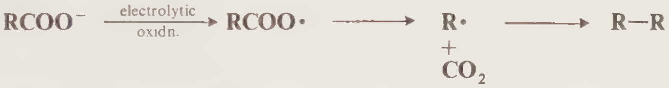
Carbon as Leaving Group

4-38 Decarboxylative Dimerization. The Kolbe Reaction

$$2RCOO^- \xrightarrow{\text{electrol}} R{-}R$$

Electrolysis of carboxylate ions, which results in decarboxylation and combination of the resulting radicals, is called the *Kolbe reaction.*[303] It is used to prepare symmetrical R—R, where R is straight- or branched-chained, except that little or no yield is obtained when there is a branching. When R is aryl, the reaction fails. Many functional groups may be present, though many others inhibit the reaction.[303] The position of the functional group is important, too. Thus $F(CH_2)_4COO^-$ gives 45% $F(CH_2)_8F$, but $F(CH_2)_3COO^-$ gives no reaction. Unsymmetrical R—R′ have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:



$$RCOO^- \xrightarrow[\text{oxidn.}]{\text{electrolytic}} RCOO\cdot \longrightarrow \underset{CO_2}{\underset{+}{R\cdot}} \longrightarrow R{-}R$$

Unlike many other organic oxidations, there is an actual loss of an electron, in an electrolytic process. There is much evidence for a free-radical mechanism, including the obtention of side products (RH, alkenes) which are characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see p. 681).

When the reaction is carried out in the presence of 1,3-dienes, additive dimerization may occur:[304]

$$2RCOO^- + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow RCH_2CH{=}CHCH_2CH_2CH{=}CHCH_2R$$

The radical $R\cdot$ adds to the conjugated system to give $RCH_2CH{=}CHCH_2\cdot$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[305]

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[300] Schut, Engberts, and Wynberg, *Synth. Commun.* **2,** 415 (1972).

[301] For a review, see Bonner and Grimm, in Kharasch and Meyers, "The Chemistry of Organic Sulfur Compounds," vol. 2, pp. 35–71, 410–413, Pergamon Press, New York, 1966.

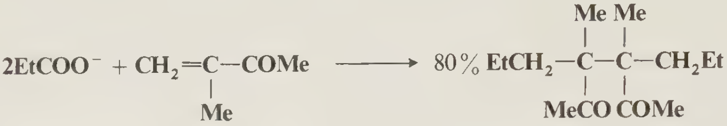
[302] Owens and Ahmberg, *Can. J. Chem.* **40,** 941 (1962).

[303] For reviews, see Gilde, *Methods Free-Radical Chem.* **3,** 1–82 (1972); Eberson, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 53–101, Interscience Publishers, New York, 1969; Svadkovskaya and Voitkevich, *Russ. Chem. Rev.* **29,** 161–180 (1960); Weedon, *Adv. Org. Chem.* **1,** 1–34 (1960); *Q. Rev., Chem. Soc.* **6,** 380–398 (1952); Vijh and Conway, *Chem. Rev.* **67,** 623–664 (1967). For a review of electrochemical reactions in general, see Eberson and Schäfer, *Fortschr. Chem. Forsch.* **21,** 1–182 (1971).

[304] Lindsey and Peterson, *J. Am. Chem. Soc.* **81,** 2073 (1959); Khrizolitova, Mirkind, and Fioshin, *J. Org. Chem. USSR* **4,** 1640 (1968); Bruno and Dubois, *Bull. Soc. Chim. Fr.* 2270 (1973).

[305] Smith and Gilde, *J. Am. Chem. Soc.* **81,** 5325 (1959), **83,** 1355 (1961); Schäfer and Pistorius, *Angew. Chem. Int. Ed. Engl.* **11,** 841 (1972) [*Angew. Chem.* **84,** 893].

Additive dimerization also takes place when the Kolbe reaction is carried out in the presence of activated monoolefins, e.g.,[306]



$$2\mathrm{EtCOO^-} + \mathrm{CH_2{=}\underset{Me}{C}{-}COMe} \longrightarrow 80\%\ \mathrm{EtCH_2{-}\overset{Me}{\underset{MeCO}{C}}{-}\overset{Me}{\underset{COMe}{C}}{-}CH_2Et}$$

OS **III**, 401; **V**, 445, 463.

4-39 Decarboxylative Bromination. The Hunsdiecker Reaction

$$\mathrm{RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr}$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction* and is a way of decreasing the length of a carbon chain by one unit.[307] The reaction is of wide scope, giving good results for normal-alkyl R from 2 to 18 carbons and for many branched R too, giving primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not α-substituted. R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used.

When iodine is the reagent, the ratio between the reactants is very important and determines the products. When a 1 : 1 ratio of salt to iodine is used, the product is the alkyl halide, as above. A 2 : 1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare esters. A 3 : 2 ratio gives both products: 1 mole of ester and 1 mole of halide from 3 moles of salt. The Simonini reaction can also be carried out with lead salts of acids.[308] A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide, instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.[309]

Other methods of accomplishing this reaction are: (1) treatment of thallium(I) carboxylates (which are easy to prepare and purify) with bromine;[310] (2) treatment of carboxylic acids with lead tetraacetate and halide *ions* ($\mathrm{Cl^-}$, $\mathrm{Br^-}$, or $\mathrm{I^-}$);[311] (3) reaction of the acids with lead tetraacetate and N-chlorosuccinimide, which gives tertiary and secondary chlorides in good yields but is not good for R = primary or phenyl;[312] and (4) the reaction between an acyl peroxide and $\mathrm{CuCl_2}$, $\mathrm{CuBr_2}$, or $\mathrm{CuI_2}$ [313] [this reaction also takes place with $\mathrm{Cu(SCN)_2}$, $\mathrm{Cu(N_3)_2}$, and $\mathrm{Cu(CN)_2}$]. The preparation of iodides has also been accomplished by treating the acid with iodine and lead tetraacetate in the presence of uv light.[314] Alkyl fluorides can be prepared in low yields by treating sodium or potassium salts of carboxylic acids with $\mathrm{F_2}$ [315]

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[306] Chkir and Lelandais, *Chem. Commun.* 1369 (1971).

[307] For reviews, see Wilson, *Org. React.* **9**, 332–388 (1957); Johnson and Ingham, *Chem. Rev.* **56**, 219–269 (1957); Sosnovsky, Ref. 66, pp. 383–386.

[308] Bachman and Wittman, *J. Org. Chem.* **28**, 65 (1963); Bachman, Kite, Tuccarbasu, and Tullman, *J. Org. Chem.* **35**, 3167 (1970).

[309] Cristol and Firth, *J. Org. Chem.* **26**, 280 (1961); Davis, Herynk, Carroll, Bunds, and Johnson, *J. Org. Chem.* **30**, 415 (1965); Bunce, *J. Org. Chem.* **37**, 664 (1972); Cason and Walba, *J. Org. Chem.* **37**, 669 (1972).

[310] McKillop, Bromley, and Taylor, *J. Org. Chem.* **34**, 1172 (1969).

[311] Kochi, *J. Am. Chem. Soc.* **87**, 2500 (1965), *J. Org. Chem.* **30**, 3265 (1965). For a review, see Sheldon and Kochi, *Org. React.* **19**, 279–421 (1972), pp. 326–334, 390–399.

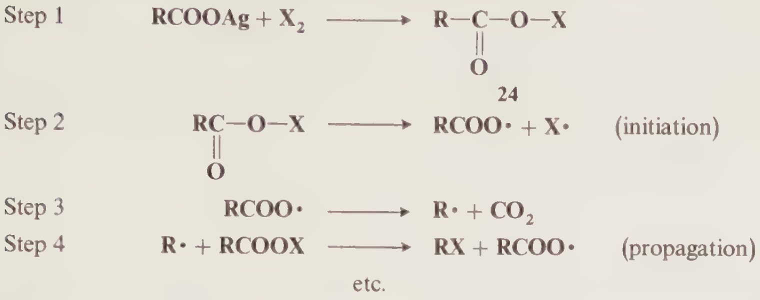
[312] Becker, Geisel, Grob, and Kuhnen, *Synthesis* 493 (1973).

[313] Jenkins and Kochi, *J. Org. Chem.* **36**, 3095, 3103 (1971).

[314] Barton, Faro, Serebryakov, and Woolsey, *J. Chem. Soc.* 2438 (1965).

[315] Grakauskas, *J. Org. Chem.* **34**, 2446 (1969).

The mechanism of the Hunsdiecker reaction is believed to be as follows:



Step 1 $\mathrm{RCOOAg + X_2 \longrightarrow R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}X}$ **24**

Step 2 $\mathrm{R\underset{\underset{\displaystyle O}{\|}}{C}{-}O{-}X \longrightarrow RCOO\cdot + X\cdot}$ (initiation)

Step 3 $\mathrm{RCOO\cdot \longrightarrow R\cdot + CO_2}$

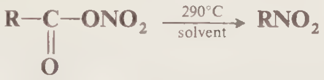
Step 4 $\mathrm{R\cdot + RCOOX \longrightarrow RX + RCOO\cdot}$ (propagation)

etc.

The first step is not a free-radical process, and its actual mechanism is not known. **24** is an acyl hypohalite and is presumed to be an intermediate, although it has never been isolated from the reaction mixture. Among the evidence for the mechanism outlined is that optical activity at R is lost (except when a neighboring bromine atom is present, see p. 625); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbonium ion; and the side products, notably R—R, are consistent with a free-radical mechanism. There is evidence that the Simonini reaction involves the same mechanism as the Hunsdiecker reaction but that the alkyl halide formed then reacts with excess RCOOAg (reaction **0-26**) to give the ester.[316] See also reaction **9-14.**

OS **III,** 578; **V,** 126; **51,** 106. See also OS **50,** 31.

4-40 Decarboxylative Nitration



$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}ONO_2 \xrightarrow[\text{solvent}]{290^\circ C} RNO_2}$$

Acyl nitrates can be smoothly decarboxylated by heating to give moderate yields of nitro compounds.[317] The reaction has been performed with R = primary, secondary, and tertiary alkyl, though only low yields have been obtained in the last case. A free-radical mechanism has been proposed, similar to that of the Hunsdiecker reaction.[317]

4-41 Decarbonylation of Aldehydes and Acyl Halides

$$\mathrm{RCHO \xrightarrow{RhCl(Ph_3P)_3} RH}$$

Aldehydes, both aliphatic and aromatic, can be decarbonylated[318] by heating with chlorotris(triphenylphosphine)rhodium[319] or other catalysts such as palladium.[320] $\mathrm{RhCl(Ph_3P)_3}$ is often called *Wilkinson's catalyst.* In an older reaction aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*t*-butyl peroxide or other peroxides,[321] usually in a solution containing a hydrogen donor, such as a mercaptan. The reaction has also been initiated with light; and thermally (without an initiator) by heating at about 500°C.

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[316] Oae, Kashiwagi, and Kozuka, *Bull. Chem. Soc. Jpn.* **39,** 2441 (1966); Bunce and Murray, *Tetrahedron* **27,** 5323 (1971).

[317] Bachman and Biermann, *J. Org. Chem.* **35,** 4229 (1970).

[318] For reviews, see Tsuji and Ohno, *Synthesis* 157–169 (1969); Bird, "Transition Metal Intermediates in Organic Synthesis," pp. 239–247, Academic Press, New York, 1967.

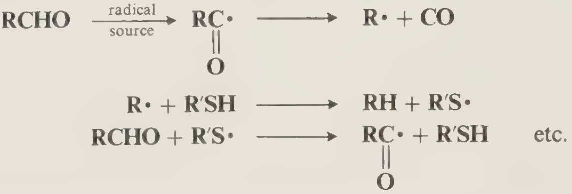
[319] Tsuji and Ohno, *Tetrahedron Lett.* 3969 (1965); Tsuji, Ohno, and Kajimoto, *Tetrahedron Lett.* 4565 (1965); Ohno and Tsuji, *J. Am. Chem. Soc.* **90,** 99 (1968); Baird, Nyman, and Wilkinson, *J. Chem. Soc. A* 348 (1968).

[320] For example, see Newman and Gill, *J. Org. Chem.* **31,** 3860 (1966); Wilt and Abegg, *J. Org. Chem.* **33,** 923 (1968). For a review, see Rylander, Ref. 170, pp. 260–267.

[321] For reviews of free-radical aldehyde decarbonylations, see Vinogradov and Nikishin, *Russ. Chem. Rev.* **40,** 916–932 (1971); Schubert and Kintner, in Patai, Ref. 138, pp. 711–735.

Wilkinson's catalyst also decarbonylates aromatic acyl halides (ArCOCl → ArCl).[322] This reaction has been carried out with acyl iodides[323] and fluorides,[324] as well as with bromides and chlorides.[322] Aliphatic acyl halides which lack an α-hydrogen also give this reaction,[325] but if an α-hydrogen is present, elimination takes place instead (see reaction **7-16**). Aromatic acyl cyanides give aryl cyanides (ArCOCN → ArCN).[326]

The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of mercaptans):[327]

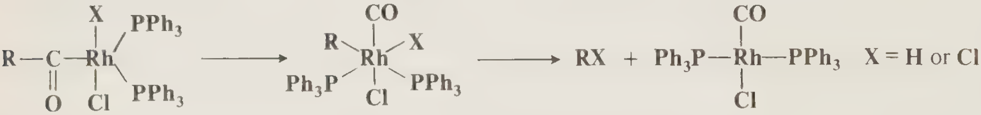


$$\mathrm{RCHO} \xrightarrow[\text{source}]{\text{radical}} \underset{\substack{\|\\ \mathrm{O}}}{\mathrm{RC}\cdot} \longrightarrow \mathrm{R}\cdot + \mathrm{CO}$$

$$\mathrm{R}\cdot + \mathrm{R'SH} \longrightarrow \mathrm{RH} + \mathrm{R'S}\cdot$$

$$\mathrm{RCHO} + \mathrm{R'S}\cdot \longrightarrow \underset{\substack{\|\\ \mathrm{O}}}{\mathrm{RC}\cdot} + \mathrm{R'SH} \qquad \text{etc.}$$

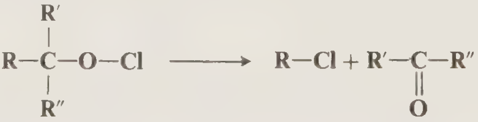
The reactions with Wilkinson's catalyst go through a complex of the form **25**, where X is H or halogen when the substrate is an aldehyde or an acyl halide, respectively. Both **25** and **26** (X = Cl)



25 **26**

have been isolated.[328] When X = H, the reaction with $\mathrm{RhCl(Ph_3P)_3}$ has been shown to give retention of configuration at a chiral R;[329] and deuterium labeling demonstrates that the reaction is intramolecular: RCOD gave RD.[330] For aldehyde decarbonylation by an electrophilic mechanism, see reaction **1-42**.

4-42 Decomposition of Tertiary Hypochlorites



$$\mathrm{R}-\overset{\substack{\mathrm{R'}\\ |}}{\underset{\substack{|\\ \mathrm{R''}}}{\mathrm{C}}}-\mathrm{O}-\mathrm{Cl} \longrightarrow \mathrm{R}-\mathrm{Cl} + \mathrm{R'}-\underset{\substack{\|\\ \mathrm{O}}}{\mathrm{C}}-\mathrm{R''}$$

When tertiary hypochlorites are heated, they spontaneously decompose to alkyl halides and ketones.[331] The reaction may be regarded as substitution at R (of $\mathrm{R_2COCl}$ by Cl). Primary and secondary hypochlorites give the reaction under much milder conditions, but the group which cleaves in these cases is always hydrogen, so that the products are HCl and an aldehyde or ketone, and the reaction is better regarded as an elimination (of HCl) rather than as a substitution. One of the R groups may be an acyl group, in which case acyl cleavage (to give an acyl halide) may take place and even predominate.[332]

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[322] Blum, *Tetrahedron Lett.* 1605 (1966); Blum, Oppenheimer, and Bergmann, *J. Am. Chem. Soc.* **89**, 2338 (1967); Tsuji and Ohno, *Tetrahedron Lett.* 4713 (1966).

[323] Blum, Rosenman, and Bergmann, *J. Org. Chem.* **33**, 1928 (1968).

[324] Olah and Kreienbühl, *J. Org. Chem.* **32**, 1614 (1967).

[325] Tsuji and Ohno, *Tetrahedron Lett.* 4713 (1966), *J. Am. Chem. Soc.* **88**, 3452 (1966).

[326] Blum, Oppenheimer, and Bergmann, Ref. 322.

[327] Slaugh, *J. Am. Chem. Soc.* **81**, 2262 (1959); Berman, Stanley, Sherman, and Cohen, *J. Am. Chem. Soc.* **85**, 4010 (1963).

[328] Ohno and Tsuji, Ref. 319; Stille and Regan, *J. Am. Chem. Soc.* **96**, 1508 (1974).

[329] Walborsky and Allen, *J. Am. Chem. Soc.* **93**, 5465 (1971); see also Tsuji and Ohno, *Tetrahedron Lett.* 2173 (1967).

[330] Prince and Raspin, *J. Chem. Soc. A* 612 (1969); Walborsky and Allen, Ref. 329.

[331] Cairns and Englund, *J. Org. Chem.* **21**, 140 (1956); Denney and Beach, *J. Org. Chem.* **24**, 108 (1959).

The mechanism has been formulated as follows:[333]

$$\begin{aligned} R_3C{-}O{-}Cl &\longrightarrow R_3C{-}O\cdot + Cl\cdot \\ R_3CO\cdot &\longrightarrow R_2C{=}O + R\cdot \\ R\cdot + R_3C{-}O{-}Cl &\longrightarrow RCl + R_3CO\cdot \end{aligned}$$

It may be noted that these three steps are exactly analogous to steps 2 to 4 of the mechanism of the Hunsdiecker reaction (**4-39**). The evidence for this mechanism is similar to that for reaction **4-39:** racemization, formation of R—R, etc.

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[332] Walsh, Witmer, McNeil, Wilcko, and Orwig, *Tetrahedron Lett.* 77 (1968).

[333] Greene, *J. Am. Chem. Soc.* **81**, 2688 (1959); Greene, Savitz, Osterholtz, Lau, Smith, and Zanet, *J. Org. Chem.* **28**, 55 (1963).

Fifteen

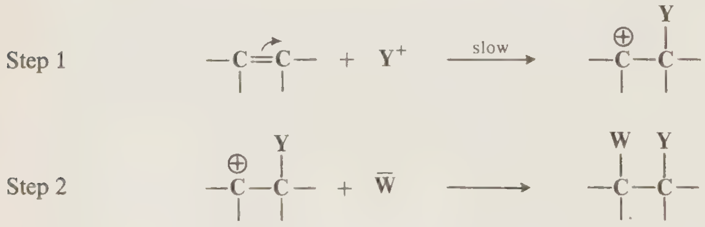
Addition to Carbon-Carbon Multiple Bonds

There are basically four ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, an electrophile, or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous. Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanisms.

MECHANISMS

Electrophilic Addition[1]

In this mechanism a positive species approaches the double or triple bond and in the first step forms a bond by converting the π pair of electrons into a σ pair:



Step 1

$$-\underset{|}{C}{=}\underset{|}{C}- \;+\; Y^+ \xrightarrow{\text{slow}} -\overset{\oplus}{\underset{|}{C}}-\overset{\overset{Y}{|}}{\underset{|}{C}}-$$

Step 2

$$-\overset{\oplus}{\underset{|}{C}}-\overset{\overset{Y}{|}}{\underset{|}{C}}- \;+\; \overline{W} \longrightarrow -\overset{\overset{W}{|}}{\underset{|}{C}}-\overset{\overset{Y}{|}}{\underset{|}{C}}-$$

1

As in electrophilic substitution (p. 454), Y need not actually be a positive ion but may be the positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. In any case, **1** has a positive charge on the other carbon. The second step, therefore, is a combination of **1** with a species carrying an electron pair and usually bearing a negative charge. This step is the same as the second step of the SN1 mechanism. There is evidence that **1** is not the actual intermediate ion in all cases. In many brominations it is fairly certain that **1**, if it is formed at all, very rapidly cyclizes to a bromonium ion (**2**):

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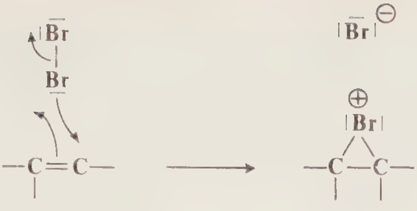
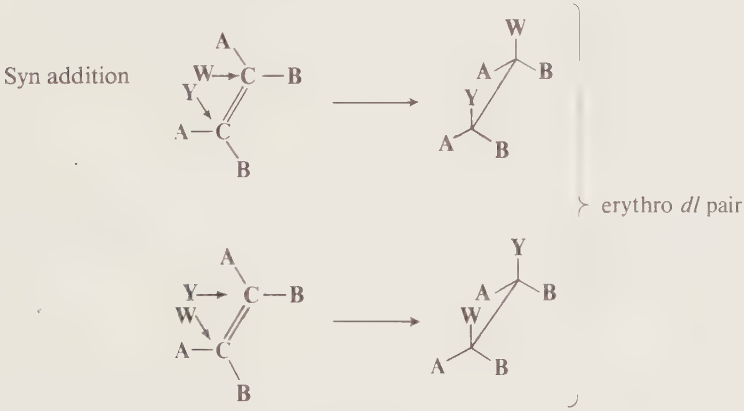
[1] For a monograph, see de la Mare and Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier Publishing Company, New York, 1966; For reviews, see Freeman, *Chem. Rev.* **75**, 439–490 (1975); Bolton, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 1–86, American Elsevier Publishing Company, Inc., New York, 1973; Dolbier, *J. Chem. Educ.* **46**, 342–344 (1969).



2

This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution, and it is likely that other potential neighboring groups (see p. 279) form similar intermediates. The attack of $\overline{W}$ on an intermediate like **2** is a nucleophilic substitution. As in the similar case of electrophilic substitution (p. 457), there has been speculation that the electrophile and the olefin might form an initial π complex,[2] which would then collapse to the open carbonium ion **1** or a cyclic intermediate like **2**. Evidence for such π complexes has been found in certain cases.[3]

In investigating the mechanism of addition to a double bond, perhaps the most useful type of information which can be obtained is the stereochemistry of the reaction.[4] The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 12), and there are thus three possibilities. Y and W may enter from the same side of the plane, in which case the addition is stereospecific and *syn*; they may enter from opposite sides for stereospecific *anti* addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the cis and trans isomers of an olefin of the form ABC=CBA. We may use the cis olefin as an example. If the addition is syn, the product will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y:



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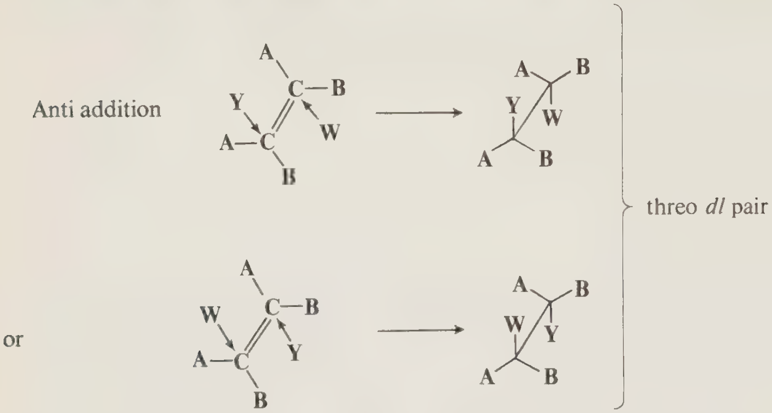
[2] For discussions, see Sergeev, Serguchev, and Smirnov, *Russ. Chem. Rev.* **42,** 697–712 (1973); Banthorpe, *Chem. Rev.* **70,** 295–322 (1970), pp. 304–308, 320–321.

[3] Olah and Hockswender, *J. Am. Chem. Soc.* **96,** 3574 (1974); Olah, Schilling, Westerman, and Lin, *J. Am. Chem. Soc.* **96,** 3581 (1974).

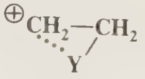
[4] For a review of the stereochemistry of electrophilic additions to double and triple bonds, see Fahey, *Top. Stereochem.* **3,** 237–342 (1968).

On the other hand, if the addition is anti, the threo *dl* pair will be formed:



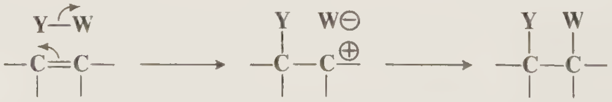
Of course, the trans isomer will give the threo pair if the addition is syn and the erythro pair if it is anti. As with the similar experiment discussed on p. 280, this experiment does not involve use of a polarimeter, and optical activity is not created, since none of the starting materials was optically active. The threo and erythro isomers have different physical properties. In the special case where Y = W (as in the addition of Br_2), the "erythro pair" becomes a meso compound. In addition to triple-bond compounds of the type AC≡CA, syn addition results in a cis olefin and anti addition in a trans olefin. By the definition given on p. 123, addition to triple bonds cannot be stereospecific, though it can be, and often is, stereoselective.

It can easily be seen that in reactions involving cyclic intermediates like **2** addition must be anti, since the second step must occur from the backside. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. On the other hand there may be some factor which maintains the configuration, in which case W may come in from the same side or from the opposite side, depending on the circumstances. For example, the carbonium ion might be stabilized by an attraction for Y which does not involve a full bond:



3

The second group would then come in anti. A circumstance which would favor syn addition would be the formation of an ion pair after the addition of Y:[5]



Since W is already on the same side of the plane as Y, collapse of the ion pair leads to syn addition. Another factor which might be responsible for anti addition is distortion of the substrate. It has been mentioned (p. 214) that ethylene, for example, in *excited* states is no longer planar. It has been suggested that anti addition may be the result of such distortion or of vibrational distortion of the substrate.[6]

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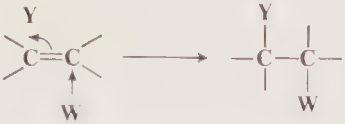
[5] Dewar, *Angew. Chem. Int. Ed. Engl.* **3**, 245–249 (1964) [*Angew. Chem.* **76**, 320–325].

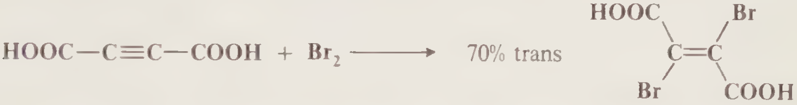
[6] Burnelle, *Tetrahedron* **20**, 2403 (1964), **21**, 49 (1965).

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially simultaneous but from opposite sides:[7]



This mechanism, which is called the Ad3 mechanism (*termolecular addition*), has the disadvantage that three molecules must come together in the transition state. However, it is the reverse of the E2 mechanism for elimination, for which the transition state is known to possess this geometry (p. 896).

There is much evidence that when the attack is by Br^+ (or a carrier of it), the bromonium ion **2** is often an intermediate, and the addition is anti. As long ago as 1912, McKenzie showed that treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, while fumaric acid (the trans isomer) gave the meso compound.[8] Many similar experiments have been performed since, with similar results. For triple bonds, stereoselective anti addition was shown even earlier. Bromination of dicarboxyacetylene gave 70% of the trans isomer:[9]



There is other evidence for mechanisms involving **2**. We have already mentioned (p. 283) that bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. Such ions have also been isolated in reactions involving addition of a Br^+ species to a double bond.[10] The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.[11] Similar results are found when the reaction is carried out in the presence of nitrate ions and of water.

However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.[12] Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90 to 100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of about 35, the addition was completely nonstereospecific.[13] Likewise in the case of triple bonds, stereoselective anti addition was found in bromination of 3-hexyne, but both cis and trans products were obtained in bromination of phenylacetylene.[14] These results indicate that a bromonium ion is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $Ph\overset{\oplus}{C}HCH_2CH_3$, which is a relatively stable benzylic cation) and that there is probably a spectrum of mechanisms between complete bromonium-ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.[15] We may recall (e.g., p. 288) that we have previously seen cases where cations required more stabilization from outside sources as they became intrinsically less stable themselves.

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[7] Hammond and Nevitt, *J. Am. Chem. Soc.* **76,** 4121 (1954); Hammond and Collins, *J. Am. Chem. Soc.* **82,** 4323 (1960); Bell and Pring, *J. Chem. Soc. B* 1119 (1966); Pincock and Yates, *J. Am. Chem. Soc.* **90,** 5643 (1968); Fahey and Lee, *J. Am. Chem. Soc.* **89,** 2780 (1967), **90,** 2124 (1968); Fahey and Monahan, *J. Am. Chem. Soc.* **92,** 2816 (1970); Fahey and McPherson, *J. Am. Chem. Soc.* **93,** 2445 (1971); Fahey, McPherson, and Smith, *J. Am. Chem. Soc.* **96,** 4534 (1974); Fahey, Payne, and Lee, *J. Org. Chem.* **39,** 1124 (1974); Pasto, Meyer, and Lepeska, *J. Am. Chem. Soc.* **96,** 1858 (1974).

[8] McKenzie, *J. Chem. Soc.* **101,** 1196 (1912).

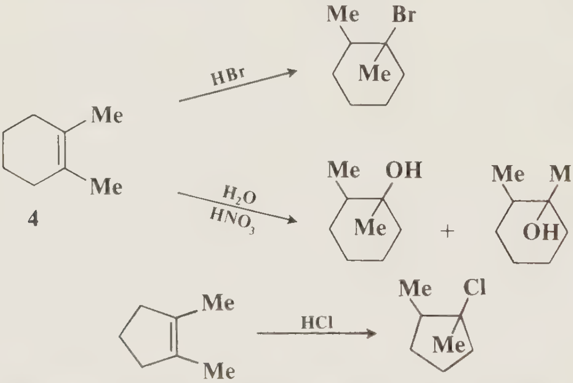
[9] Michael, *J. Prakt. Chem.* **46,** 209 (1892).

[10] Strating, Wieringa, and Wynberg, *Chem. Commun.* 907 (1969); Olah, *Angew. Chem. Int. Ed. Engl.* **12,** 173–212 (1973), p. 207 [*Angew. Chem.* **85,** 183–225].

[11] Francis, *J. Am. Chem. Soc.* **47,** 2340 (1925).

[12] Fahey and Schneider, *J. Am. Chem. Soc.* **90,** 4429 (1968). See also Rolston and Yates, *J. Am. Chem. Soc.* **91,** 1469, 1477, 1483 (1969).

For electrophilic additions in which the electrophile is not Br^+ or a carrier of it, varying results have been reported. Attack by I^+ and RS^+ usually involves cyclic intermediates[16] and hence anti addition.[17] There is evidence that iodonium ions[18] and thiiranium ions[19] are less subject to competition from open cations than bromonium ions. When the electrophile is a proton, the cyclic intermediate is not possible. Examples are known of predominant syn, anti, and non-stereoselective addition of HX. It was found that treatment of 1,2-dimethylcyclohexene (**4**) with HBr and 1,2-dimethylcyclopentene with HCl gave predominant anti addition,[20] while addition of water to **4** gave equal amounts of the cis and trans alcohols:[21]



On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant syn addition:[22]

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[13] Buckles, Bader, and Thurmaier, *J. Org. Chem.* **27**, 4523 (1962); Heublein, *J. Prakt. Chem.* [4] **31**, 84–91 (1966). See also Buckles, Miller, and Thurmaier, *J. Org. Chem.* **32**, 888 (1967); Heublein and Lauterbach, *J. Prakt. Chem.* **311**, 91 (1969); Ruasse and Dubois, *J. Am. Chem. Soc.* **97**, 1977 (1975).

[14] Pincock and Yates, *Can. J. Chem.* **48**, 3332 (1970).

[15] For other evidence for this concept, see Pincock and Yates, *Can. J. Chem.* **48**, 2944 (1970); Yates and McDonald, *J. Am. Chem. Soc.* **93**, 6297 (1971); *J. Org. Chem.* **38**, 2465 (1973); Heasley and Chamberlain, *J. Org. Chem.* **35**, 539 (1970); Dubois, Toullec, and Barbier, *Tetrahedron Lett.* 4485 (1970); Ruasse and Dubois, *J. Org. Chem.* **37**, 1770 (1972), **39**, 2441 (1974); *Tetrahedron Lett.* 4555 (1975); Dubois and Ruasse, *J. Org. Chem.* **38**, 493 (1973); Dalton and Davis, *Tetrahedron Lett.* 1057 (1972); Wilkins and Regulski, *J. Am. Chem. Soc.* **94**, 6016 (1972); Sisti and Meyers, *J. Org. Chem.* **38**, 4431 (1973); McManus and Hames, *Tetrahedron Lett.* 4549 (1973); McManus and Peterson, *Tetrahedron Lett.* 2753 (1975); Abraham and Monasterios, *J. Chem. Soc., Perkin Trans. 1* 1446 (1973); Dubois, Ruasse, and Argile, *Tetrahedron Lett.* 1713 (1976). See also McManus and Ware, *Tetrahedron Lett.* 4271 (1974).

[16] For a review of thiiranium ions as intermediates, see Mueller, *Angew. Chem. Int. Ed. Engl.* **8**, 482–492 (1969) [*Angew. Chem.* **81**, 475–484].

[17] There is evidence that Cl^+ may form cyclic intermediates: see Ref. 4, pp. 273–277.

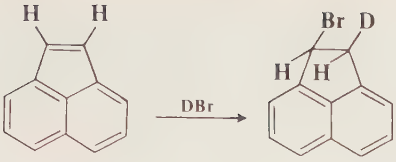
[18] Hassner, Boerwinkle, and Levy, *J. Am. Chem. Soc.* **92**, 4879 (1970).

[19] Schmid, Csizmadia, Nowlan, and Garratt, *Can. J. Chem.* **50**, 2457 (1972).

[20] Hammond and Nevitt, Ref. 7; Hammond and Collins, Ref. 7. See also Pasto, Meyer, and Kang, *J. Am. Chem. Soc.* **91**, 2162 (1969); Fahey and Monahan, Ref. 7; Pasto, Meyer, and Lepeska, Ref. 7.

[21] Collins and Hammond, *J. Org. Chem.* **25**, 911 (1960).

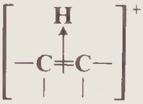
[22] Dewar and Fahey, *J. Am. Chem. Soc.* **85**, 2245, 2248 (1963). For a review of syn addition of HX, see Ref. 5.



5

In fact it has been shown that the stereoselectivity of HCl addition can be controlled by changing the reaction conditions. Addition of HCl to **4** in CH_2Cl_2 at −98°C gave predominantly syn addition, while in ethyl ether at 0°C, the addition was mostly anti.[23]

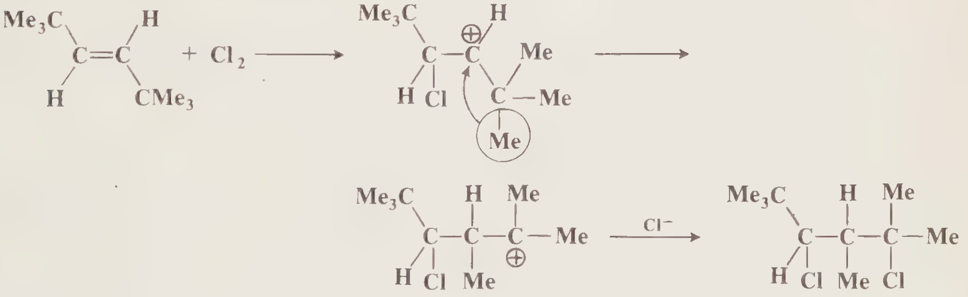
In order to explain anti addition when the attack is by a proton, an initial complex[2] of the form



$$\left[-\overset{\overset{\displaystyle H}{\uparrow}}{C{=}C}- \right]^{+}$$

has been invoked, followed by rate-determining formation of an open cation.[24] However, there is much evidence against this concept,[25] including the fact that the addition of H^+ to double bonds is general-acid- and not specific-acid-catalyzed, implying rate-determining proton transfer from the acid to the double bond (p. 236). If there is a free carbonium-ion intermediate in additions of H_2O, it cannot be reversibly formed, since unreacted olefin recovered after treatment with D_2SO_4 contained no (or very little) deuterium.[26] This has led some investigators to doubt that a free carbonium ion is involved in hydrations.[26]

However, in order to show that free carbonium intermediates are formed in at least some reactions, we may cite the result of treatment of *trans*-1,2-di-*t*-butylethylene with chlorine. The product was not the simple addition product expected, but **6**, which arose by rearrangement of the carbonium ion initially formed:[27]



6

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[23] Becker and Grob, *Synthesis* 789 (1973); see also Marcuzzi, Melloni, and Modena, *Tetrahedron Lett.* 413 (1974).

[24] Purlee and Taft, *J. Am. Chem. Soc.* **78,** 5807 (1956).

[25] See Baliga and Whalley, *Can. J. Chem.* **42,** 1019 (1964), **43,** 2453 (1965); Kresge and Chiang, *J. Chem. Soc. B* 53 (1967); Kresge, Chiang, Fitzgerald, McDonald, and Schmid, *J. Am. Chem. Soc.* **93,** 4907 (1971); Loudon and Noyce, *J. Am. Chem. Soc.* **91,** 1433 (1969); Corriu and Guenzet, *Tetrahedron* **26,** 671 (1970); Takaya, Todo, Hosoya, and Minegishi, *Bull. Chem. Soc. Jpn.* **44,** 1175, 1179 (1971); Schubert and Keeffe, *J. Am. Chem. Soc.* **94,** 559 (1972); Simandoux, Torck, Hellin, and Coussemant, *Bull. Soc. Chim. Fr.* 4402, 4410 (1972); Bernasconi and Boyle, *J. Am. Chem. Soc.* **96,** 6070 (1974).

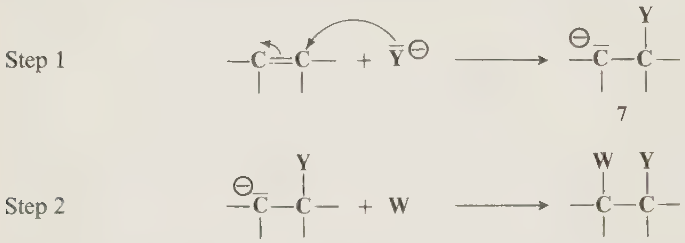
[26] Deno, Kish, and Peterson, *J. Am. Chem. Soc.* **87,** 2157 (1965).

[27] Puterbaugh and Newman, *J. Am. Chem. Soc.* **81,** 1611 (1959). For other rearrangements accompanying electrophilic addition, see Fahey, *J. Am. Chem. Soc.* **88,** 4681 (1966); Fahey and McPherson, *J. Am. Chem. Soc.* **91,** 3865 (1969); Norman and Thomas, *J. Chem. Soc. B* 598 (1967); Bilke, Collin, Duschek, Höbold, Höhn, Pritzkow, Schmidt, and Schnurpfeil, *J. Prakt. Chem.* **311,** 1037 (1969); Bundel', Ryabtsev, Sorokin, and Reutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1311 (1969); Pocker and Stevens, *J. Am. Chem. Soc.* **91,** 4205 (1969).

In all these cases (except for the Ad3 mechanisms) we have assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate is rapid, and this is probably true in most cases. However, some additions have been found in which the second step is rate-determining.[28]

Nucleophilic Addition[29]

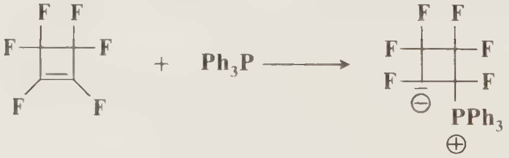
In the first step of nucleophilic addition a nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, forcing the π electrons to become centered on the other carbon, creating a carbanion. The second step is combination of this carbanion with a positive species:



7

This mechanism is the same as the simple electrophilic one shown on page 672 except that the charges are reversed. When the olefin contains a good leaving group (as defined for nucleophilic substitution, p. 325), substitution is a side reaction (this is nucleophilic substitution at a vinyl substrate, see p. 311). There are at least five other types of side reactions which intermediates like **7** can undergo.[30]

In certain cases the intermediate carbanion **7** has been isolated. An example is the betaine **8**,



8

which was isolated as a white solid when perfluorocyclobutene was treated with triphenylphosphine.[31] In this case, **8** could not undergo the normal step 2 because no electrophile was available.

In the special case of addition of HY to a substrate of the form $-\underset{|}{C}=\underset{|}{C}-Z$, where Z = CHO, COR (including quinones[32]), COOR, $CONH_2$, CN, NO_2, SOR, SO_2R, etc., addition nearly always follows a nucleophilic mechanism, with Y^- bonding with the carbon *away* from the Z group, e.g.,

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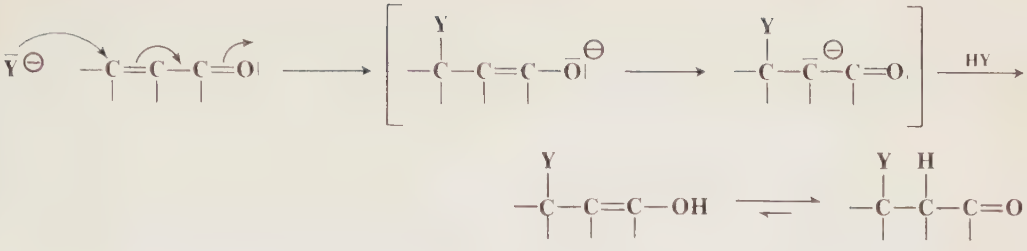
[28] See for example, Rau, Alcais, and Dubois, *Bull. Soc. Chim. Fr.* 3336 (1972); Bellucci, Berti, Ingrosso, and Mastrorilli, *Tetrahedron Lett.* 3911 (1973).

[29] For a review, see Patai and Rappoport, in Patai, "The Chemistry of Alkenes," vol. 1, pp. 469–584, Interscience Publishers, New York, 1964.

[30] Patai and Rappoport, *J. Chem. Soc.* 377, 383, 392, 396 (1962); Ref. 29.

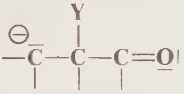
[31] Stockel, Megson, and Beachem, *J. Org. Chem.* **33**, 4395 (1968). See also Farrell, Newton, and White, *J. Chem. Soc. B* 637 (1967); Fyfe, *Can. J. Chem.* **47**, 2331 (1969).

[32] For a review of addition reactions of quinones, see Finley, in Patai, "The Chemistry of the Quinonoid Compounds," pt. 2, pp. 877–1144, John Wiley & Sons, Inc., New York, 1974.



9

Protonation of the enolate ion is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol **9**, which tautomerizes. So although the net result of the reaction is addition to a carbon-carbon double bond, the *mechanism* is 1,4 nucleophilic addition to the C=C—C=O (or similar) system and is thus very similar to the mechanism of addition to carbon-oxygen double and similar bonds (see Chapter 16). When Z is CN or a C=O group, it is also possible for Y to attack at *this* carbon, and this reaction sometimes competes. When it happens, it is called 1,2 addition. 1,4 addition to these substrates is also known as *conjugate addition.* Y^- never attacks at the 3 position, since the resulting carbanion would have no resonance stabilization:



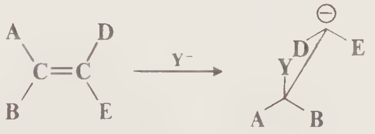
$$-\overset{\ominus}{\underline{C}}-\overset{Y}{C}-C{=}\underline{O}|$$

Perhaps the most important substrate of this type is acrylonitrile, and 1,4 addition to it is called *cyanoethylation* because the Y is cyanoethylated:[33]

$$H_2C{=}CH{-}CN + HY \longrightarrow Y{-}CH_2{-}CH_2{-}CN$$

With any substrate, when Y is an ion of the type $Z{-}\overset{\ominus}{\bar{C}}R_2$ (Z is as defined above; R may be alkyl, aryl, hydrogen, or another Z), the reaction is called the *Michael reaction* (see reaction **5-1**). In this book we shall call all other reactions which follow this mechanism *Michael-type additions.* Systems of the type C=C—C=C—Z may give 1,2, 1,4, or 1,6 addition.[34] Even 1,8 addition has been found with suitable substrates. Michael-type reactions are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to YH and $CH_2{=}CHZ$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on p. 678, the addition should be nonstereospecific, though it might well be stereoselective (see p. 123 for the distinction). For example, the cis and trans forms of an olefin ABC=CDE would give, respectively, **10** and **11**:



10

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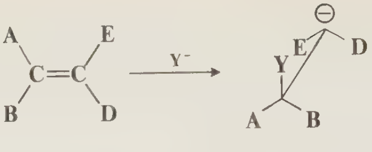
[33] For a review of cyanoethylations, see Bruson, *Org. React.* **5**, 79–135 (1949). For a review of cyanoethylations with compounds from which acrylonitrile is generated in situ, e.g., $ClCH_2CH_2CN$, and of the reverse of cyanoethylation (decyanoethylation), see Butskus, *Russ. Chem. Rev.* **30**, 583–598 (1961).

[34] For a review of 1,6 Michael-type additions, see Ralls, *Chem. Rev.* **59**, 329–344 (1959).



11

If the carbanion has even a short lifetime, **10** and **11** will assume the most favorable conformation before the attack of W. This is of course the same for both of them, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the cis and trans isomers do not give rise to different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain olefins. Except for Michael-type substrates, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the cis isomer exists. In these cases the reaction has been shown to be stereoselective, with syn addition reported in some cases[35] and anti addition in others.[36] When the reaction is performed on a Michael-type substrate, C=C—Z, the hydrogen does not arrive at the carbon directly but only through a tautomeric equilibrium. The product will naturally assume the most thermodynamically stable configuration, without relation to the direction of original attack of Y. For obvious reasons, additions to triple bonds cannot be stereospecific.[37] As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and anti,[38] though syn addition[39] and non-stereoselective addition[40] have also been reported.

Free-Radical Addition[41]

The mechanism of free-radical addition follows the pattern discussed in Chapter 14 (pp. 619–620). A radical is generated by

$$\mathrm{YW} \xrightarrow[\text{dissociation}]{h\nu \text{ or spontaneous}} \mathrm{Y}\cdot + \mathrm{W}\cdot$$

or

$$\mathrm{R}\cdot \text{ (from some other source)} + \mathrm{YW} \longrightarrow \mathrm{RW} + \mathrm{Y}\cdot$$

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[35] For example, Truce and Levy, *J. Org. Chem.* **28,** 679 (1963).

[36] For example, Truce and Levy, *J. Am. Chem. Soc.* **83,** 4641 (1961); Zefirov, Yur'ev, Prikazchikova, and Bykhovskaya, *J. Gen. Chem. USSR* **33,** 2100 (1963).

[37] For a review of nucleophilic addition to triple bonds, see Miller and Tanaka, *Sel. Org. Transform.* **1,** 143–238 (1970).

[38] Truce, Boudakian, Heine, and McManimie, *J. Am. Chem. Soc.* **78,** 2743 (1956); Truce and Simms, *J. Am. Chem. Soc.* **78,** 2756 (1956); Shostakovskii, Chekulaeva, Kondrat'eva, and Lopatin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2118 (1962); Théron and Vessière, *Bull. Soc. Chim. Fr.* 2994 (1968); Bowden and Price, *J. Chem. Soc. B* 1466, 1472 (1970); Raunio and Frey, *J. Org. Chem.* **36,** 345 (1971); Truce and Tichenor, *J. Org. Chem.* **37,** 2391 (1972).

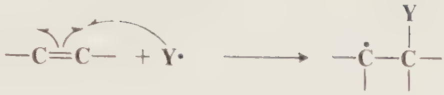
[39] Truce, Goldhamer, and Kruse, *J. Am. Chem. Soc.* **81,** 4931 (1959); Truce and Heine, *J. Am. Chem. Soc.* **79,** 5311 (1957); Dolfini, *J. Org. Chem.* **30,** 1298 (1965); Winterfeldt and Preuss, *Chem. Ber.* **99,** 450 (1966).

[40] Gracheva, Laba, Kul'bovskaya, and Shostakovskii, *J. Gen. Chem. USSR* **33,** 2431 (1963); Truce and Brady, *J. Org. Chem.* **31,** 3543 (1966); Prilezhaeva, Vasil'ev, Mikhaleshvili, and Bogdanov, *Bull. Acad. Sci., USSR, Div. Chem. Sci.* 1820 (1970).

[41] For monographs on this subject, see Huyser, "Free-Radical Chain Reactions," Interscience Publishers, New York, 1970; Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," The Macmillan Company, New York, 1964. Other books with much of interest in this field are Nonhebel and Walton, "Free-Radical Chemistry," Cambridge University Press, London, 1974; Pryor, "Free Radicals," McGraw-Hill Book Company, New York, 1965; Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, 1957. For reviews, see Minisci, *Acc. Chem. Res.* **8,** 165–171 (1975); Davies, *MTP Int. Rev. Sci.: Org. Chem., Ser. One,* **10,** 49–70 (1973); Elad, *Org. Photochem.* **2,** 168–212 (1969); Schönberg, "Preparative Organic Photochemistry," pp. 155–181, Springer-Verlag, New York, 1968; Walling and Huyser, *Org. React.* **13,** 91–149 (1963); Stacey and Harris, *Org. React.* **13,** 150–376 (1963); Cadogan and Hey, *Q. Rev., Chem. Soc.* **8,** 308–329 (1954); Cadogan and Perkins, in Patai, Ref. 29, pp. 585–632.

Propagation then occurs by

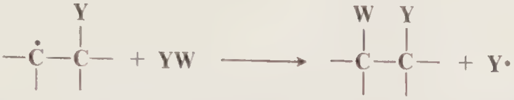
Step 1



$$-C{=}C- + Y\cdot \longrightarrow -\overset{\bullet}{C}-\overset{Y}{C}-$$

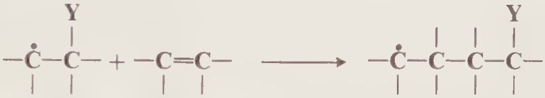
12

Step 2



$$-\overset{\bullet}{C}-\overset{Y}{C}- + YW \longrightarrow -\overset{W}{C}-\overset{Y}{C}- + Y\cdot$$

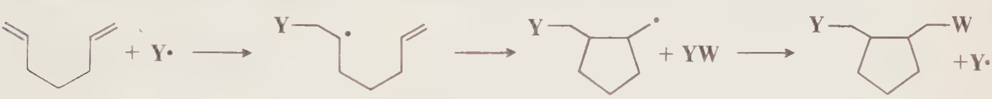
Step 2 is an abstraction, so that W is nearly always univalent, either hydrogen or halogen (p. 625). Termination of the chain may occur in any of the ways discussed in Chapter 14. If **12** adds to another olefin molecule,



$$-\overset{\bullet}{C}-\overset{Y}{C}- + -C{=}C- \longrightarrow -\overset{\bullet}{C}-C-C-\overset{Y}{C}-$$

a dimer is formed. This may now add to still another, and chains, long or short, may be built up. This is the mechanism of free-radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical can add intramolecularly to the other double bond, leading to a cyclic product, e.g.,[42]



13

Free radicals of the type **13**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions (see p. 689).

The free-radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **12** has any but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on p. 680.[43] Many free-radical additions have been found to be stereoselective, though not all. For example, addition of HBr to 1-bromocyclohexene gave only *cis*-1,2-dibromocyclohexane and none of the trans isomer (anti addition),[44] and propyne (at −78 to −60°C) gave only *cis*-1-bromopropene (anti addition).[45] However, stereospecificity has been found only in a few cases. The most important of these is addition of HBr to 2-bromo-2-butene under free-radical conditions at −80°C. Under these conditions, the cis isomer gave 92% of the meso addend, while the trans isomer gave mostly the *dl* pair.[46] This stereospecificity disappeared at room temperature, where both olefins gave the same mixture of products (about 78% of the *dl* pair and 22% of the meso compound), so that the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned on p. 624:

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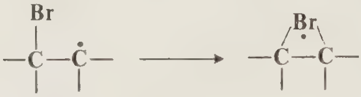
[42] For reviews of these and other free-radical cyclization reactions, see Julia, *Acc. Chem. Res.* **4**, 386–392 (1972), *Pure Appl. Chem.* **40**, 553–567 (1974), **15**, 167–183 (1967), *Rec. Chem. Prog.* **25**, 3–29 (1964); Nonhebel and Walton, Ref. 41, pp. 533–544; Wilt, in Kochi, "Free Radicals," vol. 1, pp. 418–446, John Wiley & Sons, Inc., New York, 1973.

[43] For a review of the stereochemistry of free-radical addition, see Bohm and Abell, *Chem. Rev.* **62**, 599–609 (1962).

[44] Goering, Abell, and Aycock, *J. Am. Chem. Soc.* **74**, 3588 (1952). See also LeBel, Czaja, and DeBoer, *J. Org. Chem.* **34**, 3112 (1969).

[45] Skell and Allen, *J. Am. Chem. Soc.* **80**, 5997 (1958).

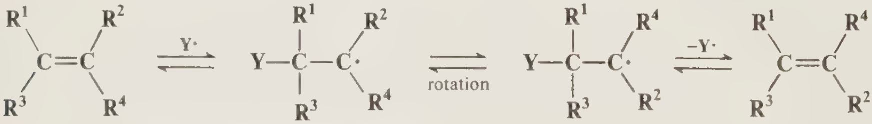
[46] Goering and Larsen, *J. Am. Chem. Soc.* **79**, 2653 (1957), **81**, 5937 (1959). Also see Skell and Allen, *J. Am. Chem. Soc.* **81**, 5383 (1959); Skell and Freeman, *J. Org. Chem.* **29**, 2524 (1964).



This species is similar to the bromonium ion, which is responsible for stereospecific anti addition in the electrophilic mechanism (p. 673). Further evidence for the existence of such bridged radicals was obtained by addition of Br• to olefins at 77 K. Esr spectra of the resulting species were consistent with bridged structures.[47] There is evidence that iodine may form similar bridges: free-radical addition of I_2 at $-42°C$ is stereospecific and anti.[48] However, addition of RSH to olefins, even at $-78°C$, is not stereospecific though it is stereoselective.[49]

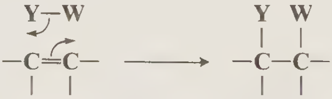
As mentioned previously, anti addition of HBr to triple bonds occurs at -78 to $-60°C$.[45] However, at room temperature this reaction, whether conducted in the liquid or in the vapor phase, is nonstereoselective. It has been shown that this is only apparent: the reaction is still stereoselective, but isomerization occurs after the initial product is formed.[50] Stereoselective syn addition has been demonstrated in the reaction between 1-bromopropyne and HBr.[51]

For many radicals step 1 (C=C + Y• → •C—C—Y) is reversible. In such cases free radicals can cause cis → trans isomerization of a double bond by the pathway[52] (see also p. 534)



Cyclic Mechanisms

There are some addition reactions where the initial attack is not at one carbon of the double bond, but both carbons are attacked simultaneously. Some of these are four-center mechanisms, which follow this pattern:



In others there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be syn. The most important reaction of this type is the Diels-Alder reaction (**5-51**).

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[47] Abell and Piette, *J. Am. Chem. Soc.* **84,** 916 (1962). See also Leggett, Kennerly, and Kohl, *J. Chem. Phys.* **60,** 3264 (1974).

[48] Skell and Pavlis, *J. Am. Chem. Soc.* **86,** 2965 (1964). The conclusion that iodine forms such bridges has been disputed by Benson, Golden, and Egger [*J. Chem. Phys.* **42,** 4265 (1965)], who hold that addition of I_2 is concerted.

[49] Skell and Allen, *J. Am. Chem. Soc.* **82,** 1511 (1960); Neureiter and Bordwell, *J. Am. Chem. Soc.* **82,** 5354 (1960).

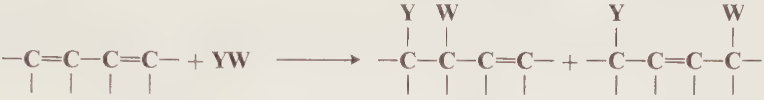
[50] Skell and Allen, *J. Am. Chem. Soc.* **86,** 1559 (1964).

[51] Bergel'son, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1145 (1960).

[52] Benson, Egger, and Golden, *J. Am. Chem. Soc.* **87,** 468 (1965); Golden, Furuyama, and Benson, *Int. J. Chem. Kinet.* **1,** 57 (1969).

Addition to Conjugated Systems

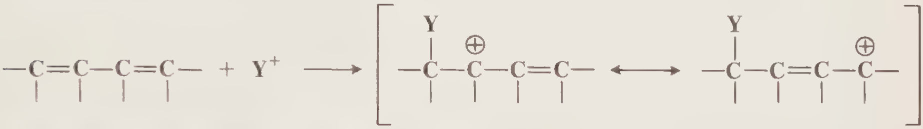
When electrophilic addition is carried out on a compound which has two double bonds in conjugation, a 1,2-addition product (**14**) is often obtained, but in most cases there is also a 1,4-addition product (**15**), often in much larger yield:



$$-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=\underset{|}{C}- + YW \longrightarrow -\underset{|}{\overset{Y}{C}}-\underset{|}{\overset{W}{C}}-\underset{|}{C}=\underset{|}{C}- + -\underset{|}{\overset{Y}{C}}-\underset{|}{C}=\underset{|}{C}-\underset{|}{\overset{W}{C}}-$$

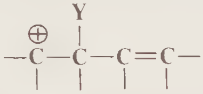
14 **15**

If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbonium ion resulting from attack by Y^+ is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



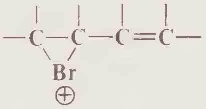
$$-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=\underset{|}{C}- + Y^+ \longrightarrow \left[-\underset{|}{\overset{Y}{C}}-\underset{|}{\overset{\oplus}{C}}-\underset{|}{C}=\underset{|}{C}- \longleftrightarrow -\underset{|}{\overset{Y}{C}}-\underset{|}{C}=\underset{|}{C}-\underset{|}{\overset{\oplus}{C}}-\right]$$

W^- may then attack either position. The original attack of Y^+ is always at the end of the conjugated system because an attack at a middle carbon would give a carbonium ion unstabilized by resonance:

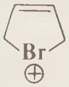


$$-\underset{|}{\overset{\oplus}{C}}-\underset{|}{\overset{Y}{C}}-\underset{|}{C}=\underset{|}{C}-$$

In the case of electrophiles like Br^+, which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an intermediate like **16**. Direct nucleophilic attack by W^- would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an SN2′-type mechanism (see p. 304). Intermediates like **17** have been postulated but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4-products.[53] If an ion like **17** were the intermediate, the 1,4-products would have to have the cis configuration.



16



17

In most cases more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic. In most cases, under the reaction conditions, **14** is converted to a mixture of **14** and **15** which is richer in **15**. That is, either isomer gives the same mixture of both, which contains more **15**. It was found that at low temperatures, butadiene and HCl gave only 20 to 25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4 product.[54]

Another aspect of the stereochemistry of 1,4 addition, besides the configuration (cis or trans) of the new double bond, is the question of whether the groups Y and W both come in from the same side of the plane (of the conjugated system) or from opposite sides. This can be determined only for dienes of the type XZC=CR—CR=CUV (where X can be the same as U and Z can be the same as V but X ≠ Z and U ≠ V). Electrophilic bromination and chlorination of such systems has shown that the addition is primarily syn, with both bromines or chlorines entering mostly from the same side of the plane.[55]

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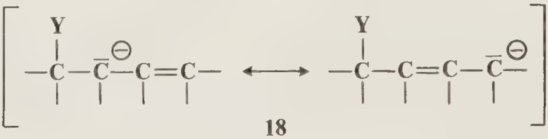
[53] Mislow and Hellman, *J. Am. Chem. Soc.* **73,** 244 (1951); Mislow, *J. Am. Chem. Soc.* **75,** 2512 (1953).

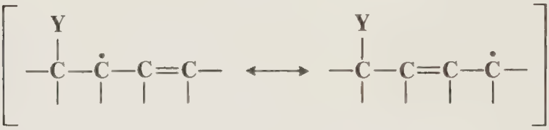
[54] Kharasch, Kritchevsky, and Mayo, *J. Org. Chem.* **2,** 489 (1938).

Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case there is a competition between 1,2 and 1,4 addition. In the case of nucleophilic or free-radical attack,[56] the intermediates (**18** and **19**) are resonance hybrids and behave like the intermediate from electrophilic attack. Dienes may give 1,4 addition by a cyclic mechanism in this way:



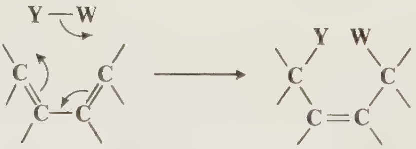
$$\left[-\underset{|}{\overset{\overset{\displaystyle Y}{|}}{C}}-\underset{|}{\overset{\ominus}{\bar{C}}}-\underset{|}{C}=\underset{|}{C}- \longleftrightarrow -\underset{|}{\overset{\overset{\displaystyle Y}{|}}{C}}-\underset{|}{C}=\underset{|}{C}-\underset{|}{\overset{\ominus}{\bar{C}}}-\right]$$

18

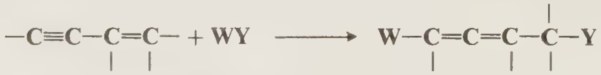


$$\left[-\underset{|}{\overset{\overset{\displaystyle Y}{|}}{C}}-\underset{|}{\dot{C}}-\underset{|}{C}=\underset{|}{C}- \longleftrightarrow -\underset{|}{\overset{\overset{\displaystyle Y}{|}}{C}}-\underset{|}{C}=\underset{|}{C}-\underset{|}{\dot{C}}-\right]$$

19



Other conjugated systems, including trienes, enynes, diynes, etc., have been studied much less but behave similarly.[57] 1,4 addition to enynes is an important way of making allenes:[58]



$$-C\equiv C-\underset{|}{C}=\underset{|}{C}- + WY \longrightarrow W-\underset{|}{C}=C=\underset{|}{C}-\underset{|}{\overset{|}{C}}-Y$$

ORIENTATION AND REACTIVITY

Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition, and electron-withdrawing groups decrease it. This is illustrated in Tables 1 and 2.[59] As a further illustration it may be

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[55] Heasley, Heasley, Manatt, Day, Hodges, Kroon, Redfield, Rold, and Williamson, *J. Org. Chem.* **38,** 4109 (1973); Heasley, Hayse, McClung, Strickland, Heasley, Davis, Ingle, Rold, and Ungermann, *J. Org. Chem.* **41,** 334 (1976).

[56] For a review of free-radical addition to conjugated dienes, see Afanas'ev and Samokhvalov, *Russ. Chem. Rev.* **38,** 318–329 (1969).

[57] For reviews of addition to conjugated enynes, see Petrov, *Russ. Chem. Rev.* **29,** 489–509 (1960); Taylor, *Chem. Rev.* **67,** 317–359 (1967), pp. 329–331.

[58] For a discussion, see Sandler and Karo, "Organic Functional Group Preparations," vol. 2, pp. 31–34, Academic Press, Inc., New York, 1971.

[59] Table 1 is from de la Mare, *Q. Rev., Chem. Soc.* **3,** 126–145 (1949), p. 145. Table 2 is from Dubois and Mouvier, *Tetrahedron Lett.* 1325 (1963).

TABLE 1 Relative reactivity of some olefins toward bromine in acetic acid at 24°C[59]

Olefin	Relative rate
$PhCH{=}CH_2$	Very fast
$PhCH{=}CHPh$	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
$PhCH{=}CHBr$	0.11
$CH_2{=}CHBr$	0.0011

TABLE 2 Relative reactivity of some olefins toward bromine in methanol[59]

Olefin	Relative rate
$CH_2{=}CH_2$	3.0×10
$CH_3CH_2CH{=}CH_2$	2.9×10^3
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

mentioned that the reactivity toward electrophilic addition of a group of olefins increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[60] For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $F_2C{=}CF_2$[61] and $(NC)_2C{=}C(CN)_2$.[62] The effect of substituents is so great that it is possible to make the statement that *simple olefins do not react by the nucleophilic mechanism and polyhalo or polycyano olefins do not generally react by the electrophilic mechanism.*[63] There are some reagents which attack only as nucleophiles, e.g., ammonia, and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $F_2C{=}CF_2$ does not react with these. In still other cases, the same reagent reacts with a simple olefin by the electrophilic mechanism and with a polyhalo olefin by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(NC)_2C{=}CHCN$ with an initial attack by Cl^- [64] and that HF adds to $F_2C{=}CClF$ with an initial attack by F^-.[65] Compounds which have a double bond conjugated with a Z group (as defined on p. 678) nearly always react by a nucleophilic mechanism. These are actually 1,4 additions, as discussed on p. 679. A number of studies have been made of the relative activating abilities of various Z groups.[66] On the basis of these studies, the following order of decreasing activating ability has been suggested: Z = NO_2, COAr, CHO, COR, SO_2Ar, CN, COOR, SOAr, $CONH_2$, CONHR.[67] When Michael-type reactions are performed on ZCH=CHZ′, then, in general, the more activating Z controls the position of attack[68] so that, for example, PhCOCH=CHCN is attacked at the carbon adjacent to the CN.[69] However, exceptions are known.

It seems obvious that electron-withdrawing groups enhance nucleophilic substitution and inhibit electrophilic substitution because they lower the electron density of the double bond. This is probably true, and yet similar reasoning does not apply to a comparison between double and triple bonds.[70] There is a higher concentration of electrons between the carbons of a triple bond than there is in a double bond, and yet triple bonds are *less* subject to electrophilic attack and *more* subject to nucleophilic attack than double bonds.[71] This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds to the double bond.[72] On the other hand, addition of hydrogen halides gives results that are far from simple. In some cases (both conjugated and nonconjugated) the electrophilic H^+ predominantly attacks the double bond and in other cases the triple bond.[73] Which bond is attacked seems to depend on the state of alkylation. When the triple bond is of the form $HC{\equiv}C{-}$, it is the bond exclusively or predominantly attacked by H^+, but internal triple bonds are not so preferred. With conjugated enynes mixtures are commonly obtained. Thus bromination of vinylacetylene gives all possible dibromides.[72] The relative reactivity of double and triple bonds also depends on the solvent. It has been shown that in the gas phase and in nonpolar solvents, double bonds are far more reactive toward bromine than triple bonds (rate ratios were about 10^5), but in water the differences disappeared and the rates were about equal.[74]

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[60] Shelton and Lee, *J. Org. Chem.* **25**, 428 (1960).

[61] For a review of additions to $F_2C{=}CF_2$ and other fluoroolefins, see Chambers and Mobbs, *Adv. Fluorine Chem.* **4**, 51–112 (1965).

[62] For reviews at tetracyanoethylene, see Dhar, *Chem. Rev.* **67**, 611–622 (1967); Cairns and McKusick, *Angew. Chem.* **73**, 520–525 (1961).

[63] Such reactions can take place under severe conditions. For example electrophilic addition could be accomplished with $F_2C{=}CHF$ in super-acid solutions [Olah and Mo, *J. Org. Chem.* **37**, 1028 (1972)] although $F_2C{=}CF_2$ did not react under these conditions. For reviews of electrophilic additions to fluoroolefins, see Dyatkin, Mochalina, and Knunyants, *Russ. Chem. Rev.* **35**, 417–427 (1966), *Fluorine Chem. Rev.* **3**, 45–71 (1969); Ref. 61, pp. 77–81.

[64] Dickinson, Wiley, and McKusick, *J. Am. Chem. Soc.* **82**, 6132 (1960).

[65] Miller, Fried, and Goldwhite, *J. Am. Chem. Soc.* **82**, 3091 (1960).

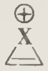
[66] See, for example, Friedman and Wall, *J. Org. Chem.* **31**, 2888 (1966); Ring, Tesoro, and Moore, *J. Org. Chem.* **32**, 1091 (1967).

[67] Shenhav, Rappoport, and Patai, *J. Chem. Soc. B* 469 (1970).

[68] For a review, see Nesmeyanov, Rybinskaya, and Rybin, *Russ. Chem. Rev.* **36**, 453–467 (1967).

[69] Nesmeyanov, Rybinskaya, and Rybin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2013 (1961).

Still, it is true that in general triple bonds are more susceptible to nucleophilic and less to electrophilic attack than double bonds, in spite of their higher electron density. One explanation for this is that the electrons in the triple bond are held more tightly because of the smaller carbon-carbon distance, and it is thus harder for an attacking electrophile to pull out a pair. There is evidence from far-uv spectra to support this conclusion.[75] Another possible explanation lies in the fact that addition of an electrophile to a carbon-carbon triple bond gives a vinyl cation, and vinyl cations are somewhat less stable than the corresponding secondary alkyl cations[76] (p. 157). On the other hand, addition of a nucleophile gives a vinyl anion, and these are more stable than the corresponding alkyl anions. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**20**) are more strained than the corresponding **21** and furthermore are antiaromatic systems (see p. 55), which **21** are not. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, etc., is slower for triple than for double bonds.[77] As might be expected, triple bonds connected to a Z group ($C{\equiv}C{-}Z$) undergo nucleophilic addition especially well.[78]



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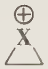

21

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[70] For reviews of ionic and free-radical additions to triple bonds, in Viehe, "Acetylenes," Marcel Dekker, Inc., New York, 1969, see, respectively, the articles by Winterfeldt, pp. 267–334, and Julia, pp. 335–354.

[71] For discussions of this, see Bohlmann, *Angew. Chem.* **69**, 82 (1957); Miller, *J. Org. Chem.* **21**, 247 (1956); Daniels and Bauer, *J. Chem. Educ.* **35**, 444 (1958).

[72] Petrov, *Russ. Chem. Rev.* **29**, 489–509 (1960).

[73] Petrov and Porfir'eva, *J. Gen. Chem. USSR* **33**, 3142 (1963).

[74] Yates, Schmid, Regulski, Garratt, Leung, and McDonald, *J. Am. Chem. Soc.* **95**, 160 (1973).

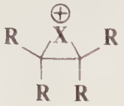
[75] Walsh, *Q. Rev., Chem. Soc.* **2**, 73–91 (1948).

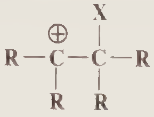
[76] For reviews of vinyl cations formed by addition of electrophiles to triple bonds and to allenes, see Stang, *Prog. Phys. Org. Chem.* **10**, 205–325 (1973); Modena and Tonellato, *Adv. Phys. Org. Chem.* **9**, 185–280 (1971), pp. 187–231; Richey and Richey, in Olah and Schleyer, "Carbonium Ions," vol. 2, pp. 906–922, Interscience Publishers, New York, 1970.

[77] Nevertheless, bridged ions **20** have been implicated in some additions to triple bonds. See, for example, Pincock and Yates, Ref. 14; Mauger and Berliner, *J. Am. Chem. Soc.* **94**, 194 (1972); Bassi and Tonellato, *J. Chem. Soc., Perkin Trans. 1* 669 (1973).

[78] For a review of additions to these substrates, see Winterfeldt, *Angew. Chem. Int. Ed. Engl.* **6**, 423–434 (1967) [*Angew. Chem.* **79**, 389–400], *Newer Methods Prep. Org. Chem.* **6**, 243–279 (1971).

Although alkyl groups in general increase the rates of electrophilic addition, there is a different pattern depending on whether the intermediate is a bridged ion or an open carbonium ion.[79] In the former case substitution of alkyl groups on $H_2C{=}CH_2$ causes a cumulative rate acceleration





$$R-\overset{\oplus}{\underset{R}{C}}-\overset{X}{\underset{R}{C}}-R$$

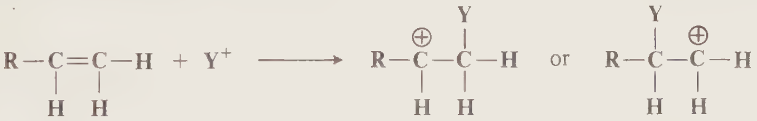
until all four hydrogens have been replaced by alkyl groups, because each group helps to stabilize the positive charge.[80] With the open ion the effect is not cumulative. Replacement of the two hydrogens on one carbon causes great rate increases (primary → secondary → tertiary carbonium ion), but additional substitution on the other carbon produces little or no acceleration.[81]

Free-radical additions may occur with any type of substrate. The determining factor is the presence of a free-radical attacking species. Some reagents, e.g., HBr, RSH, attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator, the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals, like cyclopropyl (see p. 628), behave like nucleophiles, in that the rate is increased by the presence of electron-withdrawing groups in the substrate.[82] The reverse is true for electrophilic radicals.[83]

Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. It has been shown that alkyl groups affect the rate of electrophilic addition in accord with the σ_I and E_s values of Taft (pp. 255–258) so that only inductive and steric effects are important and not resonance (hyperconjugative) effects.[84]

Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? For electrophilic attack, the answer is given by *Markovnikov's rule: the positive portion of the reagent goes to the side of the double or triple bond which has more hydrogens.*[85] A number of explanations have been suggested for this regioselectivity, but the most probable is that Y^+ adds to that side which will give the more stable carbonium ion. Thus, when an alkyl group is present, secondary carbonium ions are more stable than primary:



$$R-\underset{H}{C}=\underset{H}{C}-H + Y^+ \longrightarrow R-\overset{\oplus}{\underset{H}{C}}-\overset{Y}{\underset{H}{C}}-H \quad \text{or} \quad R-\overset{Y}{\underset{H}{C}}-\overset{\oplus}{\underset{H}{C}}-H$$

More stable

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[79] Bartlett and Sargent, *J. Am. Chem. Soc.* **87,** 1297 (1965); Schmid and Garratt, *Can. J. Chem.* **51,** 2463 (1973).

[80] See, for example, Anantakrishnan and Ingold, *J. Chem. Soc.* 1396 (1935); Swern, in Swern, "Organic Peroxides," vol. 2, pp. 451–454, Interscience Publishers, New York, 1971.

[81] Bartlett and Sargent, Ref. 79; Riesz, Taft, and Boyd, *J. Am. Chem. Soc.* **79,** 3724 (1957).

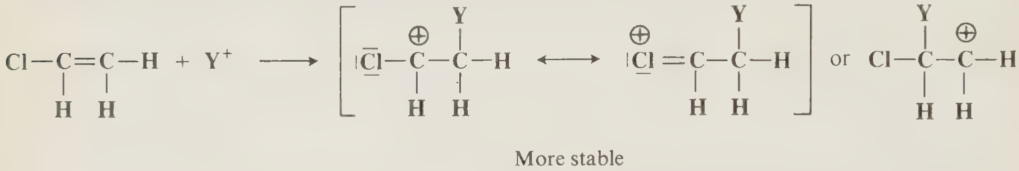
[82] Stefani, Chuang, and Todd, *J. Am. Chem. Soc.* **92,** 4168 (1970); Herk, Stefani, and Szwarc, *J. Am. Chem. Soc.* **83,** 3008 (1961).

[83] See for example, Gibb, Peters, Tedder, Walton, and Winton, *Chem. Commun.* 978 (1970).

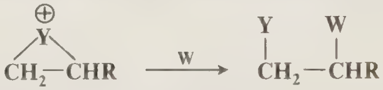
[84] Dubois and Mouvier, *Tetrahedron Lett.* 1325 (1963); Dubois and Goetz, *Tetrahedron Lett.* 303 (1965); Beverly and Hogg, *J. Chem. Soc. B* 175 (1971); Baluzow, Duschek, Just, Pritzkow, and Schmidt, *J. Prakt. Chem.* **317,** 53 (1975).

[85] For discussions of Markovnikov's rule, see Isenberg and Grdinic, *J. Chem. Educ.* **46,** 601 (1969); Grdinic and Isenberg, *Intra-Sci. Chem. Rep.* **4,** 145–162 (1970).

We may ask: How does Y^+ "know" which side will give the more stable carbonium ion? As in the similar case of electrophilic aromatic substitution (p. 459), we may invoke the Hammond postulate and say that that carbonium ion which has the lower energy is preceded by that transition state which has the lower energy. Markovnikov's rule also applies for halogen substituents because the halogen stabilizes the carbonium ion by resonance:



Markovnikov's rule is also usually followed where bromonium ions or other three-membered rings are intermediates. This means that in these cases attack by W must resemble the SN1

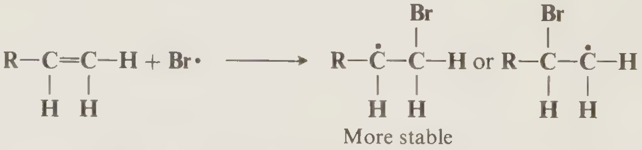


rather than the SN2 mechanism[86] (see p. 341), though the overall stereospecific anti addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration.

Olefins containing strong electron-withdrawing groups may violate Markovnikov's rule. For example, attack at the Markovnikov position of $Me_3\overset{\oplus}{N}{-}CH{=}CH_2$ would give an ion with positive charges on adjacent atoms. The compound $CF_3CH{=}CH_2$ has been reported to give electrophilic addition with acids in an anti-Markovnikov direction, but it has been shown[87] that when treated with acids, this compound does not give simple electrophilic addition at all; the apparently anti-Markovnikov products are formed by other pathways.

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type C=C—Z. Here the negative part of the reagent *always* attacks regiospecifically at the carbon which does not carry the Z (see p. 679).

In free-radical addition the radical attacks at that position which gives the more stable radical.[87a] This is usually the same position which would give the more stable carbonium ion, since the order of radical stability is the same as the order of carbonium-ion stability, namely, tertiary > secondary > primary. With a reagent such as HBr, this means that the addition is anti-Markovnikov, since it is Br• which is attacking:



Thus, the observed orientation in both kinds of HBr addition is caused by formation of the more stable intermediate, and in each case it is the secondary intermediate which is preferred to the primary (or the tertiary to the secondary or primary). The difference in orientation results from the fact that in electrophilic addition it is H^+ which attacks but in radical addition it is $Br\cdot$. Internal olefins with no groups present to stabilize the radical usually give approximately a 1 : 1 mixture. However, there are some differences in regioselectivity depending on how much electrophilic character the free radical has. For example, in additions to $FCH{=}CF_2$, the electrophilic $CCl_3\cdot$ radical attacked the FCH carbon, while the essentially nonpolar $CH_3\cdot$ radical preferred the CF_2 carbon.[88] Steric influences also play a part. A bulky radical shows a greater preference than a smaller radical[89] for the less hindered side. In *intramolecular* additions of

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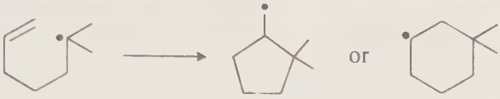
[86] SN2 attack would give anti-Markovnikov addition, and some examples of this have been found. For an example where Y^+ is RS^+, see Thaler, Mueller and Butler, *J. Am. Chem. Soc.* **90,** 2069 (1968); Mueller and Butler, *J. Am. Chem. Soc.* **90,** 2075 (1968).

[87] Myhre and Andrews, *J. Am. Chem. Soc.* **92,** 7595, 7596 (1970).

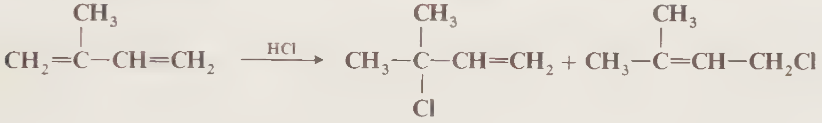
[87a] For a discussion of orientation in free-radical additions, see Tedder and Walton, *Acc. Chem. Res.* **9,** 183–191 (1976).



Favored

radicals containing a 5,6 double bond, both five- and six-membered rings may be formed, but in most cases the five-membered rings are greatly preferred, even (as in the case shown) where five-membered ring closure means generating a primary and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, but other explanations have also been offered.[90]

For conjugated dienes, attack by a positive ion, a negative ion, or a free radical is always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is the one that is formed. For example, isoprene treated with HCl gives only **22** and **23**, with none of the product arising from attack at the other end. $PhCH{=}CHCH{=}CH_2$ gives only $PhCH{=}CHCHClCH_3$ since it is

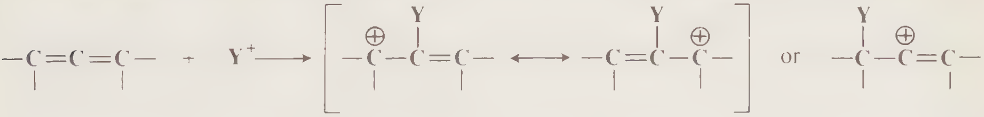


22 **23**

$$CH_2{=}\overset{\overset{CH_3}{|}}{C}{-}CH{=}CH_2 \xrightarrow{HCl} CH_3{-}\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}{-}CH{=}CH_2 + CH_3{-}\overset{\overset{CH_3}{|}}{C}{=}CH{-}CH_2Cl$$

the only one of the eight possible products which has a double bond in conjugation with the ring and which results from attack by H^+ at an end of the conjugated system.

When allenes are attacked by electrophilic reagents,[91] Markovnikov's rule would predict that the attack should be at the end of the system, since there are no hydrogens in the middle. Attack



$$-\underset{|}{C}{=}C{=}\underset{|}{C}- \;+\; Y^+ \longrightarrow \left[-\underset{|}{\overset{\oplus}{C}}-\overset{\overset{Y}{|}}{C}{=}\underset{|}{C}- \longleftrightarrow -\underset{|}{C}{=}\overset{\overset{Y}{|}}{C}-\underset{|}{\overset{\oplus}{C}}- \right] \text{ or } -\underset{|}{\overset{\overset{Y}{|}}{C}}-\overset{\oplus}{C}{=}\underset{|}{C}-$$

at the center gives a carbonium ion which is stabilized by resonance, but not immediately, because in order for such stabilization to be in effect the three *p* orbitals must be parallel, and it requires a rotation about the C—C bond for this to happen.[92] Therefore, the stability of the allyl cation has no effect on the transition state, which still has a geometry similar to that of the original allene (p. 94). Probably because of this, attack on the unsubstituted $CH_2{=}C{=}CH_2$ is most often at the end carbon,[93] to give a vinyl cation,[76] though center attack has also been reported.[94] However, as alkyl or aryl groups are substituted on the allene carbons, attack at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form $RCH{=}C{=}CH_2$ are still attacked most often at the end, but with $RCH{=}C{=}CHR'$ center attack is more prevalent. Tetramethylallene is also attacked predominantly at the center carbon.[95] Free radicals attack allenes most often at the end,[96] though attack at the middle has also been reported.[97] It has been postulated that, at least in some of these cases, attack was actually at the end, but then isomerization occurred.[98] As with electrophilic attack, and for the same reason, the stability of the allyl radical has no effect on the transition state of the reaction between a free radical and an allene. Again, as with electrophilic attack, the presence of alkyl groups increases the extent of attack by a free radical at the middle carbon.[99]

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[88] Tedder, Walton, and Winton, *Chem. Commun.* 1046 (1971).

[89] Čapka and Chvalovský, *Collect. Czech. Chem. Commun.* **33**, 2872 (1968).

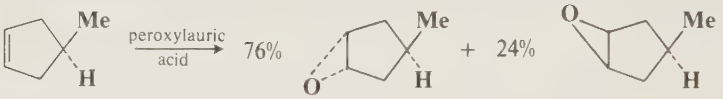
[90] For discussions, see Beckwith and Moad, *J. Chem. Soc., Chem. Commun.* 472 (1974); Beckwith, Gream, and Struble, *Aust. J. Chem.* **25**, 1081 (1972).

[91] For reviews of addition to allenes, see Modena and Tonellato, Ref. 76, pp. 215–231; Richey and Richey, Ref. 76, pp. 917–922; Caserio, *Sel. Org. Transform.* **1**, 239–299 (1970); Taylor, Ref. 57, pp. 338–346; Mavrov and Kucherov, *Russ. Chem. Rev.* **36**, 233–249 (1967); Griesbaum, *Angew. Chem. Int. Ed. Engl.* **5**, 933–946 (1966) [*Angew. Chem.* **78**, 953–966]; Petrov and Fedorova, *Russ. Chem. Rev.* **33**, 1–13 (1964).

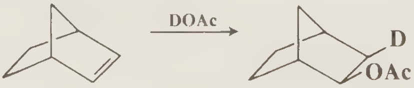
[92] For evidence that this is so, see Okuyama, Izawa, and Fueno, *J. Am. Chem. Soc.* **95**, 6749 (1973).

Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds there are further aspects of steric orientation. In syn addition to an unsymmetrical cyclic olefin, the two groups can come in from the more hindered side or from the less hindered side of the double bond. The rule is that syn addition is usually, though not always, from the less hindered side.[100] For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less hindered and 24% from the more hindered side:[101]



In anti addition to a cyclic substrate, the initial attack by the electrophile is also from the less hindered side. However, many (though not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.[102] In these cases attack is always from the exo side, e.g.,[103]



unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate; e.g., 7,7-dimethylnorbornene undergoes syn-endo epoxidation (**5-40**) and hydroboration[104] (**5-15**). However, addition of DCl and F_3CCOOD to, and oxymercuration (**5-2**) of,

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[93] See, for example, Jacobs and Johnson, *J. Am. Chem. Soc.* **82**, 6397 (1960).

[94] See Peer, *Recl. Trav. Chim. Pays-Bas* **81**, 113 (1962); Fedorova, *J. Gen. Chem. USSR* **33**, 3508 (1963).

[95] For example, see Bianchini and Guillemonat, *Bull. Soc. Chim. Fr.* 2120 (1968); Pittman, *Chem. Commun.* 122 (1969); Poutsma and Ibarbia, *J. Am. Chem. Soc.* **93**, 440 (1971).

[96] Griesbaum, Oswald, Quiram, and Naegele, *J. Org. Chem.* **28**, 1952 (1963).

[97] van der Ploeg, Knotnerus, and Bickel, *Recl. Trav. Chim. Pays-Bas* **81**, 775 (1962); Kovachic and Leitch, *Can. J. Chem.* **39**, 363 (1961); Griesbaum, Oswald, and Hall, *J. Org. Chem.* **29**, 2404 (1964); Abell and Anderson, *Tetrahedron Lett.* 3727 (1964).

[98] Heiba and Haag, *J. Org. Chem.* **31**, 3814 (1966); Tien and Abell, *J. Org. Chem.* **35**, 956 (1970).

[99] For example, see Byrd and Caserio, *J. Org. Chem.* **37**, 3881 (1972).

[100] For a review of stereoselectivity in cyclic additions, see Henbest, *Proc. Chem. Soc.* 159–165 (1963).

[101] Henbest and McCullough, *Proc. Chem. Soc.* 74 (1962).

[102] For a discussion, see Traylor, *Acc. Chem. Res.* **2**, 152–160 (1969).

[103] Cristol, Morrill, and Sanchez, *J. Org. Chem.* **31**, 2719 (1966); Brown, Kawakami, and Liu, *J. Am. Chem. Soc.* **92**, 5536 (1970). See also Bond, *J. Am. Chem. Soc.* **90**, 5326 (1968); Stille and Hughes, *J. Org. Chem.* **36**, 340 (1971).

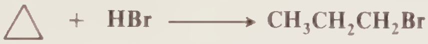
[104] Brown and Kawakami, *J. Am. Chem. Soc.* **92**, 201, 1990 (1970); Brown and Liu, *J. Am. Chem. Soc.* **93**, 7335 (1971); Brown, Kawakami, and Liu, *J. Am. Chem. Soc.* **95**, 2209 (1973).

7,7-dimethylnorbornene proceed syn-exo in spite of the methyl groups in the 7 position.[105] Similarly, free-radical additions to norbornene and similar molecules are often syn-exo, though anti additions and endo attacks are also known.[106]

It has been mentioned that additions of Br_2 and HOBr are often anti because of formation of bromonium ions and that free-radical addition of HBr is also anti, presumably because of formation of the analogous cyclic-radical intermediates. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.[107] This is so because diaxial opening of the three-membered ring preserves in the transition state a maximum coplanarity of the participating centers; indeed, on opening, epoxides also give diaxial products. However, the initial diaxial product may then pass over to the diequatorial conformer (see p. 129) unless other groups on the ring render the latter less stable than the former. Some cases have been found (in electrophilic addition of bromine) where the initial ring opening gave the diequatorial rather than the diaxial conformer.[108] Such behavior has been attributed to the second step of the reaction (ring opening) being rate-determining rather than the first (attack on the double bond by the electrophile).[109] In free-radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial attack by the radical is also usually from the axial direction,[110] resulting in a diaxial initial product if the overall addition is anti.

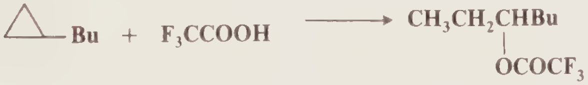
Addition to Cyclopropane Rings[111]

We have previously seen (p. 141) that in some respects, cyclopropane rings resemble double bonds.[112] It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered ring; e.g. (the reaction numbers of the analogous addition reactions are given in parentheses),



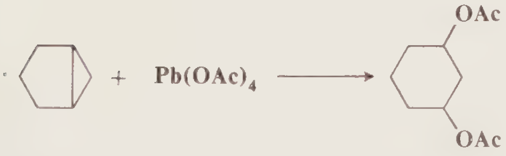
$$+ \ \mathrm{HBr} \longrightarrow \mathrm{CH_3CH_2CH_2Br}$$

(5-1)



$$\mathrm{Bu} + \mathrm{F_3CCOOH} \longrightarrow \mathrm{CH_3CH_2\underset{\displaystyle OCOCF_3}{\underset{|}{C}}HBu}$$

(5-6)[113]



$$+ \ \mathrm{Pb(OAc)_4} \longrightarrow$$

OAc

OAc

(5-39)[114]

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[105] Brown and Liu, *J. Am. Chem. Soc.* **97**, 600, 2469 (1975); Brown and Kawakami, *J. Am. Chem. Soc.* **95**, 8665 (1973); Tidwell and Traylor, *J. Org. Chem.* **33**, 2614 (1968).

[106] For a review of free-radical addition to these systems, see Azovskaya and Prilezhaeva, *Russ. Chem. Rev.* **41**, 516–528 (1972).

[107] Barton, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 127–143, Butterworth Scientific Publications, London, 1959; Goering, Abell, and Aycock, *J. Am. Chem. Soc.* **74**, 3588 (1952); Goering and Sims, *J. Am. Chem. Soc.* **77**, 3465 (1955); Shoppee, Akhtar, and Lack, *J. Chem. Soc.* 877 (1964); Readio and Skell, *J. Org. Chem.* **31**, 753, 759 (1966).

[108] Barili, Bellucci, Marioni, Morelli, and Scartoni, *J. Org. Chem.* **37**, 4353 (1972).

[109] Bellucci, Berti, Ingrosso, and Mastrorilli, Ref. 28.

[110] Huyser, Benson, and Sinnige, *J. Org. Chem.* **32**, 622 (1967); LeBel, Czaja, and DeBoer, Ref. 44.

[111] For a review, see Charton, in Zabicky, "The Chemistry of Alkenes," vol. 2, pp. 569–592, Interscience Publishers, New York, 1970.

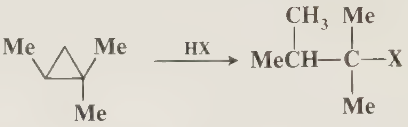
[112] For a review, see Lukina, *Russ. Chem. Rev.* **31**, 419 (1962). The analogies are by no means complete: see Gordon, *J. Chem. Educ.* **44**, 461 (1967).

[113] Peterson and Thompson, *J. Org. Chem.* **33**, 968 (1968).

[114] Moon, *J. Org. Chem.* **29**, 3456 (1964).

Other examples are discussed at reactions **5-14, 5-52,** and **5-53.**

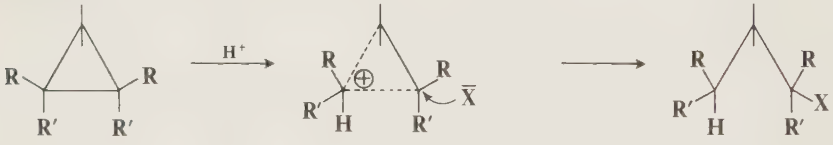
Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves electrophilic attack.[115] For substituted cyclopropanes, these reactions usually follow Markovnikov's rule, though exceptions are known, and the degree of regioselectivity is often small. The application of Markovnikov's rule to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.[116] The rule



predicts that the electrophile (in this case H^+) goes to the carbon with the most hydrogens and the nucleophile goes to the carbon which can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions, the one which becomes connected to the electrophile and the one which becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,[117] 100% inversion,[118] and with mixtures of retention and inversion.[119] At the carbon which becomes connected to the nucleophile the result is usually inversion, though retention has also been found,[120] and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for attack by HX, but analogous mechanisms can be written for other electrophiles).[121]

Mechanism *a*



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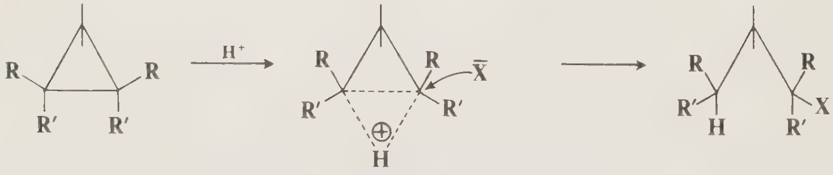
Mechanism *b*



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[115] For a review, see DePuy, *Top. Curr. Chem.* **40,** 73–101 (1973).

[116] Kramer, *J. Am. Chem. Soc.* **92,** 4344 (1970).

[117] For example, see DePuy, Breitbeil, and DeBruin, *J. Am. Chem. Soc.* **88,** 3347 (1966); Hendrickson and Boeckman, *J. Am. Chem. Soc.* **91,** 3269 (1969).

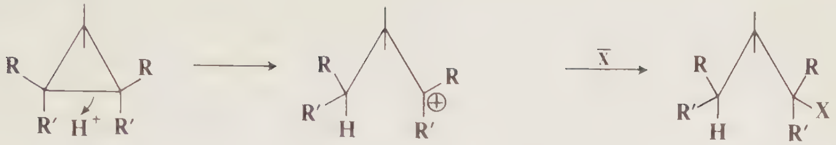
[118] For example, see LaLonde, Ding, and Tobias, *J. Am. Chem. Soc.* **89,** 6651 (1967); Warnet and Wheeler, *Chem. Commun.* 547 (1971); Hogeveen, Roobeek, and Volger, *Tetrahedron Lett.* 221 (1972); Battiste and Mackiernan, *Tetrahedron Lett.* 4095 (1972). See also Jensen, Patterson, and Dinizo, *Tetrahedron Lett.* 1315 (1974).

[119] Nickon and Hammons, *J. Am. Chem. Soc.* **86,** 3322 (1964); Hammons, Probasco, Sanders, and Whalen, *J. Org. Chem.* **33,** 4493 (1968); DePuy and McGirk, *J. Am. Chem. Soc.* **95,** 2366 (1973), **96,** 1121 (1974); DePuy, Andrist, and Fünfschilling, *J. Am. Chem. Soc.* **96,** 948 (1974).

[120] Cristol, Lim, and Dahl, *J. Am. Chem. Soc.* **92,** 4013 (1970); Hendrickson and Boeckman, *J. Am. Chem. Soc.* **93,** 4491 (1971).

[121] Ref. 115, pp. 92–93.

Mechanism *c*



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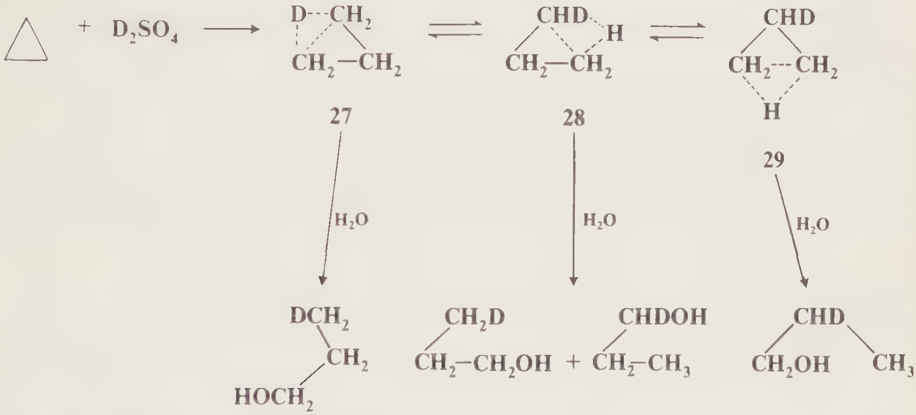
Mechanism *a* involves a corner-protonated cyclopropane[122] (**24**); we have already seen examples of such ions in the 2-norbornyl and 7-norbornenyl cations (pp. 296–297). Mechanism *b* involves an edge-protonated cyclopropane (**25**). Mechanism *c* consists of a one-step SE2-type attack by H^+ to give the classical carbonium ion **26**, which then reacts with the nucleophile. Although the three mechanisms as we have drawn them show retention of configuration at the carbon which becomes attached to the proton, mechanisms *a* and *c* at least can also lead to inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. When cyclopropane was treated with D_2SO_4 (reaction **5-2**), the deuterium was found at all three carbons of the resulting 1-propanol.[123] This result can be explained by an equilibrium among the three edge-protonated species **27** to **29**. A similar equilibrium (with CH_3CO^+ instead of D^+) can



explain the reaction of cyclopropane with CH_3COCl to give $CH_3COCH_2CH_2CH_2Cl$, CH_3CO-$CHMeCH_2Cl$, and $CH_3COCHEtCl$ (as well as $CH_3COCMe{=}CH_2$, formed by elimination of HCl from $CH_3COCHMeCH_2Cl$).[124] There are also the possibilities that three corner-protonated cyclopropanes might be in equilibrium with each other (corner-to-corner hydrogen shifts) and with the edge-protonated species and that in some cases **24** or **25** might form first and then be converted to **26**. There is evidence that corner-protonated cyclopropanes may be somewhat more stable than the edge-protonated type.[125]

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[122] For reviews of protonated cyclopropanes, see Collins, *Chem. Rev.* **69**, 543–550 (1969); Lee, *Prog. Phys. Org. Chem.* **7**, 129–187 (1970).

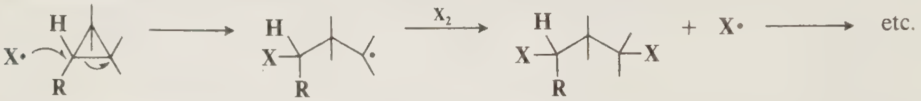
[123] Baird and Aboderin, *Tetrahedron Lett.* 235 (1963), *J. Am. Chem. Soc.* **86**, 252 (1964); Lee and Gruber, *J. Am. Chem. Soc.* **90**, 3775 (1968); Lee, Chwang, and Wan, *J. Am. Chem. Soc.* **90**, 3778 (1968); Deno, LaVietes, Mockus, and Scholl, *J. Am. Chem. Soc.* **90**, 6457 (1968). See also Deno, Billups, LaVietes, Scholl, and Schneider, *J. Am. Chem. Soc.* **92**, 3700 (1970).

[124] Hart and Schlosberg, *J. Am. Chem. Soc.* **90**, 5189 (1968).

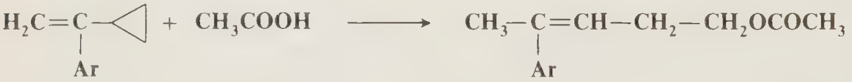
[125] Saunders, Vogel, Hagen, and Rosenfeld, *Acc. Chem. Res.* **6**, 53–59 (1973), p. 56. See also Lee, Cessna, Ko, and Vassie, *J. Am. Chem. Soc.* **95**, 5688 (1973).

The mechanism of bromination seems to depend on the substrate. Cyclopropane itself does not react with bromine in the dark in the absence of a Lewis acid catalyst. However, when $AlCl_3$ or $FeBr_3$ is present, the product is a mixture of 1,1-, 1,2-, and 1,3-dibromopropanes,[126] which can be explained, as above, by the presence of an equilibrium among edge-protonated cyclopropanes (Br^+ instead of D^+). On the other hand, the pattern of products obtained (mostly derived from rearrangements) in the bromination of alkyl-substituted cyclopropanes indicates that in this case the reaction proceeds via open classical carbonium ions (mechanism *c*).[127] Mechanism *c* has also been proposed for bromination of aryl-substituted cyclopropanes.[128]

Free-radical additions to cyclopropanes have been studied much less, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free-radical mechanism in the presence of uv light. The addition follows Markovnikov's rule, with the initial radical attacking the least substituted carbon and the second group going to the most substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but non-stereospecific at the other carbon.[129] A mechanism which accounts for this behavior is



In some cases conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is[130]


(5-6)

$$\underset{\mathrm{Ar}}{H_2C{=}\underset{|}{C}}\text{—}\triangleleft + CH_3COOH \longrightarrow CH_3\text{—}\underset{\substack{|\\ \mathrm{Ar}}}{C}{=}CH\text{—}CH_2\text{—}CH_2OCOCH_3 \qquad (5\text{-}6)$$

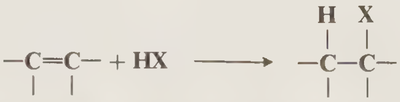
REACTIONS

Reactions are classified by type of reagent. All reactions where hydrogen adds to one side of the double bond, whether by electrophilic, nucleophilic, free-radical, or cyclic mechanisms, are treated first.

Reactions in Which Hydrogen Adds to One Side

A. Halogen on the Other Side

5-1 Addition of Hydrogen Halides



$$-\underset{|}{C}{=}\underset{|}{C}- + HX \longrightarrow -\underset{|}{\overset{\mathrm{H}}{\overset{|}{C}}}-\underset{|}{\overset{\mathrm{X}}{\overset{|}{C}}}-$$

Any of the four hydrogen halides may be added to double bonds. HI, HBr, and HF[131] add at room temperature. The addition of HCl usually requires heat. The reaction can be carried out with a large variety of double-bond compounds, including conjugated systems, where both 1,2 and 1,4 addition are possible. A convenient method for the addition of HF involves the use of a highly concentrated solution of HF in a tertiary amine such as pyridine or triethylamine, e.g., 70% HF–30% pyridine.[132] When the substrate is mixed with this solution in a solvent such as tetrahydrofuran at 0°C, alkyl fluorides are obtained in moderate to high yields.

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[126] Deno and Lincoln, *J. Am. Chem. Soc.* **88**, 5357 (1966). See also Deno and Billups, *Chem. Commun.* 1387 (1970).

[127] Lambert and Iwanetz, *J. Org. Chem.* **37**, 4082 (1972); Day, Shea, and Skell, *J. Am. Chem. Soc.* **95**, 5089 (1973); Skell, Day, and Shea, *J. Am. Chem. Soc.* **98**, 1195 (1976); Lambert and Kobayashi, *J. Org. Chem.* **41**, 671 (1976).

[128] LaLonde and Debboli, *J. Org. Chem.* **38**, 4228 (1973).

[129] Maynes and Applequist, *J. Am. Chem. Soc.* **95**, 856 (1973); Incremona and Upton, *J. Am. Chem. Soc.* **94**, 301 (1972); Shea and Skell, *J. Am. Chem. Soc.* **95**, 6728 (1973); Applequist and Searle, *J. Am. Chem. Soc.* **86**, 1389 (1964); Poutsma, *J. Am. Chem. Soc.* **87**, 4293 (1965); Jarvis, *J. Org. Chem.* **35**, 924 (1970); Upton and Incremona, *J. Org. Chem.* **41**, 528 (1976).

[130] Sarel and Ben-Shoshan, *Tetrahedron Lett.* 1053 (1965).

[131] For reviews of addition of HF, see Sharts and Sheppard, *Org. React.* **21**, 125–406 (1974), pp. 192–198, 212–214; Hudlický, "The Chemistry of Organic Fluorine Compounds," pp. 65–68, The Macmillan Company, New York, 1962; Wiechert, *Newer Methods Prep. Org. Chem.* **1**, 315–368 (1948).

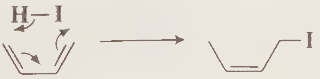
The addition of hydrogen halides to simple olefins, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.[133] When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is anti-Markovnikov (p. 688).[134] It must be emphasized that this is true only for HBr. Free-radical addition of HF and HI has never been observed, even in the presence of peroxides, and of HCl only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable *product* was formed.[135] Free-radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions on pp. 626, 635). It has often been found that anti-Markovnikov addition of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (reaction **4-8**). Markovnikov addition can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve, and it is more common to add inhibitors, e.g., phenols or quinones, which suppress the free-radical pathway. The presence of free-radical precursors such as peroxides does not inhibit the ionic mechanism, but the radical reaction, being a chain process, is much more rapid than the electrophilic reaction. In most cases it is possible to control the mechanism (and hence the orientation) by adding peroxides, to achieve complete free-radical addition, or inhibitors, to achieve complete electrophilic addition, though there are some cases where the ionic mechanism is fast enough to compete with the free-radical mechanism and complete control cannot be attained. For alternative methods of adding HBr (or HI) with anti-Markovnikov orientation, see reaction **2-28**.

It is also possible to add 1 or 2 moles of any of the four hydrogen halides to triple bonds.

$$-\mathrm{C{\equiv}C}- \xrightarrow{\mathrm{HX}} -\mathrm{CH{=}CX}- \xrightarrow{\mathrm{HX}} -\mathrm{CH_2}-\mathrm{CX_2}-$$

Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of 2 moles.

HX are electrophilic reagents, and many polyhalo and polycyano alkenes, e.g., $Cl_2C{=}CHCl$, do not react with them at all in the absence of free-radical conditions. When such reactions do occur, however, they take place by a nucleophilic addition mechanism; i.e., initial attack is by X^-. This type of mechanism also occurs with Michael-type substrates $C{=}C{-}Z$, where the orientation is always such that the halogen goes to the carbon which does not bear the Z, so that the product is of the form $X{-}C{-}CH{-}Z$, even in the presence of free-radical initiators. HI adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:[136]



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[132] Olah, Nojima, and Kerekes, *Synthesis* 779 (1973).

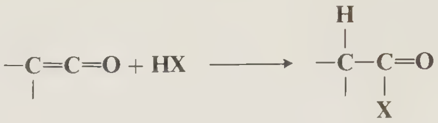
[133] For a review of electrophilic addition of HX, see Dewar, Ref. 5.

[134] For reviews of free-radical addition of HX, see Thaler, *Methods Free-Radical Chem.* **2,** 121–227 (1969), pp. 182–195; Stacey and Harris, *Org. React.* **13,** 150–376 (1963), pp. 154–164, 238–246; Sosnovsky, Ref. 41, pp. 6–18; Walling, Ref. 41, pp. 291–298.

[135] Mayo, *J. Am. Chem. Soc.* **84,** 3964 (1962).

[136] Gorton and Walsh, *J. Chem. Soc., Chem. Commun.* 782 (1972).

HX can be added to ketenes[137] to give acyl halides:[137a]

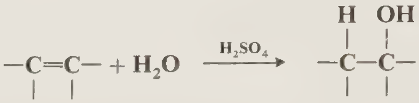


$$-\overset{}{\underset{|}{C}}=C=O + HX \longrightarrow -\overset{H}{\overset{|}{\underset{|}{C}}}-\underset{\underset{X}{|}}{C}=O$$

OS **I,** 166; **II,** 137, 336; **III,** 576; **IV,** 238, 543.

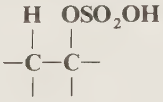
B. Oxygen on the Other Side

5-2 Hydration of Olefins



$$-\underset{|}{C}=\underset{|}{C}- + H_2O \xrightarrow{H_2SO_4} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{OH}{\overset{|}{C}}}-$$

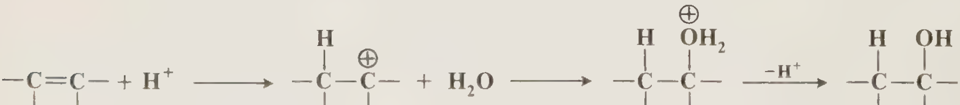
Olefins can be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids, such as nitric or perchloric, may also be used. The mechanism is electrophilic and begins with attack by a proton (see p. 676). The negative attacking species may be HSO_4^- (or similar ion in the case of other acids) to give the initial product



$$-\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{OSO_2OH}{\overset{|}{C}}}-$$

30

which can be isolated (reaction **5-4**) but, under the conditions of the reaction, is usually hydrolyzed to the alcohol (reaction **0-4**). However, the conjugate base of the acid is not the only possible species which attacks the initial carbonium ion. The attack may also be by water:



$$-\underset{|}{C}=\underset{|}{C}- + H^+ \longrightarrow -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{\oplus}{C}}- + H_2O \longrightarrow -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{\overset{\oplus}{OH_2}}{\overset{|}{C}}}- \xrightarrow{-H^+} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{|}{\overset{OH}{\overset{|}{C}}}-$$

When the reaction proceeds by this pathway, **30** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of E1 elimination of alcohols (reaction **7-1**).[138] It is likely that the mechanism involves both pathways. Sometimes the initial carbonium ion rearranges to a more stable one. For example, hydration of $CH_2{=}CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. With ordinary olefins the addition predominantly follows Markovnikov's rule. For a method of anti-Markovnikov hydration, see reaction **5-15.** With substrates of the type C=C—Z (Z is as defined on p. 678) the product is always HO—C—CH—Z, and the mechanism is usually nucleophilic,[139] although electrophilic addition gives the same product[140] since a cation $CH{-}\overset{\oplus}{C}{-}Z$ would be destabilized by the positive charges (full or partial) on two adjacent atoms. Conjugated dienes are seldom hydrated.

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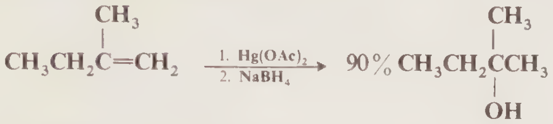
[137] For a review of the mechanisms of reactions of ketenes with HX, H_2O, ROH, RCOOH, and amines, see Satchell and Satchell, *Chem. Soc. Rev.* **4**, 231–250 (1975).

[137a] For a discussion of the mechanism, see Lillford and Satchell, *J. Chem. Soc. B* 897 (1968).

[138] For a discussion of the mechanism, see Liler, "Reaction Mechanisms in Sulphuric Acid," pp. 210–225, Academic Press, Inc., New York, 1971.

[139] For example, see Fedor, De, and Gurwara, *J. Am. Chem. Soc.* **95**, 2905 (1973); Jensen and Carré, *J. Org. Chem.* **39**, 2103 (1974).

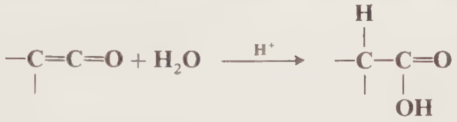
Olefins can be hydrated quickly, under mild conditions in high yields without rearrangement products, by the use of oxymercuration[141] (addition of oxygen and mercury) followed by in situ treatment with sodium borohydride[142] (reaction **2-21**). For example, 2-methyl-1-butene treated with mercuric acetate, followed by $NaBH_4$, gave 90% 2-methyl-2-butanol



$$CH_3CH_2\overset{CH_3}{\overset{|}{C}}{=}CH_2 \xrightarrow[2.\ NaBH_4]{1.\ Hg(OAc)_2} 90\%\ CH_3CH_2\underset{\underset{OH}{|}}{\overset{CH_3}{\overset{|}{C}}}CH_3$$

This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted olefins, gives almost complete Markovnikov addition.

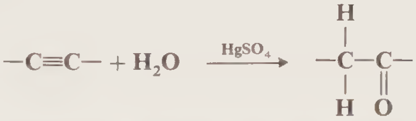
The addition of water to vinyl ethers causes hydrolysis to aldehydes or ketones (reaction **0-7**). Ketenes add water to give carboxylic acids in a reaction which is catalyzed by acids:[143]



$$-\underset{|}{C}{=}C{=}O + H_2O \xrightarrow{H^+} -\underset{|}{\overset{H}{\overset{|}{C}}}-\underset{\underset{OH}{|}}{C}{=}O$$

OS **IV**, 555, 560; **53**, 94. Also see OS **V**, 818.

5-3 Hydration of Alkynes



$$-C{\equiv}C- + H_2O \xrightarrow{HgSO_4} -\underset{\underset{H}{|}}{\overset{H}{\overset{|}{C}}}-\underset{\underset{O}{\|}}{C}-$$

Alkynes can be hydrated with mercuric ion salts (often the sulfate) as catalysts.[144] Thallium(III) salts can also be used.[145] Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones (for a method of reversing the orientation for terminal alkynes, see reaction **5-15**). With alkynes of the form $RC{\equiv}CH$ methyl ketones are formed almost exclusively, but with $RC{\equiv}CR'$ both possible products are usually obtained. However, if R is primary and R′ secondary or tertiary, the carbonyl group is formed preferentially next to the secondary or tertiary carbon.[146]

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[140] For example, see Noyce and DeBruin, *J. Am. Chem. Soc.* **90**, 372 (1968).

[141] For reviews of oxymercuration and other oxymetalation reactions, see Kitching, *Organomet. React.* **3**, 319–398 (1972), *Organomet. Chem. Rev.* **3**, 61–134 (1968); Oullette, in Trahanovsky, "Oxidation in Organic Chemistry," pt. B, pp. 140–166, Academic Press, Inc., New York, 1973; House, "Modern Synthetic Reactions," 2d ed., pp. 387–396, W. A. Benjamin, Inc., New York, 1972; Zefirov, *Russ. Chem. Rev.* **34**, 527-536 (1965); Chatt, *Chem. Rev.* **48**, 7–43 (1951).

[142] Brown and Geoghegan, *J. Am. Chem. Soc.* **89**, 1522 (1967), *J. Org. Chem.* **35**, 1844 (1970), **37**, 1937 (1972); Brown, Geoghegan, Kurek, and Lynch, *Organomet. Chem. Synth.* **1**, 7 (1970), *J. Org. Chem.* **37**, 1941 (1972); Brown and Hammar, *J. Am. Chem. Soc.* **89**, 1524 (1967); Moon and Waxman, *Chem. Commun.* 1283 (1967); Moon, Takakis, and Waxman, *J. Org. Chem.* **34**, 2951 (1969); Moon, Ganz, and Waxman, *Chem. Commun.* 866 (1969); Johnson and Rickborn, *Chem. Commun.* 1073 (1968); Klein and Levene, *Tetrahedron Lett.* 4833 (1969); Chamberlain and Whitham, *J. Chem. Soc. B* 1382 (1970); Barrelle and Apparu, *Bull. Soc. Chim. Fr.* 2016 (1972).

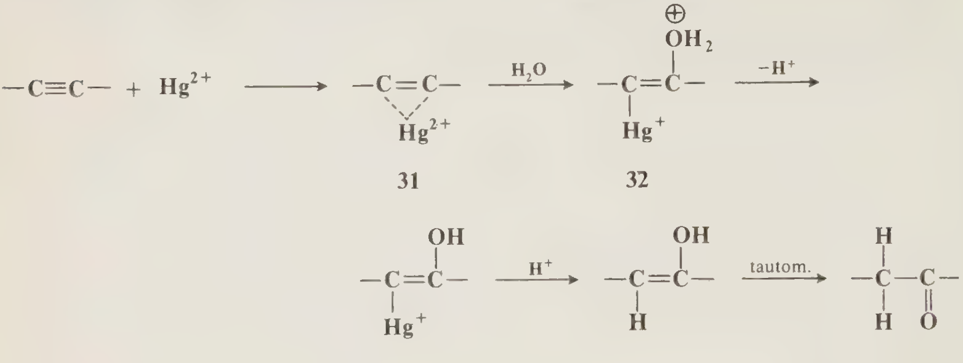
[143] For discussions of the mechanism, see Lillford and Satchell, *J. Chem. Soc. B* 889 (1968); Ref. 137.

[144] For reviews, see Khan and Martell, "Homogeneous Catalysis by Metal Complexes," vol. 2, pp. 91–95, Academic Press, Inc., New York, 1974; Miocque, Hung, and Yen, *Ann. Chim.* (*Paris*) [13] **8**, 157–174 (1963).

[145] Uemura, Kitoh, Fujita, and Ichikawa, *Bull. Chem. Soc. Jpn.* **40**, 1499 (1967).

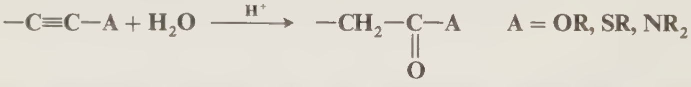
[146] Krupin and Petrov, *J. Gen. Chem. USSR* **33**, 3799 (1963).

The first step of the mechanism is probably formation of a complex (**31**), since ions like Hg^{2+} form complexes with alkynes (p. 79). Water then attacks in an SN2-type process to give the intermediate **32**, which loses a proton to give **33**. Hydrolysis of **33** (an example of reaction **2-21**) gives the enol, which tautomerizes to the product.[147] There is evidence that the mechanism is somewhat more complicated than this. A yellow color has been observed in the solution which, from spectral evidence, is attributed to a complex containing an Hg^{2+} ion and *two* acetylene molecules.[148] The isolation of **32** or **33** would be strong evidence in favor of the above mechanism. Such intermediates have not been isolated, but an analogous intermediate has been isolated from treatment of olefins with mercuric salts. Ions of the type **31** but with single C—C bonds instead of double have been prepared in stable solutions in super acids.[149]



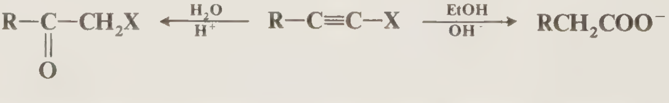
31 **32** **33**

Esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,[150] and ynamines, without a mercuric catalyst;[151]



$$-C\equiv C-A + H_2O \xrightarrow{H^+} -CH_2-\underset{\underset{O}{\|}}{C}-A \qquad A = OR, SR, NR_2$$

This is ordinary electrophilic addition, with rate-determining protonation as the first step.[152] Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts. These include $ArC\equiv CCOOH$,[153] $ArC\equiv CCH_3$,[154] and 3-hexyne.[155] When chloro or bromoalkynes are hydrolyzed in acid solution, they give the normal product, an α-halo ketone, but hydrolysis with ethanolic OH^- gives a carboxylic acid salt:[156]



$$R-\underset{\underset{O}{\|}}{C}-CH_2X \xleftarrow[H^+]{H_2O} R-C\equiv C-X \xrightarrow[OH^-]{EtOH} RCH_2COO^-$$

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[147] Rochow, Hurd, and Lewis, "The Chemistry of Organometallic Compounds," pp. 109–112, John Wiley & Sons, Inc., New York, 1957.

[148] Budde and Dessy, *Tetrahedron Lett.* 651 (1963), *J. Am. Chem. Soc.* **85**, 3964 (1963).

[149] Olah and Clifford, *J. Am. Chem. Soc.* **95**, 6067 (1973). See also Bach, Gauglhofer, and Kevan, *J. Am. Chem. Soc.* **94**, 6860 (1972).

[150] For a review of acetylenic ethers and thioethers, see Brandsma, Bos, and Arens, in Viehe, Ref. 70, pp. 751–860.

[151] Arens, *Adv. Org. Chem.* **2**, 163 (1960); Ref. 150, pp. 774–775.

[152] Hogeveen and Drenth, *Recl. Trav. Chim. Pays-Bas* **82**, 375, 410 (1963); Stamhuis and Drenth, *Recl. Trav. Chim. Pays-Bas* **82**, 385, 394 (1963); Verhelst and Drenth, *J. Am. Chem. Soc.* **96**, 6692 (1974).

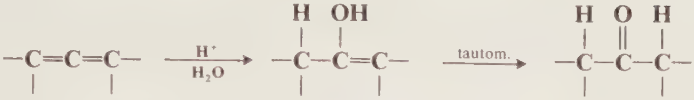
[153] Noyce, Matesich, and Peterson, *J. Am. Chem. Soc.* **89**, 6225 (1967).

[154] Noyce and Schiavelli, *J. Org. Chem.* **33**, 845 (1968), *J. Am. Chem. Soc.* **90**, 1020, 1023 (1968).

[155] Richey and Buckley, cited by Deno, *Prog. Phys. Org. Chem.* **2**, 181 (1964).

[156] For a review, see Delavarenne and Viehe, in Viehe, Ref. 70, pp. 693–696, 707–709, 719–721.

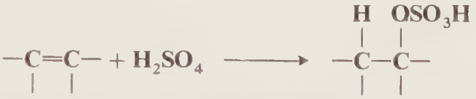
Allenes can also be hydrolyzed to ketones, with an acid catalyst:[157]



$$-\underset{|}{C}{=}C{=}\underset{|}{C}- \xrightarrow[H_2O]{H^+} -\overset{H}{\underset{|}{C}}-\overset{OH}{C}{=}\underset{|}{C}- \xrightarrow{\text{tautom.}} -\overset{H}{\underset{|}{C}}-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{|}{C}}-$$

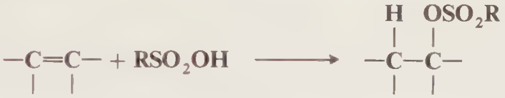
OS **III**, 22; **IV**, 13; **V**, 1024.

5-4 Formation of Inorganic Esters



$$-\underset{|}{C}{=}\underset{|}{C}- + H_2SO_4 \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{OSO_3H}{\underset{|}{C}}-$$

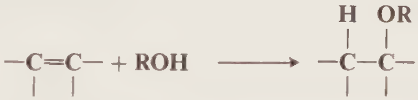
It is possible to prepare esters of sulfuric acid by treatment of olefins with H_2SO_4, but care must be taken that the esters do not hydrolyze to the alcohol (reaction **5-2**). It is also possible for the product to add to a second molecule of olefin to give a dialkyl sulfate. In practice, however, the reaction is seldom used for any olefin except ethylene. Esters of inorganic acids are most often prepared from alcohols (reaction **0-33**). Sulfonic acids add to many olefins, though not to ethylene, to give sulfonic esters:



$$-\underset{|}{C}{=}\underset{|}{C}- + RSO_2OH \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{OSO_2R}{\underset{|}{C}}-$$

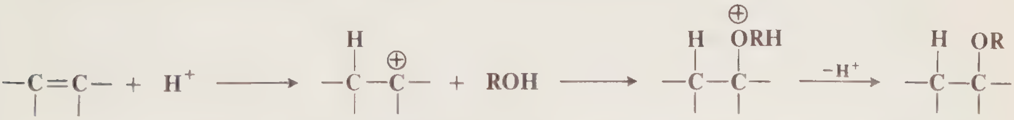
Alkyl fluorosulfates $ROSO_2F$ can be prepared by the treatment of olefins with fluorosulfuric acid HSO_3F at low temperatures.[158]

5-5 Addition of Alcohols and Phenols



$$-\underset{|}{C}{=}\underset{|}{C}- + ROH \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{OR}{\underset{|}{C}}-$$

Alcohols and phenols add to olefins in reactions which are catalyzed by acids or bases. When the reactions are acid-catalyzed, the mechanism is electrophilic, with H^+ as the attacking species. The resulting carbonium ion combines with a molecule of alcohol:



$$-\underset{|}{C}{=}\underset{|}{C}- + H^+ \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{\oplus}{\underset{|}{C}}- + ROH \longrightarrow -\overset{H}{\underset{|}{C}}-\overset{\overset{\oplus}{ORH}}{\underset{|}{C}}- \xrightarrow{-H^+} -\overset{H}{\underset{|}{C}}-\overset{OR}{\underset{|}{C}}-$$

The addition, therefore, follows Markovnikov's rule. Primary alcohols give better results than secondary, and tertiary alcohols are very inactive. This is a convenient method for the preparation of tertiary ethers by the use of a suitable olefin such as $Me_2C{=}CH_2$.

For those substrates which are more susceptible to nucleophilic attack, e.g., polyhalo olefins and olefins of the type C=C—Z, it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[159] The reactions with C=C—Z are of the Michael type, and OR always goes to the side away from the Z.[160] Since triple bonds are more susceptible to nucleophilic attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and vinyl ethers and acetals may be produced by this reaction:[161]

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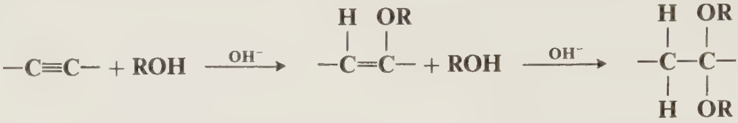
[157] For example, see Fedorova and Petrov, *J. Gen. Chem. USSR* **32**, 1740 (1962); Mühlstadt and Graefe, *Chem. Ber.* **100**, 223 (1967).

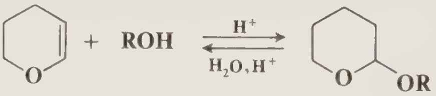
[158] See, for example, Olah, Nishimura, and Mo, *Synthesis* 661 (1973).

[159] For a review with respect to fluoroolefins, see Ref. 61, pp. 53–61.



$$-C\equiv C- + ROH \xrightarrow{OH^-} -\overset{H}{C}=\overset{OR}{C}- + ROH \xrightarrow{OH^-} -\overset{H}{\underset{H}{C}}-\overset{OR}{\underset{OR}{C}}-$$

Because vinyl ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to vinyl ethers can also be catalyzed by acids. One utilization of this reaction involves the compound dihydropyran (**34**), which is often used to protect the OH groups of primary and secondary alcohols and phenols. The acetal formed by this reaction (**35**) is stable to bases, Grignard reagents, $LiAlH_4$, and oxidizing agents, any of which may be used to react with functional groups located within the R group. When the reactions are completed, **35** is easily cleaved by treatment with dilute acids (reaction **0-7**).



34 **35**

In base-catalyzed addition to triple bonds the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Other catalysts, namely, BF_3 and mercuric salts, have also been used in addition of ROH to triple bonds. Similarly, the addition of alcohols to allenes (to give 3-alkoxyalkenes) is catalyzed by HgO–BF_3.[162]

Alcohols can be added to certain double-bond compounds (cyclohexenes, cycloheptenes) photochemically in the presence of a photosensitizer such as benzene. The mechanism is electrophilic, and Markovnikov orientation is found. The olefins react in their first excited triplet states.[163]

The oxymercuration-demercuration procedure mentioned in reaction **5-2** can be adapted to the preparation of ethers (Markovnikov orientation) if the oxymercuration is carried out in an alcohol ROH as solvent; e.g., 2-methyl-1-butene in ethanol gives $EtMe_2COEt$.[164] Primary and secondary alcohols give good yields when mercuric acetate is used, but for tertiary alcohols it is necessary to use mercuric trifluoroacetate. However, even with this reagent the method fails where the product would be a ditertiary ether. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with $NaBH_4$) is an alkyl peroxide.[165] When either of the oxymercuration-demercuration procedures is applied to α-substituted-β-unsubstituted compounds of the form $CH_2{=}CR'{-}Z$ (Z = COOH, COOR, CHO, COPh), the products are the α-alkoxy compounds $CH_3CR'(OR){-}Z$ [or the corresponding peroxy compounds $CH_3CR'(OOR){-}Z$] which have the *opposite* orientation from that normal for Michael-type substrates.[166]

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[160] For a review of addition of ROH to acrylonitrile (cyanoethylation of alcohols and phenols), see Bruson, *Org. React.* **5**, 79–135 (1949), pp. 89–95, 121–128.

[161] For reviews, see Shostakovskii, Trofimov, Atavin, and Lavrov, *Russ. Chem. Rev.* **37**, 907–919 (1968); Shostakovskii, Bogdanova, and Plotnikova, *Russ. Chem. Rev.* **33**, 66–77 (1964).

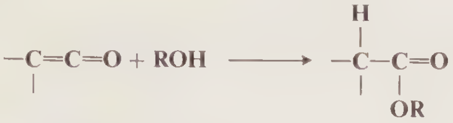
[162] Bach, *Tetrahedron Lett.* 5841 (1968).

[163] Marshall, *Acc. Chem. Res.* **2**, 33–40 (1969).

[164] Brown and Rei, *J. Am. Chem. Soc.* **91**, 5646 (1969).

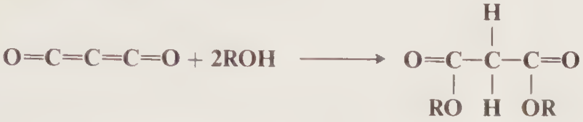
[165] Ballard and Bloodworth, *J. Chem. Soc. C* 945 (1971). See also Sokolov and Reutov, *J. Org. Chem. USSR* **5**, 168 (1969); Schmitz, Rieche, and Brede, *J. Prakt. Chem.* **312**, 30 (1970).

Both alcohols and phenols add to ketenes to give esters:[167]



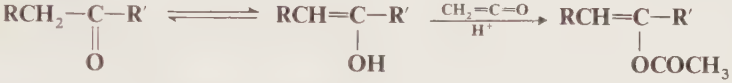
$$-\underset{|}{C}=C=O + ROH \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{OR}{|}}{C}=O$$

Similarly, carbon suboxide gives malonic esters:[168]



$$O=C=C=C=O + 2ROH \longrightarrow O=\underset{\underset{RO}{|}}{C}-\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}-\underset{\underset{OR}{|}}{C}=O$$

In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates:

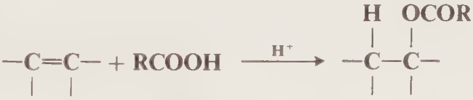


$$RCH_2-\underset{\underset{O}{\|}}{C}-R' \rightleftharpoons RCH=\underset{\underset{OH}{|}}{C}-R' \xrightarrow[H^+]{CH_2=C=O} RCH=\underset{\underset{OCOCH_3}{|}}{C}-R'$$

Alcohols can also add to olefins in a different way (see reaction **5-23**).

OS **III,** 371, 774, 813; **IV,** 184, 558; **52,** 128.

5-6 Addition of Carboxylic Acids



$$-\underset{|}{C}=\underset{|}{C}- + RCOOH \xrightarrow{H^+} -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{OCOR}{|}}{\underset{|}{C}}-$$

Esters are produced by the addition of carboxylic acids to olefins, a reaction which is usually acid-catalyzed (by proton or Lewis acids[169]) and similar in mechanism to reaction **5-5.** Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols can be prepared by addition to olefins of the form $R_2C{=}CHR$.[170] *t*-Butyl alcohol is a particularly good solvent for this reaction.[171] When a carboxylic acid which contains a double bond in the chain is treated with a strong acid, the addition occurs internally and the product is a γ- and/or a δ-lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double-bond shifts (reaction **2-2**).[172] The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. However, another reaction competes, in which the product is a cyclopentenone or a cyclohexenone. This is essentially an example of reaction **2-15.** In either case, first the double bond migrates into the proper position, and then a proton from the catalyst may attack the acid in two ways. It either adds to the double bond or removes OH^- from the carboxyl group, leaving an acylonium ion:

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[166] Normal orientation was observed for unsubstituted, β-only-substituted, and α,β-disubstituted substrates: Bloodworth and Bunce, *Chem. Commun.* 753 (1970), *J. Chem. Soc. C* 1453 (1971).

[167] Lacey, *Adv. Org. Chem.* **2,** 213–263 (1960), pp. 216–217; Quadbeck, *Angew. Chem.* **68,** 361 (1956), *Newer Methods Prep. Org. Chem.* **2,** 133–161 (1963). For discussions of the mechanism, see Tille and Pracejus, *Chem. Ber.* **100,** 196–210 (1967); Brady, Vaughn, and Hoff, *J. Org. Chem.* **34,** 843 (1969); Ref. 137.

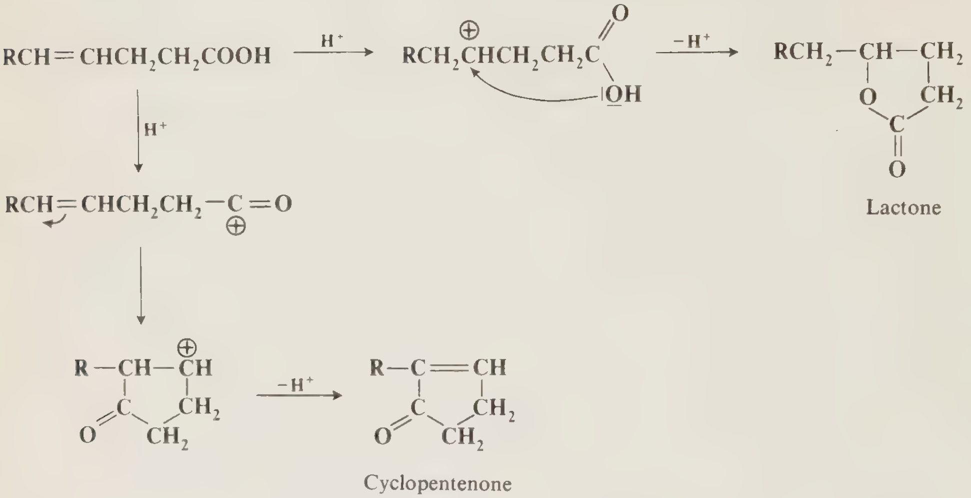
[168] For a review of carbon suboxide, see Kappe and Ziegler, *Angew. Chem. Int. Ed. Engl.* **13,** 491–504 (1974) [*Angew. Chem.* **86,** 529–542].

[169] See for example Guenzet and Camps, *Bull. Soc. Chim. Fr.* 3167 (1973), *Tetrahedron* **30,** 849 (1974).

[170] See for example Peterson and Tao, *J. Org. Chem.* **29,** 2322 (1964).

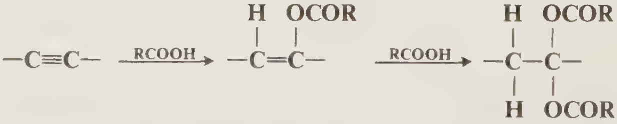
[171] Pavlov, Bogavac, and Arsenijevic, *Bull. Soc. Chim. Fr.* 2985 (1974).

[172] For a review of such lactonizations, see Ansell and Palmer, *Q. Rev., Chem. Soc.* **18,** 211–225 (1964).



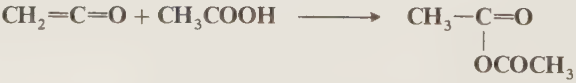
If it adds to the double bond, normal lactonization occurs, but if it creates an acylonium ion, *this* attacks the double bond and the ketone product is formed. Actually, the fact that anti addition is observed in the lactonization indicates that the two steps of this process are probably concerted or nearly so. Which type of reaction predominates depends mainly on which type of acid is used as catalyst. Proton-donating acids, e.g., H_2SO_4, HCOOH, and HF, give mostly lactones, while Lewis acids like acetic anhydride, $ZnCl_2$ in HOAc, P_2O_5, etc., are among those which give mostly ketones. Since carbonium ions are involved, rearrangements take place in both reactions.

Triple bonds may give alkenyl esters or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts:



$$-C\equiv C- \xrightarrow{RCOOH} -\overset{\displaystyle H\ \ OCOR}{\overset{|\quad |}{C=C}}- \xrightarrow{RCOOH} -\underset{\underset{\displaystyle H\ \ OCOR}{|\quad |}}{\overset{\overset{\displaystyle H\ \ OCOR}{|\quad |}}{C-C}}-$$

With ketenes, carboxylic acids give anhydrides,[173] and acetic anhydride is prepared industrially in this manner:



$$CH_2{=}C{=}O + CH_3COOH \longrightarrow CH_3-\underset{\underset{\displaystyle OCOCH_3}{|}}{C}{=}O$$

Esters can also be obtained by the addition to olefins of acyl peroxides.[174] These reactions are catalyzed by copper and are free-radical processes.

OS **III**, 853; **IV**, 261, 417, 444; **V**, 852, 863. Also see OS **I**, 317.

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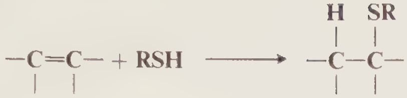
[173] For discussions of the mechanism, see Briody, Lillford, and Satchell, *J. Chem. Soc. B* 885 (1968); Corriu, Guenzet, Camps, and Reye, *Bull. Soc. Chim. Fr.* 3679 (1970); Ref. 137.

[174] Kharasch and Fono, *J. Org. Chem.* **24**, 606 (1959); Kochi, *J. Am. Chem. Soc.* **84**, 1572 (1962).

C. Sulfur on the Other Side

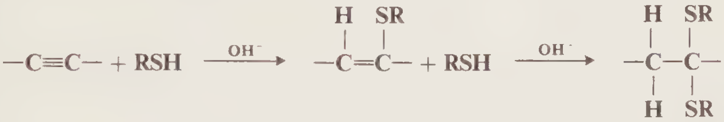
5-7 Addition of H_2S and Mercaptans



$$-\underset{|}{C}=\underset{|}{C}- + RSH \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{SR}{|}}{C}}-$$

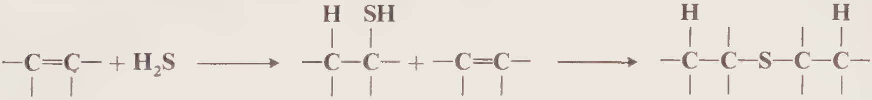
H_2S and mercaptans add to olefins by electrophilic, nucleophilic, or free-radical mechanisms.[175] In the absence of initiators the addition to simple olefins is by an electrophilic mechanism, similar to that in reaction **5-5**, and Markovnikov's rule is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless an acid catalyst is used. For example, the reaction can be performed in concentrated H_2SO_4.[176] In the presence of free-radical initiators, H_2S and mercaptans add to double and triple bonds by a free-radical mechanism, and the orientation is anti-Markovnikov.[177] In fact the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition can be done with H_2S, RSH (R may be primary, secondary, or tertiary), ArSH, RCOSH,[178] and even $(RO)_2PSSH$. R may contain various functional groups. The olefins may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR, NO_2, RSO_2, etc. With acetylenes it is possible to add 1 or 2 moles of RSH.

When mercaptans are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the Michael type[179] or may be polyhalo olefins or alkynes.[161] As with the free-radical mechanism, alkynes may give either vinyl thioethers or thioacetals:



$$-C\equiv C- + RSH \xrightarrow{OH^-} -\overset{\overset{H}{|}}{C}=\overset{\overset{SR}{|}}{C}- + RSH \xrightarrow{OH^-} -\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-\underset{\underset{SR}{|}}{\overset{\overset{SR}{|}}{C}}-$$

By any mechanism, the initial product of addition of H_2S to a double bond is a mercaptan, which is capable of adding to a second molecule of olefin, so that sulfides are often produced:



$$-\underset{|}{C}=\underset{|}{C}- + H_2S \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{SH}{|}}{C}}- + -\underset{|}{C}=\underset{|}{C}- \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{|}{C}}-S-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}-$$

Additions to conjugated dienes have been rare. For electrophilic (acid-catalyzed) conditions, 1,4 addition has been reported.[180] For free-radical addition, both 1,2[180] and 1,4 addition[181] have been demonstrated. Conjugated diynes, treated with H_2S, give thiophenes:[182]

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[175] For reviews, see Prilezhaeva and Shostakovskii, *Russ. Chem. Rev.* **32,** 399–426 (1963); Wardell, in Patai, "The Chemistry of the Thiol Group," pt. 1, pp. 169–178, John Wiley & Sons, Inc., New York, 1974; Reid, "Organic Chemistry of Bivalent Sulfur," vol. 1, pp. 18–21, vol. 2, pp. 29–42, Chemical Publishing Company, New York, 1958–1960.

[176] Shostakovskii, Kul'bovskaya, Gracheva, Laba, and Yakushina, *J. Gen. Chem. USSR* **32,** 707 (1962).

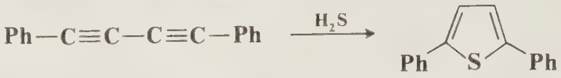
[177] For reviews of free-radical addition of H_2S and RSH, see Griesbaum, *Angew. Chem. Int. Ed. Engl.* **9,** 273–287 (1970) [*Angew. Chem.* **82,** 276–290]; Oswald and Griesbaum, in Kharasch and Meyers, "Organic Sulfur Compounds," vol. 2, pp. 233–256, Pergamon Press, New York, 1966; Stacey and Harris, *Org. React.* **13,** 150–376 (1963), pp. 165–196, 247–324; Sosnovsky, Ref. 41, pp. 62–97; Walling, Ref. 41, pp. 313–326.

[178] For a review of the addition of thio acids, see Janssen, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 720–723, Interscience Publishers, New York, 1969.

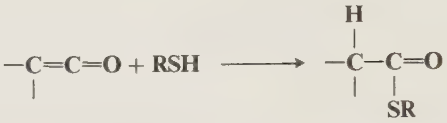
[179] For a review of additions to acrylonitrile, see Bruson, *Org. React.* **5,** 79–135 (1949), pp. 95–97, 129–130.

[180] Saville, *J. Chem. Soc.* 5040 (1962).

[181] Oswald, Griesbaum, Thaler, and Hudson, *J. Am. Chem. Soc.* **84,** 3897 (1962); Claisse and Davies, *J. Chem. Soc.* 4894 (1965), obtained both 1,2 and 1,4 products.

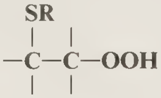


Conjugated triynes and tetraynes also give thiophenes. Ketenes add mercaptans to give thiol esters:



$$-\underset{|}{C}{=}C{=}O + RSH \longrightarrow -\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{SR}{|}}{C}{=}O$$

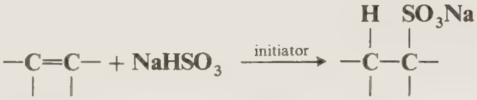
When mercaptans add to olefins by a free-radical mechanism in the presence of oxygen, β-hydroperoxy sulfides are side products:



$$-\overset{\overset{SR}{|}}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OOH$$

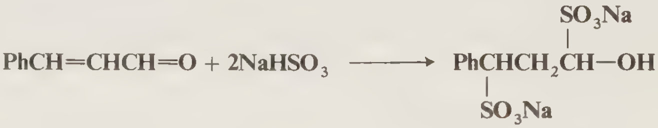
OS **III**, 458; **IV**, 669.

5-8 Addition of Sodium Bisulfite



$$-\underset{|}{C}{=}\underset{|}{C}- + NaHSO_3 \xrightarrow{\text{initiator}} -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{SO_3Na}{|}}{\underset{|}{C}}-$$

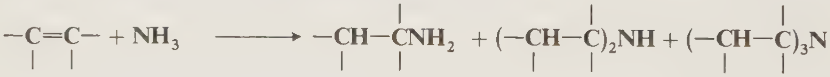
Salts of aliphatic sulfonic acids can be prepared by addition of bisulfite salts to olefins in the presence of free-radical initiators.[183] The orientation is anti-Markovnikov. On systems of the type C=C—C=O, bis addition may be observed:



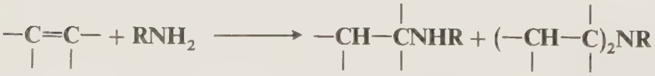
$$PhCH{=}CHCH{=}O + 2NaHSO_3 \longrightarrow Ph\underset{\underset{SO_3Na}{|}}{CH}CH_2\overset{\overset{SO_3Na}{|}}{CH}-OH$$

D. Nitrogen on the Other Side

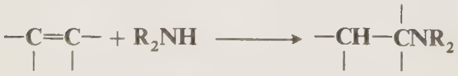
5-9 Addition of Ammonia and Amines



$$-\underset{|}{C}{=}\underset{|}{C}- + NH_3 \longrightarrow -\underset{|}{CH}-\overset{|}{\underset{|}{C}}NH_2 + (-\underset{|}{CH}-\overset{|}{\underset{|}{C}})_2NH + (-\underset{|}{CH}-\overset{|}{\underset{|}{C}})_3N$$



$$-\underset{|}{C}{=}\underset{|}{C}- + RNH_2 \longrightarrow -\underset{|}{CH}-\overset{|}{\underset{|}{C}}NHR + (-\underset{|}{CH}-\overset{|}{\underset{|}{C}})_2NR$$



$$-\underset{|}{C}{=}\underset{|}{C}- + R_2NH \longrightarrow -\underset{|}{CH}-\overset{|}{\underset{|}{C}}NR_2$$

Ammonia and primary and secondary amines add to olefins which are susceptible to nucleophilic attack.[184] Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of olefin, etc. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. Since ammonia and amines are much weaker acids than water, alcohols, and mercaptans (see reactions **5-2, 5-5, 5-7**), and since acids could hardly catalyze the reaction (because they would turn NH_3 into NH_4^+), this reaction does not occur by an electrophilic mechanism and so gives very low yields, if any, with ordinary olefins. The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo olefins,[185] Michael-type substrates, and alkynes. As expected, on Michael-type substrates the nitrogen goes to the carbon which does not carry the Z.[186] Other nitrogenous compounds, among them hydroxylamine, hydrazines, amides ($RCONH_2$ and RCONHR′ including imides and lactams), and sulfonamides, also add to olefins. In the case of amides, basic catalysts are required, since amides are not good enough nucleophiles for the reaction and must be converted to $RCONH^-$. Even with amines, basic catalysts are sometimes used, so that RNH^- or R_2N^- is the actual nucleophile. Tertiary amines (except those which are too bulky) add to Michael-type substrates in a reaction which is catalyzed by acids like HCl or HNO_3, to give the corresponding quaternary ammonium salts.[187]

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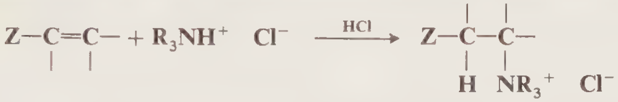
[182] Schulte, Reisch, and Hörner, *Chem. Ber.* **95**, 1943 (1962).

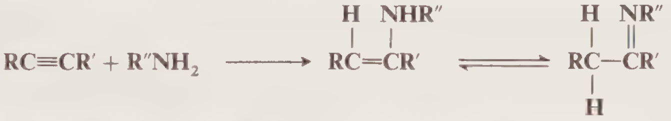
[183] For a review, see Gilbert, "Sulfonation and Related Reactions," pp. 148–156, Interscience Publishers, New York, 1965.



$$\mathrm{Z{-}\underset{|}{C}{=}\underset{|}{C}{-} + R_3NH^+\ \ Cl^- \xrightarrow{HCl} Z{-}\overset{|}{\underset{\underset{\displaystyle H}{|}}{C}}{-}\overset{|}{\underset{\underset{\displaystyle NR_3^+}{|}}{C}}{-}\ \ Cl^-}$$

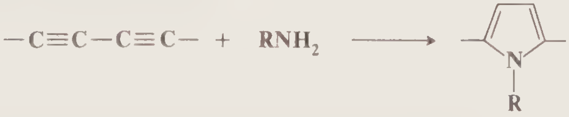
The tertiary amine may be aliphatic, cycloalkyl, or heterocyclic (including pyridine).

Triple bonds are readily attacked.[188] Primary amines add to give enamines, which have a hydrogen on the nitrogen and (analogously to enols) tautomerize to the more stable imines:



$$\mathrm{RC{\equiv}CR' + R''NH_2 \longrightarrow \overset{\overset{\displaystyle H}{|}}{R C}{=}\overset{\overset{\displaystyle NHR''}{|}}{C}R' \rightleftharpoons R\underset{\underset{\displaystyle H}{|}}{\overset{\overset{\displaystyle H}{|}}{C}}{-}\overset{\overset{\displaystyle NR''}{\|}}{C}R'}$$

These are often stable enough for isolation.[189] When ammonia is used instead of a primary amine, the corresponding $\mathrm{RCH_2{-}\overset{\overset{\displaystyle NH}{\|}}{C}R'}$ is not stable enough for isolation, but polymerizes. Secondary amines give enamines $RCH{=}CR'NR''_2$, which, lacking a hydrogen on the nitrogen, are quite stable. It has been shown that triple bonds are more susceptible than even activated double bonds to attack by amines. Thus diethylamine added to the triple bonds of *both* $CH_3COCH{=}CHC{\equiv}CH$ and $CH_3COC{\equiv}CCH{=}CH_2$.[190] Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles:[191]



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[184] For reviews, see Suminov and Kost, *Russ. Chem. Rev.* **38,** 884–899 (1969); Gibson, in Patai, "The Chemistry of the Amino Group," pp. 61–65, Interscience Publishers, New York, 1968.

[185] For a review with respect to fluoroolefins, see Chambers and Mobbs, *Adv. Fluorine Chem.* **4,** 51–112 (1965), pp. 62–68.

[186] For a review of cyanoethylation of ammonia and amines, see Bruson, *Org. React.* **5,** 79–135 (1949), pp. 79–89, 113–120.

[187] Le Berre and Delacroix, *Bull. Soc. Chim. Fr.* 640, 647 (1973).

[188] For a review of addition of ammonia and amines to triple bonds, see Chekulaeva and Kondrat'eva, *Russ. Chem. Rev.* **34,** 669–680 (1965).

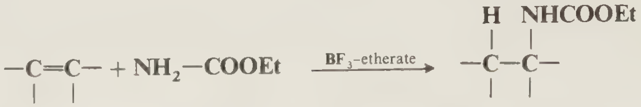
[189] For example, see Kruse and Kleinschmidt, *J. Am. Chem. Soc.* **83,** 213, 216 (1961).

[190] Bowden, Braude, Jones, and Weedon, *J. Chem. Soc.* 45 (1946).

[191] Schulte, Reisch, and Walker, *Chem. Ber.* **98,** 98 (1965).

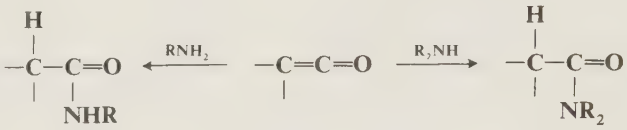
This is not 1,4 addition but 1,2 addition twice.

Carbamates add to olefins and conjugated dienes (which give 1,4 addition) in the presence of BF_3–etherate to give N-substituted carbamates:[192]



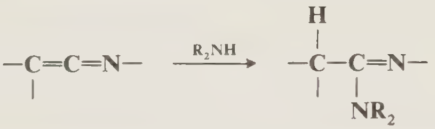
$$-\underset{|}{C}=\underset{|}{C}- + NH_2-COOEt \xrightarrow{BF_3\text{-etherate}} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{NHCOOEt}{|}}{C}}-$$

Primary and secondary amines add to ketenes, to give, respectively, N-substituted and N,N-disubstituted amides:[193]



$$-\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{\underset{NHR}{|}}{C}=O \xleftarrow{RNH_2} -\underset{|}{C}=C=O \xrightarrow{R_2NH} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{\underset{NR_2}{|}}{C}=O$$

and to ketenimines to give amidines:[194]

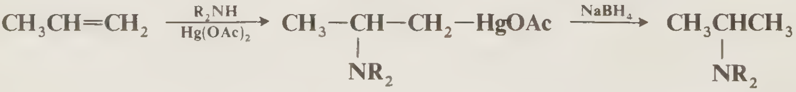


$$-\underset{|}{C}=C=N- \xrightarrow{R_2NH} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{\underset{NR_2}{|}}{C}=N-$$

R = H or alkyl

Secondary amines can be added to certain nonactivated olefins if palladium(II) complexes are used as catalysts.[195] Markovnikov orientation is observed.

NH_3 can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (**5-15**) followed by treatment with NH_2Cl or NH_2OSO_2OH (**2-29**). This produces a primary amine with anti-Markovnikov orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration followed by reduction (see **5-2** for the analogous oxymercuration-demercuration procedure), e.g.,[196]



$$CH_3CH=CH_2 \xrightarrow[Hg(OAc)_2]{R_2NH} CH_3-\underset{\underset{NR_2}{|}}{CH}-CH_2-HgOAc \xrightarrow{NaBH_4} CH_3\underset{\underset{NR_2}{|}}{CH}CH_3$$

The addition of a secondary amine (shown above) produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows Markovnikov's rule. See also reaction **6-57**.

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **53**, 13. Also see OS **53**, 98.

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[192] Müller and Merten, *Chem. Ber.* **98**, 1097 (1965).

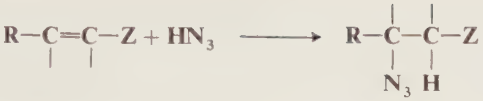
[193] For discussions of the mechanism of this reaction, see Briody and Satchell, *Tetrahedron* **22**, 2649 (1966); Lillford and Satchell, *J. Chem. Soc. B* 360 (1967), 54 (1968); Ref. 137.

[194] Stevens, Freeman, and Noll, *J. Org. Chem.* **31**, 3718 (1965).

[195] See for example, Walker, Manyik, Atkins, and Farmer, *Tetrahedron Lett.* 3817 (1970); Takahashi, Miyake, and Hata, *Bull. Chem. Soc. Jpn.* **45**, 1183 (1972); Baker, Cook, Halliday, and Smith, *J. Chem. Soc., Perkin Trans. 2* 1511 (1974); Åkermark, Bäckvall, Hegedus, Zetterberg, Siirala-Hanseń, and Sjöberg, *J. Organomet. Chem.* **72**, 127 (1974); Åkermark, Bäckvall, Siirala-Hanseń, Sjöberg, and Zetterberg, *Tetrahedron Lett.* 1363 (1974); Åkermark and Bäckvall, *Tetrahedron Lett.* 819 (1975); Hegedus, Allen, and Waterman, *J. Am. Chem. Soc.* **98**, 2674 (1976).

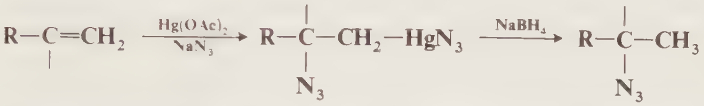
[196] Lattes and Périé, *C. R. Acad. Sci., Ser. C* **262**, 1591 (1966), *Tetrahedron Lett.* 5165 (1967); Périé and Lattes, *Tetrahedron Lett.* 2289 (1969), *Bull. Soc. Chim. Fr.* 583 (1970); Bäckvall and Åkermark, *J. Organomet. Chem.* **78**, 177 (1974).

5-10 Addition of Hydrazoic Acid



$$R-\underset{|}{C}=\underset{|}{C}-Z + HN_3 \longrightarrow R-\underset{\underset{N_3}{|}}{\overset{|}{C}}-\underset{\underset{H}{|}}{\overset{|}{C}}-Z$$

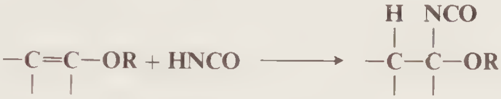
Hydrazoic acid can be added to certain Michael-type substrates (Z is as defined on p. 678) to give β-azido compounds.[197] The reaction apparently fails if R is phenyl. HN_3 can be added indirectly to ordinary olefins by azidomercuration, followed by demercuration,[198] analogous to the similar procedures mentioned in reactions **5-2**, **5-5**, and **5-9**. The method can be applied to



$$R-\underset{|}{C}=CH_2 \xrightarrow[NaN_3]{Hg(OAc)_2} R-\underset{\underset{N_3}{|}}{\overset{|}{C}}-CH_2-HgN_3 \xrightarrow{NaBH_4} R-\underset{\underset{N_3}{|}}{\overset{|}{C}}-CH_3$$

terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes.

5-11 Addition of HNCO to Vinyl Ethers

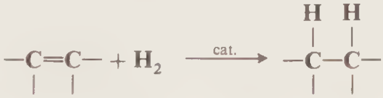


$$-\underset{|}{C}=\underset{|}{C}-OR + HNCO \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{NCO}{|}}{C}}-OR$$

α-Alkoxyisocyanates can be prepared by addition of cyanic acid to vinyl ethers.[199] The orientation is always as shown. Certain other olefins also undergo this reaction.[200]

E. Hydrogen on Both Sides

5-12 Hydrogenation of Double and Triple Bonds[201]



$$-\underset{|}{C}=\underset{|}{C}- + H_2 \xrightarrow{\text{cat.}} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}-$$

Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.[202] According to the review of Adkins and Shriner, over 99% of all known alkenes add hydrogen at temperatures between 0 and 275 C. Many functional groups may be present in the molecule, e.g., OH, COOH, NH_2, CHO, COR, COOR, or CN. Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively[203] (see Table 2 in Chapter 19, p. 1116). The catalysts used can be divided into two broad classes both of which mainly consist of transition metals and their compounds: (1) catalysts which are insoluble in the reaction medium (*heterogeneous catalysts*). These have been the ones traditionally used. Among the most effective are Raney nickel,[204] $NaBH_4$-reduced nickel[205] (also called nickel boride), platinum metal or its oxide,[206] rhodium, ruthenium, zinc oxide,[207] and palladium-on-charcoal. (2) Catalysts which are soluble in the reaction medium (*homogeneous catalysts*).[208] These are of more recent discovery. The most important is chlorotris(triphenylphosphine)rhodium $RhCl(Ph_3P)_3$,[209] often called *Wilkinson's catalyst*, which catalyzes the hydrogenation of many olefinic compounds without disturbing such groups as COOR, NO_2, CN, or COR present in the same molecule.[210] Even unsaturated aldehydes can be reduced to saturated aldehydes,[211] though in this case decarbonylation (reaction **4-41**) may be a side reaction. Among other homogeneous catalysts are chlorotris(triphenylphosphine)-hydridoruthenium(II) $(Ph_3P)_3RuClH$,[212] which is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all), and pentacyanocobaltate(II) $Co(CN)_5{}^{3-}$, which is effective for double and triple bonds only when they are part of conjugated systems[213] (the conjugation may be with C=C, C=O, or an aromatic ring). Homogeneous catalysts often have the advantages of better catalyst reproducibility and better selectivity. They are also less susceptible to catalyst poisoning[214] (heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by sulfur-containing compounds such as mercaptans and sulfides). On the other hand, heterogeneous catalysts are usually easier to separate from the reaction mixture. Optically active homogeneous (as well as heterogeneous) catalysts have been used to achieve partially asymmetric hydrogenations.[215]

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[197] Boyer, *J. Am. Chem. Soc.* **73**, 5248 (1951); Harvey and Ratts, *J. Org. Chem.* **31**, 3907 (1966). For a review, see Biffen, Miller, and Paul, in Patai, "The Chemistry of the Azido Group," pp. 120–136, Interscience Publishers, 1971.

[198] Heathcock, *Angew. Chem. Int. Ed. Engl.* **8**, 134 (1969) [*Angew. Chem.* **81**, 148].

[199] Hoover and Rothrock, *J. Org. Chem.* **28**, 2082 (1963).

[200] For a review, see Ozaki, *Chem. Rev.* **72**, 457–496 (1972), p. 461.

[201] For a review, see Mitsui and Kasahara, in Zabicky, Ref. 111, vol. 2, pp. 175–214.

[202] For a monograph on catalytic hydrogenation, see Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, 1965. For reviews, see Adkins and Shriner, in Gilman, "Advanced Organic Chemistry," 2d ed., vol. 1, pp. 779–834, John Wiley & Sons, Inc., New York, 1943; Candlin and Rennie, in Bentley and Kirby, "Elucidation of Organic Structures by Physical and Chemical Methods," 2d ed. (vol. 4 of Weissberger, "Techniques of Chemistry"), pt. 2, pp. 97–117, John Wiley & Sons, Inc., New York, 1973; McQuillin, in Bentley, "Eulicidation of Structures by Physical and Chemical Methods," 1st ed. (vol. 9 of Weissberger, "Techniques of Organic Chemistry"), pt. 1, pp. 497–580, Interscience Publishers, New York, 1963; House, Ref. 141, pp. 1–34; Carruthers, "Some Modern Methods of Organic Synthesis," pp. 299–326, Cambridge University Press, London, 1971.

Hydrogenations in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures. The resistance is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25°C and 100 atm, while tetrasubstituted double bonds may require 275°C and 100 atm. Among the double bonds which are most difficult

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[203] For a discussion, see Ref. 206, pp. 59–120.

[204] For a review of hydrogenations with Raney nickel, see Schröter, *Newer Methods Prep. Org. Chem.* **1,** 61–101 (1948).

[205] Paul, Buisson, and Joseph, *Ind. Eng. Chem.* **44,** 1006 (1952); Brown, *Chem. Commun.* 952 (1969), *J. Org. Chem.* **35,** 1900 (1970); Brown and Ahuja, *J. Org. Chem.* **38,** 2226 (1973), *J. Chem. Soc., Chem. Commun.* 553 (1973).

[206] For a treatise on hydrogenation with Pt, Ru, Rh, Pd, Os, and Ir catalysts, see Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, Inc., New York, 1967.

[207] For a review of hydrogenations with zinc oxide, see Kokes and Dent, *Adv. Catal.* **22,** 1–50 (1972).

[208] For a monograph, see James, "Homogeneous Hydrogenation," John Wiley & Sons, Inc., New York, 1973. For reviews, see Harmon, Gupta, and Brown, *Chem. Rev.* **73,** 21–52 (1973); Strohmeier, *Fortschr. Chem. Forsch.* **25,** 71–104 (1972); Heck, "Organotransition Metal Chemistry," pp. 55–65, Academic Press, Inc., New York, 1974; Rylander, "Organic Syntheses with Noble Metal Catalysts," pp. 60–76, Academic Press, Inc., New York, 1973; Lyons, Rennick, and Burmeister, *Ind. Eng. Chem., Prod. Res. Dev.* **9,** 2–20 (1970); Vol'pin and Kolomnikov, *Russ. Chem. Rev.* **38,** 273-289 (1969); Osborn, *Endeavor* **26,** 144–148 (1967); Bird, "Transition Metal Intermediates in Organic Synthesis," pp. 248–271, Academic Press, Inc., New York, 1967; Tulupov, *Russ. J. Phys. Chem.* **39,** 1251–1260 (1965); Lauer, *Ann. Chim. (Paris)* [13] **10,** 301–311 (1965).

[209] Young, Osborn, Jardine, and Wilkinson, *Chem. Commun.* 131 (1965); Osborn, Jardine, Young, and Wilkinson, *J. Chem. Soc. A* 1711 (1966); Osborn and Wilkinson, *Inorg. Synth.* **10,** 67 (1967); Biellmann, *Bull. Soc. Chim. Fr.* 3055 (1968); van Bekkum, van Rantwijk, and van de Putte, *Tetrahedron Lett.* 1 (1969).

[210] Harmon, Parsons, Cooke, Gupta, and Schoolenberg, *J. Org. Chem.* **34,** 3684 (1969).

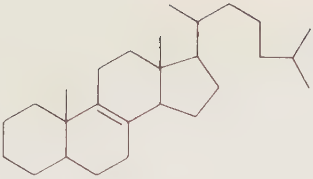
[211] Jardine and Wilkinson, *J. Chem. Soc. C* 270 (1967).

[212] Hallman, Evans, Osborn, and Wilkinson, *Chem. Commun.* 305 (1967); Hallman, McGarvey, and Wilkinson, *J. Chem. Soc. A* 3143 (1968); Jardine and McQuillin, *Tetrahedron Lett.* 5189 (1968).

[213] Kwiatek, Mador, and Seyler, *J. Am. Chem. Soc.* **84,** 304 (1962); Jackman, Hamilton, and Lawlor, *J. Am. Chem. Soc.* **90,** 1914 (1968); Funabiki, Matsumoto, and Tarama, *Bull. Chem. Soc. Jpn.* **45,** 2723 (1972).

[214] Birch and Walker, *Tetrahedron Lett.* 1935 (1967).

[215] For reviews, see Bogdanović, *Angew. Chem. Int. Ed. Engl.* **12,** 954-964 (1973) [*Angew. Chem.* **85,** 1013-1023]; Izumi, *Angew. Chem. Int. Ed. Engl.* **10,** 871-881 (1971) [*Angew. Chem.* **83,** 956-966]. See also Ref. 65 in Chapter 4.



to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in the steroid shown. Hydrogenations, even at about atmospheric pressure, are ordinarily performed in a special hydrogenator, but this is not always necessary. Both the catalyst and the hydrogen may be generated in situ, by treatment of H_2PtCl_6 or $RhCl_3$ with $NaBH_4$,[216] and then ordinary glassware may be used.

Although catalytic hydrogenation is the method which is most often used, double bonds can be reduced by other reagents as well. Among these are sodium in ethanol, sodium and *t*-butyl alcohol in HMPT,[217] lithium and aliphatic amines[218] (see also reaction **5-13**), chromous ion,[219] zinc and acids, water and precipitated nickel,[220] trifluoroacetic acid and triethylsilane Et_3SiH,[221] hydrazine (if a small amount of oxidizing agent, such as air, H_2O_2, or cupric ion is present),[222] and NH_2OSO_3H.[223] However, metallic hydrides, such as lithium aluminum hydride and sodium borohydride, do not in general reduce carbon-carbon double bonds,[224] although this can be done in special cases where the double bond is polar, as in fulvenes (p. 46). In addition, lithium aluminum hydride often reduces double bonds which are in conjugation with C=O bonds, as well as reducing the C=O bonds, e.g.,[225]

$$\mathbf{Ph{-}CH{=}CH{-}COOH} \xrightarrow{\text{LiAlH}_4} 85\%\ \mathbf{Ph{-}CH_2{-}CH_2{-}CH_2OH}$$

This double reduction can be avoided by the use of aluminum hydride[226] or diisobutylaluminum hydride,[227] which selectively reduce C=O groups in the presence of conjugated C=C bonds (see also p. 830). On the other hand, C=C bonds can be selectively reduced in the presence of conjugated C=O bonds by hydrogenation with $RhCl(PPh_3)_3$ as catalyst,[228] as well as by a number of other methods.[229] $LiAlH_4$ also reduces the double bonds of allylic alcohols.[230]

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[216] Brown and Sivasankaran, *J. Am. Chem. Soc.* **84,** 2828 (1962); Brown and Brown, *J. Am. Chem. Soc.* **84,** 1494, 1495, 2829 (1962), *J. Org. Chem.* **31,** 3989 (1966); Brown, Sivasankaran, and Brown, *J. Org. Chem.* **28,** 214 (1963). See also Brown and Brown, *Tetrahedron Suppl.* **8,** pt. 2, 149 (1966); Brown, *J. Am. Chem. Soc.* **91,** 5901 (1969), *Chem. Commun.* 139 (1970).

[217] Angibeaud, Larchevêque, Normant, and Tchoubar, *Bull. Soc. Chim. Fr.* 595 (1968); Whitesides and Ehmann, *J. Org. Chem.* **35,** 3565 (1970).

[218] Benkeser, Schroll, and Sauve, *J. Am. Chem. Soc.* **77,** 3378 (1955).

[219] For example, see Castro and Stephens, *J. Am. Chem. Soc.* **86,** 4358 (1964); Castro, Stephens, and Mojé, *J. Am. Chem. Soc.* **88,** 4964 (1966).

[220] Sakai, Ishige, Kono, Motoyama, Watanabe, and Hata, *Bull. Chem. Soc. Jpn.* **41,** 1902 (1968).

[221] Kursanov, Parnes, Bassova, Loim, and Zdanovich, *Tetrahedron* **23,** 2235 (1967); Kursanov, Parnes, and Bolestova, *Doklad. Chem.* **181,** 726 (1968). For a review, see Kursanov, Parnes, and Loim, *Synthesis* 633–651 (1974). See also Kalinkin, Parnes, Shaapuni, and Kursanov, *Doklad. Chem.* **219,** 888 (1974).

[222] Corey, Mock, and Pasto, *Tetrahedron Lett.* 347 (1961); Hünig, Müller, and Thier, *Tetrahedron Lett.* 353 (1961); Furst, Berlo, and Hooton, *Chem. Rev.* **65,** 51–68 (1965), pp. 64–65; Nagendrappa and Devaprabhakara, *Tetrahedron Lett.* 4243 (1970); Hoffman and Schlessinger, *Chem. Commun.* 1245 (1971).

[223] Appel and Büchner, *Justus Liebigs Ann. Chem.* **654,** 1 (1962); Dürckheimer, *Justus Liebigs Ann. Chem.* **721,** 240 (1969).

[224] For a review of the action of metallic hydrides on olefins and acetylenes, see Gaylord, "Reduction with Complex Metal Hydrides," pp. 925–975, Interscience Publishers, Inc., New York, 1956.

[225] Nystrom and Brown, *J. Am. Chem. Soc.* **69,** 2548 (1947), **70,** 3738 (1948).

[226] Jorgenson, *Tetrahedron Lett.* 559 (1962); Brown and Hess, *J. Org. Chem.* **34,** 2206 (1969); Dilling and Plepys, *J. Org. Chem.* **35,** 2971 (1970).

[227] Wilson, Seidner, and Masamune, *Chem. Commun.* 213 (1970).

The inertness of ordinary double bonds toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without effect on a double bond in the same molecule (see Chapter 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds, though it does reduce alkynes, allenes, conjugated dienes,[230a] certain nonconjugated dienes,[231] and aromatic rings (reaction **5-13**).

Another hydrogenation method is called *transfer hydrogenation.*[232] In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst is frequently employed. A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing 2 moles of hydrogen.

Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned. The comparative reactivity of triple and double bonds depends on the catalyst.[233] With most catalysts, e.g., Pd, triple bonds are hydrogenated more easily, and therefore it is possible to add just 1 mole of hydrogen and reduce a triple bond to a double bond (usually a stereoselective syn addition) or to reduce a triple bond without affecting a double bond present in the same molecule.[234] A particularly good catalyst for this purpose is the Lindlar catalyst ($Pd–CaCO_3–PbO$).[235] On the other hand, there are catalysts which selectively hydrogenate double bonds. Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride[236] (usually a stereoselective syn addition) or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine (a stereoselective anti addition). Terminal alkynes are not reduced by the $Na–NH_3$ procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the $Na–NH_3$ solution of $(NH_4)_2SO_4$, which liberates the free ethynyl group.[237]

An indirect method[238] of double-bond reduction involves hydrolysis of boranes (prepared by reaction **5-15**). Trialkylboranes can be hydrolyzed by refluxing with carboxylic acids,[239] while

[228] Djerassi and Gutzwiller, *J. Am. Chem. Soc.* **88,** 4537 (1966); Ref. 210.

[229] See Kadin, *J. Org. Chem.* **31,** 620 (1966); Pereyre and Valade, *Bull. Soc. Chim. Fr.* 1928 (1967), *Tetrahedron Lett.* 489 (1969); Pereyre, Colin, and Valade, *Tetrahedron Lett.* 4805 (1967); Iqbal and Jackson, *J. Chem. Soc. C* 616 (1968); Angibeaud, Larchevêque, Normant, and Tchoubar, Ref. 217; Gautier, Miocque, and Duclos, *Bull. Soc. Chim. Fr.* 4348 (1969); Buchanan and Woodgate, *Q. Rev., Chem. Soc.* **23,** 522–536 (1969); Mel'nikova and Pivnitskii, *J. Org. Chem. USSR* **6,** 2635 (1970), **8,** 2138 (1972); Sasson and Blum, *Tetrahedron Lett.* 2167 (1971); Blum, Sasson, and Iflah, *Tetrahedron Lett.* 1015 (1972); Noyori, Umeda, and Ishigami, *J. Org. Chem.* **37,** 1542 (1972); Kursanov, Loim, Baranova, Moiseeva, Zalukaev, and Parnes, *Synthesis* 420 (1973); Kitamura, Sakamoto, and Joh, *Chem. Lett.* 379 (1973); House and Kinloch, *J. Org. Chem.* **39,** 1173 (1974); Masamune, Bates, and Georghiou, *J. Am. Chem. Soc.* **96,** 3686 (1974); Mc Murry, *Acc. Chem. Res.* **7,** 281–286 (1974), p. 284; Boeckman and Michalak, *J. Am. Chem. Soc.* **96,** 1623 (1974); Schauble, Walker, and Morin, *J. Org. Chem.* **39,** 755 (1974); Ganem, *J. Org. Chem.* **40,** 146 (1975); Kitamura, Joh, and Hagihara, *Chem. Lett.* 203 (1975); Ashby and Lin, *Tetrahedron Lett.* 4453 (1975).

[230] For discussions of the mechanism of this reaction, see Snyder, *J. Org. Chem.* **32,** 3531 (1967); Borden, *J. Am. Chem. Soc.* **90,** 2197 (1968).

[230a] For a review of reductions of α,β-unsaturated carbonyl compounds with metals in liquid NH_3, see Caine, *Org. React.* **23,** 1–258 (1976).

[231] Ortiz de Montellano, Loving, Shields, and Gardner, *J. Am. Chem. Soc.* **89,** 3365 (1967).

[232] For reviews, see Brieger and Nestrick, *Chem. Rev.* **74,** 567–580 (1974); Jackman, *Adv. Org. Chem.* **2,** 329–366 (1960).

[233] For a discussion, see Wells, *Chem. Ind. (London)* 1742 (1964).

[234] For reviews of the catalytic hydrogenation of alkynes, see Marvell and Li, *Synthesis* 457–468 (1973); Gutmann and Lindlar, in Viehe, Ref. 70, pp. 355–363.

[235] Lindlar and Dubois, *Org. Synth.* **V,** 880.

[236] Wilke and Müller, *Chem. Ber.* **89,** 444 (1956); *Justus Liebigs Ann. Chem.* **629,** 224 (1960); Gensler and Bruno, *J. Org. Chem.* **28,** 1254 (1963); Eisch and Kaska, *J. Am. Chem. Soc.* **88,** 2213 (1966).

[237] Henne and Greenlee, *J. Am. Chem. Soc.* **65,** 2020 (1943).

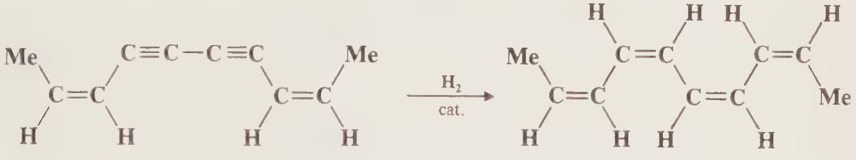
[238] For a review, see Zweifel, *Intra-Sci. Chem. Rep.* **7**(2), 181–189 (1973).

[239] Brown and Murray, *J. Am. Chem. Soc.* **81,** 4108 (1959).

monoalkylboranes RBH_2 can be hydrolyzed with base.[240] Triple bonds can be similarly reduced, to cis olefins.[241]

Conjugated dienes may add hydrogen by 1,2 or 1,4 addition. Selective 1,4 addition can be achieved by hydrogenation in the presence of carbon monoxide, with bis(cyclopentadienyl)-chromium as catalyst.[242] With allenes catalytic hydrogenation usually reduces both double bonds, but reduction of just one double bond, to give an olefin, has been accomplished by treatment with Na NH_3[243] and by hydrogenation with $RhCl(PPh_3)_3$ as catalyst.[244]

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be syn, with the hydrogens entering from the less hindered side of the molecule.[245] Stereospecificity can be investigated only for tetrasubstituted olefins (except when the reagent is D_2), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80 to 100% syn, though some of the anti addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes nearly always is stereoselective, giving the cis olefin (usually at least 80%), even when it is thermodynamically less stable. For example, **36** gave **37**, even though the steric hindrance is such that a planar molecule is impossible.[246] This is thus a useful method of preparing such cis olefins. However, when steric hindrance is too great, the trans olefin may be formed. One factor which complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogens takes place, as can be shown by hydrogenation with deuterium. Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and ethanes (including C_2H_6), as well as HD.[247] With 2-butene, it was found that double-bond migration, cis-trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur; e.g., $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst.[248] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,[249] and even without deuterium, i.e.,



36 **37**

$$CH_4 + CD_4 \longrightarrow CHD_3 + CH_2D_2$$

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[240] Weinheimer and Marisco, *J. Org. Chem.* **27**, 1926 (1962).

[241] Brown and Zweifel, *J. Am. Chem. Soc.* **81**, 1512 (1959).

[242] Miyake and Kondo, *Angew. Chem. Int. Ed. Engl.* **7**, 631 (1968) [*Angew. Chem.* **80**, 663]. See also Cais, Frankel, and Rejoan, *Tetrahedron Lett.* 1919 (1968).

[243] Gardner and Narayana, *J. Org. Chem.* **26**, 3518 (1961); Devaprabhakara, and Gardner, *J. Am. Chem. Soc.* **85**, 648 (1963); Vaidyanathaswamy, Joshi, and Devaprabhakara, *Tetrahedron Lett.* 2075 (1971).

[244] Bhagwat and Devaprabhakara, *Tetrahedron Lett.* 1391 (1972) See also Freidlin, Kopyttsev, Litvin, and Nazarova, *J. Org. Chem. USSR* **10**, 434 (1974); Pregaglia, Ferrari, Andreeta, Capparella, Genoni, and Ugo, *J. Organomet. Chem.* **70**, 89 (1974).

[245] For a review of the stereochemistry of heterogeneous catalytic hydrogenation, see Burwell, *Chem. Rev.* **57**, 895–934 (1957).

[246] Holme, Jones, and Whiting, *Chem. Ind. (London)* 928 (1956).

[247] Turkevich, Schissler, and Irsa, *J. Phys. Chem.* **55**, 1078 (1951).

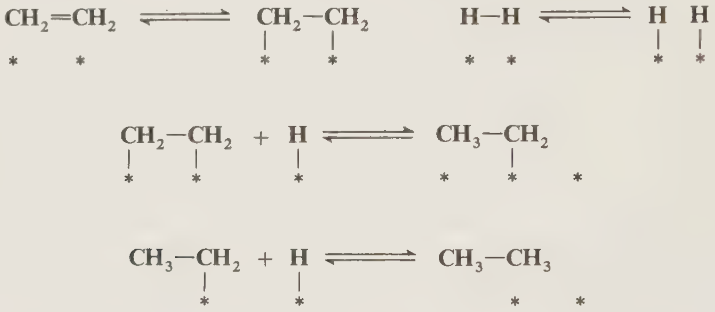
[248] Wilson, Otvos, Stevenson, and Wagner, *Ind. Eng. Chem.* **45**, 1480 (1953).

[249] For reviews, see Gudkov and Balandin, *Russ. Chem. Rev.* **35**, 756–761 (1966); Kemball, *Adv. Catal.* **11**, 223–262 (1959).

in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.

It was mentioned that catalytic hydrogenation of triple bonds and the reaction with diisobutylaluminum hydride usually give the cis olefin. Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans olefin. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with hydrazine or NH_2OSO_3H, which also give the cis products.

The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.[250] Because the reaction is heterogeneous, kinetic data, though easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.[251] According to this, the olefin is adsorbed onto the surface of the metal, though the nature of the actual bonding is unknown[252] despite many attempts to elucidate it.[253] The metallic site is usually indicated by an asterisk. For steric reasons it is apparent that adsorption of the olefin takes place with its less hindered side attached to the catalyst surface. The fact that addition of hydrogen is generally also from the less hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the olefin. It is likely that the H_2 molecule is cleaved to hydrogen atoms in the act of being adsorbed. It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.[254] In the second step one of the adsorbed hydrogen atoms becomes attached to a carbon atom, creating, in effect, an alkyl radical (which is still bound to the catalyst though only by one bond) and two vacant catalyst sites. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and two more vacant sites. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of scheme. For example, these steps may be occurring in hydrogenation of 1-butene:[255]



$$\underset{*\qquad *}{CH_2{=}CH_2} \rightleftharpoons \underset{*\qquad *}{\overset{\vert\qquad\vert}{CH_2{-}CH_2}} \qquad \underset{*\quad *}{H{-}H} \rightleftharpoons \underset{*\quad *}{\overset{}{H\quad H}}$$

$$\underset{*\qquad *}{CH_2{-}CH_2} + \underset{*}{H} \rightleftharpoons \underset{*\qquad *}{CH_3{-}CH_2}\quad *$$

$$\underset{*}{CH_3{-}CH_2} + \underset{*}{H} \rightleftharpoons CH_3{-}CH_3 \quad *\quad *$$

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[250] For reviews, see Siegel, *Adv. Catal.* **16**, 123–177 (1966); Burwell, *Chem. Eng. News* **44** (34), 56–67 (Aug. 22, 1966); Bond and Wells, *Adv. Catal.* **15**, 91–226 (1964); Bond, *Q. Rev., Chem. Soc.* **8**, 279–307 (1954); Hoelscher, Poynter, and Weger, *Chem. Rev.* **54**, 575–592 (1954).

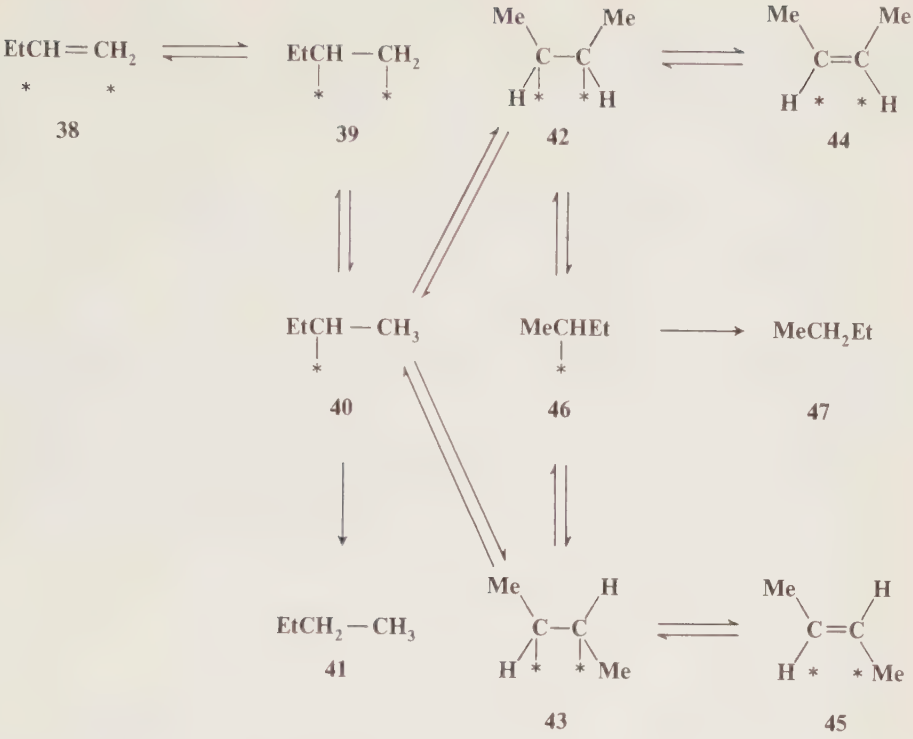
[251] Horiuti and Polanyi, *Trans. Faraday Soc.* **30**, 1164 (1934).

[252] See, for example, Burwell and Schrage, *J. Am. Chem. Soc.* **87**, 5234 (1965).

[253] See, for example, McKee, *J. Am. Chem. Soc.* **84**, 1109 (1962).

[254] Krasna, *J. Am. Chem. Soc.* **83**, 289 (1961).

[255] Smith and Burwell, *J. Am. Chem. Soc.* **84**, 925 (1962).



In this scheme the normal reaction is represented by **38** → **39** → **40** → **41**, double-bond migration by **38** → **39** → **40** → **42** → **44**, cis-trans isomerization by **45** → **43** → **40** → **42** → **44**, and hydrogen exchange by **38** → **39** → **40** → **42** → **46** → **47**. Although this mechanism is satisfactory as far as it goes, there are still questions it does not answer, among them questions involving the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst. It is certain that the bond energy, and perhaps even the type of bonding, will be different for catalysts of different structure, but what effect this has on the mechanism is not known.[256] For example, there is evidence that metals such as platinum or nickel do not form π or π-allylic complexes with olefinic substrates[257] but that zinc oxide does form π-allylic complexes.[258]

The mechanism of homogeneous hydrogenation catalyzed by $RhCl(Ph_3P)_3$ [259] involves reaction of the catalyst with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**48**), which rapidly transfers two hydrogen atoms to the alkene. The intermediate **48** can be isolated. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and nondeuterated compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one olefin molecule and that no exchange takes place.[259] Although

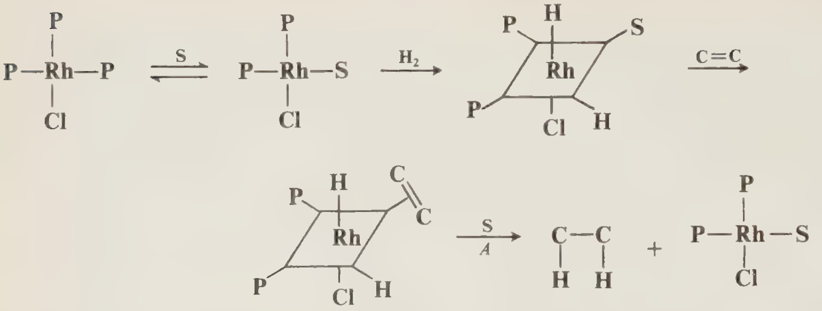
---

[256] See Trapnell, *Q. Rev., Chem. Soc.* **8**, 404–421 (1954).

[257] See however, McKervey, Rooney, and Samman, *J. Chem. Soc., Chem. Commun.* 1185 (1972).

[258] Dent and Kokes, *J. Am. Chem. Soc.* **92**, 6709, 6718 (1970); See also Ref. 207.

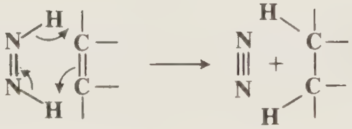
[259] Osborn, Jardine, Young, and Wilkinson, Ref. 209; Jardine, Osborn and Wilkinson, *J. Chem. Soc. A* 1574 (1967); Montelatici, van der Ent, Osborn, and Wilkinson, *J. Chem. Soc. A* 1054 (1968).



P = PPh$_3$
S = solvent

the addition is syn, there is evidence that the actual addition of the two hydrogens to the double bond (the step marked *A*) is not concerted but takes place in a stepwise fashion, at least in some cases.[260]

In the reactions with hydrazine and with NH_2OSO_3H the actual reducing species is diimide NH=NH, which is formed from the hydrazine by the oxidizing agent, and from NH_2OSO_3H by the intermediacy of NH, which dimerizes.[261] Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,[262] by a cyclic mechanism:[263]



The addition is therefore stereospecifically syn[264] and, like catalytic hydrogenation, generally takes place from the less hindered side of a double bond, though not much discrimination in this respect is observed where the difference in bulk effects is small.[265] Diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N, O=O) and are more difficult for those inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation at ordinary temperatures, though it has been prepared[266] as a yellow solid at −196°C. Substituted diimides, e.g., MeN=NH and PhN=NH, have been prepared in solution and are somewhat more stable.[267] Diimide can also be generated by acid treatment of potassium azodicarboxylate (KOOC—N=N—COOK)[268] and by base-catalyzed or thermal elimination of a proton and the substituent from an acyl or sulfonyl hydrazide.[269]

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[260] Biellmann and Jung, *J. Am. Chem. Soc.* **90,** 1673 (1968); Hussey and Takeuchi, *J. Am. Chem. Soc.* **91,** 672 (1969); Heathcock and Poulter, *Tetrahedron Lett.* 2755 (1969); Smith and Shuford, *Tetrahedron Lett.* 525 (1970); Atkinson and Luke, *Can. J. Chem.* **48,** 3580 (1970).

[261] For reviews of hydrogenations with diimide, see Miller, *J. Chem. Educ.* **42,** 254–259 (1965); House, Ref. 141, pp. 248–256. For a review of the formation and structure of diimides, see Hünig, Müller, and Thier, *Angew. Chem. Int. Ed. Engl.* **4,** 271–280 (1965) [*Angew. Chem.* **77,** 368–377].

[262] Aylward and Sawistowska, *J. Chem. Soc.* 1435 (1964).

[263] Ref. 222; van Tamelen, Dewey, Lease, and Pirkle, *J. Am. Chem. Soc.* **83,** 4302 (1961); Vidyarthi, Willis, Back, and McKitrick, *J. Am. Chem. Soc.* **96,** 7647 (1974).

[264] Corey, Pasto, and Mock, *J. Am. Chem. Soc.* **83,** 2957 (1961).

[265] van Tamelen and Timmons, *J. Am. Chem. Soc.* **84,** 1067 (1962).

[266] Wiberg, Fischer, and Bachhuber, *Chem. Ber.* **107,** 1456 (1974). See also Rosengren and Pimentel, *J. Chem. Phys.* **43,** 507 (1965); Trombetti, *Can. J. Phys.* **46,** 1005 (1968); Bondybey and Nibler, *J. Chem. Phys.* **58,** 2125 (1973); Sellmann, Brandl, and Endell, *Angew. Chem. Int. Ed. Engl.* **12,** 1019 (1973) [*Angew. Chem.* **85,** 1122].

[267] Huang and Kosower, *J. Am. Chem. Soc.* **89,** 3910, 3911 (1967); Ackerman, Ellenson, and Robison, *J. Am. Chem. Soc.* **90,** 7173 (1968).

[268] See for example, Hamersma and Snyder, *J. Org. Chem.* **30,** 3985 (1965).

[269] Dewey and van Tamelen, *J. Am. Chem. Soc.* **83,** 3729 (1961).

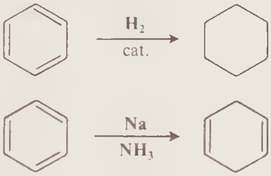
When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (reaction **5-13**). The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.[221] In accord with this mechanism, the reaction can be applied only to those olefins which when protonated can form a tertiary carbonium ion or one stabilized in some other way, e.g., by α-OR substitution.[270]

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding D_2 to a double or triple bond in a regiospecific or stereospecific manner. However, this objective can be achieved (with syn addition) by homogeneous catalytic hydrogenation, which usually adds D_2 without scrambling,[271] or by the use of one of the diimide methods.[264] Deuterium can also be regiospecifically added by the hydroboration-reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS **I,** 101, 311; **II,** 191, 491; **III,** 385, 586, 742, 794; **IV,** 136, 298, 302, 304, 408, 887; **V,** 16, 96, 277, 281, 993; **53,** 63; **54,** 1.

Catalysts and apparatus for hydrogenation are found at OS **I,** 61, 463; **II,** 142; **III,** 176, 181, 685; **V,** 880.

5-13 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,[272] but higher temperatures (100 to 200°C) are required than for ordinary double bonds. Though the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used.[273] Many functional groups, such as OH, O^-, COOH, COOR, NH_2, etc., do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (reaction **0-79**). Phenols may be reduced to *cyclohexanones*, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives tetrahydrofuran. With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since olefins are more easily reduced than aromatic rings. Thus, 1 mol of benzene, treated with 1 mol of hydrogen, gives no cyclohexadiene or cyclohexene but $\frac{1}{3}$ mol of cyclohexane and $\frac{2}{3}$ mol of recovered benzene. This is not true for all aromatic systems. With phenanthrene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 43).

When aromatic rings are reduced by sodium (or potassium or lithium) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol

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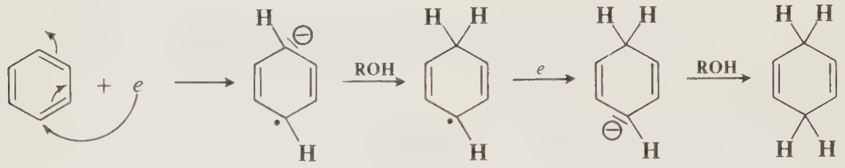
[270] Parnes, Bolestova, and Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **21,** 1927 (1972).

[271] Biellmann and Liesenfelt, *Bull. Soc. Chim. Fr.* 4029 (1966); Birch and Walker, *Tetrahedron Lett.* 4939 (1966), *J. Chem. Soc. C* 1894 (1966); Morandi and Jensen, *J. Org. Chem.* **34,** 1889 (1969). See however, Atkinson and Luke, Ref. 260.

[272] For reviews, see Smith, in Augustine, "Reduction Techniques and Applications in Organic Synthesis," pp. 309–395, Marcel Dekker, Inc., New York, 1968; Weitkamp, *Adv. Catal.* **18,** 1–110 (1968) (for naphthalenes); Freifelder, *Adv. Catal.* **14,** 203–253 (1963) (for pyridines and quinolines).

[273] Muetterties and Hirsekorn, *J. Am. Chem. Soc.* **96,** 4063 (1974); Hirsekorn, Rakowski, and Muetterties, *J. Am. Chem. Soc.* **97,** 237 (1975).

(often ethyl, isopropyl, or *t*-butyl alcohol), 1,4 addition of hydrogen takes place and nonconjugated cyclohexadienes are produced. This reaction is called the *Birch reduction.*[274] Ammonia obtained commercially often has iron salts as impurities which lower the yield in the Birch reduction. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl or alkoxyl decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene and not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups such as COOH or $CONH_2$ increase the reaction rate and are found on the reduced positions of the product. The mechanism involves direct transfer of electrons from the metal:[275]

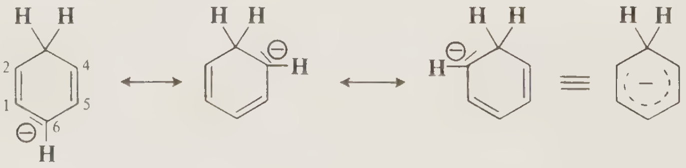


49 **50**

The sodium transfers an electron to the ring, becoming oxidized to Na^+ and creating a radical ion (**49**).[276] There is a great deal of evidence from esr spectra for these species.[277] The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **50** accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of **49** are frequently obtained. There is evidence[278] at least with some substrates, e.g., biphenyl, that the radical ion corresponding to **49** is converted to the carbanion corresponding to **50** by a different pathway, in which the order of the steps is reversed: first a second electron is lost to give a dianion,[276] which then acquires a proton, producing the intermediate corresponding to **50**.

Ordinary olefins are usually unaffected by Birch-reduction conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated olefins, internal alkynes (p. 710), and conjugated olefins (with C=C or C=O) are reduced under these conditions.

It may be noted that **50** is a resonance hybrid; i.e., we can write two additional canonical forms:



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[274] For a monograph, see Akhrem, Reshotova, and Titov, "Birch Reduction of Aromatic Compounds," Plenum Press, New York, 1972. For reviews, see Birch and Subba Rao, *Adv. Org. Chem.* **8,** 1–65 (1972); Kaiser, *Synthesis* 391 415 (1972); Harvey, *Synthesis* 161–172 (1970); House, Ref. 141, pp. 145-150, 173-209; Carruthers, Ref. 202, pp. 335 346, 350 351; Hückel, *Fortschr. Chem. Forsch.* **6,** 197 250 (1966); Smith, Ref. 272, pp. 95-170; Birch and Smith, *Q. Rev., Chem. Soc.* **12,** 17–33 (1958); Birch, *Q. Rev., Chem. Soc.* **4,** 69–93 (1950).

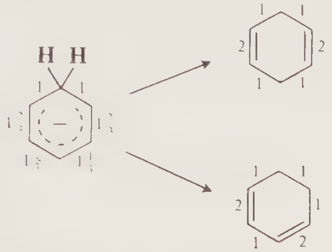
[275] Birch and Nasipuri, *Tetrahedron* **6,** 148 (1959).

[276] For a review of radical ions and diions generated from aromatic compounds, see Holy, *Chem. Rev.* **74,** 243 277 (1974).

[277] For example, see Jones, in Kaiser and Kevan, "Radical Ions," pp. 245 274, Interscience Publishers, New York, 1968; Bowers, *Adv. Magn. Reson.* **1,** 317–396 (1965); Carrington, *Q. Rev., Chem. Soc.* **17,** 67–99 (1963).

[278] Lindow, Cortez, and Harvey, *J. Am. Chem. Soc.* **94,** 5406 (1972); Harvey, Lindow, and Rabideau, *J. Am. Chem. Soc.* **94,** 5412 (1972).

The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene? An answer to this question has been proposed by Hine, who has suggested that this case is an illustration of the operation of the *principle of least motion*.[279] According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[279] The principle can be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 29) for the six carbon-carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3}+\frac{1}{3}+\frac{1}{3}+\frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3}+\frac{2}{3}+\frac{2}{3}+\frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ^{13}C nmr spectrum of **50** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.[280]

Reduction of aromatic rings with lithium in amines (instead of ammonia) proceeds further, and cyclohexenes are obtained.[281] It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced. It has been shown that it is possible to reduce either one or two double bonds by electrochemical reduction.[282]

OS **I,** 99, 499; **II,** 566; **III,** 278, 742; **IV,** 313, 887, 903; **V,** 398, 400, 467, 591, 670, 743, 989; **50,** 50, 88; **51,** 103; **52,** 66; **54,** 11.

5-14 Reductive Cleavage of Cyclopropanes

$\xrightarrow[\text{cat.}]{H_2}$ $CH_3CH_2CH_3$

Cyclopropanes can be cleaved by catalytic hydrogenolysis.[283] Among the catalysts used have been Ni, Pd, and Pt. The reaction can often be run under mild conditions.[284] Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,[285] can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.[286]

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[279] Hine, *J. Org. Chem.* **31,** 1236 (1966). See also Tee, *J. Am. Chem. Soc.* **91,** 7144 (1969).

[280] Bates, Brenner, Cole, Davidson, Forsythe, McCombs, and Roth, *J. Am. Chem. Soc.* **95,** 926 (1973).

[281] Benkeser, Robinson, Sauve, and Thomas, *J. Am. Chem. Soc.* **77,** 3230 (1955); Reggel, Friedel, and Wender, *J. Org. Chem.* **22,** 891 (1957); Benkeser, Agnihotri, and Burrous, *Tetrahedron Lett.* no. 16, 1 (1960); Benkeser, Burrous, Hazdra, and Kaiser, *J. Org. Chem.* **28,** 1094 (1963); Benkeser, Agnihotri, Burrous, Kaiser, Mallan, and Ryan, *J. Org. Chem.* **29,** 1313 (1964); Kwart and Conley, *J. Org. Chem.* **38,** 2011 (1973).

[282] Benkeser and Kaiser, *J. Am. Chem. Soc.* **85,** 2858 (1963).

[283] For reviews, see Charton, Ref. 111, pp. 588–592; Rylander, Ref. 206, pp. 469–474; Newham, *Chem. Rev.* **63,** 123–137 (1963); Liberman, *Russ. Chem. Rev.* **30,** 237–251 (1961).

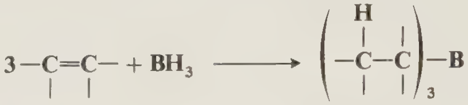
[284] See for example, Woodworth, Buss, and Schleyer, *Chem. Commun.* 569 (1968).

[285] See for example, Walborsky and Pierce, *J. Org. Chem.* **33,** 4102 (1968); Walborsky, Aronoff, and Schulman, *J. Org. Chem.* **36,** 1036 (1970).

[286] For a review, see Staley, *Sel. Org. Transform.* **2,** 309–348 (1972).

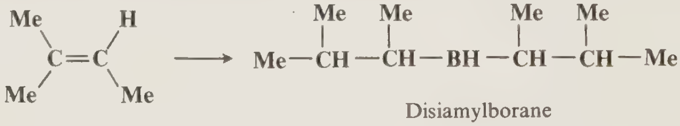
F. A Metal on the Other Side

5-15 Hydroboration

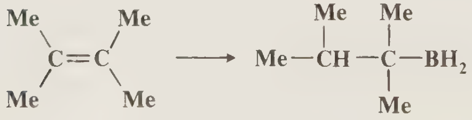


$$3\,-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}-\;+\;BH_3 \longrightarrow \left(-\overset{H\;\;|}{\underset{|\;\;\,|}{C-C}}\right)_3\!-B$$

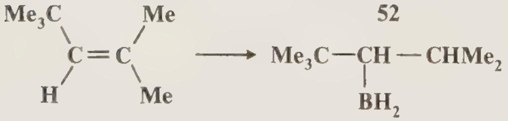
When olefins are treated with borane in ether solvents, BH_3 adds across the double bond.[287] Borane cannot be prepared as a stable pure compound[288] (it dimerizes to diborane B_2H_6), but it is commercially available in the form of complexes with tetrahydrofuran, dimethyl sulfide,[289] or tertiary amines, The olefins can be treated with a solution of one of these complexes (THF–BH_3 reacts at 0°C and is the most convenient to use; $R_3N–BH_3$ generally require temperatures of about 100°C; however, the latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by the moisture in air) or with a mixture of $NaBH_4$ and BF_3 etherate (or $NaBH_4$ and acetic acid[290]), which generates borane in situ. Ordinarily, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of olefin to give R_2BH, which in turn adds to a third olefin molecule, so that the isolated product is a trialkylborane R_3B. The reaction can be performed on alkenes with one to four substituents, including cyclic olefins, but when the olefin is highly hindered, the product *is* the dialkylborane R_2BH or even the monoalkylborane RBH_2.[291] For example, **51** (*disiamylborane*), **52** (*thexylborane*), and **54** have been prepared in this manner:



Disiamylborane
51



Thexylborane
52



53 **54**

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[287] For books on this reaction and its manifold applications, see Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N.Y., 1972, "Organic Syntheses Via Boranes," John Wiley & Sons, Inc., New York, 1975; "Hydroboration," W. A. Benjamin, Inc., New York, 1962; Cragg, "Organoboranes in Organic Synthesis," Marcel Dekker, Inc., New York, 1973. For reviews, see Zweifel and Brown, *Org. React.* **13,** 1–54 (1963); Brown, *Tetrahedron* **12,** 117–138 (1961).

[288] Mappes and Fehlner, *J. Am. Chem. Soc.* **92,** 1562 (1970); Mappes, Fridmann, and Fehlner, *J. Phys. Chem.* **74,** 3307 (1970); Fehlner, *J. Am. Chem. Soc.* **93,** 6366 (1971).

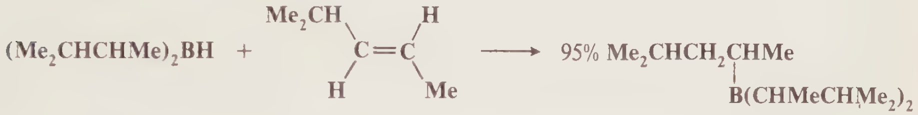
[289] Braun, Braun, Crissman, Opperman, and Adams, *J. Org. Chem.* **36,** 2388 (1971); Lane, *J. Org. Chem.* **39,** 1437 (1974).

[290] Hach, *Synthesis* 340 (1974).

[291] Unless coordinated with a strong Lewis base such as a tertiary amine, mono and dialkylboranes actually exist as dimers, e.g., $R_2B\overset{H}{\underset{H}{\langle\,\rangle}}BR_2$: Brown and Klender, *Inorg. Chem.* **1,** 204 (1962).

Monoalkylboranes RBH_2 (which can be prepared from hindered olefins, as above, or from simple olefins either by reaction **9-56** or by the method described below) and dialkylboranes R_2BH also add to olefins, to give the mixed trialkylboranes RR'_2B and $R_2R'B$, respectively. Mixed trialkylboranes $R_2R'B$ can also be prepared by addition to alkenes of dialkylthioboranes R_2BSR'', followed by treatment with $LiAlH_4$.[292]

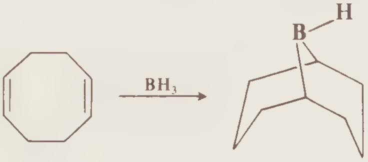
In all cases the boron goes to the side of the double bond which has more hydrogens, whether the substituents are aryl or alkyl.[293] Thus the reaction of **53** with BH_3 gives 98% **54** and only 2% of the other product. This actually follows Markovnikov's rule, since boron is more positive than hydrogen. However, the regioselectivity is caused mostly by steric factors, though electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of substituted styrenes showed that the attack by boron has electrophilic character.[294] When both sides of the double bond are monosubstituted or both disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large attacking molecule. For example, treatment of iso-PrCH=CHMe with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with disiamylborane (**51**) gave 95% of **55** and only 5% of the other isomer:[295]



51

55

Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN), which is prepared by hydroboration of 1,5-cyclooctadiene:[296]



9-BBN

9-BBN has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and will preferentially attack less hindered bonds, so that it is often possible to hydroborate one double bond in a molecule selectively and leave others unaffected or to hydroborate one olefin in the presence of a less reactive olefin.[297] For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a cis olefin can be selectively hydroborated in a mixture of the cis and trans isomers.

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[292] Pelter and Sharrocks, *J. Chem. Soc., Chem. Commun.* 566 (1972).

[293] For a thorough discussion of the regioselectivity with various types of substrate and hydroborating agents, see Cragg, Ref. 287, pp. 63–84, 137–197.

[294] Brown and Sharp, *J. Am. Chem. Soc.* **88,** 5851 (1966); Klein, Dunkelblum, and Wolff, *J. Organomet. Chem.* **7,** 377 (1967).

[295] Brown and Zweifel, *J. Am. Chem. Soc.* **83,** 1241 (1961).

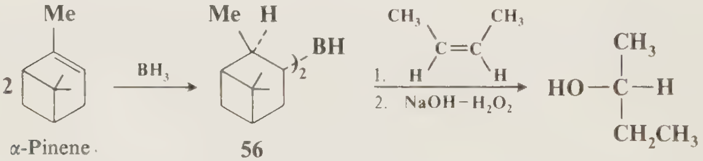
[296] Knights and Brown, *J. Am. Chem. Soc.* **90,** 5280, 5281 (1968); Scouten and Brown, *J. Org. Chem.* **38,** 4092 (1973); Brown, Knights, and Scouten, *J. Am. Chem. Soc.* **96,** 7765 (1974).

[297] Brown and Moerikofer, *J. Am. Chem. Soc.* **85,** 2063 (1963); Zweifel and Brown, *J. Am. Chem. Soc.* **85,** 2066 (1963); Zweifel, Ayyangar, and Brown, *J. Am. Chem. Soc.* **85,** 2072 (1963); Ref. 295.

Another hydroboration reagent with even greater regioselectivity than BH_3 (for terminal alkenes or those of the form $R_2C{=}CHR$) is monochloroborane BH_2Cl in ether (the hydroboration product is a dialkylchloroborane R_2BCl).[298] For example, 1-hexene gave 94% of the anti-Markovnikov product with BH_3–THF, but > 99.5% with BH_2Cl–OEt_2. This additional regioselectivity is caused by electronic rather than steric factors, so that alkenes with the same number of alkyl groups on both sides of the double bond give significant yields of both isomers. Treatment of alkenes with dichloroborane-etherate $BHCl_2$–OEt_2 in the presence of BCl_3 gives alkyldichloroboranes $RBCl_2$.[299]

An important use of the hydroboration reaction is that alkylboranes, when oxidized with hydrogen peroxide and NaOH, are converted to alcohols (reaction **2-26**). This thus becomes an indirect way of adding H_2O across a double bond in an anti-Markovnikov manner. However, boranes undergo other reactions as well. Among other things, they react with α-halo carbonyl compounds to give alkylated products (**0-101**), with α,β-unsaturated carbonyl compounds to give Michael-type addition of R and H (**5-21**), with CO to give alcohols and ketones (**8-27** to **8-29**); they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (reaction **5-12**), or they can be oxidized with chromic acid to give ketones,[300] dimerized with silver nitrate and NaOH (**4-35**), isomerized (**8-14**), or converted to amines (**2-29**) or halides (**2-28**, **4-32**). They are thus useful intermediates for the preparation of a wide variety of compounds. In addition to alkyl and aryl groups, such functional groups as OR, OH, NH_2, SMe, halogen, and COOR may be present in the molecule,[301] but not groups which are reducible by borane.

Use of the reagent diisopinocampheylborane **56** (prepared by treating optically active α-pinene with BH_3) results in asymmetric hydroboration-oxidation.[302] Alcohols with optical purities of 70 to 90% have been obtained in this way, making it one of the most efficient asymmetric syntheses known.

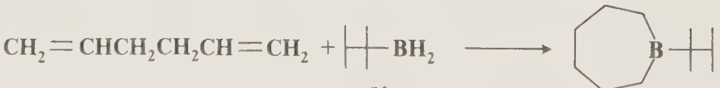


α-Pinene

56

Optically active

The double bonds in a conjugated diene are hydroborated separately; i.e., there is no 1,4 addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. Thexylborane[303] (**52**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated,[304] e.g.,



52

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[298] Brown and Ravindran, *J. Am. Chem. Soc.* **98**, 1785 (1976).

[299] Brown and Ravindran, *J. Am. Chem. Soc.* **98**, 1798 (1976).

[300] Brown and Garg, *J. Am. Chem. Soc.* **83**, 2951 (1961). See also Lansbury and Nienhouse, *Chem. Commun.* 273 (1966).

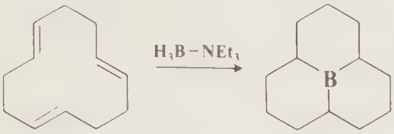
[301] See for example, Brown and Unni, *J. Am. Chem. Soc.* **90**, 2902 (1968); Brown and Gallivan, *J. Am. Chem. Soc.* **90**, 2906 (1968); Brown and Sharp, *J. Am. Chem. Soc.* **90**, 2915 (1968).

[302] Zweifel and Brown, *J. Am. Chem. Soc.* **86**, 393 (1964); Brown, Ayyangar, and Zweifel, *J. Am. Chem. Soc.* **86**, 397 (1964). See also Brown, Kettle, McKenna, and McKenna, *Chem. Commun.* 667 (1967); Streitwieser, Verbit, and Bittman, *J. Org. Chem.* **32**, 1530 (1967); Varma and Caspi, *Tetrahedron* **24**, 6365 (1968).

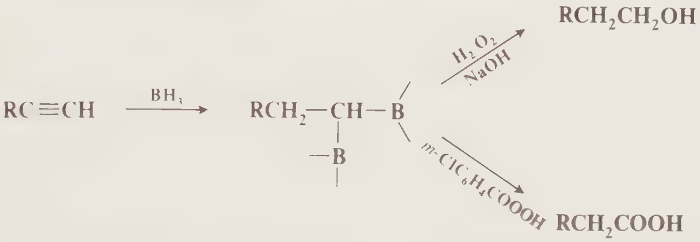
[303] For a review of the chemistry of thexylborane, see Negishi and Brown, *Synthesis* 77–89 (1974).

[304] Brown and Pfaffenberger, *J. Am. Chem. Soc.* **89**, 5475 (1967); Brown and Negishi, *J. Am. Chem. Soc.* **94**, 3567 (1972).

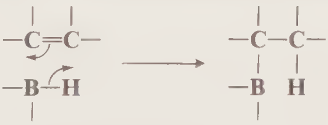
Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.[305] One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene:[306]



Triple bonds can be monohydroborated to give unsaturated boranes, which can be reduced with carboxylic acids to cis alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed at reaction **5-3**. However, terminal alkynes give unsaturated boranes (and hence aldehydes) only when treated with a hindered borane such as **51**, **52**, or catecholborane[307] (p. 560), or with $BH_2Cl\text{-}OEt_2$.[308] The reaction between terminal alkynes and BH_3 produces 1,1-dibora compounds, which can be oxidized either to primary alcohols (with $NaOH\text{-}H_2O_2$) or to carboxylic acids (with *m*-chloroperbenzoic acid).[309] Acetylenic acetals $RC{\equiv}CCH(OEt)_2$ (which can be prepared from ortho esters by reaction **0-92**) can be similarly hydroborated, with concomitant reduction of the acetal group (reaction **0-80**), to give alkenylborane ethers, which can be oxidized or hydrolyzed in situ to give α-keto ethers RCH_2COCH_2OEt or cis allylic ethers $RCH{=}CHCH_2OEt$, respectively.[310]



The addition in hydroboration has been shown to be stereospecific and syn, with attack taking place from the less hindered side.[311] Where the reaction rates are measurable (most are too fast), the reaction is second order.[312] The mechanism is probably a cyclic four-center one:[313]



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[305] Brown, Negishi, and Burke, *J. Am. Chem. Soc.* **94**, 3561 (1972); Brown and Negishi, *Pure Appl. Chem.* **29**, 527–545 (1972); Negishi and Brown, *J. Am. Chem. Soc.* **95**, 6757 (1973).

[306] Rotermund and Köster, *Justus Liebigs Ann. Chem.* **686**, 153 (1965); Brown and Negishi, *J. Am. Chem. Soc.* **89**, 5478 (1967).

[307] Brown and Gupta, *J. Am. Chem. Soc.* **94**, 4370 (1972), **97**, 5249 (1975). For a review of catecholborane, see Lane and Kabalka, *Tetrahedron* **32**, 981–990 (1976).

[308] Brown and Ravindran, *J. Org. Chem.* **38**, 1617 (1973).

[309] Zweifel and Arzoumanian, *J. Am. Chem. Soc.* **89**, 291 (1967).

[310] Zweifel, Horng, and Plamondon, *J. Am. Chem. Soc.* **96**, 316 (1974).

[311] Kabalka and Bowman, *J. Org. Chem.* **38**, 1607 (1973); Brown and Zweifel, *J. Am. Chem. Soc.* **83**, 2544 (1961).

[312] Brown and Moerikofer, *J. Am. Chem. Soc.* **83**, 3417 (1961); Pasto and Kang, *J. Am. Chem. Soc.* **90**, 3797 (1968); Pasto, Lepeska, and Cheng, *J. Am. Chem. Soc.* **94**, 6083 (1972).

[313] Brown and Zweifel, *J. Am. Chem. Soc.* **81**, 247 (1959); Pasto, Lepeska, and Balasubramaniyan, *J. Am. Chem. Soc.* **94**, 6090 (1972); Pasto, Lepeska, and Cheng, Ref. 312. See, however, Jones, *J. Org. Chem.* **37**, 1886 (1972).

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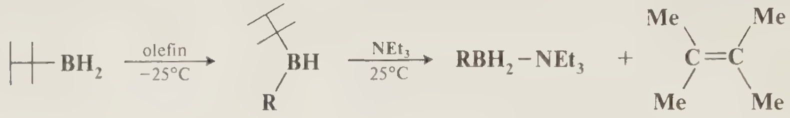
In the case of thexylmonoalkylboranes (**57**, prepared by addition of **52** to olefins), hydroboration can be reversed by treatment with triethylamine.[314] The monoalkylborane–triethylamine complexes **58** can be used to hydroborate olefins to give the trialkylboranes RR'_2B. **57** can also

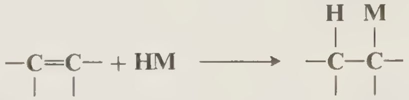


52 **57** **58**

be added to terminal alkenes to give trialkylboranes with three different R groups RR′R″B, one of which is the thexyl group.[315] However, if the terminal alkene is sufficiently hindered, a thexyl group is lost and again the product is RR'_2B.[315]

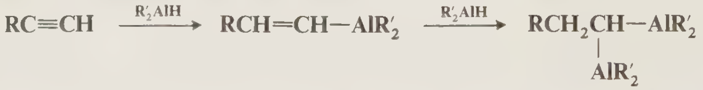
OS **50,** 88; **52,** 59; **53,** 77.

5-16 Other Hydrometalation



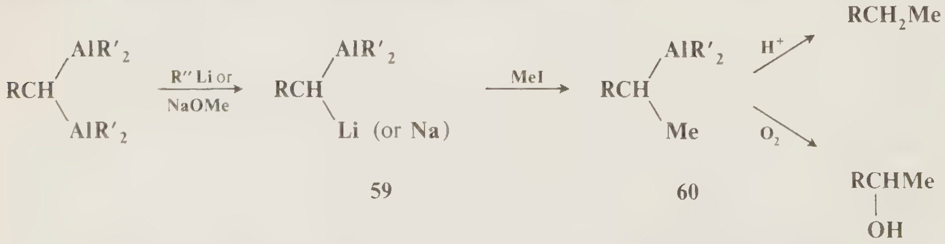
$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + HM \longrightarrow -\overset{H}{\underset{|}{\overset{|}{C}}}-\overset{M}{\underset{|}{\overset{|}{C}}}-$$

Metal hydrides of groups IIIA and IVA of the periodic table (e.g., AlH_3, GaH_3) as well as many of their alkyl and aryl derivatives (e.g., R_2AlH, Ar_3SnH) add to double bonds to give organometallic compounds.[316] The hydroboration reaction (**5-15**) is an important example. The mechanism with group IIIA hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with group IVA hydrides a mechanism involving free radicals seems more likely. With some reagents triple bonds can add 1 or 2 moles, e.g.,[317]



$$RC{\equiv}CH \xrightarrow{R'_2AlH} RCH{=}CH{-}AlR'_2 \xrightarrow{R'_2AlH} RCH_2\underset{\underset{\displaystyle AlR'_2}{|}}{CH}{-}AlR'_2$$

When 2 moles are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products. 1,1-Dialuminum compounds react with alkyllithium reagents or sodium methoxide to give the inter-



59 **60**

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[314] Brown, Negishi, and Katz, *J. Am. Chem. Soc.* **94,** 5893 (1972), **97,** 2791 (1975).

[315] Lane and Brown. *J. Organomet. Chem.* **34,** C29 (1972); Brown, Katz, Lane, and Negishi, *J. Am. Chem. Soc.* **97,** 2799 (1975).

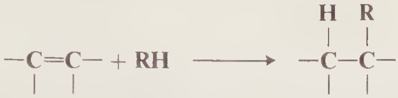
[316] Eisch, "The Chemistry of Organometallic Compounds," pp. 107–111, The Macmillan Company, New York, 1967.

[317] Wilke and Müller, *Justus Liebigs Ann. Chem.* **629,** 222 (1960); Eisch and Kaska, *J. Am. Chem. Soc.* **88,** 2213 (1966); Eisch and Foxton, *J. Org. Chem.* **36,** 3520 (1971); Eisch and Rhee, *Justus Liebigs Ann. Chem.* 565 (1975).

mediates **59**.[318] **59** can be treated with methyl iodide to give the trialkylaluminum compounds **60**, which can be hydrolyzed to alkanes or oxidized to alcohols.[318]

G. Carbon on the Other Side

5-17 Addition of Alkanes and Alkenes



$$-\underset{|}{C}=\underset{|}{C}- + RH \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{R}{|}}{C}}-$$

There are two important ways of adding alkanes to olefins, the thermal method and the acid-catalysis method.[319] Both give chiefly mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method the reactants are heated to high temperatures (about 500°C) at high pressures (150 to 300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[320] The mechanism is undoubtedly of a free-radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:

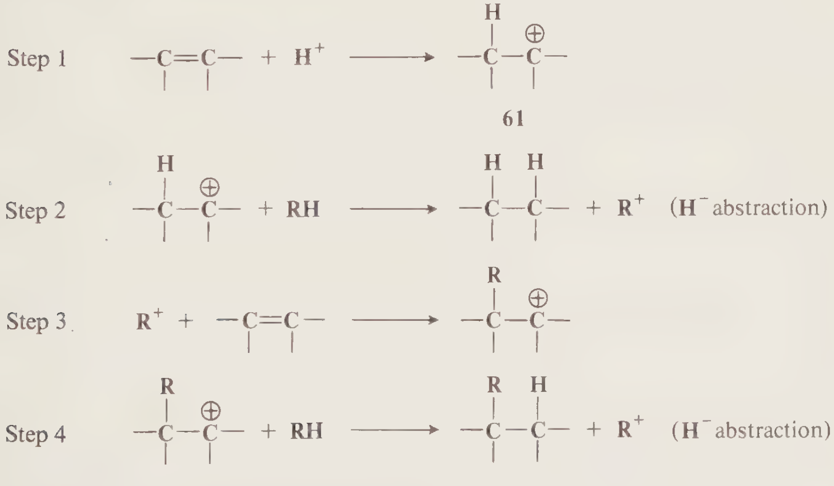
Step 1 $CH_3CH_2CH_3 \xrightarrow{\Delta} CH_3\cdot + CH_3CH_2\cdot$

Step 2 $CH_3\cdot + CH_3CH_2CH_3 \longrightarrow CH_4 + CH_3\underset{\bullet}{C}HCH_3$

Step 3 $CH_3\underset{\bullet}{C}HCH_3 + CH_2{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CH_2\cdot$

Step 4 $(CH_3)_2CHCH_2CH_2\cdot + CH_3CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 + CH_3\underset{\bullet}{C}HCH_3$

In the acid-catalysis method, a proton or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between −30 and 100°C. This is a Friedel-Crafts process with a carbonium-ion mechanism (illustrated for a proton acid catalyst):



Step 1 $$-\underset{|}{C}=\underset{|}{C}- + H^+ \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\oplus}{C}}-$$

Step 2 $$-\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\oplus}{C}}- + RH \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}- + R^+ \quad (H^- \text{ abstraction})$$

Step 3 $$R^+ + -\underset{|}{C}=\underset{|}{C}- \longrightarrow -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{\oplus}{C}}-$$

Step 4 $$-\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{\oplus}{C}}- + RH \longrightarrow -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{\overset{H}{|}}{C}}- + R^+ \quad (H^- \text{ abstraction})$$

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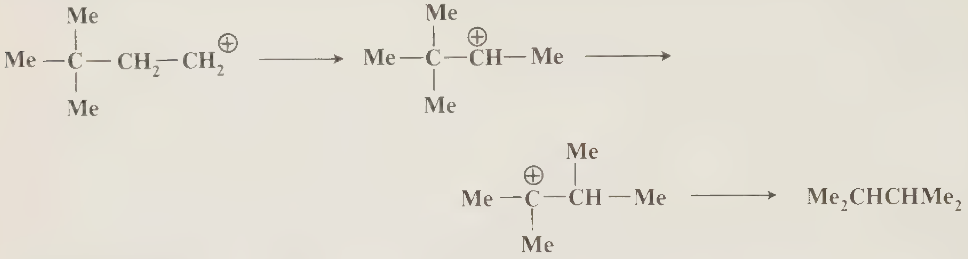
[318] Zweifel and Steele, *Tetrahedron Lett.* 6021 (1966).

[319] For reviews, see Shuikin and Lebedev, *Russ. Chem. Rev.* **35**, 448-455 (1966); Schmerling, in Olah, "Friedel-Crafts and Related Reactions," vol. 2, pp. 1075–1111, 1121–1122, Interscience Publishers, New York, 1964.

[320] Frey and Hepp, *Ind. Eng. Chem.* **28**, 1439 (1936).

62 often rearranges before it abstracts a hydride ion, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane:



$$Me_3C-CH_2-\overset{\oplus}{C}H_2 \longrightarrow Me_3C-\overset{\oplus}{C}H-Me \longrightarrow Me_2\overset{\oplus}{C}-CHMe-Me \longrightarrow Me_2CHCHMe_2$$

It is also possible for **61** (or **62**, for that matter), instead of abstracting a hydride ion, to add to another mole of olefin, so that not only rearrangement products but also dimeric and polymeric products are frequent.

The addition of secondary or tertiary carbonium ions (generated from the corresponding alcohols, esters, or alkenes) to 1,1-dichloroethene gives carboxylic acids by hydrolysis of the intermediate ions (see reaction **0-3**):[321]

$$R_3COH \xrightarrow{H^+} R_3C^+ + CH_2{=}CCl_2 \longrightarrow$$

$$R_3C-CH_2-\overset{\oplus}{C}Cl_2 \xrightarrow{H_2O} R_3CCH_2COOH$$

The reaction may also be base-catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.[322] Carbanions most often used are those stabilized by one or more α-aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:[323]

$$PhCH_3 \xrightarrow{Na} Ph\overset{\ominus}{\bar{C}}H_2 + PhCH{=}CH_2 \longrightarrow$$

$$Ph\overset{\ominus}{\bar{C}}H-CH_2CH_2Ph \xrightarrow{\text{solvent}} PhCH_2CH_2CH_2Ph$$

Conjugated dienes give 1,4 addition.[324] This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids[325] (see also reaction **0-98**):

$$CH_3COOK \xrightarrow{NaNH_2} \overset{\ominus}{\bar{C}}H_2COOK + CH_2{=}CH_2 \longrightarrow \overset{\ominus}{\bar{C}}H_2-CH_2CH_2COOK$$

Two and even three alkyl groups can be put on this way.

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[321] For a review, see Bott and Hellmann, *Angew. Chem. Int. Ed. Engl.* **5,** 870–874 (1966) [*Angew. Chem.* **78,** 932–936]. *Newer Methods Prep. Org. Chem.* **6,** 67–80 (1971).

[322] For reviews, see Pines, *Acc. Chem. Res.* **7,** 155–162 (1974); Pines and Schaap, *Adv. Catal.* **12,** 117–148 (1960), pp. 126–146.

[323] Pines and Wunderlich, *J. Am. Chem. Soc.* **80,** 6001 (1958).

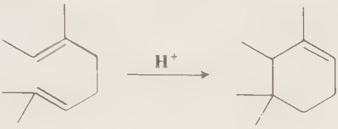
[324] Eberhardt and Peterson, *J. Org. Chem.* **30,** 82 (1965); Pines and Stalick, *Tetrahedron Lett.* 3723 (1968).

[325] Schmerling and Toekelt, *J. Am. Chem. Soc.* **84,** 3694 (1962). See also Kuo, Yahner, and Ainsworth, *J. Am. Chem. Soc.* **93,** 6321 (1971).

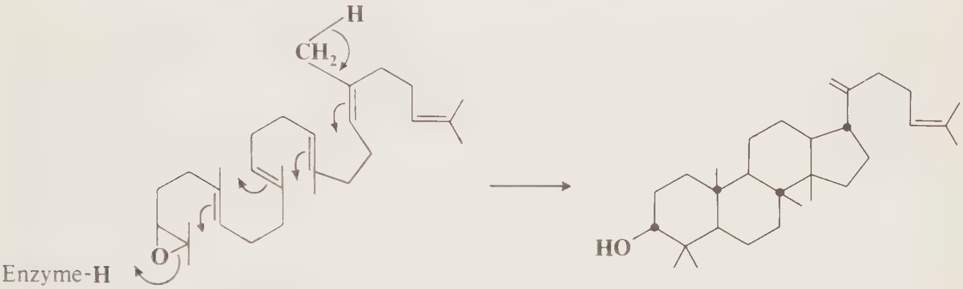
As pointed out above, it is possible in the acid-catalyzed process for an olefin to add to an olefin so that the product is a dimer which contains one double bond, e.g.,

$$CH_2{=}CH_2 + CH_2{=}CH_2 \longrightarrow CH_2{=}CH{-}CH_2{-}CH_3$$

This reaction has also been carried out internally, e.g.,



Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymic catalysis to dammaradienol.

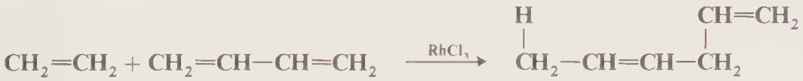


Squalene 2,3-oxide

Dammaradienol

The squalene → lanosterol biosynthesis (which is a key step in the biosynthesis of cholesterol) is similar.[326]

The addition of olefins to olefins can also be accomplished by bases[327] as well as by the use of catalyst systems[328] consisting of nickel complexes and alkylaluminum compounds (known as *Ziegler catalysts*)[329] and by catalysts derived from rhodium chloride.[330] These and similar catalysts also catalyze the 1,4 addition of olefins to dienes,[331] e.g.,



$$CH_2{=}CH_2 + CH_2{=}CH{-}CH{=}CH_2 \xrightarrow{RhCl_3} \overset{\overset{\displaystyle H}{|}}{C}H_2{-}CH{=}CH{-}\overset{\overset{\displaystyle CH{=}CH_2}{|}}{C}H_2$$

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[326] For reviews, see Johnson, *Angew. Chem. Int. Ed. Engl.* **15,** 9–17 (1976) [*Angew. Chem.* **88,** 33–40], *Bioorg. Chem.* **5,** 51–98 (1976), *Acc. Chem. Res.* **1,** 1–8 (1968); van Tamelen, *Acc. Chem. Res.* **8,** 152–158 (1975).

[327] For a review, see Pines, *Synthesis* 309–327 (1974).

[328] For reviews, see Jira and Freiesleben, *Organomet. React.* **3,** 1–190 (1972), pp. 117–130; Heck, Ref. 208, pp. 84–94, 150–157; Khan and Martell, Ref. 144, vol. 2, pp. 135–158; Rylander, Ref. 208, pp. 175–196; Tsuji, *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 213–220.

[329] See for example, Onsager, Wang, and Blindheim, *Helv. Chim. Acta* **52,** 187, 196, 215, 224, 230 (1969); Jones and Symes, *J. Chem. Soc. C* 1124 (1971); Fischer, Jonas, Misbach, Stabba, and Wilke, *Angew. Chem. Int. Ed. Engl.* **12,** 943 (1973) [*Angew. Chem.* **85,** 1002]. See also McClure and Barnett, *J. Organomet. Chem.* **80,** 385 (1974).

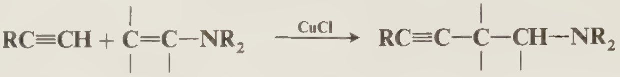
[330] Cramer, *J. Am. Chem. Soc.* **87,** 4717 (1965), *Acc. Chem. Res.* **1,** 186–191 (1968); Kobayashi and Taira, *Tetrahedron* **24,** 5763 (1968); Takahashi, Okura, and Keii, *J. Am. Chem. Soc.* **97,** 7489 (1975).

[331] See, for example, Alderson, Jenner, and Lindsey, *J. Am. Chem. Soc.* **87,** 5638 (1965); Cramer, *J. Am. Chem. Soc.* **89,** 1633 (1967); Miller, Kealy, and Barney, *J. Am. Chem. Soc.* **89,** 3756 (1967); Hata and Aoki, *J. Org. Chem.* **32,** 3754 (1967); Hata and Miyake, *Bull. Chem. Soc. Jpn.* **41,** 2762 (1968); Tajima and Kunioka, *Chem. Commun.* 603 (1968); Adler, Beger, Duschek, Gericke, Pritzkow, and Schmidt, *J. Prakt. Chem.* **316,** 449 (1974).

In the presence of cuprous chloride and ammonium chloride, acetylene adds to another molecule of itself to give vinylacetylene:

$$HC{\equiv}CH + HC{\equiv}CH \xrightarrow[NH_4Cl]{CuCl} HC{\equiv}C{-}CH{=}CH_2$$

Similarly, terminal alkynes add to the double bond of enamines:[332]

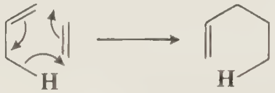


$$RC{\equiv}CH + \overset{|}{\underset{|}{C}}{=}\underset{|}{C}{-}NR_2 \xrightarrow{CuCl} RC{\equiv}C{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}H{-}NR_2$$

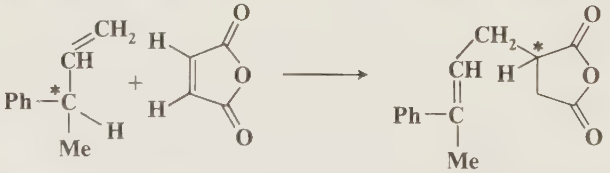
Olefins and alkynes may also add to each other to give cyclic products (see reactions **5-52** and **5-54**).

OS **I,** 229; **IV,** 665.

5-18 The Ene Synthesis

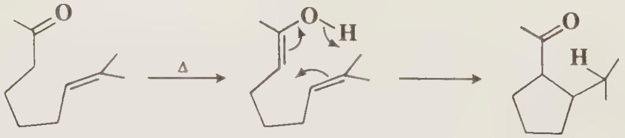


Olefins can add to double bonds in a reaction different from those discussed in **5-17,** which, however, is still formally the addition of RH to a double bond. This reaction is called the *ene synthesis*[333] and bears a certain similarity to the Diels-Alder reaction (**5-51**). One of the components must be a reactive dienophile[334] (see reaction **5-51** for a definition of this word) such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene such as propene. There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise mechanisms have been suggested. The reaction between maleic anhydride and optically active PhCHMeCH=CH$_2$ gave an optically active product,[335]



which is strong evidence for a concerted rather than a stepwise mechanism. Incidentally, this is another case of asymmetric synthesis (p. 106).

6,7-Unsaturated ketones give internal ene reactions, which proceed through the enol forms, e.g.,[336]



OS **IV,** 766; **V,** 459.

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[332] Brannock, Burpitt, and Thweatt, *J. Org. Chem.* **28,** 1462 (1963).

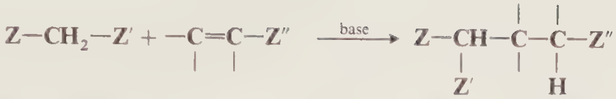
[333] Alder and Brachel, *Justus Liebigs Ann. Chem.* **651,** 141 (1962). For reviews, see Keung and Alper, *J. Chem. Educ.* **49,** 97-100 (1972); Hoffmann, *Angew. Chem. Int. Ed. Engl.* **8,** 556-577 (1969) [*Angew. Chem.* **81,** 597-618].

[334] However, good yields can be obtained even from less reactive dienophiles, e.g., methyl acrylate, if the reaction is catalyzed by AlCl$_3$: Snider, *J. Org. Chem.* **39,** 255 (1974).

[335] Hill and Rabinovitz, *J. Am. Chem. Soc.* **86,** 965 (1964). See also Hill, Morgan, Shetty, and Synerholm, *J. Am. Chem. Soc.* **96,** 4201 (1974); Garsky, Koster, and Arnold, *J. Am. Chem. Soc.* **96,** 4207 (1974).

[336] For a review, see Conia and Le Perchec, *Synthesis* 1-19 (1975).

5-19 The Michael Reaction

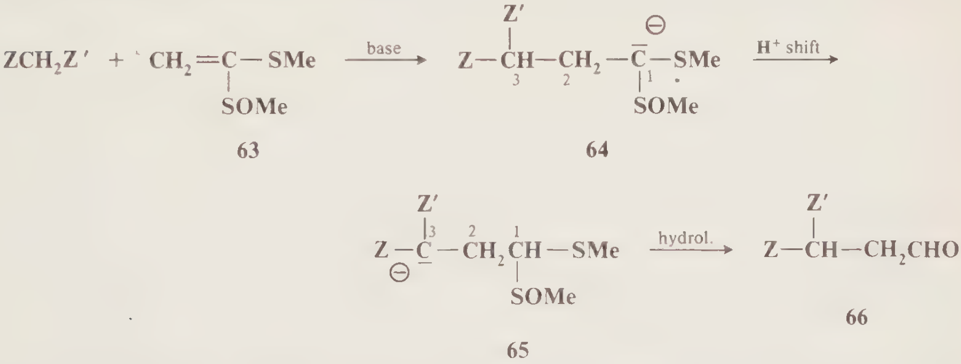


$$Z{-}CH_2{-}Z' + {-}C{=}C{-}Z'' \xrightarrow{\text{base}} Z{-}CH(Z'){-}C{-}CH{-}Z''$$

Compounds containing electron-withdrawing groups (Z is defined on p. 678) add, in the presence of bases, to olefins of the form C=C—Z (including quinones). This is called the *Michael reaction* and involves conjugate addition.[337] The base removes the acidic proton, and then the mechanism is as outlined on p. 679. The reaction has been carried out with malonates, cyanoacetates, acetoacetates, other β-keto esters, and compounds of the form $Z{-}CH_3$, ZCH_2R, $ZCHR_2$, and ZCHRZ', including esters, ketones, aldehydes, nitriles, nitro compounds,[338] and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes. These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (reaction **5-23**). 1,2 addition (to the C=O or C≡N group) often competes and sometimes predominates (reaction **6-42**).

Mannich bases (see reaction **6-17**) and β-halo carbonyl compounds may also be used as substrates; these are converted to the C=C—Z compounds in situ by the basic catalyst (reactions **6-17**, **7-13**).[339] Substrates of this kind are especially useful in cases where the C=C—Z compound is unstable. The reaction of C=C—Z compounds with enamines (**2-17**) can also be considered a Michael reaction. Michael reactions are reversible (**7-17**).

The ketene thioacetal monoxide **63** reacts with ZCH_2Z' compounds to give adducts which can be hydrolyzed to the substituted aldehydes **66**.[340] **63** is thus a synthon for the $-CH_2CHO$ group.



The reaction has been performed with Z, Z' = COR and COOR, as well as with simple esters $R'CH_2COOR$ and with enamines (see reaction **2-17**). When the reagent is ZCH_2Z', if an alkyl halide R″X is added to the reaction mixture before hydrolysis, the enolate ion **65** is alkylated at C-3, so that the product after hydrolysis is $ZCR''Z'CH_2CHO$.[341] On the other hand, if the reagent is a simple ester $R'CH_2COOR$, addition of R″X alkylates the more stable **64** (i.e., **65** does not form, and alkylation takes place at C-1), so that the product after hydrolysis is a γ-keto ester ROOCCHR′CH$_2$COR″.[341]

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[337] For reviews, see Bergmann, Ginsburg, and Pappo, *Org. React.* **10**, 179–560 (1959); Bruson, *Org. React.* **5**, 79–135 (1949) (for acrylonitrile); and House, Ref. 141, pp. 595–623.

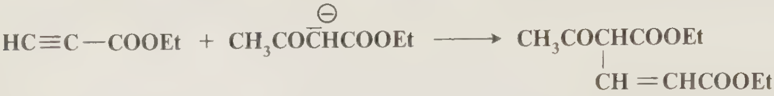
[338] For a review of Michael reactions where Z, Z', or Z″ is nitro, see Baer and Urbas, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pt. 2, pp. 130–148, Interscience Publishers, New York, 1970.

[339] Mannich bases react with ketones *without* basic catalysts to give 1,5-diketones, but this process, known as the *thermal-Michael reaction*, has a different mechanism: Brown, Buchanan, Curran, and McLay, *Tetrahedron* **24**, 4565 (1968); Gill, James, Lions, and Potts, *J. Am. Chem. Soc.* **74**, 4923 (1952).

[340] Herrmann, Kieczykowski, Romanet, Wepplo, and Schlessinger, *Tetrahedron Lett.* 4711 (1973).

[341] Herrmann, Kieczykowski, Romanet, and Schlessinger, *Tetrahedron Lett.* 4715 (1973).

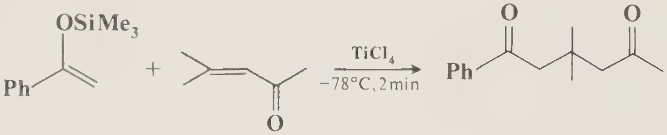
Michael reactions are sometimes applied to substrates of the type C≡C—Z, e.g.,



$$\mathrm{HC{\equiv}C{-}COOEt} + \mathrm{CH_3CO\overset{\ominus}{C}HCOOEt} \longrightarrow \mathrm{CH_3CO\underset{\substack{|\\ CH=CHCOOEt}}{C}HCOOEt}$$

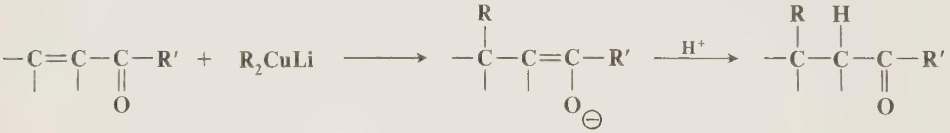
Indeed, because of the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes, e.g., acetylene, to be substrates in this reaction.[342]

In a closely related reaction, silyl enol ethers add to α,β-unsaturated ketones and esters when catalyzed by TiCl$_4$, e.g.,[342a]



OS **I**, 272; **II**, 200; **III**, 286; **IV**, 630, 652, 662, 776; **V**, 486, 1135; **53**, 1; **55**, 99.

5-20 1,4 Addition of Organometallic Compounds to Activated Double Bonds



$$-\underset{|}{C}=\underset{|}{C}-\underset{\parallel}{\underset{O}{C}}-R' + R_2CuLi \longrightarrow -\overset{\overset{R}{|}}{\underset{|}{C}}-\underset{|}{C}=\underset{\underset{O^{\ominus}}{|}}{C}-R' \xrightarrow{H^+} -\overset{\overset{R}{|}}{\underset{|}{C}}-\overset{\overset{H}{|}}{\underset{|}{C}}-\underset{\underset{O}{\parallel}}{C}-R'$$

67

Lithium dialkylcopper reagents (see reaction **0-87**) add to α,β-unsaturated aldehydes and ketones (R′ = H, R, Ar) to give conjugate addition products,[343] in a reaction which is closely related to the Michael reaction. α,β-Unsaturated esters are less reactive, and the corresponding acids do not react at all. R may be primary alkyl, vinyl, or aryl. Various functional groups such as OH and unconjugated C=O groups may be present in the substrate. A characteristic of the reaction is that only one of the R groups of R$_2$CuLi adds to the substrate; the other is wasted. This can be a limitation where the precursor (RLi or RCu, see p. 410) is expensive or available in limited amounts. The difficulty can be overcome by using one of the mixed reagents R(R′C≡C)-CuLi,[344] R(O—*t*-Bu)CuLi,[345] or R(PhS)CuLi,[346] each of which transfers only the R group. These reagents are easily prepared by the reaction of RLi with R′C≡CCu (R′ = *n*-Pr or *t*-Bu), *t*-BuOCu, or PhSCu, respectively. A further advantage of these mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagent R(CN)CuLi, prepared from RLi and CuCN, also selectively transfers the R group.[347]

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[342] See for example Makosza, *Tetrahedron Lett*. 5489 (1966).

[342a] Narasaka, Soai, and Mukaiyama, *Chem. Lett*. 1223 (1974).

[343] House, Respess, and Whitesides, *J. Org. Chem*. **31**, 3128 (1966). For reviews, see Posner, *Org. React*. **19**, 1–113 (1972); House, *Acc. Chem. Res*. **9**, 59–67 (1976).

[344] Corey and Beames, *J. Am. Chem. Soc*. **94**, 7210 (1972); House and Umen, *J. Org. Chem*. **38**, 3893 (1973).

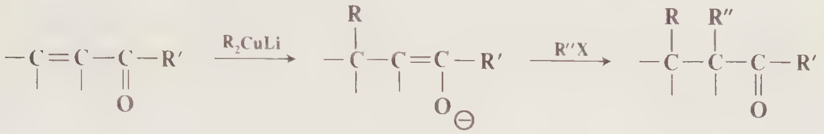
[345] Posner and Whitten, *Tetrahedron Lett*. 1815 (1973).

[346] Posner, Whitten, and Sterling, *J. Am. Chem. Soc*. **95**, 7788 (1973).

[347] Gorlier, Hamon, Levisalles, and Wagnon, *J. Chem. Soc., Chem. Commun*. 88 (1973).

There is generally little or no competition from 1,2 addition (to the C=O). However, when R is allyl, 1,4 addition is observed with some substrates and 1,2 addition with others.[348] R_2CuLi also add to α,β-unsaturated sulfones ($C{=}C{-}SO_2Ar$)[349] but not to simple α,β-unsaturated nitriles.[350] Organocopper reagents RCu (as well as certain R_2CuLi) add to α,β-unsaturated sulfoxides C=C—SOR.[351]

When the solvent is 1,2-dimethoxyethane, instead of hydrolyzing the enolate ion **67**, it is

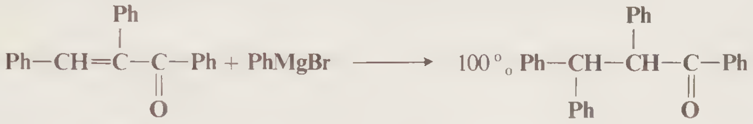


$$-\underset{|}{C}=\underset{|}{C}-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{R_2CuLi} -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{C}=\underset{\underset{O^{\ominus}}{|}}{C}-R' \xrightarrow{R''X} -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{\overset{R''}{|}}{C}}-\underset{\underset{O}{\|}}{C}-R'$$

67

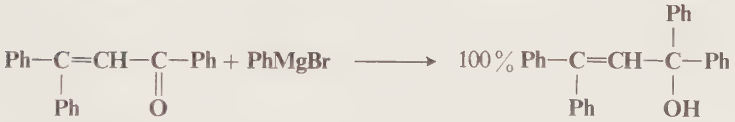
possible to alkylate it directly with an alkyl halide, where R″ is primary alkyl or allylic[352] (reaction **0-97**). Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation.

Grignard reagents also add to these substrates, but with these reagents, 1,2 addition may seriously compete: the product is often controlled by steric factors. Thus, **68** with phenylmagnesium bromide gives 100% 1,4 addition, while **69** gives 100% 1,2 addition:



$$Ph-CH=\overset{\overset{Ph}{|}}{C}-\underset{\underset{O}{\|}}{C}-Ph + PhMgBr \longrightarrow 100\%\ Ph-\underset{\underset{Ph}{|}}{CH}-\overset{\overset{Ph}{|}}{CH}-\underset{\underset{O}{\|}}{C}-Ph$$

68



$$Ph-\underset{\underset{Ph}{|}}{C}=CH-\underset{\underset{O}{\|}}{C}-Ph + PhMgBr \longrightarrow 100\%\ Ph-\underset{\underset{Ph}{|}}{C}=CH-\overset{\overset{Ph}{|}}{\underset{\underset{OH}{|}}{C}}-Ph$$

69

In general, substitution at the carbonyl group increases 1,4 addition, while substitution at the double bond increases 1,2 addition. In most cases both products are obtained, but α,β-unsaturated *aldehydes* nearly always give exclusive 1,2 addition when treated with Grignard reagents. However, the extent of 1,4 addition of Grignard reagents can be increased by the use of a copper-ion catalyst, e.g., CuCl, $Cu(OAc)_2$.[353] It is likely that alkylcopper reagents, formed from RMgX and Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual attacking species in these cases.[343] Alkyllithiums, treated with compounds of the form $C{=}C{-}COCH_3$ and $C{=}C{-}COOC_2H_5$, gave only 1,2 addition.[354] In some cases, with Grignard reagents, it is possible to get a diaddition product (1,2 *and* 1,4).[355]

However, neither Grignard reagents nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds. Grignard reagents in general add only to double bonds susceptible to nucleophilic attack, e.g., fluoroolefins, tetracyanoethylene,[355a] and fulvenes. However, active Grignard reagents (benzyl, allyl) also add to the double bonds of allylic amines[356] and of allylic and homoallylic alcohols[357] as well as to the triple bonds of propargyl alcohols and certain other alkynols.[358] It is likely that cyclic intermediates are involved in these cases, in which the magnesium coordinates with the hetero arom. Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) also add to the double and triple bonds of allylic and propargylic alcohols[359] (in this case tetramethylethylenediamine is a catalyst) and to certain other olefins containing hetero groups such as OR, NR_2 or SR.[360] Allylic, benzylic, and tertiary Grignard reagents also add to 1-alkenes and to strained internal alkenes, e.g., norbornene, if the reaction is carried out not in ether but in a hydrocarbon solvent such as pentane or in the alkene itself as solvent, heated, under pressure if necessary, to 60 to 130°C.[361] Yields are variable. *Intramolecular* addition of RMgX to completely unactivated double and triple bonds has been demonstrated;[362] e.g., refluxing of 6-chloro-1-heptene with Mg for 5 hr gave, after hydrolysis, an 88% yield of 1,2-dimethylcyclopentane. Also, certain catalysts [e.g., tris(triphenylphosphine)-bromorhodium $(Ph_3P)_3RhBr$, bis(triphenylphosphine)dichloronickel $(Ph_3P)_2NiCl_2$] catalyze the addition of methylmagnesium bromide to diphenylacetylene.[363]

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[348] House and Fischer, *J. Org. Chem.* **34**, 3615 (1969). See also Daviaud and Miginiac, *Tetrahedron Lett.* 3345 (1973).

[349] Posner and Brunelle, *Tetrahedron Lett.* 935 (1973).

[350] House and Umen, Ref. 344.

[351] Truce and Lusch, *J. Org. Chem.* **39**, 3174 (1974).

[352] Coates and Sandefur, *J. Org. Chem.* **39**, 275 (1974). See also Posner, Whitten, Sterling, and Brunelle, *Tetrahedron Lett.* 2591 (1974); Heng and Smith, *Tetrahedron Lett.* 589 (1975).

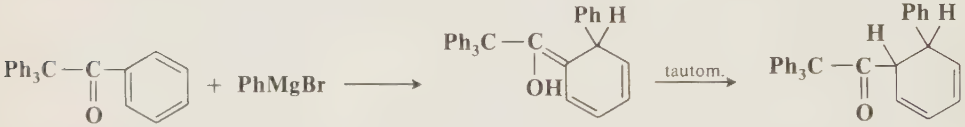
[353] Posner, Ref. 343.

[354] Rozhkov and Makin, *J. Gen. Chem. USSR* **34**, 57 (1964).

[355] Fuson, San, and Dieckmann, *J. Org. Chem.* **27**, 1221 (1962).

An alkynyl group can be added to the double bond of an α,β-unsaturated ketone by use of the diethylalkynylalane reagents $Et_2AlC{\equiv}CR$.[364] In a similar manner, the alkenyl reagents $R_2AlCH{=}CR'$ transfer an alkenyl group.[365] Trialkylalanes R_3Al also add 1,4 to such ketones in the presence of nickel acetylacetonate.[366]

In certain cases, Grignard reagents add 1,4 to *aromatic* systems, e.g.,[367]



[355a] Gardner and Kochi, *J. Am. Chem. Soc.* **98,** 558 (1976).

[356] Richey, Erickson, and Heyn, *Tetrahedron Lett.* 2183 (1971).

[357] Eisch and Husk, *J. Am. Chem. Soc.* **87,** 4194 (1965); Chérest, Felkin, Frajerman, Lion, Roussi, and Swierczewski, *Tetrahedron Lett.* 875 (1966); Eisch and Merkley, *J. Organomet. Chem.* **20,** P27 (1969); Felkin and Kaeseberg, *Tetrahedron Lett.* 4587 (1970); Richey and Szucs, *Tetrahedron Lett.* 3785 (1971).

[358] Eisch and Merkley, Ref. 357; Richey and Von Rein, *J. Organomet. Chem.* **20,** P32 (1969); Von Rein and Richey, *Tetrahedron Lett.* 3777 (1971). See also Vermeer, de Graaf, and Meijer, *Recl. Trav. Chim. Pays-Bas* **93,** 24 (1974); Jousseaume and Duboudin, *J. Organomet. Chem.* **91,** C1 (1975).

[359] Felkin, Swierczewski, and Tambuté, *Tetrahedron Lett.* 707 (1969); Crandall and Clark, *Tetrahedron Lett.* 325 (1969), *J. Org. Chem.* **37,** 4236 (1972); Dimmel and Huang, *J. Org. Chem.* **38,** 2756 (1973); Olsson and Claesson, *Tetrahedron Lett.* 2161 (1974).

[360] Veefkind, Bickelhaupt, and Klumpp, *Recl. Trav. Chim. Pays-Bas* **88,** 1058 (1969); Veefkind, Schaaf, Bickelhaupt, and Klumpp, *Chem. Commun.* 722 (1971).

[361] Lehmkuhl and Reinehr, *J. Organomet. Chem.* **25,** C47 (1970); **57,** 29 (1973); Lehmkuhl, Reinehr, Brandt, and Schroth, *J. Organomet. Chem.* **57,** 39 (1973); Lehmkuhl, Reinehr, Schomburg, Henneberg, Damen, and Schroth, *Justus Liebigs Ann. Chem.* 103 (1975); Lehmkuhl, Reinehr, Henneberg, Schomburg, and Schroth, *Justus Liebigs Ann. Chem.* 119 (1975); Lehmkuhl, Bergstein, Henneberg, Janssen, Olbrysch, Reinehr, and Schomburg, *Justus Liebigs Ann. Chem.* 1176 (1975).

[362] See, for example, Richey and Rees, *Tetrahedron Lett.* 4297 (1966); Kossa, Rees, and Richey, *Tetrahedron Lett.* 3455 (1971); Richey and Veale, *J. Am. Chem. Soc.* **96,** 2641 (1974), *Tetrahedron Lett.* 615 (1975); Drozd, Ustynyuk, Tsel'eva, and Dmitriev, *J. Gen. Chem. USSR* **39,** 1951 (1969); Felkin, Umpleby, Hagaman, and Wenkert, *Tetrahedron Lett.* 2285 (1972).

[363] Michman and Balog, *J. Organomet. Chem.* **31,** 395 (1971); Duboudin and Jousseaume, *J. Organomet. Chem.* **44,** C1 (1972).

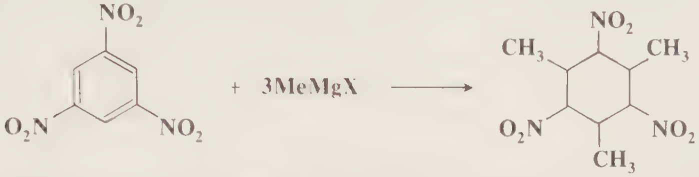
[364] Hooz and Layton, *J. Am. Chem. Soc.* **93,** 7320 (1971).

[365] Hooz and Layton, *Can. J. Chem.* **51,** 2098 (1973).

[366] Jeffery, Meisters, and Mole, *J. Organomet. Chem.* **74,** 365 (1974); Bagnell, Jeffery, Meisters, and Mole, *Aust. J. Chem* **28,** 801 (1975); Bagnell, Meisters, and Mole, *Aust. J. Chem.* **28,** 817 (1975); Ashby and Heinsohn, *J. Org. Chem.* **39,** 3297 (1974). See also Kabalka and Daley, *J. Am. Chem. Soc.* **95,** 4428 (1973).

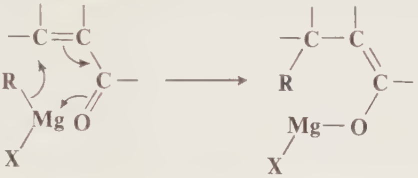
[367] This example is from Schmidlin and Wohl, *Ber.* **43,** 1145 (1910), and Mosher and Huber, *J. Am. Chem. Soc.* **75,** 4604 (1953). For a review of such reactions, see Fuson, *Adv. Organomet. Chem.* **1,** 221–238 (1964).

Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so that this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds:[368]



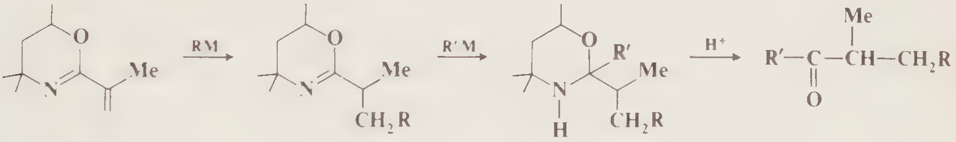
Both Grignard and R_2CuLi reagents[369] have also been added to triple-bond systems of the form C≡C—C=O.

The mechanisms of most of these reactions are not well known. The 1,4 uncatalyzed Grignard reaction has been postulated to proceed by a cyclic mechanism



but there is evidence against it.[370] The R_2CuLi and copper-catalyzed Grignard additions may involve a free-radical mechanism of some type,[371] though the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.[372] The addition of R_3Al takes place by a free-radical mechanism.[366]

Grignard reagents and alkyllithiums add to the double bond of the commercially available 2-isopropenyldihydro-1,3-oxazine **70** (see reaction **0-100**), and then without isolation of **71**, a second



70 71 72

mole of RM (the same or different) can be added to give **72**, which can be hydrolyzed to a ketone.[373] R may be aryl or primary, secondary, or tertiary alkyl, but R′ is limited to aryl and primary alkyl groups. Borohydride reduction of **71**, followed by hydrolysis (see reaction **0-100**), gives the α-alkyl aldehyde $RCH_2CHMeCHO$. Similar reactions have been carried out on 2-(1-phenyl-1-ethenyl)dihydro-1,3-oxazine, the phenyl analog of **70**. The addition of RM to **70** is not a simple 1,4-addition but involves ring opening to a ketenimine intermediate (similar to **162**, shown on p. 430), which then closes to give **71**.

OS **IV**, 93; **V**, 762; **50**, 38; **52**, 109; **55**, 1.

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[368] Severin and Schmitz, *Chem. Ber.* **96**, 3081 (1963).

[369] For example, see Corey and Katzenellenbogen, *J. Am. Chem. Soc.* **91**, 1851 (1969); Siddall, Biskup, and Fried, *J. Am. Chem. Soc.* **91**, 1853 (1969); Corey, Kim, Chen, and Takeda, *J. Am. Chem. Soc.* **94**, 4395 (1972); Anderson, Corbin, Cotterrell, Cox, Henrick, Schaub, and Siddall, *J. Am. Chem. Soc.* **97**, 1197 (1975).

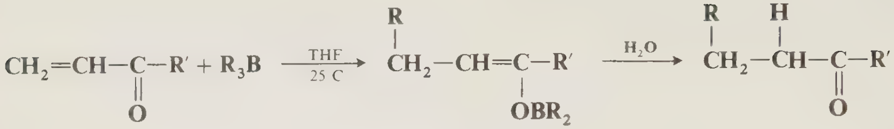
[370] House and Thompson, *J. Org. Chem.* **28**, 360 (1963); Klein, *Tetrahedron* **20**, 465 (1964). See however Marets and Rivière, *Bull. Soc. Chim. Fr.* 4320 (1970).

[371] See for example House and Umen, *J. Am. Chem. Soc.* **94**, 5495 (1972); Ruden and Litterer, *Tetrahedron Lett.* 2043 (1975). See, however, Hannah, and Smith, *Tetrahedron Lett.* 187 (1975).

[372] Näf and Degen, *Helv. Chim. Acta* **54**, 1939 (1971); Whitesides and Kendall, *J. Org. Chem.* **37**, 3718 (1972). See also Ref. 343.

[373] Meyers, Kovelesky, and Jurjevich, *J. Org. Chem.* **38**, 2136 (1973).

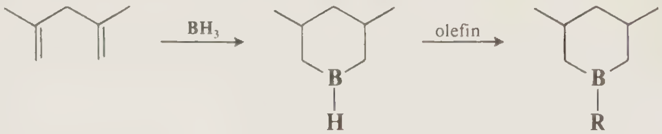
5-21 The Addition of Boranes to Activated Double Bonds



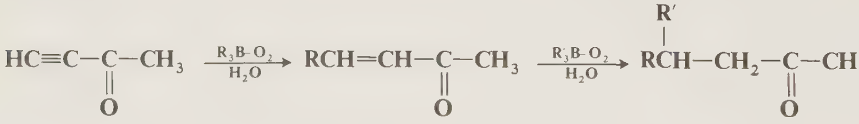
$$CH_2{=}CH{-}\underset{\underset{O}{\|}}{C}{-}R' + R_3B \xrightarrow[25\ C]{THF} \overset{\overset{R}{|}}{CH_2}{-}CH{=}\underset{\underset{OBR_2}{|}}{C}{-}R' \xrightarrow{H_2O} \overset{\overset{R}{|}}{CH_2}{-}\overset{\overset{H}{|}}{CH}{-}\underset{\underset{O}{\|}}{C}{-}R'$$

$R' = H, Me$

Trialkylboranes rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain of their derivatives, e.g., 2-bromo- and 2-methylacrolein, in tetrahydrofuran at 25°C, to give enol borinates, which can be hydrolyzed to aldehydes or ketones.[374] The water may be present from the beginning, so that the reaction can be run in one laboratory step. Since the boranes can be prepared from olefins (reaction **5-15**), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group, such as crotonaldehyde $CH_3CH{=}CHCHO$ and 3-penten-2-one, fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of O_2 or by initiation with peroxides or uv light.[375] As in the Michael reaction, the α,β-unsaturated compound can be generated in situ from the corresponding Mannich base (reaction **6-17**).[376] A disadvantage is that only one of the three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a B-alkyl borinate such as **74**[377] (the reagents B-R-9-BBN are not useful here, since the R group of these reagents does not preferentially add to the substrate). **74** can be prepared by hydroboration of 2,4-dimethyl-1,4-pentadiene, followed by addition of the borinane **73** to an olefin. **74** (R = *t*-butyl) can be prepared by treatment of **74** (R = OMe) with *t*-BuLi. The use of this reagent permits *t*-butyl groups to be added. Like the three substrates mentioned above, 3-butyn-2-one fails to react in the absence of air but undergoes the reaction when exposed to a slow stream of air.[378]



73 **74**



$$HC{\equiv}C{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow[H_2O]{R_3B{-}O_2} RCH{=}CH{-}\underset{\underset{O}{\|}}{C}{-}CH_3 \xrightarrow[H_2O]{R'_3B{-}O_2} \overset{\overset{R'}{|}}{RCH}{-}CH_2{-}\underset{\underset{O}{\|}}{C}{-}CH_3$$

75

Since the product is an α,β-unsaturated ketone, it can be made to react with another BR_3, the same or different, to produce a wide variety of ketones **75**. Similarly, the monoepoxides of

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[374] Suzuki, Arase, Matsumoto, Itoh, Brown, Rogić, and Rathke, *J. Am. Chem. Soc.* **89,** 5708 (1967); Brown, Rogić, Rathke, and Kabalka, *J. Am. Chem. Soc.* **89,** 5709 (1967); Brown, Kabalka, Rathke, and Rogić, *J. Am. Chem. Soc.* **90,** 4165 (1968). For reviews, see Brown and Midland, *Angew. Chem. Int. Ed. Engl.* **11,** 692–700 (1972), pp. 694–698 [*Angew. Chem.* **84,** 702–710]; Kabalka, *Intra-Sci. Chem. Rep.* 7(1), 57–64 (1973); Brown, "Boranes in Organic Chemistry," Ref. 287, pp. 413–433.

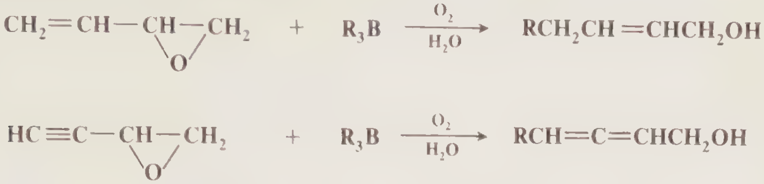
[375] Brown and Kabalka, *J. Am. Chem. Soc.* **92,** 712, 714 (1970). See also Utimoto, Tanaka, Furubayashi, and Nozaki, *Tetrahedron Lett.* 787 (1973); Miyaura, Kashiwagi, Itoh, and Suzuki, *Chem. Lett.* 395 (1974).

[376] Brown, Rathke, Kabalka, and Rogić, *J. Am. Chem. Soc.* **90,** 4166 (1968).

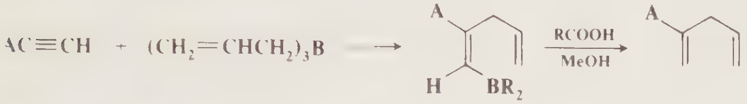
[377] Brown and Negishi, *J. Am. Chem. Soc.* **93,** 3777 (1971).

[378] Suzuki, Nozawa, Itoh, Brown, Kabalka, and Holland, *J. Am. Chem. Soc.* **92,** 3503 (1970).

1,3-butadiene and butenyne react with BR_3 in the presence of oxygen to give 4-alkyl-2-buten-1-ols and 4-alkyl-2,3-butadien-1-ols, respectively:[379]



Triallylboranes add to unactivated triple bonds to give vinylboranes which can be hydrolyzed to 1,4-dienes:[380]



A = H, R, OR, Ar, vinyl, or Me_3Si

The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl[381] (a free-radical inhibitor) indicates that free-radical mechanisms are involved. The attacking species is R•, and the following mechanism[381] (shown for peroxide initiation) is likely:

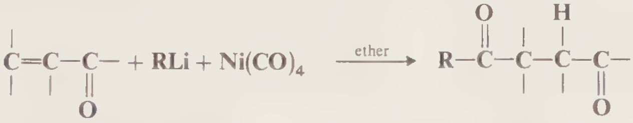
Initiation $\mathrm{R'OOR' \longrightarrow 2R'O\cdot}$

$$\mathrm{R'O\cdot + R_3B \longrightarrow R{-}\overset{\oplus}{\dot{O}}{-}\overset{\ominus}{\bar{B}}R_3 \longrightarrow R'O{-}BR_2 + R\cdot}$$

Propagation $\mathrm{R\cdot + C{=}C{-}C{=}O \longrightarrow R{-}C{-}C{=}C{-}O\cdot}$

$$\mathrm{R{-}C{-}C{=}C{-}O\cdot + R_3B \longrightarrow R{-}C{-}C{=}C{-}OBR_2 + R\cdot}$$

5-22 Acylation of Activated Double Bonds and of Triple Bonds



$$\overset{|}{\underset{|}{\mathrm{C}}}=\underset{|}{\mathrm{C}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}- + \mathrm{RLi} + \mathrm{Ni(CO)_4} \xrightarrow{\text{ether}} \mathrm{R}-\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-\overset{|}{\underset{|}{\mathrm{C}}}-\overset{\overset{\mathrm{H}}{|}}{\underset{|}{\mathrm{C}}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-$$

76

An acyl group can be introduced into the 4 position of an α,β-unsaturated ketone by treatment with an organolithium compound and nickel carbonyl.[382] The product is a 1,4-diketone. R may be aryl or primary alkyl. The reaction can also be applied to alkynes (which need not be activated), in which case 2 moles add and the product is also a 1,4-diketone, e.g., $R'C{\equiv}CH \rightarrow RCOCHR'CH_2COR$.[383]

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[379] Suzuki, Miyaura, Itoh, Brown, Holland, and Negishi, *J. Am. Chem. Soc.* **93**, 2792 (1971); Suzuki, Miyaura, Itoh, Brown, and Jacob, *Synthesis* 305 (1973).

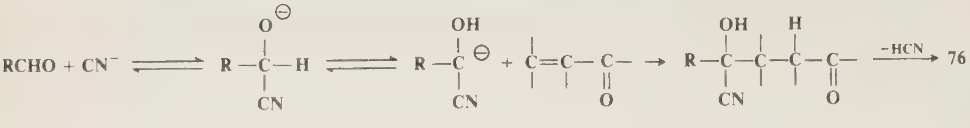
[380] Bubnov, Frolov, Kiselev, Bogdanov, and Mikhailov, *Organomet. Chem. Synth.* **1**, 37 (1970); Mikhailov, Bubnov, Korobeinikova, and Frolov, *J. Organomet. Chem.* **27**, 165 (1971).

[381] Kabalka, Brown, Suzuki, Honma, Arase, and Itoh, *J. Am. Chem. Soc.* **92**, 710 (1970).

[382] Corey and Hegedus, *J. Am. Chem. Soc.* **91**, 4926 (1969).

[383] Sawa, Hashimoto, Ryang, and Tsutsumi, *J. Org. Chem.* **33**, 2159 (1968).

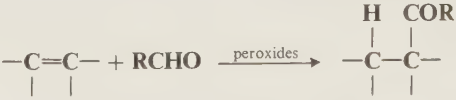
Another method involves treatment with an aldehyde and cyanide ion (see reaction **6-50**) in a polar aprotic solvent such as dimethylformamide or dimethyl sulfoxide[384]



77

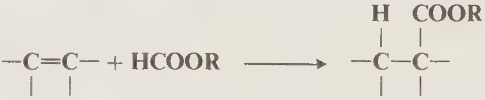
This method has been applied to α,β-unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ-keto esters, and γ-keto nitriles, respectively (see also reaction **6-56**). The ion **77** is a synthon for the unavailable $R\bar{C}\overset{\ominus}{=}O$ anion (see also p. 427); it may be considered a "masked" $\underset{\bigcirc}{R}\bar{C}\overset{\ominus}{=}O$ anion. Other masked carbanions which have been used in this reaction are the $EtS\underset{\ominus}{\bar{C}}RSOEt$ ion[385] (see p. 427), the $CH_2{=}\overset{\ominus}{\bar{C}}OEt$ ion,[385a] and the $R\overset{\ominus}{\bar{C}}$-(OCHMeOEt)CN ion[386] (see p. 423). In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes (reaction **0-99**) do not give 1,4 addition to these substrates but instead add 1,2 to the C=O group (reaction **6-42**).

5-23 Addition of Alcohols, Amines, Esters, Aldehydes, etc.

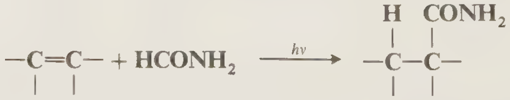


$$-\underset{|}{C}=\underset{|}{C}- + RCHO \xrightarrow{\text{peroxides}} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{COR}{|}}{C}}-$$

Aldehydes, formates, primary and secondary alcohols, amines, ethers,[387] alkyl halides,[388] compounds of the type $Z{-}CH_2{-}Z'$, and a few other compounds add to double bonds in the presence of free-radical initiators.[389] This is formally the addition of RH to a double bond, but the "R" is not just any carbon but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as on p. 419). The addition of aldehydes is illustrated above. Formates and formamides[390] add similarly:



$$-\underset{|}{C}=\underset{|}{C}- + HCOOR \longrightarrow -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{COOR}{|}}{C}}-$$



$$-\underset{|}{C}=\underset{|}{C}- + HCONH_2 \xrightarrow{h\nu} -\underset{|}{\overset{\overset{H}{|}}{C}}-\underset{|}{\overset{\overset{CONH_2}{|}}{C}}-$$

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[384] Stetter and Schreckenberg, *Tetrahedron Lett.* 1461 (1973), *Angew. Chem. Int. Ed. Engl.* **12,** 81 (1973) [*Angew. Chem.* **85,** 89], *Chem. Ber.* **107,** 210, 2453 (1974). See also Stetter and Kuhlmann, *Angew. Chem. Int. Ed. Engl.* **13,** 539 (1974) [*Angew. Chem.* **86,** 589].

[385] Herrmann, Richman, and Schlessinger, *Tetrahedron Lett.* 3271, 3275 (1973).

[385a] Boekman, Bruza, Baldwin, and Lever, *J. Chem. Soc., Chem. Commun.* 519 (1975).

[386] Stork and Maldonado, *J. Am. Chem. Soc.* **96,** 5272 (1974).

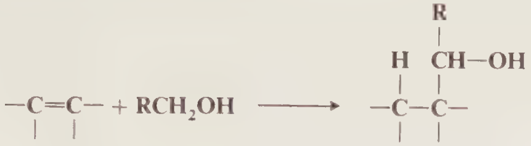
[387] Rosenthal and Elad, *Tetrahedron* **23,** 3193 (1967).

[388] Trecker and Henry, *Chem. Commun.* 258 (1966).

[389] For reviews, see Vogel, *Synthesis* 99–140 (1970); Huyser, Ref. 41, pp. 152–159; Elad, *Fortschr. Chem. Forsch.* **7,** 528–558 (1967); Walling and Huyser, Ref. 41, pp. 108–112, 132–146; Sosnovsky, Ref. 41, pp. 121–152; Walling, Ref. 41, pp. 273–289.

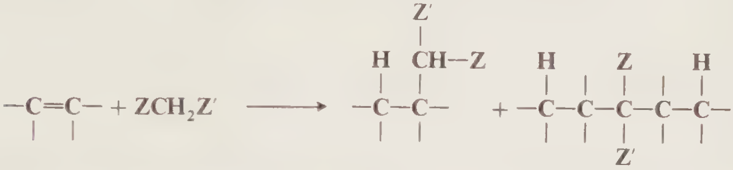
[390] Elad, Ref. 389, pp. 530–543.

Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{RCH_2OH} \longrightarrow -\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-\underset{|}{\overset{\overset{\overset{\overset{\mathrm{R}}{|}}{\mathrm{CH-OH}}}{|}}{\mathrm{C}}}-$$

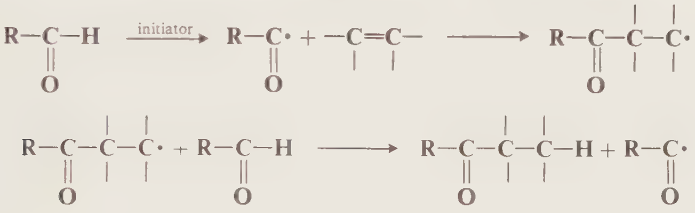
ZCH_2Z' compounds react at the carbon bearing the active hydrogen:[391]



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{ZCH_2Z'} \longrightarrow -\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-\underset{|}{\overset{\overset{\overset{\overset{\mathrm{Z'}}{|}}{\mathrm{CH-Z}}}{|}}{\mathrm{C}}}- \quad + -\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{\underset{\mathrm{Z'}}{|}}{\overset{\overset{\mathrm{Z}}{|}}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-$$

Similar additions have been successfully carried out with carboxylic acids, anhydrides,[392] acyl halides, esters, nitriles, and other types of compounds.[393]

These reactions are most successful when the olefin contains electron-withdrawing groups such as halo or carbonyl groups. A free-radical initiator is required, usually peroxides or uv light. The mechanism is illustrated for aldehydes but is similar for the other compounds:



$$\mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{H} \xrightarrow{\text{initiator}} \mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\cdot + -\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- \longrightarrow \mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}\cdot$$

$$\mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}\cdot + \mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{H} \longrightarrow \mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\mathrm{H} + \mathrm{R}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\cdot$$

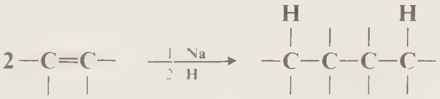
etc.

Polymers are often side products.

Similar reactions have been carried out on acetylene.[394]

OS **IV**, 430; **V**, 93; **55**, 57.

5-24 Reductive Coupling of Olefins



$$2\,-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- \xrightarrow[2.\ \mathrm{H}^{+}]{1.\ \mathrm{Na}} -\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{|}{\mathrm{C}}}-\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-$$

Certain olefins have been coupled by treatment with sodium, followed by acid. The reaction has been performed with styrene, 1,1-diphenylethylene, acrylonitrile, and butadiene, among others.[395]

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[391] For example, see Allen, Cadogan, Harris, and Hey, *J. Chem. Soc.* 4468 (1962); Cadogan, Hey, and Sharp, *J. Chem. Soc. C* 1743 (1966), *J. Chem. Soc. B* 803 (1967).

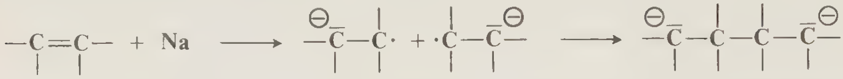
[392] de Klein, *Recl. Trav. Chim. Pays-Bas* **94**, 48 (1975).

[393] Allen, Cadogan, and Hey, *J. Chem. Soc.* 1918 (1965); Cadogan, *Pure Appl. Chem.* **15**, 153–165 (1967), pp. 153–158.

[394] For example, see Cywinski and Hepp, *J. Org. Chem.* **31**, 3814 (1965); DiPietro and Roberts, *Angew. Chem. Int. Ed. Engl.* **5**, 415 (1966) [*Angew. Chem.* **78**, 388].

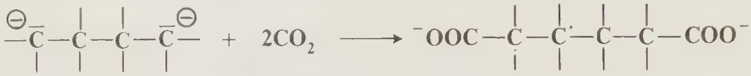
[395] Frank and Foster, *J. Org. Chem.* **26**, 303 (1961); Frank, Leebrick, Moormeier, Scheben, and Homberg, *J. Org. Chem.* **26**, 307 (1961); Suga, Watanabe, and Takahashi, *Bull. Chem. Soc. Jpn.* **40**, 2432 (1967).

The coupling is head to head. The first step is probably an electron transfer from the sodium, creating a radical ion, which dimerizes:



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + \text{Na} \longrightarrow \ominus\,-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\cdot + \cdot\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\,\ominus \longrightarrow \ominus\,-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\,\ominus$$

That the dicarbanion is an intermediate may be shown by treatment of the mixture with carbon dioxide, instead of acid, whereupon a dicarboxylate ion is obtained:

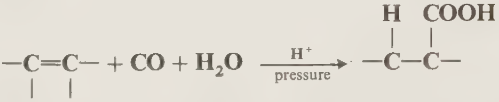


$$\ominus\,-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\,\ominus + 2CO_2 \longrightarrow {}^{-}OOC-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-COO^{-}$$

Mixed coupling can be achieved in certain cases; e.g., a mixture of acrylonitrile and ethyl acrylate gave 80% ethyl δ-cyanovalerate.[396]

Similar reactions have been carried out electrolytically.[397]

5-25 Hydrocarboxylation



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + CO + H_2O \xrightarrow[\text{pressure}]{H^+} -\overset{H}{\overset{|}{C}}-\overset{COOH}{\overset{|}{C}}-$$

The acid-catalyzed hydrocarboxylation of olefins (the *Koch reaction*) can be performed in a number of ways.[398] In one method, the olefin is treated with carbon monoxide and water at 100 to 350°C and 500 to 1000 atm pressure, with a mineral-acid catalyst. However, the reaction can also be performed under milder conditions. If the olefin is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0 to 50°C and 1 to 100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.[399] The formic acid procedure is called the *Koch-Haaf reaction* (the Koch-Haaf reaction can also be applied to alcohols, see reaction **0-105**). Nearly all olefins can be hydrocarboxylated by one or more of these procedures. However, conjugated dienes are polymerized instead. If the olefin contains a functional group such as OH, NH_2, or $CONH_2$, the corresponding lactone (reaction **0-24**), lactam (reaction **0-56**), or cyclic imide may be the product.[400] Cyclic ketones can be produced from 1,5- and 1,6-dienes.

Hydrocarboxylation can also be accomplished under mild conditions (160°C and 50 atm) by the use of nickel carbonyl as catalyst. This is more often applied to triple bonds, to give α,β-unsaturated acids, in which cases the conditions are milder still. Acid catalysts are used along with the nickel carbonyl, but basic catalysts may also be employed.[401] Other metallic salts and complexes, e.g., bis(triphenylphosphine)palladium dichloride $(Ph_3P)_2PdCl_2$,[402] have also been used.

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[396] Matsuda, *Tetrahedron Lett.* 6193 (1966).

[397] Baizer, *Tetrahedron Lett.* 973 (1963); Baizer and Anderson, *J. Org. Chem.* **30,** 1357 (1965); Anderson and Baizer, *Tetrahedron Lett.* 511 (1965); Anderson, Baizer, and Petrovich, *J. Org. Chem.* **31,** 3890 (1966); Petrovich, Anderson, and Baizer, *J. Org. Chem.* **31,** 3897 (1966); Schäfer and Steckhan, *Tetrahedron Lett.* 3835 (1970).

[398] For reviews of hydrocarboxylation of double and triple bonds catalyzed by acids or metallic compounds, see Eidus, Lapidus, Puzitskii, and Nefedov, *Russ. Chem. Rev.* **42,** 199–213 (1973); Eidus, Puzitskii, Lapidus, and Nefedov, *Russ. Chem. Rev.* **40,** 429–440 (1971); Falbe, "Carbon Monoxide in Organic Synthesis," pp. 78–174, Springer-Verlag OHG, Berlin, 1970; Bird, Ref. 208, pp. 149-204, *Chem. Rev.* **62,** 283-302 (1962); Olah and Olah, in Olah, Ref. 319, vol. 3, pp. 1272–1296 (1964).

[399] Koch and Haaf, *Justus Liebigs Ann. Chem.* **618,** 251 (1958); Haaf, *Chem. Ber.* **99,** 1149 (1966); Christol and Solladié, *Bull. Soc. Chim. Fr.* 1307 (1966).

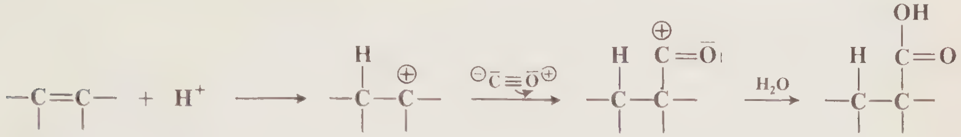
[400] For reviews of these ring closures, see Falbe, Ref. 398, pp. 147–174, *Angew. Chem. Int. Ed. Engl.* **5,** 435–446 (1966) [*Angew. Chem.* **78,** 532–544], *Newer Methods Prep. Org. Chem.* **6,** 193–222 (1971).

[401] Sternberg, Markby, and Wender, *J. Am. Chem. Soc.* **82,** 3638 (1960).

[402] For a review, see Bittler, Kutepow, Neubauer, and Reis, *Angew. Chem. Int. Ed. Engl.* **7,** 329–335 (1968) [*Angew. Chem.* **7,** 329–335]. See also Fenton, *J. Org. Chem.* **38,** 3192 (1973).

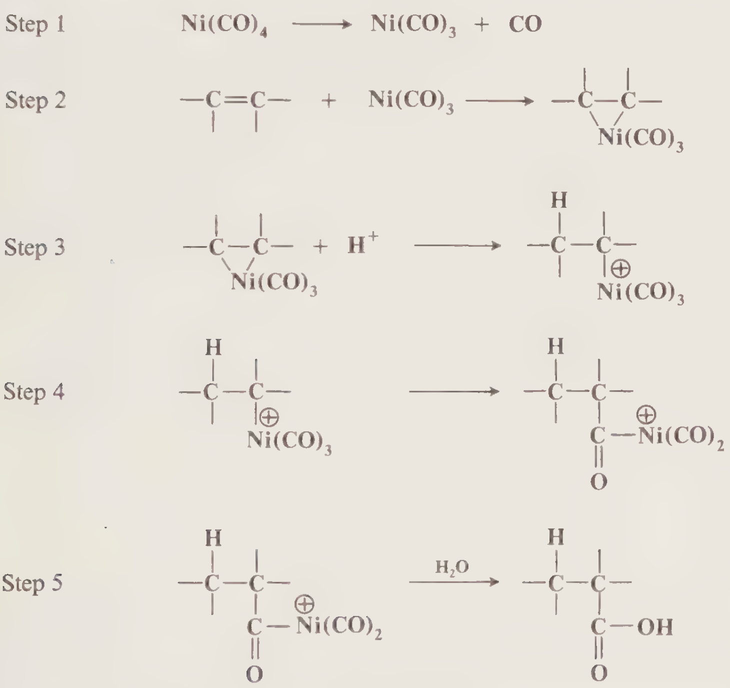
In another method, the palladium chloride complex of the olefin is treated with CO in ethanol at about 100°C.[403] The product in this case is the ethyl ester.

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism[404] involves initial attack by a proton, followed by attack of the resulting carbonium ion on carbon monoxide to give an acylonium ion, which, with water, gives the product:


H⁺
H
⊕
$^{\ominus}\bar{C}\equiv\bar{O}^{\oplus}$
H
⊕
C=O
H₂O
OH
H
C=O

Therefore, Markovnikov's rule is followed, and carbon skeleton rearrangements and double-bond isomerizations (prior to attack by CO) are frequent.

For the nickel carbonyl reaction, the addition is syn, for both alkenes and alkynes.[405] The following mechanism has been proposed:[405]


Step 1
$Ni(CO)_4 \longrightarrow Ni(CO)_3 + CO$
Step 2
$Ni(CO)_3$
$Ni(CO)_3$
Step 3
H⁺
$Ni(CO)_3$
H
⊕
$Ni(CO)_3$
Step 4
H
⊕
$Ni(CO)_3$
H
⊕
$Ni(CO)_2$
O
Step 5
H
⊕
$Ni(CO)_2$
O
H₂O
H
OH
O

Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

In either the acid catalysis or the nickel carbonyl (or other metallic catalyst) method, if alcohols, mercaptans, amines, etc., are used instead of water, the product is the corresponding ester, thiol ester, or amide, instead of the carboxylic acid.

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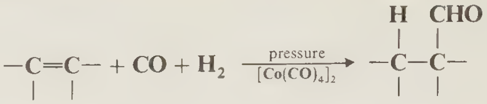
[403] Tsuji, Morikawa, and Kiji, *J. Am. Chem. Soc.* **86,** 4851 (1964); Tsuji, Kiji, Imamura, and Morikawa, *J. Am. Chem. Soc.* **86,** 4350 (1964). For a review, see Tsuji, *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 153–159.

[404] For a review, see Hogeveen, *Adv. Phys. Org. Chem.* **10,** 29–52 (1973).

[405] Bird, Cookson, Hudec, and Williams, *J. Chem. Soc.* 410 (1963).

5-26 Hydroformylation

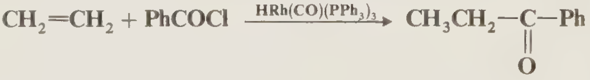


$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + CO + H_2 \xrightarrow[{[Co(CO)_4]_2}]{\text{pressure}} -\overset{H}{\underset{|}{\overset{|}{C}}}-\overset{CHO}{\underset{|}{\overset{|}{C}}}-$$

Olefins can be hydroformylated[406] by treatment with carbon monoxide and hydrogen over a catalyst which is usually a cobalt carbonyl but may also be a rhodium complex[407] [e.g., hydridocarbonyltris(triphenylphosphine)rhodium] or another transition-metal compound. Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal olefins > straight-chain internal olefins > branched-chain olefins. Conjugated dienes give dialdehydes when rhodium catalysts are used[408] but saturated monoaldehydes (the second double bond is reduced) with cobalt carbonyls. Many functional groups, e.g., OH, CHO, COOR, CN, may be present in the molecule, though halogens usually interfere. Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.[409] Among the side reactions are aldol condensation (**6-40**), acetal formation, the Tishchenko reaction (**9-75**), and polymerization.

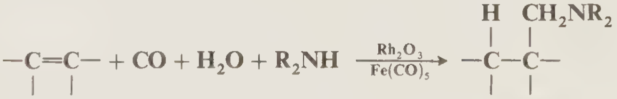
When dicobalt octacarbonyl $[Co(CO)_4]_2$ is the catalyst, the species which actually adds to the double bond[410] is tetracarbonylhydrocobalt $HCo(CO)_4$.[411] There then follows a rearrangement and a reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in reaction **5-25.** The reducing agent in the reduction step is either $HCo(CO)_4$ or, less likely, H_2. Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up. It has been shown[412] that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that $HCo(CO)_3$ is the reducing agent.

An indirect method for the hydroformylation of olefins involves formation of the trialkylborane (reaction **5-15**) and treatment of this with carbon monoxide and a reducing agent (see reaction **8-29**). *Hydroacylation* of alkenes has been accomplished, in variable yields, by treatment with an acyl halide and a rhodium complex catalyst, e.g.,[413]



$$CH_2=CH_2 + PhCOCl \xrightarrow{HRh(CO)(PPh_3)_3} CH_3CH_2-\underset{\underset{O}{\|}}{C}-Ph$$

5-27 Aminomethylation of Alkenes



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + CO + H_2O + R_2NH \xrightarrow[Fe(CO)_5]{Rh_2O_3} -\overset{H}{\underset{|}{\overset{|}{C}}}-\overset{CH_2NR_2}{\underset{|}{\overset{|}{C}}}-$$

78

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[406] For reviews, see Heck, Ref. 208, pp. 215–224; Khan and Martell, Ref. 144, vol. 2, pp. 39–60; Falbe, Ref. 398, pp. 3–77; Bird, Ref. 208, 117–148; Chalk and Harrod, *Adv. Organomet. Chem.* **6**, 119–170 (1968).

[407] For example, see Osborn, Wilkinson, and Young, *Chem. Commun.* 17 (1965); Evans, Osborn, and Wilkinson, *J. Chem. Soc. A* 3133 (1968); Brown and Wilkinson, *Tetrahedron Lett.* 1725 (1969), *J. Chem. Soc. A* 2753 (1970); Yagupsky, Brown, and Wilkinson, *J. Chem. Soc. A* 1392 (1970); Pruett and Smith, *J. Org. Chem.* **34,** 327 (1969); Heil, Markó and Bor, *Chem. Ber.* **104,** 3418 (1971); Fell and Müller, *Monatsh. Chem.* **103,** 1222 (1972); Stefani, Consiglio, Botteghi, and Pino, *J. Am. Chem. Soc.* **95,** 6504 (1973); Arai, Kaneko, and Kunugi, *Chem. Lett.* 265 (1975); Bott, *Chem. Ber.* **108,** 997 (1975).

[408] Fell and Rupilius, *Tetrahedron Lett.* 2721 (1969).

[409] For examples with rhodium catalysts, see Fell and Beutler, *Tetrahedron Lett.* 3455 (1972); Botteghi and Salomon, *Tetrahedron Lett.* 4285 (1974).

[410] It is also possible that tricarbonylhydrocobalt $HCo(CO)_3$, formed by loss of CO from $HCo(CO)_4$, may be adding to the double bond.

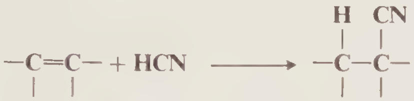
[411] Heck and Breslow, *Chem. Ind. (London)* 467 (1960), *J. Am. Chem. Soc.* **83,** 4023 (1961); Karapinka and Orchin, *J. Org. Chem.* **26,** 4187 (1961); Taylor and Orchin, *J. Am. Chem. Soc.* **93,** 6504 (1971); Clark, Terapane, and Orchin, *J. Org. Chem.* **39,** 2405 (1974); Whyman, *J. Organomet. Chem.* **81,** 97 (1974).

[412] Aldridge and Jonassen, *J. Am. Chem. Soc.* **85,** 886 (1963).

[413] Schwartz and Cannon, *J. Am. Chem. Soc.* **96,** 4721 (1974).

Alkenes react with carbon monoxide, water, and a secondary amine, to give the tertiary amines **78**.[414] Rhodium oxide may serve as a catalyst, but higher yields ($> 90\%$) are obtained when iron pentacarbonyl is also present.

5-28 Addition of HCN



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{HCN} \longrightarrow -\underset{|}{\overset{\overset{\mathrm{H}}{|}}{\mathrm{C}}}-\underset{|}{\overset{\overset{\mathrm{CN}}{|}}{\mathrm{C}}}-$$

Ordinary olefins do not react with HCN, but polyhalo olefins and olefins of the form C=C—Z add HCN to give nitriles.[415] The reaction is therefore a nucleophilic addition and is base-catalyzed. When Z is COR or, more especially, CHO, 1,2 addition (reaction **6-52**) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH_4Cl, and HCl. One or two moles of HCN may be added to a triple bond, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared in this way, by the addition of HCN to acetylene. Alkylaluminum cyanides, e.g., Et_2AlCN, or mixtures of HCN and trialkylalanes R_3Al are especially good reagents for conjugate addition of HCN[416] to α,β-unsaturated ketones and α,β-unsaturated acyl halides. HCN may be added to ordinary olefins in the presence of either dicobalt octacarbonyl[417] or of tetrakis(triphenylphosphite)palladium(0) $Pd[P(OPh)_3]_4$ and triphenyl phosphite.[418]

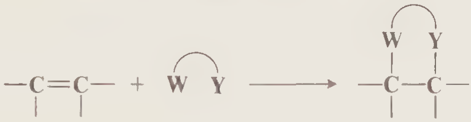
OS **I,** 451; **II,** 498; **III,** 615; **IV,** 392, 393, 804; **V,** 239, 572; **52,** 100.

5-29 Addition of ArH

See reaction **1-13** (Friedel-Crafts alkylation).

Reactions in Which Hydrogen Adds to Neither Side

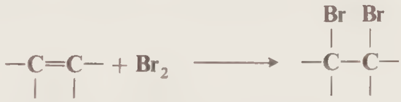
Some of these reactions are *cycloadditions* (reactions **5-40, 5-41, 5-45, 5-47,** and **5-50** to **5-55**). In such cases addition to the multiple bond closes a ring:



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \overset{\frown}{\mathrm{W}\;\;\mathrm{Y}} \longrightarrow -\underset{|}{\overset{\overset{\mathrm{W}}{|}}{\mathrm{C}}}-\underset{|}{\overset{\overset{\mathrm{Y}}{|}}{\mathrm{C}}}-$$

A. Halogen on One or Both Sides

5-30 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)



$$-\underset{|}{\mathrm{C}}=\underset{|}{\mathrm{C}}- + \mathrm{Br_2} \longrightarrow -\underset{|}{\overset{\overset{\mathrm{Br}}{|}}{\mathrm{C}}}-\underset{|}{\overset{\overset{\mathrm{Br}}{|}}{\mathrm{C}}}-$$

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[414] Iqbal, *Helv. Chim. Acta* **54,** 1440 (1971).

[415] For a review, see Friedrich and Wallenfels, in Rappoport, "The Chemistry of the Cyano Group," pp. 68–72, Interscience Publishers, New York, 1970.

[416] Nagata, Okumura, and Yoshioka, *J. Chem. Soc. C* 2347 (1970); Nagata, Yoshioka, Okumura, and Murakami, *J. Chem. Soc. C* 2355 (1970); Nagata, Yoshioka, and Hirai, *J. Am. Chem. Soc.* **94,** 4635 (1972); Nagata, Yoshioka, and Murakami, *J. Am. Chem. Soc.* **94,** 4644, 4654 (1972); Nagata, Yoshioka, and Terasawa, *J. Am. Chem. Soc.* **94,** 4672 (1972).

[417] Arthur, England, Pratt, and Whitman, *J. Am. Chem. Soc.* **76,** 5364 (1954).

[418] Brown and Rick, *Chem. Commun.* 112 (1969).

Most double bonds are easily halogenated with bromine, chlorine, or interhalogen compounds.[419] Iodination has also been accomplished, but the reaction is slower.[420] Under free-radical conditions, iodination proceeds more easily.[421] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the olefin. The order of activity for some of the reagents is $BrCl > ICl > Br_2 > IBr > I_2$.[422] Mixed halogenations have also been achieved by other methods. Mixtures of Br_2 and Cl_2 have been used to give bromochlorination;[423] iodochlorination has been achieved with $CuCl_2$ and either I_2, HI, CdI_2, or other iodine donors;[424] iodofluorination[425] with mixtures of AgF and I_2;[426] and mixtures of N-bromo amides in anhydrous HF give bromofluorination.[427] Bromo-, iodo-, and chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2, I_2, or an N-chloro-, N-bromo-, or N-iodo amide in 70% HF–30% pyridine.[428] Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds, and mixtures are obtained.[429] However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (−78°C).[430] Addition of fluorine has also been accomplished with other reagents, e.g., CoF_3;[431] XeF_2;[432] and a mixture of PbO_2 and SF_4.[433] XeF_4 has also been used for this purpose,[434] but isomerization takes place, so that ethylene gave 45% 1,2-difluoroethane but also 35% of the 1,1-difluoro isomer. With perfluoroethylene, where isomerization is not a factor, XeF_4 gave good yields of the normal addition product.

The reaction with bromine is very rapid and is easily carried out at room temperature. Bromine is often used as a test, qualitative or quantitative, for unsaturation.[435] The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, etc., functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster.

Several other reagents add Cl_2 to double bonds, among them NCl_3,[436] SO_2Cl_2,[437] PCl_5,[438] $SbCl_5$,[439] $MoCl_5$,[440] and iodobenzene dichloride $PhICl_2$.[441] A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide $C_5H_5NH^+ \; Br_3^-$.[442] Br_2 or Cl_2 can also be added with $CuBr_2$ or $CuCl_2$ in the presence of a compound such as acetonitrile, methanol, or triphenylphosphine.[443]

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[419] For a review, see House, Ref. 141, pp. 422–431.

[420] Sumrell, Wyman, Howell, and Harvey, *Can. J. Chem.* **42**, 2710 (1964); Zanger and Rabinowitz, *J. Org. Chem.* **40**, 248 (1975).

[421] Skell and Pavlis, *J. Am. Chem. Soc.* **86**, 2956 (1964); Ayres, Michejda, and Rack, *J. Am. Chem. Soc.* **93**, 1389 (1971).

[422] White and Robertson, *J. Chem. Soc.* 1509 (1939).

[423] Buckles, Forrester, Burham, and McGee, *J. Org. Chem.* **25**, 24 (1960). See also Uemura, Onoe, and Okano, *Bull. Chem. Soc. Jpn.* **47**, 143 (1974).

[424] Baird, Surridge, and Buza, *J. Org. Chem.* **36**, 2088, 3324 (1971).

[425] For a review of mixed halogenations where one side is fluorine, see Sharts and Sheppard, *Org. React.* **21**, 125–406 (1974), pp. 137–157.

[426] Hall and Jones, *Can. J. Chem.* **51**, 2902 (1973); see also Kreespan, *J. Org. Chem.* **27**, 1813 (1962); Knunyants and German, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1016 (1966).

[427] Robinson, Finckenor, Oliveto, and Gould, *J. Am. Chem. Soc.* **81**, 2191 (1959); Bowers, *J. Am. Chem. Soc.* **81**, 4107 (1959); Pattison, Peters, and Dean, *Can. J. Chem.* **43**, 1689 (1965).

[428] Olah, Nojima, and Kerekes, *Synthesis* 780 (1973).

[429] See, for example, Fuller, Stacey, Tatlow, and Thomas, *Tetrahedron* **18**, 123 (1962).

[430] Merritt and Stevens, *J. Am. Chem. Soc.* **88**, 1822 (1966); Merritt and Johnson, *J. Org. Chem.* **31**, 1859 (1966); Merritt, *J. Am. Chem. Soc.* **89**, 609 (1967).

[431] Rausch, Davis, and Osborne, *J. Org. Chem.* **28**, 494 (1963).

[432] Zupan and Pollak, *J. Chem. Soc., Chem. Commun.* 845 (1973), *J. Org. Chem.* **39**, 2646 (1974), *Tetrahedron Lett.* 1015 (1974).

[433] Bissell and Fields, *J. Org. Chem.* **29**, 1591 (1964).

[434] Shieh, Yang, and Chernick, *J. Am. Chem. Soc.* **86**, 5021 (1964).

[435] For a review of this, see Kuchar, in Patai, Ref. 29, pp. 273–280.

[436] Field and Kovacic, *Synthesis* 135 (1969); Strand and Kovacic, *Synth. Commun.* **2**, 129 (1972).

[437] Kharasch and Brown, *J. Am. Chem. Soc.* **61**, 3432 (1939).

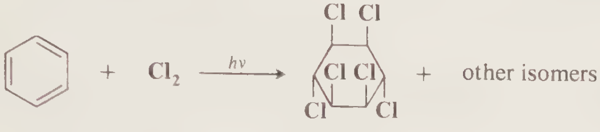
[438] Spiegler and Tinker, *J. Am. Chem. Soc.* **61**, 940 (1939).

[439] Uemura, Onoe, and Okano, *Bull. Chem. Soc. Jpn.* **47**, 692 (1974).

[440] Uemura, Onoe, and Okano, *Bull. Chem. Soc. Jpn.* **47**, 3121 (1974); San Filippo, Sowinski, and Romano, *J. Am. Chem. Soc.* **97**, 1599 (1975).

[441] See for example, Tanner and Gidley, *J. Org. Chem.* **33**, 38 (1968); Masson and Thuillier, *Bull. Soc. Chim. Fr.* 4368 (1969); Lasne and Thuillier, *Bull. Soc. Chim. Fr.* 249 (1974).

The mechanism is usually electrophilic (see p. 675), but when free-radical initiators (or uv light) are present, then addition may occur by a free-radical mechanism.[444] Once Br• or Cl• radicals are formed, however, substitution may compete (reactions **4-1** and **4-2**). This is especially important when the olefin has allylic hydrogens. Under free-radical conditions (uv light) bromine or chlorine adds to the benzene ring to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see p. 118). In the case of chlorination one of these isomers, which is called *gammexane* and constitutes about 10 to 12% of the mixture, is used as an insecticide. Toluene not only undergoes addition under these conditions but also α-halogenation[445] (reaction **4-1**).

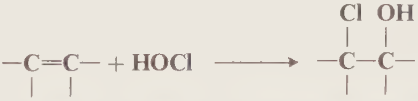


Gammexane

Conjugated systems give both 1,2 and 1,4 addition.[446] Triple bonds add bromine, though generally more slowly than double bonds (see p. 686). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Two moles of bromine may be added to triple bonds to give tetrabromo products. There is evidence that the addition of the first mole of bromine to a triple bond may take place by a nucleophilic mechanism.[447] With allenes it is very easy to stop the reaction after only 1 mole has added, to give X—C—CX=C.[448] In most cases a second mole of halogen can be added only by forced treatment. Addition of halogen to ketenes gives α-halo acyl halides, but the yields are not good. When bromine was added to *cis*- and *trans*-cyclodecenes, the products were, respectively, *cis*- and *trans*-1,6-dibromocyclodecane.[449] In this case there was a transannular hydride shift.

OS **I,** 205, 521; **II,** 171, 177, 270, 408; **III,** 105, 123, 127, 209, 350, 526, 531, 731, 785; **IV,** 130, 195, 748, 851, 969; **V,** 136, 370, 403, 467, 921; **50,** 36; **55,** 32, 62, 86.

5-31 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)



$$-\underset{|}{C}=\underset{|}{C}- + HOCl \longrightarrow -\underset{|}{\overset{\overset{Cl}{|}}{C}}-\underset{|}{\overset{\overset{OH}{|}}{C}}-$$

HOCl, HOBr, and HOI can be added to olefins to produce halohydrins.[450] HOBr and HOCl are often generated in situ by the reaction between water and Br_2 or Cl_2, respectively. HOI can also be generated from I_2 and H_2O, but in this case an oxidizing agent such as HIO_3, HgO, or O_2 and HNO_2 must be present.[451] HOBr can also be conveniently added by the use of a reagent consisting of an N-bromo amide [e.g., N-bromosuccinimide (NBS) or N-bromoacetamide] and a small amount of water in a solvent such as dimethyl sulfoxide or dioxane.[452] The mechanism of HOX addition is electrophilic, with initial attack by the positive halogen end of the HOX dipole. Following Markovnikov's rule, the positive halogen goes to the side of the double bond which has more hydrogens. The resulting carbonium ion (or bromonium or iodonium ion) reacts with OH^- or H_2O to give the product. In the NBS–dimethyl sulfoxide method, the initial product is $\mathrm{Br{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}O\overset{\oplus}{S}Me_2}$, which is hydrolyzed by the water to the bromohydrin. If the substrate is treated with Br_2 or Cl_2 (or another source of positive halogen such as NBS or BrN_3[453]) in an alcohol or a carboxylic acid solvent, it is possible to obtain, directly, $\mathrm{X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OR}$ or $\mathrm{X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OCOR}$, respectively (also see reaction **5-39**). HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds $—CX_2—CO—$.

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[442] Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, pp. 967–970, John Wiley & Sons, Inc., New York, 1967.

[443] Koyano, *Bull. Chem. Soc. Jpn.* **43,** 1439, 3501 (1970); Koyano and Watanabe, *Bull. Chem. Soc. Jpn.* **44,** 1378 (1971); Uemura, Tabata, Kimura, and Ichikawa, *Bull. Chem. Soc. Jpn.* **44,** 1973 (1971); Or, Levy, Asscher, and Vofsi, *J. Chem. Soc., Perkin Trans. 2* 857 (1974); Uemura, Onoe, and Okano, *J. Chem. Soc., Chem. Commun.* 925 (1975); Ref. 424. See also Arganbright and Yates, *J. Org. Chem.* **27,** 1205 (1962).

[444] For example, see Poutsma, *J. Am. Chem. Soc.* **87,** 2161, 2172 (1965), *J. Org. Chem.* **31,** 4167 (1966).

[445] Kharasch and Berkman, *J. Org. Chem.* **6,** 810 (1941).

[446] For a review, see Cais, in Patai, Ref. 29, pp. 993–999.

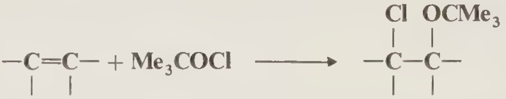
[447] Sinn, Hopperdietzel, and Sauermann, *Monatsh. Chem.* **96,** 1036 (1965).

[448] However, formation of side products may be extensive. See, for example, Poutsma, *J. Org. Chem.* **33,** 4080 (1968).

[449] Závada and Sicher, *Proc. Chem. Soc.* 199 (1961).

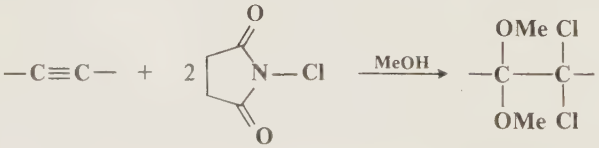
[450] For a review, see Boguslavskaya, *Russ. Chem. Rev.* **41,** 740–749 (1972).

t-Butyl hypochlorite and hypobromite add to double bonds to give *t*-butyl ethers, e.g.,[454]



$$\mathrm{{-}\underset{|}{C}{=}\underset{|}{C}{-} + Me_3COCl \longrightarrow {-}\overset{Cl}{\underset{|}{\overset{|}{C}}}{-}\overset{OCMe_3}{\underset{|}{\overset{|}{C}}}{-}}$$

This is a convenient method for the preparation of tertiary ethers. Me_3COCl adds 1,2 to some conjugated dienes[454] and 1,4 to others.[455] When Me_3COCl or Me_3COBr is added to olefins in the presence of excess ROH, the ether produced is $\mathrm{X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OR}$.[456] Vinyl ethers give β-halo acetals.[457] Two moles of "MeOCl" can be added to triple bonds by treatment with N-chlorosuccinimide in methanol.[458]



These acetals can then be hydrolyzed to α,α-dichloro ketones. Alkenyl boronic acids RCH=CHB(OH)$_2$ (p. 560) react with bromine and NaOMe at −78°C to give α-bromo acetals RCHBrCH(OMe)$_2$.[459] Chlorine acetate [solutions of which are prepared by treating Cl_2 with

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[451] See for example, Cornforth and Green, *J. Chem. Soc. C* 846 (1970).

[452] For examples, see Dalton, Hendrickson, and Jones, *Chem. Commun.* 591 (1966); Dalton, Dutta, and Jones, *J. Am. Chem. Soc.* **90**, 5498 (1968); Dalton and Dutta, *J. Chem. Soc. B* 85 (1971); Sisti, *J. Org. Chem.* **35**, 2670 (1970).

[453] Boerwinkle and Hassner, *Tetrahedron Lett.* 3921 (1968).

[454] For a review, see Anbar and Ginsburg, *Chem. Rev.* **54**, 925–958 (1954), pp. 929–933.

[455] Riemschneider and Nehring, *Justus Liebigs Ann. Chem.* **660**, 41 (1962).

[456] Geneste and Kergomard, *Bull. Soc. Chim. Fr.* 470 (1963); Bresson, Dauphin, Geneste, Kergomard, and Lacourt, *Bull. Soc. Chim. Fr.* 2432 (1970), 1080 (1971).

[457] Weissermel and Lederer, *Chem. Ber.* **96**, 77 (1963).

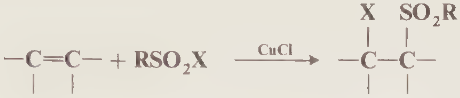
[458] Reed, *J. Org. Chem.* **30**, 2195 (1965).

[459] Hamaoka and Brown, *J. Org. Chem.* **40**, 1189 (1975).

$Hg(OAc)_2$ in an appropriate solvent] adds to olefins to give acetoxy chlorides.[460] The latter are also produced by treatment of olefins with a mixture of $PdCl_2$ and $CuCl_2$ in acetic acid.[461]

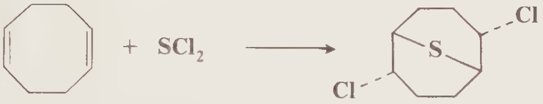
OS **I,** 158; **IV,** 130, 157.

5-32 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)



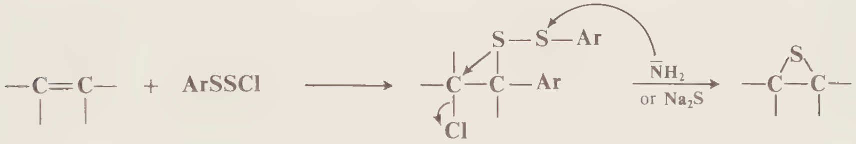
$$-\underset{|}{C}=\underset{|}{C}- + RSO_2X \xrightarrow{CuCl} -\underset{|}{\overset{X}{\overset{|}{C}}}-\underset{|}{\overset{SO_2R}{\overset{|}{C}}}-$$

Sulfonyl halides add to double bonds, to give β-halo sulfones, in the presence of free-radical initiators. A particularly good catalyst is cuprous chloride.[462] Triple bonds behave similarly, to give β-halo-α,β-unsaturated sulfones.[463] In a similar reaction, sulfenyl chlorides, RSCl, give β-halo thioethers,[464] $Cl-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-SR$. The latter may be free-radical or electrophilic additions, depending on conditions. Other sulfur compounds also add to double bonds by free-radical mechanisms.[465] Sulfur dichloride adds to cyclic dienes in a transannular fashion to give sulfur-bridged dichlorides,[466] e.g.,



Linear dienes undergo a similar reaction, to give sulfur heterocycles.[467]

β-Halo disulfides, formed by addition of arenethiosulfenyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.[468]



The overall episufidation is a stereospecific syn addition.

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[460] de la Mare, Wilson, and Rosser, *J. Chem. Soc., Perkin Trans 2* 1480 (1973); de la Mare, O'Connor, and Wilson, *J. Chem. Soc., Perkin Trans. 2* 1150 (1975). For the addition of bromine acetate, see Wilson and Woodgate, *J. Chem. Soc., Perkin Trans. 2* 141 (1976).

[461] Henry, *J. Org. Chem.* **32,** 2575 (1967), **38,** 1681 (1973).

[462] Asscher and Vofsi, *J. Chem. Soc* 4962 (1964); Truce, Goralski, Christensen, and Bavry, *J. Org. Chem.* **35,** 4217 (1970); Sinnreich and Asscher, *J. Chem. Soc., Perkin Trans. 1* 1543 (1972).

[463] Truce and Wolf, *J. Org. Chem.* **36,** 1727 (1971); Amiel, *J. Org. Chem.* **36,** 3691, 3697 (1971), **39,** 3867 (1974); Zakharkin and Zhigareva, *J. Org. Chem. USSR* **9,** 918 (1973); Okuyama, Izawa, and Fueno, *J. Org. Chem.* **39,** 351 (1974).

[464] For a review, see Kühle, *Synthesis* 563–586 (1971).

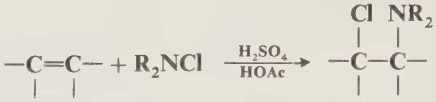
[465] For reviews, see Stacey and Harris, *Org. React.* **13,** 150–376 (1963), pp. 200–207, 327–332; Sosnovsky, Ref. 41, pp. 103–115; Walling, Ref. 41, pp. 326–332.

[466] Corey and Block, *J. Org. Chem.* **31,** 1663 (1966); Lautenschlaeger, *J. Org. Chem.* **31,** 1679 (1966), **33,** 2627 (1968); Weil, Smith, and Gruber, *J. Org. Chem.* **31,** 1669 (1966).

[467] Lautenschlaeger, *J. Org. Chem.* **33,** 2620 (1968); Mühlstädt, Schneider, and Martinetz, *J. Prakt. Chem.* **315,** 929 (1973).

[468] Fujisawa and Kobori, *Chem. Lett.* 935 (1972).

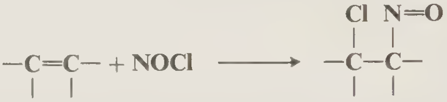
5-33 Addition of Halogen and an Amino Group (Addition of Halogen, Nitrogen)



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + R_2NCl \xrightarrow[HOAc]{H_2SO_4} -\overset{Cl}{\overset{|}{\underset{|}{C}}}-\overset{NR_2}{\overset{|}{\underset{|}{C}}}-$$

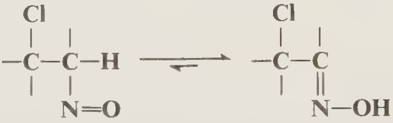
The groups R_2N and Cl can be added directly to olefins, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-N-chloroamines and acids.[469] These are free-radical additions, with initial attack by the $R_2NH\cdot^+$ radical ion. N-Halo amides RCONHX add RCONH and X to double bonds under the influence of uv light.[470] For an indirect way of adding NH_2 and I to a double bond, see reaction **5-36.**

5-34 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + NOCl \longrightarrow -\overset{Cl}{\overset{|}{\underset{|}{C}}}-\overset{N=O}{\overset{|}{\underset{|}{C}}}-$$

There are three possible products when NOCl is added to olefins.[471] The initial product is always the β-halo nitroso compound, but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime:



$$-\overset{Cl}{\overset{|}{\underset{|}{C}}}-\underset{\underset{N=O}{|}}{\overset{|}{C}}-H \rightleftharpoons -\overset{Cl}{\overset{|}{\underset{|}{C}}}-\underset{\underset{N-OH}{\|}}{\overset{|}{C}}$$

With some olefins, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.[472] Many functional groups may be present without interference, e.g., COOH, COOR, CN, OR. In the past, the reaction was invaluable in the characterization of terpenes. The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, although syn addition has been reported in some cases.[473] Markovnikov's rule is followed, the positive NO going to the carbon which has more hydrogens.

Nitryl chloride NO_2Cl also adds to olefins, to give β-halo nitro compounds, but this is a free-radical process. The NO_2 goes to the less substituted carbon.[474] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro olefins.[475] β-Halo nitro compounds can also be prepared by treatment of olefins with N_2O_4 and bromine (or iodine), but another possible product is the β-halo nitrate.[476] Which product is formed depends on the substrate. FNO_2 can be added to olefins[477] by treatment with HF in HNO_3[478] or by addition of the olefin to a solution of nitronium tetrafluoroborate $NO_2^+\ BF_4^-$ (see reaction **1-2**) in 70% HF–30% pyridine solution[479] (see also reaction **5-30**).

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[469] Neale and Hinman, *J. Am. Chem. Soc.* **85,** 2666 (1963); Neale, *Tetrahedron Lett.* 483 (1966), *J. Org. Chem.* **32,** 3263 (1967); Neale and Marcus, *J. Org. Chem.* **32,** 3273 (1967); Minisci, Galli, and Cecere, *Tetrahedron Lett.* 3163 (1966). See also Scholz and Viehe, *Chimia* **29,** 512 (1975). For reviews, see Neale, *Synthesis* 1–15 (1971); Sosnovsky and Rawlinson, *Adv. Free-Radical Chem.* **4,** 203–284 (1972), pp. 238–249.

[470] Touchard and Lessard, *Tetrahedron Lett.* 4425 (1971), 3827 (1973). See also Peiffer, Traynard, and Guillemonat, *Bull. Soc. Chim. Fr.* 1910 (1966); Ohashi, Sugie, Okahara, and Komori, *Tetrahedron Lett.* 4195 (1968).

[471] For reviews, see Kadzyauskas and Zefirov, *Russ. Chem. Rev.* **37,** 543–550 (1968); Beckham, Fessler, and Kise, *Chem. Rev.* **48,** 319–396 (1951); Sosnovsky, Ref. 41, pp. 247–251, 272–275.

[472] For a review of the preparation of halo nitro compounds, see Shvekhgeimer, Smirnyagin, Sadykov, and Novikov, *Russ. Chem. Rev.* **37,** 351–363 (1968).

[473] For example, see Meinwald, Meinwald, and Baker, *J. Am. Chem. Soc.* **86,** 4074 (1964).

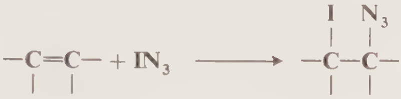
[474] Shechter, *Rec. Chem. Prog.* **25,** 55–76 (1964).

[475] Schlubach and Braun, *Justus Liebigs Ann. Chem.* **627,** 28 (1959).

[476] Bachman, Logan, Hill, and Standish, *J. Org. Chem.* **25,** 1312 (1960). See also Hassner, Kropp, and Kent, *J. Org. Chem.* **34,** 2628 (1969).

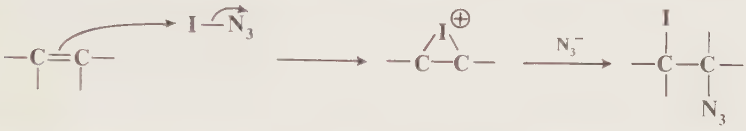
OS **IV**, 711; **V**, 266, 863.

5-35 Addition of XN_3 (Addition of Halogen, Nitrogen)



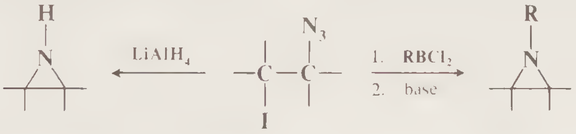
$$-\underset{|}{C}=\underset{|}{C}- + IN_3 \longrightarrow -\overset{\overset{I}{|}}{\underset{|}{C}}-\overset{\overset{N_3}{|}}{\underset{|}{C}}-$$

The addition of iodine azide to double bonds[480] gives β-iodo azides.[481] The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium-ion intermediate



(see p. 676). The reaction has been performed on many double-bond compounds, including α,β-unsaturated ketones. Similar reactions can be performed with BrN_3 and ClN_3. 1,4 addition has been found with acyclic conjugated dienes.[482] In the case of BrN_3 both electrophilic and free-radical mechanisms are important,[483] while with ClN_3 the additions are chiefly free-radical.[484] Free-radical addition of ClN_3 can also be achieved by treatment of the alkene with NaN_3, $FeCl_3$, $FeSO_4$, and H_2O_2.[485] IN_3 also adds to triple bonds, to give β-iodo-α,β-unsaturated azides.[486]

β-iodo azides can be reduced to aziridines with $LiAlH_4$,[487] or converted to N-alkyl- or N-arylaziridines by treatment with an alkyl- or aryldichloroborane followed by a base.[488] In both



cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (reaction **0-46**) follows. β-Iodo azides can also be converted to 1-azirines (reaction **5-46**).

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[477] For a review, see Sharts and Sheppard, *Org. React.* **21,** 125–406 (1974), pp. 236–243.

[478] Knunyants, German, and Rozhkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1794 (1963).

[479] Olah and Nojima, *Synthesis* 785 (1973).

[480] For reviews, see Hassner, *Acc. Chem. Res.* **4,** 9–16 (1971); Biffin, Miller, and Paul, Ref. 197, pp. 136–147.

[481] Hassner and Levy, *J. Am. Chem. Soc.* **87,** 4203 (1965); Fowler, Hassner, and Levy, *J. Am. Chem. Soc.* **89,** 2077 (1967).

[482] Hassner and Keogh, *Tetrahedron Lett.* 1575 (1975).

[483] Hassner and Boerwinkle, *J. Am. Chem. Soc.* **90,** 217 (1968); Hassner and Teeter, *J. Org. Chem.* **36,** 2176 (1971).

[484] Even IN_3 can be induced to add by a free-radical mechanism. For a review of free-radical additions of XN_3, see Hassner, *Intra-Sci. Chem. Rep.* **4,** 109–114 (1970).

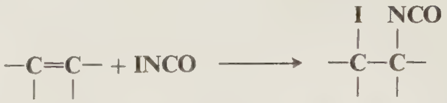
[485] Minisci and Galli, *Tetrahedron Lett.* 357 (1963). See also Van Ende and Krief, *Angew. Chem. Int. Ed. Engl.* **13,** 279 (1974) [*Angew. Chem.* **86,** 311].

[486] Hassner, Isbister, and Friederang, *Tetrahedron Lett.* 2939 (1969).

[487] Hassner, Matthews, and Fowler, *J. Am. Chem. Soc.* **91,** 5046 (1969).

[488] Levy and Brown, *J. Am. Chem. Soc.* **95,** 4067 (1973).

5-36 Addition of INCO (Addition of Halogen, Nitrogen)



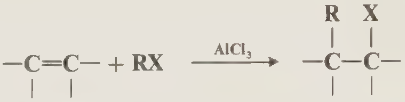
$$-\underset{|}{C}=\underset{|}{C}- + \text{INCO} \longrightarrow -\underset{|}{\overset{\overset{\text{I}}{|}}{C}}-\underset{|}{\overset{\overset{\text{NCO}}{|}}{C}}-$$

In a reaction similar to **5-35**, iodine isocyanate adds to double bonds to give β-iodo isocyanates.[489] The addition is stereospecific and anti, and the mechanism is similar to that shown in reaction **5-35.** The reaction has been applied to mono-, di-, and some trisubstituted olefins. The orientation generally follows Markovnikov's rule, the positive iodine adding to the less highly substituted side. α,β-Unsaturated carbonyl compounds do not react. Triple bonds give β-iodo-α,β-unsaturated isocyanates in low yields.[490] Allenes add 1 mole of INCO to give β-iodo-β,γ-unsaturated isocyanates.[491]

Since an isocyanate group can be hydrolyzed to an amino group ($RNCO \rightarrow RNH_2$, reaction **6-3**), the method is an indirect way of adding H_2N and I to double bonds.

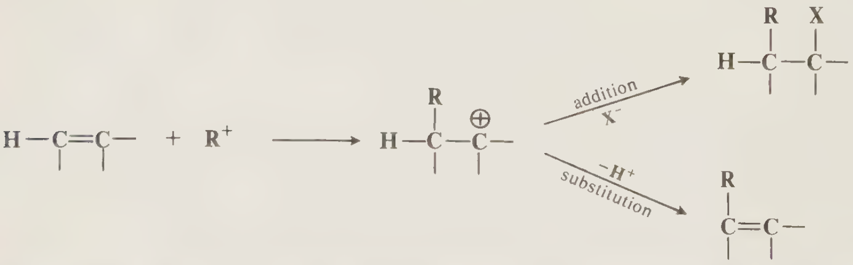
OS **51,** 112.

5-37 Addition of Alkyl Halides (Addition of Halogen, Carbon)



$$-\underset{|}{C}=\underset{|}{C}- + \text{RX} \xrightarrow{\text{AlCl}_3} -\underset{|}{\overset{\overset{\text{R}}{|}}{C}}-\underset{|}{\overset{\overset{\text{X}}{|}}{C}}-$$

Alkyl halides can be added to olefins in the presence of a Friedel-Crafts catalyst, most often $AlCl_3$.[492] The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with reaction **1-13**). Methyl and ethyl halides, which cannot rearrange, give no reaction at all. The attacking species is the carbonium ion formed from the alkyl halide and the catalyst (see reaction **1-13**). The addition therefore follows Markovnikov's rule, with the carbonium ion going to the carbon with more hydrogens. Substitution is a side reaction, arising from loss of hydrogen from the carbonium ion formed when the original carbonium ion attacks the double bond:



Conjugated dienes can add 1,4.[493] Triple bonds also undergo the reaction, to give vinyl halides.[494]

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[489] Heathcock and Hassner, *Angew. Chem. Int. Ed. Engl.* **2,** 213 (1963) [*Angew. Chem.* **75,** 344]; Hassner and Heathcock, *Tetrahedron Lett.* 393 (1963), 1125 (1964), *Tetrahedron* **20,** 1037 (1964), *J. Org. Chem.* **30,** 1748 (1965); Birckenbach and Linhard, *Ber.* **64B,** 961, 1076 (1931); Drehfahl and Ponsold, *Chem. Ber.* **93,** 519 (1960); Hassner, Lorber, and Heathcock, *J. Org. Chem.* **32,** 540 (1967); Hassner, Hoblitt, Heathcock, Kropp, and Lorber, *J. Am. Chem. Soc.* **92,** 1326 (1970); Gebelein, Swift, and Swern, *J. Org. Chem.* **32,** 3314 (1967); Gebelein and Swern, *J. Org. Chem.* **33,** 2758 (1968); Gebelein, Rosen, and Swern, *J. Org. Chem.* **34,** 1677 (1969); Gebelein, *Chem. Ind.* (*London*) 57 (1970).

[490] Grimwood and Swern, *J. Org. Chem.* **32,** 3665 (1967).

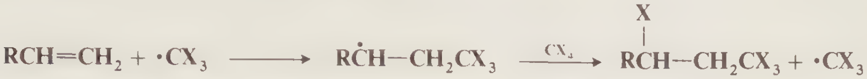
[491] Greibrokk, *Acta Chem. Scand.* **27,** 3368 (1973).

[492] For a review, see Schmerling, in Olah, Ref. 319, vol. 2, pp. 1133–1174.

[493] Kolyaskina and Petrov, *J. Gen. Chem. USSR* **32,** 1067 (1962).

[494] See, for example, Maroni, Melloni, and Modena, *J. Chem. Soc., Perkin Trans. 1* 2491 (1973), 353 (1974); Marcuzzi and Melloni, *Gazz. Chim. Ital.* **105,** 495 (1975).

CCl_4, $BrCCl_3$, ICF_3, and similar simple polyhalo alkanes add to olefins in good yield.[495] These are free-radical additions and require initiation by peroxides, metal halides (e.g., $FeCl_2$, CuCl),[496] or uv light. The initial attack is by the carbon, and it goes to the carbon which has more hydrogens, as in most free-radical attack:

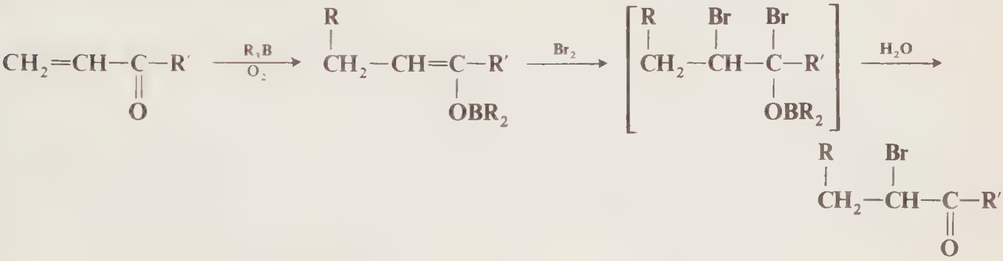


$$\mathrm{RCH{=}CH_2 + \cdot CX_3 \longrightarrow R\dot{C}H{-}CH_2CX_3 \xrightarrow{CX_4} R\overset{\overset{\textstyle X}{|}}{C}H{-}CH_2CX_3 + \cdot CX_3}$$

This type of polyhalo alkane adds to halogenated olefins in the presence of $AlCl_3$ by an electrophilic mechanism.[497] This is called the *Prins reaction* (not to be confused with the other Prins reaction, **6-54**).

ArX can be added across double bonds, in a free-radical process, by treatment of olefins with diazonium salts, though Meerwein arylation (substitution) (reaction **4-17**) competes.[498] This addition may be either 1,2 or 1,4 with conjugated dienes.[499] Addition of ArX can also be accomplished by treatment with an arylmercury halide ArHgX in the presence of CuX_2, LiX, and a palladium compound catalyst, usually Li_2PdCl_4.[500] In this case also, substitution (reaction **4-18**) is a side reaction. Yields of addition product are increased by increasing the concentration of CuX_2.

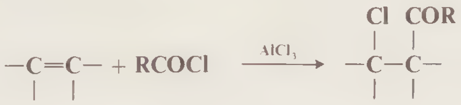
R and X can be added to double bonds of α,β-unsaturated ketones in an indirect manner. The substrate is treated with an organoboron compound (reaction **5-21**), and to the resulting enol borinate is added bromine, followed by hydrolysis.[501]



$$\mathrm{CH_2{=}CH{-}\underset{\underset{\textstyle O}{\|}}{C}{-}R' \xrightarrow[O_2]{R_3B} \overset{\overset{\textstyle R}{|}}{CH_2}{-}CH{=}\underset{\underset{\textstyle OBR_2}{|}}{C}{-}R' \xrightarrow{Br_2} \left[\overset{\overset{\textstyle R}{|}}{CH_2}{-}\overset{\overset{\textstyle Br}{|}}{CH}{-}\overset{\overset{\textstyle Br}{|}}{\underset{\underset{\textstyle OBR_2}{|}}{C}}{-}R'\right] \xrightarrow{H_2O} \overset{\overset{\textstyle R}{|}}{CH_2}{-}\overset{\overset{\textstyle Br}{|}}{CH}{-}\underset{\underset{\textstyle O}{\|}}{C}{-}R'}$$

OS **II,** 312; **IV,** 727; **V,** 1076; **51,** 1.

5-38 Addition of Acyl Halides (Addition of Halogen, Carbon)



$$\mathrm{{-}\underset{|}{C}{=}\underset{|}{C}{-} + RCOCl \xrightarrow{AlCl_3} {-}\underset{|}{\overset{\overset{\textstyle Cl}{|}}{C}}{-}\underset{|}{\overset{\overset{\textstyle COR}{|}}{C}}{-}}$$

Acyl halides have been added to many olefins, in the presence of Friedel-Crafts catalysts. The reaction has been applied to straight-chain, branched, and cyclic olefins, but to very few containing functional groups, except halogen.[502] The mechanism is similar to that of reaction **5-37**, and, as in that case, substitution competes (see reaction **2-15**). Increasing temperature favors substitution,[503] and good yields of addition products can be achieved if the temperature is kept under 0°C. The reaction usually fails with conjugated dienes, since polymerization predominates. The reaction can be performed on triple-bond compounds, producing compounds of the form $\text{RCO}-\underset{|}{\text{C}}=\underset{|}{\text{C}}-\text{Cl}$.[504] A *formyl* group and a halogen can be added to triple bonds by treatment with N,N-disubstituted formamides and $POCl_3$ (Vilsmeier conditions, see reaction **1-16**).[505]

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[495] For reviews, see Freidlina and Chukovskaya, *Synthesis* 477–488 (1974); Walling and Huyser, *Org. React.* **13,** 91–149 (1963), pp. 107–108, 122–131; Huyser, Ref. 41, pp. 148–151; Sosnovsky, Ref. 41, pp. 19–61; Walling, Ref. 41, pp. 247–272.

[496] For example, see Asscher and Vofsi, *J. Chem. Soc.* 1887, 3921 (1963), *J. Chem. Soc. B* 947 (1968); Murai and Tsutsumi, *J. Org. Chem.* **31,** 3000 (1966).

[497] Ref. 492, pp. 1150, 1162.

[498] For example, see Iurkevich, Dombrovskii, and Terent'ev, *J. Gen. Chem. USSR* **28,** 226 (1958); Fedorov, Pribytkova, Kanishchev, and Dombrovskii, *J. Org. Chem. USSR* **9,** 1517 (1973); Cleland, *J. Org. Chem.* **26,** 3362 (1961), **34,** 744 (1969).

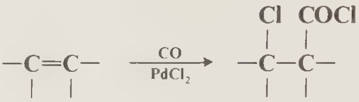
[499] For example, see Dombrovskii and Ganushchak, *J. Gen. Chem. USSR* **31,** 1191 (1961), **32,** 1867 (1962); Ganushchak, Golik, and Migaichuk, *J. Org. Chem. USSR* **8,** 2403 (1972).

[500] Heck, *J. Am. Chem. Soc.* **90,** 5538 (1968).

[501] Miyaura, Harada, Itoh, and Suzuki, *Chem. Lett.* 1145 (1973).

[502] For reviews, see Groves, *Chem. Soc. Rev.* **1,** 73–97 (1972); House, Ref. 141, pp. 786–797; Nenitzescu and Balaban, in Olah, Ref. 319, vol. 3, pp. 1033–1152 (1964).

When olefins are treated with carbon monoxide in the presence of $PdCl_2$, β-chloro acyl halides are produced:[506]



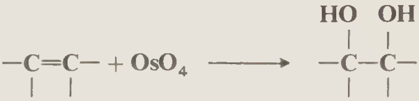
$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- \xrightarrow[\text{PdCl}_2]{\text{CO}} -\underset{|}{\overset{\text{Cl}}{\overset{|}{\text{C}}}}-\underset{|}{\overset{\text{COCl}}{\overset{|}{\text{C}}}}-$$

though not in high yield. The carbon goes to the side with more hydrogens.

OS **IV**, 186; **51,** 115.

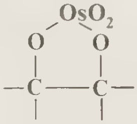
B. Oxygen or Nitrogen on One or Both Sides

5-39 Hydroxylation (Addition of Oxygen, Oxygen)

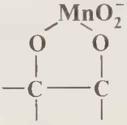


$$-\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{OsO}_4 \longrightarrow -\underset{|}{\overset{\text{HO}}{\overset{|}{\text{C}}}}-\underset{|}{\overset{\text{OH}}{\overset{|}{\text{C}}}}-$$

There are many reagents which add two OH groups to a double bond.[507] OsO_4 and alkaline $KMnO_4$ give syn addition, from the less hindered side of the double bond. Osmium tetroxide[508] adds rather slowly but almost quantitatively.[509] The cyclic ester **79** is an intermediate and can be isolated, but is usually decomposed in solution, with sodium sulfite in ethanol or other reagents. Bases catalyze the reaction by coordinating with the ester. The chief drawback to this reaction is that OsO_4 is expensive and highly toxic, so that its use has been limited to small-scale preparations of scarce materials. However, the same result (syn addition) can be accomplished more economically, by the use of H_2O_2, with OsO_4 present in catalytic amounts.[510] *t*-Butyl hydroperoxide in alkaline solution may be substituted for H_2O_2 in this procedure.[510a]



79



80

[503] Jones, Taylor, and Rudd, *J. Chem. Soc.* 1342 (1961).

[504] For example, see Nifant'ev, Grachev, Bakinovskii, Kara-Murza, and Kochetkov, *J. Appl. Chem. USSR* **36,** 646 (1963); Savenkov, Khokhlov, Nazarova, and Mochalkin, *J. Org. Chem. USSR* **9,** 914 (1973); Martens, Janssens, and Hoornaert, *Tetrahedron* **31,** 177 (1975).

[505] Yen, *Ann. Chim. (Paris)* [13] **7,** 785 (1962).

[506] Tsuji, Morikawa, and Kiji, *J. Am. Chem. Soc.* **86,** 4851 (1964); Tsuji, *Acc. Chem. Res.* **2,** 144–152 (1969), *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 150–153.

[507] For a review, see Gunstone, *Adv. Org. Chem.* **1,** 103–147 (1960).

[508] First used for this purpose by Criegee, *Justus Liebigs Ann. Chem.* **522,** 75 (1936).

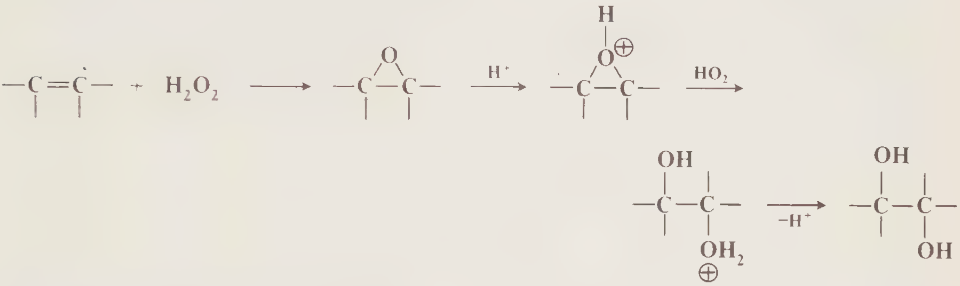
[509] For a discussion, see Fieser and Fieser, Ref. 442, vol. 1, pp. 759–764.

[510] Milas and Sussman, *J. Am. Chem. Soc.* **58,** 1302 (1936), **59,** 2345 (1937). For a review, see Rylander, Ref. 208, pp. 121–133.

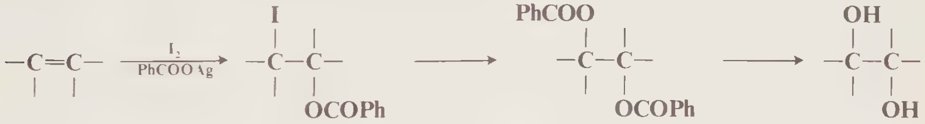
[510a] Sharpless and Akashi, *J. Am. Chem. Soc.* **98,** 1986 (1976).

Potassium permanganate is a strong oxidizing agent and can oxidize the glycols which are the products of this reaction (see reactions **9-8** and **9-11**). In acid and neutral solution it always does so; hence it is not feasible to prepare glycols in this manner. Glycols can be prepared with alkaline permanganate, but the conditions must be mild. Even so, yields are seldom above 50%. As with OsO_4, it is likely that cyclic esters (**80**) are intermediates; species which are believed to be such intermediates have been detected spectrally.[511] This reaction is the basis of the *Baeyer test* for the presence of double bonds.

Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (reaction **5-40**) occurs first, followed by an SN2 reaction, resulting in overall anti addition:

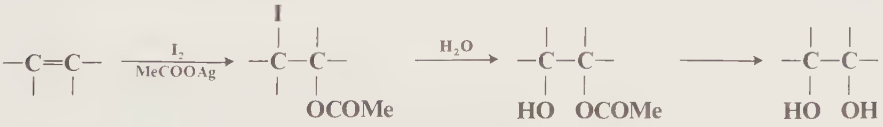


The same result can be achieved in one step with monopersuccinic acid.[512] Overall anti addition can also be achieved by the method of Prevost.[513] In this method the olefin is treated with iodine and silver benzoate in a 1 : 2 molar ratio. The initial addition is anti and results in a β-halo benzoate (**81**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism (p. 279), so that the groups are still anti:



81

Hydrolysis of the ester does not change the configuration. The method of Woodward is similar, but results in overall syn hydroxylation. The olefin is treated with iodine and silver acetate in a 1 : 1 molar ratio in acetic acid-containing water. Here again, the initial product is a β-halo ester; the addition is anti, and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal SN2 process, so that the monoacetate is syn.



[511] Lee and Brownridge, *J. Am. Chem. Soc.* **95,** 3033 (1973), **96,** 5517 (1974); Wiberg, Deutsch and Roček, *J. Am. Chem. Soc.* **95,** 3034 (1973).

[512] Lombard and Schroeder, *Bull. Soc. Chim. Fr.* 2800 (1963).

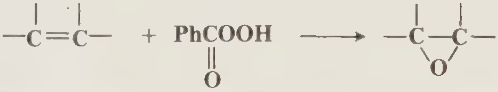
[513] For reviews of Prevost's and Woodward's methods, see Wilson, *Org. React.* **9,** 332-387 (1957), pp. 350 352.

Hydrolysis gives the glycol which is the product of overall syn addition. With cyclic trisubstituted olefins, both the Woodward and the Prevost methods may give allylic alcohols and ketones rather than the normal products.[514] Although the Woodward method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more hindered side of the olefin. Both the Prevost and the Woodward methods have also been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.[515] Addition of IOCOMe has also been accomplished with I_2 and peracetic acid[516] and with I_2 and potassium iodate in acetic acid.[517] The resulting β-iodo acetate can then be converted to the diol which is the product of syn addition by treatment with cupric acetate or potassium acetate. By a combination of the I_2–KIO_3 and $Cu(OAc)_2$ or KOAc methods, a double bond can be converted to the diol without the use of the expensive silver acetate.[517]

Olefins can also be oxidized with metallic acetates such as lead tetraacetate or thallium acetate to give bisacetates of glycols.[518]

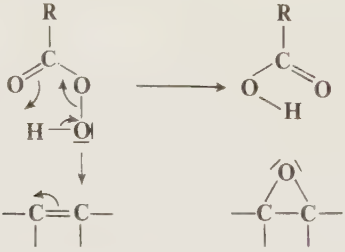
OS **II,** 307; **III,** 217; **IV,** 317; **V,** 647; **50,** 24.

5-40 Epoxidation (Addition of Oxygen, Oxygen)



Olefins can be epoxidized with any of a number of peracids, of which perbenzoic is the most often used. The reaction, which is called the *Prilezhaev reaction*, has wide utility.[519] Alkyl, aryl, hydroxyl, ester, and other groups may be present, though not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl olefins. Conditions are mild, and yields are high. Other peracids, especially peracetic and *m*-chloroperbenzoic, are also used; trifluoroperacetic acid is a particularly reactive one.[520] Occasionally the reaction is performed with H_2O_2 and a carboxylic acid, so that the peracid is generated in situ. Glycols and glycol esters (reaction **5-39**) are side products.

The following one-step mechanism was proposed by Bartlett:[521]



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[514] Parrilli, Adinolfi, Dovinola, and Mangoni, *Gazz. Chim. Ital.* **104,** 819 (1974); Parrilli, Dovinola, and Mangoni, *Gazz. Chim. Ital.* **104,** 829 (1974), and references cited in these papers.

[515] Cambie, Hayward, Roberts, and Rutledge, *J. Chem. Soc., Chem. Commun.* 359 (1973); *J. Chem. Soc., Perkin Trans. 1* 1858, 1864 (1974).

[516] Ogata and Aoki, *J. Org. Chem.* **31,** 1625 (1966). See also Aoki and Ogata, *Bull. Chem. Soc. Jpn.* **41,** 1476 (1968).

[517] Mangoni, Adinolfi, Barone, and Parrilli, *Tetrahedron Lett.* 4485 (1973), *Gazz. Chim. Ital.* **105,** 377 (1975).

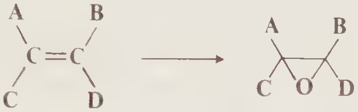
[518] For a review with respect to lead tetraacetate, see Moriarty, *Sel. Org. Transform.* **2,** 183 237 (1972).

[519] For reviews, see Swern, in Swern, "Organic Peroxides," vol. 2, pp. 355–533, Interscience Publishers, New York, 1971; Metelitsa, *Russ. Chem. Rev.* **41,** 807–821 (1972); Hiatt, in Augustine and Trecker, "Oxidation," vol. 2, pp. 113 140, Marcel Dekker, Inc., New York, 1971; House, Ref. 141, pp. 292 321; Swern, *Org. React.* **7,** 378–433 (1953). For a review pertaining to the stereochemistry of the reaction, see Berti, *Top. Stereochem.* **7,** 93–251 (1973), pp. 95–187.

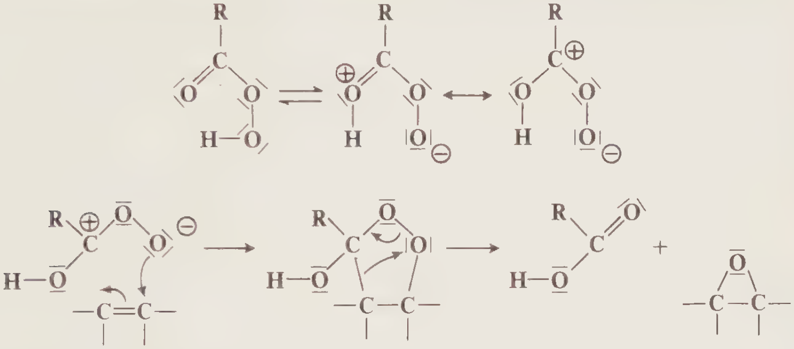
[520] Emmons and Pagano, *J. Am. Chem. Soc.* **77,** 89 (1955).

[521] Bartlett, *Rec. Chem. Prog.* **18,** 111 (1957).

Evidence for this mechanism is as follows:[522] (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peracid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited. (3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbonium-ion character in the transition state.[523] (4) The addition is stereospecific; i.e., a trans olefin gives a trans epoxide and a cis olefin a cis epoxide:

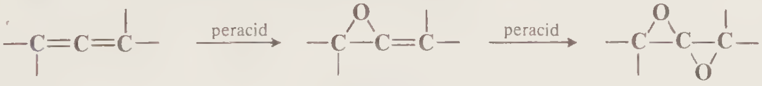


Another mechanism, postulated more recently, is also in accord with the above facts:[524]



The key step of this mechanism is the 1,3-dipolar addition (see reaction **5-50**) of a tautomer of the peroxy acid. The five-membered cyclic adduct then rearranges to the products. Evidence against the 1,3-dipolar mechanism has been reported by Bingham and coworkers,[525] who found that the rates of epoxidation of cyclohexene and norbornene by perlauric acid were approximately the same, though in typical 1,3-dipolar additions norbornene reacts 10^3 to 10^4 times faster than cyclohexene.

Conjugated dienes can be epoxidized (1,2 addition), though the reaction is slower than for corresponding olefins, but α,β-unsaturated ketones do not generally give epoxides when treated with peracids.[526] However, α,β-unsaturated esters react normally, to give glycidic esters.[527] When a carbonyl group is in the molecule but not conjugated with the double bond, the Baeyer-Villiger reaction (**8-23**) may compete. It has been shown that 2-allylcyclohexanone treated with peracetic acid gives the Baeyer-Villiger reaction, but with H_2O_2 and benzonitrile it gives epoxidation.[528] Allenes are converted by peracids to allene oxides (**82**) or spiro dioxides (**83**),



82 83

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[522] Ogata and Tabushi, *J. Am. Chem. Soc.* **83,** 3440 (1961).

[523] Khalil and Pritzkow, *J. Prakt. Chem.* **315,** 58 (1973).

[524] Kwart and Hoffman, *J. Org. Chem.* **31,** 419 (1966). For another mechanism, see Hanzlik and Shearer, *J. Am. Chem. Soc.* **97,** 5231 (1975).

[525] Bingham, Meakins, and Whitham, *Chem. Commun.* 445 (1966); see, however, Kwart, Starcher, and Tinsley, *Chem. Commun.* 335 (1967).

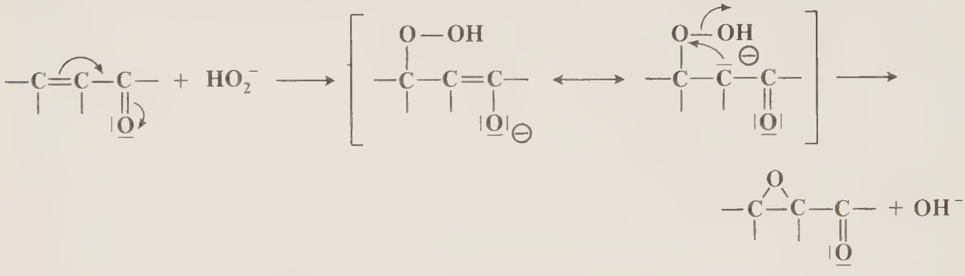
[526] A few exceptions are known. For example, see Hart, Verma, and Wang, *J. Org. Chem.* **38,** 3418 (1973).

[527] MacPeek, Starcher, and Phillips, *J. Am. Chem. Soc.* **81,** 680 (1959).

[528] Payne, *Tetrahedron* **18,** 763 (1962).

which in certain cases can be isolated[529] but more often are unstable under the reaction conditions and react further to give other products.[530]

α,β-Unsaturated ketones (including quinones), aldehydes, and sulfones can be epoxidized with alkaline H_2O_2,[531] but this is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-:[532]



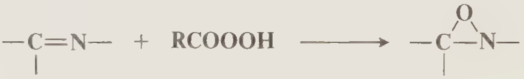
Epoxides can also be prepared by treating olefins with oxygen or with an alkyl peroxide,[533] catalyzed by a complex of V or Mo. The reaction with oxygen, which can also be carried out without a catalyst, is probably a free-radical process.[534]

It would be useful if triple bonds could be simply epoxidized to give oxirenes (**84**). However, oxirenes are unknown. They probably form in the reaction[535] but react further before they can

84

be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (see p. 55).

Peracids react with C=N bonds to give oxaziridines.[536]



OS **I**, 494; **IV**, 552, 860; **V**, 191, 414, 467, 1007; **55**, 52, 86.

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[529] Crandall, Machleder, and Thomas, *J. Am. Chem. Soc.* **90**, 7346 (1968); Camp and Greene, *J. Am. Chem. Soc.* **90**, 7349 (1968); Crandall, Conover, Komin, and Machleder, *J. Org. Chem.* **39**, 1723 (1974).

[530] For example, see Crandall and Machleder, *J. Am. Chem. Soc.* **90**, 7292, 7347 (1968); Crandall, Machleder, and Sojka, *J. Org. Chem.* **38**, 1149 (1973).

[531] For example, see Payne and Williams, *J. Org. Chem.* **24**, 54 (1959), **26**, 651 (1961); Zwanenburg and ter Wiel, *Tetrahedron Lett.* 935 (1970).

[532] Bunton and Minkoff, *J. Chem. Soc.* 665 (1949); Temple, *J. Org. Chem.* **35**, 1275 (1970). For a review, see Patai and Rappoport, in Patai, Ref. 29, vol. 1, pp. 512–517.

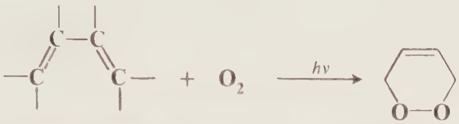
[533] For example, see Gould, Hiatt, and Irwin, *J. Am. Chem. Soc.* **90**, 4573 (1968); Sharpless and Michaelson, *J. Am. Chem. Soc.* **95**, 6136 (1973); Baker, Mains, Sheng, and Zajacek, *J. Org. Chem.* **38**, 1145 (1973); Sheldon, *Recl. Trav. Chim. Pays-Bas* **92**, 253 (1973); Hart and Lavrik, *J. Org. Chem.* **39**, 1793 (1974); Arakawa, Moro-oka, and Ozaki, *Bull. Chem. Soc. Jpn.* **47**, 2958 (1974); Tanaka, Yamamoto, Nozaki, Sharpless, Michaelson, and Cutting, *J. Am. Chem. Soc.* **96**, 5254 (1974); Kaloustian, Lena, and Metzger, *Tetrahedron Lett.* 599 (1975).

[534] Brill, *J. Am. Chem. Soc.* **85**, 141 (1963); Moss and Steiner, *J. Chem. Soc.* 2372 (1965); Sérée de Roch, *Bull. Soc. Chim. Fr.* 1979 (1965).

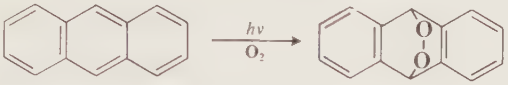
[535] McDonald and Schwab, *J. Am. Chem. Soc.* **86**, 4866 (1964); Stille and Whitehurst, *J. Am. Chem. Soc.* **86**, 4871 (1964); Ciabattoni, Campbell, Renner, and Concannon, *J. Am. Chem. Soc.* **92**, 3286 (1970); Ibne-Rasa, Pater, Ciabattoni, and Edwards, *J. Am. Chem. Soc.* **95**, 7894 (1973); Ogata, Sawaki, and Inoue, *J. Org. Chem.* **38**, 1044 (1973).

[536] Emmons, *J. Am. Chem. Soc.* **79**, 5739 (1957); Horner and Jürgens, *Chem. Ber.* **90**, 2184 (1957); Krimm, *Chem. Ber.* **91**, 1057 (1958); Madan and Clapp, *J. Am. Chem. Soc.* **91**, 6078 (1969); Ogata and Sawaki, *J. Am. Chem. Soc.* **95**, 4687, 4692 (1973); Schmitz, *Adv. Heterocycl. Chem.* **2**, 83–130 (1963).

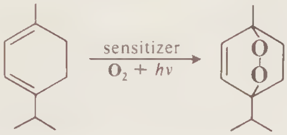
5-41 Photooxidation of Dienes (Addition of Oxygen, Oxygen)



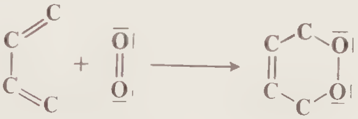
Conjugated dienes react with oxygen under the influence of light to give internal peroxides.[537] The reaction has mostly been applied to cyclic dienes. The scope extends to certain aromatic compounds,[538] e.g.,



In addition to those dienes and aromatic rings which can be photooxidized directly, there is a larger group which give the reaction in the presence of a photosensitizer such as eosin (see p. 218). Among these is α-terpinene, which is converted to ascaridole:



At first it may seem strange that oxygen, which is a diradical, needs photosensitization, either by light or a photosensitizer, to cause it to add to the conjugated system. But, as in reaction **4-8**, it is not the ground-state oxygen (the triplet) which reacts, and the purpose of the photosensitization is to elevate the oxygen to the singlet state,[539] so that the reaction is actually a Diels-Alder reaction (see **5-51**) with singlet oxygen as dienophile:[540]



Like reaction **5-51**, this reaction is reversible.

We have previously discussed the reaction of singlet oxygen with double-bond compounds to give hydroperoxides (reaction **4-8**), but singlet oxygen can also react with double bonds in another way, to give a dioxetane intermediate (**85**), which usually cleaves to aldehydes or ketones[541] but has been isolated in certain cases.[542]

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[537] For reviews, see Denny and Nickon, *Org. React.* **20,** 133–336 (1973); Adams, in Augustine and Trecker, Ref. 519, vol. 2, pp. 65–112; Gollnick, *Adv. Photochem.* **6,** 1–122 (1968); Schönberg, Ref. 41, pp. 382–397; Gollnick and Schenck, in Hamer, "1,4-Cycloaddition Reactions," pp. 255–344, Academic Press, Inc., New York, 1967; Arbuzov, *Russ. Chem. Rev.* **34,** 558–574 (1965).

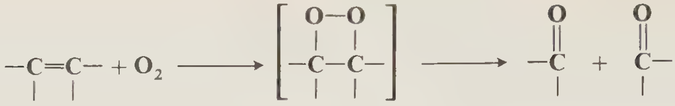
[538] For a review, see Rigaudy, *Pure Appl. Chem.* **16,** 169–186 (1968).

[539] For reviews of singlet oxygen, see Ref. 156 in Chapter 14.

[540] Foote and Wexler, *J. Am. Chem. Soc.* **86,** 3880 (1964); Corey and Taylor, *J. Am. Chem. Soc.* **86,** 3881 (1964); Foote, Wexler, and Ando, *Tetrahedron Lett.* 4111 (1965).

[541] For discussions, see Kearns, *Chem. Rev.* **71,** 395–427 (1971), pp. 422–424; Bartlett, *Pure Appl. Chem.* **27,** 597–609 (1971); Foote, *Pure Appl. Chem.* **27,** 635–645 (1971).

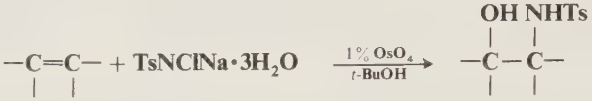
[542] For example, see Bartlett and Schaap, *J. Am. Chem. Soc.* **92,** 3223 (1970); Mazur and Foote, *J. Am. Chem. Soc.* **92,** 3225 (1970); Bartlett, Mendenhall, and Schaap, *Ann. N.Y. Acad. Sci.* **171,** 79 (1970); Schaap, *Tetrahedron Lett.* 1757 (1971); Schaap and Tontapanish, *J. Chem. Soc., Chem. Commun.* 490 (1972); Wieringa, Strating, Wynberg, and Adam, *Tetrahedron Lett.* 169 (1972); Hasty and Kearns, *J. Am. Chem. Soc.* **95,** 3380 (1973); Burns and Foote, *J. Am. Chem. Soc.* **96,** 4339 (1974); Kopecky, Filby, Mumford, Lockwood, and Ding, *Can. J. Chem.* **53,** 1103 (1975).



$$-\overset{|}{\underset{|}{C}}=\overset{|}{\underset{|}{C}}- + O_2 \longrightarrow \left[\begin{matrix} O-O \\ | \quad | \\ -C-C- \\ | \quad | \end{matrix}\right] \longrightarrow -\overset{O}{\overset{\|}{\underset{|}{C}}} + \overset{O}{\overset{\|}{\underset{|}{C}}}-$$

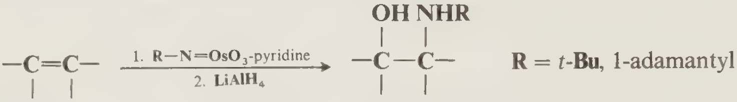
85

5-42 Oxyamination (Addition of Oxygen, Nitrogen)



$$-\underset{|}{C}=\underset{|}{C}- + \text{TsNClNa}\cdot 3H_2O \xrightarrow[t\text{-BuOH}]{1\%\ OsO_4} -\overset{OH}{\overset{|}{\underset{|}{C}}}-\overset{NHTs}{\overset{|}{\underset{|}{C}}}-$$

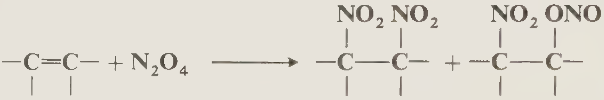
N-Tosylated β-hydroxy alkylamines (which can be easily hydrolyzed to β-hydroxyamines) can be prepared by treatment of alkenes with the trihydrate of Chloramine-T.[542a] In some cases $AgNO_3$ must be added. In another procedure, certain β-hydroxy secondary alkylamines can be prepared by treatment of alkenes with the osmium compounds $R{-}N{=}OsO_3$ (R = *t*-butyl or 1-adamantyl), followed by reductive cleavage with $LiAlH_4$ of the initially-formed osmic esters.[543] It is presumed



$$-\underset{|}{C}=\underset{|}{C}- \xrightarrow[2.\ LiAlH_4]{1.\ R-N=OsO_3\text{-pyridine}} -\overset{OH}{\overset{|}{\underset{|}{C}}}-\overset{NHR}{\overset{|}{\underset{|}{C}}}- \qquad R = t\text{-Bu, 1-adamantyl}$$

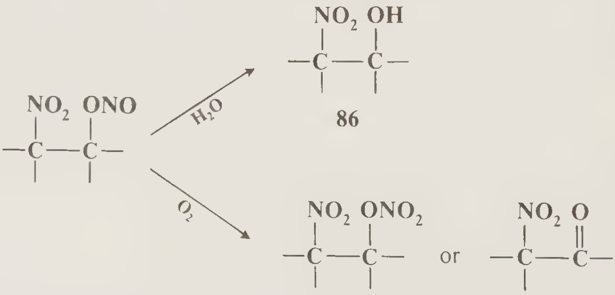
that $R{-}N{=}OsO_3$ (R = Ts) is an intermediate in the Chloramine-T reaction. Another oxyamination reaction involves treatment of a palladium complex of the olefin with a secondary amine, followed by lead tetraacetate.[543a]

5-43 Addition of N_2O_4 and Related Reactions (Addition of Nitrogen, Nitrogen or Nitrogen, Oxygen):



$$-\underset{|}{C}=\underset{|}{C}- + N_2O_4 \longrightarrow -\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{NO_2}{\overset{|}{\underset{|}{C}}}- + -\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{ONO}{\overset{|}{\underset{|}{C}}}-$$

When olefins are treated with N_2O_4 in an ether, ester, or alkane[544] as solvent, *vic*-dinitro compounds and β-nitro alkyl nitrites are produced.[545] The reaction may be successfully performed with all kinds of olefins and acetylenes. Generally, both products are produced. The dinitro compound is usually stable, but the ester is quite reactive. Upon addition of water or alcohol it is hydrolyzed to a β-nitro alcohol. If oxygen is added, it is oxidized to a β-nitro alkyl nitrate or an α-nitro aldehyde or ketone.



$$-\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{ONO}{\overset{|}{\underset{|}{C}}}- \xrightarrow{H_2O} -\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{OH}{\overset{|}{\underset{|}{C}}}-$$

86

$$-\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{ONO}{\overset{|}{\underset{|}{C}}}- \xrightarrow{O_2} -\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{ONO_2}{\overset{|}{\underset{|}{C}}}- \text{ or } -\overset{NO_2}{\overset{|}{\underset{|}{C}}}-\overset{O}{\overset{\|}{C}}-$$

[542a] Sharpless, Chong, and Oshima, *J. Org. Chem.* **41,** 177 (1976).

[543] Sharpless, Patrick, Truesdale, and Biller, *J. Am. Chem. Soc.* **97,** 2305 (1975).

[543a] Bäckvall, *Tetrahedron Lett.* 2225 (1975).

[544] Bonetti, DeSavigny, Michalski, and Rosenthal, *J. Org. Chem.* **33,** 237 (1968).

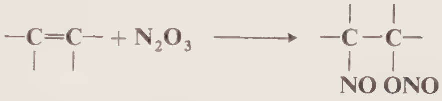
[545] For reviews, see Larson, in Feuer, Ref. 338, pt. 1, pp. 316–323 (1969); Stacey and Harris, *Org. React.* **13,** 150–376 (1963), pp. 224–229, 361–367; Shechter, *Rec. Chem. Prog.* **25,** 55–76 (1964); Sosnovsky, Ref. 41, pp. 252–269; Noble, Borgardt, and Reed, *Chem. Rev.* **64,** 19–57 (1964), pp. 20–22.

The nitrate is stable. Even without deliberate addition of oxygen, it is not uncommon to find some nitrate or ketone. It is therefore possible to prepare four types of compound in this reaction, not counting the nitrite.

The mechanism is probably of the free-radical type,[546] with initial attack by NO_2 to give $-\underset{\bullet}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-NO_2$ as the intermediate for both products. In accord with this, the nitro group (in the nitrite derivatives) is found on the side with more hydrogens. There is evidence that a β-nitro alkyl peroxynitrate $O_2NCHRCHROONO_2$ is an intermediate in the formation of the α-nitro carbonyl compound.[547] When oxygen is completely absent, the product is a β-nitroso nitrate $O_2NOCR_2CR_2NO$, and it is likely that in this case N_2O_4 adds by a heterolytic mechanism.[548]

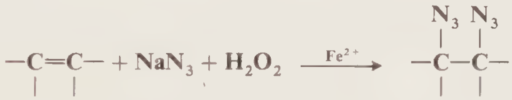
β-Nitro alcohols (**86**) can also be prepared indirectly, by addition of acetyl nitrate $AcONO_2$ to double bonds.[549] The resulting β-nitro acetate can be hydrolyzed to the alcohol. Side products of the addition of $AcONO_2$ are nitro olefins. The addition follows Markovnikov's rule, with the nitro group going to the carbon with more hydrogens.

N_2O_3 adds to olefins to give β-nitroso alkyl nitrites:[550]



$$-\underset{|}{C}=\underset{|}{C}- + N_2O_3 \longrightarrow -\underset{\underset{NO}{|}}{\overset{|}{C}}-\underset{\underset{ONO}{|}}{\overset{|}{C}}-$$

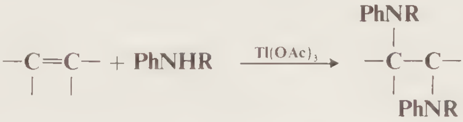
β-Nitroso formates can be prepared by treatment of alkenes with nitrosyl formate HCOONO, generated in situ from isoamyl nitrite and formic acid.[551] Two azide groups can be added to double bonds by treatment with sodium azide and hydrogen peroxide, in the presence of ferrous ion:[552]



$$-\underset{|}{C}=\underset{|}{C}- + NaN_3 + H_2O_2 \xrightarrow{Fe^{2+}} -\underset{|}{\overset{\overset{N_3}{|}}{C}}-\underset{|}{\overset{\overset{N_3}{|}}{C}}-$$

OS **50**, 84.

5-44 Bisamination (Addition of Nitrogen, Nitrogen)



$$-\underset{|}{C}=\underset{|}{C}- + PhNHR \xrightarrow{Tl(OAc)_3} -\underset{|}{\overset{\overset{PhNR}{|}}{C}}-\underset{\underset{PhNR}{|}}{C}-$$

Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.[553] The reaction is not successful for primary aliphatic amines.

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[546] Shechter, Gardikes, and Pagano, *J. Am. Chem. Soc.* **81**, 5420 (1959); Shechter, Gardikes, Cantrell, and Tiers, *J. Am. Chem. Soc.* **89**, 3005 (1967).

[547] Lachowicz and Kreuz, *J. Org. Chem.* **32**, 3885 (1967); Duynstee, Hennekens, Housmans, van Raayen, and Voskuil, *Recl. Trav. Chim. Pays-Bas* **92**, 1272 (1973).

[548] Duynstee, Housmans, Voskuil, and Berix, *Recl. Trav. Chim. Pays-Bas* **92**, 698 (1973).

[549] Bordwell and Garbisch, *J. Am. Chem. Soc.* **82**, 3588 (1960), *J. Org. Chem.* **27**, 2322, 3049 (1962), **28**, 1765 (1963); Bordwell and Biranowski, *J. Org. Chem.* **32**, 629 (1967).

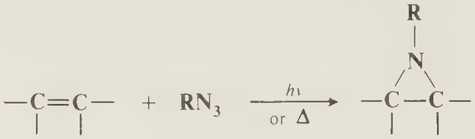
[550] Park and Williams, *Chem. Commun.* 332 (1969).

[551] Hamann and Swern, *J. Am. Chem. Soc.* **90**, 6481 (1968).

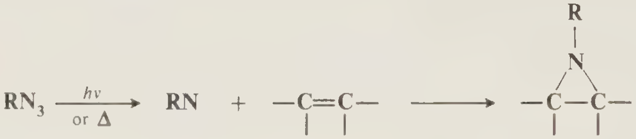
[552] Minisci and Galli, *Tetrahedron Lett.* 533 (1962).

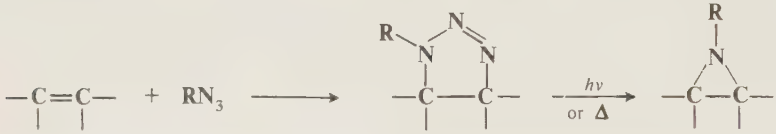
[553] Gómez Aranda, Barluenga, and Aznar, *Synthesis* 504 (1974).

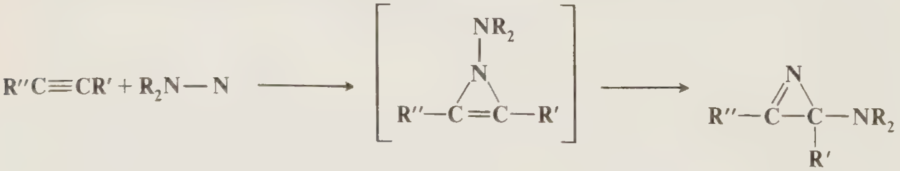
5-45 Formation of Aziridines (Addition of Nitrogen, Nitrogen)



Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.[554] The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO_2, as well as other groups. The reaction can take place by at least two pathways. In one, the azide is converted to a nitrene (p. 184), which adds to the double bond in a manner analogous to that of carbene addition (reaction **5-53**). In the other pathway a 1,3 dipolar addition (reaction **5-50**) takes place to give a triazoline (which can be isolated), followed by extrusion of nitrogen (reaction **7-48**). Evidence for the nitrene pathway is most compelling for R = acyl groups. As discussed on p. 184, singlet nitrenes add stereospecifically while triplet nitrenes do not. Aminonitrenes R_2NN have been shown to add to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.[555] Like oxirenes (p. 752), 2-azirines are unknown, probably because they are predicted to be antiaromatic.







Nitrenes can also add to aromatic rings to give ring-expansion products analogous to those mentioned in reaction **5-53**.[556] Nitrenoids can also add to C=N bonds and to C=O bonds, to give diaziridines and oxaziranes, respectively.[557]

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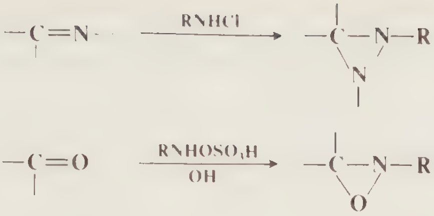
[554] For reviews, see Dermer and Ham, "Ethylenimine and Other Aziridines," pp. 68–79, Academic Press, Inc., New York, 1969; Muller and Hamer, "1,2-Cycloaddition Reactions," pp. 5–43, Interscience Publishers, New York, 1967.

[555] Anderson, Gilchrist, and Rees, *Chem. Commun.* 147 (1969).

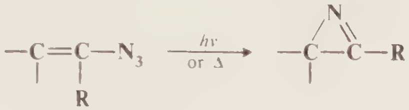
[556] For example, see Hafner and König, *Angew. Chem. Int. Ed. Engl.* **2**, 96 (1963) [*Angew. Chem.* **75**, 89]; Lwowski and Johnson, *Tetrahedron Lett.* 891 (1967).

[557] For reviews, see Muller and Hamer, Ref. 554; Schmitz, *Adv. Heterocycl. Chem.* **2**, 83–130 (1963).



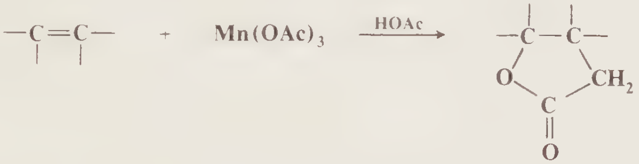
OS **55,** 114.

5-46 The Formation of 1-Azirines from Vinyl Azides



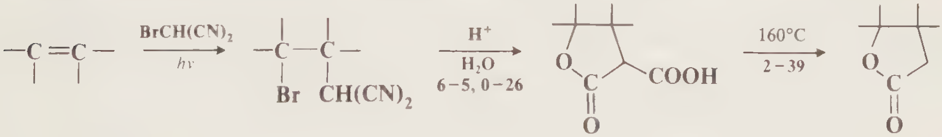
1-Azirines can be prepared by the photolysis or thermolysis of vinyl azides.[558] The thermolysis is catalyzed by tertiary amines.[559] The reaction may be regarded as a kind of addition of a nitrene to a double bond. R may be alkyl, aryl, or hydrogen,[560] though 1-azirines in which R = hydrogen are unstable and difficult to isolate. Vinyl azides are easily prepared from olefins in two steps: addition of iodine azide (reaction **5-35**) followed by elimination of HI (reaction **7-13**).

5-47 The Conversion of Olefins to γ-Lactones (Addition of Oxygen, Carbon)



Olefins react with manganese(III) acetate to give γ-lactones.[561] The mechanism is probably free-radical, involving addition of $\cdot CH_2COOH$ to the double bond. Similar lactone formation has also been accomplished with lead tetraacetate.[562]

Olefins can also be converted to γ-lactones by the following indirect route:[563] bromodicyano-



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[558] Smolinsky, *J. Org. Chem.* **27,** 3557 (1962); Smolinsky and Pryde, *J. Org. Chem.* **33,** 2411 (1968); Horner, Christmann, and Gross, *Chem. Ber.* **96,** 399 (1963); Harvey and Ratts, *J. Org. Chem.* **31,** 3907 (1966); Hassner and Fowler, *Tetrahedron Lett.* 1545 (1967), *J. Am. Chem. Soc.* **90,** 2869 (1968); Woerner, Reimlinger, and Arnold, *Angew. Chem. Int. Ed. Engl.* **7,** 130 (1968) [*Angew. Chem.* **80,** 119].

[559] Komatsu, Ichijima, Ohshiro, and Agawa, *J. Org. Chem.* **38,** 4341 (1973).

[560] Isomura, Kobayashi, and Taniguchi, *Tetrahedron Lett.* 3499 (1968); Isomura, Okada, and Taniguchi, *Tetrahedron Lett.* 4073 (1969).

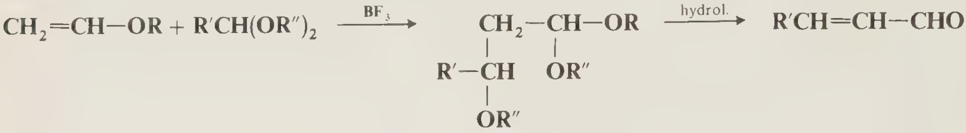
[561] Bush and Finkbeiner, *J. Am. Chem. Soc.* **90,** 5903 (1968); Heiba, Dessau, and Koehl, *J. Am. Chem. Soc.* **90,** 5905 (1968); Heiba, Dessau, and Rodewald, *J. Am. Chem. Soc.* **96,** 7977 (1974).

[562] Heiba, Dessau, and Koehl, *J. Am. Chem. Soc.* **90,** 2706 (1968).

[563] For another indirect route, see Das Gupta, Felix, Kempe, and Eschenmoser, *Helv. Chim. Acta* **55,** 2198 (1972).

methane adds to double bonds under the influence of uv light to give adducts (reaction **5-37**) which are easily hydrolyzed and decarboxylated. In the overall process a double-bond compound is converted to a γ-lactone.[564]

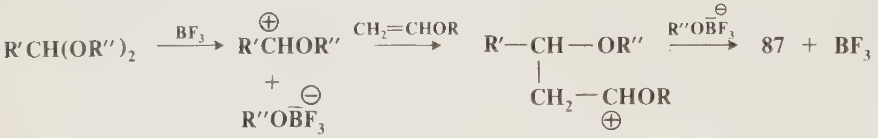
5-48 The Addition of Acetals to Vinyl Ethers (Addition of Oxygen, Carbon)



$$\mathrm{CH_2{=}CH{-}OR + R'CH(OR'')_2 \xrightarrow{BF_3} \begin{array}{ccc} & CH_2 & {-}CH{-}OR \\ & | & | \\ R'{-} & CH & OR'' \\ & | & \\ & OR'' & \end{array} \xrightarrow{hydrol.} R'CH{=}CH{-}CHO}$$

87

Acetals add to vinyl ethers in the presence of BF_3, to give alkoxy acetals which can be hydrolyzed to α,β-unsaturated aldehydes.[565] Other Lewis acids, e.g., $ZnCl_2$, $AlCl_3$, have also been used as catalysts. Because of transetherification (reaction **0-19**) the product acetal (when $R \neq R''$) may contain $R''OCHR'CH_2CH(OR'')_2$ as well as **87.** For this reason it is usually advisable to begin with an acetal and a vinyl ether in which $R = R''$. The mechanism of the addition reaction has been formulated as[566]

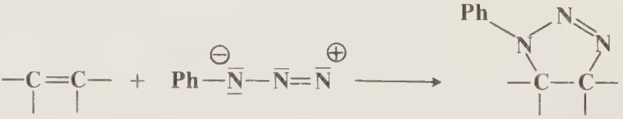


$$\mathrm{R'CH(OR'')_2 \xrightarrow{BF_3} \begin{array}{c} \overset{\oplus}{R'CHOR''} \\ + \\ R''O\overset{\ominus}{B}F_3 \end{array} \xrightarrow{CH_2{=}CHOR} \begin{array}{l} R'{-}CH{-}OR'' \\ \quad\ | \\ \quad CH_2{-}\overset{}{\underset{\oplus}{CHOR}} \end{array} \xrightarrow{R''O\overset{\ominus}{B}F_3} 87 + BF_3}$$

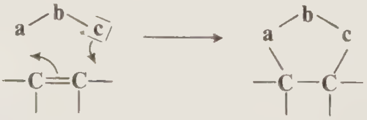
5-49 Addition of Aldehydes and Ketones (Addition of Oxygen, Carbon).

See the Prins reaction (**6-54**), reactions **6-55,** and **6-68** to **6-70.**

5-50 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



Azides add to double bonds to give triazolines. This is one example of a large group of reactions (2 + 3 cycloadditions) in which five-membered heterocyclic compounds are prepared by addition to double bonds of 1,3-dipolar compounds.[567] These are compounds which have a sequence of three atoms a—b—c, of which a has a sextet of electrons in the outer shell and c an octet with at least one unshared pair. The reaction can then be formulated as



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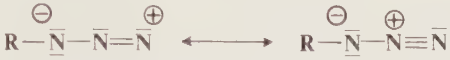
[564] Boldt, Thielecke, and Etzemüller, *Chem. Ber.* **102,** 4157 (1969).

[565] For a review, see Povarov, *Russ. Chem. Rev.* **34,** 639-656 (1965).

[566] Hoaglin and Hirsch, *J. Am. Chem. Soc.* **71,** 3468 (1949).

[567] For reviews, see Huisgen, in "Aromaticity," *Chem. Soc. Spec. Publ.* no. 21, 51–73 (1967), *Helv. Chim. Acta* **50,** 2421 2439 (1967), *Bull. Soc. Chim. Fr.* 3431 (1965), *Angew. Chem. Int. Ed. Engl.* **2,** 565–598, 633–645 (1963) [*Angew. Chem.* **75,** 604–637, 742 754], *Proc. Chem. Soc.* 357 369 (1961); Beltrame, in Bamford and Tipper, Ref. 1, vol. 9, pp. 117 131; Huisgen, Grashey, and Sauer, in Patai, Ref. 29, vol. 1, pp. 806–878; Black, Crozier, and Davis, *Synthesis* 205–221 (1975); Stuckwisch, *Synthesis* 469–483 (1973). For a review of intramolecular 1,3-dipolar additions, see Padwa, *Angew. Chem. Int. Ed. Engl.* **15,** 123–136 (1976) [*Angew. Chem.* **88,** 131–144].

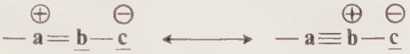
Since compounds with six electrons in the outer shell of an atom are usually not stable, the a—b—c system is actually one canonical structure of a resonance hybrid, for which at least one other structure may be drawn, e.g., for azides



$$R-\overset{\ominus}{\underline{\overline{N}}}-\overline{N}=\overset{\oplus}{N} \longleftrightarrow R-\overset{\ominus}{\underline{\overline{N}}}-\overset{\oplus}{N}\equiv\overline{N}$$

1,3-Dipolar compounds can be divided into two main types:

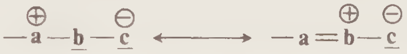
1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form a triple bond on that atom:



$$-\overset{\oplus}{a}=\underline{b}-\overset{\ominus}{\underline{c}} \longleftrightarrow -\overset{\oplus}{a}\equiv b-\overset{\ominus}{\underline{c}}$$

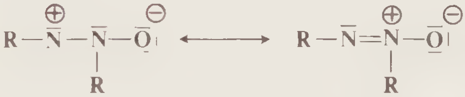
If we limit ourselves to the first row of the periodic table, b can only be nitrogen, a can be carbon or nitrogen, and c can be carbon, oxygen, or nitrogen; hence there are six types which fit this description. Among these are azides (a = b = c = N), illustrated above, and diazoalkanes ($R_2\overset{\ominus}{\overline{C}}-\overline{N}=\overset{\oplus}{\overline{N}}$).

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form a double bond:



$$-\overset{\oplus}{a}-\underline{b}-\overset{\ominus}{\underline{c}} \longleftrightarrow -\overset{\oplus}{a}=b-\overset{\ominus}{\underline{c}}$$

Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N—N—C is only another form of C—N—N. Examples are azoxy compounds:



$$R-\overset{\oplus}{\overline{N}}-\overline{N}(R)-\overset{\ominus}{\underline{\overline{O}}}| \longleftrightarrow R-\overline{N}=\overset{\oplus}{N}(R)-\overset{\ominus}{\underline{\overline{O}}}|$$

Of the 18 systems, some of which are unstable and must be generated in situ, the reaction has been accomplished for at least 15, though not in all cases with a carbon-carbon double bond (the reaction also can be carried out with other double bonds). Not all olefins undergo 1,3-dipolar addition equally well. The reaction is most successful for those which are good dienophiles in the Diels-Alder reaction (**5-51**). The addition is stereoselective and syn, and the mechanism is probably a one-step synchronous process, as illustrated above.[568] As expected for this type of mechanism, the rates do not vary much with changes in solvent.[569] There are no simple rules covering orientation in 1,3-dipolar additions when both the reagent and the substrate are unsymmetrical. Regioselectivities are complicated but have been explained by molecular-orbital treatments.[570]

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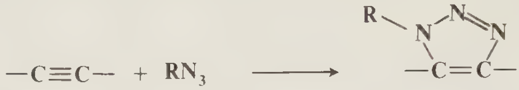
[568] For discussions, see Huisgen, *J. Org. Chem.* **33,** 2291 (1968), **41,** 403 (1976); Harcourt, *J. Mol. Struct.* **12,** 351–366 (1972); Firestone, *J. Org. Chem.* **33,** 2285 (1968).

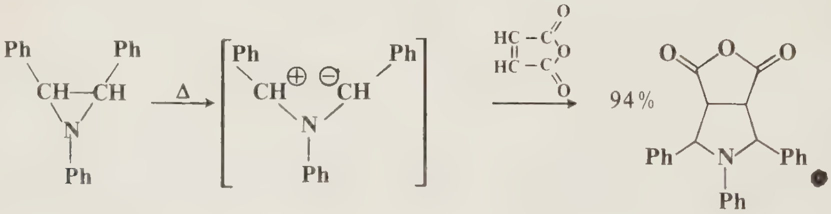
[569] For a review of the role of solvents in this reaction, see Kadaba, *Synthesis* 71–84 (1973).

[570] Sustmann, *Tetrahedron Lett.* 2717 (1971), *Pure Appl. Chem.* **40,** 569–593 (1974), Sustmann and Trill, *Angew. Chem. Int. Ed. Engl.* **11,** 838 (1972) [*Angew. Chem.* **84,** 887]; Houk, *J. Am. Chem. Soc.* **94,** 8953 (1972); Houk, Sims, Duke, Strozier, and George, *J. Am. Chem. Soc.* **95,** 7287 (1973); Houk, Sims, Watts, and Luskus, *J. Am. Chem. Soc.* **95,** 7301 (1973); Bastide, Ghandour and Henri-Rousseau, *Tetrahedron Lett.* 4225 (1972), *Bull. Soc. Chim. Fr.* 2290 (1973); Bastide and Henri-Rousseau, *Bull. Soc. Chim. Fr.* 2294 (1973), 1037 (1974); Caramella and Cellerino, *Tetrahedron Lett.* 229 (1974).

Carbon-carbon triple bonds may also undergo 1,3-dipolar addition.[571] For example, azides give triazoles:

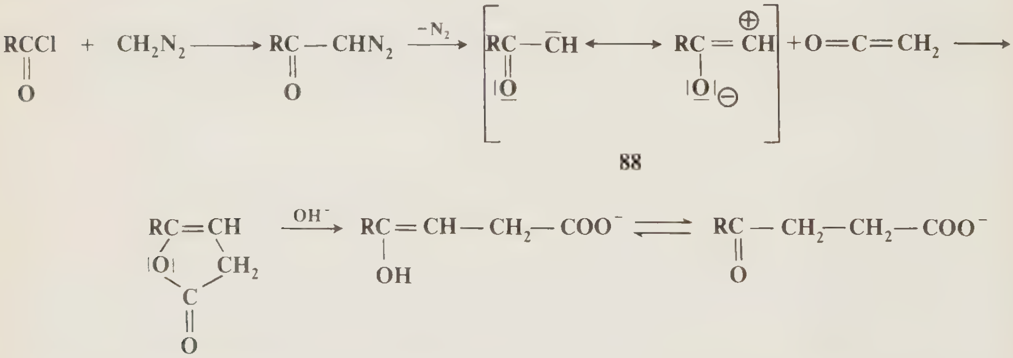


The 1,3-dipolar reagent can in some cases be generated by the in situ opening of a suitable three-membered ring system. For example, aziridines can add to activated double bonds to give pyrrolidines, e.g.,[572]



Aziridines also add to C≡C triple bonds as well as to other unsaturated linkages, including C=O, C=N, and C≡N.[573] In some of these reactions it is a C—N bond of the aziridine which opens rather than the C—C bond.

The 1,3-dipolar addition to ketene of a carbene derived from a diazo ketone provides a method of increasing the length of a carbon chain by three:[574]



88

The first step is an example of reaction **0-116.** In the last step the enol lactone (butenolide) formed by the 1,3-dipolar addition is hydrolyzed by base. It may be noted that the 1,3-dipolar species **88** does not fit into either of the two main categories mentioned above. Although **88** adds to the double bond of ketene, it normally undergoes rearrangement (reaction **8-9**) before it can add to most other double bonds.[575]

2 + 3 cycloadditions are also known in which the compound which adds to the double or triple bond is not a 1,3-dipolar compound but an anion with a partial negative charge at *both*

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[571] For reviews, see Bastide, Hamelin, Texier, and Quang, *Bull. Soc. Chim. Fr.* 2555–2579; 2871–2887 (1973); Fuks and Viehe, in Viehe, Ref. 70, pp. 460–477.

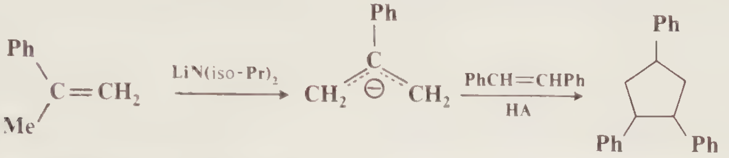
[572] Heine and Peavy, *Tetrahedron Lett.* 3123 (1965); Heine, Peavy, and Durbetaki, *J. Org. Chem.* **31**, 3924 (1966).

[573] For reviews, see Lown, *Rec. Chem. Prog.* **32**, 51–83 (1971); Gladysheva, Sineokov, and Etlis, *Russ. Chem. Rev.* **39**, 118–129 (1970).

[574] Ried and Mengler, *Justus Liebigs Ann. Chem.* **678**, 113 (1964).

[575] Huisgen, Binsch, and Ghosez, *Chem. Ber.* **97**, 2628 (1964).

ends. Such reactions are called 1,3-*anionic cycloadditions*.[576] An important example is the case where the anion is an allyl carbanion and the product a cyclopentane. For example, α-methylstyrene adds to stilbene after being treated with the strong base lithium diisopropylamide.[577]

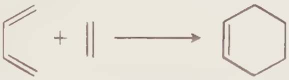


In this case the reagent is an allylic anion,[578] but similar 2 + 3 cycloadditions involving allylic cations have also been reported.[579]

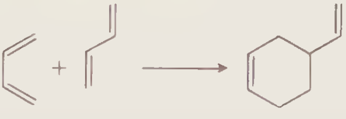
OS V, 96, 127; **53,** 59. Also see OS **IV**, 380.

C. Carbon on Both Sides. Reactions **5-51** to **5-55** are cycloaddition reactions.[580]

5-51 The Diels-Alder Reaction



In the *Diels-Alder reaction* a double bond adds 1,4 to a conjugated diene (a 4 + 2 cycloaddition)[581] so that the product is always a six-membered ring. The double-bond compound is called a *dienophile*. The reaction is easy and rapid and of very broad scope. Ethylene and simple olefins make poor dienophiles, although the reaction has been carried out with these compounds. Most dienophiles are of the form $-\underset{|}{C}=\underset{|}{C}-Z$ or $Z-\underset{|}{C}=\underset{|}{C}-Z'$, where Z and Z′ are CHO, COR, COOH, COOR, COCl, COAr, CN,[582] NO_2,[583] Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2COOH, halogen, or C=C.[584] In the latter case, the dienophile is itself a diene:



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[576] For a review, see Kauffmann, *Angew. Chem. Int. Ed. Engl.* **13,** 627–639 (1974) [*Angew. Chem.* **86,** 715-727].

[577] Eidenschink and Kauffmann, *Angew. Chem. Int. Ed. Engl.* **11,** 292 (1972) [*Angew. Chem.* **84,** 292].

[578] For other examples, see Ford, Radue, and Walker, *Chem. Commun.* 966 (1970); Boche and Martens, *Angew. Chem. Int. Ed. Engl.* **11,** 724 (1972) [*Angew. Chem.* **84,** 768]; Marino and Mesbergen, *J. Am. Chem. Soc.* **96,** 4050 (1974); Klumpp and Schmitz, *Tetrahedron Lett.* 2911 (1974).

[579] For example, see Noyori, Yokoyama, and Hayakawa, *J. Am. Chem. Soc.* **95,** 2722 (1973).

[580] For a system of classification of cycloaddition reactions, see Huisgen, *Angew. Chem. Int. Ed. Engl.* **7,** 321–328 (1968) [*Angew. Chem.* **80,** 329–337].

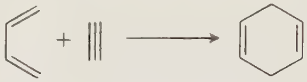
[581] For a monograph, see Wasserman, "Diels-Alder Reactions," American Elsevier Publishing Company, Inc., New York, 1965. For reviews, see Beltrame, in Bamford and Tipper, Ref. 1, vol. 9, pp. 94–117; Huisgen, Grashey, and Sauer, in Patai, Ref. 29, vol. 1, pp. 878–929; Carruthers, Ref. 202, pp. 115–168; Sauer, *Angew. Chem. Int. Ed. Engl.* **5,** 211–230 (1966), **6,** 16–33 (1967) [*Angew. Chem.* **78,** 233–252, **79,** 76–94]; Alder, *Newer Methods Prep. Org. Chem.* **1,** 381-511 (1948).

[582] For a review of the Diels-Alder reaction with acrylonitrile, see Butskus, *Russ. Chem. Rev.* **31,** 283-284 (1962). For a review of tetracyanoethylene as a dienophile, see Ciganek, Linn, and Webster, in Rappoport, Ref. 415, pp. 449–453.

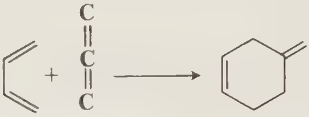
[583] For a review of the Diels-Alder reaction with nitro compounds, see Novikov, Shuekhgeimer, and Dudinskaya, *Russ. Chem. Rev.* **29,** 79–94 (1960).

[584] For a review of Diels-Alder reactions with many ethylenic and acetylenic dienophiles, see Holmes, *Org. React.* **4,** 60–173 (1948).

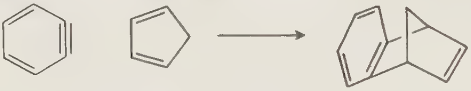
When two dienes react, mixtures are quite possible. Thus, butadiene and isoprene ($CH_2{=}CH{-}CMe{=}CH_2$) gave all nine possible Diels-Alder adducts, as well as eight-membered rings and trimers.[585] Particularly common dienophiles are maleic anhydride[586] and quinones.[587] Triple bonds ($-C{\equiv}C{-}Z$ or $Z{-}C{\equiv}C{-}Z'$) may be dienophiles[588]



as may allenes



Benzynes, although not isolable, act as dienophiles, and can be trapped with dienes;[589] e.g.,



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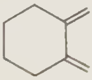
Besides carbon-carbon multiple bonds, other double- and triple-bond compounds may be dienophiles, giving rise to heterocyclic compounds. Among these are $N{\equiv}C{-}$, $-N{=}C{-}$, $-N{=}N{-}$, $O{=}N$, and $-C{=}O$ compounds[590] and, as we have seen (reaction **5-41**), even molecular oxygen.

Dienes may be open-chain, inner-ring (e.g., **89**), outer-ring (e.g., **90**), across rings (e.g., **91**), or inner-outer (e.g., **92**), except that they may not be frozen into a transoid conformation (see p. 764). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.[591]



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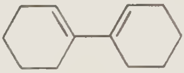

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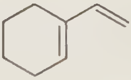

92

Aromatic compounds may also behave as dienes. Benzene is very unreactive toward dienophiles, and very few dienophiles (one of them is benzyne) have been reported to give Diels-Alder adducts with it.[592] Naphthalene and phenanthrene are also quite resistant, though naphthalene has given

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[585] Johnstone and Quan, *J. Chem. Soc.* 935 (1963).

[586] For a review of Diels-Alder reactions with maleic anhydride, see Kloetzel, *Org. React.* **4,** 1–59 (1948).

[587] For reviews of Diels-Alder reactions with quinones, see Finley, in Patai, Ref. 32, pt. 2, pp. 986–1018; Butz and Rytina, *Org. React.* **5,** 136–192 (1949).

[588] For a review of triple bonds as dienophiles, see Fuks and Viehe, in Viehe, Ref. 70, pp. 477–508.

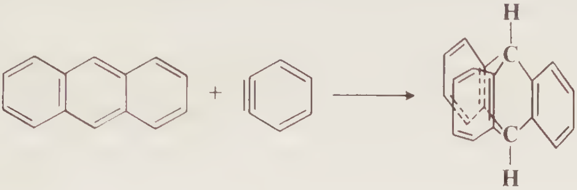
[589] Wittig and Pohmer, *Chem. Ber.* **89,** 1334 (1956); Wittig and Knauss, *Chem. Ber.* **91,** 895 (1958); Wittig and Dürr, *Justus Liebigs Ann. Chem.* **672,** 55 (1964). For a review of benzynes as dienophiles, with a table listing 155 examples, see Hoffmann, "Dehydrobenzene and Cycloalkynes," pp. 200–239, Academic Press, Inc., New York, 1967.

[590] For a monograph on dienes and dienophiles with hetero atoms, see Hamer, Ref. 537. For reviews, see Desimoni and Tacconi, *Chem. Rev.* **75,** 651–692 (1975); Kresze and Firl, *Fortschr. Chem. Forsch.* **11,** 245–284 (1969); Arbuzov, *Russ. Chem. Rev.* **33,** 407–424 (1964); Needleman and Chang Kuo, *Chem. Rev.* **62,** 405–431 (1962).

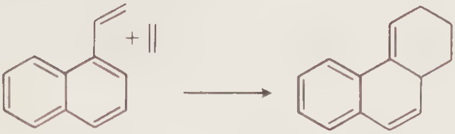
[591] For a review of Diels-Alder reactions with cyclopentadienone as diene, see Allen, *Chem. Rev.* **62,** 653-664 (1962). For a review with perchlorocyclopentadiene, see Ungnade and McBee, *Chem. Rev.* **58,** 249–320 (1958), pp. 254–305. For a review with 2-pyrones, see Shusherina, *Russ. Chem. Rev.* **43,** 851–861 (1974).

[592] Miller and Stiles, *J. Am. Chem. Soc.* **85,** 1798 (1963); Meyerson and Fields, *Chem. Ind.* (*London*) 1230 (1966); Ciganek, *Tetrahedron Lett.* 3321 (1967); Friedman, *J. Am. Chem. Soc.* **89,** 3071 (1967); Liu and Krespan, *J. Org. Chem.* **34,** 1271 (1969).

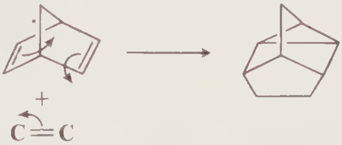
Diels-Alder addition at high pressures.[593] However, anthracene and other compounds with at least three linear benzene rings give Diels-Alder reactions readily. The interesting compound triptycene can be prepared by a Diels-Alder reaction between benzyne and anthracene:[594]



It is possible for a diene to have one double bond in an aromatic system and the other outside it, e.g.,

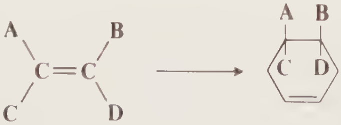


Even styrene has been shown to react in this manner.[595] Certain heterocyclic aromatic rings (among them furan) may also behave as dienes in the Diels-Alder reaction. Some hetero dienes which give the reaction are —C=C—C=O, O=C—C=O, and N=C—C=N.[590] For both all-carbon and hetero systems, the "diene" may be a conjugated enyne. If the geometry of the molecule is suitable, the diene may even be nonconjugated, e.g.,[596]



The stereochemistry of the Diels-Alder reaction can be considered from several aspects:[597]

1. With respect to the dienophile, the addition is almost always syn. Very few exceptions are known.[598] This means that groups which are cis in the olefin will be cis in the cyclohexene ring:



The addition is thus stereospecific.

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[593] Jones, Mangold, and Plieninger, *Tetrahedron* **18**, 267 (1962); Plieninger, Wild, and Westphal, *Tetrahedron* **25**, 5561 (1969). See also Dufraisse, Rigaudy, and Ricard, *Tetrahedron Suppl.* **8**, 491 (1966).

[594] Wittig and Niethammer, *Chem. Ber.* **93**, 944 (1960); Wittig, Härle, Knauss, and Niethammer, *Chem. Ber.* **93**, 951 (1960). For a review of triptycene, see Skvarchenko, Shalaev, and Klabunovskii, *Russ. Chem. Rev.* **43**, 951–966 (1974).

[595] Lora-Tamayo, *Tetrahedron* **4**, 17 (1958); Ciganek, *J. Org. Chem.* **34**, 1923 (1969).

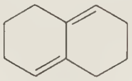
[596] Cookson, Dance, and Hudec, *J. Chem. Soc.* 5416 (1964).

[597] For a review, see Martin and Hill, *Chem. Rev.* **61**, 537–562 (1961).

[598] For some exceptions, see Mark, *J. Org. Chem.* **39**, 3179, 3181 (1974).

2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans,trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives.

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **93**, the reaction does not take place. For example, 7,9-cholestadiene has such a transoid system and is inert to maleic anhydride. The diene therefore either must be frozen into the cisoid conformation or must be able to achieve it during the reaction.



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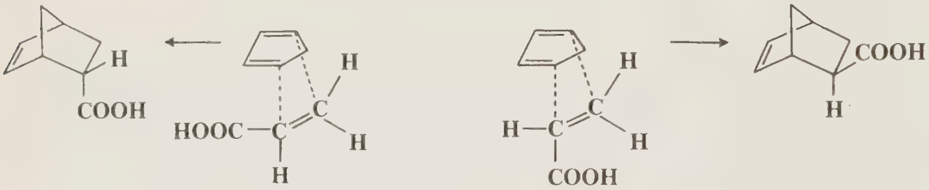
4. When the diene is cyclic, there are two possible ways in which addition can occur if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo addition*), or it may be the smaller side (*exo addition*):

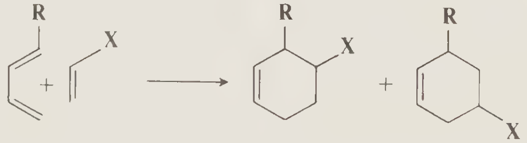


Endo addition

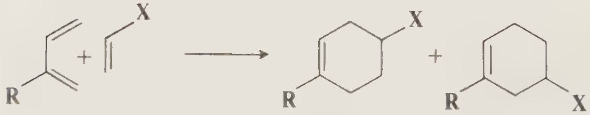
Exo addition

Most of the time, the addition is predominantly endo; i.e., the more bulky side of the olefin is under the ring, and this is probably true for open-chain dienes also. However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.[599]

When an unsymmetrical diene adds to an unsymmetrical dienophile, there are two possible products (not counting stereoisomers):



Mostly



Mostly

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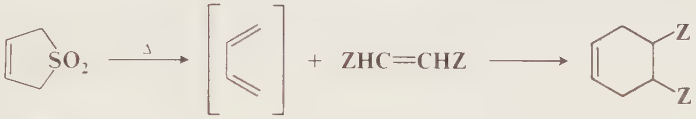
[599] See, for example, Alder and Günzl, *Chem. Ber.* **93**, 809 (1960); Stockmann, *J. Org. Chem.* **26**, 2025 (1961); Kobuke, Fueno, and Furukawa, *J. Am. Chem. Soc.* **92**, 6548 (1970); Jones and Wife, *J. Chem. Soc., Chem. Commun.* 421 (1973).

Although mixtures are often obtained, usually one predominates,[600] the one indicated above. This regioselectivity, in which the "ortho" or "para" product is favored over the "meta," has been explained by molecular-orbital considerations.[601]

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it. For the dienophile it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. Cyclic dienes, in which the cisoid conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation.[602]

As should be apparent from the foregoing, many interesting compounds can be prepared by the Diels-Alder reaction, some of which we would be hard put to make in any other way. It has thus been exceedingly useful. Competing reactions are polymerization of the diene or dienophile, or both, and 1,2 cycloaddition (reaction **5-52**). However, yields are usually quite high. No catalyst is needed, although it has been found that Lewis acids catalyze some Diels-Alder reactions,[603] usually those in which Z in the dienophile is a C=O or C=N group. A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above)[604] and the extent of endo addition.[605] The Diels-Alder reaction is usually reversible and has been used to protect double bonds.[606] A convenient substitute for butadiene in the Diels-Alder reaction is the compound 3-sulfolene (**94**), since the latter is a solid which is easy to handle while the former is a gas.[607] Butadiene is generated in situ by a reverse Diels-Alder reaction (see reaction **7-23**).



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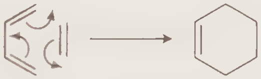
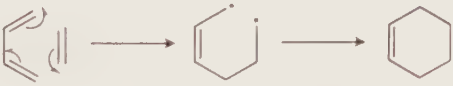
There are, broadly speaking, three possible mechanisms which have been considered for the Diels-Alder reaction.[608] In mechanism *a* there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In mechanism *b* one end of the

Mechanism *a*



Mechanism *b*



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[600] For a review, see Titov, *Russ. Chem. Rev.* **31,** 267–282 (1962).

[601] Feuer, Herndon, and Hall, *Tetrahedron* **24,** 2575 (1968); Eisenstein, Lefour, and Anh, *Chem. Commun.* 969 (1971); Eisenstein and Anh, *Bull. Soc. Chim. Fr.* 2723 (1973); Inukai, Sato, and Kojima, *Bull. Chem. Soc. Jpn.* **45,** 891 (1972); Houk, *J. Am. Chem. Soc.* **95,** 4092 (1973); Epiotis, *J. Am. Chem. Soc.* **95,** 5624 (1973); Alston, Ottenbrite, and Shillady, *J. Org. Chem.* **38,** 4075 (1973); Sustmann, *Pure Appl. Chem.* **40,** 569–593 (1974). See also Fleming, Gianni, and Mah, *Tetrahedron Lett.* 881 (1976).

[602] Sauer, Lang, and Mielert, *Angew. Chem. Int. Ed. Engl.* **1,** 268 (1962) [*Angew. Chem.* **74,** 352]; Sauer and Wiest, *Angew. Chem. Int. Ed. Engl.* **1,** 269 (1962) [*Angew. Chem.* **74,** 353].

[603] Yates and Eaton, *J. Am. Chem. Soc.* **82,** 4436 (1960); Fray and Robinson, *J. Am. Chem. Soc.* **83,** 249 (1961); Inukai and Kojima, *J. Org. Chem.* **32,** 869, 872 (1967); Ciganek, Ref. 592.

[604] For an exception, see Stojanac, Dickinson, Stojanac, Woznow, and Valenta, *Can. J. Chem.* **53,** 616 (1975).

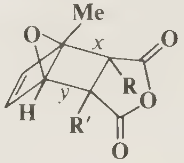
[605] For discussions, see Houk and Strozier, *J. Am. Chem. Soc.* **95,** 4094 (1973); Alston and Ottenbrite, *J. Org. Chem.* **40,** 1111 (1975).

[606] For a review of the reverse Diels-Alder reaction, see Kwart and King, *Chem. Rev.* **68,** 415–447 (1968).

[607] Sample and Hatch, *Org. Synth.* **50,** 43 (1970).

[608] For reviews, see Seltzer, *Adv. Alicyclic Chem.* **2,** 1–57 (1968); Ref. 581.

diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened. A diradical formed in this manner must be a singlet; i.e., the two unpaired electrons must have opposite spins, by an argument similar to that outlined on p. 179. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. There have been many mechanistic investigations of the Diels-Alder reaction, and the bulk of the evidence suggests that most Diels-Alder reactions take place by the one-step cyclic mechanism *a*, although it is possible that a diradical or even a diion mechanism may be taking place in some cases. The main evidence in support of mechanism *a* is as follows: (1) The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of Diels-Alder reactions depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions which develop charges in the transition state. (3) It was shown that, in the decomposition of **95**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[609] If bond x broke before bond y, there should surely be a secondary isotope effect. This result strongly indicates that the bond breaking of x and y is simultaneous. This is the reverse of a Diels-Alder reaction, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds x and y. Subsequently, a similar experiment was carried out on the forward reaction,[610] and the result was the same. There is also other evidence for mechanism *a*.[611] However, the fact that the mechanism is concerted does not necessarily mean that in the transition state both new σ bonds have been formed to the same extent. It could very well be that one bond has been formed to a greater degree than the other.[612]



95

I: R=H, R′=D
II: R=D, R′=H

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (p. 685) indicate that the diene is behaving as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, though the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels-Alder reactions.[613]

We have emphasized that the Diels-Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of olefins to cyclobutanes (reaction

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[609] Seltzer, *J. Am. Chem. Soc.* **85,** 1360 (1963), **87,** 1534 (1965); for other isotope effect evidence, see Taagepera and Thornton, *J. Am. Chem. Soc.* **94,** 1168 (1972).

[610] Van Sickle and Rodin, *J. Am. Chem. Soc.* **86,** 3091 (1964).

[611] See, for example, Dewar and Pyron, *J. Am. Chem. Soc.* **92,** 3098 (1970); Brun and Jenner, *Tetrahedron* **28,** 3113 (1972); Doering, Franck-Neumann, Hasselmann, and Kaye, *J. Am. Chem. Soc.* **94,** 3833 (1972); McCabe and Eckert, *Acc. Chem. Res.* **7,** 251–257 (1974).

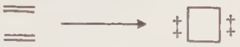
[612] Woodward and Katz, *Tetrahedron* **5,** 70 (1959); Liu and Schmidt, *Tetrahedron* **27,** 5289 (1971); Dewar and Pyron, Ref. 611.

[613] Sauer and Wiest, *Angew. Chem. Int. Ed. Engl.* **1,** 269 (1962) [*Angew. Chem.* **74,** 353]. For another example, see Bradsher and Stone, *J. Org. Chem.* **33,** 519 (1968), **34,** 1700 (1969).

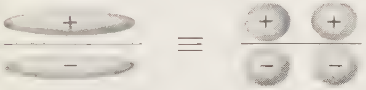
5-52) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*,[614] which predicts that certain reactions are allowed and others forbidden. The orbital-symmetry rules (also called the Woodward-Hoffmann rules) apply *only to concerted reactions*, e.g., mechanism *a*, and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, of which we shall discuss two: the correlation-diagram method and the frontier-orbital method.[615]

The Correlation-Diagram Method[616]

In this method we shall draw a correlation diagram for each reaction, in which the symmetry of the orbitals in the starting compounds will be compared with the symmetry of the orbitals of the products. First let us consider the dimerization of two ethylenes to give cyclobutane.

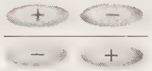


We shall ignore the σ bonds of the ethylenes and the two previously existing σ bonds of the cyclobutane and focus our attention on the two π bonds of the ethylenes and the two newly created σ bonds (marked ‡) in the cyclobutane. We recall (p. 12) that each ethylene has two π orbitals, one bonding and one antibonding. In this book we represent the bonding π orbital as shown on the left (**A**).



A **B**

Bonding orbital



Antibonding orbital

Note that many other books prefer to represent it as in **B**. The two methods of representation

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[614] For monographs, see Woodward and Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, Inc., New York, 1970 [the text of this book also appears in *Angew. Chem. Int. Ed. Engl.* **8,** 781–853 (1969); *Angew. Chem.* **81,** 797–869]. Gilchrist and Storr, "Organic Reactions and Orbital Symmetry," Cambridge University Press, London, 1972; Lehr and Marchand, "Orbital Symmetry," Academic Press, Inc., New York, 1972. For reviews, see, in Klopman, "Chemical Reactivity and Reaction Paths," John Wiley & Sons, Inc., New York, 1974, the articles by Fujimoto and Fukui, pp. 23–54, Klopman, pp. 55–165, Herndon, Feuer, Giles, Otteson, and Silber, pp. 275–299, and Michl, pp. 301–338; Simonetta, *Top. Curr. Chem.* **42,** 1–47 (1973); Houk, *Surv. Prog. Chem.* **6,** 113–208 (1973); Vollmer and Servis, *J. Chem. Educ.* **47,** 491–500 (1970); Gill, *Essays Chem.* **1,** 43–76 (1970), *Q. Rev., Chem. Soc.* **22,** 338–389 (1968); Seebach, *Fortschr. Chem. Forsch.* **11,** 177–215 (1969); Miller, *Adv. Phys. Org. Chem.* **6,** 185–332 (1968); Woodward, in "Aromaticity," Ref. 567, pp. 217–249; Millie, *Bull. Soc. Chim. Fr.* 4031 (1966). For reviews of applications to inorganic chemistry, see Pearson, *Top. Curr. Chem.* **41,** 75–112 (1973), *Chem. Eng. News* **48** (41), 66–72 (Sept. 28, 1970).

[615] For other approaches, see Dewar, *Angew. Chem. Int. Ed. Engl.* **10,** 761–775 (1971) [*Angew. Chem.* **83,** 859–875]; Zimmerman, *Acc. Chem. Res.* **4,** 272–280 (1971); Shen, *J. Chem. Educ.* **50,** 238–242 (1973); Salem, *J. Am. Chem. Soc.* **90,** 543, 553 (1968); Trindle, *J. Am. Chem. Soc.* **92,** 3251, 3255 (1970); Mulder and Oosterhoff, *Chem. Commun.* 305, 307 (1970); Goddard, *J. Am. Chem. Soc.* **92,** 7520 (1970), **94,** 793 (1972); Herndon, *Chem. Rev.* **72,** 157–179 (1972); Perrin, *Chem. Br.* **8,** 163–173 (1972); Langlet and Malrieu, *J. Am. Chem. Soc.* **94,** 7254 (1972); Epiotis, *J. Am. Chem. Soc.* **94,** 1924 (1972), **95,** 1191, 1200, 1206, 1935, 1941, 1946 (1973), *Angew. Chem. Int. Ed. Engl.* **13,** 751–780 (1974) [*Angew. Chem.* **86,** 825–855]; Pearson, *J. Am. Chem. Soc.* **94,** 8287 (1972); Mathieu, *Bull. Soc. Chim. Fr.* 807 (1973); Dewar, Kirschner, and Kollmar, *J. Am. Chem. Soc.* **96,** 5240 (1974); Silver and Karplus, *J. Am. Chem. Soc.* **97,** 2645 (1975); Day, *J. Am. Chem. Soc.* **97,** 2431 (1975); Halevi, *Helv. Chim. Acta* **58,** 2136 (1975); Mok and Nye, *J. Chem. Soc., Perkin Trans 2* 1810 (1975).

[616] Longuet-Higgins and Abrahamson, *J. Am. Chem. Soc.* **87,** 2045 (1965); Hoffmann and Woodward, *J. Am. Chem. Soc.* **87,** 2046 (1965).

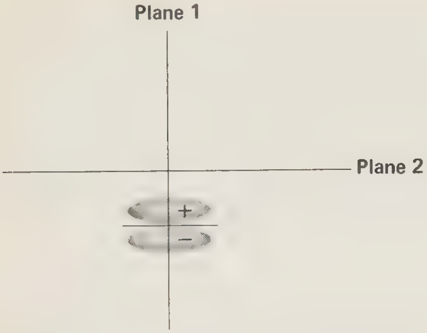
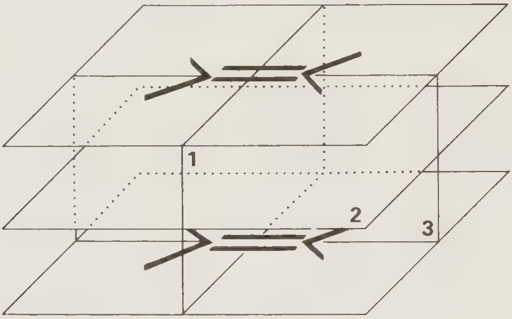


Figure 1 Cross section of the bonding π orbital of a single ethylene molecule.

are completely equivalent. The most probable approach of the two ethylene molecules, in order for a concerted reaction to take place, is in two parallel planes[617]



In this configuration two planes of symmetry, marked 1 and 2 in the diagram, are present throughout the course of the reaction (plane 3 is also a plane of symmetry, but we ignore it because there is nothing to be learned from it). In order to construct a correlation diagram it is necessary to choose molecular orbitals *which are either symmetric or antisymmetric with respect to any plane of symmetry or other symmetry operation which may be present*. A choice of the bonding π orbital of a single ethylene molecule will not fulfill this condition, for the following reason. For an orbital to be symmetric with respect to a plane of symmetry, it must appear on both sides of the plane; and the signs of its lobes must be unchanged. To be antisymmetric with respect to a plane of symmetry, an orbital must also appear on both sides of the plane, but in this case the signs of all its lobes must be changed. It is obvious (Figure 1) that the bonding orbital of a single ethylene molecule is symmetric with respect to plane 1 but neither symmetric nor antisymmetric with respect to plane 2.[617a] Choosing the bonding orbital of the other ethylene molecule will not help either, because its symmetry properties are the same. We can fulfill the condition by examining the *interaction* of the orbitals in the transition state. As the two molecules approach each other, we can imagine the bonding orbital of one overlapping the bonding orbital of the other, to form two new transition-state orbitals which are the *sum* and the *difference* of the two original orbitals, respectively. In taking the sum of two orbitals, we simply merge them together. In taking the difference, we change the signs of one, and then merge them together. Likewise, the two antibonding orbitals interact in a similar fashion. Thus four orbitals arise (present in the transition state only), which can be represented in cross section as follows:

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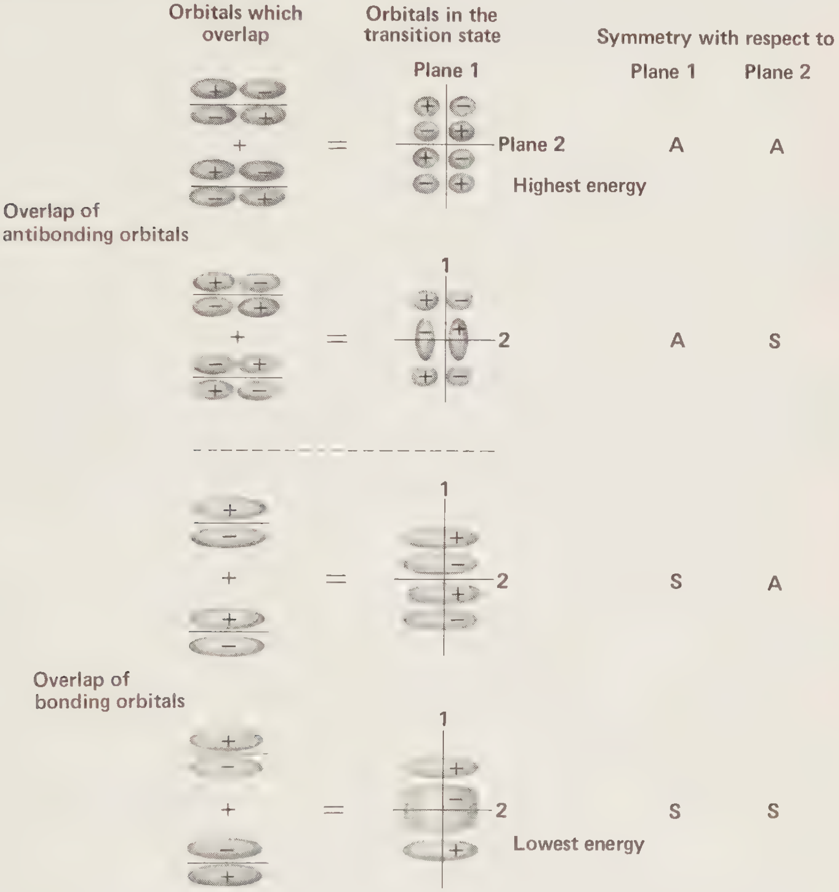
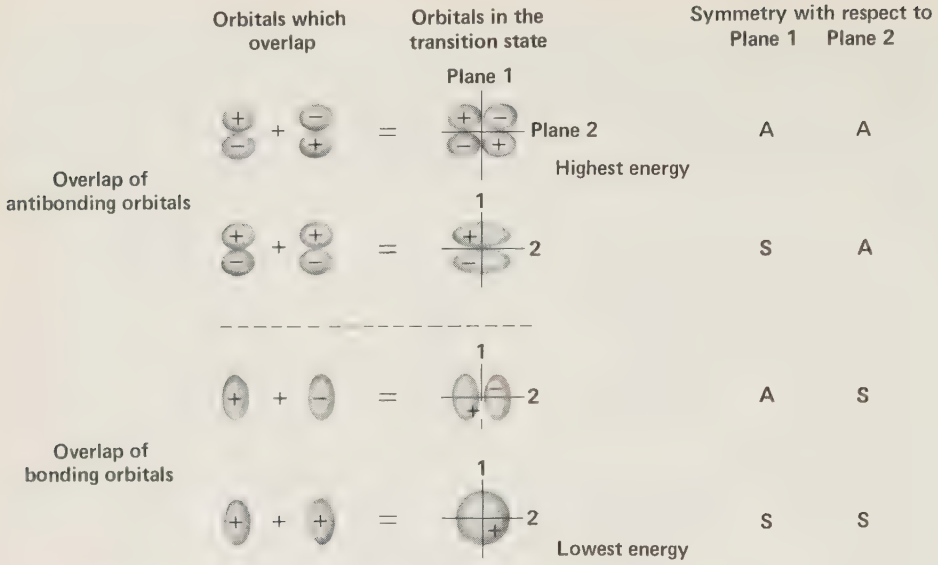
[617] This figure is adapted from Woodward and Hoffmann, Ref. 614.

[617a] The bonding π orbital of a single ethylene molecule is antisymmetric with respect to the plane of its own node, but this is irrelevant to the present case because this plane is not a plane of symmetry throughout the course of the reaction.

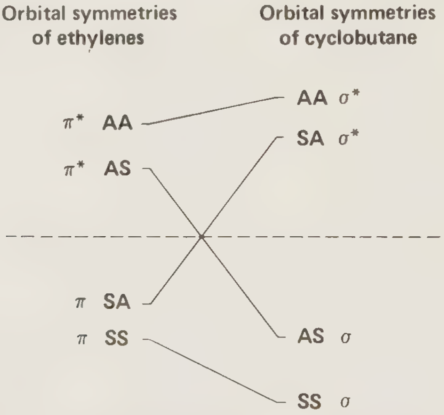

Orbitals which overlap
Orbitals in the transition state
Symmetry with respect to
Plane 1
Plane 2
Plane 1
Plane 2
Highest energy
Overlap of antibonding orbitals
Overlap of bonding orbitals
Lowest energy
1
2
A
S
+
−
=

All four of these transition-state orbitals are either symmetric or antisymmetric with respect to planes 1 and 2 as shown above.

We now consider the two σ bonds (marked ‡) of the product. We may recall (p. 8, Figure 5) that a σ orbital consists of a single lobe, while a σ^* orbital has two lobes, of opposite signs. Once again we examine the interaction of the four orbitals involved (two σ and two σ^* orbitals). We take the sum and the difference of the two σ orbitals and the sum and the difference of the two σ^* orbitals. Note that we have shown the interaction of lowest energy as the sum of two + orbitals. We could just as easily have shown the sum of two − orbitals, which would have been equivalent. The important thing is that it is the sum of orbitals of the same sign.


Orbitals which overlap
Orbitals in the transition state
Symmetry with respect to
Plane 1
Plane 2
Plane 1
Plane 2
Highest energy
Overlap of antibonding orbitals
+
−
=
A
A
1
2
S
A
1
2
A
S
Overlap of bonding orbitals
1
2
S
S
Lowest energy

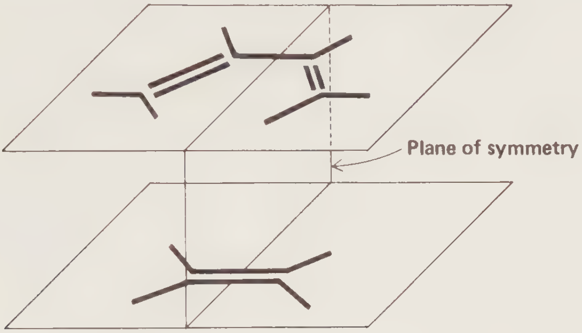
We are now ready to draw a correlation diagram, which correlates the orbitals of the starting compounds (in this case the transition state orbitals) with those of the product.


Orbital symmetries of ethylenes
Orbital symmetries of cyclobutane
π* AA
π* AS
π SA
π SS
AA σ*
SA σ*
AS σ
SS σ

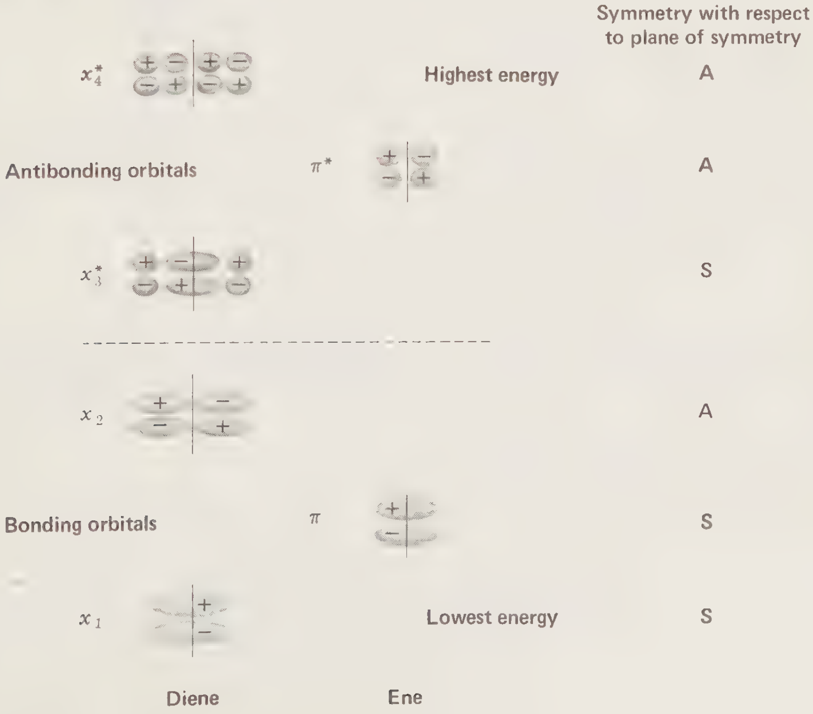
In an uncatalyzed reaction (called *thermal* to distinguish it from a photochemical, or light-induced reaction) the π electrons of the two ethylene molecules are in the bonding π orbitals (the π* orbitals are vacant). The principle of conservation of orbital symmetry says that orbital symmetry must be conserved for the reaction to be allowed. Therefore, the orbitals marked SS and SA in the starting compounds must convert into the orbitals marked SS and SA, respectively, in the product. This is no problem for the SS orbital, which in the product is a bonding orbital. But the SA orbital of the product is antibonding. Thus for the thermal reaction to take place, a bonding orbital *must*, in order to preserve its symmetry, be converted to an antibonding orbital; but the energy involved is unacceptably high, and the reaction is "forbidden." Note that this is true *in either direction*. Although thermal cleavage of cyclobutane to give two ethylene molecules is much more favored by entropy factors than is the reverse reaction, it too is forbidden to proceed by a cyclic mechanism.

However, if the reaction, in either direction, is photochemically induced, *it becomes allowed.* The uv light promotes an electron from a bonding to an antibonding orbital, so that the orbitals marked SS, SA, and AS are all occupied. In this case conversion of starting material to product (in either direction) involves conversion of two bonding and one antibonding orbitals to two bonding and one antibonding orbitals, which, of course, does not involve a prohibitive energy cost.

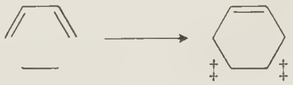
Let us now analyze the Diels-Alder reaction in a similar manner. In this case, approach of the two molecules results in a configuration with only one plane of symmetry,[617]


Plane of symmetry

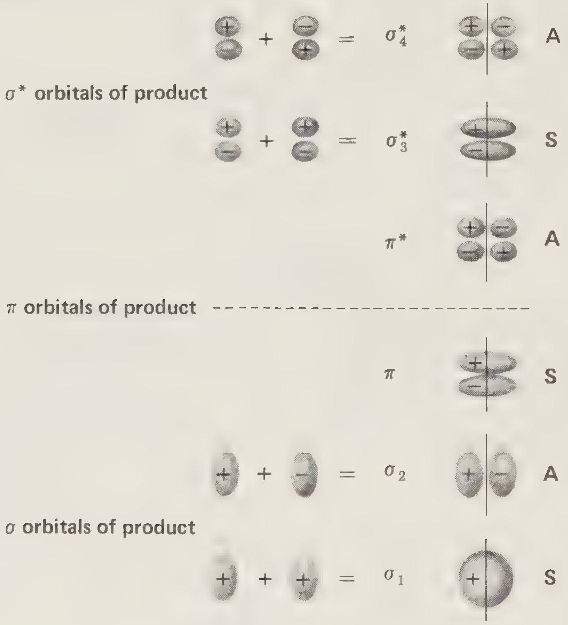
and the orbitals involved are all symmetric or antisymmetric with respect to this plane, so that it is not necessary to consider the interaction of orbitals in the transition state. It will be sufficient to correlate the orbitals of the starting materials with those of the products. The orbitals of the starting compounds can be represented thus (see p. 33) for the orbitals of butadiene):


Symmetry with respect to plane of symmetry
x_4^*
Highest energy
A
Antibonding orbitals
π^*
A
x_3^*
S
x_2
A
Bonding orbitals
π
S
x_1
Lowest energy
S
Diene
Ene

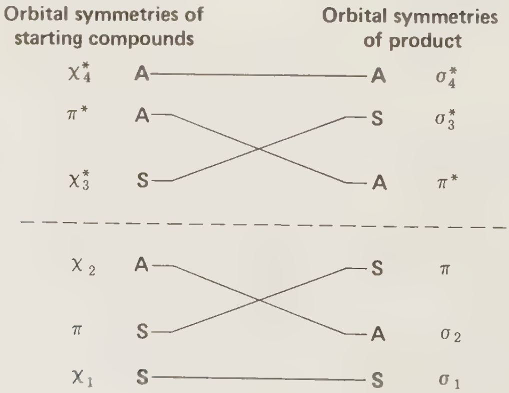
The product in this case is a cyclohexene, and we need consider only the new π bond and the two new σ bonds (marked ‡). The two orbitals of the π bond can be considered individually,



but the four σ orbitals interact as before. The orbitals of the product are therefore


σ* orbitals of product
σ_4^*
A
σ_3^*
S
π^*
A
π orbitals of product
π
S
σ_2
A
σ orbitals of product
σ_1
S

Drawing a correlation diagram as before, we have

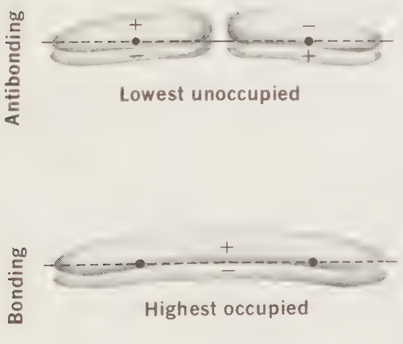

Orbital symmetries of starting compounds
Orbital symmetries of product
χ_4^*
A
A
σ_4^*
π^*
A
S
σ_3^*
χ_3^*
S
A
π^*
χ_2
A
S
π
π
S
A
σ_2
χ_1
S
S
σ_1

Inspection of this correlation diagram shows us that the reaction can proceed by a cyclic transition state, in either direction, without any orbital going from a bonding to an antibonding condition. So the thermal reaction is *allowed*, in either direction. On the other hand, a photochemical reaction would require (for the forward direction) that a χ_3^* orbital convert to a σ_3^* orbital. Although both are antibonding, such a conversion bypasses the π^* orbital of the product and is therefore forbidden.[618] A photochemically induced reverse reaction is also forbidden for a similar reason: the π^* orbital of the cyclohexene would have to correlate with the π^* orbital of the ene component, bypassing the χ_3^* orbital of the diene.

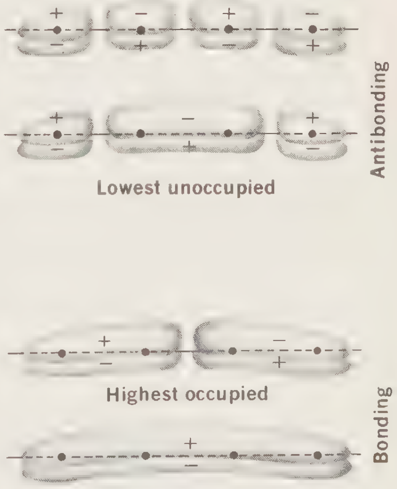
Note that, strictly speaking, the treatment we have given above applies only to cases possessing elements of symmetry and would not, strictly speaking, apply, say, to a reaction between ethylene and propylene to give methylcyclobutane because the presence of the extra methyl group destroys the symmetry of the reactants, transition state, and products. Nevertheless, we may make the reasonable assumption that the presence of substituents causes only small perturbations in the properties of the orbitals and does not greatly affect the reactions. Therefore, the principle of conservation of orbital symmetry covers these cases also. However, in some cases, where the olefin or diene contains hetero atoms (e.g., O=N—C=O) or is part of an aromatic ring, the symmetry of the orbitals involved may be so different that the general rules we have derived do not apply, and correlation diagrams must be individually drawn for each case.[618a]

The Frontier-Orbital Method[619]

As applied to cycloaddition reactions the rule is that *reactions are allowed only when all overlaps between the highest-occupied molecular orbital of one reactant and the lowest-unoccupied molecular orbital of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*. For monoolefins and dienes these orbitals are



π orbitals of an isolated C=C bond



π orbitals of a conjugated diene

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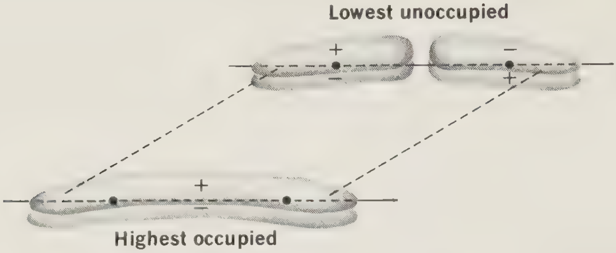
[618] For a discussion, see Epiotis and Yates, *J. Org. Chem.* **39**, 3150 (1974).

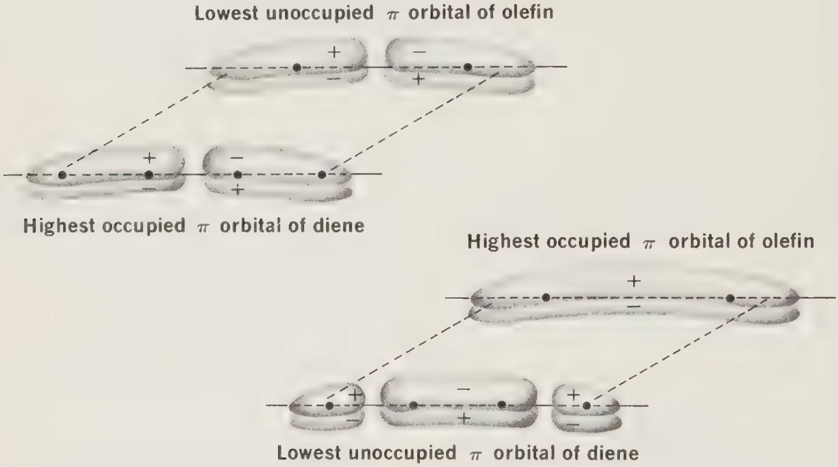
[618a] For a discussion, see Schilling and Snyder, *J. Am. Chem. Soc.* **97**, 4422 (1975).

[619] Fukui and Fujimoto, *Bull. Chem. Soc. Jpn.* **40**, 2018 (1967), **42**, 3399 (1969); Fukui, *Fortschr. Chem. Forsch.* **15**, 1–85 (1970), *Acc. Chem. Res.* **4**, 57–64 (1971); Houk, *Acc. Chem. Res.* **8**, 361–369 (1975).

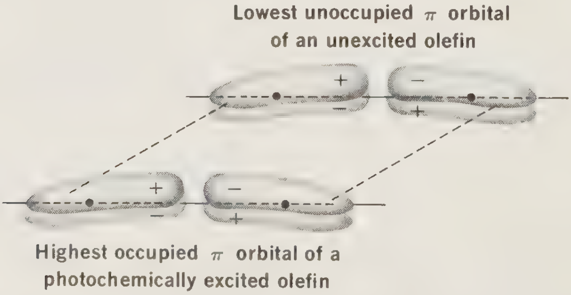
A concerted cyclization of two monoolefins (a 2 + 2 reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe:


Lowest unoccupied
+
−
−
+
+
−
Highest occupied

On the other hand, the Diels-Alder reaction (a 4 + 2 reaction) is allowed, whether considered from either direction:


Lowest unoccupied π orbital of olefin
+
−
−
+
+
−
−
+
Highest occupied π orbital of diene
Highest occupied π orbital of olefin
+
−
+
−
−
+
+
−
Lowest unoccupied π orbital of diene

These considerations are reversed when the ring closures are photochemically induced since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the 2 + 2 reaction is now allowed:

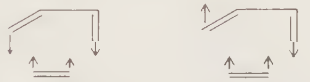

Lowest unoccupied π orbital
of an unexcited olefin
+
−
−
+
+
−
−
+
Highest occupied π orbital of a
photochemically excited olefin

and the 4 + 2 reaction disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, Diels-Alder adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

Thus, the correlation-diagram method and the frontier-orbital method lead to the same conclusions: thermal 2 + 4 cycloadditions and photochemical 2 + 2 cycloadditions (and the reverse ring openings) are allowed, while photochemical 2 + 4 and thermal 2 + 2 ring closings (and openings) are forbidden. Application of the same procedures to other ring closures shows that 4 + 4 and 6 + 2 ring closures and openings require photochemical induction while the 6 + 4 and 8 + 2 reactions can take place only thermally (see reaction **5-55**). In general cycloaddition reactions allowed thermally are those with $4n + 2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions which take place by cyclic mechanisms, i.e., where two σ bonds are formed (or broken) at about the same time. The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal Diels-Alder reaction (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given Diels-Alder reaction proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal 2 + 2 cycloadditions in which the molecules assume the geometry we have pictured above cannot[620] take place by a cyclic mechanism (however, see below). As we shall see (**5-52**), such reactions largely occur by two-step mechanisms. Similarly, 4 + 2 photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism[621] (mechanism *b*[622]).

In all of the above discussion we have assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript s is used to designate this geometry, and a normal Diels-Alder reaction would be called a $[_{\pi}4_s + {}_{\pi}2_s]$ cycloaddition (the subscript π indicates that π electrons are involved in the cycloaddition.) However, we can conceive of another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system; i.e., they point in opposite directions.



Normal Diels-Alder reaction **$[4_s + 2_s]$**

Twisted Diels-Alder reaction **$[4_a + 2_s]$**

This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[_{\pi}4_a + {}_{\pi}2_s]$ cycloaddition (a stands for antarafacial). Formal correlation diagrams cannot be drawn in this case, but we can easily show by the frontier-orbital method that this reaction (and consequently the reverse ring-opening reaction) are thermally forbidden and photochemically allowed. Thus in order for a $[_{\pi}4_a + {}_{\pi}2_s]$ reaction to proceed, overlap between the highest occupied π orbital of the olefin and the lowest unoccupied π orbital of the diene would have to occur as follows, with a + lobe overlapping a − lobe:

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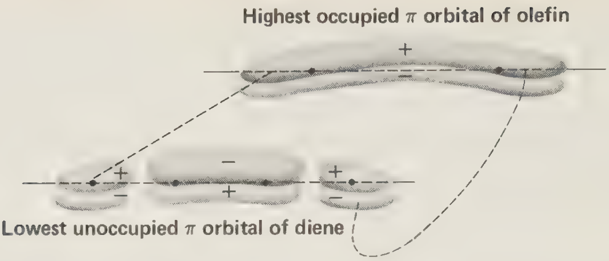
[620] The possibility has been raised that some disallowed reactions may nevertheless proceed by concerted mechanisms: see Schmidt, *Helv. Chim. Acta* **54**, 862 (1971), *Tetrahedron Lett.* 581 (1972); Muszkat and Schmidt, *Helv. Chim. Acta* **54**, 1195 (1971); Baldwin, Andrist, and Pinschmidt, *Acc. Chem. Res.* **5**, 402–406 (1972); Berson, *Acc. Chem. Res.* **5**, 406–414 (1972); Berson and Salem, *J. Am. Chem. Soc.* **94**, 8917 (1972).

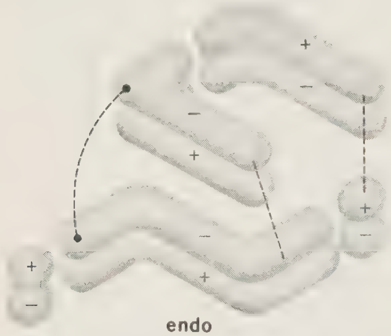
[621] It has been contended that 2 + 2 thermal and 2 + 4 photochemical cycloadditions occur by concerted mechanisms and the observed nonstereospecificity stems from completely concerted processes: Epiotis, *J. Am. Chem. Soc.* **95**, 1191, 1935, 1941 (1972).

[622] For example, see Sieber, Heimgartner, Hansen, and Schmid, *Helv. Chim. Acta* **55**, 3005 (1972). For discussions, see Bartlett, Helgeson, and Wersel, *Pure Appl. Chem.* **16**, 187 200 (1968); Seeley, *J. Am. Chem. Soc.* **94**, 4378 (1972); Kaupp, *Angew. Chem. Int. Ed. Engl.* **11**, 313, 718 (1972) [*Angew. Chem.* **84**, 259, 718].


Highest occupied π orbital of olefin
Lowest unoccupied π orbital of diene

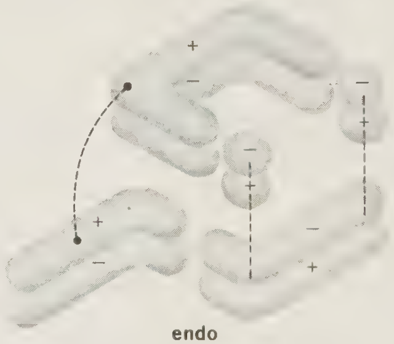
Since like signs are no longer overlapping, the thermal reaction is now forbidden. Similarly, thermal $[_\pi 4_s + {}_\pi 2_a]$ and $[_\pi 2_a + {}_\pi 2_a]$ cyclizations are forbidden, while thermal $[_\pi 4_a + {}_\pi 2_a]$ and $[_\pi 2_s + {}_\pi 2_a]$ cyclizations are allowed, and these considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a 2 + 4 cyclization,[623] but larger ring closures could take place by such a pathway, and 2 + 2 thermal cyclizations, where the $[_\pi 2_s + {}_\pi 2_s]$ pathway is forbidden, can also do so in certain cases (see reaction **5-52**). We therefore see that whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved, since each manner of approach gives rise to different symmetry elements.

Symmetry considerations have also been advanced to explain predominant endo addition.[624] In the case of 4 + 2 addition of butadiene to itself, the approach may be exo or endo:



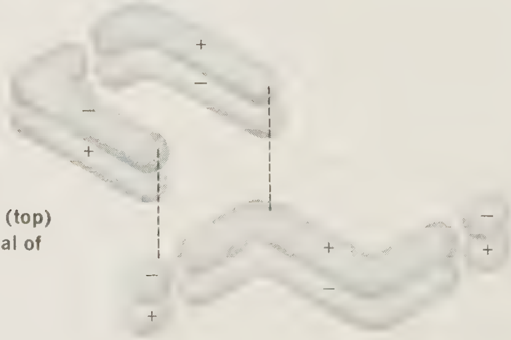
endo

Highest-occupied orbital of diene (top) overlaps lowest-unoccupied orbital of "olefin" (bottom)



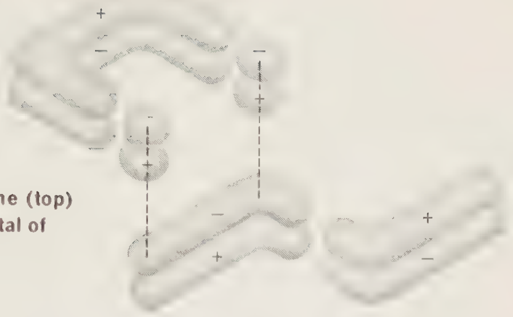
endo

Lowest-unoccupied orbital of diene (top) overlaps highest occupied orbital of "olefin" (bottom)



exo

Highest-occupied orbital of diene (top) overlaps lowest-unoccupied orbital of "olefin" (bottom)



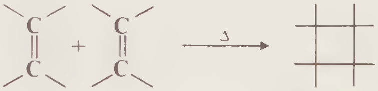
exo

Lowest unoccupied orbital of diene (top) overlaps highest-occupied orbital of "olefin" (bottom)

It can be seen that whether the highest-occupied molecular orbital of the diene overlaps with the lowest-unoccupied molecular orbital of the olefin or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that 6 + 4 cycloaddition is predicted by similar considerations to proceed with predominant exo orientation, and that is what is found.[625] However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional π orbitals, and a number of alternative explanations have also been offered.[626]

OS **II,** 102; **III,** 310, 807; **IV,** 238, 311, 738, 890, 964; **V,** 60, 96, 414, 424, 604, 985, 1037; **50,** 24, 36, 43.

5-52 Dimerization of Olefins



The thermal reaction between two molecules of olefin to give cyclobutane derivatives (a 2 + 2 cycloaddition) can be carried out where the olefins are the same or different, but the reaction is not a general one for olefins.[627] Dimerization of like olefins occurs with the following compounds: $F_2C{=}CX_2$ (X = F or Cl) and certain other fluorinated alkenes, though not $F_2C{=}CH_2$, allenes (to give derivatives of **96**),[628] benzynes [to give biphenylene (**97**) derivatives], activated olefins

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[623] A possible photochemical $[_{\pi}4_s + _{\pi}2_a]$ cycloaddition has been reported: Hart, Miyashi, Buchanan, and Sasson, *J. Am. Chem. Soc.* **96,** 4857 (1974).

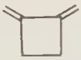
[624] Hoffmann and Woodward, *J. Am. Chem. Soc.* **87,** 4388 (1965). See also Williamson, Hsu, Lacko, and Youn, *J. Am. Chem. Soc.* **91,** 6129 (1969); Cárdenas, *Chem. Commun.* 134 (1970); Seguchi, Sera, and Maruyama, *Tetrahedron Lett.* 1585 (1973).

[625] See for example, Cookson, Drake, Hudec, and Morrison, *Chem. Commun.* 15 (1966); Itô, Fujise, Okuda, and Inoue, *Bull. Chem. Soc. Jpn.* **39,** 1351 (1966); Paquette and Barrett, *J. Am. Chem. Soc.* **88,** 2590 (1966); Paquette, Barrett, and Kuhla, *J. Am. Chem. Soc.* **91,** 3616 (1969); Houk and Woodward, *J. Am. Chem. Soc.* **92,** 4143, 4145 (1970); Jones and Kneen, *J. Chem. Soc., Chem. Commun.* 420 (1973).

[626] See, for example, Houk, *Tetrahedron Lett.* 2621 (1970); Houk and Luskus, *J. Am. Chem. Soc.* **93,** 4606 (1971); Kobuke, Fueno, and Furukawa, *J. Am. Chem. Soc.* **92,** 6548 (1970); Kobuke, Sugimoto, Furukawa, and Fueno, *J. Am. Chem. Soc.* **94,** 3633 (1972); Jacobson, *J. Am. Chem. Soc.* **95,** 2579 (1973); Mellor and Webb, *J. Chem. Soc., Perkin Trans. 2* 17, 26 (1974); Cantello, Mellor, and Webb, *J. Chem. Soc., Perkin Trans. 2* 22 (1974).

[627] For reviews, see Roberts and Sharts, *Org. React.* **12,** 1–56 (1962); Gilchrist and Storr, Ref. 614, pp. 141–191; Beltrame, in Bamford and Tipper, Ref. 1, vol. 9, pp. 131–152; Huisgen, Grashey, and Sauer, in Patai, Ref. 29, pp. 779–802; Wilson and Goldhamer, *J. Chem. Educ.* **40,** 599–603 (1963).

[628] For a review, see Fischer, in Patai, Ref. 29, pp. 1064–1067.



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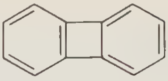

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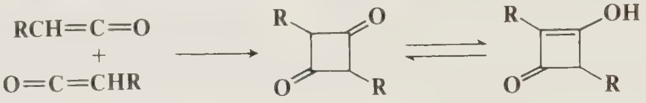
(e.g., styrene, acrylonitrile, butadiene), and certain methylenecyclopropanes.[629] Substituted ketenes dimerize to give cyclobutenone derivatives (**98**) as the major primary products, though ketene



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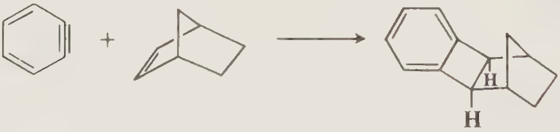
itself dimerizes in a different manner, to give an unsaturated β-lactone (reaction **6-68**).[630]

Different olefins combine as follows:

1. $F_2C{=}CX_2$ (X = F or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many olefins. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels-Alder reactions.[631]

2. Allenes[632] and ketenes[633] react with activated olefins and alkynes. Ketenes give 1,2 addition even with conjugated dienes.[634] Ketenes also add to unactivated olefins if sufficiently long reaction times are used.[635] A synthon for a ketene in this reaction is a ketenimmonium salt $R_2C{=}C{=}NR_2'^{+}\ ZnCl_3^{-}$.[636] The product is readily hydrolyzed (reaction **6-2**) to the same cyclobutanone which would be obtained from the corresponding ketene. Allenes and ketenes also add to each other.[637]

3. Benzynes react with certain olefins,[638] e.g.,



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[629] Dolbier, Lomas, Garza, Harmon, and Tarrant, *Tetrahedron* **28,** 3185 (1972).

[630] Farnum, Johnson, Hess, Marshall, and Webster, *J. Am. Chem. Soc.* **87,** 5191 (1965). For a review, see Hanford and Sauer, *Org. React.* **3,** 127–132 (1946).

[631] Bartlett, Montgomery, and Seidel, *J. Am. Chem. Soc.* **86,** 616 (1964).

[632] For a review of 2 + 2 cycloadditions of allenes, see Baldwin and Fleming, *Fortschr. Chem. Forsch.* **15,** 281–310 (1970).

[633] For reviews of cycloadditions of ketenes, see Brady, *Synthesis* 415–422 (1971); Luknitskii and Vovsi, *Russ. Chem. Rev.* **38,** 487–494 (1969); Ulrich, "Cycloaddition Reactions of Heterocumulenes," pp. 38–121, Academic Press, Inc., New York, 1967; Holder, *J. Chem. Educ.* **53,** 81–85 (1976).

[634] See, for example, Martin, Gott, Goodlett, and Hasek, *J. Org. Chem.* **30,** 4175 (1965); Brady and O'Neal, *J. Org. Chem.* **32,** 2704 (1967); Huisgen and Otto, *Tetrahedron Lett.* 4491 (1968), *Chem. Ber.* **102,** 3475 (1969); Ghosez, Montaigne, Roussel, Vanlierde, and Mollet, *Tetrahedron* **27,** 615 (1971). For indirect methods of the 1,4 addition of the elements of ketene to a diene, see Freeman, Balls, and Brown, *J. Org. Chem.* **33,** 2211 (1968); Corey, Ravindranathan, and Terashima, *J. Am. Chem. Soc.* **93,** 4326 (1971).

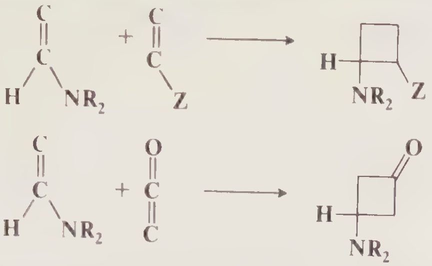
[635] Huisgen and Feiler, *Chem. Ber.* **102,** 3391 (1969); Brady and Patel, *J. Org. Chem.* **38,** 4106 (1973).

[636] Marchand-Brynaert and Ghosez, *J. Am. Chem. Soc.* **94,** 2870 (1972); Sidani, Marchand-Brynaert and Ghosez, *Angew. Chem. Int. Ed. Engl.* **13,** 267 (1974) [*Angew. Chem.* **86,** 272].

[637] Bampfield, Brook, and McDonald, *J. Chem. Soc., Chem. Commun.* 132 (1975); Bertrand, Maurin, Gras, and Gil, *Tetrahedron* **31,** 849 (1975).

[638] Simmons, *J. Am. Chem. Soc.* **83,** 1657 (1961). See also Crews and Beard, *J. Org. Chem.* **38,** 522, 529 (1973). For a review, see Hoffmann, Ref. 589, pp. 200–205.

4. Enamines[639] form four-membered rings with Michael-type olefins[640] and with ketenes.[641] In both cases, only enamines from aldehydes give stable four-membered rings:



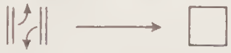
The reaction of enamines with ketenes can conveniently be carried out by generating the ketene in situ from an acyl halide and a tertiary amine. Ynamines react with ketenes to give the corresponding 3-dialkylaminocyclobutenones.[642]

5. Olefins with electron-withdrawing groups may form cyclobutanes with olefins containing electron-donating groups. The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with olefins of the form C=C—A, where A may be OR, SR (enol and thioenol ethers),[643] cyclopropyl,[644] or certain aryl groups.[645]

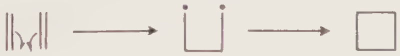
Solvents are not necessary for 2 + 2 cycloadditions. They are usually carried out at 100 to 225°C under pressure, though the reactions in group 5 occur under milder conditions.

The reaction is similar to the Diels-Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, though most olefins react with a diene either entirely by 1,2 or entirely by 1,4 addition. We may propose three mechanisms,[646] analogous to those proposed for the Diels-Alder reaction. Mechanism *a* is a concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical and a diion intermediate. As in reaction 5-51, a diradical intermediate must be a singlet. In searching for ways to tell which mechanism is operating in a given case, we would expect mechanism *c* to be sensitive to changes in solvent

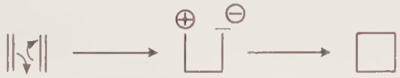
Mechanism *a*



Mechanism *b*



Mechanism *c*



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[639] For reviews of cycloaddition reactions of enamines, see Cook, in Cook, "Enamines," pp. 211–252, Marcel Dekker, Inc., New York, 1969; Szmuszkovicz, *Adv. Org. Chem.* **4,** 1–113 (1963); pp. 39–42.

[640] Brannock, Bell, Burpitt, and Kelly, *J. Org. Chem.* **29,** 801 (1964); Brannock, Bell, Goodlett, and Thweatt, *J. Org. Chem.* **29,** 813 (1964).

[641] Berchtold, Harvey, and Wilson, *J. Org. Chem.* **26,** 4776 (1961); Hasek and Martin, *J. Org. Chem.* **28,** 1468 (1963); Opitz and Kleeman, *Justus Liebigs Ann. Chem.* **665,** 114 (1963); Hasek, Gott, and Martin, *J. Org. Chem.* **31,** 1931 (1966).

[642] Delaunois and Ghosez, *Angew. Chem. Int. Ed. Engl.* **8,** 72 (1969) [*Angew. Chem.* **81,** 36].

[643] Williams, Wiley, and McKusick, *J. Am. Chem. Soc.* **84,** 2210 (1962).

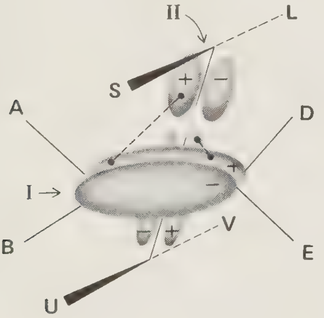
[644] Nishida, Moritani, and Teraji, *J. Org. Chem.* **38,** 1878 (1973).

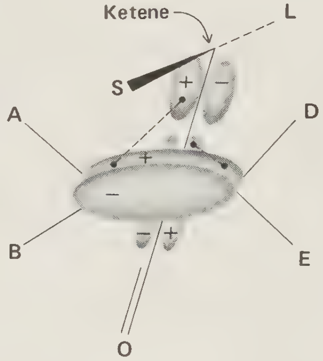
[645] Nagata, Shirota, Nogami, and Mikawa, *Chem. Lett.* 1087 (1973); Shirota, Yoshida, Nogami, and Mikawa, *Chem. Lett.* 1271 (1973).

[646] For a review, see Bartlett, *Q. Rev., Chem. Soc.* **24,** 473–497 (1970).

polarity, while mechanisms *a* and *b* should be insensitive, and we would expect mechanism *a* to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific, though if the second step of these processes takes place very rapidly, before the intermediate diradical or diion has a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations such rapid ring closure might be more likely here than in a $4 + 2$ cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[{}_{\pi}2_{s} + {}_{\pi}2_{s}]$ mechanism is ruled out for most of these substrates by the principle of conservation of orbital symmetry, but a $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ mechanism is allowed (p. 776), and there is much evidence that ketenes and certain other linear molecules in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ cycloaddition the molecules must approach each other in such a way that the + lobe of the highest-occupied π orbital of one molecule (molecule I) overlaps with both + lobes of the lowest unoccupied π orbital of the other (molecule II), even though these lobes are on opposite sides of the nodal plane of molecule II.





The geometry of this approach requires that the groups S and U of molecule II project *into* the plane of molecule I. This has not been found to happen for ordinary alkenes,[647] but if molecule II is a ketene, the group marked U is not present and the $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ reaction can take place. Among the evidence[648] for this mechanism is the following: (1) The reactions are stereospecific.[649] (2) The isomer which forms is the *more hindered one*. Thus methylketene plus cyclopentadiene gave only the endo product (**99**, A = H, R = CH_3).[650] Even more remarkably, when haloalkyl ketenes RXC=C=O were treated with cyclopentadiene, the endo-exo ratio of the product (**99**, **100**, A = halogen) actually *increased* substantially when R was changed from Me to

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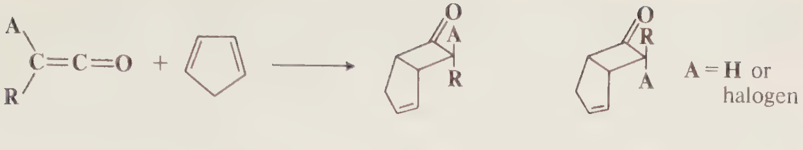
[647] See for example Padwa, Koehn, Masaracchia, Osborn, and Trecker, *J. Am. Chem. Soc.* **93,** 3633 (1971); Bartlett, Cohen, Elliott, Hummel, Minns, Sharts, and Fukunaga, *J. Am. Chem. Soc.* **94,** 2899 (1972).

[648] For other evidence, see Baldwin and Kapecki, *J. Am. Chem. Soc.* **92,** 4874 (1970); (1970); Brook and Griffiths, *Chem. Commun.* 1344 (1970); Frey and Isaacs, *J. Chem. Soc. B* 830 (1970); Egger, *Int. J. Chem. Kinet.* **5,** 285 (1973); Moon and Kolesar, *J. Org. Chem.* **39,** 995 (1974); Isaacs and Hatcher, *J. Chem. Soc., Chem. Commun.* 593 (1974).

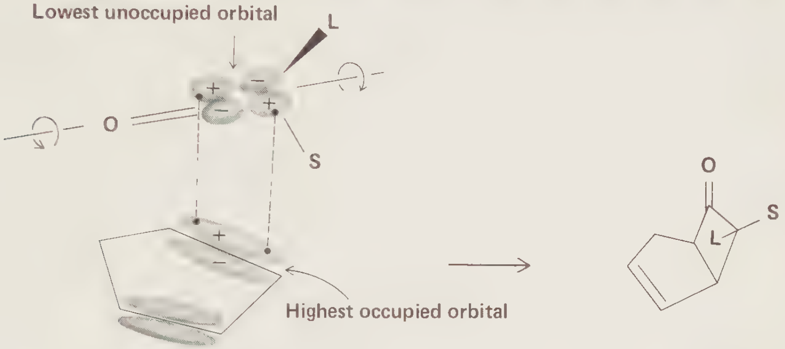
[649] Huisgen, Feiler, and Binsch, *Angew. Chem. Int. Ed. Engl.* **3,** 753 (1964) [*Angew. Chem.* **76,** 892], *Chem. Ber.* **102,** 3460 (1969); Binsch, Feiler, and Huisgen, *Tetrahedron Lett.* 4497 (1968); Martin, Goodlett, and Burpitt, *J. Org. Chem.* **30,** 4309 (1965); Montaigne and Ghosez, *Angew. Chem. Int. Ed. Engl.* **7,** 221 (1968) [*Angew. Chem.* **80,** 194]; Bertrand, Gras, and Gore, *Tetrahedron* **31,** 857 (1975); Marchand-Brynaert and Ghosez, Ref. 636; Huisgen and Mayr, *Tetrahedron Lett.* 2965, 2969 (1975).

[650] Brady, Hoff, Roe, and Parry, *J. Am. Chem. Soc.* **91,** 5679 (1969); Rey, Roberts, Dieffenbacher, and Dreiding, *Helv. Chim. Acta* **53,** 417 (1970). See also Brady, Parry, Roe, and Hoff, *Tetrahedron Lett.* 819 (1970); Brady and Roe, *J. Am. Chem. Soc.* **93,** 1662 (1971); Brady, Parry, and Stockton, *J. Org. Chem.* **36,** 1486 (1971); DoMinh and Strausz, *J. Am. Chem. Soc.* **92,** 1766 (1970); Isaacs and Stanbury, *Chem. Commun.* 1061 (1970); Brook, Harrison, and Duke, *Chem. Commun.* 589 (1970); Dehmlow, *Tetrahedron Lett.* 2573 (1973); Bampfield, Brook, and McDonald, Ref. 637.



endo **99** exo **100**

iso-Pr to *t*-Bu![651] One would expect preferential formation of the exo products (**100**) from $[{}_{\pi}2_{s} + {}_{\pi}2_{s}]$ cycloadditions where the molecules approach each other as in the diagram on p. 768, but a $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group directed toward the olefin) must twist as shown



(L = larger; S = smaller group) in order for the + lobes to interact and this swings the larger group into the endo position.[652] The experimental results in which the amount of endo isomer increases with the increasing size of the R group have been called *masochistic steric effects*, though, as we have seen, they are just what would be expected from a $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ reaction. (3) There is only moderate polar solvent acceleration.[653] (4) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.[654] Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the $[{}_{\pi}2_{s} + {}_{\pi}2_{a}]$ mechanism,[655] but the evidence in these cases is more consistent with the diradical mechanism *b*.[656]

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes. These reactions are generally not stereospecific[657] and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C{=}CFCl$ gives **101** and not **102.** If

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[651] Brady and Roe, *J. Am. Chem. Soc.* **92,** 4618 (1970).

[652] Brook, Harrison, and Duke, Ref. 650.

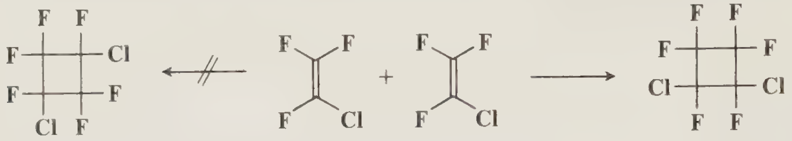
[653] Brady and O'Neal, *J. Org. Chem.* **32,** 612 (1967); Huisgen and Otto, *J. Am. Chem. Soc.* **90,** 5342 (1968); Huisgen, Feiler, and Otto, *Tetrahedron Lett.* 4485 (1968), *Chem. Ber.* **102,** 3444 (1969); Sterk, *Z. Naturforsch., Teil B,* **27,** 143 (1972).

[654] Baldwin and Kapecki, *J. Am. Chem. Soc.* **92,** 4868 (1970); Isaacs and Stanbury, *J. Chem. Soc., Perkin Trans. 2* 166 (1973).

[655] For example, see Kiefer and Okamura, *J. Am. Chem. Soc.* **90,** 4187 (1968); Baldwin and Roy, *Chem. Commun.* 1225 (1969); Moore, Bach, and Ozretich, *J. Am. Chem. Soc.* **91,** 5918 (1969).

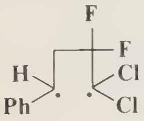
[656] Muscio and Jacobs, *Tetrahedron Lett.* 2867 (1969); Taylor, Warburton, and Wright, *J. Chem. Soc. C* 385 (1971); Taylor and Wright, *J. Chem. Soc. C* 391 (1971); Dai and Dolbier, *J. Am. Chem. Soc.* **94,** 3946 (1972); Duncan, Weyler, and Moore, *Tetrahedron Lett.* 4391 (1973); Roth, Heiber and Erker, *Angew. Chem. Int. Ed. Engl.* **12,** 504 (1973) [*Angew. Chem.* **85,** 511]; Grimme and Rother, *Angew. Chem. Int. Ed. Engl.* **12,** 505 (1973) [*Angew. Chem.* **85,** 512]; Levek and Kiefer, *J. Am. Chem. Soc.* **98,** 1875 (1976).

[657] Montgomery, Schueller, and Bartlett, *J. Am. Chem. Soc.* **86,** 621 (1964); Bartlett, Hummel, Elliott, and Minns, *J. Am. Chem. Soc.* **94,** 2898 (1972).



102 **101**

one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other. Still more evidence is that when unsymmetrical olefins couple, the orientation of the product can almost always be predicted on the basis of the relative stability of the radicals; e.g., styrene and $F_2C{=}CCl_2$ can give four intermediates (**103** to **106**). On the basis of radical stability, **105** and **106** can be ruled out, since in **103** and **104**



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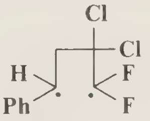

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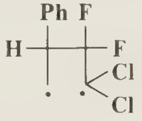

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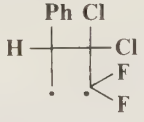

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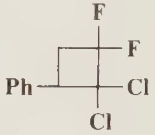

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there is resonance of an unpaired electron with a phenyl group. **103** is more likely than **104,** since a dichloromethyl type of radical should be more stable than a difluoromethyl type. In accord with this prediction, the product is actually **107.**[658] Similarly, for an unsymmetrical diene, it is possible to predict which double bond will be attacked on the basis of which radical is more stable.[631]

The diion mechanism[659] *c* has been reported for at least some of the reactions in categories 4 and 5.[660] For example, the rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether was strongly influenced by changes in solvent polarity.[661] Some of these reactions are nonstereospecific, but others are stereospecific.[662] As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups[663] and that it is possible to trap the diionic intermediates.[664]

[658] Silversmith, Kitahara, Caserio, and Roberts, *J. Am. Chem. Soc.* **80,** 5840 (1958).

[659] For a review of cycloadditions with polar intermediates, see Gompper, *Angew. Chem. Int. Ed. Engl.* **8,** 312–327 (1969) [*Angew. Chem.* **81,** 348–363].

[660] The reactions of ketenes with enamines and ynamines are apparently not concerted but take place by the diionic mechanism: Otto, Feiler, and Huisgen, *Angew. Chem. Int. Ed. Engl.* **7,** 737 (1968) [*Angew. Chem.* **80,** 759]; Ref. 642.

[661] Proskow, Simmons, and Cairns, *J. Am. Chem. Soc.* **88,** 5254 (1966). See also Steiner and Huisgen, *Tetrahedron Lett.* 3769 (1973), *J. Am. Chem. Soc.* **95,** 5056 (1973).

[662] Proskow, Simmons, and Cairns, Ref. 661; Huisgen and Steiner, *J. Am. Chem. Soc.* **95,** 5054, 5055 (1973).

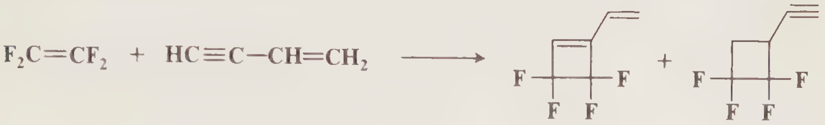
[663] Huisgen and Steiner, *Tetrahedron Lett.* 3763 (1973).

[664] Huisgen, Schug, and Steiner, *Angew. Chem. Int. Ed. Engl.* **13,** 80, 81 (1974) [*Angew. Chem.* **86,** 47, 48]. For additional evidence see Fleischmann and Kelm, *Tetrahedron Lett.* 3773 (1973); Ref. 646.

The reactions with benzynes are nonstereospecific,[665] ruling out a concerted mechanism, but there is doubt whether diradicals or diions are involved.[666]

Thermal cleavage of cyclobutanes[667] to give two olefin molecules (the reverse of 2 + 2 cycloaddition) operates by the diradical mechanism, and the $[{}_\sigma 2_s + {}_\sigma 2_a]$ pathway has not been found[668] (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds; e.g.,



About equal amounts

The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed except where these rearrange before they can be isolated (see reaction **5-54**).[669]

Although thermal 2 + 2 cycloaddition reactions are essentially limited to the cases described above, many (though by no means all) double-bond compounds undergo such reactions *when photochemically excited* (either directly or by a photosensitizer—see p. 218) even if they are not in the above categories.[670] Simple alkenes absorb in the far uv (p. 212), which is difficult to reach experimentally, though this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes[671] (especially to strained compounds such as cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,[672] α,β-unsaturated ketones,[673] acids or acid derivatives, or quinones, since these compounds, because they are conjugated, absorb at longer wavelengths (p. 211). Both dimerizations and mixed additions are common, some examples being (see also the example on p. 222)

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[665] Tabushi, Oda, and Okazaki, *Tetrahedron Lett.* 3743 (1968); Jones and Levin, *Tetrahedron Lett.* 5593 (1968), *J. Am. Chem. Soc.* **91,** 6411 (1969); Wasserman, Solodar, and Keller, *Tetrahedron Lett.* 5597 (1968); Friedman, Osiewicz, and Rabideau, *Tetrahedron Lett.* 5735 (1968).

[666] See Gassman and Benecke, *Tetrahedron Lett.* 1089 (1969); Tabushi, Okazaki, and Oda, *Tetrahedron* **25,** 4401 (1969); Ahlgren and Åkermark, *Tetrahedron Lett.* 3047 (1970); Ref. 665.

[667] See Frey, *Adv. Phys. Org. Chem.* **4,** 147–193 (1966), pp. 170–175, 180–183.

[668] See, for example, Cocks, Frey, and Stevens, *Chem. Commun.* 458 (1969); Srinivasan and Hsu, *J. Chem. Soc., Chem. Commun.* 1213 (1972); Paquette and Kukla, *Tetrahedron Lett.* 1241 (1973). See however, Cant, Coxon, and Hartshorn, *Aust. J. Chem.* **28,** 391 (1975).

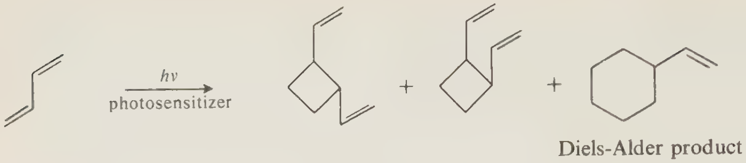
[669] For a review of these cases, and of cycloadditions of triple bonds to double bonds, see Fuks and Viehe, in Viehe, Ref. 70, pp. 435–442.

[670] For reviews, see Kricka and Ledwith, *Synthesis* 539–549 (1974); Herndon, *Top. Curr. Chem.* **46,** 141–179 (1974); Sammes, *Q. Rev., Chem. Soc.* **24,** 37–68 (1970), pp. 46–55; Crowley and Mazzocchi, in Zabicky, Ref. 111, pp. 297–316; Scharf, *Fortschr. Chem. Forsch.* **11,** 216–244 (1969); Steinmetz, *Fortschr. Chem. Forsch.* **7,** 445–527 (1967); Warrener and Bremner, *Rev. Pure Appl. Chem.* **16,** 117–173 (1966), pp. 122–128; Turro, Dalton, and Weiss, *Org. Photochem.* **2,** 1–62 (1969); Trecker, *Org. Photochem.* **2,** 63–116 (1969); Fonken, *Org. Photochem.* **1,** 197–246 (1967); Chapman and Lenz, *Org. Photochem.* **1,** 283–321 (1967); Schönberg, Ref. 41, pp. 70–96, 109–117; Neckers, "Mechanistic Organic Photochemistry," pp. 98–130, 138–148, Reinhold Publishing Corporation, New York, 1967; Kan, "Organic Photochemistry," pp. 155–198, McGraw-Hill Book Company, New York, 1966; Turro, "Molecular Photochemistry," pp. 196–208, 212–220, W. A. Benjamin, Inc., New York, 1965.

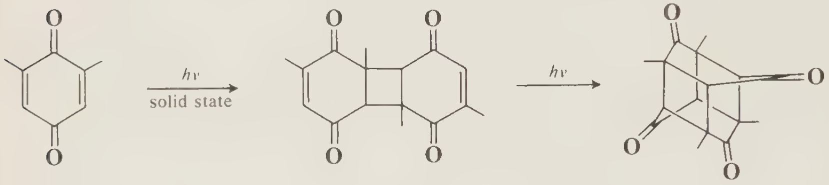
[671] For examples of nonphotosensitized dimerization of simple alkenes, see Arnold and Abraitys, *Chem. Commun.* 1053 (1967); Yamazaki and Cvetanović, *J. Am. Chem. Soc.* **91,** 520 (1969).

[672] For a review, see Dilling, *Chem. Rev.* **69,** 845–877 (1969).

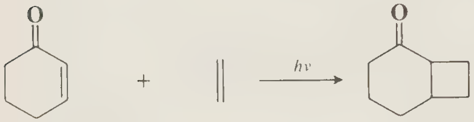
[673] For reviews, see Margaretha, *Chimia* 203–209 (1975); Bauslaugh, *Synthesis* 287–300 (1970); Eaton, *Acc. Chem. Res.* **1,** 50–57 (1968).


hν
photosensitizer
+
+
Diels-Alder product

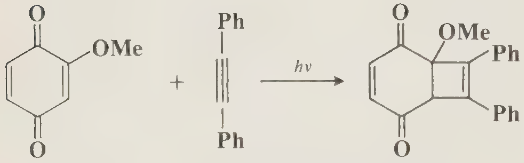
Ref. 674


O
O
hν
solid state
O
O
O
O
hν
O
O
O
O

Ref. 675

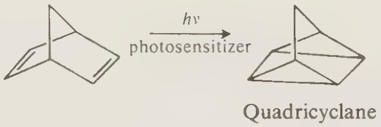


Ref. 676

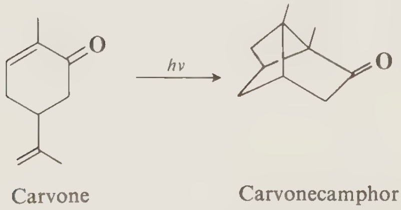

O
OMe
O
+
Ph
Ph
hν
O
OMe
Ph
Ph
O

Ref. 677

Photochemical 2 + 2 cycloadditions can also take place intramolecularly if a molecule has two double bonds which are properly oriented.[678] The cyclization of the quinone dimer shown above is one example. Other examples are


hν
photosensitizer
Quadricyclane

Ref. 679


O
hν
O
Carvone
Carvonecamphor

Ref. 680

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[674] Hammond, Turro, and Fischer, *J. Am. Chem. Soc.* **83,** 4674 (1961); Hammond, Turro, and Liu, *J. Org. Chem.* **28,** 3297 (1963); Liu, Turro, and Hammond, *J. Am. Chem. Soc.* **87,** 3406 (1965); Cundall and Griffiths, *Trans. Faraday Soc.* **61,** 1968 (1965); DeBoer, Turro, and Hammond, *Org. Synth.* **V,** 528.

[675] Cookson, Cox, and Hudec, *J. Chem. Soc.* 4499 (1961).

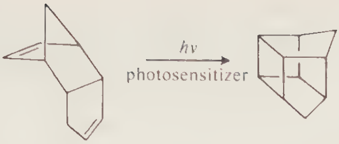
[676] Owsley and Bloomfield, *J. Chem. Soc. C* 3445 (1971). See also Corey, Bass, LeMathieu, and Mitra, *J. Am. Chem. Soc.* **86,** 5570 (1964).

[677] Pappas and Pappas, *Tetrahedron Lett.* 1597 (1967).

[678] For reviews, see Prinzbach, *Pure Appl. Chem.* **16,** 17–46 (1968); Dilling, *Chem. Rev.* **66,** 373–393 (1966).

[679] Hammond, Turro, and Fischer, Ref. 674; Dauben and Cargill, *Tetrahedron* **15,** 197 (1961). See also Cristol and Snell, *J. Am. Chem. Soc.* **80,** 1950 (1958).

[680] Ciamician and Silber, *Ber.* **41,** 1928 (1908); Büchi and Goldman, *J. Am. Chem. Soc.* **79,** 4741 (1957).



Ref. 681

It is obvious that many molecules can be constructed in this way which would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases polymeric or other side products are obtained instead of the desired product.

It is possible that some of these photochemical cycloadditions take place by a $[_{\pi}2_s + {_{\pi}2_s}]$ mechanism (which is of course allowed by orbital symmetry); when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state.[682] The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,[683] making it likely that the $[_{\pi}2_s + {_{\pi}2_s}]$ mechanism is operating in these reactions. However, in most cases it is a triplet excited state which reacts with the ground-state molecule, and in these cases the diradical (or in certain cases the diionic) mechanism is taking place. Photosensitized $2\pi + 2\pi$ cycloadditions almost always involve the triplet state and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state (which is of course a singlet). Thus, in order to conserve spin,[684] the initially formed diradical must be a triplet; i.e., the two electrons must have the same spin. Consequently the second, or ring-closing, step of the mechanism cannot take place at once, because a new bond cannot form from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. We would therefore predict nonstereospecificity, and that is what is found.[685] At least some 2 + 2 photocycloadditions take place by way of exciplex intermediates[686] [an *exciplex* is an excited EDA complex (p. 79) which is dissociated in the ground state; in this case one double bond is the donor and the other the acceptor].

Many 2 + 2 photochemical cycloadditions are neither stereospecific nor regiospecific, though others display one or both of these characteristics. However, dimerizations which occur in the solid state are almost always both regiospecific and stereospecific. Since molecules in the solid state have no freedom, the only reactions which can occur are those where only a minimum of atomic or molecular motion is required. Only the electrons can move much. The dimerization of olefins is well suited to these limitations. In the solid state, closely related compounds may react quite differently. For example, $PhCH{=}CH{-}CH{=}C(COOH)_2$ gives a dimer where the two molecules are connected at the γ and δ positions, while $PhCH{=}CH{-}CH{=}CHCOOH$ gives a dimer where one molecule is connected by its α and β positions and the other by its γ and δ positions.[687] This result is found because the molecules are stacked differently in the lattice and

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[681] Schenck and Steinmetz, *Chem. Ber.* **96**, 520 (1963).

[682] We have previously seen (p. 220) that reactions between two excited molecules are extremely rare.

[683] Yamazaki and Cvetanović, Ref. 671. For another likely example, see Lewis, Hoyle, and Johnson, *J. Am. Chem. Soc.* **97**, 3267 (1975).

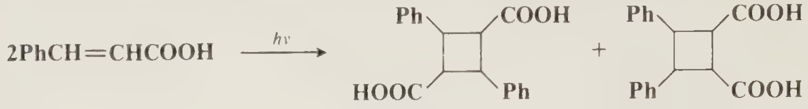
[684] This is an example of the Wigner spin conservation rule (p. 218). Note that spin conservation is something entirely different from symmetry conservation.

[685] See for example Liu and Hammond, *J. Am. Chem. Soc.* **89**, 4936 (1967); Kramer and Bartlett, *J. Am. Chem. Soc.* **94**, 3934 (1972).

[686] See for example Farid, Doty, and Williams, *J. Chem. Soc., Chem. Commun.* 711 (1972); Mizuno, Pac, and Sakurai, *J. Am. Chem. Soc.* **96**, 2993 (1974); Caldwell and Smith, *J. Am. Chem. Soc.* **96**, 2994 (1974); Creed and Caldwell, *J. Am. Chem. Soc.* **96**, 7369 (1974).

[687] Cohen and Schmidt, *J. Chem. Soc.* 1996 (1964).

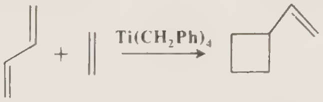
the principle of minimum motion is followed. A given compound may react one way in the solid phase and another way in freer phases. For example, the dimerization of *trans*-cinnamic acid



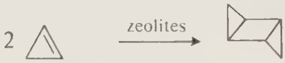
Truxillic acids Truxinic acids

occurs *only* in the solid state. Also different crystalline modifications of a compound may react differently, since the stacking is not the same. *trans*-Cinnamic acid supplies an example here too, since it is different crystalline forms which give rise to truxillic acid on the one hand and truxinic acid on the other (there are several stereoisomers of both truxillic and truxinic acid, but each crystalline form of *trans*-cinnamic acid produces just one stereoisomer). The study of reactions in the solid state is called *topochemistry*.[688]

It has been found that certain 2 + 2 cycloadditions which do not occur thermally can be made to take place without photochemical initiation by the use of certain catalysts, usually transition-metal compounds.[689] Examples are:



Ref. 690



Ref. 691

Among the catalysts used are Lewis acids[692] and phosphine-nickel complexes.[693] Certain of the reverse cyclobutane ring openings can also be catalytically induced (reaction **8-42**). The role of the catalyst is not certain and may well be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or σ bonds of the substrate.[694] In such a case the reaction would of course be a concerted $2_s + 2_s$ process. However, it is also possible that the catalysts cause the reactions to take place by nonconcerted mechanisms.[695] Evidence that the latter pathway has been followed in at least one case is the isolation of a metal-carbon σ-bonded intermediate in the dimerization of norbornadiene, catalyzed by iridium complexes.[696] Photodimerizations of olefins are catalyzed by copper(I) triflate.[697]

[688] Cohen, Hirschberg, and Schmidt, *J. Chem. Soc.* 2060 (1964), and seven preceding papers. For reviews of topochemistry, see Cohen, *Angew. Chem. Int. Ed. Engl.* **14**, 386–393 (1975) [*Angew. Chem.* **87**, 439–447 (1974)], *Pure Appl. Chem.* **9**, 567–574 (1965); Cohen and Green, *Chem. Br.* **9**, 490–497 (1973); Schmidt, *Pure. Appl. Chem.* **27**, 647–678 (1971).

[689] For a review, see Kricka and Ledwith, Ref. 670.

[690] Cannell, *J. Am. Chem. Soc.* **94**, 6867 (1972).

[691] Schipperijn and Lukas, *Tetrahedron Lett.* 231 (1972).

[692] West and Kwitowski, *J. Am. Chem. Soc.* **90**, 4697 (1968).

[693] See for example, Hoover and Lindsey, *J. Org. Chem.* **34**, 3051 (1969); Noyori, Ishigami, Hayashi, and Takaya, *J. Am. Chem. Soc.* **95**, 1674 (1973); Yoshikawa, Aoki, Kiji, and Furukawa, *Tetrahedron* **30**, 405 (1974).

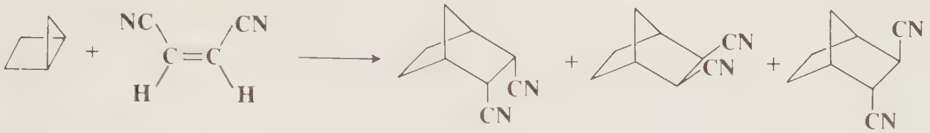
[694] For discussions, see Labunskaya, Shebaldova, and Khidekel', *Russ. Chem. Rev.* **43**, 1–16 (1974); Mango, *Top. Curr. Chem.* **45**, 39–91 (1974), *Tetrahedron Lett.* 1509 (1973), *Intra-Sci. Chem. Rep.* **6** (3), 171–187 (1972), *Chem. Technol.* **1**, 758–765 (1971), *Adv. Catal.* **20**, 291–325 (1969); Mango and Schachtschneider, *J. Am. Chem. Soc.* **93**, 1123 (1971), **91**, 2484 (1969); van der Lugt, *Tetrahedron Lett.* 2281 (1970); Wristers, Brener, and Pettit, *J. Am. Chem. Soc.* **92**, 7499 (1970).

[695] See for example Cassar and Halpern, *Chem. Commun.* 1082 (1970).

[696] Fraser, Bird, Bezman, Shapley, White, and Osborn, *J. Am. Chem. Soc.* **95**, 597 (1973).

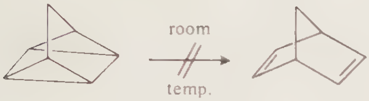
[697] Salomon and Kochi, *J. Am. Chem. Soc.* **96**, 1137 (1974); Salomon, Folting, Streib, and Kochi, *J. Am. Chem. Soc.* **96**, 1145 (1974).

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne[698] bearing electron-withdrawing groups.[699] These reactions are ${}_{\pi}2 + {}_{\sigma}2$ cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes[700] and bicyclo[2.1.0]pentanes.

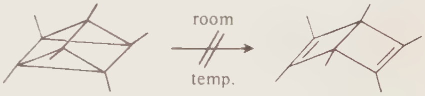


For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.[701] The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism. Photochemical[702] and metal-catalyzed[703] ${}_{\pi}2 + {}_{\sigma}2$ cycloadditions have also been reported.

In reaction **5-51** we used the principle of conservation of orbital symmetry to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable though highly strained. For example, quadricyclane and hexamethylprismane[704] are thermodynamically much less stable (because much more strained) than their corresponding isomeric dienes, norbornadiene and hexamethylbicyclo[2.2.0]hexadiene (**108**).[705] Yet the former two compounds can be kept indefinitely at room temperature, although



Quadricyclane Norbornadiene



108

Hexamethylprismane (A Dewar benzene)

in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over, to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a ${}_{\sigma}2 + {}_{\sigma}2$ process) and, as we have seen, a thermal process of this sort is forbidden by the Woodward-Hoffmann rules. The process is allowed photochemically, and we are not surprised to find that both quadricyclane and hexamethylprismane can be photochemically converted to the respective dienes at room temperature or below.[706] It is also possible to conceive of simple bond rearrange-

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[698] Gassman and Mansfield, *J. Am. Chem. Soc.* **90,** 1517, 1524 (1968).

[699] For a review, see Gassman, *Acc. Chem. Res.* **4,** 128–136 (1971).

[700] Cairncross and Blanchard, *J. Am. Chem. Soc.* **88,** 496 (1966).

[701] Gassman, Mansfield, and Murphy, *J. Am. Chem. Soc.* **91,** 1684 (1969).

[702] Freeman and Balls, *J. Org. Chem.* **32,** 2354 (1967); Wiskott and Schleyer, *Angew. Chem. Int. Ed. Engl.* **6,** 694 (1967) [*Angew. Chem.* **79,** 680]; Prinzbach and Eberbach, *Chem. Ber.* **101,** 4083 (1968); Prinzbach and Klaus, *Angew. Chem. Int. Ed. Engl.* **8,** 276 (1969) [*Angew. Chem.* **81,** 289].

[703] See for example, Volger, Hogeveen, and Gaasbeek, *J. Am. Chem. Soc.* **91,** 218 (1969); Katz and Cerefice, *J. Am. Chem. Soc.* **91,** 2405, 6519 (1969).

[704] This compound can be prepared by photolysis of **108,** another example of an intramolecular photochemical 2 + 2 cycloaddition: Lemal and Lokensgard, *J. Am. Chem. Soc.* **88,** 5934 (1966); Schäfer, Criegee, Askani, and Grüner, *Angew. Chem. Int. Ed. Engl.* **6,** 78 (1967) [*Angew. Chem.* **79,** 54].

[705] For a review of this compound, see Schäfer and Hellmann, *Angew. Chem. Int. Ed. Engl.* **6,** 518–525 (1967) [*Angew. Chem.* **79,** 566–573].

[706] These conversions can also be carried out by the use of transition methyl catalysts: Hogeveen and Volger, *Chem. Commun.* 1133 (1967), *J. Am. Chem. Soc.* **89,** 2486 (1967); Kaiser, Childs, and Maitlis, *J. Am. Chem. Soc.* **93,** 1270 (1971); Ref. 695.

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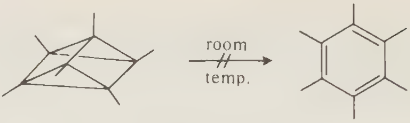
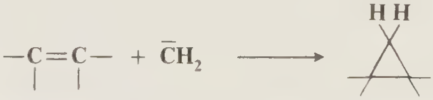


ments whereby hexamethylprismane is converted to hexamethylbenzene, which of course is far more stable than either hexamethylprismane or **108.** It has been calculated that hexamethylbenzene is at least 90 kcal/mol more stable than hexamethylprismane. The fact that hexamethylprismane does not spontaneously undergo this reaction has prompted the observation[707] that the prismane has "the aspect of an angry tiger unable to break out of a paper cage." However, a correlation diagram for this reaction[707] discloses that it too is a symmetry-forbidden process. All three of these "forbidden" reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.[708]

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[709] These compounds actually have the structures which in the nineteenth century were proposed for benzenes. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula.[710] On p. 29 it was mentioned that Dewar formulas are canonical forms (though not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS **V,** 54, 235, 277, 297, 370, 393, 424, 459, 528; **51,** 133; **53,** 30; **55,** 43. For the reverse reaction, see OS **V,** 734.

5-53 The Addition of Carbenes and Carbenoids to Double and Triple Bonds



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives (2 + 1 cycloaddition).[711] Many derivatives of carbene, e.g., PhCH, ROCH,[712] $Me_2C{=}C$, $C(CN)_2$, have been added to double bonds, but the reaction is most often performed with CH_2 itself, with halo and dihalocarbenes,[713] and with carbalkoxycarbenes[714] (generated from diazoacetic esters). Alkylcarbenes HCR have been added to olefins,[715] but more often these rearrange to give olefins (p. 183). The carbene can be generated in any of the ways normally used (p. 181). However, not all reactions in which a cyclopropane is formed by treatment of an olefin with a carbene "precursor" actually involve free carbene intermediates. In some cases, e.g., the Simmons-Smith procedure, p. 793, it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (p. 182) is actually involved.

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[707] Woodward and Hoffmann, Ref. 614, pp. 107–112.

[708] See for example, Oth, *Recl. Trav. Chim. Pays-Bas* **87,** 1185 (1968).

[709] For reviews of valence isomers of benzene, see van Tamelen, *Acc. Chem. Res.* **5,** 186–192 (1972), *Angew. Chem. Int. Ed. Engl.* **4,** 738–745 (1965) [*Angew. Chem.* **77,** 759–767]; Bolesov, *Russ. Chem. Rev.* **37,** 666–670 (1968); Viehe, *Angew. Chem. Int. Ed. Engl.* **4,** 746–751 (1965) [*Angew. Chem.* **77,** 768–773]; Ref. 705.

[710] Because of this, bicyclo[2.2.0]hexadiene is often called Dewar benzene.

[711] For reviews, see Bethell, in McManus, "Organic Reactive Intermediates," pp. 101–113, Academic Press, Inc., New York, 1973; in Patai, Ref. 29, the articles by Cadogan and Perkins, pp. 633–671 and Huisgen, Grashey, and Sauer, pp. 755–776; Kirmse, "Carbene Chemistry," 2d ed., pp. 85–122, 267–406, Academic Press, Inc., New York, 1971, *Angew. Chem.* **73,** 161–166 (1961); Hine, "Divalent Carbon," especially pp. 20–28, 42–44, 55–60, 73–78, 122–130, The Ronald Press Company, New York, 1964.

[712] For a review, see Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **7,** 588–598 (1968) [*Angew. Chem.* **80,** 603–613].

[713] For a review of the addition of halocarbenes, see Parham and Schweizer, *Org. React.* **13,** 55–90 (1963).

[714] For a review, see Dave and Warnhoff, *Org. React.* **18,** 217–401 (1970).

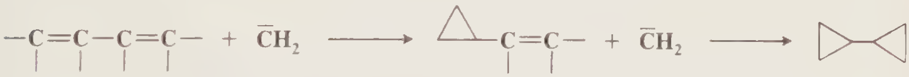
[715] For example, see Frey, *J. Chem. Soc.* 2293 (1962).

Carbene itself is extremely reactive and gives many side reactions, especially insertion reactions (**2-18**), which greatly reduce yields.[716] When it is desired to add CH_2 for preparative purposes, free carbene is not used, but the Simmons-Smith procedure or some other method which does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere. The order of reactivity is $CH_2 > CHCl > CCl_2 > CBr_2 > CF_2$. A few of the many ways[717] in which halocarbenes or carbenoids are generated for this reaction are the following,[718] most of which involve formal α elimination (the first two steps of the SN1cB mechanism, p. 330):

$$\begin{array}{rcll}
CH_2Cl_2 + RLi & \longrightarrow & CHCl & \\
N_2CHBr & \xrightarrow{h\nu} & CHBr & \\
CHCl_3 + OH^- & \longrightarrow & CCl_2 & \\
CHCl_3 + LiOCEt_3 & \longrightarrow & CCl_2 & \text{(Ref. 719)} \\
PhHgCCl_2Br & \xrightarrow{\Delta} & CCl_2 & \text{(Ref. 720)} \\
PhHgCBr_3 & \xrightarrow{80^\circ C} & CBr_2 & \text{(Ref. 720)} \\
Me_3SnCF_3 + NaI & \longrightarrow & CF_2 & \text{(Ref. 721)} \\
CHBr_2F + RLi & \longrightarrow & CFBr & \text{(Ref. 721)}
\end{array}$$

It has been shown that the reaction between $PhCHCl_2$ and *t*-BuOK produces a carbenoid but when the reaction is run in the presence of a crown ether (p. 82), the free PhCCl is formed instead.[722] This is therefore a method for generating a free carbene.[723] Dihalocyclopropanes are very useful compounds[724] which can be reduced to cyclopropanes, treated with magnesium or sodium to give allenes (reaction **8-3**), or converted to a number of other products.

Olefins of all types can be converted to cyclopropane derivatives by this reaction. Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[725] Conjugated dienes give 1,2 addition:[726]



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[716] For a review of additions of CH_2, see Bell, *Prog. Phys. Org. Chem.* **2**, 1–61 (1964), pp. 8–27, 43–45.

[717] Much of the work in this field has been carried out by Seyferth and coworkers; see, for example, Seyferth, Burlitch, Minasz, Mui, Simmons, Treiber, and Dowd, *J. Am. Chem. Soc.* **87**, 4259 (1965); Seyferth, Simmons, and Singh, *J. Organomet. Chem.* **3**, 336 (1965); Seyferth and Haas, *J. Organomet. Chem.* **46**, C33 (1972), *J. Org. Chem.* **40**, 1620 (1975); Seyferth and Shih, *Organomet. Chem. Synth.* **1**, 415 (1972); Seyferth and Hopper, *J. Org. Chem.* **37**, 4070 (1972), *J. Organomet. Chem.* **51**, 77 (1973); Seyferth, Haas, and Dagani, *J. Organomet. Chem.* **104**, 9 (1976).

[718] A much longer list, with references, is given in Kirmse, "Carbene Chemistry," Ref. 711, pp. 313–319.

[719] Prager and Brown, *Synthesis* 736 (1974).

[720] For a review of the use of phenyl(trihalomethyl)mercury compounds as dihalocarbene or dihalocarbenoid precursors, see Seyferth, *Acc. Chem. Res.* **5**, 65–74 (1972).

[721] For reviews of fluorinated carbenes, see Seyferth, in Moss and Jones, "Carbenes," vol. 2, pp. 101–158, John Wiley & Sons, Inc., New York, 1975; Sheppard and Sharts, "Organic Fluorine Chemistry," pp. 237–270, W. A. Benjamin, Inc., New York, 1969.

[722] Moss and Pilkiewicz, *J. Am. Chem. Soc.* **96**, 5632 (1974).

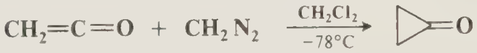
[723] See Moss, Joyce, and Pilkiewicz, *Tetrahedron Lett.* 2425 (1975).

[724] For a review of reactions of dihalocyclopropanes, see Barlet and Vo-Quang, *Bull. Soc. Chim. Fr.* 3729–3760 (1969).

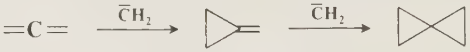
[725] Cairns and McKusick, *Angew. Chem.* **73**, 520 (1961).

[726] Woodworth and Skell, *J. Am. Chem. Soc.* **79**, 2542 (1957).

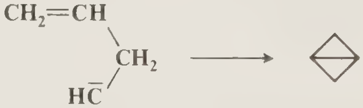
Addition of a second mole gives bicyclopropyl derivatives.[727] 1,4 addition is rare but has been reported for addition of $C(CN)_2$ to cyclooctatetraene.[728] In the addition of carbenes to unsymmetrical dienes, that double bond is attacked first which has a larger number of alkyl groups, since that makes it more susceptible to electrophilic attack. Carbene adds to ketene to give cyclopropanone.[729]



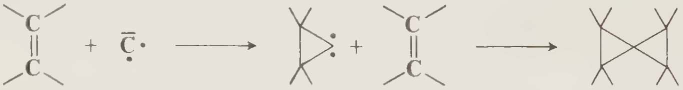
Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:[730]



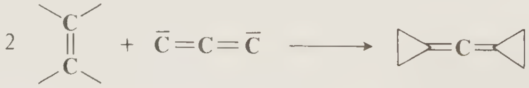
A second mole gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.[731] Allylcarbene gives internal addition, forming bicyclobutane:[732]



Spiropentanes are also formed upon reaction of olefins with atomic carbon aged on a paraffin hydrocarbon surface at −196°C:[733]



The first addition is stereospecific and the second nonstereospecific, in accord with the $2s^22p_x{}^12p_y{}^1$ outer-shell configuration for the ground state of carbon. The C_3 species which is found in carbon vapor (p. 180) gives bisethanoallenes:[734]



Triple-bond compounds[735] react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.[736] Cyclopropenones (p. 54) are obtained by hydrolysis of dihalocyclopropenes.[737] It has proved possible to add 2 moles of a carbene to an alkyne, to give a bicyclobutane:[738]

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[727] Orchin and Herrick, *J. Org. Chem.* **24**, 139 (1959); Nakhapetyan, Safonova, and Kazanskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 840 (1962); Skattebøl, *J. Org. Chem.* **29**, 2951 (1964).

[728] Anastassiou, Cellura, and Ciganek, *Tetrahedron Lett.* 5267 (1970). See also Jefford, Kabengele, Kovacs, and Burger, *Tetrahedron Lett.* 257 (1974), *Helv. Chim. Acta* **57**, 104 (1974); Jefford, Mareda, Gehret, Kabengele, Graham, and Burger, *J. Am. Chem. Soc.* **98**, 2585 (1976).

[729] Turro and Hammond, *Tetrahedron* **24**, 6017 (1968); Rothgery, Holt, and McGee, *J. Am. Chem. Soc.* **97**, 4971 (1975).

[730] For a review of the addition of carbenes and carbenoids to allenes, see Bertrand, *Bull. Soc. Chim. Fr.* 3044–3054 (1968).

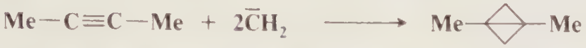
[731] See, for example, Funakubo, Moritani, Murahashi, and Tuji, *Tetrahedron Lett.* 539 (1962).

[732] Lemal, Menger, and Clark, *J. Am. Chem. Soc.* **85**, 2529 (1963).

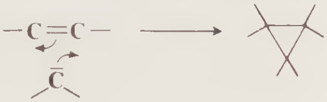
[733] Skell and Engel, *J. Am. Chem. Soc.* **88**, 3749 (1966).

[734] Skell, Wescott, Goldstein, and Engel, *J. Am. Chem. Soc.* **87**, 2829 (1965).

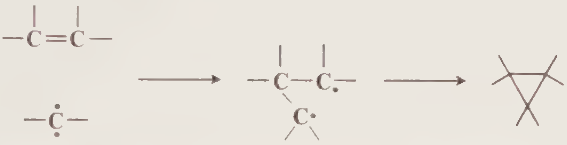
[735] For reviews, see Fuks and Viehe, in Viehe, Ref. 70, pp. 427–434; Closs, *Adv. Alicyclic Chem.* **1**, 53–127 (1966), pp. 58–65.



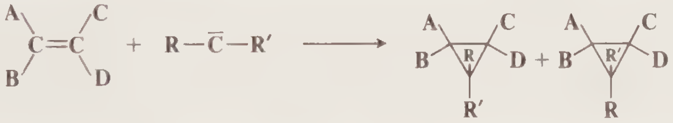
Carbenes are electrophiles, and, in accord with this, electron-donating substituents on the olefin increase the rate of the reaction, and electron-withdrawing groups decrease it,[739] though the range of relative rates is not very great.[740] As discussed on p. 179 carbenes in the singlet state (which is the most common state) react stereospecifically and syn,[741] probably by a one-step mechanism, similar to mechanism *a* of reactions **5-51** and **5-52:**



Carbenes in the triplet state react nonstereospecifically,[742] probably by a diradical mechanism, similar to mechanism *b* of reactions **5-51** and **5-52:**



For carbenes or carbenoids of the type R—C—R′ there is another aspect of stereochemistry.[743] When these species are added to all but symmetrical olefins, two isomers are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



Which isomer is predominantly formed depends on R, R′, and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species (R′ = H), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show anti stereoselectivity. When R = halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.

Carbenes are so reactive that they add to the "double bonds" of aromatic rings. The products are usually not stable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene:[744]

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[736] Frey, *Chem. Ind.* (*London*) 1266 (1960).

[737] Vol'pin, Koreshkov, and Kursanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 535 (1959).

[738] Doering and Coburn, *Tetrahedron Lett.* 991 (1965). Also see Mahler, *J. Am. Chem. Soc.* **84,** 4600 (1962).

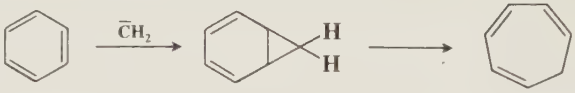
[739] Skell and Garner, *J. Am. Chem. Soc.* **78,** 5430 (1956); Doering and Henderson, *J. Am. Chem. Soc.* **80,** 5274 (1958); Mitsch and Rodgers, *Int. J. Chem. Kinet.* **1,** 439 (1969).

[740] For a review of reactivity in this reaction, with many comprehensive tables of data, see Moss, in Jones and Moss, "Carbenes," vol. 1, pp. 153–304, John Wiley & Sons, Inc., New York, 1973.

[741] Woodworth and Skell, *J. Am. Chem. Soc.* **81,** 3383 (1959); Jones, Ando, Hendrick, Kulczycki, Howley, Hummel, and Malament, *J. Am. Chem. Soc.* **94,** 7469 (1972).

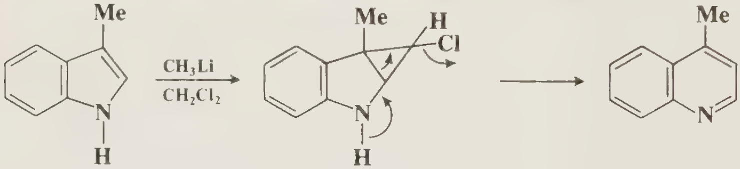
[742] Skell and Klebe, *J. Am. Chem. Soc.* **82,** 247 (1960).

[743] For reviews of the stereochemistry of carbene and carbenoid addition to double bonds, see Moss, *Sel. Org. Transform.* **1,** 35–88 (1970); Closs, *Top. Stereochem.* **3,** 193–235 (1968).



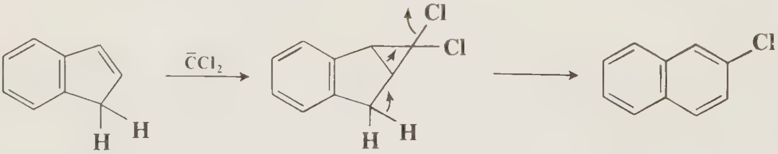
109

but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate (**109**) cannot be isolated in this case (it undergoes an electrocyclic rearrangement, p. 1024), though certain substituted norcaradienes, e.g., the product of addition of $C(CN)_2$ to benzene,[745] have been isolated.[746] With CH_2, insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding CH_2 to benzene rings without the use of free carbene is the catalytic decomposition of CH_2N_2 in the aromatic compound as solvent with CuCl or CuBr.[747] By this method better yields of cycloheptatrienes are obtained without insertion side products.[748] CHCl is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines, by treatment with halocarbenes,[749] e.g.,



110

The intermediate in this reaction (**110**) has not been isolated, but it has been trapped, as the N-acetate,[750] which with alcoholic KOH gives the quinoline product. In the reaction between indene and CCl_2, the intermediate has been isolated:[751]



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[744] Doering and Knox, *J. Am. Chem. Soc.* **75,** 297 (1951).

[745] Ciganek, *J. Am. Chem. Soc.* **89,** 1454 (1967).

[746] See for example, Mukai, Kubota, and Toda, *Tetrahedron Lett.* 3581 (1967); Maier and Heep, *Chem. Ber.* **101,** 1371 (1968); Jones, *Angew. Chem. Int. Ed. Engl.* **8,** 76 (1969) [*Angew. Chem.* **81,** 83]; Jones, Harrison, and Rettig, *J. Am. Chem. Soc.* **91,** 7462 (1969); Schönleber, *Angew. Chem. Int. Ed. Engl.* **8,** 76 [*Angew. Chem.* **81,** 83]; Ciganek, *J. Am. Chem. Soc.* **93,** 2207 (1971); Dürr and Kober, *Tetrahedron Lett.* 1255, 1259 (1972); Vogel, Wiedemann, Roth, Eimer, and Günther, *Justus Liebigs Ann. Chem.* **759,** 1 (1972); Klärner, *Tetrahedron Lett.* 19 (1974); Bannerman, Cadogan, Gosney, and Wilson, *J. Chem. Soc., Chem. Commun.* 618 (1975).

[747] Wittig and Schwarzenbach, *Justus Liebigs Ann. Chem.* **650,** 1 (1961); Müller and Fricke, *Justus Liebigs Ann. Chem.* **661,** 38 (1963); Müller, Kessler, Fricke, and Kiedaisch, *Justus Liebigs Ann. Chem.* **675,** 63 (1961).

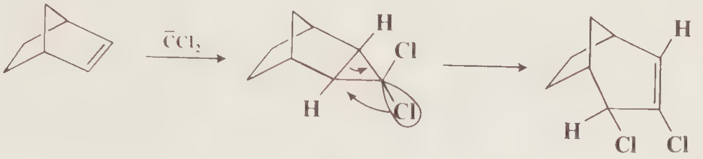
[748] For a review of catalyzed reactions of diazomethane, see Müller, Kessler, and Zeeh, *Fortschr. Chem. Forsch.* **7,** 128–171 (1966).

[749] For a review of the reactions of heterocyclic compounds with carbenes, see Rees and Smithen, *Adv. Heterocycl. Chem.* **3,** 57–78 (1964).

[750] Dobbs, *Chem. Commun.* 56 (1965). See also Dobbs, *J. Org. Chem.* **33,** 1093 (1968).

[751] Parham and Reiff, *J. Am. Chem. Soc.* **77,** 1177 (1955); Parham, Reiff, and Swartzentruber, *J. Am. Chem. Soc.* **78,** 1437 (1956).

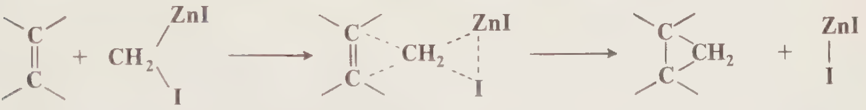
In such cases a side reaction which sometimes occurs is expansion of the *six-membered* ring. Ring expansion may occur even with nonaromatic compounds, when the driving force is supplied by relief of strain,[752] e.g.,



111

111 is so strained that it rearranges,[753] though it has been isolated.[754]

As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons-Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion side products.[755] This procedure involves treatment of the double-bond compound with CH_2I_2 and a Zn–Cu couple and leads to cyclopropane derivatives in good yields.[756] The Zn–Cu couple can be prepared in several ways,[757] of which heating Zn dust with CuCl in ether under nitrogen[758] is particularly convenient. The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn\cdot ZnI_2$. This intermediate is stable enough for solutions of it to be isolable.[759] These solutions give CH_2I_2 when treated with I_2 (reaction **2-28**). and CH_3I when treated with H_2O (reaction **2-21**). The addition is stereospecifically syn, and a concerted mechanism is likely, perhaps[760]



With the Simmons-Smith procedure, as with free carbenes, conjugated dienes give 1,2 addition,[761] and allenes give methylenecyclopropanes or spiropentanes. An alternative way of carrying out the Simmons-Smith reaction is by treatment of the substrate with CH_2I_2 or another dihalomethane and Et_2Zn in ether. This method can be adapted to the introduction of RCH and ArCH by the use of $RCHI_2$ or $ArCHI_2$ instead of the dihalomethane.[762] Another method uses a dihalo compound and copper.[762a]

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[752] Jefford, Gunsher, Hill, Brun, Le Gras, and Waegell, *Org. Synth.* **51,** 60 (1971). For a review of the addition of halocarbenes to bridged bicyclic olefins, see Jefford, *Chimia* **24,** 357–363 (1970).

[753] Bergman, *J. Org. Chem.* **28,** 2210 (1963).

[754] Moore, Moser, and LaPrade, *J. Org. Chem.* **28,** 2200 (1963); DeSelms and Combes, *J. Org. Chem.* **28,** 2206 (1963).

[755] For reviews, see Simmons, Cairns, Vladuchick, and Hoiness, *Org. React.* **20,** 1–131 (1973); Furukawa and Kawabata, *Adv. Organomet. Chem.* **12,** 83–134 (1974); pp. 84–103.

[756] Simmons and Smith, *J. Am. Chem. Soc.* **81,** 4256 (1959).

[757] Shank and Shechter, *J. Org. Chem.* **24,** 1525 (1959); LeGoff, *J. Org. Chem.* **29,** 2048 (1964). For the use of a Zn Ag couple, see Denis, Girard, and Conia, *Synthesis* 549 (1972).

[758] Rawson and Harrison, *J. Org. Chem.* **35,** 2057 (1970).

[759] Blanchard and Simmons, *J. Am. Chem. Soc.* **86,** 1337 (1964).

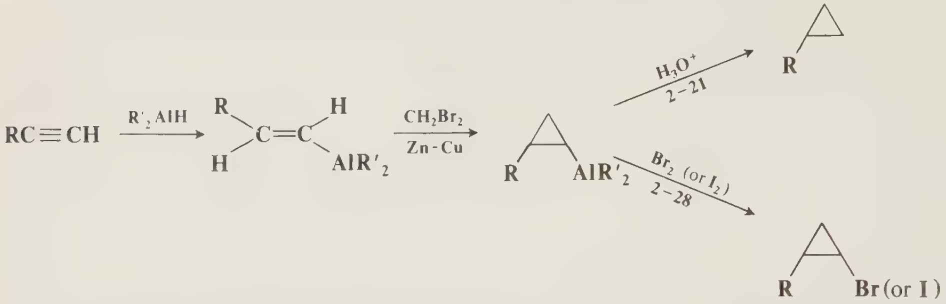
[760] Simmons, Blanchard, and Smith, *J. Am. Chem. Soc.* **86,** 1347 (1964).

[761] Overberger and Halek, *J. Org. Chem.* **28,** 867 (1963).

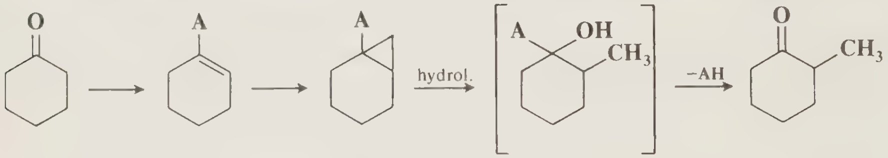
[762] Furukawa, Kawabata, and Nishimura, *Tetrahedron* **24,** 53 (1968), *Tetrahedron Lett.* 3495 (1968); Nishimura, Kawabata, and Furukawa, *Tetrahedron* **25,** 2647 (1969); Miyano and Hashimoto, *Bull. Chem. Soc. Jpn.* **46,** 892 (1973). See also Sawada and Inouye, *Bull. Chem. Soc. Jpn.* **42,** 2669 (1969).

[762a] Kawabata, Naka, and Yamashita, *J. Am. Chem. Soc.* **98,** 2676 (1976).

Alkynes can be converted to cyclopropanes or cyclopropyl halides by carbene transfer to the alkenylaluminum compound formed from the alkyne and a dialkylalane (reaction **5-16**):[763]

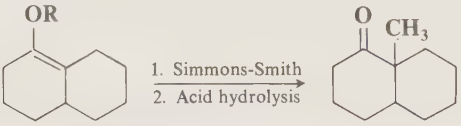


The Simmons-Smith reaction has been used as the basis of a method for the indirect α-methylation of a ketone.[764] The ketone (illustrated for cyclohexanone) is first converted to the enol ether, e.g., by reaction **6-6**, or to the enamine (reaction **6-15**) or silyl ether. Application of the Simmons-Smith reaction gives the cyclopropane compound **112**, which is then cleaved (addition of water to a cyclopropane ring) to an intermediate **113**, which loses ROH, RNH_2, or R_3SiH, producing the methylated ketone. Cleavage of **112** is carried out by acid hydrolysis if A is OR, by basic hydrolysis if A is SiR_3, and by neutral hydrolysis in aqueous methanol at 150 to 170°C if A is NR_2. If the double bond is at a bridgehead, the reaction is a means of angular methylation, e.g.,[765]



112 **113**

$A = OR, NR_2, SiR_3$



Olefins which undergo the Michael reaction (**5-19**) can be converted to cyclopropane derivatives with sulfur ylides.[765a] Among the most common of these is dimethyloxosulfonium methylide (**114**),[766] which is widely use to transfer CH_2 to activated double bonds, but other sulfur ylides,

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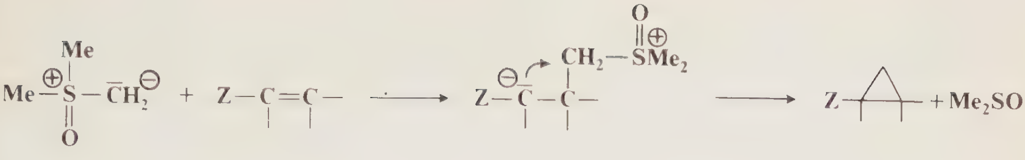
[763] Zweifel, Clark, and Whitney, *J. Am. Chem. Soc.* **93,** 1305 (1971).

[764] See Wenkert, Mueller, Reardon, Sathe, Scharf, and Tosi, *J. Am. Chem. Soc.* **92,** 7428 (1970) for the enol ether procedure; Kuehne and King, *J. Org. Chem.* **38,** 304 (1973) for the enamine procedure; and Conia and Girard, *Tetrahedron Lett.* 2767 (1973) and Girard and Conia, *Tetrahedron Lett.* 3327 (1974) for the silyl ether procedure.

[765] Wenkert and Berges, *J. Am. Chem. Soc.* **89,** 2507 (1967); Ireland, Marshall, and Tilley, *J. Am. Chem. Soc.* **92,** 4754 (1970). See also Sims, *J. Org. Chem.* **32,** 1751 (1967); Whitlock and Overman, *J. Org. Chem.* **34,** 1962 (1969).

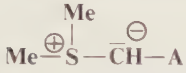
[765a] For a monograph, see Trost and Melvin, "Sulfur Ylides," Academic Press, Inc., New York, 1975.

[766] Truce and Badiger, *J. Org. Chem.* **29,** 3277 (1964); Corey and Chaykovsky, *J. Am. Chem. Soc.* **87,** 1353 (1965); Agami, *Bull. Soc. Chim. Fr.* 1391 (1967); Agami and Prevost, *Bull. Soc. Chim. Fr.* 2299 (1967). For a review, see Durst, *Adv. Org. Chem.* **6,** 285–388 (1969), pp. 333–339.



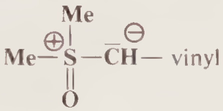
114

e.g., **115** (A = acyl,[767] carbethoxy[768]), **116**,[769] and **117**,[770] which transfer CHA, CH—vinyl, and CMe_2, respectively, have also been used. CHR and CR_2 can be added in a similar manner with



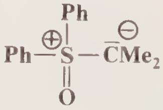
$\mathrm{Me_2\overset{\oplus}{S}{-}\overset{\ominus}{C}H{-}A}$

115



$\mathrm{Me_2\overset{\oplus}{S}(=O){-}\overset{\ominus}{C}H{-}vinyl}$

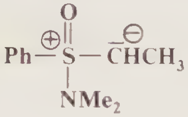
116



$\mathrm{Ph_2\overset{\oplus}{S}(=O){-}\overset{\ominus}{C}Me_2}$

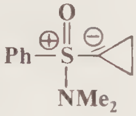
117

certain nitrogen-containing compounds. For example, the nitrogen ylides **118** and **119** and the carbanion **120** can be used, respectively, to add CHMe, cyclopropylidene, and CMe_2 to activated

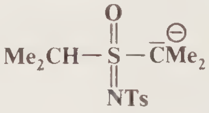


$\mathrm{Ph{-}\overset{\oplus}{S}(=O)(NMe_2){-}\overset{\ominus}{C}HCH_3}$

118



119



$\mathrm{Me_2CH{-}S(=O)(=NTs){-}\overset{\ominus}{C}Me_2}$

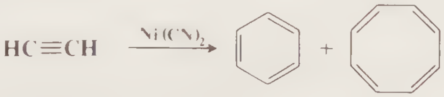
120

double bonds.[771] Similar reactions have been performed with phosphorus ylides.[772] The reactions with ylides are of course nucleophilic addition.

Many substituted cyclopropanes have been made by treatment of olefins with HCWZX, where W = H, R, Ar, Cl, or COOR; Z = COOR, CN, or COAr, and X = Cl or Br.[773] This is a syn addition.

OS **V**, 306, 855, 859, 874; **50**, 94; **51**, 60; **52**, 132; **54**, 11; **55**, 12.

5-54 Trimerization and Tetramerization of Alkynes



When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[774] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes.[775] This reaction has been used to prepare very crowded molecules. Diisopropylacetylene was trimerized over $Co_2(CO)_8$ and over $Hg[Co(CO)_4]_2$ to hexaisopropylbenzene, which had previously been unknown.[776] The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Even more interesting was the *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF to give 1,2,3-tri-*t*-butyl-4,5,6-trifluorobenzene (**122**), the first time three adjacent *t*-butyl groups had been put onto a benzene ring.[777] The fact that this is a head-to-head joining makes the following sequence likely:

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[767] Trost, *J. Am. Chem. Soc.* **89**, 138 (1967). See also Nozaki, Takaku, and Kondô, *Tetrahedron* **22**, 2145 (1966).

[768] Payne, *J. Org. Chem.* **32**, 3351 (1967).

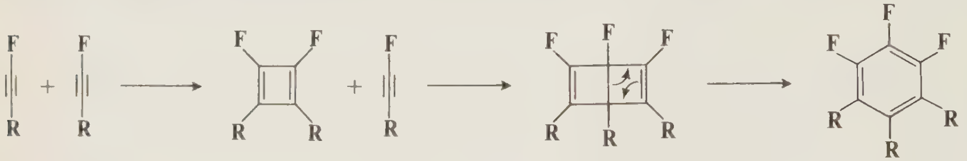
[769] LaRochelle, Trost, and Krepski, *J. Org. Chem.* **36**, 1126 (1971); Marino and Kaneko, *Tetrahedron Lett.* 3971 3975 (1973).

[770] Corey and Jautelat, *J. Am. Chem. Soc.* **89**, 3912 (1967).

[771] For reviews, see Kennewell and Taylor, *Chem. Soc. Rev.* **4**, 189–209 (1975); Trost, *Acc. Chem. Res.* **7**, 85–92 (1974); Johnson, *Acc. Chem. Res.* **6**, 341–347 (1973). See also Johnson, Kirchhoff, Reischer, and Katekar, *J. Am. Chem. Soc.* **95**, 4287 (1973); Johnson and Janiga, *J. Am. Chem. Soc.* **95**, 7692 (1973).

[772] Bestmann and Seng, *Angew. Chem. Int. Ed. Engl.* **1**, 116 (1962) [*Angew. Chem.* **74**, 154]; Grieco and Finkelhor, *Tetrahedron Lett.* 3781 (1972).

[773] Warner, *J. Org. Chem.* **24**, 1536 (1959); McCoy, *J. Org. Chem.* **25**, 2078 (1960), *J. Am. Chem. Soc.* **84**, 2246 (1962).



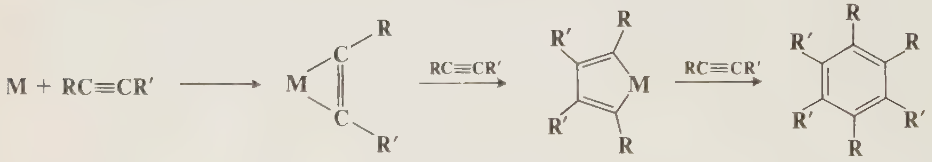
R = *t*-butyl

121

122

The fact that **121** (a bicyclo[2.2.0]hexadiene) was also isolated lends support to this scheme.

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene RC≡CH. The chief product is usually the 1,2,4-isomer, with lesser amounts of the 1,3,5-isomer also generally obtained but little if any of the 1,2,3-isomer. Mechanisms of the catalyzed reactions are not well established, although coordination of the metal with the triple bond is believed to be involved.[778] However, it has been shown that at least some of these reactions proceed through three- and five-membered heterocyclic intermediates (**123** and **124**). Such intermediates (where M = Rh, Ir, or Ni) have been isolated and



123

124

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[774] For reviews, see Yur'eva, *Russ. Chem. Rev.* **43**, 48–68 (1974); Khan and Martell, Ref. 144, pp. 163–168; Maitlis, *Pure Appl. Chem.* **30**, 427–448 (1972); Reppe, Kutepow, and Magin, *Angew. Chem. Int. Ed. Engl.* **8**, 727–733 (1969) [*Angew. Chem.* **81**, 717–723]; Fuks, and Viehe, in Viehe, Ref. 70, pp. 450–460; Hoogzand and Hübel, in Wender and Pino, "Organic Syntheses Via Metal Carbonyls," vol. 1, pp. 343–371, Interscience Publishers, New York, 1968; Bird, Ref. 208, pp. 1–29; Reikhsfel'd and Makovetskii, *Russ. Chem. Rev.* **35**, 510–523 (1966); Schrauzer, Glockner, and Eichler, *Angew. Chem. Int. Ed. Engl.* **3**, 185–191 (1964) [*Angew. Chem.* **76**, 28–35]; Maitlis, *Acc. Chem. Res.* **9**, 93–99 (1976).

[775] See, for example, Franzus, Canterino, and Wickliffe, *J. Am. Chem. Soc.* **81**, 1514 (1959); Reikhsfel'd, Makovetskii, and Erokhina, *J. Gen. Chem. USSR* **32**, 646 (1962).

[776] Arnett and Bollinger, *J. Am. Chem. Soc.* **86**, 4729 (1964); Hopff, *Chimia* **18**, 140 (1964); Hopff and Gati, *Helv. Chim. Acta* **48**, 509 (1965).

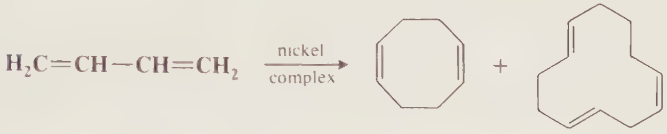
[777] Viehe, Merényi, Oth, and Valange, *Angew. Chem. Int. Ed. Engl.* **3**, 746 (1964) [*Angew. Chem.* **76**, 888]; Viehe, Merényi, Oth, Senders, and Valange, *Angew. Chem. Int. Ed. Engl.* **3**, 755 (1964) [*Angew. Chem.* **76**, 923]. Also see Arnett and Bollinger, *Tetrahedron Lett.* 3803 (1964); Schäfer, *Angew. Chem. Int. Ed. Engl.* **5**, 669 (1966) [*Angew. Chem.* **78**, 716].

[778] For a review of transition metal complexes of acetylenes, see Bowden and Lever, *Organomet. Chem. Rev.* **3**, 227–279 (1968).

shown to give benzenes when treated with alkynes.[779] Note that this pathway accounts for the predominant formation of the 1,2,4-isomer.

For addition of triple bonds to triple bonds, but not with ring formation, see reaction **5-17.**

5-55 Other Cycloaddition Reactions



Conjugated dienes can be dimerized or trimerized at their 1,4 positions (formally, $4+4$ and $4+4+4$ cycloadditions) by treatment with certain nickel complexes or other transition-metal compounds.[780] Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.[781] The relative amount of each product can be controlled by use of the proper catalyst. For example, Ni : $P(OC_6H_4\text{-}o\text{-}Ph)_3$ gives predominant dimerization, while $Ni(cyclooctadiene)_2$ gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise mechanisms involving metal-olefin complexes.[782] Treatment of a mixture of ethylene and butadiene with the appropriate nickel compound gives 1,5-cyclodecadiene, formed from two molecules of the diene and one of the olefin[783] (a $4+4+2$ cycloaddition). In a similar manner, cocyclization of butadiene and triple-bond compounds gives 1,4,7-cyclodecatrienes.[784]

As we have seen in reaction **5-51,** the Woodward-Hoffmann rules allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is $4n+2$ and photochemically if the number is $4n$. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight-membered or greater, concerted mechanisms, though allowed by orbital symmetry for the cases stated, become difficult to achieve because of the entropy factor (the two ends of one system must simultaneously encounter the two ends of the other), unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight-membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct 4 + 4 or 4 + 4 + 4 cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes. Some examples are

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[779] Collman and Kang, *J. Am. Chem. Soc.* **89,** 844 (1967); Collman, Kang, Little, and Sullivan, *Inorg. Chem.* **7,** 1298 (1968); Collman, *Acc. Chem. Res.* **1,** 136–143 (1968); Yamazaki and Hagihara, *J. Organomet. Chem.* **7,** P22 (1967); Wakatsuki, Kuramitsu, and Yamazaki, *Tetrahedron Lett.* 4549 (1974); Moseley and Maitlis, *J. Chem. Soc., Dalton Trans.* 169 (1974); Müller, *Synthesis* 761–774 (1974); Eisch and Galle, *J. Organomet. Chem.* **96,** C23 (1975).

[780] For reviews, see Heimbach, *Angew. Chem. Int. Ed. Engl.* **12,** 975–989 (1973) [*Angew. Chem.* **85,** 1035–1049]; Baker, *Chem. Rev.* **73,** 487–530 (1973), pp. 489–512; Semmelhack, *Org. React.* **19,** 115–198 (1972), pp. 128–143; Heimbach, Jolly, and Wilke, *Adv. Organomet. Chem.* **8,** 29–86 (1970), pp. 48–83; Wilke, *Angew. Chem. Int. Ed. Engl.* **2,** 105–115 (1963) [*Angew. Chem.* **75,** 10–20]; Khan and Martell, Ref. 144, pp. 159–163; Heck, Ref. 208, pp. 157–164; Bird, Ref. 208, pp. 30–68.

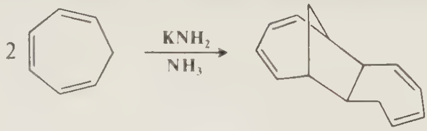
[781] For a review of the 1,5,9-cyclododecatrienes (there are four stereoisomers, of which the *t,t,t* is shown above), See Rona, *Intra-Sci. Chem. Rep.* **5,** 105–148 (1971).

[782] For example, see Heimbach and Wilke, *Justus Liebigs Ann. Chem.* **727,** 183 (1969); Barnett, Büssemeier, Heimbach, Jolly, Krüger, Tkatchenko, and Wilke, *Tetrahedron Lett.* 1457 (1972); Barker, Green, Howard, Spencer, and Stone, *J. Am. Chem. Soc.* **98,** 3373 (1976).

[783] Heimbach and Wilke, Ref. 782.

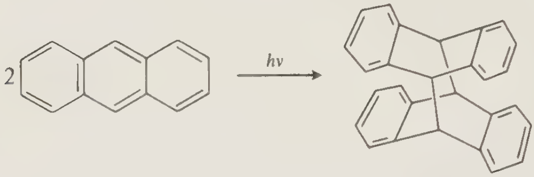
[784] Heimbach, *Angew. Chem. Int. Ed. Engl.* **5,** 961 (1966) [*Angew. Chem.* **78,** 983]; Heimbach and Brenner, *Angew. Chem. Int. Ed. Engl.* **5,** 961 (1966) [*Angew. Chem.* **78,** 983]; Brenner, Heimbach, and Wilke, *Justus Liebigs Ann. Chem.* **727,** 194 (1969).

6 + 2



Ref. 785

4 + 4



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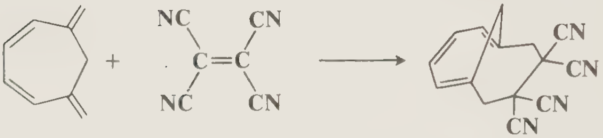
8 + 2



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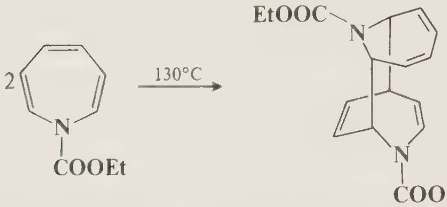
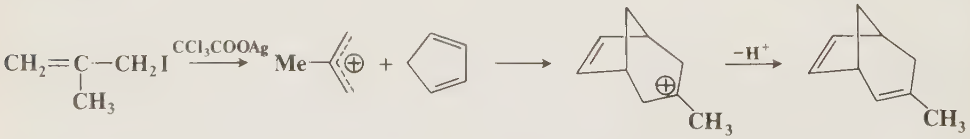
6 + 4



Ref. 788

The suprafacial thermal addition of an allylic cation to a diene (a 4 + 3 cycloaddition[789]) is allowed by the Woodward-Hoffmann rules (note that the highest occupied molecular orbital of an allylic cation, p. 34, has the same symmetry as the highest occupied orbital of a simple alkene, so that this reaction would be expected to follow the same rules as the Diels-Alder reaction). Such cycloadditions can be carried out[790] by treatment of a diene with an allylic halide in the presence of a suitable silver salt, e.g.,[791]



This reaction has even been carried out with benzene assuming the role of the diene.[792]

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[785] Staley and Orvedal, *J. Am. Chem. Soc.* **96**, 1618 (1974). In this case the reagent converted one molecule of cycloheptatriene to the cycloheptatrienyl anion (p. 48), which then added stepwise to the other molecule.

[786] Shönberg, Ref. 41, pp. 97–99.

[787] Farrant and Feldmann, *Tetrahedron Lett.* 4979 (1970).

[788] Paquette, Barrett, and Kuhla, *J. Am. Chem. Soc.* **91**, 3616 (1969); Paul, Johnson, Barrett, and Paquette, *Chem. Commun.* 6 (1969).

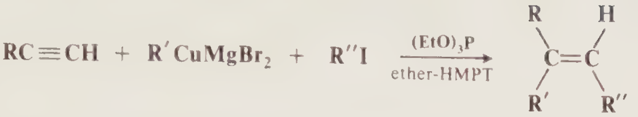
[789] For 4 + 3 cycloaddition reactions which do not proceed through allyl cations, see Noyori, Makino, and Takaya, *J. Am. Chem. Soc.* **93**, 1272 (1971); Meinwald and Gruber, *J. Am. Chem. Soc.* **93**, 3802 (1971).

[790] For a review, see Hoffmann, *Angew. Chem. Int. Ed. Engl.* **12**, 819–835 (1973) [*Angew. Chem.* **85**, 877–894].

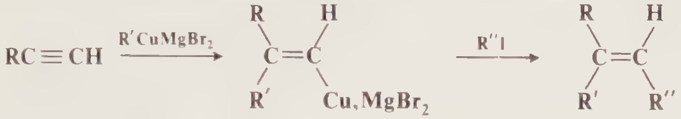
[791] Hoffmann, Joy, and Suter, *J. Chem. Soc. B* 57 (1968).

[792] Hoffmann and Hill, *Angew. Chem. Int. Ed. Engl.* **13**, 136 (1974) [*Angew. Chem.* **86**, 127].

5-56 The Addition of Two Alkyl Groups to an Alkyne

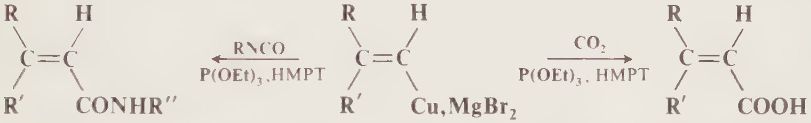


Two different alkyl groups can be added to a terminal alkyne in one laboratory step by treatment with an alkylcopper magnesium bromide reagent and an alkyl iodide in ether-HMPT containing triethyl phosphite.[793] The groups add stereoselectively syn. The reaction, which has been applied to primary R′ and to primary, allylic, benzylic, and α-alkoxyalkyl R″, involves initial addition of the alkylcopper reagent, followed by a coupling reaction (**0-87**):



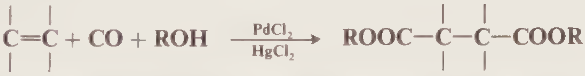
125

If the alkyl iodide is omitted, the vinylcopper intermediate **125** can be converted to a carboxylic acid by the addition of CO_2 (see reaction **6-35**) or to an amide by the addition of an isocyanate



(see reaction **6-37**), in either case in the presence of HMPT and a catalytic amount of triethyl phosphite.[794]

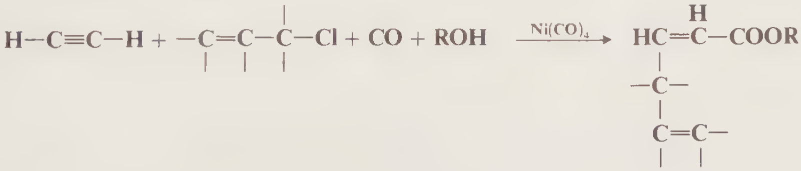
5-57 Dicarbalkoxylation of Olefins and Acetylenes



$$\text{C=C} + \text{CO} + \text{ROH} \xrightarrow[\text{HgCl}_2]{\text{PdCl}_2} \text{ROOC-C-C-COOR}$$

Alkenes can be converted to succinic esters by reaction with carbon monoxide, an alcohol, and palladium chloride in the presence of mercuric chloride.[795] The addition is mostly syn. In a similar reaction, both terminal and internal alkynes can be converted to esters of maleic acid. For an indirect method of adding two carbon groups to a double bond, see reaction **2-44.**

5-58 Carboxylation of Halides with Insertion of Acetylene



$$\text{H-C}\equiv\text{C-H} + \text{-C=C-C-Cl} + \text{CO} + \text{ROH} \xrightarrow{\text{Ni(CO)}_4} \text{HC=C(H)-COOR (with -C-C=C- on HC)}$$

---

[793] Normant, Cahiez, Chuit, Alexakis, and Villieras, *J. Organomet. Chem.* **40,** C49 (1972); Normant, Cahiez, Chuit, and Villieras, *Tetrahedron Lett.* 2407 (1973).

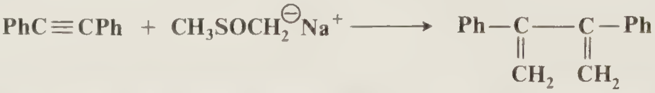
[794] Normant, Cahiez, Chuit, and Villieras, *J. Organomet. Chem.* **54,** C53 (1973).

[795] Heck, *J. Am. Chem. Soc.* **94,** 2712 (1972). See also Fenton and Steinwand, *J. Org. Chem.* **37,** 2034 (1972); James, Hines, and Stille, *J. Am. Chem. Soc.* **98,** 1806 (1976); James and Stille, *J. Am. Chem. Soc.* **98,** 1810 (1976).

Treatment of acetylene at ordinary temperatures and pressures with an allylic halide, CO, an alcohol (or water), and a $Ni(CO)_4$ catalyst results in the preparation of an $\alpha,\beta{:}\delta,\varepsilon$-bis-unsaturated ester (or acid).[796] The use of ethylene instead of acetylene gives the corresponding δ,ε-unsaturated ester (or acid).[797] However, substituted acetylenes or ethylenes do not give the reaction; other products are formed instead.[798] The halide may be any of various primary or secondary allylic halides which do not have electron-withdrawing groups on the double-bond carbons. With respect to the halide, this is an SN1 reaction, and allylic shifts are found. Secondary allylic halides give almost exclusively the allylic-shift product. When ordinary alkyl or aryl halides are used (in the acetylene reaction), another CO is found in the product and the double bond is hydrogenated.[799]

$$\mathrm{HC{\equiv}CH + R'X + ROH \xrightarrow[H_2O]{Ni(CO)_4} R'COCH_2CH_2COOR}$$

5-59 The Conversion of Diphenylacetylene to a Butadiene



$$\mathrm{PhC{\equiv}CPh + CH_3SOCH_2^{\ominus}Na^+ \longrightarrow Ph{-}\underset{\underset{\textstyle CH_2}{\Vert}}{C}{-}\underset{\underset{\textstyle CH_2}{\Vert}}{C}{-}Ph}$$

Diphenylacetylene reacts with methylsulfinyl carbanion to give 2,3-diphenylbutadiene.[800] Neither the scope nor the mechanism of this reaction seems to have been investigated. .

OS **50**, 62.

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[796] Chiusoli, Dubini, Ferraris, Guerrieri, Merzoni, and Mondelli, *J. Chem. Soc. C* 2889 (1968). For reviews, see Chiusoli, *Angew. Chem.* **72**, 74–76 (1960); *Bull. Soc. Chim. Fr.* 1139–1147 (1969); Chiusoli and Cassar, *Angew. Chem. Int. Ed. Engl.* **6**, 124–133 (1967) [*Angew. Chem.* **79**, 177–186].

[797] Chiusoli and Cometti, *J. Chem. Soc., Chem. Commun.* 1015 (1972); Chiusoli, Cometti, and Bellotti, *Gazz. Chim. Ital.* **103**, 569 (1974).

[798] Chiusoli, Bottaccio, and Venturello, *Tetrahedron Lett.* 2875 (1965); Cassar and Chiusoli, *Tetrahedron Lett.* 3295 (1965); 2805 (1966); Chiusoli, *Acc. Chem. Res.* **6**, 422–427 (1973).

[799] Chiusoli, Merzoni, and Mondelli, *Tetrahedron Lett.* 2777 (1964).

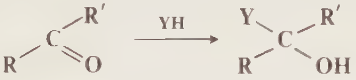
[800] Iwai and Ide, *Org. Synth.* **50**, 62 (1970).

Sixteen

Addition to Carbon-Hetero Multiple Bonds

MECHANISM AND REACTIVITY

The reactions considered in this chapter involve addition to the carbon-oxygen, carbon-nitrogen, and carbon-sulfur double bonds and to the carbon-nitrogen triple bond. The mechanistic study of these reactions is much simpler than of the additions to carbon-carbon multiple bonds considered in Chapter 15.[1] Most of the questions which concerned us there either do not arise here or can be answered very simply. Since C═O, C═N, and C≡N bonds are strongly polar, with the carbon always the positive end (except for isonitriles, see p. 890), there is never any doubt about *orientation* of unsymmetrical addition to these bonds. Nucleophilic attacking species always go the carbon and electrophilic ones to the oxygen or nitrogen. Additions to C═S bonds are much less common, but in these cases the addition can be in the other direction. For example, thiobenzophenone $Ph_2C{=}S$, when treated with phenyllithium gives, after hydrolysis, benzhydryl phenyl sulfide Ph_2CHSPh.[2] The *stereochemistry* of addition is not generally a factor because it is not normally possible to determine whether the addition is syn or anti. In addition of YH to a ketone, for example,



the product has an asymmetric carbon, but unless there is asymmetry in R or R′ or unless YH is optically active, the product must be a racemic mixture and there is no way to tell from its steric nature whether the addition of Y and H was syn or anti. The same holds true for C═N and C═S bonds, since in none of these cases can asymmetry be present at the hetero atom. The stereochemistry of additions of a single YH to the carbon-nitrogen triple bond could be investigated, since the product can exist in syn and anti forms (p. 114), but these reactions are not very important. Of course if R or R′ *is* chiral, a racemic mixture will not always arise and the stereochemistry of addition can be studied in such cases. Cram's rule (p. 106) allows us to predict in many cases the direction of attack of Y. Another such rule is Prelog's rule.[3] However, even in this type of study, the relative directions of attack of Y and H are not determined but only the direction of attack of Y with respect to the rest of the substrate molecule.

Not only are questions of orientation and stereochemistry not of great importance in the study of these mechanisms, but the picture is further simplified by the fact that free-radical additions to carbon-hetero double bonds are rare.[4] The principal question remaining is which attacks first, the nucleophile or electrophile. In most cases it is the nucleophile, and these reactions are regarded as *nucleophilic additions*, which can be represented thus (for the C=O bond, analogously for the others):

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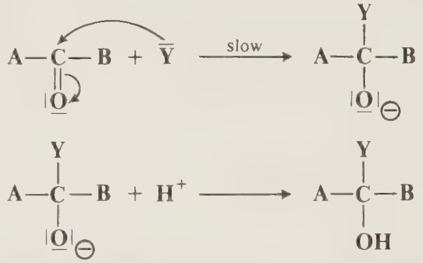
[1] For a discussion, see Jencks, *Prog. Phys. Org. Chem.* **2,** 63–118 (1964).

[2] Beak and Worley, *J. Am. Chem. Soc.* **94,** 597 (1972). See also Dagonneau and Vialle, *Tetrahedron Lett.* 3017 (1973), *Tetrahedron* **30,** 3119 (1974); Schaumann and Walter, *Chem. Ber.* **107,** 3562 (1974); Ohno, Nakamura, Uohama, and Oka, *Chem. Lett.* 983 (1975).

[3] Prelog, *Helv. Chim. Acta* **36,** 308 (1953); for a discussion of these rules, see Eliel, "The Stereochemistry of Carbon Compounds," pp. 68–74, McGraw-Hill Book Company, New York, 1962. For reviews of the stereochemistry of addition to carbonyl compounds, see Ashby and Laemmle, *Chem. Rev.* **75,** 521–546 (1975); Goller, *J. Chem. Educ.* **51,** 182–185 (1974); Toromanoff, *Top. Stereochem.* **2,** 157–198 (1967); Kamernitskii and Akhrem, *Russ. Chem. Rev.* **30,** 43–61 (1961) [the last review can also be found in *Tetrahedron* **18,** 705–750 (1962)].



Step 1

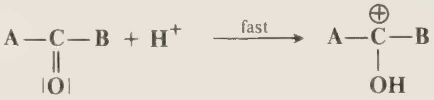
$$\mathrm{A{-}\underset{\overset{\|}{|\underline{O}}}{C}{-}B} + \overline{\mathrm{Y}} \xrightarrow{\text{slow}} \mathrm{A{-}\underset{|\underline{O}|^{\ominus}}{\overset{Y}{C}}{-}B}$$

Step 2

$$\mathrm{A{-}\underset{|\underline{O}|^{\ominus}}{\overset{Y}{C}}{-}B} + \mathrm{H}^+ \longrightarrow \mathrm{A{-}\underset{OH}{\overset{Y}{C}}{-}B}$$

The electrophile shown in step 2 is the proton. In almost all the reactions considered in this chapter the electrophilic attacking atom is either hydrogen or carbon. It may be noted that step 1 is exactly the same as step 1 of the tetrahedral mechanism of nucleophilic substitution at a carbonyl carbon (p. 308), and it might be expected that substitution would compete with addition. However, this is seldom the case. When A and B are H, R, or Ar, the substrate is an aldehyde or ketone and these almost never undergo substitution, owing to the extremely poor nature of H, R, and Ar as leaving groups. For acids and their derivatives (B = OH, OR, NH_2, etc.) addition is seldom found, because these are much better leaving groups. It is thus the nature of A and B which determines whether a nucleophilic attack at a carbon-hetero multiple bond will lead to substitution or addition.

As is the case in the tetrahedral mechanism, it is also possible for the electrophilic species to attack first, in which case it goes to the hetero atom. This species is most often a proton, and the mechanism is

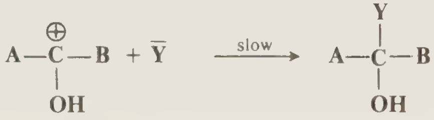


Step 1

1

2

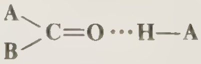
$$\mathrm{A{-}\underset{\overset{\|}{|O|}}{C}{-}B} + \mathrm{H}^+ \xrightarrow{\text{fast}} \mathrm{A{-}\underset{OH}{\overset{\oplus}{C}}{-}B}$$



Step 2

$$\mathrm{A{-}\underset{OH}{\overset{\oplus}{C}}{-}B} + \overline{\mathrm{Y}} \xrightarrow{\text{slow}} \mathrm{A{-}\underset{OH}{\overset{Y}{C}}{-}B}$$

The two mechanisms just mentioned are not usually regarded as being very different, and in each case the rate-determining step is usually the one involving nucleophilic attack. It may be observed that many of these reactions can be catalyzed by both acids and bases. Bases catalyze the reaction by converting a reagent of the form YH to the more powerful nucleophile Y^- (see p. 322). Acids catalyze it by converting the substrate, e.g., **1**, to an ion (**2**) in which the positive charge on the carbon is greatly increased, thus making it more attractive to nucleophilic attack. The latter type of catalysis may also take place with acids which are not so acidic that a proton is actually transferred to the substrate but which are able to form a hydrogen bond with it:



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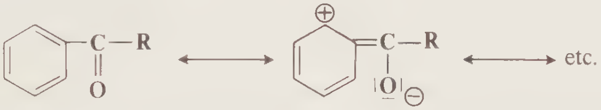
[4] For examples, see Kaplan, *J. Am. Chem. Soc.* **88**, 1833 (1966); Urry, Nishihara, and Niu, *J. Org. Chem.* **32**, 347 (1967); Maruyama, Taniuchi, and Oka, *Bull. Chem. Soc. Jpn.* **47**, 712 (1974).

TABLE 1 Percentage yields in the Perkin reaction (**6-44**) run on benzaldehydes substituted in the ring by methyl and chloro[7]

R in RCHO	Yield, %	R in RCHO	Yield, %
Phenyl	45–50	2-Chlorophenyl	71
2-Methylphenyl	15	3-Chlorophenyl	63
3-Methylphenyl	23	4-Chlorophenyl	52
4-Methylphenyl	33	2,6-Dichlorophenyl	82
2,6-Dimethylphenyl	0		

also resulting in a decreased electron density at the carbon. Similar catalysis can also be found with metallic ions, such as Ag^+, which may act here as Lewis acids.[5] We have mentioned before (p. 156) that ions of type **2** are comparatively stable carbonium ions because the positive charge is spread by resonance.

Reactivity factors in additions to carbon-hetero multiple bonds are similar to those for the tetrahedral mechanism of nucleophilic substitution.[6] If A and/or B are electron-donating groups, rates are decreased. Electron-attracting substituents increase rates. This means that aldehydes are more reactive than ketones. Table 1 illustrates these generalizations.[7] Aryl groups are somewhat deactivating compared to alkyl, because of resonance, which stabilizes the substrate molecule but is lost on going to the intermediate:

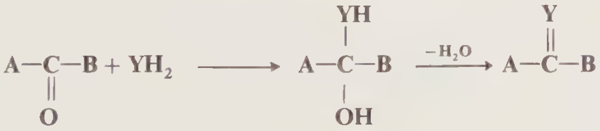


Double bonds in conjugation with the carbon-hetero multiple bond also lower addition rates, for similar reasons but, more important, may provide competition from 1,4 addition (p. 679). Steric factors are also quite important and contribute to the decreased reactivity of ketones compared with aldehydes. Highly hindered ketones like hexamethylacetone and dineopentyl ketone[8] either do not undergo many of these reactions or require extreme conditions.

REACTIONS

Many of the reactions in this chapter are simple additions to carbon-hetero multiple bonds, with the reaction ending as soon as the two groups have been added. But in many other cases subsequent reactions take place. We shall meet a number of such reactions, but most of them are of two types:

Type *A*



$$\mathrm{A}-\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{B} + \mathrm{YH}_2 \longrightarrow \mathrm{A}-\overset{\overset{\displaystyle \mathrm{YH}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{B} \xrightarrow{-\mathrm{H_2O}} \mathrm{A}-\overset{\overset{\displaystyle \mathrm{Y}}{\|}}{\mathrm{C}}-\mathrm{B}$$

---

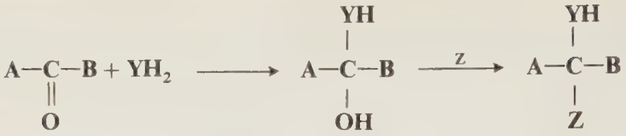
[5] Toromanoff, *Bull. Soc. Chim. Fr.* 1190 (1962).

[6] For a review of the reactivity of nitriles, see Schaefer, in Rappoport, "The Chemistry of the Cyano Group," pp. 239–305, Interscience Publishers, New York, 1970.

[7] Böck, Lock, and Schmidt, *Monatsh. Chem.* **64**, 399 (1934).

[8] Liberman and Vasina, *J. Gen. Chem. USSR* **32**, 3179 (1962).

Type *B*



$$\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{A{-}C{-}B}} + \mathrm{YH_2} \longrightarrow \mathrm{A{-}}\overset{\substack{\mathrm{YH} \\ |}}{\underset{\substack{| \\ \mathrm{OH}}}{\mathrm{C}}}\mathrm{{-}B} \xrightarrow{\mathrm{Z}} \mathrm{A{-}}\overset{\substack{\mathrm{YH} \\ |}}{\underset{\substack{| \\ \mathrm{Z}}}{\mathrm{C}}}\mathrm{{-}B}$$

In type *A*, the adduct loses water (or, in the case of addition to C=NH, ammonia, etc.), and the net result of the reaction is the substitution of C=Y for C=O (or C=NH, etc.). In type *B* there is a rapid substitution, and the OH (or NH_2, etc.) is replaced by another group Z, which is often another YH moiety. This substitution is in most cases nucleophilic, since Y usually has an unshared pair, and SN1 reactions occur very well on this type of compound (see p. 319), even when the leaving group is as poor as OH or NH_2. In this chapter we shall classify reactions according to what is initially adding to the carbon-hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct. It is true that this involves a certain danger, since we cannot always be sure just which reaction occurred first (e.g., reactions **6-7** and **6-17**). In such cases we shall make the assumptions which seem most reasonable from the mechanistic data at hand.

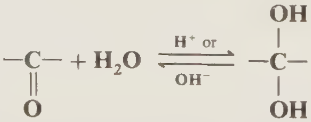
Most of the reactions considered in this chapter can be reversed. In many cases we shall consider the reverse reactions with the forward ones, in the same section. The reverses of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another, e.g., reactions **6-2** and **6-15.** For reactions which are reversible, the principle of microscopic reversibility (p. 195) applies.

We shall discuss first reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the hetero atom and then reactions in which carbon adds to the hetero atom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isonitriles, which are somewhat different in character, are treated at the end.

Reactions in Which Hydrogen or a Metallic Ion Adds to the Hetero Atom

A. Attack by OH (Addition of H_2O)

6-1 The Addition of Water to Aldehydes and Ketones. Formation of Hydrates



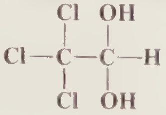
$$\underset{\substack{\| \\ \mathrm{O}}}{\mathrm{{-}C{-}}} + \mathrm{H_2O} \underset{\mathrm{OH^-}}{\overset{\mathrm{H^+\ or}}{\rightleftharpoons}} \mathrm{{-}}\overset{\substack{\mathrm{OH} \\ |}}{\underset{\substack{| \\ \mathrm{OH}}}{\mathrm{C}}}\mathrm{{-}}$$

The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or a *gem*-diol.[9] These compounds are usually stable only in water solution and decompose on distillation; i.e., the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20°C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.[10] It has been found, by exchange with ^{18}O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.[11] Acetone hydrate *has* been shown to exist in the solid state (frozen mixtures of acetone and water).[12] Since methyl, a $+I$ group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral[13] (**3**) is a stable crystalline substance. In order for **3** to revert to chloral, OH^- or H_2O must leave, and this is made difficult by the electron-withdrawing character of the Cl_3C group. Other polychlorinated and polyfluorinated aldehydes and ketones[14] and α-keto aldehydes also form stable hydrates, as do cyclopropanones. In the last case[15] formation of the hydrate (**4**) relieves some of the I strain (p. 250) of the parent ketone. Higher-molecular-weight aldehydes, e.g., C_7 and up, form solid hemihydrates (**5**), which are stable at low temperatures (near 0°C) but decompose to the aldehyde and water at about 40 to 50°C.[16]

---

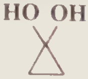
[9] For reviews, see Bell, "The Proton in Chemistry," 2d ed., pp. 183–187, Cornell University Press, Ithaca, N.Y., 1973, *Adv. Phys. Org. Chem.* **4**, 1–29 (1966); Le Hénaff, *Bull. Soc. Chim. Fr.* 4687–4700 (1968).

[10] Bell and Clunie, *Trans. Faraday Soc.* **48**, 439 (1952). See also Bell and McDougall, *Trans. Faraday Soc.* **56**, 1281 (1960).

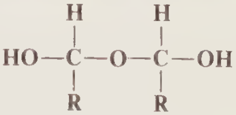


$$\mathrm{Cl{-}\overset{Cl}{\underset{Cl}{C}}{-}\overset{OH}{\underset{OH}{C}}{-}H}$$

3



4

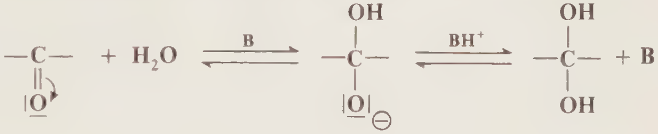


$$\mathrm{HO{-}\overset{H}{\underset{R}{C}}{-}O{-}\overset{H}{\underset{R}{C}}{-}OH}$$

5

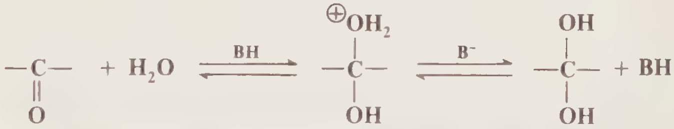
The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively:[17]

Mechanism *a*



$$-\underset{\underline{|O|}}{\underset{\|}{C}}- + H_2O \overset{B}{\rightleftharpoons} -\overset{OH}{\underset{\underline{|O|}^{\ominus}}{C}}- \overset{BH^+}{\rightleftharpoons} -\overset{OH}{\underset{OH}{C}}- + B$$

Mechanism *b*

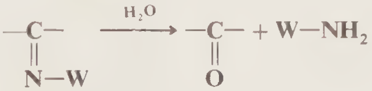


$$-\underset{O}{\underset{\|}{C}}- + H_2O \overset{BH}{\rightleftharpoons} -\overset{\oplus OH_2}{\underset{OH}{C}}- \overset{B^-}{\rightleftharpoons} -\overset{OH}{\underset{OH}{C}}- + BH$$

In mechanism *a*, as the H_2O attacks, the base pulls off a proton, and the net result is addition of OH^-. This can happen because the base is already hydrogen-bonded to the H_2O molecule before the attack. In mechanism *b*, because HB is already hydrogen-bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way B and HB accelerate the reaction even beyond the extent that they form OH^- or H_3O^+ by reaction with water.

For the reaction between ketones and H_2O_2, see reaction **7-51**.

6-2 Hydrolysis of the Carbon-Nitrogen Double Bond



$$-\underset{N-W}{\underset{\|}{C}}- \xrightarrow{H_2O} -\underset{O}{\underset{\|}{C}}- + W{-}NH_2$$

---

[11] Cohn and Urey, *J. Am. Chem. Soc.* **60,** 679 (1938).

[12] Wilson and Davidson, *Can. J. Chem.* **41,** 264 (1963).

[13] For a review of chloral, see Luknitskii, *Chem. Rev.* **75,** 259–289 (1975).

[14] For a review of additions to fluorinated ketones, see Gambaryan, Rokhlin, Zeifman, Ching-Yun, and Knunyants, *Angew. Chem. Int. Ed. Engl.* **5,** 947–956 (1966) [*Angew. Chem.* **78,** 1008–1017].

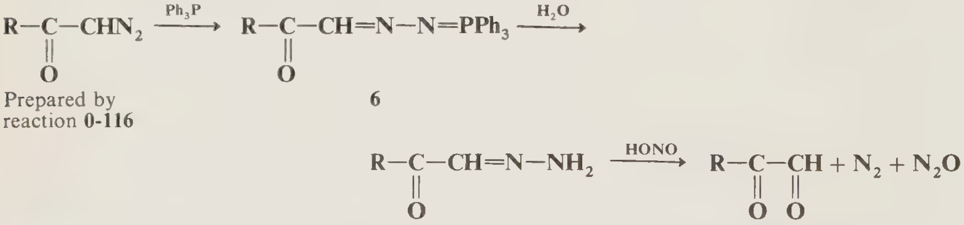
[15] Turro and Hammond, *J. Am. Chem. Soc.* **89,** 1028 (1967); Schaafsma, Steinberg, and de Boer, *Recl. Trav. Chim. Pays-Bas* **86,** 651 (1967). For a review of cyclopropanone chemistry, see Wasserman, Clark, and Turley, *Top. Curr. Chem.* **47,** 73–156 (1974).

[16] Klass, Jensen, Blair, and Martinek, *J. Org. Chem.* **28,** 3029 (1963).

[17] Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.* **52,** 1093 (1956); Pocker, *Proc. Chem. Soc.* 17 (1960); Ogata and Kawasaki, in Zabicky, "The Chemistry of the Carbonyl Group," vol. 2, pp. 3–11, Interscience Publishers, New York, 1970.

Compounds containing carbon-nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones. For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, but hydrolysis is often done in situ, without isolation. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires acid or basic catalysis. Oximes (W = OH), arylhydrazones (W = NHAr), and, most easily, semicarbazones (W = $NHCONH_2$) can also be hydrolyzed. Often a reactive aldehyde is added to combine with the liberated amine. Formaldehyde is generally used for this purpose, but levulinic acid is excellent for hydrolyzing oximes and arylhydrazones.[18]

A number of other reagents have been used to cleave C═N bonds, especially those which are not easily hydrolyzable with acidic or basic catalysts or which contain other functional groups which are attacked under these conditions. In particular, oximes have been converted to the corresponding aldehyde or ketone by treatment with, among other reagents, thallium(III) nitrate,[19] aqueous $TiCl_3$ and acetic acid,[20] aqueous $NaHSO_3$,[21] iron pentacarbonyl and BF_3,[22] aluminum isopropoxide in isopropyl alcohol,[23] lead tetraacetate,[24] cerium(IV) ions,[25] and by treatment of the O-acetate of the oxime with chromium(II) acetate.[26] Tosylhydrazones can be hydrolyzed to the corresponding ketones with NaOCl.[27] Among other reagents which have been used to cleave C═N bonds are nitrous acid (as well as nitrosonium salts such as $NO^+ \ BF_4^-$)[28] and ozone[29] (see reaction **9-10**). Aldehydes and ketones can be purified by conversion to the oxime, semicarbazone, or arylhydrazone derivative (reactions **6-21** and **6-22**), which is then recrystallized and hydrolyzed back to the starting compound. Conversion of a hydrazone to an aldehyde is the key step in the transformation of a carboxylic acid to an α-keto aldehyde, a method of increasing the carbon chain by 1:[30]



$$\text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{CHN}_2 \xrightarrow{\text{Ph}_3\text{P}} \text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{CH}=\text{N}-\text{N}=\text{PPh}_3 \xrightarrow{\text{H}_2\text{O}}$$

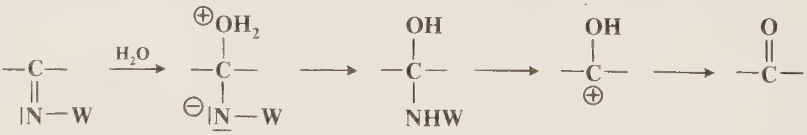
Prepared by
reaction **0-116**

6

$$\text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{CH}=\text{N}-\text{NH}_2 \xrightarrow{\text{HONO}} \text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{O}}{\|}}{\text{CH}} + \text{N}_2 + \text{N}_2\text{O}$$

Direct treatment of the α-ketotriphenylphosphazine (**6**) with HONO also gives the product.

The hydrolysis of carbon-nitrogen double bonds involves initial addition of water and elimination of a nitrogen moiety:



$$-\underset{\underset{|\text{N}-\text{W}}{\|}}{\text{C}}- \xrightarrow{\text{H}_2\text{O}} -\overset{\overset{\oplus\text{OH}_2}{|}}{\underset{\underset{\ominus|\underline{\text{N}}-\text{W}}{|}}{\text{C}}}- \longrightarrow -\overset{\overset{\text{OH}}{|}}{\underset{\underset{\text{NHW}}{|}}{\text{C}}}- \longrightarrow -\overset{\overset{\text{OH}}{|}}{\underset{\oplus}{\text{C}}}- \longrightarrow -\overset{\overset{\text{O}}{\|}}{\text{C}}-$$

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[18] DePuy and Ponder, *J. Am. Chem. Soc.* **81,** 4629 (1959).

[19] McKillop, Hunt, Naylor, and Taylor, *J. Am. Chem. Soc.* **93,** 4918 (1971).

[20] Timms and Wildsmith, *Tetrahedron Lett.* 195 (1971). See also Mc Murry and Silvestri, *J. Org. Chem.* **40,** 1502 (1975).

[21] Pines, Chemerda, and Kozlowski, *J. Org. Chem.* **31,** 3446 (1966).

[22] Alper and Edward, *J. Org. Chem.* **32,** 2938 (1967).

[23] Sugden, *Chem. Ind.* (*London*) 680 (1972).

[24] Yukawa, Sakai, and Suzuki, *Bull. Chem. Soc. Jpn.* **39,** 2266 (1966).

[25] Bird and Diaper, *Can. J. Chem.* **47,** 145 (1969).

[26] Corey and Richman, *J. Am. Chem. Soc.* **92,** 5276 (1970).

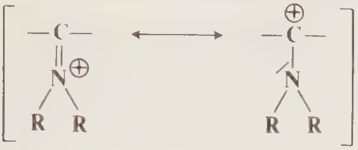
[27] Ho and Wong, *J. Org. Chem.* **39,** 3453 (1974).

[28] Doyle, Wierenga, and Zaleta, *J. Org. Chem.* **37,** 1597 (1972); Doyle, Zaleta, DeBoer, and Wierenga, *J. Org. Chem.* **38,** 1663 (1973).

[29] For example, see Erickson, Andrulis, Collins, Lungle, and Mercer, *J. Org. Chem.* **34,** 2961 (1969).

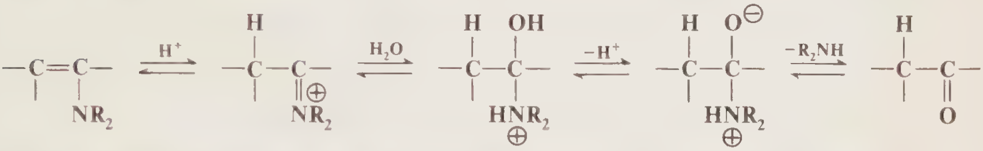
[30] Bestmann, Klein, Göthlich, and Buckschewski, *Chem. Ber.* **96,** 2259 (1963).

It is thus an example of reaction type *A* (p. 803). The sequence shown is generalized.[31] In specific cases there are variations in the order of the steps, depending on acid or basic catalysis or other conditions.[32] Which step is rate-determining also depends on acidity and on the nature of W and of the groups connected to the carbonyl.[33] Iminium ions (**7**) would be expected to undergo hydrolysis quite readily, since there is a contributing form with a positive charge on the carbon.



7

Indeed, they react with water at room temperature.[34] Acid-catalyzed hydrolysis of enamines (the last step of the Stork reaction, reaction **2-17**) involves conversion to iminium ions:[35]



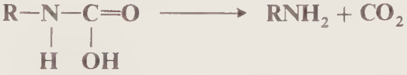
The mechanism of enamine hydrolysis is thus similar to that of vinyl ether hydrolysis (**0-7**).

OS **I,** 217, 298, 318, 381; **II,** 49, 223, 234, 284, 310, 333, 395, 519, 522; **III,** 20, 172, 626, 818; **IV,** 120; **V,** 139, 277, 736, 758; **50,** 66; **51,** 31; **53,** 98, 104.

6-3 Hydrolysis of Isocyanates and Isothiocyanates

$$R\text{—}N\text{=}C\text{=}O + H_2O \xrightarrow{OH^- \text{ or } H^+} R\text{—}NH_2 + CO_2$$

A common method for the preparation of primary amines involves the hydrolysis of isocyanates or isothiocyanates.[36] The latter react more slowly, and more vigorous conditions are required. The reaction is catalyzed by acids or bases. In this case simple addition of water to the carbon-nitrogen double bond would give an N-substituted carbamic acid (**8**). Such compounds are unstable, however, and break down to carbon dioxide (or COS in the case of isothiocyanates) and the amine:



$$R\text{—}\underset{H}{\underset{|}{N}}\text{—}\underset{OH}{\underset{|}{C}}\text{=}O \longrightarrow RNH_2 + CO_2$$

8

In the absence of a basic catalyst, disubstituted ureas, RNHCONHR, can be obtained by a nucleophilic substitution of RNH_2 on the carbamic acid or by addition of RNH_2 to another mole of RNCO.[36a]

OS **II,** 24; **IV,** 819; **V,** 273; **51,** 48.

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[31] For reviews of the mechanism, see Bruylants and Feytmants-de Medicis, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," pp. 465–504, Interscience Publishers, New York, 1970; Salomaa, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 199–205, Interscience Publishers, New York, 1966.

[32] For example, see Reeves, *J. Am. Chem. Soc.* **84,** 3332 (1962).

[33] Cordes and Jencks, *J. Am. Chem. Soc.* **85,** 2843 (1963).

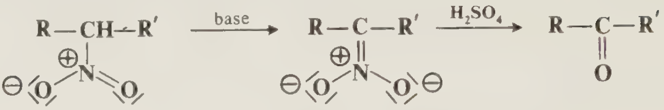
[34] Hauser and Lednicer, *J. Org. Chem.* **24,** 46 (1959).

[35] Stamhuis and Maas, *J. Org. Chem.* **30,** 2156 (1965); Maas, Janssen, Stamhuis, and Wynberg, *J. Org. Chem.* **32,** 1111 (1967); Sollenberger and Martin, *J. Am. Chem. Soc.* **92,** 4261 (1970). For a review of enamine hydrolysis, see Stamhuis, in Cook, "Enamines," pp. 101–113, Marcel Dekker, Inc., New York, 1969.

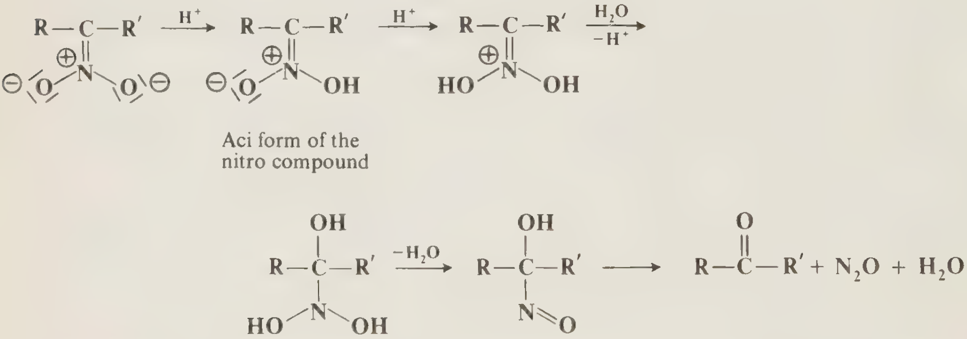
[36] For a review of the mechanisms of reactions of isocyanates with various nucleophiles, see Satchell and Satchell, *Chem. Soc. Rev.* **4,** 231–250 (1975).

[36a] Arnold, Nelson, and Verbang, *Chem. Rev.* **57,** 47 (1957).

6-4 Hydrolysis of Aliphatic Nitro Compounds



Primary or secondary aliphatic nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their salts with sulfuric acid. This is called the *Nef reaction.*[37] Tertiary aliphatic nitro compounds do not give the reaction because they cannot be converted to the salt form. Like reaction **6-2**, this reaction involves hydrolysis of a carbon-nitrogen double bond. A possible mechanism is[38]



Aci form of the
nitro compound

The conversion of nitro compounds to aldehydes or ketones has been carried out with better yields and fewer side reactions by several alternative methods. Among these are treatment of the nitro compound with aqueous $TiCl_3$ [39] or with a mixture of $NaNO_2$ and an alkyl nitrite;[40] and treatment of the salt of the nitro compound with $KMnO_4$[41] or ozone.[42] When the Nef reaction is run with methanol instead of water, primary nitro compounds give high yields of the corresponding dimethyl acetals [$RCH_2NO_2 \rightarrow RCH(OMe)_2$].[43]

When *primary* nitro compounds are treated with sulfuric acid without previous conversion to the salt form, they give carboxylic acids. Hydroxamic acids are intermediates and can be isolated, so that this is also a method for preparing *them.* Both the Nef reaction and the hydroxamic acid process involve the aci form, and the difference in products arises from higher acidity; e.g., a difference in sulfuric acid concentration from 4 *N* to 31 *N* changes the product from the aldehyde to the hydroxamic acid.[44] The mechanism of the hydroxamic acid reaction is not known with certainty, but if higher acidity is required, it may be that the protonated aci form of the nitro compound is further protonated. The following rationalization has been proposed:[44]

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[37] For a review, see Noland, *Chem. Rev.* **55**, 137–155 (1955).

[38] Hawthorne, *J. Am. Chem. Soc.* **79**, 2510 (1957). A similar mechanism, but with some slight differences, was suggested earlier by van Tamelen and Thiede, *J. Am. Chem. Soc.* **74**, 2615 (1952). See also Sun and Folliard, *Tetrahedron* **27**, 323 (1971).

[39] Mc Murry and Melton, *J. Org. Chem.* **38**, 4367 (1973); Mc Murry, *Acc. Chem. Res.* **7**, 281 286 (1974), pp. 282–284.

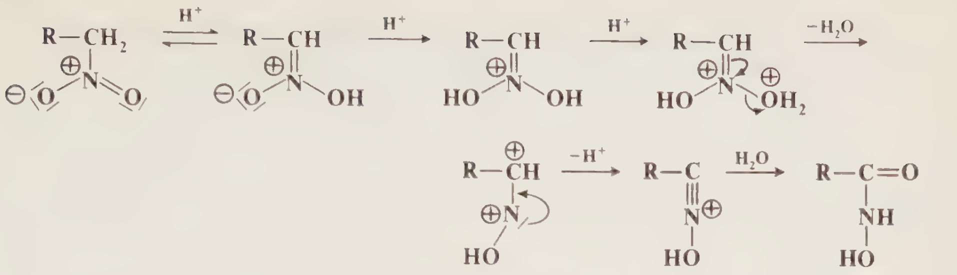
[40] Kornblum and Wade, *J. Org. Chem.* **38**, 1418 (1973).

[41] Shechter and Williams, *J. Org. Chem.* **27**, 3699 (1962); Freeman and Yeramyan, *J. Org. Chem.* **35**, 2061 (1970); Freeman and Lin, *J. Org. Chem.* **36**, 1335 (1971).

[42] Mc Murry, Melton, and Padgett, *J. Org. Chem.* **39**, 259 (1974).

[43] Jacobson, *Tetrahedron Lett.* 3215 (1974).

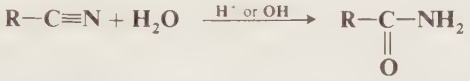
[44] Kornblum and Brown, *J. Am. Chem. Soc.* **87**, 1742 (1965). See also Cundall and Locke, *J. Chem. Soc. B* 98 (1968); Edward and Tremaine, *Can. J. Chem.* **49**, 3483, 3489, 3493 (1971).

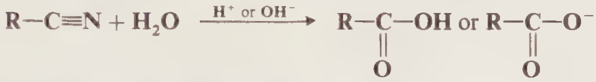


Hydrolysis of the hydroxamic acid produces the carboxylic acid.

There are no OS references, but see OS **IV**, 573, for a related reaction.

6-5 Hydrolysis of Nitriles


$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+ \text{ or } OH^-} R{-}\underset{\underset{O}{\|}}{C}{-}NH_2$$


$$R{-}C{\equiv}N + H_2O \xrightarrow{H^+ \text{ or } OH^-} R{-}\underset{\underset{O}{\|}}{C}{-}OH \text{ or } R{-}\underset{\underset{O}{\|}}{C}{-}O^-$$

Nitriles can be hydrolyzed to give either amides or carboxylic acids.[45] The amide is the initial product, but since amides are also hydrolyzed with acid or basic treatment, the carboxylic acid is the more common product. When the carboxylic acid is desired, the reagent of choice is aqueous NaOH containing about 6 to 12% H_2O_2, though acid-catalyzed hydrolysis is also frequently carried out. However, there are a number of procedures for stopping at the amide stage,[46] among them the use of concentrated H_2SO_4; formic acid and HCl or HBr;[47] acetic acid and BF_3; H_2O_2 and OH^-; and dry HCl followed by H_2O. The same result can also be obtained by use of water and certain metal ions or complexes;[48] MnO_2 in methylene chloride;[49] or $TiCl_4$ and water,[50] in which cases no acid or base is used.

The hydrolysis of nitriles to carboxylic acids is one of the best methods for the preparation of these compounds. Nearly all nitriles give the reaction, with either acid or basic catalysts. The sequences

$$RX + NaCN \longrightarrow RCN \longrightarrow RCOOH \qquad (0\text{-}103)$$

$$RCHO + HCN \longrightarrow RCH(OH)CN \longrightarrow RCH(OH)COOH \qquad (6\text{-}50)$$

$$RCHO + NaCN + NH_4Cl \longrightarrow RCH(NH_2)CN \longrightarrow RCH(NH_2)COOH \qquad (6\text{-}51)$$

are very common. The last two sequences are often carried out without isolation of the cyanide intermediates.

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[45] For reviews, see Compagnon and Miocque, *Ann. Chim. (Paris)* [14] **5**, 11–22, 23–37 (1970); Zil'berman, *Russ. Chem. Rev.* **31**, 615–633 (1962).

[46] For a discussion, see Beckwith, in Zabicky, "The Chemistry of Amides," pp. 119–125, Interscience Publishers, New York, 1970.

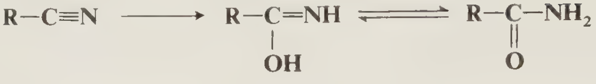
[47] Becke, Fleig, and Pässler, *Justus Liebigs Ann. Chem.* **749**, 198 (1971).

[48] For example see Watanabe, *Bull. Chem. Soc. Jpn.* **32**, 1280 (1959), **37**, 1325 (1964); Bennett and Yoshida, *J. Am. Chem. Soc.* **95**, 3030 (1973); Paraskewas, *Synthesis* 574 (1974). See also Diamond, Grant, Tom, and Taube, *Tetrahedron Lett.* 4025 (1974).

[49] Cook, Forbes, and Kahn, *Chem. Commun.* 121 (1966).

[50] Mukaiyama, Kamio, Kobayashi, and Takei, *Chem. Lett.* 357 (1973).

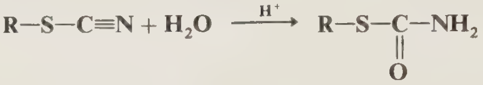
The first addition product is **9**, which tautomerizes to the amide.



$$R{-}C{\equiv}N \longrightarrow R{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}NH \rightleftharpoons R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NH_2$$

9

Thiocyanates can be converted to thiocarbamates, in a similar reaction:[51]



$$R{-}S{-}C{\equiv}N + H_2O \xrightarrow{H^+} R{-}S{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NH_2$$

Hydrolysis of cyanamides gives amines, produced by the breakdown of the unstable carbamic acid intermediates: $R_2NCN \rightarrow [R_2NCOOH] \rightarrow R_2NH$.

Nitriles exchange with carboxylic acids when heated together in an autoclave:[52]

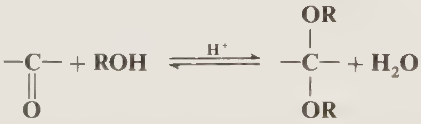
$$RCN + R'COOH \xrightarrow{300°C} RCOOH + R'CN$$

The reaction proceeds as shown if RCOOH is a weaker acid (has a higher pK value) than R′COOH. Labeling studies have shown that it is nitrogen and oxygen which are being exchanged; i.e., the R—C and R′—C bonds are not broken.

OS **I,** 21, 131, 201, 289, 298, 321, 336, 406, 436, 451; **II,** 29, 44, 292, 376, 512, 586 (see, however, **V,** 1054), 588; **III,** 34, 66, 84, 88, 114, 221, 557, 560, 615, 851; **IV,** 58, 93, 496, 506, 664, 760, 790; **V,** 239; **53,** 98. Also see OS **III,** 609; **IV,** 359, 502.

B. Attack by OR (Addition of ROH)

6-6 The Addition of Alcohols to Aldehydes and Ketones



$$-\underset{\displaystyle O}{\underset{\|}{C}}- + ROH \underset{}{\overset{H^+}{\rightleftharpoons}} -\overset{\displaystyle OR}{\overset{|}{\underset{\displaystyle OR}{\underset{|}{C}}}}- + H_2O$$

Acetals and ketals are formed by treatment of aldehydes and ketones, respectively, with alcohols in the presence of acid catalysts.[53] This is a reversible reaction, and acetals and ketals can be hydrolyzed by treatment with acid (reaction **0-7**). With small unbranched aldehydes the equilibrium lies to the right. If it is desired to prepare ketals, or acetals of larger molecules, the equilibrium must be shifted, usually by removal of water. One way of removing the water is by the use of molecular sieves.[54] The reaction in neither direction is catalyzed by bases, and so acetals and ketals are quite stable to bases, though they are easily hydrolyzed by acids. This makes this reaction a useful method of protection of aldehyde or ketone functions from attack by bases. The reaction is of wide scope. Most aldehydes are easily converted to acetals. With ketones the process is more difficult, presumably for steric reasons, and the reaction often fails, though many ketals, especially from cyclic ketones, have been made in this manner. Many functional groups may be present without being affected. 1,2-Glycols and 1,3-glycols form cyclic acetals and ketals, e.g.,

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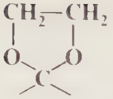
[51] Zil'berman and Lazaris, *J. Gen. Chem. USSR* **33,** 1012 (1963).

[52] Becke and Burger, *Justus Liebigs Ann. Chem.* **716,** 78 (1968). See also Klein, *J. Org. Chem.* **36,** 3050 (1971); Zil'berman, Minizov, Danov, Efremov, and Drachkova, *J. Org. Chem. USSR* **10,** 200 (1974).

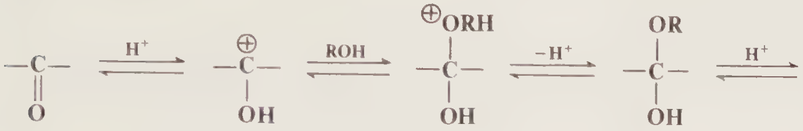
[53] For reviews, see Sandler and Karo, "Organic Functional Group Preparations," vol. 3, pp. 4–17, 34–42, Academic Press, Inc., New York, 1972; Ogata and Kawasaki, Ref. 17, pp. 14–20; Schmitz and Eichhorn, in Patai, "The Chemistry of the Ether Linkage," pp. 309–351, Interscience Publishers, New York, 1967.

[54] Roelofsen, Wils, and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **90,** 1141 (1971).



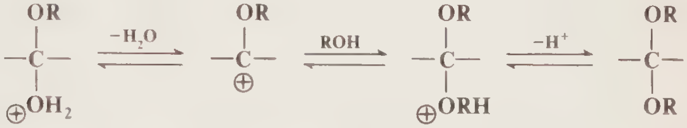
and these are often used to protect aldehydes and ketones.

The mechanism, which involves initial formation of a *hemiacetal*[55] **(10)**, is the reverse of that given for acetal hydrolysis **(0-7)**:



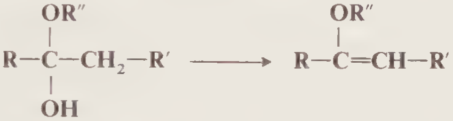
$$\underset{\text{O}}{\overset{}{\underset{\|}{-\text{C}-}}} \xrightleftharpoons{\text{H}^+} \underset{\text{OH}}{\underset{|}{\overset{\oplus}{-\text{C}-}}} \xrightleftharpoons{\text{ROH}} \underset{\text{OH}}{\underset{|}{\overset{\overset{\oplus}{\text{ORH}}}{\overset{|}{-\text{C}-}}}} \xrightleftharpoons{-\text{H}^+} \underset{\text{OH}}{\underset{|}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}}} \xrightleftharpoons{\text{H}^+}$$

10



$$\underset{\oplus\text{OH}_2}{\underset{|}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}}} \xrightleftharpoons{-\text{H}_2\text{O}} \underset{\oplus}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}} \xrightleftharpoons{\text{ROH}} \underset{\oplus\text{ORH}}{\underset{|}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}}} \xrightleftharpoons{-\text{H}^+} \underset{\text{OR}}{\underset{|}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}}}$$

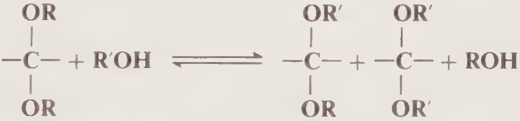
If the original aldehyde or ketone has an α-hydrogen, it is possible for water to split out in that way and enol ethers can be prepared in this manner:



$$\text{R}-\underset{\text{OH}}{\underset{|}{\overset{\text{OR}''}{\overset{|}{\text{C}}}}}-\text{CH}_2-\text{R}' \longrightarrow \text{R}-\overset{\text{OR}''}{\overset{|}{\text{C}}}=\text{CH}-\text{R}'$$

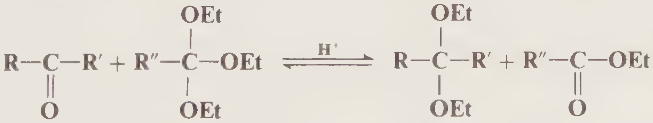
Hemiacetals themselves are no more stable than the corresponding hydrates (reaction **6-1**). As with hydrates, hemiacetals of polychloro and polyfluoro aldehydes and ketones may be quite stable.

When acetals or ketals are treated with an alcohol of higher molecular weight than the one already there, it is possible to get a *transacetalation* (reaction **0-19**):



$$\underset{\text{OR}}{\underset{|}{\overset{\text{OR}}{\overset{|}{-\text{C}-}}}} + \text{R}'\text{OH} \rightleftharpoons \underset{\text{OR}}{\underset{|}{\overset{\text{OR}'}{\overset{|}{-\text{C}-}}}} + \underset{\text{OR}'}{\underset{|}{\overset{\text{OR}'}{\overset{|}{-\text{C}-}}}} + \text{ROH}$$

In the equilibrium mixture are present three acetals and two alcohols, and in order for the reaction to be useful, a way must be found to shift the equilibria in the desired directions.[56] In another type of transacetalation, aldehydes or ketones can be converted to acetals or ketals by treatment with another acetal or ketal or with an ortho ester,[57] in the presence of an acid catalyst (shown for an ortho ester):



$$\text{R}-\underset{\text{O}}{\underset{\|}{\text{C}}}-\text{R}' + \text{R}''-\underset{\text{OEt}}{\underset{|}{\overset{\text{OEt}}{\overset{|}{\text{C}}}}}-\text{OEt} \xrightleftharpoons{\text{H}^+} \text{R}-\underset{\text{OEt}}{\underset{|}{\overset{\text{OEt}}{\overset{|}{\text{C}}}}}-\text{R}' + \text{R}''-\underset{\text{O}}{\underset{\|}{\text{C}}}-\text{OEt}$$

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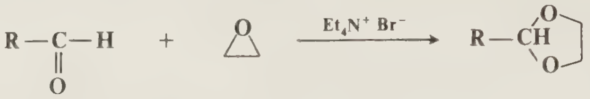
[55] For a review of hemiacetals, see Hurd, *J. Chem. Educ.* **43,** 527–531 (1966).

[56] Juvet and Chiu, *J. Am. Chem. Soc.* **83,** 1560 (1961).

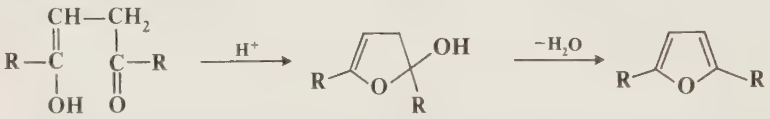
[57] For a review with respect to ortho esters, see DeWolfe, "Carboxylic Ortho Ester Derivatives," pp. 154–164, Academic Press, Inc., New York, 1970.

This method is especially useful for the conversion of ketones to ketals, since the direct reaction of a ketone with an alcohol often gives poor results. In a variation of this method, aldehydes are converted to cyclic acetals by heating in an autoclave with an epoxide and a quaternary ammonium salt:[58]



A feature of this method is that acid catalysts are not required.

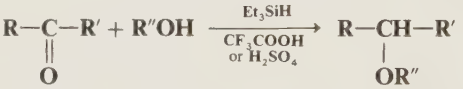
1,4-Diketones give furans when treated with acids. This is actually an example of an intramolecular addition of an alcohol to a ketone, since it is the enol form which adds:



Similarly, 1,5-diketones give pyrans. Formic acid reacts with alcohols to give orthoformates.

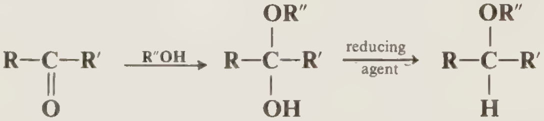
OS **I,** 1, 298, 364, 381; **II,** 137; **III,** 123, 387, 502, 536, 644, 731, 800; **IV,** 21, 479, 679; **V,** 5, 292, 303, 450, 539. Also see OS **IV,** 558, 588; **V,** 25.

6-7 Reductive Alkylation of Alcohols



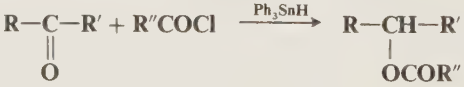
$$R-\underset{\underset{\displaystyle O}{\|}}{C}-R' + R''OH \xrightarrow[\text{or } H_2SO_4]{Et_3SiH \atop CF_3COOH} R-\underset{\underset{\displaystyle OR''}{|}}{CH}-R'$$

Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid[59] or by hydrogenation in alcoholic acid in the presence of platinum oxide.[60] The process can formally be regarded as addition of ROH to give a hemiacetal, followed by reduction of the OH:



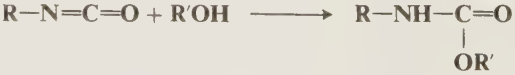
$$R-\underset{\underset{\displaystyle O}{\|}}{C}-R' \xrightarrow{R''OH} R-\overset{\overset{\displaystyle OR''}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-R' \xrightarrow[\text{agent}]{\text{reducing}} R-\overset{\overset{\displaystyle OR''}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-R'$$

In this respect it is similar to reaction **6-16**. In a similar reaction, ketones can be converted to esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.[61]



$$R-\underset{\underset{\displaystyle O}{\|}}{C}-R' + R''COCl \xrightarrow{Ph_3SnH} R-\underset{\underset{\displaystyle OCOR''}{|}}{CH}-R'$$

6-8 The Addition of Alcohols to Isocyanates



$$R-N{=}C{=}O + R'OH \longrightarrow R-NH-\underset{\underset{\displaystyle OR'}{|}}{C}{=}O$$

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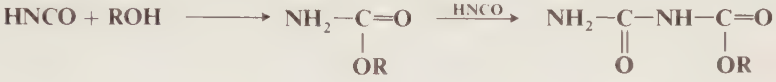
[58] Nerdel, Buddrus, Scherowsky, Klamann, and Fligge, *Justus Liebigs Ann. Chem.* **710,** 85 (1967).

[59] Doyle, DeBruyn, and Kooistra, *J. Am. Chem. Soc.* **94,** 3659 (1972).

[60] Verzele, Acke, and Anteunis, *J. Chem. Soc.* 5598 (1963). For still another method, see Loim, Parnes, Vasil'eva, and Kursanov, *J. Org. Chem. USSR* **8,** 902 (1972).

[61] Kaplan, *J. Am. Chem. Soc.* **88,** 4970 (1966).

Substituted urethans (carbamates) are prepared when isocyanates are treated with alcohols.[36] This is an excellent reaction, of wide scope, and gives good yields. The carbamates are often used as derivatives of the alcohols. Cyanic acid HNCO gives unsubstituted carbamates. Addition of a second mole of HNCO gives *allophanates*, which make good derivatives for many alcohols.



$$\mathrm{HNCO + ROH \longrightarrow NH_2{-}\underset{\displaystyle OR}{\underset{|}{C}}{=}O \xrightarrow{HNCO} NH_2{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NH{-}\underset{\displaystyle OR}{\underset{|}{C}}{=}O}$$

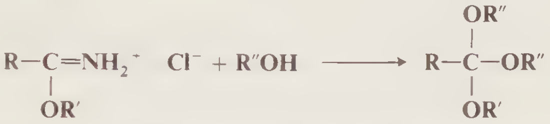
Allophanate

Polyurethans are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiocarbamates[62] RNHCSOR′, though they react slower than the corresponding isocyanates.

The details of the mechanism are poorly understood,[63] though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.[64] The addition of ROH to isocyanates can also be catalyzed by organometallic compounds.[65]

OS **I,** 140; **V,** 162; **51,** 112.

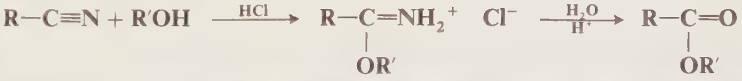
6-9 The Reaction between Imino Ester Salts and Alcohols



$$\mathrm{R{-}\underset{\displaystyle OR'}{\underset{|}{C}}{=}NH_2^+\ \ Cl^- + R''OH \longrightarrow R{-}\overset{\displaystyle OR''}{\overset{|}{\underset{\displaystyle OR'}{\underset{|}{C}}}}{-}OR''}$$

Imino ester salts (prepared by reaction **6-10**) react with alcohols to give ortho esters.[66] The reaction gives good yields.

6-10 Alcoholysis of Nitriles



$$\mathrm{R{-}C{\equiv}N + R'OH \xrightarrow{HCl} R{-}\underset{\displaystyle OR'}{\underset{|}{C}}{=}NH_2^+\ \ Cl^- \xrightarrow[H^+]{H_2O} R{-}\underset{\displaystyle OR'}{\underset{|}{C}}{=}O}$$

The addition of dry HCl to a mixture of a nitrile and an alcohol, in the absence of water, leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.[67] The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl can be used and the need for adding gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.[68]

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[62] For a review of thiocarbamates, see Walter and Bode, *Angew. Chem. Int. Ed. Engl.* **6,** 281–293 (1967) [*Angew. Chem.* **79,** 285–297].

[63] For a review, see Entelis and Nesterov, *Russ. Chem. Rev.* **35,** 917–930 (1966).

[64] See for example, Robertson and Stutchbury, *J. Chem. Soc.* 4000 (1964); Lammiman and Satchell, *J. Chem. Soc., Perkin Trans. 2* 2300 (1972), 877 (1974).

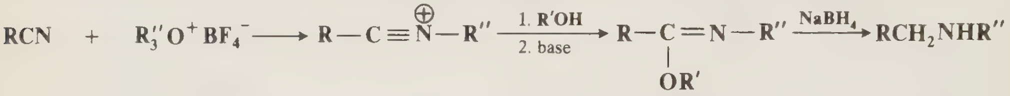
[65] For example, see Davies and Puddephatt, *J. Chem. Soc. C* 2663 (1967), 1479 (1968).

[66] For reviews, see DeWolfe, *Synthesis* 153–172 (1974), pp. 154–160, Ref. 57, pp. 2–11; Sandler and Karo, Ref. 53, vol. 2, pp. 43–48 (1971).

[67] For reviews, see Compagnon and Miocque, *Ann. Chim. (Paris)* [14] **5,** 23–27 (1970), pp. 24–26; Zil'berman, *Russ. Chem. Rev.* **31,** 615–633 (1962), p. 621; Sandler and Karo, Ref. 53, vol. 3, pp. 268–281 (1972). For a review of imino esters, see Neilson, in Patai, "The Chemistry of Amidines and Imidates," pp. 385–489, John Wiley & Sons, New York, 1975.

[68] Schaefer and Peters, *J. Org. Chem.* **26,** 412 (1961).

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group esterified and with no diester or diacid present. Addition of alcohols to nitrilium salts (prepared by treatment of nitriles with $R_3O^+ \quad BF_4^-$, see p. 373) gives



$$\mathrm{RCN} + \mathrm{R_3''O^+BF_4^-} \longrightarrow \mathrm{R{-}C{\equiv}\overset{\oplus}{N}{-}R''} \xrightarrow[\text{2. base}]{\text{1. R'OH}} \mathrm{R{-}\underset{\displaystyle OR'}{\underset{|}{C}}{=}N{-}R''} \xrightarrow{\mathrm{NaBH_4}} \mathrm{RCH_2NHR''}$$

N-alkylimino esters.[69] These imino esters can be reduced with $NaBH_4$ to yield secondary amines[70] (see also reactions **6-28, 6-29**).

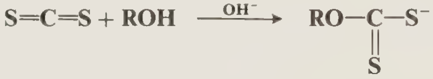
Cyanogen chloride reacts with alcohols in the presence of an acid catalyst such as dry HCl or $AlCl_3$ to give carbamates:[71]

$$\mathrm{ClCN + 2ROH \xrightarrow[\text{or } AlCl_3]{HCl} ROCONH_2 + RCl}$$

ROH can also be added to nitriles in another manner (reaction **6-57**).

OS **I**, 5, 270; **II**, 284, 310; **IV**, 645.

6-11 The Formation of Xanthates



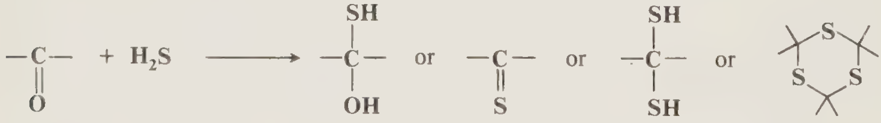
$$\mathrm{S{=}C{=}S + ROH \xrightarrow{OH^-} RO{-}\underset{\displaystyle S}{\underset{\|}{C}}{-}S^-}$$

The addition of alcohols to carbon disulfide in the presence of a base produces xanthates. The base is often OH^-, but in some cases better results can be obtained by using methylsulfinyl carbanion $MeSOCH_2^-$.[72] In a similar manner, alkoxide ions add to CO_2 to give carbonate ester salts $ROCOO^-$.

OS **V**, 439; **50**, 9.

C. Sulfur Nucleophiles

6-12 The Addition of H_2S and Mercaptans to Carbonyl Compounds



11 **12** **13** **14**

The addition of H_2S to an aldehyde or ketone may result in a variety of products.[73] The most usual product is the trithiane **14**.[74] α-Hydroxy thiols (**11**) can be prepared from polychloro and polyfluoro aldehydes and ketones.[75] Apparently **11** are stable only when prepared from these compounds, and not even for all of them. Thioketones[76] (**12**) can be prepared from certain ketones, such as diaryl ketones, by treatment with H_2S and an acid catalyst, usually HCl. They are often unstable and tend to trimerize (to **14**) or to react with air. Thioaldehydes are even less stable and apparently have never been prepared. Thioketones can also be prepared by treatment of ketones with P_4S_{10}.[77] *gem*-Dithiols (**13**) are much more stable than the corresponding hydrates or α-hydroxy thiols.[78] They have been prepared by the treatment of ketones with H_2S under pressure[79] and under mild conditions with HCl as a catalyst.[80] *gem*-Dithiols can also be prepared by the treatment of imines with H_2S,[81] and this can be accomplished without isolation of the imine if the aldehyde or ketone is treated with H_2S in the presence of ammonia or an amine.[82] In some cases *gem*-dithiols can be converted to thioketones by elimination of H_2S.[83]

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[69] Borch, *J. Org. Chem.* **34**, 627 (1969); Pilotti, Reuterhäll, Torssell, and Lindblad, *Acta Chem. Scand.* **23**, 818 (1969).

[70] Borch, Ref. 69.

[71] Bodrikov and Danova, *J. Org. Chem. USSR* **4**, 1611 (1968), **5**, 1558 (1969); Fuks and Hartemink, *Bull. Soc. Chim. Belg.* **82**, 23 (1973).

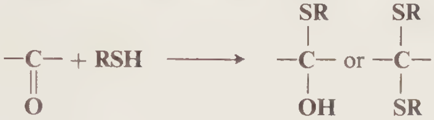
[72] Meurling, Sjöberg, and Sjöberg, *Acta Chem. Scand.* **26**, 279 (1972).

[73] For a review, see Campaigne, in Kharasch, "Organic Sulfur Compounds," vol. 1, pp. 134–145, Pergamon Press, New York, 1961.

[74] Campaigne and Edwards, *J. Org. Chem.* **27**, 3760 (1962).

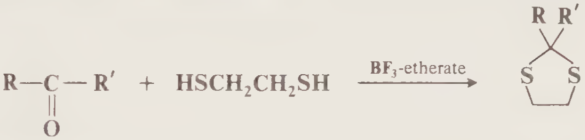
[75] Harris, *J. Org. Chem.* **25**, 2259 (1960).

Mercaptans add to aldehydes and ketones to give hemimercaptals (**15**) and mercaptals[84] (**16**).[85] Hemimercaptals are ordinarily unstable[86] though they are more stable than the corresponding hemiacetals and can be isolated in certain cases.[87] Mercaptals, like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one[88] (see reaction **0-99**). A common method for the protection of ketones involves treatment with ethanedithiol to give a cyclic thioketal.[88a] After subsequent reactions involving the R or R′ group, the protecting group can then be removed by reaction **0-7**. Alternatively, the thioketal can be desulfurized with Raney nickel (reaction **4-37**), giving the overall conversion C═O → CH_2. The C═O group of lactones and esters can be protected by a somewhat different, though related, procedure.[89] Mercaptals can also be prepared from aldehydes or ketones by treatment with orthothioborates



$$\underset{\Vert \atop \mathrm{O}}{-\mathrm{C}-} + \mathrm{RSH} \longrightarrow \underset{\mid \atop \mathrm{OH}}{\overset{\mathrm{SR} \atop \mid}{-\mathrm{C}-}} \text{ or } \underset{\mid \atop \mathrm{SR}}{\overset{\mathrm{SR} \atop \mid}{-\mathrm{C}-}}$$

15 **16**



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[76] For reviews of thioketones, see Mayer, in Janssen, "Organosulfur Chemistry," pp. 219–240, Interscience Publishers, New York, 1967; Campaigne, in Patai, "The Chemistry of the Carbonyl Group," Ref. 31, pp. 917–959; Mayer, Morganstern, and Fabian, *Angew. Chem. Int. Ed. Engl.* **3**, 277–286 (1964) [*Angew. Chem.* **76**, 157–167].

[77] See for example Scheeren, Ooms, and Nivard, *Synthesis* 149 (1973).

[78] For a review of the preparation of *gem*-dithiols, see Mayer, Hiller, Nitzchke, and Jentzsch, *Angew. Chem. Int. Ed. Engl.* **2**, 370–373 (1963) [*Angew. Chem.* **75**, 1011–1014].

[79] Cairns, Evans, Larchar, and McKusick, *J. Am. Chem. Soc.* **74**, 3982 (1952).

[80] Ref. 74; Demuynck and Vialle, *Bull. Soc. Chim. Fr.* 1213 (1967).

[81] Magnusson, *Acta Chem. Scand.* **16**, 1536 (1962), **17**, 273 (1963).

[82] Jentzsch, Fabian, and Mayer, *Chem. Ber.* **95**, 1764 (1962).

[83] Bleisch and Mayer, *Chem. Ber.* **99**, 1771 (1966); Demuynck and Vialle, *Bull. Soc. Chim. Fr.* 2748 (1967).

[84] When derived from aldehydes, these compounds are called *mercaptals* or *thioacetals*. When derived from ketones, they are often called *mercaptoles* or *thioketals*.

[85] For reviews, see Reid, "Organic Chemistry of Bivalent Sulfur," vol. 3, pp. 320–348, Chemical Publishing Company, New York, 1960; Campaigne, Ref. 73.

[86] See for example Fournier, Lamaty, Natat, and Roque, *Tetrahedron* **31**, 809 (1975).

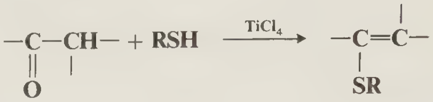
[87] For example, see Field and Sweetman, *J. Org. Chem.* **34**, 1799 (1969).

[88] Truce and Roberts, *J. Org. Chem.* **28**, 961 (1963).

[88a] For a review, see Olsen and Currie, in Patai, "The Chemistry of the Thiol Group," pt. 2, pp. 521–532, John Wiley & Sons, Inc., New York, 1974.

[89] Corey and Beames, *J. Am. Chem. Soc.* **95**, 5829 (1973).

$(RS)_3B$,[90] or with methylthiotrimethylsilane $MeSSiMe_3$.[91] If an aldehyde or ketone possesses an α-hydrogen, it can be converted to the corresponding vinyl sulfide by treatment with a mercaptan in the presence of titanium tetrachloride:[92]



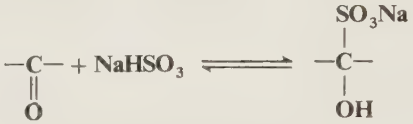
$$-\underset{\substack{\|\\ O}}{C}-\underset{|}{CH}- + RSH \xrightarrow{TiCl_4} -\underset{\substack{|\\ SR}}{C}=\overset{|}{C}-$$

Acyl halides treated with mercaptans give ortho thioesters:[93]

$$RCOCl + R'SH \longrightarrow RC(SR')_3$$

OS **II**, 610; **IV**, 927. Also see OS **III**, 332; **IV**, 967; **V**, 780; **50**, 72.

6-13 Formation of Bisulfite Addition Products



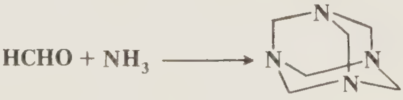
$$-\underset{\substack{\|\\ O}}{C}- + NaHSO_3 \rightleftharpoons -\overset{\substack{SO_3Na\\ |}}{\underset{\substack{|\\ OH}}{C}}-$$

Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite. Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base) and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.

OS **I**, 241, 336; **III**, 438; **IV**, 903; **V**, 437.

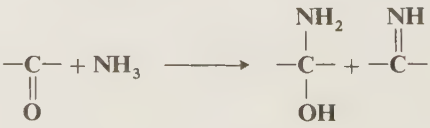
D. Attack by NH_2, NHR, or NR_2 (Addition of NH_3, RNH_2, R_2NH)

6-14 The Addition of Ammonia to Aldehydes and Ketones



17

The addition of ammonia to aldehydes or ketones does not generally give useful products. According to the pattern followed by analogous nucleophiles, the initial products would be expected to be *hemiaminals* (also called "aldehyde ammonias") (**18**) and/or imines (**19**):



$$-\underset{\substack{\|\\ O}}{C}- + NH_3 \longrightarrow -\overset{\substack{NH_2\\ |}}{\underset{\substack{|\\ OH}}{C}}- + -\overset{\substack{NH\\ \|}}{C}-$$

18 **19**

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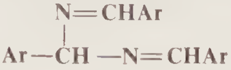
[90] Bessette, Brault, and Lalancette, *Can. J. Chem.* **43**, 307 (1965); Lalancette and Lachance, *Can. J. Chem.* **47**, 859 (1969).

[91] Evans, Grimm, and Truesdale, *J. Am. Chem. Soc.* **97**, 3229 (1975).

[92] Mukaiyama and Saigo, *Chem. Lett.* 479 (1973).

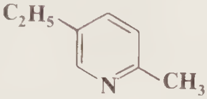
[93] Rinzema, Stoffelsma, and Arens, *Recl. Trav. Chim. Pays-Bas* **79**, 354 (1959).

However, these compounds are generally unstable. Imines with a hydrogen on the nitrogen spontaneously polymerize and have never been isolated in this reaction in the pure state, though cobalt complexes of such imines have been prepared and are stable enough to be storable under an inert-gas atmosphere at room temperature.[94] Stable hemiaminals can be prepared from polychlorinated and polyfluorinated aldehydes and ketones. Aside from these, when stable compounds *are* prepared in this reaction, they are the result of combinations and condensations of one or more molecules of **18** and or **19** with each other or with additional molecules of ammonia or carbonyl compound. The most important example of such a product is hexamethylenetetramine (**17**), prepared from ammonia and formaldehyde. Analogs of this compound have been prepared from aromatic aldehydes and ammonium carbonate.[95] Aromatic aldehydes give hydrobenzamides (**20**) derived from three molecules of aldehyde and two of ammonia.[96] Similar compounds can be prepared from aldehydes of the form R_2CHCHO and R_3CCHO.[97] Acetaldehyde and α,β-unsaturated aldehydes give alkylpyridine derivatives.[98] For example, 5-ethyl-2-picoline (**21**) can be obtained from acetaldehyde. Cyclic trimers of **19** can sometimes be isolated as crystalline compounds, but these are unstable in solution.[99]



$$\mathrm{Ar{-}\overset{\displaystyle N{=}CHAr}{\overset{|}{C}H}{-}N{=}CHAr}$$

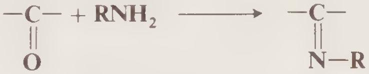
20



21

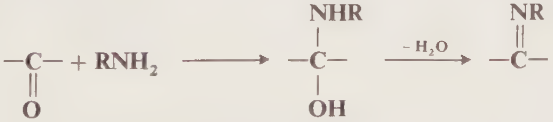
OS II, 214, 219; IV, 451; 50, 81; 52, 135. Also see OS III, 471; V, 897.

6-15 The Addition of Amines to Aldehydes and Ketones



$$\underset{\displaystyle O}{\underset{\|}{-C-}} + RNH_2 \longrightarrow \underset{\displaystyle N-R}{\underset{\|}{-C-}}$$

Primary, secondary, and tertiary amines can add to aldehydes[100] and ketones to give different kinds of products. Primary amines give imines.[101] In contrast to imines in which the nitrogen is attached to a hydrogen (reaction **6-14**), these imines are stable enough for isolation. However, in most cases they rapidly decompose or polymerize unless there is at least one aryl group on the nitrogen or the carbon. When there is an aryl group, the compounds are quite stable. They are usually called *Schiff bases*, and this reaction is the best way to prepare them. The reaction is straightforward and proceeds in high yields. The initial N-substituted hemiaminals lose water to give the stable Schiff bases:



$$\underset{\displaystyle O}{\underset{\|}{-C-}} + RNH_2 \longrightarrow \overset{\displaystyle NHR}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{-C-}}}} \xrightarrow{-H_2O} \overset{\displaystyle NR}{\overset{\|}{-C-}}$$

---

[94] Rhee, Ryang, and Tsutsumi, *Tetrahedron Lett.* 3419 (1970).

[95] Kamal, Ahmad, and Qureshi, *Tetrahedron* **19,** 869 (1963).

[96] Ogata, Kawasaki, and Okumura, *J. Org. Chem.* **29,** 1985 (1964); Crowell and McLeod, *J. Org. Chem.* **32,** 4030 (1967).

[97] Hasek, Elam, and Martin, *J. Org. Chem.* **26,** 1822 (1961).

[98] For a review, see Gelas, *Bull. Soc. Chim. Fr.* 3093–3101 (1967).

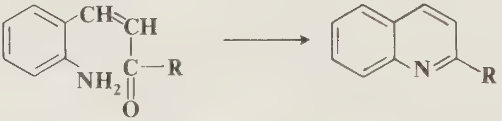
[99] For example, see Nielsen, Atkins, Moore, Scott, Mallory, and LaBerge, *J. Org. Chem.* **38,** 3288 (1973); Nielsen, Atkins, DiPol, and Moore, *J. Org. Chem.* **39,** 1349 (1974).

[100] For a review of the reactions between amines and formaldehyde, see Farrar, *Rec. Chem. Prog.* **29,** 85–101 (1968).

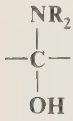
[101] For reviews of reactions of carbonyl compounds leading to the formation of C=N bonds, see Dayagi and Degani, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Ref. 31, pp. 64–83; Reeves, in Patai, "The Chemistry of the Carbonyl Group," Ref. 31, pp. 600–614. For a review of the chemistry of imines, see Layer, *Chem. Rev.* **63,** 489–510 (1963).

In general, ketones react more slowly than aldehydes, and higher temperatures and longer reaction times are often required. In addition, the equilibrium must often be shifted, usually by removal of the water, either azeotropically by distillation, or with a drying agent such as $TiCl_4$,[102] or with a molecular sieve.[103]

The reaction is often used to effect ring closure. The *Friedlander quinoline synthesis* is an example:

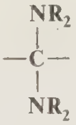


When secondary amines are added to aldehydes or ketones, the initially formed N,N-disubstituted hemiaminals (**22**) cannot lose water in the same way, and it is possible to isolate them.[104] However, they are generally unstable, and under the reaction conditions usually react further. If no α-hydrogen is present, **22** is converted to the more stable *aminal* (**23**). However, if an α-hydrogen is present, water (from **22**) or RNH_2 (from **23**) can be lost in that direction to give an enamine:[105]



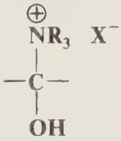
$$\begin{array}{c} NR_2 \\ | \\ -C- \\ | \\ OH \end{array}$$

22



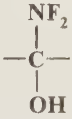
$$\begin{array}{c} NR_2 \\ | \\ -C- \\ | \\ NR_2 \end{array}$$

23



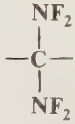
$$\begin{array}{c} \overset{\oplus}{NR_3}\ X^- \\ | \\ -C- \\ | \\ OH \end{array}$$

24



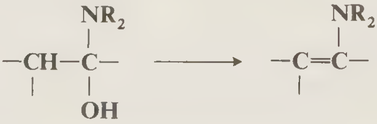
$$\begin{array}{c} NF_2 \\ | \\ -C- \\ | \\ OH \end{array}$$

25



$$\begin{array}{c} NF_2 \\ | \\ -C- \\ | \\ NF_2 \end{array}$$

26



$$\begin{array}{c} \quad NR_2 \\ \quad | \\ -CH-C- \\ |\quad\ | \\ \quad OH \end{array} \longrightarrow \begin{array}{c} \quad NR_2 \\ \quad | \\ -C{=}C- \\ | \quad\ \ \end{array}$$

This is the most common method for the preparation of enamines and usually takes place when an aldehyde or ketone containing an α-hydrogen is treated with a secondary amine. The water is usually removed azeotropically or with a drying agent,[106] but molecular sieves can also be used.[107] Secondary amine perchlorates react with aldehydes and ketones to give iminium salts (**7**, p. 807).[108] Tertiary amines can only give salts (**24**). Difluoramine NF_2H adds to aldehydes and ketones to give stable α-difluoraminocarbinols (**25**)[109] or, if concentrated H_2SO_4 is present, *gem*-bis(difluoro)amines (**26**).[110]

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[102] Weingarten, Chupp, and White, *J. Org. Chem.* **32,** 3246 (1947).

[103] Bonnett and Emerson, *J. Chem. Soc.* 4508 (1965); Kyba, *Org. Prep. Proced.* **2,** 149 (1970); Roelofsen and van Bekkum, *Recl. Trav. Chim. Pays-Bas* **91,** 605 (1972).

[104] For example, see Duhamel and Cantacuzène, *Bull. Soc. Chim. Fr.* 1843 (1962).

[105] For reviews of the preparation of enamines, see, in Cook, Ref. 35, the articles by Haynes, pp. 55–100, and Kuehne, 315–341; Szmuszkovicz, *Adv. Org. Chem.* **4,** 1–113 (1963), pp. 9–12; Sandler and Karo, Ref. 53, vol. 2, pp. 86–94 (1971).

[106] For example $TiCl_4$: White and Weingarten, *J. Org. Chem.* **32,** 213 (1967); Kuo and Daly, *J. Org. Chem.* **35,** 1861 (1970).

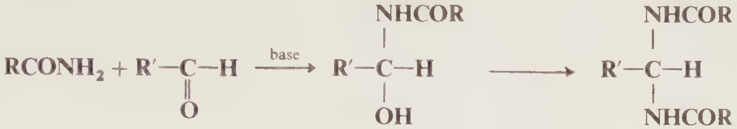
[107] Brannock, Bell, Burpitt, and Kelly, *J. Org. Chem.* **29,** 801 (1964); Taguchi and Westheimer, *J. Org. Chem.* **36,** 1570 (1971); Roelofsen and van Bekkum, Ref. 103.

[108] Leonard and Paukstelis, *J. Org. Chem.* **28,** 3021 (1963).

[109] Freeman, Graham, and Parker, *J. Am. Chem. Soc.* **90,** 121 (1968).

[110] Baum, *J. Am. Chem. Soc.* **90,** 7083 (1968).

Amides can add to aldehydes in the presence of bases (so the nucleophile is actually $\mathrm{RCONH^-}$) or acids to give acylated amino alcohols, which often react further to give alkylidene or arylidene bisamides:[111]

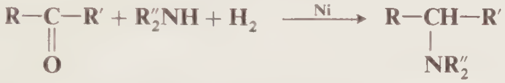


$$\mathrm{RCONH_2 + R'-\underset{\underset{O}{\|}}{C}-H \xrightarrow{base} R'-\overset{\overset{NHCOR}{|}}{\underset{\underset{OH}{|}}{C}}-H \longrightarrow R'-\overset{\overset{NHCOR}{|}}{\underset{\underset{NHCOR}{|}}{C}}-H}$$

If the R′ group contains an α-hydrogen, water may split out.

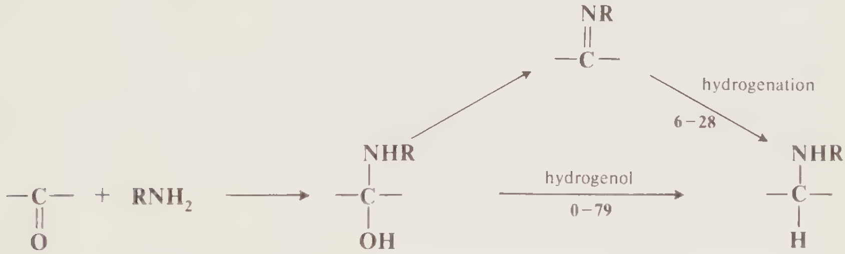
OS **I,** 80, 355, 381; **II,** 31, 49, 65, 202, 231, 422; **III,** 95, 328, 329, 332, 358, 374, 513, 753, 827; **IV,** 210, 605, 638, 824; **V,** 191, 277, 533, 567, 627, 703, 716, 736, 758, 808, 941, 1070; **50,** 66; **53,** 44, 48, 59; **54,** 39, 46, 93. Also see OS **IV,** 283, 464.

6-16 Reductive Alkylation of Ammonia or Amines



$$\mathrm{R-\underset{\underset{O}{\|}}{C}-R' + R''_2NH + H_2 \xrightarrow{Ni} R-\underset{\underset{NR''_2}{|}}{CH}-R'}$$

When an aldehyde or a ketone is treated with ammonia or a primary or secondary amine in the presence of hydrogen and a hydrogenation catalyst (heterogeneous or homogeneous[112]), *reductive alkylation* takes place.[113] The reaction can formally be regarded as occurring in the following manner (shown for a primary amine), which probably *does* correspond to the actual sequence of steps:[114]



For ammonia and primary amines there are thus two possible pathways, but when secondary amines are involved, only the hydrogenolysis pathway is possible. Other reducing agents can be used instead of hydrogen and a catalyst, among them zinc and HCl, sodium cyanoborohydride $\mathrm{NaBH_3CN}$,[115] sodium borohydride,[116] iron pentacarbonyl and alcoholic KOH,[117] and formic acid. When the last is used, the process is called the *Wallach reaction.* In the particular case where primary or secondary amines are reductively methylated with *formaldehyde* and formic acid, the method is called the *Eschweiler-Clarke procedure*. It is possible to use ammonium (or amine) salts of formic acid, or formamides, as a substitute for the Wallach conditions. This method is called the *Leuckart reaction*,[118] and in this case the products obtained are often the N-formyl derivatives of the amines instead of the free amines. Primary and secondary aromatic amines can be N-ethylated (e.g., ArNHR → ArNREt) by treatment with $NaBH_4$ in acetic acid.[119]

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[111] For reviews, see Challis and Challis, in Zabicky, Ref. 46, pp. 754–759; Zaugg and Martin, *Org. React.* **14,** 52–269 (1965), pp. 91–95, 104–112. For a discussion, see Gilbert, *Synthesis* 30 (1972).

[112] Markó and Bakos, *J. Organomet. Chem.* **81,** 411 (1974).

[113] For reviews, see Rylander, "Catalytic Hydrogenation over Platinum Metals," pp. 291–303, Academic Press, Inc., New York, 1967; Emerson, *Org. React.* **4,** 174–255 (1948).

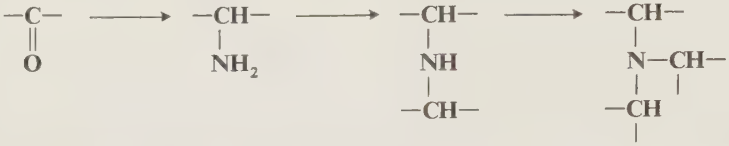
[114] See, for example, Le Bris, Lefebvre, and Coussemant, *Bull. Soc. Chim. Fr.* 1366, 1374, 1584, 1594 (1964).

[115] Borch, Bernstein, and Durst, *J. Am. Chem. Soc.* **93,** 2897 (1971). See also Boutigue and Jacquesy, *Bull. Soc. Chim. Fr.* 750 (1973). For a review of $\mathrm{NaBH_3CN}$, see Lane, *Synthesis* 135–146 (1975).

[116] Schellenberg, *J. Org. Chem.* **28,** 3259 (1963).

[117] Watanabe, Yamashita, Mitsudo, Tanaka, and Takegami, *Tetrahedron Lett.* 1879 (1974); Watanabe, Mitsudo, Yamashita, Shim, and Takegami, *Chem. Lett.* 1265 (1974). See also Boldrini, Panunzio, and Umani-Ronchi, *Synthesis* 733 (1974).

When the reagent is ammonia, it is possible for the initial product to react again and for this product to react again, so that secondary and tertiary amines are usually obtained as side products:



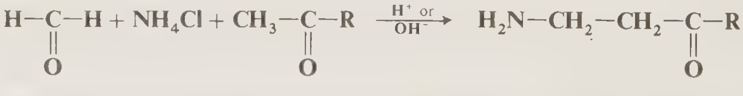
Similarly, primary amines give tertiary as well as secondary amines. In order to minimize this, the aldehyde or ketone is treated with an excess of ammonia or primary amine (unless of course the higher amine is desired).

Primary amines have been prepared from many aldehydes with at least five carbons and from many ketones by treatment with ammonia and a reducing agent. Smaller aldehydes are usually too reactive to permit isolation of the primary amine. Secondary amines have been prepared by both possible procedures: 2 moles of ammonia and 1 mole of aldehyde or ketone, and 1 mole of primary amine and 1 mole of carbonyl compound, the latter method being better for all but aromatic aldehydes. Tertiary amines can be prepared in three ways, but the method is seldom carried out with 3 moles of ammonia and 1 mole of carbonyl compound. Much more often they are prepared from primary or secondary amines.[120] The most common method for this purpose is the Eschweiler-Clarke procedure; i.e., treatment of the primary or secondary amine with formaldehyde and formic acid. Amines of the form $RNMe_2$ and R_2NMe are prepared in this manner.[121] Another method for accomplishing the conversions $RNH_2 \rightarrow RNMe_2$ and $R_2NH \rightarrow R_2NMe$ is to treat the amine with aqueous formaldehyde and $NaBH_4$[122] or $NaBH_3CN$.[123]

Reductive alkylation has also been carried out on nitro, nitroso, azo, and other compounds which are reduced in situ to primary or secondary amines.

OS **I,** 347, 528, 531; **II,** 503; **III,** 328, 501, 717, 723; **IV,** 603; **V,** 552; **52,** 124.

6-17 The Mannich Reaction



$$\underset{\displaystyle O}{\overset{}{H-\underset{\|}{C}-H}} + NH_4Cl + CH_3-\underset{\underset{\displaystyle O}{\|}}{C}-R \xrightarrow[OH^-]{H^+\text{ or}} H_2N-CH_2-CH_2-\underset{\underset{\displaystyle O}{\|}}{C}-R$$

In the *Mannich reaction*, formaldehyde (or sometimes another aldehyde) is condensed with ammonia, in the form of its salt, and a compound containing an active hydrogen.[124] This can formally be considered as an addition of ammonia to give H_2NCH_2OH, followed by a nucleophilic substitution (see the discussion of the mechanism on p. 822). Instead of ammonia, the reaction can be carried out with salts of primary or secondary amines, or with amides,[125] in which cases the product is substituted on the nitrogen with R, R_2, and RCO, respectively. Arylamines do not normally give the reaction. In any case, the product is referred to as a *Mannich base*. Many active hydrogen compounds give the reaction. Among these are the following types, with the active hydrogen underlined:

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[118] For a review, see Moore, *Org. React.* **5,** 301–330 (1949); for a discussion of the mechanism, see Lukasiewicz, *Tetrahedron* **19,** 1789 (1963).

[119] Gribble, Lord, Skotnicki, Dietz, Eaton, and Johnson, *J. Am. Chem. Soc.* **96,** 7812 (1974). See also Marchini, Liso, Reho, Liberatore, and Moracci, *J. Org. Chem.* **40,** 3453 (1975).

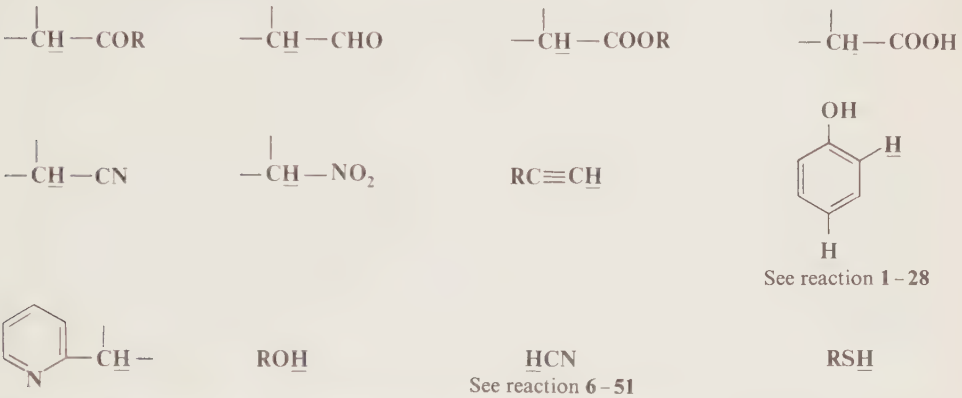
[120] For a review of the preparation of tertiary amines by reductive alkylation, see Spialter and Pappalardo, "The Acyclic Aliphatic Tertiary Amines," pp. 44–52, The Macmillan Company, New York, 1965.

[121] For a discussion, see Pine and Sanchez, *J. Org. Chem.* **36,** 829 (1971).

[122] Sondengam, Hentchoya Hémo, and Charles, *Tetrahedron Lett.* 261 (1973).

[123] Borch and Hassid, *J. Org. Chem.* **37,** 1673 (1972).

[124] For reviews, see Tramontini, *Synthesis* 703–775 (1973); Blicke, *Org. React.* **2,** 303–341 (1942); House, "Modern Synthetic Reactions," 2d ed, pp. 654–660, W. A. Benjamin, Inc., New York, 1972. For a review of Mannich reactions in which the active-hydrogen component is a nitro compound, see Baer and Urbas, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," pp. 117–130, Interscience Publishers, New York, 1970.



$-\overset{|}{C}\underline{H}-COR$ $-\overset{|}{C}\underline{H}-CHO$ $-\overset{|}{C}\underline{H}-COOR$ $-\overset{|}{C}\underline{H}-COOH$

$-\overset{|}{C}\underline{H}-CN$ $-\overset{|}{C}\underline{H}-NO_2$ $RC{\equiv}C\underline{H}$

See reaction **1-28**

$RO\underline{H}$ $\underline{H}CN$ $RS\underline{H}$

See reaction **6-51**

The Mannich base can react further, in three ways. If it is a primary or secondary amine, then it may condense with one or two additional molecules of aldehyde and active compound, e.g.,

$$H_2NCH_2CH_2COR \xrightarrow[CH_3COR]{HCHO} HN(CH_2CH_2COR)_2 \xrightarrow[CH_3COR]{HCHO} N(CH_2CH_2COR)_3$$

If the active hydrogen compound has two or three active hydrogens, the Mannich base may condense with one or two additional molecules of aldehyde and ammonia or amine, e.g.,

$$H_2NCH_2CH_2COR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_2CHCOR \xrightarrow[NH_3]{HCHO} (H_2NCH_2)_3CCOR$$

Another further reaction consists of condensation of the Mannich base with excess formaldehyde:

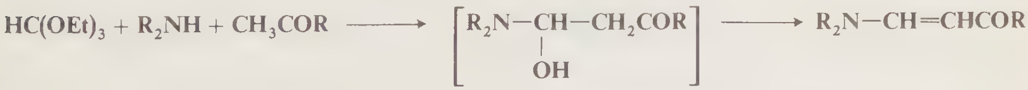
$$H_2NCH_2CH_2COR + HCHO \longrightarrow H_2C{=}NCH_2CH_2COR$$

Sometimes it is possible to obtain these products of further condensation as the main products of the reaction. At other times they are side products.

When the Mannich base contains an amino group β to a carbonyl (and it usually does), ammonia is easily eliminated and this is a route to α,β-unsaturated aldehydes, ketones, esters, etc.:

$$H_2NCH_2CH_2COR \xrightarrow{\Delta} H_2C{=}CHCOR$$

Enamines can be prepared by a Mannich reaction involving a secondary amine and formic acid (in the form of ethyl orthoformate) instead of formaldehyde, e.g.,



$$HC(OEt)_3 + R_2NH + CH_3COR \longrightarrow \left[R_2N-\underset{OH}{\underset{|}{C}H}-CH_2COR\right] \longrightarrow R_2N-CH{=}CHCOR$$

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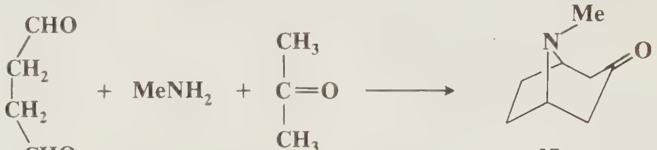
[125] Hellmann, *Angew. Chem.* **69,** 463 (1957), *Newer Methods Prep. Org. Chem.* **2,** 277–302 (1963).

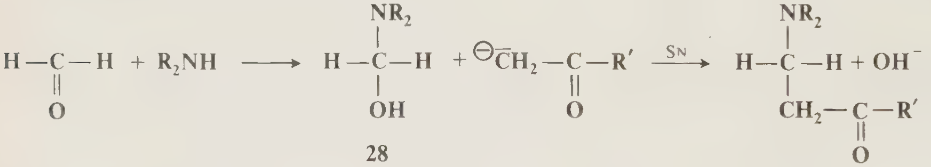
The Mannich reaction is an important biosynthetic route to natural products, mainly alkaloids, and some of these routes have been duplicated in the laboratory. A classic example is the synthesis of tropinone by Robinson in 1917. Atropine, a natural product, is an ester of tropic acid $\mathrm{PhCH(COOH)CH_2OH}$ and tropine. Tropine is a secondary alcohol which can be oxidized to the corresponding ketone, tropinone (**27**). Robinson synthesized tropinone by a Mannich reaction involving succindialdehyde, methylamine, and acetone:[126]



27

Over the years there has been much controversy about the mechanism of the Mannich reaction, especially whether the aldehyde is first attacked by the active hydrogen compound (as in reaction **6-40**) or by the ammonia or amine (as in reaction **6-15**). It is now generally agreed that the latter pathway is the correct one. Studies of the reaction kinetics have led to the following mechanistic proposals:[127]

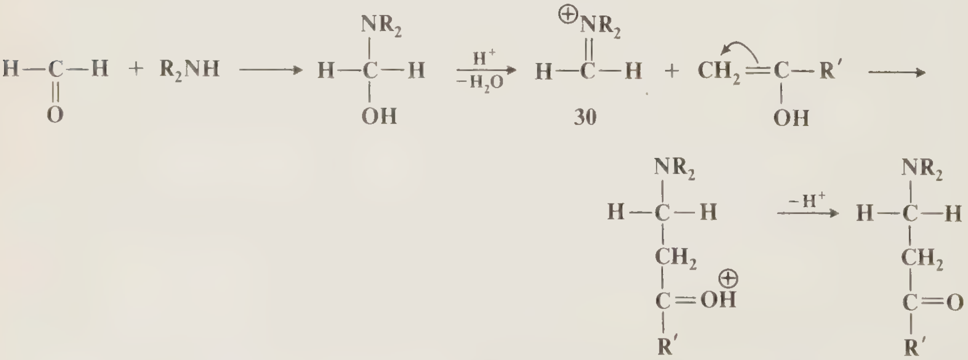
The base-catalyzed reaction



$$\underset{\overset{\|}{\mathrm{O}}}{\mathrm{H{-}C{-}H}} + \mathrm{R_2NH} \longrightarrow \underset{\underset{\mathbf{28}}{\mathrm{OH}}}{\overset{\mathrm{NR_2}}{\mathrm{H{-}C{-}H}}} + {}^{\ominus}\mathrm{CH_2{-}}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{{-}R'} \xrightarrow{\mathrm{S_N}} \underset{\mathrm{CH_2{-}}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{{-}R'}}{\overset{\mathrm{NR_2}}{\mathrm{H{-}C{-}H}}} + \mathrm{OH^-}$$

There is evidence that in basic media the intermediate which undergoes the nucleophilic substitution may be $\mathrm{H_2C(NR_2)_2}$ (**29**) instead of **28**,[128] but it has been shown that **28** are more reactive than **29** in this type of step.[129]

The acid-catalyzed reaction



$$\underset{\overset{\|}{\mathrm{O}}}{\mathrm{H{-}C{-}H}} + \mathrm{R_2NH} \longrightarrow \underset{\mathrm{OH}}{\overset{\mathrm{NR_2}}{\mathrm{H{-}C{-}H}}} \xrightarrow[-\mathrm{H_2O}]{\mathrm{H^+}} \underset{\mathbf{30}}{\overset{\overset{\oplus}{\mathrm{NR_2}}}{\overset{\|}{\mathrm{H{-}C{-}H}}}} + \mathrm{CH_2{=}}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{{-}R'} \longrightarrow$$

$$\underset{\underset{\underset{\mathrm{R'}}{\mathrm{C{=}\overset{\oplus}{O}H}}}{\mathrm{CH_2}}}{\overset{\mathrm{NR_2}}{\mathrm{H{-}C{-}H}}} \xrightarrow{-\mathrm{H^+}} \underset{\underset{\underset{\mathrm{R'}}{\mathrm{C{=}O}}}{\mathrm{CH_2}}}{\overset{\mathrm{NR_2}}{\mathrm{H{-}C{-}H}}}$$

According to this mechanism, it is the free amine and not the salt which reacts, even in acid solution; and the active-hydrogen compound (in the acid-catalyzed process) reacts as the enol when that is possible. This latter step is similar to that in reaction **2-4.** There is kinetic evidence for the intermediacy of the iminium ion (**30**).[130]

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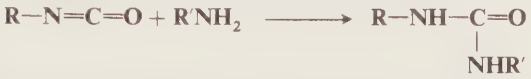
[126] Robinson, *J. Chem. Soc.* **111**, 762 (1917).
[127] Cummings and Shelton, *J. Org. Chem.* **25**, 419 (1960).
[128] Burckhalter, Wells, and Mayer, *Tetrahedron Lett.* 1353 (1964).
[129] Fernandez, *Tetrahedron Lett.* 2889 (1964).

When it is desired to use an unsymmetrical ketone as the active-hydrogen component, it is possible to get two products. Regioselectivity has been obtained by treatment of the ketone with preformed iminium ions:[131] the use of $Me_2\overset{\oplus}{N}{=}CH_2 \quad CF_3COO^-$ in CF_3COOH gives substitution at the more highly substituted position, while with iso-$Pr_2\overset{\oplus}{N}{=}CH_2 \quad ClO_4^-$ the reaction takes place at the less highly substituted position.[132] Regioselective synthesis of Mannich bases can also be carried out in an indirect manner (see reaction **6-36**). Also see reactions **6-51** and **1-28.**

OS **III,** 305; **IV,** 281, 515, 816.

6-18 The Addition of Amines to Isocyanates

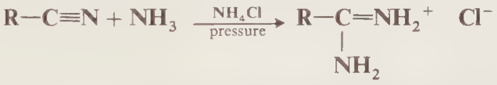


$$R{-}N{=}C{=}O + R'NH_2 \longrightarrow R{-}NH{-}\underset{\displaystyle NHR'}{\underset{|}{C}}{=}O$$

Ammonia and primary and secondary amines can be added to isocyanates to give substituted ureas.[36] Isothiocyanates give thioureas. This is an excellent method for the preparation of ureas and thioureas, and these compounds are often used as derivatives for primary and secondary amines. Cyanic acid HNCO also gives the reaction; usually its salts, e.g., NaNCO, are used. Wöhler's famous synthesis of urea involved the addition of ammonia to a salt of cyanic acid.[133]

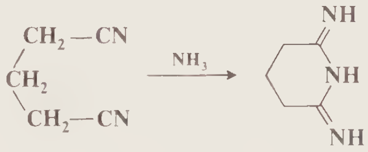
OS **II,** 79; **III,** 76, 617, 735; **IV,** 49, 180, 213, 515, 700; **V,** 555, 801, 802, 967; **51,** 121.

6-19 The Addition of Ammonia or Amines to Nitriles



$$R{-}C{\equiv}N + NH_3 \xrightarrow[\text{pressure}]{NH_4Cl} R{-}\underset{\displaystyle NH_2}{\underset{|}{C}}{=}NH_2^+ \quad Cl^-$$

Unsubstituted amidines (in the form of their salts) can be prepared by addition of ammonia to nitriles.[133a] Many amidines have been made in this way.[134] Dinitriles of suitable chain length may give imidines:[135]



Primary and secondary amines can be used instead of ammonia, to give substituted amidines, but only if the nitrile contains electron-withdrawing groups; e.g., Cl_3CCN gives the reaction. Ordinary nitriles do not react, and, in fact, acetonitrile is often used as a solvent in this reaction.[136] However, aniline can be added to benzonitrile with $AlCl_3$ as catalyst. The addition of ammonia to cyanamide NH_2CN gives guanidine $(NH_2)_2C{=}NH$.

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[130] Benkovic, Benkovic, and Comfort, *J. Am. Chem. Soc.* **91,** 1860 (1969).

[131] For earlier use of preformed iminium ions in the Mannich reaction, see Ahond, Cavé, Kan-Fan, Husson, de Rostolan, and Potier, *J. Am. Chem. Soc.* **90,** 5622 (1968); Ahond, Cavé, Kan-Fan, and Potier, *Bull. Soc. Chim. Fr.* 2707 (1970); Schreiber, Maag, Hashimoto, and Eschenmoser, *Angew. Chem. Int. Ed. Engl.* **10,** 330 (1971) [*Angew. Chem.* **83,** 355 (1971)].

[132] Jasor, Luche, Gaudry, and Marquet, *J. Chem. Soc., Chem. Commun.* 253 (1974).

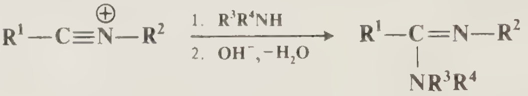
[133] For a discussion of the mechanism of this reaction, see Williams and Jencks, *J. Chem. Soc., Perkin Trans. 2* 1753, 1760 (1974).

[133a] For a review of amidines, see Gautier, Miocque, and Farnoux, in Patai, Ref. 67, pp. 283–348.

[134] See, for example, Schaefer and Krapcho, *J. Org. Chem.* **27,** 1255 (1962).

[135] Elvidge, Linstead, and Salaman, *J. Chem. Soc.* 208 (1959).

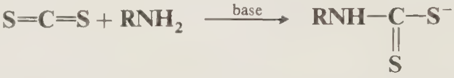
Ammonia and primary and secondary amines add to nitrilium salts to give substituted amidines (shown for secondary amines):[137]



$$R^1{-}C{\equiv}\overset{\oplus}{N}{-}R^2 \xrightarrow[2.\ OH^-,\ -H_2O]{1.\ R^3R^4NH} R^1{-}\underset{\displaystyle NR^3R^4}{\underset{|}{C}}{=}N{-}R^2$$

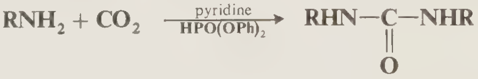
OS **I,** 302 [but also see OS **V,** 589]; **IV,** 245, 247, 515, 566, 769. See also OS **V,** 39.

6-20 The Addition of Amines to Carbon Disulfide and Carbon Dioxide



$$S{=}C{=}S + RNH_2 \xrightarrow{\text{base}} RNH{-}\underset{\displaystyle S}{\underset{\|}{C}}{-}S^-$$

Salts of dithiocarbamic acid can be prepared by the addition of primary amines to carbon disulfide. This reaction is similar to reaction **6-11.** H_2S can be eliminated from the product, directly or indirectly, to give isothiocyanates RNCS. Isothiocyanates can be obtained directly by the reaction of primary amines and CS_2 in pyridine in the presence of dicyclohexylcarbodiimide.[138] In the presence of diphenyl phosphite and pyridine, primary amines add to CO_2 and to CS_2 to give, respectively, symmetrically substituted ureas and thioureas:[139]

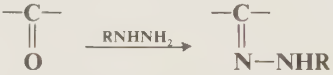


$$RNH_2 + CO_2 \xrightarrow[HPO(OPh)_2]{\text{pyridine}} RHN{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NHR$$

OS **I,** 447; **III,** 360, 394, 599, 763; **V,** 223.

E. Other Nitrogen Nucleophiles

6-21 The Addition of Hydrazine Derivatives to Carbonyl Compounds



$$-\underset{\displaystyle O}{\underset{\|}{C}}- \xrightarrow{RNHNH_2} -\underset{\displaystyle N{-}NHR}{\underset{\|}{C}}-$$

The product of condensation of a hydrazine and an aldehyde or ketone is called a *hydrazone*. Hydrazine itself gives hydrazones only with aryl ketones. With other aldehydes and ketones, either no useful product can be isolated, or the remaining NH_2 group condenses with a second mole of carbonyl compound to give an *azine*. This type of product is especially important for aromatic aldehydes:

$$ArCH{=}N{-}NH_2 + ArCHO \longrightarrow \underset{\text{An azine}}{ArCH{=}N{-}N{=}CHAr}$$

However, in some cases azines can be converted to hydrazones by treatment with excess hydrazine and NaOH.[140] Arylhydrazines, especially phenyl, *p*-nitrophenyl, and 2,4-dinitrophenyl, are used much more often and give the corresponding hydrazones with most aldehydes and ketones.[141]

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[136] Grivas and Taurins, *Can. J. Chem.* **39,** 761 (1961).

[137] Fuks, *Tetrahedron Lett.* 2147, 2153 (1973).

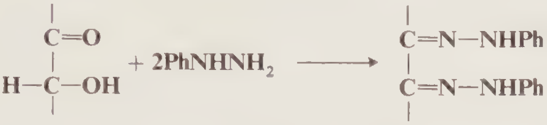
[138] Jochims and Seeliger, *Angew. Chem. Int. Ed. Engl.* **6,** 174 (1967) [*Angew. Chem.* **79,** 151]; Jochims, *Chem. Ber.* **101,** 1746 (1968). For another method, see Sakai, Aizawa, and Fujinami, *J. Org. Chem.* **39,** 1970 (1974).

[139] Yamazaki, Higashi, and Iguchi, *Tetrahedron Lett.* 1191 (1974).

[140] For example, see Day and Whiting, *Org. Synth.* **50,** 3 (1970).

[141] For a review of arylhydrazones, see Buckingham, *Q. Rev., Chem. Soc.* **23,** 37–56 (1969).

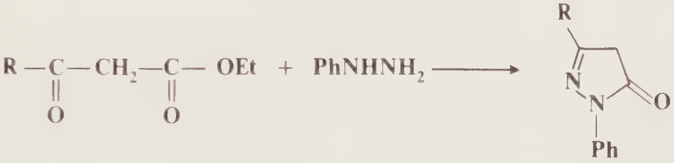
Since these are usually solids, they make excellent derivatives and are commonly employed for this purpose. α-Hydroxy aldehydes and ketones and α-dicarbonyl compounds give *osazones*, in which two adjacent carbons have carbon-nitrogen double bonds:



$$\begin{matrix} | \\ C{=}O \\ | \\ H{-}C{-}OH \\ | \end{matrix} + 2PhNHNH_2 \longrightarrow \begin{matrix} | \\ C{=}N{-}NHPh \\ | \\ C{=}N{-}NHPh \\ | \end{matrix}$$

An osazone

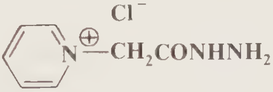
Osazones are particularly important in carbohydrate chemistry. In contrast to this behavior, β-diketones and β-keto esters give *pyrazoles* and *pyrazolones*, respectively (illustrated for β-keto esters):



Other hydrazine derivatives frequently used to prepare the corresponding hydrazone are semicarbazide $NH_2NHCONH_2$, in which case the hydrazone is called a semicarbazone, and *Girard's reagents T and P*, in which case the hydrazone is water-soluble because of the ionic group. Girard's reagents are often used for purification of carbonyl compounds.

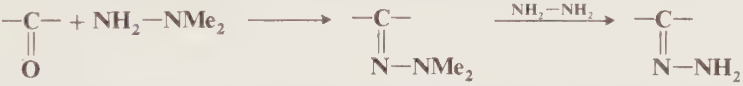
$Cl^- \quad Me_3NCH_2CONHNH_2$

Girard's reagent T



Girard's reagent P

Simple N-unsubstituted hydrazones can be obtained by an exchange reaction. The N,N-dimethylhydrazone is prepared first and then treated with hydrazine:[142]

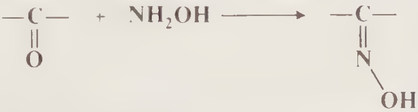


$$\underset{\displaystyle O}{\overset{}{\underset{\|}{-C-}}} + NH_2{-}NMe_2 \longrightarrow \underset{\displaystyle N{-}NMe_2}{\underset{\|}{-C-}} \xrightarrow{NH_2-NH_2} \underset{\displaystyle N{-}NH_2}{\underset{\|}{-C-}}$$

No azines are formed under these conditions.

OS **II,** 395; **III,** 96, 351; **IV,** 351, 377, 536, 884; **V,** 27, 258, 747, 929; **50,** 3, 102, **52,** 122; **55,** 52, 73. Also see OS **III,** 708; **50,** 6.

6-22 The Formation of Oximes



$$\underset{\displaystyle O}{\underset{\|}{-C-}} + NH_2OH \longrightarrow \underset{\displaystyle N{-}OH}{\underset{\|}{-C-}}$$

In a reaction very much like **6-21,** oximes can be prepared by the addition of hydroxylamine to aldehydes or ketones.[143] Derivatives of hydroxylamine, e.g., H_2NOSO_3H and $HON(SO_3Na)_2$, have also been used. For hindered ketones, such as hexamethylacetone, high pressures, e.g., 10,000 atm, may be necessary.[144] Another procedure, successful for hindered ketones, is to allow the ketone to stand with hydroxylamine and a strongly basic catalyst for 1 to 6 months. High yields of oximes are achieved in this way by those who have the patience to wait. Reactions which proceed over a long time but cannot be rushed by increase in temperature have been called *lethargic reactions*.[145]

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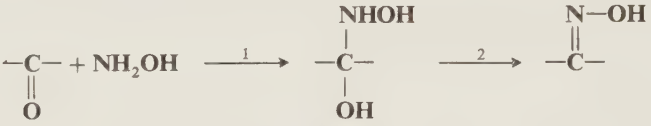
[142] Newkome and Fishel, *J. Org. Chem.* **31,** 677 (1966).

[143] For a review, see Sandler and Karo, Ref. 53, vol. 3, pp. 372–381.

It has been shown[146] that the rate of formation of oximes is at a maximum at a pH which depends on the substrate but is usually about 4, and that the rate decreases as the pH is either raised or lowered from this point. We have previously seen (p. 309) that bell-shaped curves like this are often caused by changes in the rate-determining step. In this case, at low pH values step 2 is rapid (because it is acid-catalyzed), and step 1 is slow (and rate-determining) because under these acidic conditions most of the NH_2OH molecules have been converted to the conjugate NH_3OH^+ ions, which cannot attack the substrate. As the pH is slowly increased, the fraction of free NH_2OH molecules increases and consequently so does the reaction rate, until the maximum rate is reached at about pH = 4. As the rising pH has been causing an increase in the rate of step 1, it has also been causing a *decrease* in the rate of the acid-catalyzed step 2, although this latter process has not affected the overall rate since step 2 was still faster than step 1. However, when the pH goes above about 4, step 2 becomes rate-determining, and although the rate of step 1 is still increasing (as it will until essentially all the NH_2OH is unprotonated), it is now step 2 which determines the rate, and this step is slowed by the decrease in acid concentration. Thus the overall rate decreases as the pH rises beyond about 4. It is likely that similar considerations apply to the reaction of aldehydes and ketones with amines, hydrazines, and other nitrogen nucleophiles.[147] There is evidence that when the nucleophile is 2-methylthiosemicarbazide, there is a second change in the rate-determining step: above pH about 10 *basic* catalysis of step 2 has increased the rate of this step to the point where step 1 is again rate-determining.[148] Still a third change in rate-determining step has been found at about pH = 1, showing that at least in some cases step 1 actually consists of two steps: formation of a zwitterion, e.g., $HO\overset{\oplus}{N}H_2-\underset{|}{\overset{|}{C}}-O^{\ominus}$ in the case shown above, and conversion of this to **31**.[149] The intermediate **31** has been detected by nmr in the reaction between NH_2OH and acetaldehyde.[149a]



$$-\underset{\underset{O}{\|}}{C}- + NH_2OH \xrightarrow{1} -\underset{\underset{OH}{|}}{\overset{\overset{NHOH}{|}}{C}}- \xrightarrow{2} -\overset{\overset{N-OH}{\|}}{C}-$$

31

Ketones can also be converted to oximes by treatment with other oximes, in a transoximation reaction.[150]

OS **I,** 318, 327; **II,** 70, 204, 313, 622; **III,** 690; **IV,** 229; **V,** 139, 1031.

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[144] Jones, Tristram, and Benning, *J. Am. Chem. Soc.* **81,** 2151 (1959).

[145] Pearson and Keaton, *J. Org. Chem.* **28,** 1557 (1963).

[146] Jencks, *J. Am. Chem. Soc.* **81,** 475 (1959), *Prog. Phys. Org. Chem.* **2,** 63–128 (1964).

[147] For a review of the mechanism of such reactions, see Sollenberger and Martin, in Patai, "The Chemistry of the Amino Group," pp. 367–392, Interscience Publishers, New York, 1968.

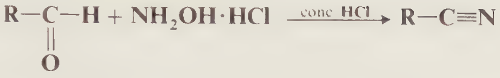
[148] Sayer and Jencks, *J. Am. Chem. Soc.* **94,** 3262 (1972).

[149] Rosenberg, Silver, Sayer, and Jencks, *J. Am. Chem. Soc.* **96,** 7986 (1974); Sayer, Pinsky, Schonbrunn, and Washtien, *J. Am. Chem. Soc.* **96,** 7998 (1974).

[149a] Cocivera, Fyfe, Effio, Vaish, and Chen, *J. Am. Chem. Soc.* **98,** 1573 (1976).

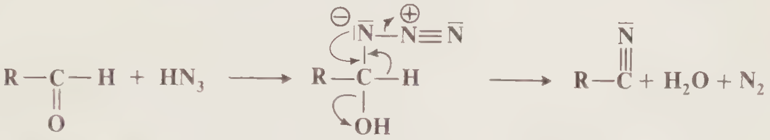
[150] For example, see Block and Newman, *Org. Synth.* **V,** 1031.

6-23 The Conversion of Aldehydes to Nitriles



$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H + NH_2OH{\cdot}HCl \xrightarrow{\text{conc HCl}} R{-}C{\equiv}N}$$

Aldehydes can be converted to nitriles in one step by refluxing with hydroxylamine hydrochloride and either concentrated HCl[151] or sodium formate in formic acid or sodium acetate in acetic acid.[152] The reaction is a combination of reactions **6-22** and **7-39.** Direct nitrile formation has also been accomplished with certain derivatives of NH_2OH, notably N,O-bistrifluoroacetylhydroxylamine $F_3CCONHOCOCF_3$[153] and NH_2OSO_2OH.[154] Another method involves treatment with hydrazoic acid, though the Schmidt reaction (**8-20**) may compete. A possible rationalization is the following:



Aromatic aldehydes have been converted to nitriles in good yield with $NH_4H_2PO_4$ and nitropropane in acetic acid[155] and with ammonia and iodine or lead tetraacetate.[156] Also see reaction **9-6.**

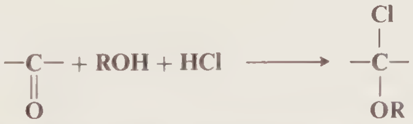
OS V, 656.

6-24 The Addition of Nitriles to Aldehydes

See reaction **6-61.**

F. Halogen Nucleophiles

6-25 The Formation of α-Halo Ethers



$$\mathrm{{-}\underset{\underset{\displaystyle O}{\|}}{C}{-} + ROH + HCl \longrightarrow {-}\overset{\displaystyle Cl}{\underset{\displaystyle OR}{C}}{-}}$$

α-Halo ethers can be prepared by treatment of aldehydes and ketones with an alcohol and HX, though α-halo ethers from simple aldehydes such as formaldehyde are unstable and the reaction tends to reverse. The reaction is applicable to aliphatic aldehydes and ketones and to primary and secondary alcohols. Aromatic aldehydes and ketones react poorly.[157]

The addition of HX to an aldehyde or ketone gives α-halo alcohols, which are usually unstable, though exceptions are known, especially with perfluoro and perchloro species. For example, **32** (X = any of the four halogens) were prepared in this way.[158] Unstable α-halo alcohols may be

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[151] Findlay and Tang, *Can. J. Chem.* **45,** 1014 (1967).

[152] Hunt, *Chem. Ind.* (*London*) 1873 (1961); van Es, *J. Chem. Soc.* 1564 (1965).

[153] Pomeroy and Craig, *J. Am. Chem. Soc.* **81,** 6340 (1959).

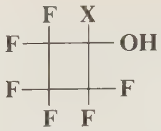
[154] Fizet and Streith, *Tetrahedron Lett.* 3187 (1974).

[155] Blatter, Lukaszewski, and de Stevens, *J. Am. Chem. Soc.* **83,** 2203 (1961).

[156] Misono, Osa, and Koda, *Bull. Chem. Soc. Jpn.* **39,** 854 (1966), **40,** 2875 (1967); Parameswaran and Friedman, *Chem. Ind.* (*London*) 988 (1965).

[157] Klages and Mühlbauer, *Chem. Ber.* **92,** 1818 (1959).

[158] Andreades and England, *J. Am. Chem. Soc.* **83,** 4670 (1961).

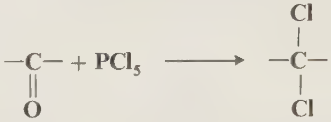


32

quite stable in the dimeric form $2XCR_2OH \rightarrow XCR_2OCR_2X$.

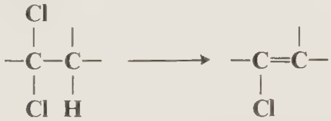
OS **I,** 377; **IV,** 101 (see, however, OS **V,** 218), 748; **52,** 16.

6-26 The Formation of *gem*-Dihalides from Aldehydes and Ketones



$$-\underset{\underset{O}{\|}}{C}- + PCl_5 \longrightarrow -\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-$$

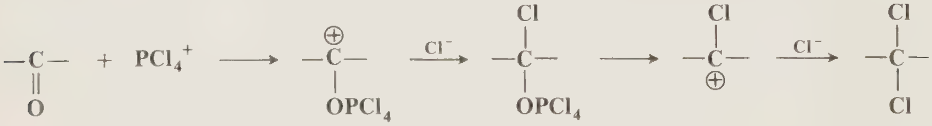
Aliphatic aldehydes and ketones can be converted to *gem*-dichlorides by treatment with PCl_5. The reaction fails for perhalo ketones.[159] If the aldehyde or ketone has an α-hydrogen, elimination of HCl may follow and a vinyl chloride is a frequent side product:[160]



$$-\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-\overset{|}{\underset{\underset{H}{|}}{C}}- \longrightarrow -\underset{\underset{Cl}{|}}{C}=\overset{|}{C}-$$

These compounds may even become the main products.[161] PBr_5 does not give good yields of *gem*-dibromides.

The mechanism of *gem*-dichloride formation involves initial attack of PCl_4^+ (which is present in solid PCl_5) at the oxygen, followed by addition of Cl^- to the carbon:[162]



$$-\underset{\underset{O}{\|}}{C}- + PCl_4^+ \longrightarrow -\overset{\oplus}{\underset{\underset{OPCl_4}{|}}{C}}- \xrightarrow{Cl^-} -\overset{\overset{Cl}{|}}{\underset{\underset{OPCl_4}{|}}{C}}- \longrightarrow -\overset{\overset{Cl}{|}}{\underset{\oplus}{C}}- \xrightarrow{Cl^-} -\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-$$

33 34 35

This chloride ion may come from PCl_6^- (which is also present in solid PCl_5). There follows a two-step S_N1 process. Alternatively, **33** can be converted to **35** without going through **34,** by an S_Ni process.

This reaction has sometimes been performed on esters, though these compounds very seldom undergo any addition to the C=O bond. An example is the conversion of $F_3CCOOPh$ to F_3CCCl_2OPh.[163] However, formates commonly give the reaction. PCl_5 converts hydrazides $RCONHNH_2$ to di- or trichlorides $RCHCl_2$ or $RCCl_3$.[164] R may be alkyl or aryl.

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[159] Farah and Gilbert, *J. Org. Chem.* **30,** 1241 (1965).

[160] For example, see Nikolenko and Popov, *J. Gen. Chem. USSR* **32,** 29 (1962).

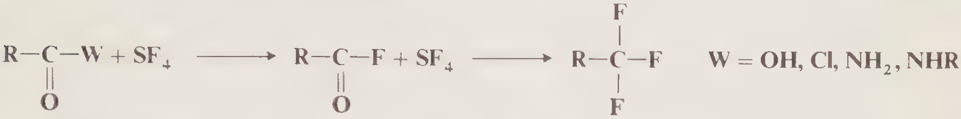
[161] See, for example, Newman, Fraenkel, and Kirn, *J. Org. Chem.* **28,** 1851 (1963).

[162] Newman and Wood, *J. Am. Chem. Soc.* **81,** 4300 (1959); Newman, *J. Org. Chem.* **34,** 741 (1969).

[163] Kirsanov and Molosnova, *J. Gen. Chem. USSR* **28,** 31 (1958); Clark and Simons, *J. Org. Chem.* **26,** 5197 (1961).

[164] Mikhailov, Matyushecheva, Derkach, and Yagupol'skii, *J. Org. Chem. USSR* **6,** 147 (1970); Yagupol'skii, Mikhailov, and Matyushecheva, *J. Org. Chem. USSR* **6,** 1658 (1970), **8,** 846 (1972); Mikhailov, Matyushecheva, and Yagupol'skii, *J. Org. Chem. USSR* **9,** 1847 (1973).

Many aldehydes and ketones have been converted to *gem*-difluoro compounds with sulfur tetrafluoride SF_4,[165] including quinones, which give 1,1,4,4-tetrafluorocyclohexadiene derivatives. Carboxylic acids, acyl chlorides, and amides react with SF_4 to give 1,1,1-trifluorides. In these cases the first product is the acyl fluoride, which then undergoes the *gem*-difluorination reaction:



$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}W + SF_4 \longrightarrow R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}F + SF_4 \longrightarrow R{-}CF_2{-}F \qquad W = OH, Cl, NH_2, NHR$$

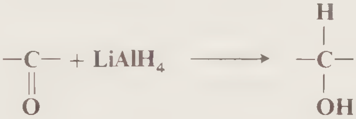
The acyl fluoride can be isolated. Esters also give trifluorides, though more vigorous conditions are required, but in this case the carbonyl group of the ester is attacked first, and RCF_2OR' can be isolated from RCOOR′ and then converted to the trifluoride. Anhydrides can react in either manner, and both types of intermediate are isolable under the right conditions. SF_4 even converts carbon dioxide to CF_4. A disadvantage of reactions with SF_4 is that they require a pressure vessel lined with stainless steel. Selenium tetrafluoride SeF_4 gives similar reactions, but atmospheric pressure and ordinary glassware can be used.[166] Other reagents which have been used to convert aldehydes and ketones to *gem*-difluorides are phenylsulfur trifluoride $PhSF_3$,[167] carbonyl fluoride COF_2,[168] molybdenum hexafluoride MoF_6,[169] and dialkylaminosulfur trifluorides R_2NSF_3.[170]

The mechanism with SF_4 is probably similar in general nature, if not in specific detail, to that with PCl_5.

OS **II,** 549; **V,** 365, 396, 1082. Also see OS **I,** 506.

G. Attack by Hydrogen

6-27 Reduction of Aldehydes and Ketones to Alcohols



$$-\underset{\displaystyle O}{\underset{\|}{C}}- + LiAlH_4 \longrightarrow -\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-$$

Aldehydes can be reduced to primary alcohols and ketones to secondary alcohols by a number of reducing agents, of which lithium aluminum hydride and other metallic hydrides are the most commonly used.[171] These reagents have two main advantages over most of the reagents which were used before the discovery of $LiAlH_4$: they do not reduce carbon-carbon double (or triple) bonds, and they generally contain a lot of hydrogen in a small amount of reagent—with $LiAlH_4$, all four hydrogens are usable for reduction. The reaction is broad and general. $LiAlH_4$ easily reduces aliphatic, aromatic, alicyclic, and heterocyclic aldehydes, containing double or triple bonds and or nonreducible groups such as NR_3, OH, OR, F, etc. If the molecule contains a group reducible by $LiAlH_4$ (e.g., NO_2, CN, COOR), then it is reduced also. $LiAlH_4$ reacts readily with water and alcohols, so that these compounds must be rigorously excluded. Common solvents are ether and tetrahydrofuran. $NaBH_4$ has a similar scope but is more selective and so may be used with NO_2, Cl, COOR, CN, etc., in the molecule. Another advantage of $NaBH_4$ is that it can be used in water or alcoholic solvents and so reduces compounds such as sugars that are not soluble in ethers. The double bonds which are generally not affected by metallic hydrides may be isolated or conjugated, but double bonds which are conjugated with the C=O group may or may not be reduced depending on the substrate, reagent, and reaction conditions. For example, it has proved possible to reduce only the C=O bonds of α,β-unsaturated ketones with AlH_3 and with diisobutylaluminum hydride (p. 709). Also, examples are known where both $NaBH_4$[172] and $LiAlH_4$[173] predominantly reduce only the C=O bond of a C=C—C=O system. On the other hand, $LiAlH_4$ reduces both double bonds of cinnamaldehyde (p. 709), and $NaBH_4$ has been shown to give substantial amounts of fully saturated alcohol products in the reduction of a number of conjugated aldehydes and ketones.[173] The scope of these reagents with ketones is similar to that with aldehydes. $LiAlH_4$ reduces even sterically hindered ketones. With suitable hydrides a degree of selectivity is possible: the reagent tetrabutylammonium cyanoborohydride $Bu_4N^+\ \ BH_3CN^-$ in HMPT reduces both aldehydes and ketones when enough acid is added to the medium to bring the acid concentration to about 1.5 *N*, but at an acid concentration of about 0.1 *N* only aldehydes are reduced, while ketones are essentially unaffected.[174] Similarly, $NaBH_4$ in isopropyl alcohol,[175] sodium triacetoxyborohydride,[175a] and 2-propanol on dehydrated alumina[176] reduce aldehydes much faster than ketones. The reagent lithium N-dihydropyridylaluminum hydride reduces diaryl ketones much better than it does dialkyl or alkyl aryl ketones.[176a] Most other hydrides reduce diaryl ketones more slowly than other types of ketones. It is obvious that reagents can often be found to reduce one kind of carbonyl function in the presence of another. Aldehydes and ketones can often be reduced in the presence of other reducible groups if a suitable reagent is used. For a discussion of selectivity in reduction reactions, see p. 1116. Quinones are reduced to hydroquinones by $LiAlH_4$, $SnCl_2$–HCl, or sodium hydrosulfite $Na_2S_2O_4$, as well as by other reducing agents.

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[165] For reviews, see Boswell, Ripka, Scribner, and Tullock, *Org. React.* **21,** 1–124 (1974); Smith, *Angew. Chem. Int. Ed. Engl.* **1,** 467–475 (1962) [*Angew. Chem.* **74,** 742–751].

[166] Olah, Nojima, and Kerekes, *J. Am. Chem. Soc.* **96,** 925 (1974).

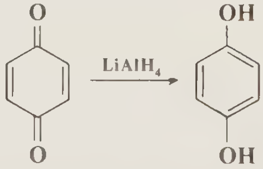
[167] Sheppard, *J. Am. Chem. Soc.* **84,** 3058 (1962).

[168] Fawcett, Tullock, and Coffman, *J. Am. Chem. Soc.* **84,** 4275 (1962).

[169] Mathey and Bensoam, *Tetrahedron* **27,** 3965 (1971), **31,** 391 (1975).

[170] Markovskii, Pashinnik, and Kirsanov, *Synthesis* 787 (1973); Middleton, *J. Org. Chem.* **40,** 574 (1975).

[171] A treatise on reduction with metal hydrides is Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956. For reviews see House, Ref. 124, pp. 49–71; Wheeler, in Patai, "The Chemistry of the Carbonyl Group," Ref. 31, pp. 507–566; Brown, *J. Chem. Educ.* **38,** 173–179 (1961); Schenker, *Angew. Chem.* **73,** 81–106 (1961), *Newer Methods Prep. Org. Chem.* **4,** 196–235 (1968); Hörmann, *Angew. Chem.* **68,** 601–604 (1956), *Newer Methods Prep. Org. Chem.* **2,** 213–226 (1963); Brown, *Org. React.* **6,** 469–509 (1951).



The reagent lithium tri-*sec*-butylborohydride $LiBH(sec\text{-}Bu)_3$, prepared by treatment of tri-*sec*-butylborane with lithium trimethoxyaluminum hydride $LiAlH(OMe)_3$, reduces cyclic and bicyclic ketones in a highly stereoselective manner, giving the less stable isomer.[177] For example, 2-methylcyclohexanone gave *cis*-2-methylcyclohexanol with an isomeric purity greater than 99%. The more usual reagents, e.g., $LiAlH_4$, $NaBH_4$, reduce relatively unhindered cyclic ketones either with little or no stereoselectivity or give predominant formation of the more stable isomer. The less stable axial alcohol is also predominantly formed when cyclohexanones are reduced with

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[172] Chaikin and Brown, *J. Am. Chem. Soc.* **71,** 122 (1949). See also Ref. 188.

[173] Johnson and Rickborn, *J. Org. Chem.* **35,** 1041 (1970).

[174] Hutchins and Kandasamy, *J. Am. Chem. Soc.* **95,** 6131 (1973).

[175] Brown, Wheeler, and Ichikawa, *Tetrahedron* **1,** 214 (1957).

[175a] Gribble and Ferguson, *J. Chem. Soc., Chem. Commun.* 535 (1975).

[176] Posner and Runquist, *Tetrahedron Lett.* 3601 (1975).

[176a] Lansbury and Peterson, *J. Am. Chem. Soc.* **84,** 1756 (1962).

[177] Brown and Krishnamurthy, *J. Am. Chem. Soc.* **94,** 7159 (1972); Krishnamurthy and Brown, *J. Am. Cheri. Soc.* **98,** 3383 (1976).

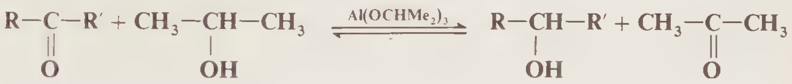
(among other reagents) AlH_3 in ether at $-70^\circ C$,[178] with triethyl phosphite and iridium tetrachloride in aqueous isopropyl alcohol,[179] with potassium triisopropoxyborohydride,[180] or with lithium dimesitylborohydride bis(dimethoxyethane).[181] Cyclohexanones which have a large degree of steric hindrance near the carbonyl group usually give predominant formation of the axial alcohol even with $LiAlH_4$ and $NaBH_4$.

Among other reagents which reduce aldehydes and ketones to alcohols are the following:

1. *Hydrogen and a catalyst.*[182] The most common catalysts are platinum and ruthenium, but homogeneous catalysts have also been used.[183] Before the discovery of the metal hydrides this was one of the most common ways of effecting this reduction, but it suffers from the fact that C=C, C≡C, C=N, and C≡N bonds are more susceptible to attack than C=O bonds. However, α,β-unsaturated aldehydes RCH=CHCHO (though not ketones) can be reduced to the corresponding unsaturated alcohols $RCH=CHCH_2OH$ by hydrogenation over reduced osmium supported on alumina or activated charcoal.[184] An iridium catalyst has also been used for this conversion.[185]

2. *Sodium in ethanol.*[186] This is called the *Bouveault-Blanc procedure* and was more popular for the reduction of esters (reaction **9-44**) than of aldehydes or ketones before the discovery of $LiAlH_4$.

3. *Isopropyl alcohol and aluminum isopropoxide.* This is called the *Meerwein-Ponndorf-Verley reduction.*[187] It is reversible, and the reverse reaction is known as the *Oppenauer oxidation* (reaction **9-4**).



$$R-\underset{\underset{\displaystyle O}{\|}}{C}-R' + CH_3-\underset{\underset{\displaystyle OH}{|}}{CH}-CH_3 \xrightleftharpoons{Al(OCHMe_2)_3} R-\underset{\underset{\displaystyle OH}{|}}{CH}-R' + CH_3-\underset{\underset{\displaystyle O}{\|}}{C}-CH_3$$

The equilibrium is shifted by removal of the acetone by distillation. The reaction takes place under very mild conditions and is highly specific for aldehydes and ketones, so that C=C bonds (including those conjugated with the C=O bonds) and many other functional groups may be present without themselves being reduced. This includes acetals, so that one of two carbonyl groups in a molecule may be specifically reduced if the other is first converted to an acetal. β-Keto esters, β-diketones, and other ketones and aldehydes with a relatively high enol content do not give this reaction.

4. Borane BH_3 and substituted boranes[188] reduce aldehydes and ketones in a manner similar to their addition to C=C bonds (reaction **5-15**).[189] That is, the boron adds to the oxygen and the hydrogen to the carbon:[190]

[178] Ayres and Sawdaye, *J. Chem. Soc. B* 581 (1967); Ayres, Kirk, and Sawdaye, *J. Chem. Soc. B* 505 (1970).

[179] Henbest and Mitchell, *J. Chem. Soc. C* 785 (1970); Eliel, Doyle, Hutchins, and Gilbert, *Org. Synth.* **50,** 13 (1970). See also Henbest and Zurqiyah, *J. Chem. Soc., Perkin Trans. 1* 604 (1974).

[180] Brown, Krishnamurthy, and Kim, *J. Chem. Soc., Chem. Commun.* 391 (1973).

[181] Hooz, Akiyama, Cedar, Bennett, and Tuggle, *J. Am. Chem. Soc.* **96,** 274 (1974).

[182] For a review, see Rylander, Ref. 113, pp. 238–290.

[183] For a review, see Heck, "Organotransition Metal Chemistry," pp. 65–70, Academic Press, Inc., New York, 1974.

[184] Rylander and Steele, *Tetrahedron Lett.* 1579 (1969).

[185] Bakhanova, Astakhova, Brikenshtein, Dorokhov, Savchenko, and Khidekel', *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **21,** 1934 (1972).

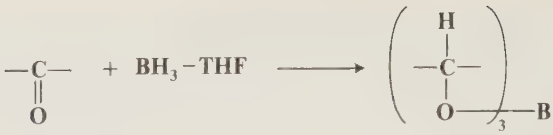
[186] For a discussion, see House, Ref. 124, pp. 152–160.

[187] For a review, see Wilds, *Org. React.* **2,** 178–223 (1944).

[188] See for example Brown and Varma, *J. Org. Chem.* **39,** 1631 (1974). 9-BBN (p. 432) reduces only the C=O group of conjugated aldehydes and ketones: Krishnamurthy and Brown, *J. Org. Chem.* **40,** 1864 (1975).

[189] For a review, see Cragg, "Organoboranes in Organic Synthesis," pp. 324–335, Marcel Dekker, Inc., New York, 1973.

[190] Brown and Subba Rao, *J. Am. Chem. Soc.* **82,** 681 (1960); Brown and Korytnyk, *J. Am. Chem. Soc.* **82,** 3866 (1960).



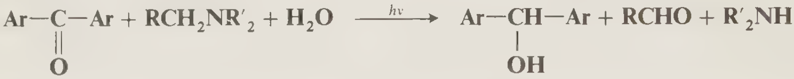
$$-\underset{\underset{\textstyle O}{\|}}{C}- \;+\; BH_3\text{-}THF \longrightarrow \left(-\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle O}{|}}{C}}-\right)_3\!\!-B$$

The borate is then hydrolyzed to the alcohol.

5. *Polymethylhydrosiloxane* $(MeHSiO)_n$, with an organotin catalyst, bis(dibutylacetoxytin) oxide, is a selective reducing agent for aldehydes and ketones under neutral conditions (refluxing 95% alcohol).[191] Under these conditions, carboxylic acids, esters, amides, alkyl halides, and nitro compounds are not reduced.

6. *Diimide* (N_2H_2, see p. 714) reduces aromatic aldehydes[192] and ketones, but aliphatic carbonyl compounds react very poorly.[193]

7. In certain cases ketones can be reduced to secondary alcohols by photochemical methods (see also p. 223). For example, diaryl ketones are reduced by irradiation in the presence of water and a tertiary amine (which is cleaved to a secondary amine and an aldehyde):[194]

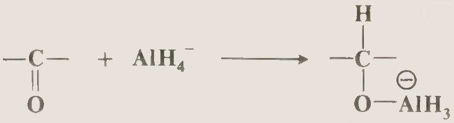


$$Ar-\underset{\underset{\textstyle O}{\|}}{C}-Ar + RCH_2NR'_2 + H_2O \xrightarrow{h\nu} Ar-\underset{\underset{\textstyle OH}{|}}{CH}-Ar + RCHO + R'_2NH$$

8. A single carbonyl group of an α-diketone can be reduced (to give an α-hydroxy ketone) by heating with zinc powder in aqueous dimethylformamide.[195]

9. In the Cannizzaro reaction (**9-74**) aldehydes without an α-hydrogen are reduced to alcohols.

With most reagents there is an initial attack on the carbon of the carbonyl group by H^- or some carrier of it, though with BH_3 the initial attack is on the oxygen. Detailed mechanisms are not known in most cases. With metallic hydrides of aluminum or boron, the attacking species is the AlH_4^- (or BH_4^-) ion, which, in effect, transfers H^- to the carbon.[196] The freed AlH_3



$$-\underset{\underset{\textstyle O}{\|}}{C}- \;+\; AlH_4^- \longrightarrow -\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle O-AlH_3}{|\;\ominus}}{C}}-$$

36

then complexes with the oxygen from the same molecule, or from a different one. However, it has been shown that in certain cases the cation plays an essential role. When the Li^+ was effectively removed from $LiAlH_4$ (by the addition of a crown ether, p. 82), the reaction did not take place.[197] The complex **36** must now be hydrolyzed to the alcohol. If the reaction is performed in a protic solvent, AlH_3 coordinates with the solvent instead and a proton from the solvent goes to the oxygen. Free H^- cannot be the attacking entity in most reductions with boron or aluminum hydrides because the reactions are frequently sensitive to the size of the MH_4^- [or $MR_mH_n^-$ or $M(OR)_mH_n^-$, etc.]. It has been shown that $NaBH_4$ *molecules* are not the attacking species either, since they react only in solvents in which they are ionized to Na^+ and BH_4^-.[198]

[191] Lipowitz and Bowman, *J. Org. Chem.* **38**, 162 (1973).

[192] Curry, Uff, and Ward, *J. Chem. Soc. C* 1120 (1967).

[193] van Tamelen, Davis, and Deem, *Chem. Commun.* 71 (1965).

[194] Cohen, Stein, and Chao, *J. Am. Chem. Soc.* **90**, 521 (1968).

[195] Kreiser, *Justus Liebigs Ann. Chem.* **745**, 164 (1971).

[196] Vail and Wheeler, *J. Org. Chem.* **27**, 3803 (1962).

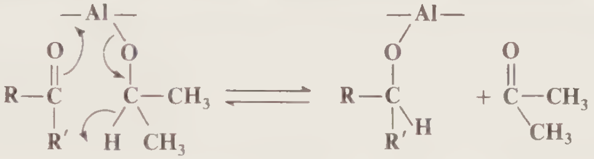
[197] Pierre and Handel, *Tetrahedron Lett.* 2317 (1974).

[198] Brown and Ichikawa, *J. Am. Chem. Soc.* **83**, 4372 (1961).

There has been much controversy about whether the initial complex (**36**) can reduce another carbonyl to give $(\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}O})_2\mathrm{AlH}_2$, and so on. It has been shown[199] that this is probably not the case but that, more likely, **36** disproportionates to $(\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}O})_4\mathrm{Al}$ and AlH_4^-, which is the only attacking species.

36 is essentially LiAlH_4 with one of the hydrogens replaced by an alkoxy group, i.e., $\mathrm{LiAlH}_3\mathrm{OR}$. The fact that **36** and other alkoxy derivatives of LiAlH_4 are less reactive than LiAlH_4 itself has led to the use of such compounds as reducing agents which are less reactive and hence more selective than LiAlH_4.[200] We have already met some of these, e.g., $\mathrm{LiAlH(O\text{-}}t\mathrm{\text{-}Bu)}_3$ (reactions **0-83** to **0-85**; see also Table 5, Chapter 19, p. 1118). As an example of selectivity in this reaction it may be mentioned that $\mathrm{LiAlH(O\text{-}}t\mathrm{\text{-}Bu)}_3$ has been used to reduce only the keto group in a molecule containing both keto and ester groups.[201] However, the use of such reagents is sometimes complicated by the disproportionation mentioned above, which may cause LiAlH_4 to be the active species even if the reagent is an alkoxy derivative. Another highly selective reagent (reducing aldehydes and ketones, but not other functional groups), which does not disproportionate, is potassium triisopropoxyborohydride.[180] The use of tin hydrides, such as $\mathrm{Ph_2SnH_2}$, gives alcohols from aldehydes or ketones directly; i.e., both hydrogens come from the hydride, and no hydrolysis is needed.[202]

The Meerwein-Ponndorf-Verley reaction usually involves a cyclic transition state:



but in some cases 2 moles of aluminum alkoxide are involved, one attacking the carbon and the other the oxygen, a conclusion which stems from the finding that in these cases the reaction was 1.5 order in alkoxide.[203] It has been shown by deuterium labeling that it is the α-hydrogen of the alkoxide which appears at the carbonyl carbon of the starting aldehyde or ketone.[204] Although we have depicted a cyclic mechanism, it is possible to visualize it as occurring in three phases: (1) coordination of the ketone with the alkoxide, (2) hydride transfer, and (3) separation of the new complex. There is controversy over which step is rate-determining: some feel that it is hydride transfer,[205] and others claim that it is none of these but a subsequent step, in which the alkoxide is hydrolyzed.[206] Although, for simplicity, we have shown the alkoxide as a monomer, it actually exists as trimers and tetramers, and it is these which react.[207]

The mechanism of the reaction with sodium in ethanol is similar to that of the Birch reduction (**5-13**) and involves a ketyl intermediate, which can be isolated.

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[199] Haubenstock and Eliel, *J. Am. Chem. Soc.* **84,** 2363 (1962).

[200] For a review of reductions with alkoxyalumino hydrides, see Málek and Černý, *Synthesis* 217–234 (1972).

[201] Levine and Eudy, *J. Org. Chem.* **35,** 549 (1970); Heusler, Wieland, and Meystre, *Org. Synth.* **V,** 692.

[202] Kuivila and Beumel, *J. Am. Chem. Soc.* **83,** 1246 (1961). For a review of reductions with organotin hydrides, see Kuivila, *Synthesis* 499–509 (1970).

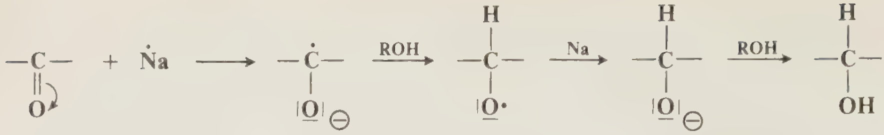
[203] Moulton, Van Atta, and Ruch, *J. Org. Chem.* **26,** 290 (1961).

[204] Williams, Krieger, and Day, *J. Am. Chem. Soc.* **75,** 2404 (1953).

[205] Shiner, Whittaker, and Fernandez, *J. Am. Chem. Soc.* **85,** 2318 (1963); Shiner and Whittaker, *J. Am. Chem. Soc.* **85,** 2337 (1963).

[206] Yager and Hancock, *J. Org. Chem.* **30,** 1174 (1965).

[207] Ref. 204; Shiner and Whittaker, *J. Am. Chem. Soc.* **91,** 394 (1969).



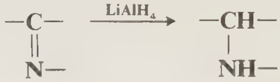
A ketyl

The mechanism of catalytic hydrogenation of aldehydes and ketones is probably similar to that of reaction **5-12**, though not much is known about it.[208]

For other reduction reactions of aldehydes and ketones, see reactions **9-39** and **9-67**. Also see reaction **9-74**.

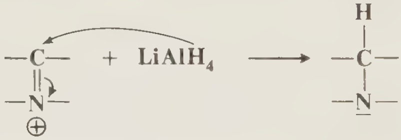
OS **I**, 90, 304, 554; **II**, 317, 545, 598; **III**, 286; **IV**, 15, 25, 216, 660; **V**, 175, 294, 595, 692; **50**, 13.

6-28 Reduction of the Carbon-Nitrogen Double Bond

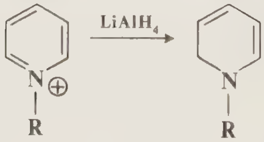


$$-\mathrm{C}(=\mathrm{N}-)- \xrightarrow{\mathrm{LiAlH_4}} -\mathrm{CH}(\mathrm{NH}-)-$$

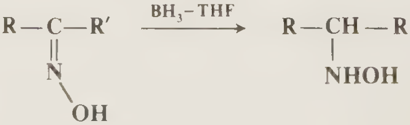
Imines, Schiff bases, hydrazones, and other C=N compounds can be reduced with $\mathrm{LiAlH_4}$, $\mathrm{NaBH_4}$, Na-EtOH, hydrogen and a catalyst, as well as with other reducing agents.[209] Iminium salts are also reduced by $\mathrm{LiAlH_4}$, though here there is no "addition" to the nitrogen:[210]



$\mathrm{LiAlH_4}$ similarly reduces N-alkylpyridinium salts to 1,2-dihydropyridines:



Oximes are generally reduced to amines (reaction **9-53**), but simple addition of H_2 to give hydroxylamines can be accomplished with borane at 25°C[211] or with sodium cyanoborohydride.[115]



$$\mathrm{R-C(=N-OH)-R'} \xrightarrow{\mathrm{BH_3-THF}} \mathrm{R-CH(NHOH)-R'}$$

OS **III**, 328, 827; **51**, 24. Also see OS **IV**, 283.

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[208] For example, see Newham and Burwell, *J. Am. Chem. Soc.* **86**, 1179 (1964).

[209] For a review, see Harada, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Ref. 31, pp. 276 293. For a review with respect to catalytic hydrogenation, see Rylander, Ref. 113, pp. 123–138.

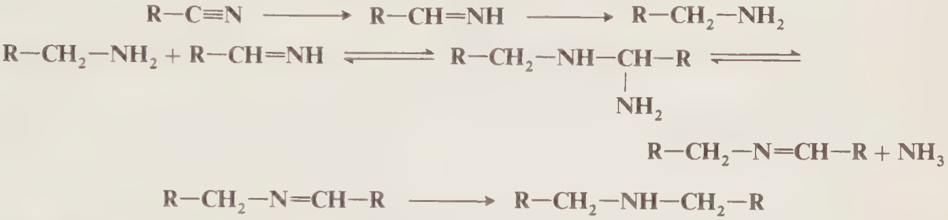
[210] For a review of nucleophilic additions to iminium salts, see Paukstelis, in Cook, Ref. 35, pp. 169-209.

[211] Feuer and Vincent, *J. Am. Chem. Soc.* **84**, 3771 (1962); Feuer, Vincent, and Bartlett, *J. Org. Chem.* **30**, 2877 (1965); Ioffe, Tartakovskii, Medvedeva, and Novikov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1446 (1964).

6-29 The Reduction of Nitriles to Amines

$$\mathrm{R{-}C{\equiv}N + LiAlH_4 \longrightarrow R{-}CH_2{-}NH_2}$$

Nitriles can be reduced to primary amines with many reducing agents,[212] including $LiAlH_4$, BH_3 THF, NaOEt, and hydrogen and a catalyst.[213] $NaBH_4$ does not generally reduce nitriles but does so in alcoholic solvents when a $CoCl_2$ catalyst is added[214] or in the presence of Raney nickel.[215] The reaction is of wide scope and has been applied to many nitriles. Secondary amines are often side products, arising from the following sequence of steps:



$$\mathrm{R{-}C{\equiv}N \longrightarrow R{-}CH{=}NH \longrightarrow R{-}CH_2{-}NH_2}$$

$$\mathrm{R{-}CH_2{-}NH_2 + R{-}CH{=}NH \rightleftharpoons R{-}CH_2{-}NH{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}R \rightleftharpoons R{-}CH_2{-}N{=}CH{-}R + NH_3}$$

$$\mathrm{R{-}CH_2{-}N{=}CH{-}R \longrightarrow R{-}CH_2{-}NH{-}CH_2{-}R}$$

These side products can be avoided by adding a compound such as acetic anhydride, which removes the primary amine as soon as it is formed,[216] or by the use of excess ammonia to drive the equilibria backward.[217]

It is not possible to stop with the addition of only 1 mole of hydrogen, i.e., to convert the nitrile to an imine, except where the imine is subsequently hydrolyzed (reaction **6-30**).

N-Alkylnitrilium ions are reduced to secondary amines by $NaBH_4$[218]

$$\mathrm{RCN \xrightarrow{R_3'O^+\ \ BF_4^-} R{-}C{\equiv}\overset{\oplus}{N}{-}R' \xrightarrow[\text{diglyme}]{NaBH_4} RCH_2{-}NH{-}R'}$$

Since nitrilium salts can be prepared by treatment of nitriles with trialkyloxonium salts (see reaction **6-10**), this is a method for the conversion of nitriles to secondary amines. In contrast, triethylsilane reduces nitrilium ions to imines: $\mathrm{R{-}C{\equiv}\overset{\oplus}{N}{-}R' \rightarrow R{-}CH{=}N{-}R'}$.[219] The imines can be hydrolyzed to aldehydes RCHO, making this an indirect method for the conversion of nitriles to aldehydes.

OS **III**, 229, 358, 720; **53**, 21.

6-30 The Reduction of Nitriles to Aldehydes

$$\mathrm{R{-}C{\equiv}N \xrightarrow[\text{2. hydrol.}]{\text{1. HCl, SnCl}_2} R{-}CH{=}O}$$

There are two principal methods for the reduction of nitriles to aldehydes.[220] In one of these, known as the *Stephen reduction*, the nitrile is treated with HCl to form

$$\mathrm{RCCl{=}NH_2^+\ \ Cl^-}$$

37

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[212] For a review, see Rabinovitz, in Rappoport, "The Chemistry of the Cyano Group," pp. 307–340, Interscience Publishers, New York, 1970.

[213] For reviews of catalytic hydrogenation of nitriles, see Rylander, Ref. 113, pp. 203–226; Freidlin and Sladkova, *Russ. Chem. Rev.* **33**, 319–330 (1964).

[214] Satoh and Suzuki, *Tetrahedron Lett.* 4555 (1969).

[215] Egli, *Helv. Chim. Acta* **53**, 47 (1970).

[216] For example, see Carothers and Jones, *J. Am. Chem. Soc.* **47**, 3051 (1925); Gould, Johnson, and Ferris, *J. Org. Chem.* **25**, 1658 (1960).

[217] For example, see Freifelder, *J. Am. Chem. Soc.* **82**, 2386 (1960).

[218] Borch, *Chem. Commun.* 442 (1968).

[219] Fry, *J. Chem. Soc., Chem. Commun.* 45 (1974).

[220] For reviews, see Mosettig, *Org. React.* **8**, 218–257 (1954); Ref. 212.

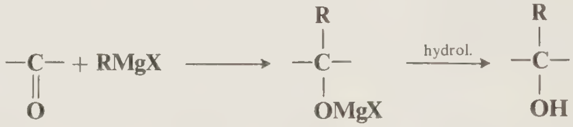
This is reduced with anhydrous $SnCl_2$ to RCH=NH, which precipitates as a complex with $SnCl_4$ and is then hydrolyzed (reaction **6-2**) to the aldehyde. The Stephen reduction is most successful when R is aromatic, but it can be done for aliphatic R up to about six carbons.[221] It is also possible to prepare **37** in a different way, by treating ArCONHPh with PCl_5. The **37** obtained in this way can then be converted to the aldehyde. This is known as the *Sonn-Müller method.*

The other way of reducing nitriles to aldehydes involves using a metal hydride reducing agent to add 1 mole of hydrogen and hydrolysis, in situ, of the resulting imine (which is undoubtedly coordinated to the metal). This has been carried out with $LiAlH_4$, $LiAlH(OEt)_3$,[222] $AlH(CH_2CHMe_2)_2$,[223] and $NaAlH_4$.[224] The metal hydride method is useful for aliphatic and aromatic nitriles. Reduction to the aldehyde has also been accomplished by treatment of the nitrile with sodium hypophosphate and Raney nickel in aqueous acetic acid-pyridine or formic acid;[225] with Raney nickel in aqueous tetrahydrofuran containing H_2SO_4;[226] and photochemically, by irradiation of the nitrile in 0.01 *M* NaOH solution.[227] Another method for the conversion of nitriles to aldehydes (by way of the nitrilium ion) was mentioned at reaction **6-29.**

OS **III,** 626, 818; **51,** 20.

H. Carbon Attack by Organometallic Compounds

6-31 The Addition of Organometallic Compounds to Aldehydes and Ketones



$$\underset{\displaystyle \overset{\|}{O}}{-C-} + RMgX \longrightarrow -\overset{\displaystyle R}{\underset{\displaystyle OMgX}{C}}- \xrightarrow{\text{hydrol.}} -\overset{\displaystyle R}{\underset{\displaystyle OH}{C}}-$$

The addition of Grignard reagents to aldehydes and ketones is known as the *Grignard reaction.*[228] Formaldehyde gives primary alcohols; other aldehydes give secondary alcohols; and ketones give tertiary alcohols. The reaction is of very broad scope, and hundreds of alcohols have been prepared in this manner. R may be alkyl or aryl. In many cases the hydrolysis step is carried out with dilute HCl or H_2SO_4, but this cannot be done for tertiary alcohols in which at least one R group is alkyl because such alcohols are easily dehydrated under acidic conditions (reaction **7-1**). In such cases (and often for primary and secondary alcohols as well) an aqueous solution of ammonium chloride is used instead of a strong acid. Other organometallic compounds may also be used, but only if they are of active metals; e.g., alkylmercurys and alkylcadmiums do not react. In practice, the only organometallic compounds used to any extent, besides Grignard reagents, are alkyl- and aryllithiums, though alkylzinc reagents were used in the past.[228a] For the addition of acetylenic groups, sodium may be the metal used: RC≡CNa (reaction **6-42**); while vinylalanes (prepared as in reaction **5-16**) are the reagents of choice for the addition of vinyl groups.[229] The reaction with alkyl- and aryllithium reagents has also been carried out without preliminary formation of RLi: a mixture of RX and the carbonyl compound was added to a suspension of lithium pieces in tetrahydrofuran.[230] Yields were generally satisfactory. Lithium dimethylcopper Me_2CuLi reacts with aldehydes[230a] but not with ketones, though a reagent prepared from Me_2CuLi and MeLi does convert cyclohexanones stereoselectively to tertiary alcohols, with the axial alcohol preferred.[231]

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[221] Zil'berman and Pyryalova, *J. Gen. Chem. USSR* **33,** 3348 (1964).

[222] Brown and Shoaf, *J. Am. Chem. Soc.* **86,** 1079 (1964); Brown and Garg, *J. Am. Chem. Soc.* **86,** 1085 (1964); de Peretti, Strzalko-Bottin, and Seyden-Penne, *Bull. Soc. Chim. Fr.* 2925 (1974).

[223] Miller, Biss, and Schwartzman, *J. Org. Chem.* **24,** 627 (1959); Marshall, Andersen, and Schlicher, *J. Org. Chem.* **35,** 858 (1970).

[224] Zakharkin, Maslin, and Gavrilenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1415 (1964).

[225] Backeberg and Staskun, *J. Chem. Soc.* 3961 (1962); Staskun and Backeberg, *J. Chem. Soc.* 5880 (1964); van Es and Staskun, *J. Chem. Soc.* 5775 (1965), *Org. Synth.* **51,** 20 (1971).

[226] Tinapp, *Chem. Ber.* **102,** 2770 (1969), **104,** 2266 (1971).

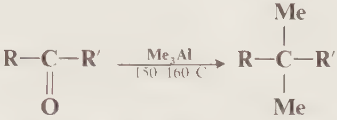
[227] Ferris and Antonucci, *J. Am. Chem. Soc.* **94,** 8091 (1972).

[228] For reviews of the addition of organometallic compounds to carbonyl groups, see Eicher, in Patai, "The Chemistry of the Carbonyl Group," Ref. 31, pp. 621–693; Kharasch and Reinmuth, "Grignard Reactions of Nonmetallic Substances," pp. 138–528, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1954.

[228a] For a review, see Furukawa and Kawabata, *Adv. Organomet. Chem.* **12,** 103–112 (1974).

[229] Newman, *Tetrahedron Lett.* 4571 (1971).

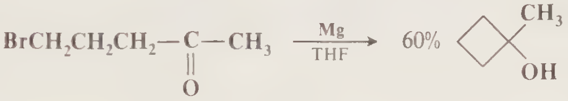
Trimethylaluminum exhaustively methylates ketones to give *gem*-dimethyl compounds[231a] (see also reaction **0-90**):



$$R-\underset{\underset{\textstyle O}{\|}}{C}-R' \xrightarrow[150-160^\circ C]{Me_3Al} R-\overset{\overset{\textstyle Me}{|}}{\underset{\underset{\textstyle Me}{|}}{C}}-R'$$

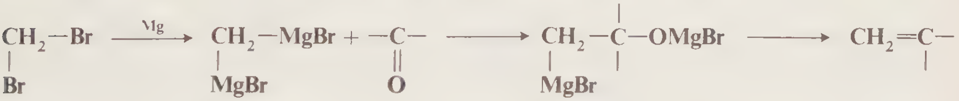
α,β-Unsaturated aldehydes or ketones can give 1,4 addition as well as normal 1,2 addition (see p. 729). In general, alkyllithiums give less 1,4 addition than the corresponding Grignard reagents.[232] Quinones may add Grignard reagents on one or both sides or give 1,4 addition. In a compound containing both an aldehydic and a ketonic carbonyl group it is possible to add RMgX selectively to the aldehydic function without significantly disturbing the ketonic group.[233]

The Grignard reaction can be performed intramolecularly. For example, treatment of 5-bromo-2-pentanone with magnesium and a small amount of mercuric chloride in tetrahydrofuran



produced 1-methyl-1-cyclobutanol in 60% yield.[234] Other four- and five-membered ring compounds were also prepared by this procedure. Similar closing of five- and six-membered rings was achieved by treatment of a δ- or ε-halocarbonyl compound, not with a metal, but with a dianion derived from nickel tetraphenylporphine.[235] The cyclization of a δ-halo γ,δ-unsaturated ketone (to give a cyclopentenol) was accomplished by treatment of the substrate with di-*n*-butylcopperlithium in pentane-ether at 0°C.[235]

The *gem*-disubstituted magnesium compounds formed from CH_2Br_2 or CH_2I_2 (reaction **2-37**) react with aldehydes or ketones to give olefins in moderate to good yields.[236] The reaction



$$\underset{\underset{\textstyle Br}{|}}{CH_2}-Br \xrightarrow{Mg} \underset{\underset{\textstyle MgBr}{|}}{CH_2}-MgBr + -\underset{\underset{\textstyle O}{\|}}{C}- \longrightarrow \underset{\underset{\textstyle MgBr}{|}}{CH_2}-\overset{|}{\underset{|}{C}}-OMgBr \longrightarrow CH_2=\underset{|}{C}-$$

could not be extended to other *gem*-dihalides. Similar reactions with *gem*-dimetallic compounds prepared with metals other than magnesium have also produced olefins, though usually with low yields.[237] However, exceptions are the α,α-dimetallic derivatives of phenyl sulfones $PhSO_2CM_2R$ ($M = Li$ or Mg), which react with aldehydes or ketones R′COR″ to give good yields of the α,β-unsaturated sulfones $PhSO_2CR{=}CR'R''$,[238] which can be reduced with aluminum amalgam (see reaction **0-96**) or with $LiAlH_4$-$CuCl_2$ to give the olefins $CHR{=}CR'R''$.[239] These reactions are closely related to the Wittig reaction (**6-47**) and, like it, provide a means of achieving the conversion $R_2C{=}O \rightarrow R_2C{=}R'_2$. On the other hand, *gem*-dihalides treated with a carbonyl compound and Li or BuLi give epoxides[240] (see also reaction **6-65**). In another use of *gem*-dihalo compounds, methylene halides add the CHX_2 group to aldehydes or ketones when treated with lithium dicyclohexylamide at low temperatures.[241]

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[230] Pearce, Richards, and Scilly, *J. Chem. Soc., Perkin Trans. 1* 1655 (1972). See also Agnès, Chiusoli, and Marraccini, *J. Organomet. Chem.* **49,** 239 (1973); Cameron and Milton, *J. Chem. Soc., Perkin Trans. 2* 378 (1976).

[230a] Barreiro, Luche, Zweig, and Crabbé, *Tetrahedron Lett.* 2353 (1975); Zweig, Luche, Barreiro, and Crabbé, *Tetrahedron Lett.* 2355 (1975).

[231] Macdonald and Still, *J. Am. Chem. Soc.* **97,** 5280 (1975).

[231a] Meisters and Mole, *Aust. J. Chem.* **27,** 1655 (1974). See also Jeffery, Meisters, and Mole, *Aust. J. Chem.* **27,** 2569 (1974).

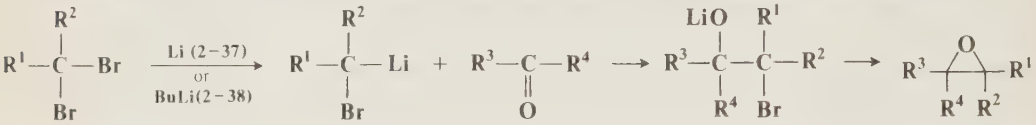
[232] An example was given on p. 729. Another can be found in Wessely, Budzikiewicz, and Janda, *Monatsh. Chem.* **92,** 621 (1961).

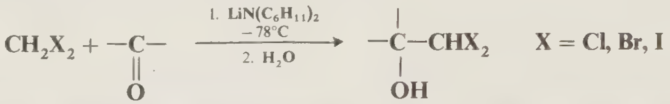
[233] Vaskan and Kovalev, *J. Org. Chem. USSR* **9,** 501 (1973).

[234] Leroux, *Bull. Soc. Chim. Fr.* 359 (1968).

[235] Corey and Kuwajima, *J. Am. Chem. Soc.* **92,** 395 (1970).

[236] Bertini, Grasselli, Zubiani, and Cainelli, *Tetrahedron Lett.* **26,** 1281 (1970). See also Hasselmann, *Chem. Ber.* **107,** 3486 (1974).

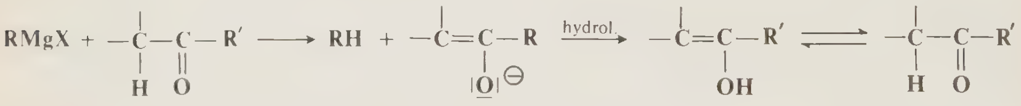




$$\mathrm{CH_2X_2} + -\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}- \xrightarrow[2.\ \mathrm{H_2O}]{1.\ \mathrm{LiN(C_6H_{11})_2},\ -78^\circ\mathrm{C}} -\overset{|}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}-\mathrm{CHX_2} \qquad \mathrm{X = Cl, Br, I}$$

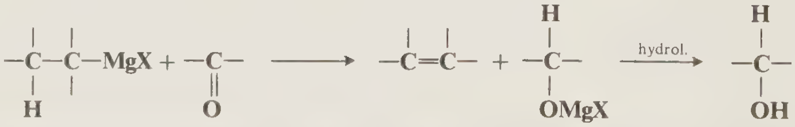
Although most aldehydes and ketones react very nicely with most Grignard reagents, there are several types of side reaction which occur mostly with hindered ketones and with bulky Grignard reagents. The two most important of these are *enolization* and *reduction*. The former requires that the aldehyde or ketone have an α-hydrogen, and the latter requires that the Grignard reagent have a β-hydrogen:

Enolization



$$\mathrm{RMgX} + -\overset{|}{\underset{\underset{\displaystyle \mathrm{H}}{|}}{\mathrm{C}}}-\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R'} \longrightarrow \mathrm{RH} + -\overset{|}{\mathrm{C}}{=}\underset{\underset{\displaystyle \mathrm{|\underline{O}|^{\ominus}}}{|}}{\mathrm{C}}-\mathrm{R} \xrightarrow{\text{hydrol.}} -\overset{|}{\mathrm{C}}{=}\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}-\mathrm{R'} \rightleftharpoons -\overset{|}{\underset{\underset{\displaystyle \mathrm{H}}{|}}{\mathrm{C}}}-\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R'}$$

Reduction



$$-\overset{|}{\underset{\underset{\displaystyle \mathrm{H}}{|}}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{MgX} + -\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}- \longrightarrow -\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}- + -\overset{\overset{\displaystyle \mathrm{H}}{|}}{\underset{\underset{\displaystyle \mathrm{OMgX}}{|}}{\mathrm{C}}}- \xrightarrow{\text{hydrol.}} -\overset{\overset{\displaystyle \mathrm{H}}{|}}{\underset{\underset{\displaystyle \mathrm{OH}}{|}}{\mathrm{C}}}-$$

Enolization is an acid-base reaction (**2-21**) in which a proton is transferred from the α-carbon to the Grignard reagent. The Grignard reagent RMgX is converted to RH and the carbonyl compound to its enolate-ion form, which, on hydrolysis, is reconverted to original ketone or aldehyde. Enolization is important not only for hindered ketones but also for those which have a relatively high percentage of enol form, e.g., β-keto esters, etc. Another factor which affects enolization is the relative freedom of R in the organometallic compound. Thus, acetophenone gave addition with RMgX and RLi but enolization with RNa and RK, in which the R has greater carbonionic character.[242] In reduction, the carbonyl compound is reduced to an alcohol (reaction **6-27**) by the Grignard reagent, which itself undergoes elimination to give an olefin. Two other side reactions are condensation (between enolate ion and excess ketone) and Wurtz-type coupling (reaction **0-92**). Such highly hindered tertiary alcohols as triisopropylcarbinol, tri-*t*-butylcarbinol, and diisopropylneopentylcarbinol cannot be prepared (or can be prepared only in extremely low yields) by the addition of Grignard reagents to ketones, because reduction and/or enolization become prominent.[243] However, these carbinols can be prepared by the use of alkyllithiums at −80°C,[244] under which conditions enolization and reduction are much less important.[245] Another method of increasing the degree of addition at the expense of reduction consists in complexing the Grignard reagent with $LiClO_4$ or $Bu_4N^+ \quad Br^-$.[246]

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[237] For example, see Zweifel and Steele, *Tetrahedron Lett.* 6021 (1966); Cainelli, Dal Bello, and Zubiani, *Tetrahedron Lett.* 4315 (1966); Cainelli, Bertini, Grasselli, and Zubiani, *Tetrahedron Lett.* 1581 (1967); Hashimoto, Hida, and Miyano, *J. Organomet. Chem.* **10**, 518 (1967); Miyano, Hida, and Hashimoto, *J. Organomet. Chem.* **12**, 263 (1968); Harrison, Rawson, Turnbull, and Fried, *J. Org. Chem.* **36**, 3515 (1971); Bongini, Savoia, and Umani-Ronchi, *J. Organomet. Chem.* **72**, C4 (1974).

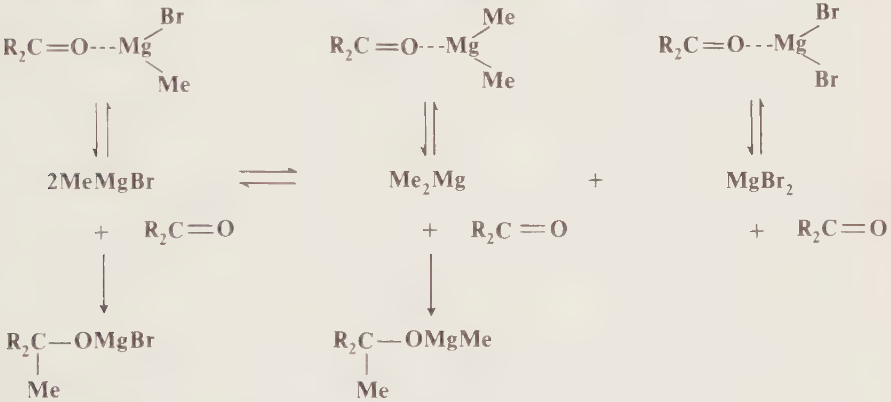
[238] Pascali, Tangari, and Umani-Ronchi, *J. Chem. Soc., Perkin Trans. 1* 1166 (1973).

[239] Pascali and Umani-Ronchi, *J. Chem. Soc., Chem. Commun.* 351 (1973).

[240] Cainelli, Umani-Ronchi, Bertini, Grasselli, and Zubiani, *Tetrahedron* **27**, 6109 (1971); Cainelli, Tangari, and Umani-Ronchi, *Tetrahedron* **28**, 3009 (1972). See also Köbrich and Werner, *Tetrahedron Lett.* 2181 (1969); Shanklin, Johnson, Ollinger, and Coates, *J. Am. Chem. Soc.* **95**, 3429 (1973).

[241] Taguchi, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **96**, 3010 (1974).

There has been much controversy regarding the mechanism of addition of Grignard reagents to aldehydes and ketones.[247] The reaction is difficult to study because of the variable nature of the species present in the Grignard solution (p. 167) and because the presence of small amounts of impurities in the magnesium seems to have a great effect on the kinetics of the reaction, making reproducible experiments difficult.[248] Furthermore, the mechanism seems to be quite complicated, since both RMgX and R_2Mg can react with the ketone, since both of these species as well as Mg_2X form complexes (Chapter 3) with the ketone,[249] and since the products initially formed can then react further (as described below). A detailed mechanism for the reaction between methylmagnesium bromide and 2-methylbenzophenone has been proposed by Ashby and co-workers,[250] based on the discovery that this reaction proceeds by two paths, one first order in MeMgBr and the other first order in Me_2Mg.[251] The initial stages of this mechanism, which starts with the three complexes formed from MeMgBr, Me_2Mg, and $MgBr_2$ are [252]



38 **39**

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[242] O'Sullivan, Swamer, Humphlett, and Hauser, *J. Org. Chem.* **26,** 2306 (1961).

[243] Whitmore and George, *J. Am. Chem. Soc.* **64,** 1239 (1942).

[244] Bartlett and Lefferts, *J. Am. Chem. Soc.* **77,** 2804 (1955); Zook, March, and Smith, *J. Am. Chem. Soc.* **81,** 1617 (1959); Bartlett and Tidwell, *J. Am. Chem. Soc.* **90,** 4421 (1968).

[245] Buhler, *J. Org. Chem.* **38,** 904 (1973). See also Huet and Emptoz, *J. Organomet. Chem.* **101,** 139 (1975).

[246] Chastrette and Amouroux, *Chem. Commun.* 470 (1970), *Bull. Soc. Chim. Fr.* 4348 (1970).

[247] For reviews, see Ashby, Laemmle, and Neumann, *Acc. Chem. Res.* **7,** 272–280 (1974); Ashby, *Bull. Soc. Chim. Fr.* 2133–2142 (1972); *Q. Rev., Chem. Soc.* **21,** 259–285 (1967); Blomberg, *Bull. Soc. Chim. Fr.* 2143–2149 (1972). For a review of the stereochemistry of the reaction, see Ashby and Laemmle, Ref. 3.

[248] See for example, Ashby, Walker, and Neumann, *Chem. Commun.* 330 (1970); Ashby, Neumann, Walker, Laemmle, and Chao, *J. Am. Chem. Soc.* **95,** 3330 (1973).

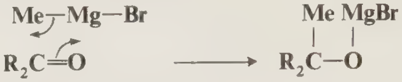
[249] Smith, *Tetrahedron Lett.* 409 (1963).

[250] Ashby, Laemmle, and Neumann, *J. Am. Chem. Soc.* **94,** 5421 (1972).

[251] Ashby, Laemmle, and Neumann, *J. Am. Chem. Soc.* **93,** 4601 (1971); Laemmle, Ashby, and Neumann, *J. Am. Chem. Soc.* **93,** 5120 (1971). See also Rudolph, Charbonneau, and Smith, *J. Am. Chem. Soc.* **95,** 7083 (1973).

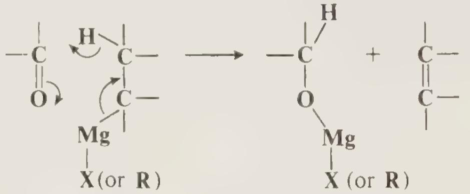
[252] The coefficient 2 in front of the MeMgBr refers only to the Schlenk equilibrium, presented horizontally, and not to the reactions between MeMgBr and the ketone, presented vertically.

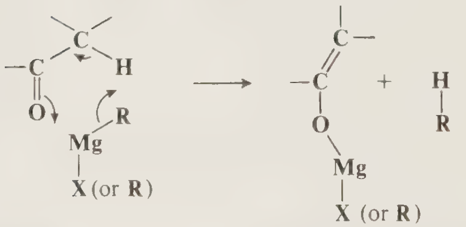
When excess Grignard reagent is present, the steps shown are essentially all that are required to describe the mechanism, but when the ketone-to-Grignard ratio is about 1 : 1, or when excess ketone is present, **38** and **39** react further—with each other and with additional molecules of RMgX and of ketone to give dimeric and trimeric species. Although the formation of these species complicates the mechanistic picture, they present no synthetic problem, since the hydrolysis step at the end of the reaction converts them all to the same alcohol, in this case R_2MeCOH. The exact nature of the step by which MeMgBr or Me_2Mg reacts with the substrate is not certain. One possibility is a four-centered cyclic transition state:[253]



The mechanism just outlined is probably not the only one. There are indications that in some cases, at least part of the reaction may go through a ketyl (p. 177) intermediate[254] [this pathway is called the *single-electron-transfer* (SET) *pathway*]. The SET pathway is favored by the presence of small amounts of transition metals[255] (which are often found as impurities in the magnesium).

There is general agreement that the mechanisms leading to reduction[256] and enolization are as follows:





Aromatic aldehydes and ketones can be alkylated and reduced in one reaction vessel by treatment with an alkyl- or aryllithium, followed by lithium and ammonia and then by ammonium chloride.[257]

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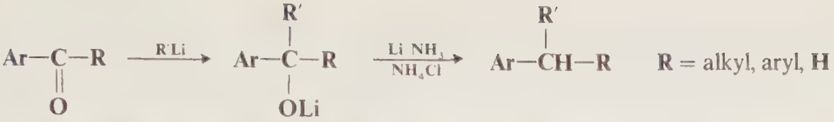
[253] Tuulmets, *Org. React.* (*USSR*) **4,** 5 (1967); House and Oliver, *J. Org. Chem.* **33,** 929 (1968); Ashby, Yu, and Roling, *J. Org. Chem.* **37,** 1918 (1972). See also Smith and Billet, *J. Am. Chem. Soc.* **89,** 6948 (1967); Billet and Smith, *J. Am. Chem. Soc.* **90,** 4108 (1968); Holm, *Acta Chem. Scand.* **23,** 579 (1969).

[254] Maruyama, *Bull. Chem. Soc. Jpn.* **37,** 897 (1964); Blomberg and Mosher, *J. Organomet. Chem.* **13,** 519 (1968); Fauvarque and Rouget, *C. R. Acad. Sci., Ser. C* **267,** 1355 (1968); Holm and Crossland, *Acta Chem. Scand.* **25,** 59 (1971); Lopp, Buhler, and Ashby, *J. Am. Chem. Soc.* **97,** 4966 (1975). See also Eisch and Harrell, *J. Organomet. Chem.* **21,** 21 (1970); House and Weeks, *J. Am. Chem. Soc.* **97,** 2770, 2778, 2785 (1975).

[255] Ashby and Wiesemann, *J. Am. Chem. Soc.* **96,** 7117 (1974); Ashby, Lopp, and Buhler, *J. Am. Chem. Soc.* **97,** 1964 (1975).

[256] For discussions of the mechanism of reduction, see Singer, Salinger, and Mosher, *J. Org. Chem.* **32,** 3821 (1967); Denise, Fauvarque, and Ducom, *Tetrahedron Lett.* 335 (1970); Chauvière and Welvart, *Bull. Soc. Chim. Fr.* 765, 771, 774 (1970); Cabaret and Welvart, *J. Organomet. Chem.* **80,** 199 (1974); Holm, *J. Organomet. Chem.* **29,** C45 (1971), *Acta Chem. Scand.* **27,** 1552 (1973).

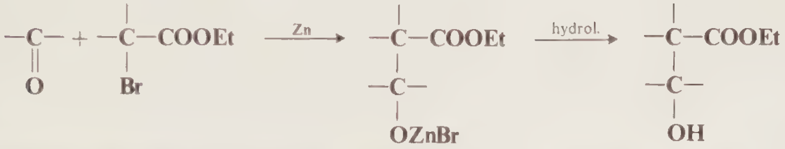
[257] Hall and Lipsky, *J. Org. Chem.* **38,** 1735 (1973); Hall, *J. Org. Chem.* **38,** 1738 (1973); Hall and McEnroe, *J. Org. Chem.* **40,** 271 (1975); Lipsky and Hall, *Org. Synth.* **55,** 7 (1976); Hall, Sha, and Jordan, *J. Org. Chem.* **41,** 1494 (1976).



$$\mathrm{Ar{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R} \xrightarrow{\mathrm{R'Li}} \mathrm{Ar{-}\overset{\overset{\displaystyle R'}{|}}{\underset{\underset{\displaystyle OLi}{|}}{C}}{-}R} \xrightarrow[\mathrm{NH_4Cl}]{\mathrm{Li\ NH_3}} \mathrm{Ar{-}\overset{\overset{\displaystyle R'}{|}}{CH}{-}R} \qquad \mathrm{R = alkyl, aryl, H}$$

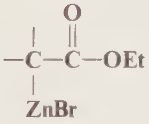
OS **I,** 188; **II,** 406, 606; **III,** 200, 696, 729, 757; **IV,** 771, 792; **V,** 46, 452, 608, 1058; **53,** 56, 116; **54,** 97; **55,** 7.

6-32 The Reformatsky Reaction



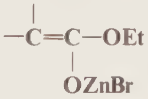
$$\mathrm{{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}} + \mathrm{{-}\overset{|}{\underset{\underset{\displaystyle Br}{|}}{C}}{-}COOEt} \xrightarrow{\mathrm{Zn}} \mathrm{{-}\overset{|}{\underset{\underset{\underset{\underset{\displaystyle OZnBr}{|}}{{-}C{-}}}{|}}{C}}{-}COOEt} \xrightarrow{\text{hydrol.}} \mathrm{{-}\overset{|}{\underset{\underset{\underset{\underset{\displaystyle OH}{|}}{{-}C{-}}}{|}}{C}}{-}COOEt}$$

The *Reformatsky reaction* is very similar to reaction **6-31.**[258] An aldehyde or ketone is treated with zinc and a halide;[259] the halide is nearly always an α-halo ester or a vinylog of an α-halo ester (e.g., RCHBrCH=CHCOOEt) though α-halo nitriles,[260] α-halo N,N-disubstituted amides, and the zinc salts of α-halo carboxylic acids[261] have also been used. With the last reagent the product is an α-hydroxy acid. The reaction has also been carried out with activated indium instead of zinc.[261a] The aldehyde or ketone may be aliphatic, aromatic, or heterocyclic or contain various functional groups. Formally, the reaction can be regarded as if it were analogous to the Grignard reaction (**6-31**), with **40** as an intermediate analogous to RMgX. There *is* an intermediate derived from zinc and the ester, but whether it has the structure **40** or the enolate structure **41** has been a matter of some controversy. There is some evidence for **40,**[262] but most of the evidence favors **41.**[263] The following pericyclic mechanism, involving **41,** has been proposed:[264]



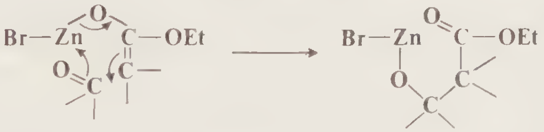
$$\mathrm{{-}\overset{|}{\underset{\underset{\displaystyle ZnBr}{|}}{C}}{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OEt}$$

40



$$\mathrm{{-}\overset{|}{C}{=}\underset{\underset{\displaystyle OZnBr}{|}}{C}{-}OEt}$$

41



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[258] For reviews, see Rathke, *Org. React.* **22,** 423-460 (1975); Gaudemar, *Organomet. Chem. Rev., Sect. A* **8,** 183-233 (1972); Diaper and Kuksis, *Chem. Rev.* **59,** 89–178 (1959); Shriner, *Org. React.* **1,** 1–37 (1942).

[259] Various improvements in the reaction procedures have been suggested by Curé and Gaudemar, *Bull. Soc. Chim. Fr.* 2471 (1969); Frankenfeld and Werner, *J. Org. Chem.* **34,** 3689 (1969); Cornforth, Opara, and Read, *J. Chem. Soc. C* 2799 (1969); Rathke and Lindert, *J. Org. Chem.* **35,** 3966 (1970); Ruppert and White, *J. Org. Chem.* **39,** 269 (1974).

[260] Vinograd and Vul'fson, *J. Gen. Chem. USSR* **29,** 248, 1118, 2658, 2659 (1960).

[261] Bellassoued, Couffignal, and Gaudemar, *J. Organomet. Chem.* **61,** 9 (1973).

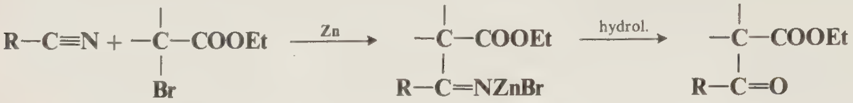
[261a] Chao and Rieke, *J. Org. Chem.* **40,** 2253 (1975).

[262] Canceill, Gabard, and Jaques, *Bull. Soc. Chim. Fr.* 231 (1968); Goasdoué and Gaudemar, *J. Organomet. Chem.* **39,** 17 (1972).

[263] Zimmerman and Traxler, *J. Am. Chem. Soc.* **79,** 1920 (1957); Vaughan, Bernstein, and Lorber, *J. Org. Chem.* **30,** 1790 (1965); Vaughan and Knoess, *J. Org. Chem.* **35,** 2394 (1970); Matsumoto, Tanaka, and Fukui, *Bull. Chem. Soc. Jpn.* **44,** 3378 (1971); Matsumoto, Hosoda, Mōri, and Fukui, *Bull. Chem. Soc. Jpn.* **45,** 3156 (1972).

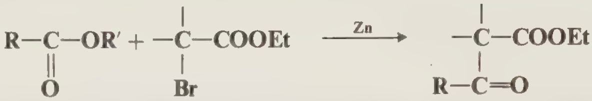
[264] Guetté, Capillon, and Guetté, *Tetrahedron* **29,** 3659 (1973); Balsamo, Barili, Crotti, Ferretti, Macchia, and Macchia, *Tetrahedron Lett.* 1005 (1974).

Usually, after hydrolysis, the alcohol is the product, but sometimes (especially with aryl aldehydes) elimination follows directly and the product is an olefin. Since Grignard reagents cannot be formed from α-halo esters, the method is quite useful, although there are competing reactions and yields are sometimes low. A similar reaction has been carried out on nitriles:[265]



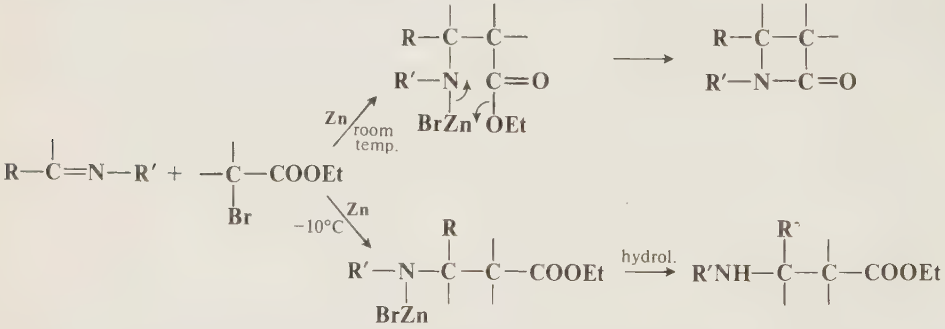
$$\mathrm{R{-}C{\equiv}N} + \underset{\mathrm{Br}}{\overset{|}{\underset{|}{-\mathrm{C}-}}}\mathrm{COOEt} \xrightarrow{\mathrm{Zn}} \underset{\mathrm{R-C=NZnBr}}{\overset{|}{\underset{|}{-\mathrm{C}-}}}\mathrm{COOEt} \xrightarrow{\text{hydrol.}} \underset{\mathrm{R-C=O}}{\overset{|}{\underset{|}{-\mathrm{C}-}}}\mathrm{COOEt}$$

Esters have also been used as substrates, but then, as might be expected (p. 802), the result is substitution and not addition:

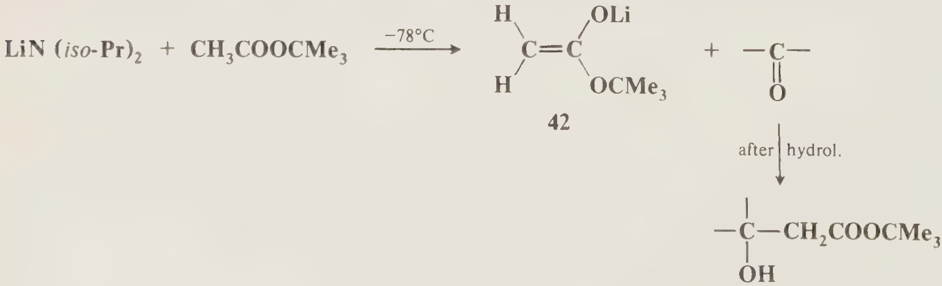


$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}OR'} + \underset{\mathrm{Br}}{\overset{|}{\underset{|}{-\mathrm{C}-}}}\mathrm{COOEt} \xrightarrow{\mathrm{Zn}} \underset{\mathrm{R-C=O}}{\overset{|}{\underset{|}{-\mathrm{C}-}}}\mathrm{COOEt}$$

The product in this case is the same as with the corresponding nitrile, though the pathways are different. Imines give β-amino esters (after hydrolysis) when the reaction is carried out at −10°C,[266] but at room temperature the product is the corresponding β-lactam:[267]



Addition of *t*-butyl acetate to lithium diisopropylamide in hexane at −78°C gives the lithium salt of *t*-butyl acetate[268] (reaction **2-20**) as a stable white solid. The nmr and ir spectra of this salt in benzene show it to have the enolate structure **42**, similar to the structure **41** given above



42

43

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[265] Cason, Rinehart, and Thornton, *J. Org. Chem.* **18**, 1594 (1953); Bellassoued and Gaudemar, *J. Organomet. Chem.* **81**, 139 (1974).

[266] Gilman and Speeter, *J. Am. Chem. Soc.* **65**, 2255 (1943).

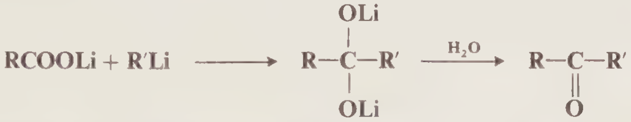
[267] Dardoize, Moreau, and Gaudemar, *Bull. Soc. Chim. Fr.* 3841 (1972), 1668 (1973). See also Dardoize and Gaudemar, *Bull. Soc. Chim. Fr.* 939 (1974).

[268] Rathke and Sullivan, *J. Am. Chem. Soc.* **95**, 3050 (1973).

for the Reformatsky reagent. Reaction of **42** with a ketone provides a simple rapid alternative to the Reformatsky reaction as a means of preparing β-hydroxy *t*-butyl esters with the structure **43.** A similar reaction involves treatment of a ketone R_2CO with ethyl or *t*-butyl lithiotrimethylsilylacetate $Me_3SiCHLiCOOR'$, but in this case the product is the α,β-unsaturated ester $R_2C{=}CHCOOR'$.[269]

OS **III**, 408; **IV**, 120, 444.

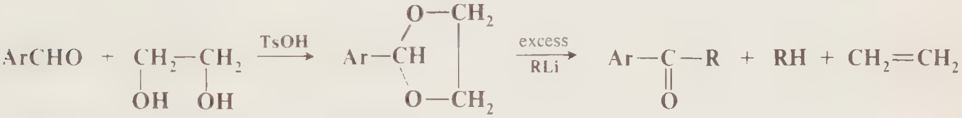
6-33 The Conversion of Carboxylic Acid Salts to Ketones with Organometallic Compounds



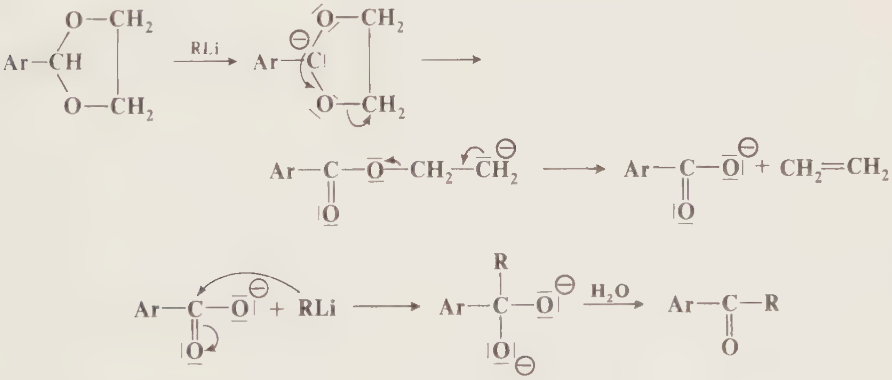
$$\text{RCOOLi} + \text{R'Li} \longrightarrow \text{R}-\underset{\text{OLi}}{\overset{\text{OLi}}{\text{C}}}-\text{R'} \xrightarrow{H_2O} \text{R}-\underset{\text{O}}{\overset{}{\text{C}}}-\text{R'}$$

Good yields of ketones can often be obtained by treatment of the lithium salt of a carboxylic acid with an alkyllithium reagent, followed by hydrolysis.[270] The reaction can be run in two ways: the acid can be treated with 2 moles of R′Li, or the lithium carboxylate can be independently prepared and treated with 1 mole of R′Li. R′ may be aryl or primary, secondary, or tertiary alkyl. MeLi and PhLi have been employed most often. R may be alkyl or aryl, though lithium acetate generally gives low yields. Tertiary alcohols are side products.

A reaction between ArCOOLi and RLi is one step in a conversion of an aromatic aldehyde to an alkyl aryl ketone. The aldehyde is converted to the corresponding cyclic acetal, which is treated with excess RLi.[271]



The mechanism is



OS **V**, 775.

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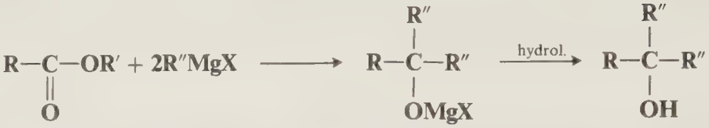
[269] Hartzell, Sullivan, and Rathke, *Tetrahedron Lett.* 1403 (1974); Shimoji, Taguchi, Oshima, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **96**, 1620 (1974). For a similar reaction, see Chan, Chang, and Vinokur, *Tetrahedron Lett.* 1137 (1970).

[270] For a review, see Jorgenson, *Org. React.* **18**, 1–97 (1970).

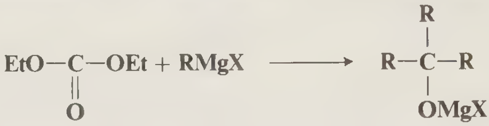
[271] Berlin, Rathore, and Peterson, *J. Org. Chem.* **30**, 226 (1965).

6-34 The Addition of Grignard Reagents to Acid Derivatives



$$R-\underset{\underset{O}{\|}}{C}-OR' + 2R''MgX \longrightarrow R-\overset{\overset{R''}{|}}{\underset{\underset{OMgX}{|}}{C}}-R'' \xrightarrow{\text{hydrol.}} R-\overset{\overset{R''}{|}}{\underset{\underset{OH}{|}}{C}}-R''$$

When esters are treated with Grignard reagents, there is usually concomitant addition to the carbonyl (reaction **6-31**) and substitution of R″ for OR′ (reaction **0-106**), so that tertiary alcohols are formed in which two R groups are the same. Formates give secondary alcohols, and carbonates give tertiary alcohols in which all three R groups are the same:

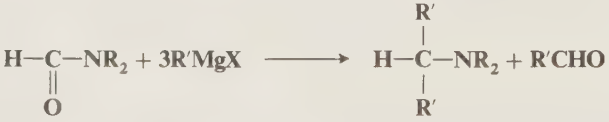


$$EtO-\underset{\underset{O}{\|}}{C}-OEt + RMgX \longrightarrow R-\overset{\overset{R}{|}}{\underset{\underset{OMgX}{|}}{C}}-R$$

Acyl halides and anhydrides behave similarly, though these substrates are employed less often.[272] There are many side reactions possible, especially when there is branching in the acid derivative or in the Grignard reagent: enolizations, reductions (not for esters, but for halides), condensations, and cleavages, but the most important is simple substitution (reaction **0-106**), which in some cases may be made to predominate. Trimethylaluminum, which exhaustively methylates ketones (reaction **6-31**), also exhaustively methylates carboxylic acids, to give *t*-butyl compounds[273] (see also reaction **0-90**):

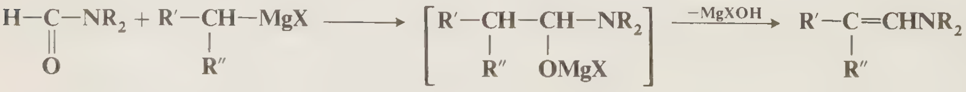
$$RCOOH + \text{excess } Me_3Al \xrightarrow{120\ C} RCOOAlMe_2 \xrightarrow{Me_3Al} RCMe_3$$

Disubstituted formamides can give addition of 2 moles of Grignard reagent.



$$H-\underset{\underset{O}{\|}}{C}-NR_2 + 3R'MgX \longrightarrow H-\overset{\overset{R'}{|}}{\underset{\underset{R'}{|}}{C}}-NR_2 + R'CHO$$

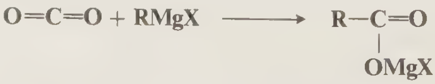
The products of this reaction (called the *Bouveault reaction*) are an aldehyde and a tertiary amine.[274] The use of an amide other than a formamide can give a ketone instead of an aldehyde, but yields are generally low. Alternatively, if R′ contains an α-hydrogen, the product may be an enamine, and enamines have been synthesized in good yields by this method.[275]



$$H-\underset{\underset{O}{\|}}{C}-NR_2 + R'-\underset{\underset{R''}{|}}{CH}-MgX \longrightarrow \left[R'-\underset{\underset{R''}{|}}{CH}-\underset{\underset{OMgX}{|}}{CH}-NR_2\right] \xrightarrow{-MgXOH} R'-\underset{\underset{R''}{|}}{C}=CHNR_2$$

OS **I,** 226; **II,** 179, 602; **III,** 237, 831, 839; **IV,** 601; **52,** 19; **55,** 39.

6-35 The Addition of Organometallic Compounds to CO_2



$$O=C=O + RMgX \longrightarrow R-\underset{\underset{OMgX}{|}}{C}=O$$

Grignard reagents add to one C=O bond of CO_2 exactly as they do to an aldehyde or a ketone.[276] Here, of course, the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice, but it is also possible to bubble CO_2 through a Grignard solution. However, the latter procedure usually gives lower yields, since the salt can react with additional molecules of Grignard reagent to give a ketone and a tertiary alcohol (reactions **6-31** and **6-34**). Sometimes this can be turned to preparative use; e.g., hexamethylacetone can be made in this way from CO_2 and *t*-butylmagnesium bromide.

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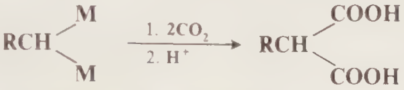
[272] For a review of these reactions, see Kharasch and Reinmuth, Ref. 228, pp. 549–766, 846–869.

[273] Meisters and Mole, *Aust. J. Chem.* 27, 1665 (1974).

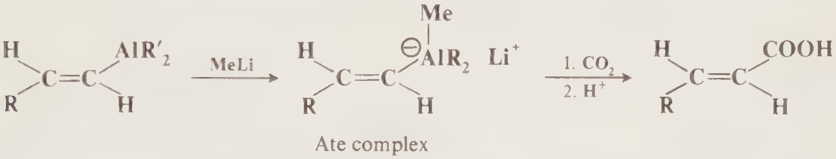
[274] For a review, see Ref. 120, pp. 59–63.

[275] Hansson and Wickberg, *J. Org. Chem.* **38,** 3074 (1973).

Many carboxylic acids have been prepared in this manner, and, along with the sequence **0-103–6-5** and reaction **8-9**, this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO_2 is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi, RNa, RCaX, etc.) but much less often. The formation of the salt of a carboxylic acid after the addition of CO_2 to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also reaction **6-43**). Addition of CO_2 to *gem*-dimetallic compounds gives replacement of both metal atoms, the product being a malonic acid.[277]



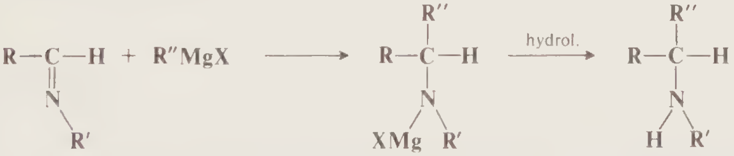
α,β-Unsaturated acids can be prepared by carbonation of an ate complex of a vinylalane.[278]



Vinylalanes can be prepared by addition of a dialkylalane to a triple bond (reaction **5-16**).

OS **I**, 361, 524; **II**, 425; **III**, 413, 553, 555; **V**, 890, 1043.

6-36 The Addition of Organometallic Compounds to Imines



Aldimines can be converted to secondary amines by treatment with Grignard reagents.[279] Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.[280] Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents;

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[276] For reviews of the reaction between organometallic compounds and CO_2, see Volpin and Kolomnikov, *Organomet. React.* **5**, 313–386 (1975); Sneeden, in Patai, "The Chemistry of Carboxylic Acids and Esters," pp. 137–173, Interscience Publishers, New York, 1969; Kharasch and Reinmuth, Ref. 228, pp. 913–948.

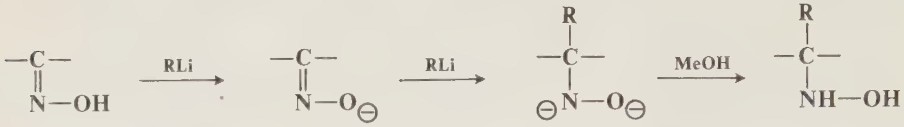
[277] For examples, see Cainelli, Dal Bello, and Zubiani, *Tetrahedron Lett.* 3429 (1965); Zweifel and Steele, Ref. 237; Bertini, Grasselli, Zubiani, and Cainelli, Ref. 236.

[278] Zweifel and Steele, *J. Am. Chem. Soc.* **89**, 2754, 5085 (1967).

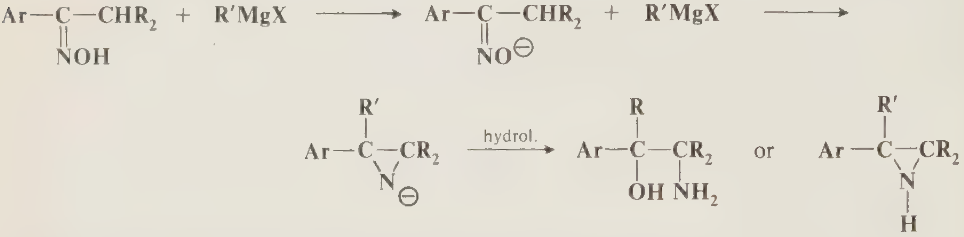
[279] For reviews of the addition of organometallic reagents to C=N bonds, see Harada, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Ref. 31, pp. 266–272; Kharasch and Reinmuth, Ref. 228, pp. 1204–1227.

[280] Huet, *Bull. Soc. Chim. Fr.* 952, 960, 967, 973 (1964).

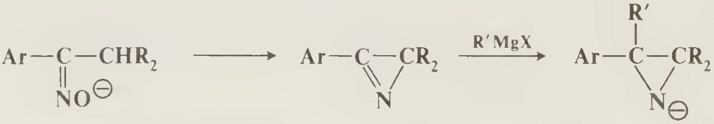
others give reduction; others (oximes) give an active hydrogen to the Grignard reagent; and still others give miscellaneous reactions. Oximes can be converted to hydroxylamines by treatment with two moles of an alkyllithium reagent, followed by methanol.[280a] Aryl alkyl oximes containing an α hydrogen react with 2 moles of Grignard reagent to give α-amino alcohols, with a net migration of N, or aziridines, depending on the method of hydrolysis.[281]



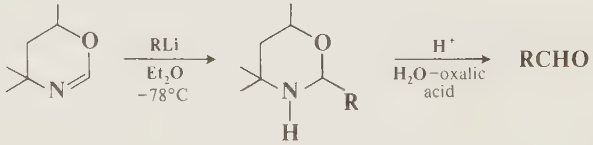
$$\underset{\substack{\| \\ \text{N—OH}}}{-\text{C}-} \xrightarrow{\text{RLi}} \underset{\substack{\| \\ \text{N—O}^{\ominus}}}{-\text{C}-} \xrightarrow{\text{RLi}} \overset{\substack{\text{R} \\ |}}{\underset{\substack{| \\ {}^{\ominus}\text{N—O}^{\ominus}}}{-\text{C}-}} \xrightarrow{\text{MeOH}} \overset{\substack{\text{R} \\ |}}{\underset{\substack{| \\ \text{NH—OH}}}{-\text{C}-}}$$



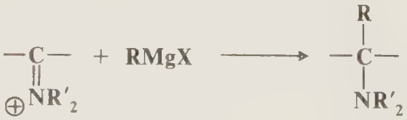
The mechanism involves initial formation of an azirine (see reaction **8-16**).[282]



Alkyllithium compounds add to the C=N bond of the dihydro-1,3-oxazine **44**.[283] Since the products **45** can be hydrolyzed to aldehydes, this is a method for the conversion of RLi to RCHO (see also reaction **2-31**).



Iminium salts[210] give tertiary amines directly, with just R adding:



$$\underset{\substack{\| \\ {}^{\oplus}\text{NR}'_2}}{-\text{C}-} + \text{RMgX} \longrightarrow \overset{\substack{\text{R} \\ |}}{\underset{\substack{| \\ \text{NR}'_2}}{-\text{C}-}}$$

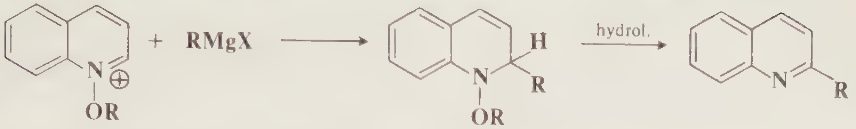
[280a] Richey, McLane, and Phillips, *Tetrahedron Lett.* 233 (1976).

[281] Campbell, Campbell, McKenna, and Chaput, *J. Org. Chem.* **8**, 103 (1943); Freeman, *Chem. Rev.* **73**, 283–292 (1973), pp. 288–190. See also Alvernhe, Arsenyiadis, Chaabouni, and Laurent, *Tetrahedron Lett.* 355 (1975).

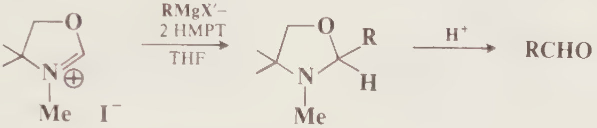
[282] Eguchi and Ishii, *Bull. Chem. Soc. Jpn.* **36**, 1434 (1963); Laurent and Muller, *Tetrahedron Lett.* 759 (1969); Alvernhe and Laurent, *Bull. Soc. Chim. Fr.* 3003 (1970).

[283] Meyers and Adickes, *Tetrahedron Lett.* 5151 (1969).

Salts of nitrogen heterocycles have also been alkylated in this manner, e.g.,[284]

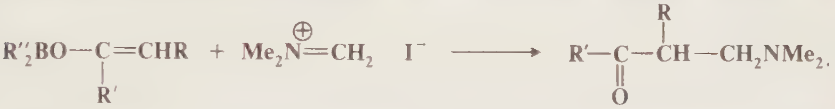


Application of this reaction to N-alkyl derivatives of 2-oxazolines (in the presence of HMPT) provides a means of conversion of an aryl, benzyl, or vinyl Grignard reagent RMgX to the corresponding aldehyde RCHO[285] (see reaction **0-100** for the similar conversion of Grignard reagents to ketones):



However, the method is not applicable to simple Grignard reagents.

Enol borinates react with iminium ions to give β-dialkylamino ketones (Mannich bases).[286]



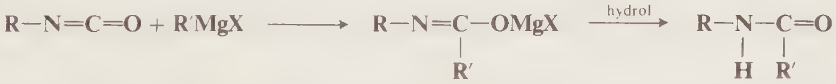
$$R''_2BO-\underset{R'}{\underset{|}{C}}=CHR + Me_2\overset{\oplus}{N}=CH_2 \quad I^- \longrightarrow R'-\underset{O}{\underset{\|}{C}}-\overset{R}{\overset{|}{C}}H-CH_2NMe_2.$$

This reaction provides a means of constructing a Mannich base from a given ketone in a regioselective manner, since either enol borinate can be prepared at will. The enol borinates (which need not be isolated) are prepared as in reaction **0-101.**

For the addition of alkyllithium compounds to the C═N bond of ketenimines, see reaction **2-17.**

OS **IV,** 605; **54,** 42. Also see OS **III,** 329.

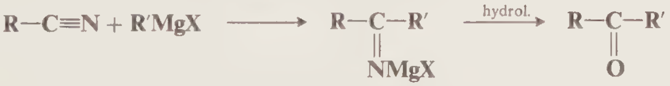
6-37 The Addition of Grignard Reagents to Isocyanates



$$R-N=C=O + R'MgX \longrightarrow R-N=\underset{R'}{\underset{|}{C}}-OMgX \xrightarrow{\text{hydrol}} R-\underset{H}{\underset{|}{N}}-\underset{R'}{\underset{|}{C}}=O$$

The addition of Grignard reagents to isocyanates gives, after hydrolysis, N-substituted amides. The reaction is written above as involving addition to C═O, but the ion is a resonance hybrid and the addition might just as well have been shown as occurring on the C═N. In any event, hydrolysis gives the amide. This is a very good reaction and may be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.[287] Isothiocyanates give N-substituted thioamides.

6-38 The Addition of Grignard Reagents to Nitriles



$$R-C\equiv N + R'MgX \longrightarrow R-\underset{NMgX}{\underset{\|}{C}}-R' \xrightarrow{\text{hydrol.}} R-\underset{O}{\underset{\|}{C}}-R'$$

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[284] Červinka, Fábryová, and Matouchová, *Collect. Czech. Chem. Commun.* **28,** 535 (1963).

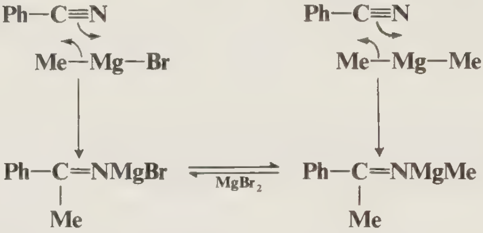
[285] Meyers and Collington, *J. Am. Chem. Soc.* **92,** 6676 (1970).

[286] Hooz and Bridson, *J. Am. Chem. Soc.* **95,** 602 (1973).

[287] LeBel, Cherluck, and Curtis, *Synthesis* 678 (1973).

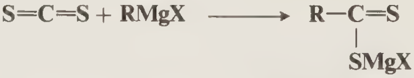
Ketones can be prepared by addition of Grignard reagents to nitriles and subsequent hydrolysis. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.[288] The ketimine salt does not in general react with Grignard reagents; hence tertiary alcohols or tertiary alkyl amines are not often side products.[289] By careful hydrolysis of the salt it is sometimes possible to isolate ketimines $\mathrm{R{-}\underset{\underset{NH}{\|}}{C}{-}R'}$.[290] The addition of Grignard reagents to the C≡N group is normally slower than to the C=O group, and CN-containing aldehydes add the Grignard reagent without disturbing the CN group.[291] In a similar reaction, triethylaluminum[292] reacts with nitriles (in a 2 : 1 ratio) to give, after hydrolysis, ethyl ketones.[293]

The following mechanism has been proposed for the reaction of the methyl Grignard reagent with benzonitrile:[294]



OS **III,** 26, 562; **V,** 520.

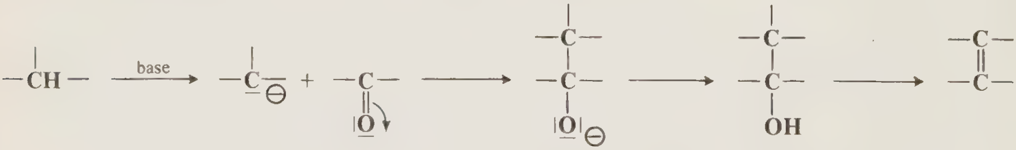
6-39 The Addition of Grignard Reagents to CS_2



$$S{=}C{=}S + RMgX \longrightarrow \mathrm{R{-}\underset{\underset{SMgX}{|}}{C}{=}S}$$

This reaction is analogous to reaction **6-34.**[294a] See also reaction **6-43.**

I. Carbon Attack by Active Hydrogen Compounds. Reactions **6-40** through **6-49** are base-catalyzed condensations (although some of them are catalyzed by acids too).[295] In reaction **6-40** through **6-47,** a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α-hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



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[288] For a review, see Kharasch and Reinmuth, Ref. 228, pp. 767–845.

[289] For an example where tertiary amines have been made the main products, see Alvernhe and Laurent, *Tetrahedron Lett.* 1057 (1973).

[290] Pickard and Tolbert, *J. Org. Chem.* **26,** 4886 (1961).

[291] Cason, Kraus, and McLeod, *J. Org. Chem.* **24,** 392 (1959). See also Borch, Levitan, and Van-Catledge, *J. Org. Chem.* **37,** 726 (1972).

[292] For a review of the reactions of organoaluminum compounds, see Reinheckel, Haage, and Jahnke, *Organomet. Chem. Rev., Sect. A* **4,** 47–136 (1969).

[293] Reinheckel and Jahnke, *Chem. Ber.* **97,** 2661 (1964). See also Bagnell, Jeffery, Meisters, and Mole, *Aust. J. Chem.* **27,** 2577 (1974).

[294] Ashby, Chao, and Neuman, *J. Am. Chem. Soc.* **95,** 4896, 5186 (1973).

[294a] For a review of the addition of Grignard reagents to C=S bonds, see Paquer, *Bull. Soc. Chim. Fr.* 1439–1449 (1975).

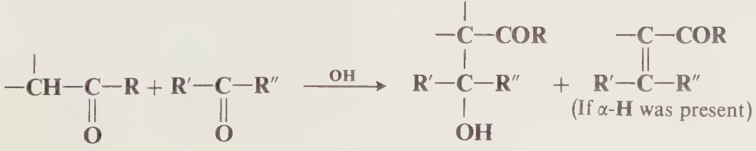
[295] For reviews, see House, Ref. 124, pp. 629–682; Reeves, in Patai, "The Chemistry of the Carbonyl Group," Ref. 31, pp. 567–619.

TABLE 2 Base-catalyzed condensations showing the active-hydrogen components and the carbonyl components

Reaction	Active-hydrogen component	Carbonyl component	Subsequent reactions
6-40 Aldol condensation	Aldehyde $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{CHO}$ Ketone $-\underset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{COR}$	Aldehyde, ketone	Dehydration may follow
6-41	Ester $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{COOR}$	Aldehyde, ketone (usually without α-hydrogens)	Dehydration may follow
6-42 Knoevenagel reaction	$\mathrm{Z}-\mathrm{CH_2}-\mathrm{Z'}$, $\mathrm{Z}-\mathrm{CHR}-\mathrm{Z'}$, and similar molecules	Aldehyde, ketone (usually without α-hydrogens)	Dehydration usually follows
6-43	$-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{Z}$ $\quad \mathrm{Z} = \mathrm{COR, COOR, NO_2}$	$\mathrm{CO_2}$, $\mathrm{CS_2}$	
6-44 Perkin reaction	Anhydride $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{COOCOR}$	Aromatic aldehyde	Dehydration usually follows
6-45 Darzen's reaction	α-Halo ester $\mathrm{X}\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{COOR}$	Aldehyde, ketone	Epoxidation (SN reaction) follows
6-46 Tollens' reaction	Aldehyde $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{CHO}$ Ketone $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{COR}$	Formaldehyde	Crossed Cannizzaro reaction follows
6-47 Wittig reaction	Phosphorus ylide $\mathrm{Ph_3}\overset{\oplus}{\mathrm{P}}-\overset{\vert}{\underset{\ominus}{\underline{\mathrm{C}}}}-$	Aldehyde, ketone	"Dehydration" always follows
6-48 Thorpe reaction	Nitrile $-\overset{\vert}{\mathrm{C}}\mathrm{H}-\mathrm{CN}$	Nitrile	
6-49	Phosphorus ylide $\mathrm{Ph_3}\overset{\oplus}{\mathrm{P}}-\overset{\vert}{\underset{\ominus}{\underline{\mathrm{C}}}}-$	Nitrile	

The reactions differ in the nature of the active hydrogen component and of the carbonyl component. Table 2 illustrates the differences. Reactions **6-48** and **6-49** are analogous reactions involving addition to C≡N.

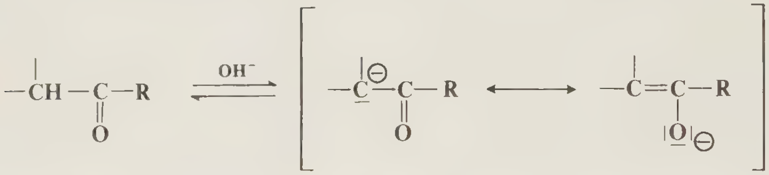
6-40 The Aldol Condensation



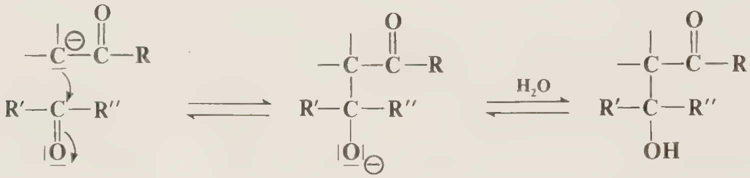
$$-\overset{|}{\mathrm{C}}\mathrm{H}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R} + \mathrm{R'}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R''} \xrightarrow{\mathrm{OH}} \mathrm{R'}-\overset{\overset{|}{-\mathrm{C}-\mathrm{COR}}}{\overset{|}{\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}}}-\mathrm{R''} + \mathrm{R'}-\overset{-\mathrm{C}-\mathrm{COR}}{\overset{\|}{\mathrm{C}}}-\mathrm{R''}$$

(If α-H was present)

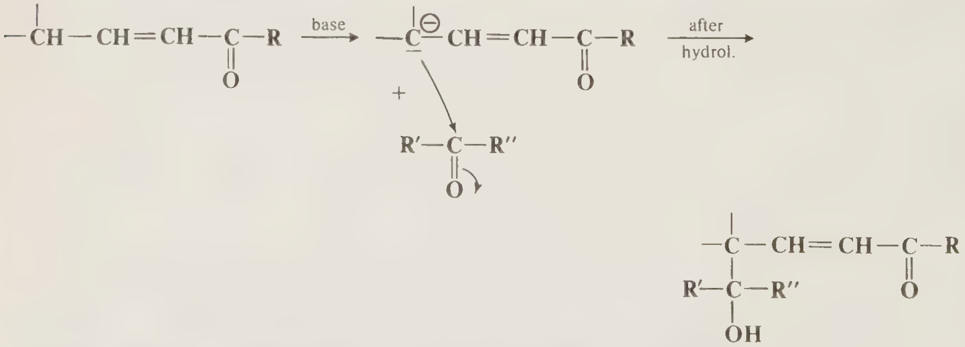
In the *aldol condensation* the α-carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.[296] The base most often used is OH^-, though stronger bases, e.g., aluminum *t*-butoxide, are sometimes employed. Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate ion; i.e., the equilibrium



lies well to the left, for both aldehydes and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



The product is a β-hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. Even if the dehydration is not spontaneous, it can usually easily be done, since the new double bond will be in conjugation with the C═O bond; so that this is a method of preparing α,β-unsaturated aldehydes and ketones as well as β-hydroxy aldehydes and ketones. The entire reaction is an equilibrium (including the dehydration step), and α,β-unsaturated and β-hydroxy aldehydes and ketones may be cleaved by treatment with OH^-. This reverse reaction is known as the *retrograde aldol reaction.* Under the principle of vinylogy, the active hydrogen may be one in the γ position of an α,β-unsaturated carbonyl compound:



The scope of the aldol condensation may be discussed under five headings:

1. *Condensation between two molecules of the same aldehyde.* This equilibrium lies far over to the right, and the reaction is quite feasible. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must be one with an α-hydrogen. Aldol itself, the condensation product of acetaldehyde, is actually a trimer:[297]

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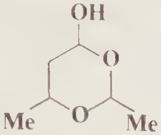
[296] For a book-length review, see Nielsen and Houlihan, *Org. React.* **16,** 1–438 (1968).

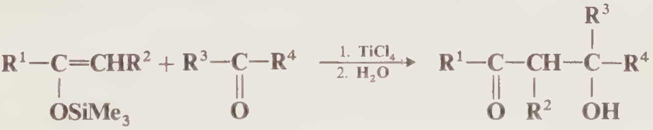


2. *Condensation between two molecules of the same ketone.* In this case the equilibrium lies well over to the left, and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (for example, see OS **I,** 199). In this method the ketone is refluxed in such a way that the condensate drips into a separate chamber, in which the base is present. In this chamber the reaction proceeds to the small extent permitted by the unfavorable equilibrium. When the chamber is full, the mixture of the ketone and its dimer is siphoned back into the original flask, out of contact with the base. Since the boiling point of the dimer is higher than that of the ketone, only the ketone is volatilized back to the chamber containing the base, where a little more of it is converted to dimer, and the process is repeated until a reasonable yield of dimer is obtained. Two molecules of the same ketone can also be condensed without a Soxhlet extractor, by use of the reagent barium pernitride Ba_3N_4.[298] Unsymmetrical ketones condense on the side which has more hydrogens. (An exception is butanone, which with acid catalysts reacts at the CH_2 group, though with basic catalysts it too reacts at the CH_3 group.)

3. *Condensation between two different aldehydes.* In the most general case this will produce a mixture of four products (eight, if the olefins are counted). However, if one aldehyde does not have an α-hydrogen, only two aldols are possible, and in many cases the crossed product is the main one. The crossed aldol condensation is often called the *Claisen-Schmidt reaction.*

4. *Condensation between two different ketones.* This is seldom attempted, but similar considerations apply.

5. *Condensation between an aldehyde and a ketone.* This is usually feasible, especially when the aldehyde has no α-hydrogen, since there is no competition from ketone condensing with itself. This is also called the *Claisen-Schmidt reaction.* Even when the aldehyde has an α-hydrogen, it is the α-carbon of the ketone which adds to the carbonyl of the aldehyde, and not the other way around. The reaction is ordinarily carried out by adding a base to a mixture of the aldehyde and ketone, but it has been done by preparing the lithium enolate of the ketone separately (reaction **2-20**) and then adding this to the aldehyde in the presence of $ZnCl_2$,[299] a method which has the advantages that coupling will take place on the desired side of an unsymmetrical ketone, and that the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion. Another way to ensure coupling on the desired side of a ketone is to treat the silyl ether of the ketone (instead of the ketone itself) with an aldehyde or ketone, with $TiCl_4$ as catalyst.[300] This reaction



$$\underset{\displaystyle OSiMe_3}{R^1-\underset{|}{C}}{=}CHR^2 + R^3-\underset{\displaystyle O}{\underset{\|}{C}}-R^4 \xrightarrow[2.\ H_2O]{1.\ TiCl_4} R^1-\underset{\displaystyle O}{\underset{\|}{C}}-\underset{\displaystyle R^2}{\underset{|}{CH}}-\overset{\displaystyle R^3}{\overset{|}{\underset{\displaystyle OH}{\underset{|}{C}}}}-R^4$$

46

can also be run with the aldehyde or ketone in the form of its acetal $R^3R^4C(OR')_2$, in which case the product is the ether $RCOCHR^2CR^3R^4OR'$, instead of **46.**[301] Enol acetates also give this product when treated with acetals and $TiCl_4$ or a similar catalyst.[302]

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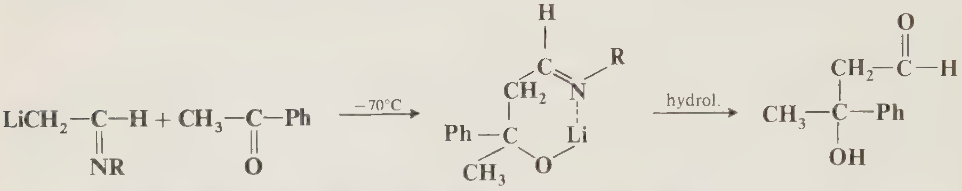
[297] Gruèn and McTigue, *Aust. J. Chem.* **17,** 953 (1964).

[298] Okamoto and Goswami, *Bull. Chem. Soc. Jpn.* **39,** 2778 (1966).

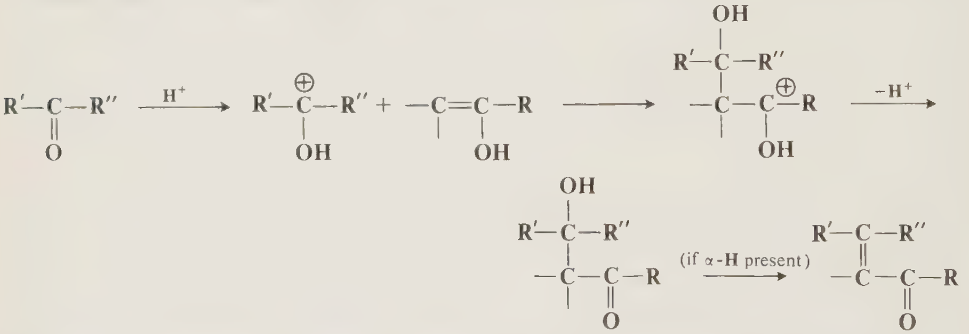
[299] House, Crumrine, Teranishi, and Olmstead, *J. Am. Chem. Soc.* **95,** 3310 (1973). See also Stork, Kraus, and Garcia, *J. Org. Chem.* **39,** 3459 (1974); Stork and d'Angelo, *J. Am. Chem. Soc.* **96,** 7114 (1974).

[300] Mukaiyama, Banno, and Narasaka, *J. Am. Chem. Soc.* **96,** 7503 (1974).

It is possible to make the α-carbon of the aldehyde add to the carbonyl carbon of the ketone, by using the Schiff base instead of the aldehyde, and $LiN(iso\text{-}Pr)_2$ as the base:[303]



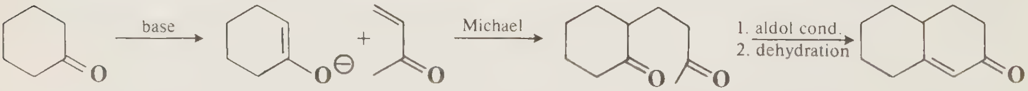
The aldol condensation can also be performed with acid catalysts, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group, which attacks the α-carbon of the *enol* form of the other molecule:



With respect to the enol, this mechanism is similar to that of α halogenation (reaction **2-4**).

A side reaction which is sometimes troublesome is further condensation, since the product of an aldol condensation is still an aldehyde or ketone.

Aldol condensations are often used to close five- and six-membered rings. Because of the favorable entropy (p. 193), such ring closures generally take place with ease, even where a ketone condenses with a ketone. An important example is the *Robinson annulation reaction*,[304] which has often been used in the synthesis of steroids and terpenes. In this reaction a cyclic ketone is converted to another cyclic ketone, with one additional six-membered ring containing a double bond. The substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.[305] The enolate ion of the substrate adds to the methyl vinyl ketone in a



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[301] Mukaiyama and Hayashi, *Chem. Lett.* 15 (1974).

[302] Mukaiyama, Izawa, and Saigo, *Chem. Lett.* 323 (1974). See also Kitazawa, Imamura, Saigo, and Mukaiyama, *Chem. Lett.* 569 (1975).

[303] Wittig, Frommeld, and Suchanek, *Angew. Chem. Int. Ed. Engl.* **2**, 683 (1963) [*Angew. Chem.* **75**, 303]; Wittig and Frommeld, *Chem. Ber.* **97**, 3548 (1964); Wittig and Suchanek, *Tetrahedron Suppl.* **8**, 347 (1966). For reviews, see Wittig and Reiff, *Angew. Chem. Int. Ed. Engl.* **7**, 7-14 (1968); [*Angew. Chem.* **80**, 8-15]; Reiff, *Newer Methods Prep. Org. Chem.* **6**, 48-66 (1971); Wittig, *Rec. Chem. Prog.* **28**, 45-60 (1967). See also Wittig and Hesse, *Justus Liebigs Ann. Chem.* **746**, 149, 174 (1971).

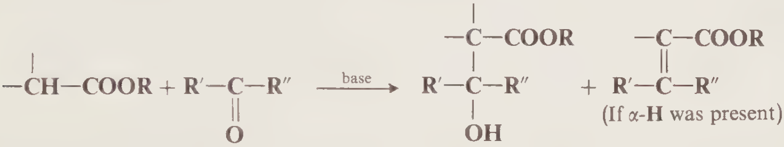
[304] For reviews of this and related reactions, see Jung, *Tetrahedron* **32**, 1-31 (1976); Mundy, *J. Chem. Educ.* **50**, 110-113 (1973).

[305] Acid catalysis has also been used; see Heathcock, Ellis, Mc Murry, and Coppolino, *Tetrahedron Lett.* 4995 (1971).

Michael reaction (**5-19**) to give a diketone which undergoes or is made to undergo an internal aldol condensation and subsequent dehydration to give the product. Because methyl vinyl ketone has a tendency to polymerize, precursors are often used instead, i.e., compounds which will give methyl vinyl ketone when treated with a base. One common example, $MeCOCH_2CH_2NEt_2Me^+ I^-$ (see reaction **7-8**), is easily prepared by quaternization of $MeCOCH_2CH_2NEt_2$, which itself is prepared by a Mannich reaction (**6-17**) involving acetone, formaldehyde, and dimethylamine. The Robinson annulation reaction has also been carried out with 3-butyn-2-one, in which case the new ring of the product contains two double bonds.[306] α-Silylated vinyl ketones $RCOC(SiMe_3){=}CH_2$ have also been used successfully in annulation reactions.[307] The $SiMe_3$ group is easily removed. 1,5-Diketones prepared in other ways are also frequently cyclized by internal aldol condensations.

OS **I,** 77, 78, 81, 199, 283, 341; **II,** 167, 214; **III,** 317, 353, 367, 747, 806, 829; **V,** 486, 869; **50,** 66; **53,** 48, 70; **54,** 49.

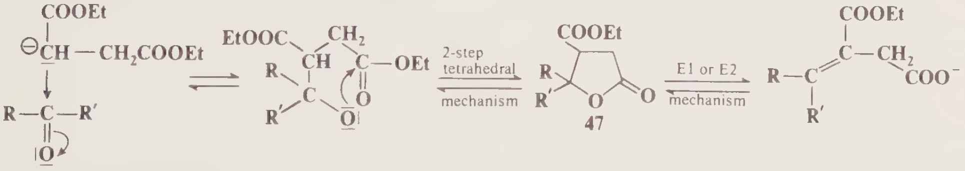
6-41 Condensations between Esters and Aldehydes or Ketones



In the presence of a strong base, the α-carbon of an ester may condense with the carbonyl carbon of an aldehyde or ketone to give a β-hydroxy ester, which may or may not be dehydrated to the α,β-unsaturated ester. This reaction is sometimes called the Claisen condensation,[308] an unfortunate usage since that name is more firmly connected to reaction **0-111.** It is also possible for the α-carbon of an aldehyde or ketone to add to the carbonyl carbon of an ester, but this is a different reaction (**0-112**) involving nucleophilic substitution and not addition to a C=O bond. It can, however, be a side reaction if the aldehyde or ketone has an α-hydrogen.

Besides ordinary esters (containing an α-hydrogen), the reaction can also be carried out with lactones and, as in reaction **6-40**, with the γ position of α,β-unsaturated esters (vinylology).

For most esters, a much stronger base is needed than for aldol condensations; Ph_3CNa and $LiNH_2$[309] are among those employed. However, one type of ester reacts more easily, and such strong bases are not needed: diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt, NaH, or $KOCMe_3$. This reaction is called the *Stobbe condensation.*[310] One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (1) the fact that succinic esters react so much better than others; (2) one ester group is always cleaved; and (3) the alcohol is not the product but the olefin. In addition, intermediate lactones **47** have been isolated from the mixture:[311]



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[306] For example, see Woodward, and Singh, *J. Am. Chem. Soc.* **72,** 494 (1950).

[307] Stork and Ganem, *J. Am. Chem. Soc.* **95,** 6152 (1973); Stork and Singh, *J. Am. Chem. Soc.* **96,** 6181 (1974); Boeckman, *J. Am. Chem. Soc.* **96,** 6179 (1974).

[308] Because it was discovered by Claisen: *Ber.* **23,** 977 (1890).

[309] Dunnavant and Hauser, *J. Org. Chem.* **25,** 503, 1693 (1960).

[310] For a review, see Johnson and Daub, *Org. React.* **6,** 1 73 (1951).

[311] Robinson and Seijo, *J. Chem. Soc.* 582 (1941).

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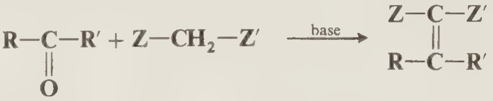
The Stobbe condensation has been extended to di-*t*-butyl esters of glutaric acid.[312]

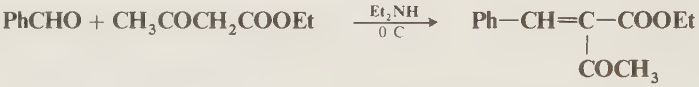
OS **I,** 252; **III,** 132; **V,** 80, 564. Also see OS **IV,** 278, 478; **V,** 251.

6-42 The Knoevenagel Condensation



$$\underset{\displaystyle\overset{\|}{\mathrm{O}}}{\mathrm{R{-}C{-}R'}} + \mathrm{Z{-}CH_2{-}Z'} \xrightarrow{\text{base}} \begin{array}{c}\mathrm{Z{-}C{-}Z'}\\ \|\\ \mathrm{R{-}C{-}R'}\end{array}$$

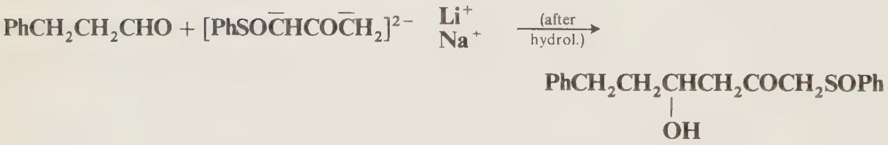
The condensation of aldehydes or ketones, usually not containing an α-hydrogen, with compounds of the form Z—CH$_2$—Z′ or Z—CHR—Z′ is usually called the *Knoevenagel reaction*,[313] although some limit the use of this name to only some of the active-hydrogen compounds which give the reaction. Z and Z′ may be CHO, COR, COOH, COOR, CN, NO$_2$,[314] SOR, SO$_2$R, SO$_2$OR, or similar groups. When Z = COOH, decarboxylation of the product often takes place in situ. If a strong enough base is used, the reaction can be performed on compounds possessing only a single Z; e.g., CH$_3$Z or RCH$_2$Z. Other active hydrogen compounds can also be employed, among them CHCl$_3$, 2-methylpyridines, terminal acetylenes, cyclopentadienes, etc.; in fact any compound which contains a C—H bond the hydrogen of which can be removed by a base. The following examples illustrate the wide scope of the reaction:



$$\mathrm{PhCHO + CH_3COCH_2COOEt \xrightarrow[0\ C]{Et_2NH} Ph{-}CH{=}\underset{\displaystyle\underset{\mathrm{COCH_3}}{|}}{C}{-}COOEt}$$

48

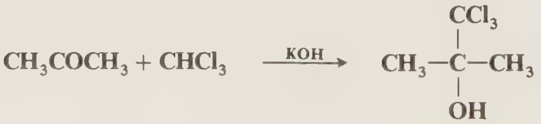
$$\mathrm{PhCHO + CH_3NO_2 \xrightarrow{\textit{n}\text{-}C_5H_{11}NH_2} Ph{-}CH{=}CH{-}NO_2} \qquad \text{(Ref. 314)}$$



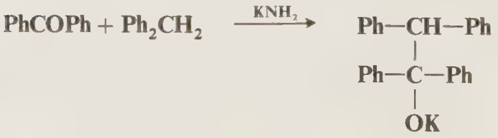
$$\mathrm{PhCH_2CH_2CHO + [PhSO\bar{C}HCO\bar{C}H_2]^{2-}\ \begin{matrix}Li^+\\ Na^+\end{matrix} \xrightarrow[\text{hydrol.)}]{\text{(after}} PhCH_2CH_2\underset{\displaystyle\underset{\mathrm{OH}}{|}}{C}HCH_2COCH_2SOPh} \qquad \text{(Ref. 315)}$$

49

$$\mathrm{PrCHO + HOOCCH_2COOH \xrightarrow[\text{piperidine}]{\text{pyridine-}} PrCH{=}CHCOOH}$$



$$\mathrm{CH_3COCH_3 + CHCl_3 \xrightarrow{KOH} CH_3{-}\overset{\displaystyle\overset{\mathrm{CCl_3}}{|}}{\underset{\displaystyle\underset{\mathrm{OH}}{|}}{C}}{-}CH_3}$$



$$\mathrm{PhCOPh + Ph_2CH_2 \xrightarrow{KNH_2} \begin{array}{c}\mathrm{Ph{-}CH{-}Ph}\\ |\\ \mathrm{Ph{-}C{-}Ph}\\ |\\ \mathrm{OK}\end{array}} \qquad \text{(Ref. 316)}$$

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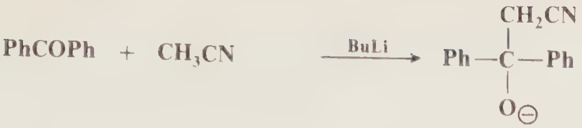
[312] Puterbaugh, *J. Org. Chem.* **27,** 4010 (1962).

[313] For a review, see Jones, *Org. React.* **15,** 204–599 (1967).

[314] For a review of this reaction with respect to nitroalkanes, (often called the *Henry reaction*), see Baer and Urbas, in Feuer, Ref. 124, pp. 76–117.

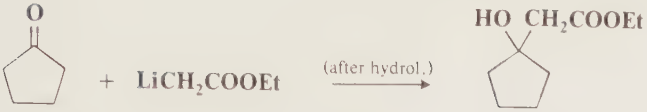
[315] Kuwajima and Iwasawa, *Tetrahedron Lett.* 107 (1974). See also Huckin and Weiler, *Can. J. Chem.* **52,** 2157 (1974).

[316] Hamrick and Hauser, *J. Am. Chem. Soc.* **81,** 2096, 3144 (1959).

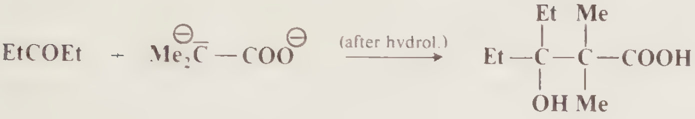


$$\mathrm{PhCOPh} + \mathrm{CH_3CN} \xrightarrow{\mathrm{BuLi}} \mathrm{Ph{-}\overset{CH_2CN}{\underset{O^{\ominus}}{C}}{-}Ph}$$

(Ref. 317)

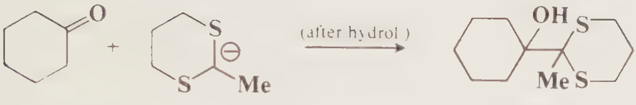


(Ref. 318)



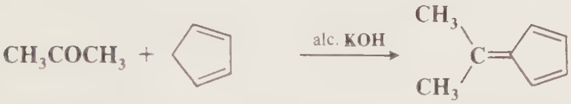
$$\mathrm{EtCOEt} + \mathrm{Me_2\overset{\ominus}{C}{-}COO^{\ominus}} \xrightarrow{\text{(after hydrol.)}} \mathrm{Et{-}\overset{Et}{\underset{OH}{C}}{-}\overset{Me}{\underset{Me}{C}}{-}COOH}$$

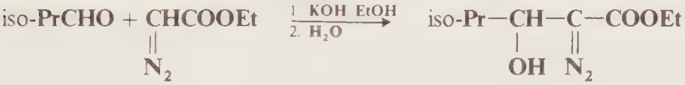
(Ref. 319)



50

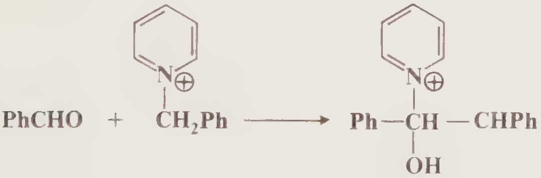
(Ref. 320)





$$\mathrm{iso\text{-}PrCHO} + \underset{\mathrm{N_2}}{\underset{\|}{\mathrm{CHCOOEt}}} \xrightarrow[2.\ \mathrm{H_2O}]{1.\ \mathrm{KOH\ EtOH}} \mathrm{iso\text{-}Pr{-}\underset{OH}{\underset{|}{CH}}{-}\underset{N_2}{\underset{\|}{C}}{-}COOEt}$$

(Ref. 321)



(Ref. 322)

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[317] Kaiser and Hauser, *J. Org. Chem.* **33**, 3402 (1968).

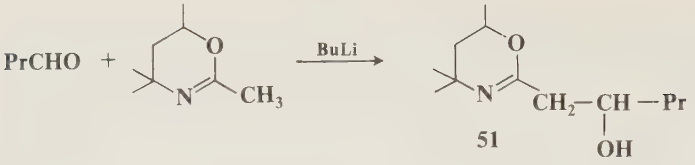
[318] Rathke, *J. Am. Chem. Soc.* **92**, 3222 (1970). See also reaction **6-32**.

[319] Moersch and Burkett, *J. Org. Chem.* **36**, 1149 (1971). See also Caron and Lessard, *Can. J. Chem.* **51**, 981 (1973); Cainelli, Cardillo, Contento, Trapani, and Umani-Ronchi, *J. Chem. Soc., Perkins Trans. 1* 400 (1973); Cainelli, Cardillo, Contento, and Umani-Ronchi, *Gazz. Chim. Ital.* **104**, 625 (1974). When the nucleophile is $\mathrm{PhCHCO\overset{\ominus}{O}}$, the reaction is known as the *Ivanov reaction.*

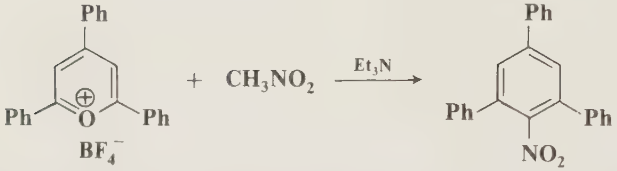
[320] Corey and Seebach, *Angew. Chem. Int. Ed. Engl.* **4**, 1075 (1965) [*Angew. Chem.* **77**, 1134]. For other examples of the addition of 1,3-dithianes and similar reagents to aldehydes, ketones, and compounds containing C=N bonds, see Seebach, *Synthesis* 17-36 (1969), pp. 27-29; Corey and Crouse, *J. Org. Chem.* **33**, 298 (1968); Ogura and Tsuchihashi, *Tetrahedron Lett.* 1383, 2681 (1972); Seebach, Kolb, and Gröbel, *Tetrahedron Lett.* 3171 (1974); Duhamel, Duhamel, and Mancelle, *Bull. Soc. Chim. Fr.* 331 (1974).

[321] Wenkert and McPherson, *J. Am. Chem. Soc.* **94**, 8084 (1972). See also Schöllkopf, Bánhidai, Frasnelli, Meyer, and Beckhaus, *Justus Liebigs Ann. Chem.* 1767 (1974).

[322] For a review of these reactions with pyridinium salts, see Kröhnke, *Angew. Chem. Int. Ed. Engl.* **2**, 225-237 (1963) [*Angew. Chem.* **75**, 181-194].



51 (Ref. 323)



(Ref. 324)

We see from these examples that many of the carbon nucleophiles we encountered in Chapter 10 are also nucleophiles toward aldehydes and ketones (compare reactions **0-96** through **0-100** and **0-102**). As we have seen in Chapter 10, the initial products in many of these cases, e.g., **48** through **51**, can be converted by relatively simple procedures (hydrolysis, reduction, decarboxylation, etc.) to various other products. In the reaction with terminal acetylenes,[325] sodium acetylides are the most common reagents (when they are used, the reaction is often called the *Nef reaction*), but lithium,[325a] magnesium, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide–ethylenediamine complex,[326] a stable, free-flowing powder which is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of a base, so that the acetylide is generated in situ. This procedure is called the *Favorskii reaction*, not to be confused with the Favorskii rearrangement (**8-8**). 1,4-Diols can be prepared by the treatment of aldehydes with dimetalloacetylenes MC≡CM.[327] The reaction with cyclopentadiene is a good method for the preparation of fulvenes.

With most of these reagents the alcohol is not isolated (but only the olefin) if the alcohol has a hydrogen in the proper position. However, in some cases it is the alcohol which is the major product. When the reactant is of the form ZCH_2Z', aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of olefin from the condensation of ethyl malonate $CH_2(COOEt)_2$ with ketones, as well as with aldehydes, if the reaction is run with $TiCl_4$ and pyridine in tetrahydrofuran.[328] In reactions with ZCH_2Z', the catalyst is most often a secondary amine (piperidine is the most common), though many other catalysts have been used, among them certain amino acids, e.g., β-alanine, α-aminophenylacetic acid. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the Knoevenagel reaction. In some cases amine salts make better catalysts than the free amines, but this is not always true. Alkoxides are also common catalysts. In some cases it is possible to get a second molecule of active compound to add to the initial product in a Michael reaction; e.g.,

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[323] Meyers, Nabeya, Adickes, Fitzpatrick, Malone, and Politzer, *J. Am. Chem. Soc.* **91,** 764 (1969). For other examples, see Meyers and Temple, *J. Am. Chem. Soc.* **92,** 6644 (1970); Fitzpatrick, Malone, Politzer, Adickes, and Meyers, *Org. Prep. Proced.* **1,** 193 (1969); Meyers, Nabeya, Adickes, Politzer, Malone, Kovelesky, Nolen, and Portnoy, *J. Org. Chem.* **38,** 36, (1973).

[324] Dimroth, Berndt, and Reichardt, *Org. Synth.* **V,** 1128. See also Dimroth, *Angew. Chem.* **72,** 331–342 (1960); Dimroth and Wolf, *Newer Methods Prep. Org. Chem.* **3,** 357–423 (1964).

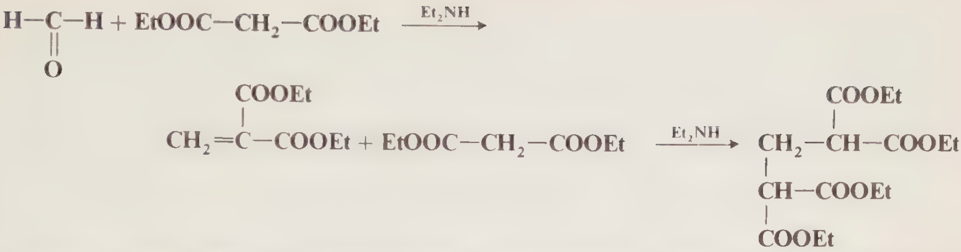
[325] For reviews, see Ziegenbein, in Viehe, "Acetylenes," pp. 207–241, Marcel Dekker, Inc., New York, 1969; Ried, *Newer Methods Prep. Org. Chem.* **4,** 95–138 (1968).

[325a] See Midland, *J. Org. Chem.* **40,** 2250 (1975), for the use of amine-free monolithium acetylide.

[326] Beumel and Harris, *J. Org. Chem.* **28,** 2775 (1963).

[327] Sudweeks and Broadbent, *J. Org. Chem.* **40,** 1131 (1975).

[328] Lehnert, *Tetrahedron Lett.* 4723 (1970), *Tetrahedron* **28,** 663 (1972), **29,** 635 (1973), *Synthesis* 667 (1974).



$$\mathrm{H{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H + EtOOC{-}CH_2{-}COOEt} \xrightarrow{\mathrm{Et_2NH}}$$

$$\mathrm{CH_2{=}\overset{\overset{\displaystyle COOEt}{|}}{C}{-}COOEt + EtOOC{-}CH_2{-}COOEt} \xrightarrow{\mathrm{Et_2NH}} \mathrm{\overset{\overset{\displaystyle COOEt}{|}}{\quad\ \ } CH_2{-}CH{-}COOEt;\ CH_2{-}CH(COOEt)_2}$$

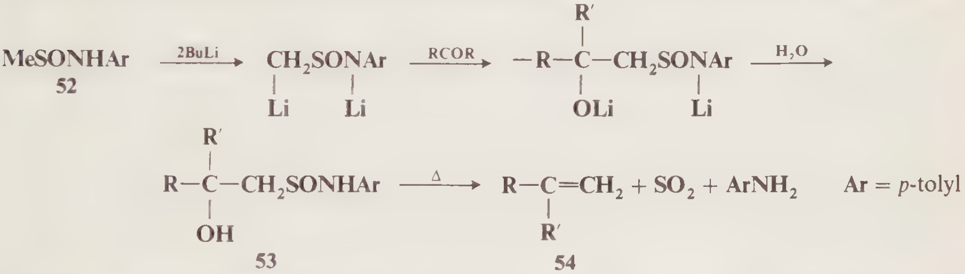
It has also proved possible to have one active hydrogen compound add to an aldehyde and then, in situ, to have a *different* one add to the olefin in the Michael manner.[329]

As with reaction **6-40**, these reactions have sometimes been performed with acid catalysts.[330]

Imines can be employed instead of aldehydes or ketones; the products are the same, an amine being lost instead of water.[331]

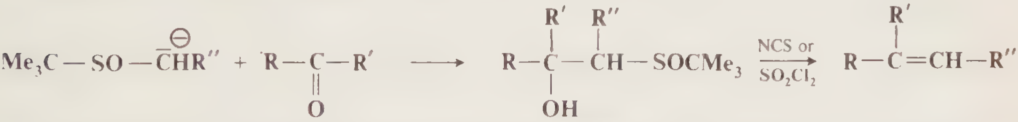
A number of special applications of the Knoevenagel reaction follow.

1. The dilithio derivative of N-methanesulfinyl-*p*-toluidine[332] (**52**) adds to aldehydes and ketones to give, after hydrolysis, the hydroxysulfinamides **53**, which, upon heating, undergo stereospecifically syn eliminations to give the olefins **54**.[333] The reaction is thus a method for achieving the conversion $\mathrm{RR'CO \rightarrow RR'C{=}CH_2}$ and represents an alternative to the Wittig reaction. In a similar reaction, the lithio derivatives of alkyl *t*-butyl sulfoxides add to aldehydes and ketones to give β-hydroxy sulfoxides, which eliminate SO_2 when treated with N-chlorosuccinimide or sulfuryl chloride.[333a] Another similar method involves treatment of the aldehyde or ketone with the sulfoximine derivative **55**, followed by reduction of the product with aluminum

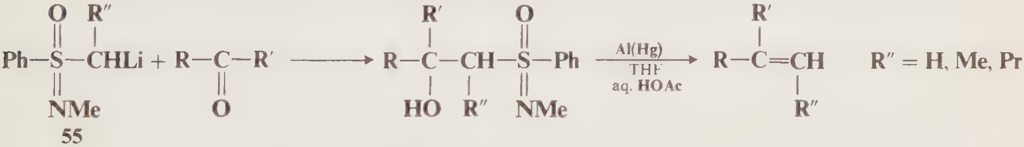


$$\underset{\mathbf{52}}{\mathrm{MeSONHAr}} \xrightarrow{\mathrm{2BuLi}} \mathrm{\underset{Li}{CH_2}SON\underset{Li}{Ar}} \xrightarrow{\mathrm{RCOR}} \mathrm{R{-}\overset{R'}{\underset{OLi}{C}}{-}CH_2SO\underset{Li}{N}Ar} \xrightarrow{\mathrm{H_2O}}$$

$$\underset{\mathbf{53}}{\mathrm{R{-}\overset{R'}{\underset{OH}{C}}{-}CH_2SONHAr}} \xrightarrow{\Delta} \underset{\mathbf{54}}{\mathrm{R{-}\underset{R'}{C}{=}CH_2}} + \mathrm{SO_2 + ArNH_2} \qquad \mathrm{Ar} = p\text{-tolyl}$$



$$\mathrm{Me_3C{-}SO{-}\overset{\ominus}{C}HR'' + R{-}\underset{O}{\overset{}{\underset{\|}{C}}}{-}R'} \longrightarrow \mathrm{R{-}\overset{R'}{\underset{OH}{C}}{-}\overset{R''}{C}H{-}SOCMe_3} \xrightarrow[\mathrm{SO_2Cl_2}]{\mathrm{NCS\ or}} \mathrm{R{-}\overset{R'}{C}{=}CH{-}R''}$$



$$\underset{\mathbf{55}}{\mathrm{Ph{-}\overset{O}{\underset{NMe}{S}}{-}\overset{R''}{C}HLi}} + \mathrm{R{-}\underset{O}{C}{-}R'} \longrightarrow \mathrm{R{-}\overset{R'}{\underset{HO}{C}}{-}\underset{R''}{C}H{-}\overset{O}{\underset{NMe}{S}}{-}Ph} \xrightarrow[\mathrm{aq.\ HOAc}]{\mathrm{Al(Hg)},\ \mathrm{THF}} \mathrm{R{-}\overset{R'}{C}{=}\underset{R''}{C}H} \qquad \mathrm{R''} = \mathrm{H, Me, Pr}$$

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[329] For example, see Russell and Becker, *J. Am. Chem. Soc.* **85**, 3406 (1963).

[330] For example, see Rappoport and Patai, *J. Chem. Soc.* 731 (1962).

[331] Charles, *Bull. Soc. Chim. Fr.* 1559, 1566, 1573, 1576 (1963); Siegrist, Liechti, Meyer, and Weber, *Helv. Chim. Acta* **52**, 2521 (1969).

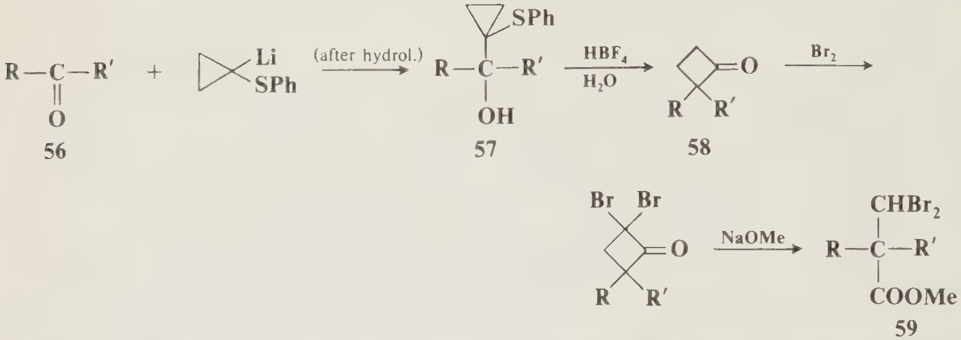
[332] For a method of preparing **52**, see Bowlus and Katzenellenbogen, *Synth. Commun.* **4**, 137 (1974).

[333] Corey and Durst, *J. Am. Chem. Soc.* **90**, 5548, 5553 (1968).

[333a] Jung, Sharma, and Durst, *J. Am. Chem. Soc.* **95**, 3420 (1973). See also Kuwajima and Uchida, *Tetrahedron Lett.* 649 (1972).

amalgam in aqueous tetrahydrofuran containing acetic acid.[334] Still other similar reactions have been reported in which a carbanion was generated α to a silicon rather than a sulfur atom.[335]

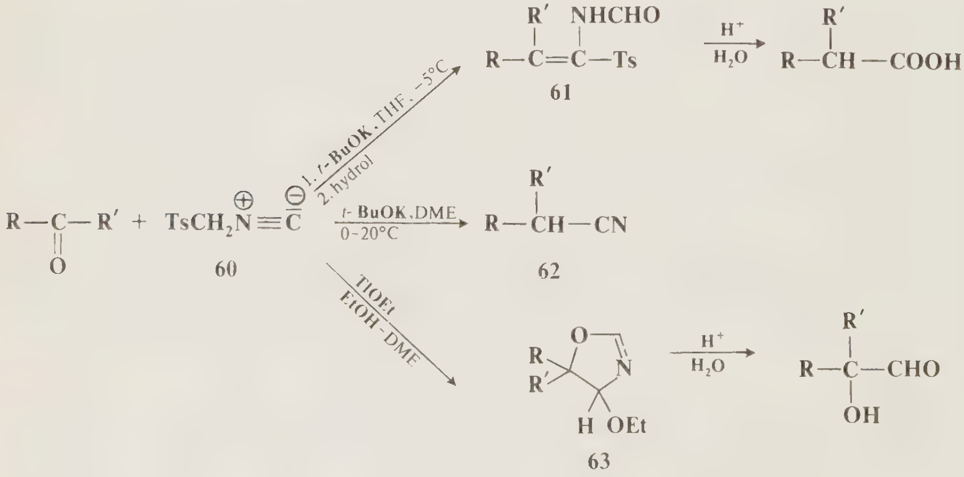
2. Another kind of conversion which can be realized with the aid of a type of Knoevenagel reaction is that of $C{=}O \rightarrow CR_2$.[336] Treatment of a ketone (**56**) with 1-lithiocyclopropyl phenyl sulfide gives the cyclopropylcarbinol **57**, which is rearranged (reaction **8-3**) to the cyclobutanone



56 **57** **58** **59**

58. Bromination of **58** (reaction **2-4**), followed by treatment with NaOMe, cleaves the cyclobutane ring (reaction **2-44**) to give compound **59**, which has two functional groups and so can be converted to a variety of other products. The conversion of **56** to **59** can also be accomplished by the use of a sulfur ylide (see reaction **6-65**). Other $C{=}O \rightarrow CR_2$ conversions are mentioned at reactions **6-31** (p. 837) and **6-47** (p. 871).

3. The reaction of ketones with tosylmethylisocyanide (**60**) gives different products[337] depending on the reaction conditions. When the reaction is run with potassium *t*-butoxide in tetrahydrofuran



61 **60** **62** **63**

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[334] Johnson, Shanklin, and Kirchhoff, *J. Am. Chem. Soc.* **95**, 6462 (1973).

[335] For example, see Chan and Chang, *J. Org. Chem.* **39**, 3264 (1974); Taguchi, Shimoji, Yamamoto, and Nozaki, *Bull. Chem. Soc. Jpn.* **47**, 2529 (1974).

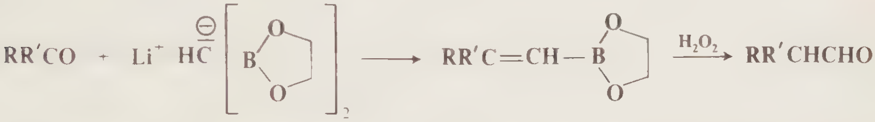
[336] Trost, Keeley, and Bogdanowicz, *J. Am. Chem. Soc.* **95**, 3068 (1973); Trost and Bogdanowicz, *J. Am. Chem. Soc.* **95**, 2038 (1973); Trost, Bogdanowicz, and Kern, *J. Am. Chem. Soc.* **97**, 2218 (1975).

[337] For a review of α-metalated isocyanides, see Hoppe, *Angew. Chem. Int. Ed. Engl.* **13**, 789–804 (1974) [*Angew. Chem.* **86**, 878–893].

at −5°C, one obtains (after hydrolysis) the normal Knoevenagel product **61**, except that the isonitrile group has been hydrated (reaction **6-71**).[338] With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile **62**.[339] When the ketone is treated with **60** and thallium(I) ethoxide in a 4 : 1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline **63**.[340] Since **61** can be hydrolyzed[341] to a carboxylic acid[338] and **63** to an α-hydroxy aldehyde,[340] this versatile reaction provides a means for achieving the conversion of RCOR′ to RCHR′COOH, RCHR′CN, or RCR′(OH)CHO, as desired. The conversion to RCHR′COOH has also been carried out with certain aldehydes (R′ = H).[342]

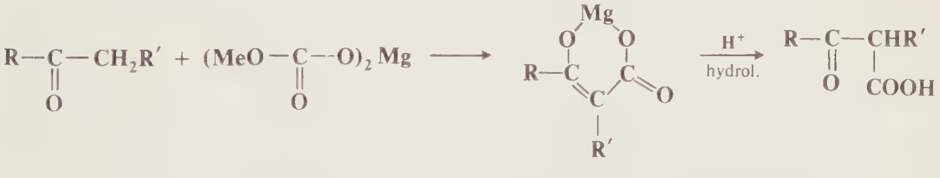
4. Aldehydes and ketones RCOR′ react with α-methoxyvinyllithium $CH_2=C(Li)OMe$ to give hydroxy enol ethers $RR'C(OH)C(OMe)=CH_2$, which are easily hydrolyzed to acyloins RR′C(OH)COMe.[343] In this reaction, the $CH_2=C(Li)OMe$ is a synthon for the unavailable $CH_3-\overset{\ominus}{\bar{C}}=O$ ion. The reagent also reacts with esters RCOOR′ to give $RC(OH)(COMe=CH_2)_2$. A synthon for the $Ph-\overset{\ominus}{C}=O$ ion is $Ph\overset{\ominus}{\bar{C}}(CN)OSiMe_3$, which adds to aldehydes and ketones RCOR′ to give, after hydrolysis, the α-hydroxy ketones RR′C(OH)COPh.[343a]

5. A procedure for converting an aldehyde or ketone RR′CO to the homologous aldehyde RR′CHCHO consists of treating the substrate with lithium bis(ethylenedioxyboryl)methide, followed by oxidation with aqueous H_2O_2:[344]



OS **I,** 181, 290, 413; **II,** 202; **III,** 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; **IV,** 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; **V,** 130, 381, 572, 585, 627, 833, 1088, 1128; **50,** 36; **53,** 66; **54,** 19. Also see OS **III,** 395; **V,** 450.

6-43 The Addition of Active Hydrogen Compounds to CO_2 and CS_2



64 65

Ketones of the form $RCOCH_3$ and $RCOCH_2R'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate **64**.[344a] Because formation of the chelate **65** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α-position. The reaction has also been performed on CH_3NO_2 and compounds of the form RCH_2NO_2 [345] and on certain lactones[346] and hydantoins[347] (p. 861). Direct carboxylation has been reported in a number of instances. Various ketones, esters, and other active hydrogen compounds have been carboxylated in the α position with the aid of the base PhONa, though yields are generally low.[348] Malonic acid monoalkyl esters can be directly prepared from carboxylic esters of the form RCH_2COOR' and $R_2CHCOOR'$ by treatment of the lithium salt with carbon dioxide.[349] Best yields are obtained from anions which are rather severely crowded around the anionic carbon atom. In a similar reaction, ketones have been carboxylated in the α position to give β-keto acids.[350] The base here was lithium 4-methyl-2,6-di-*t*-butylphenoxide (**66**). This base has also been used in the addition

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[338] Schöllkopf, Schröder, and Blume, *Justus Liebigs Ann. Chem.* **766,** 130 (1972); Schöllkopf and Schröder, *Angew. Chem. Int. Ed. Engl.* **11,** 311 (1972) [*Angew. Chem.* **84,** 289].

[339] Oldenziel and van Leusen, *Synth. Commun.* **2,** 281 (1972), *Tetrahedron Lett.* 1357 (1973).

[340] Oldenziel and van Leusen, *Tetrahedron Lett.* 163, 167 (1974).

[341] **61** can also be converted to a nitrile; see reaction **7-40.**

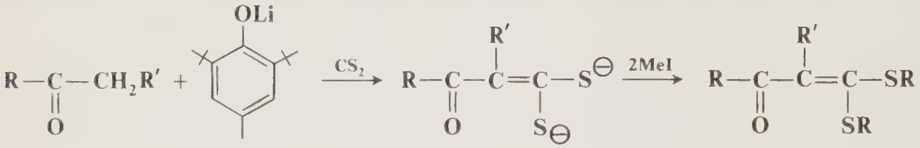
[342] For another method of achieving the conversion RCHO → RCH_2COOH, see Gross and Costisella, *Angew. Chem. Int. Ed. Engl.* **7,** 391 (1968) [*Angew. Chem.* **80,** 364].

[343] Baldwin, Höfle, and Lever, *J. Am. Chem. Soc.* **96,** 7125 (1974).

[343a] Hünig and Wehner, *Synthesis* 391 (1975).

[344] Matteson, Moody, and Jesthi, *J. Am. Chem. Soc.* **97,** 5608 (1975).

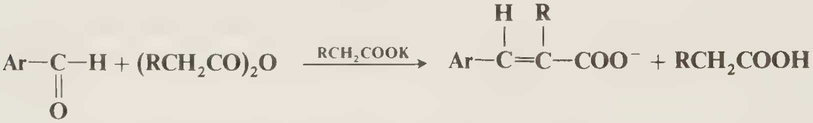
[344a] Stiles, *J. Am. Chem. Soc.* **81,** 2598 (1959), *Ann. N.Y. Acad. Sci.* **88,** 332 (1960); Crombie, Hemesley, and Pattenden, *Tetrahedron Lett.* 3021 (1968).



66 **67** **68**

of ketones to CS_2 to give dianions (**67**), which are easily alkylated to α-dithiomethylene ketones **68**.[351] Compounds of the form ZCH_2Z' also react with bases and CS_2 to give dianions analogous to **67**.[352]

6-44 The Perkin Reaction



$$\mathrm{Ar{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}H + (RCH_2CO)_2O \xrightarrow{RCH_2COOK} Ar{-}\overset{H}{\overset{|}{C}}{=}\overset{R}{\overset{|}{C}}{-}COO^- + RCH_2COOH}$$

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.[353] When the anhydride has two α-hydrogens (as shown), dehydration always occurs; the β-hydroxy acid salt is never isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the sodium or potassium salt of the acid corresponding to the anhydride. Besides aromatic aldehydes, their vinylogs ArCH=CHCHO also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.[354] There is a possible side reaction: decarboxylation of the initial β-hydroxy acid salt instead of simple dehydration. Sometimes this is the main reaction:

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[345] Finkbeiner and Stiles, *J. Am. Chem. Soc.* **85**, 616 (1963); Finkbeiner and Wagner, *J. Org. Chem.* **28**, 215 (1963).

[346] Martin, Watts, and Johnson, *Chem. Commun.* 27 (1970).

[347] Finkbeiner, *J. Org. Chem.* **30**, 3414 (1965).

[348] Bottaccio, Chiusoli, and Felicioli, *Gazz. Chim. Ital.* **103**, 105 (1973). See also Ito and Takami, *Chem. Lett.* 1035 (1974).

[349] Reiffers, Strating, and Wynberg, *Tetrahedron Lett.* 2339 (1971); Reiffers, Wynberg, and Strating, *Tetrahedron Lett.* 3001 (1971).

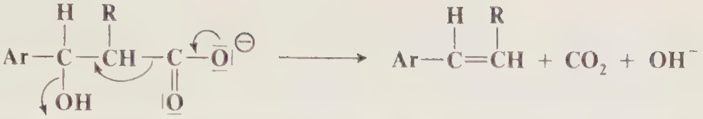
[350] Corey and Chen, *J. Org. Chem.* **38**, 4086 (1973).

[351] Corey and Chen, *Tetrahedron Lett.* 3817 (1973).

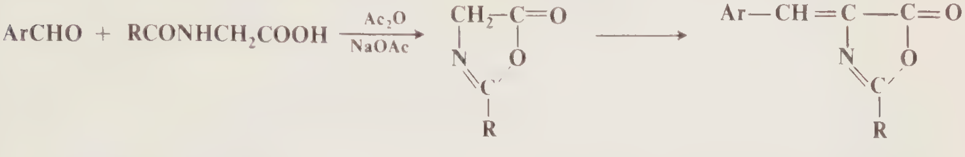
[352] Larsson and Lawesson, *Tetrahedron* **28**, 5341 (1972); Jensen, Dalgaard, and Lawesson, *Tetrahedron* **30**, 2413 (1974); and references cited in these papers.

[353] For a review of the Perkin reaction and the related Erlenmeyer synthesis, see Johnson, *Org. React.* **1**, 210-266 (1942).

[354] Crawford and Little, *J. Chem. Soc.* 722 (1959).

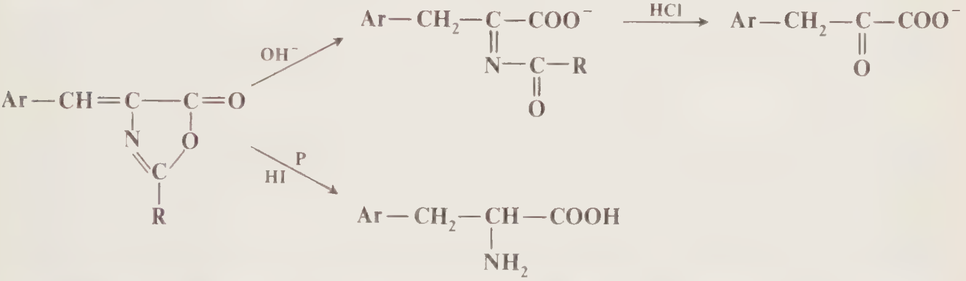


An important variation of the Perkin reaction is the *Erlenmeyer azlactone synthesis*.[355] In this reaction aromatic aldehydes are condensed with N-acyl derivatives of glycine, in the presence of acetic anhydride and sodium acetate. The product is an azlactone:

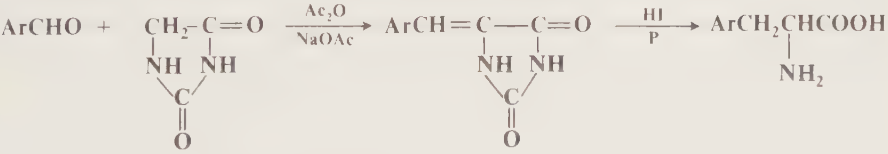


The intermediate **69** is formed first and then condenses with the aldehyde. When **69** was prepared independently, it reacted with aromatic aldehydes to give azlactones.[356] The Erlenmeyer reaction can be extended to aliphatic aldehydes by the use of tetrahydrofuran as solvent and replacement of NaOAc by $Pb(OAc)_2$.[357]

Azlactones are useful because they can be converted into other compounds. Treatment with NaOH, followed by HCl, gives arylpyruvic acids, the preparation of which represents a method of increasing the carbon chain by two (from the original aldehyde). Reduction of an azlactone by phosphorus and HI, or other reducing agents, produces an amino acid, also increasing the chain by two:



Further variations of the Perkin reaction involve condensation with hydantoin (**70**) and with rhodanine (**71**). The product from hydantoin condensation may also be reduced to an amino acid. The product from the rhodanine condensation may be converted, in high yield, by a three-step process to a nitrile with one more carbon than the original aldehyde:



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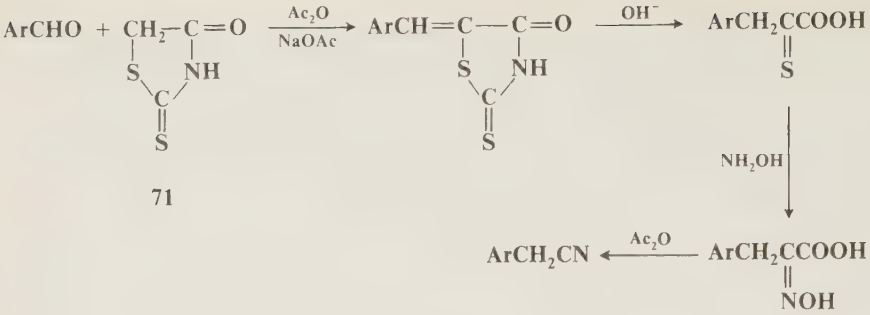
[355] For reviews, see Ref. 354; Carter, *Org. React.* 3, 198–239 (1946); and Baltazzi, *Q. Rev., Chem. Soc.* 9, 150–173 (1955).

[356] Crawford and Little, *J. Chem. Soc.* 729 (1959).

[357] Baltazzi and Robinson, *Chem. Ind.* (*London*) 191 (1954).



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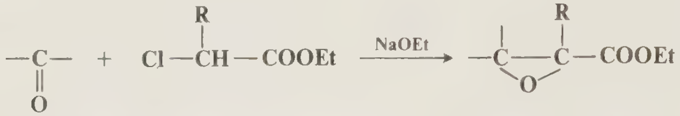
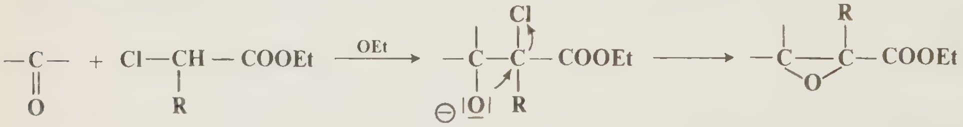
OS **I,** 398; **II,** 1, 55, 61, 229, 489; **III,** 426. Also see OS **II,** 333, 519.

6-45 Darzen's Glycidic Ester Condensation



Aldehydes and ketones condense with α-halo esters in the presence of bases to give α,β-epoxy esters, called *glycidic esters.* This is called *Darzen's condensation.*[358] The reaction consists of an initial Knoevenagel-type condensation (**6-42**) followed by an internal SN2 reaction (**0-15**):[359]



Although the intermediate halo alkoxide is generally not isolated, it has been done, not only with α-fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions) but also with α-chloro esters.[360] This is only one of several types of evidence that rule out a carbene intermediate.[361] Sodium ethoxide is often used as the base, although other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields, but aliphatic aldehydes react poorly. However, the reaction can be made to give good yields (~80%) with simple aliphatic aldehydes as well as with aromatic aldehydes and ketones by treatment of the α-halo ester with the base lithium bis(trimethylsilyl)amide $LiN(SiMe_3)_2$ in tetrahydrofuran at −78°C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.[362] The Darzen's reaction has also been carried out on α-halo ketones, α-halo nitriles,[363] α-halo sulfones,[364] α-halo N,N-disubstituted amides,[365] and even on benzylic halides. Glycidic esters can easily be converted to aldehydes (reaction **2-39**). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α-halo ester or an α-halo N,N-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.[366] However, yields were not high. Acid-catalyzed Darzen's reactions have also been reported.[367] See also reaction **6-65.**

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[358] For reviews, see Berti, *Top. Stereochem.* **7,** 93–251 (1973); pp. 210–218; Newman and Magerlein, *Org. React.* **5,** 413–440 (1949); Ballester, *Chem. Rev.* **55,** 283–300 (1955).

[359] For discussions of the mechanism of the reaction, and especially of the stereochemistry, see Bachelor and Bansal, *J. Org. Chem.* **34,** 3600 (1969); Roux-Schmitt, Seyden-Penne, and Wolfe, *Tetrahedron* **28,** 4965 (1972).

[360] Martynov and Titov. *J. Gen. Chem. USSR* **30,** 4072 (1960), **32,** 716 (1962), **33,** 1350 (1963), **34,** 2139 (1964); Elkik and Francesch, *Bull. Soc. Chim. Fr.* 1277, 1281 (1973).

[361] Another, based on the stereochemistry of the products, is described by Zimmerman and Ahramjian, *J. Am. Chem. Soc.* **82,** 5459 (1960).

[362] Borch, *Tetrahedron Lett.* 3761 (1972).

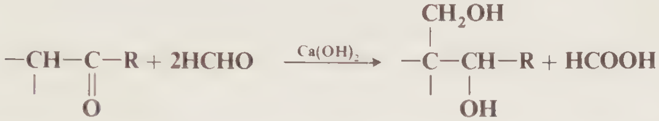
[363] See White and Wu, *J. Chem. Soc., Chem. Commun.* 988 (1974).

[364] Vogt and Tavares, *Can. J. Chem.* **47,** 2875 (1969).

[365] Tung, Speziale, and Frazier, *J. Org. Chem.* **28,** 1514 (1963).

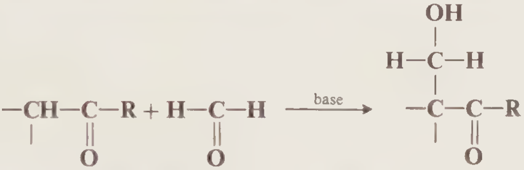
OS **III,** 727; **IV,** 459, 649.

6-46 Tollens' Reaction



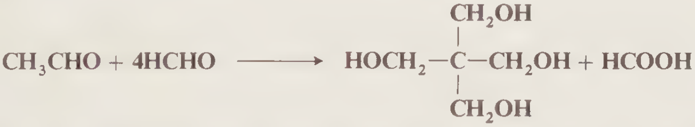
$$-\underset{|}{\mathrm{CH}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R}+2\mathrm{HCHO}\xrightarrow{\mathrm{Ca(OH)_2}}-\overset{\overset{\mathrm{CH_2OH}}{|}}{\underset{|}{\mathrm{C}}}-\underset{\underset{\mathrm{OH}}{|}}{\mathrm{CH}}-\mathrm{R}+\mathrm{HCOOH}$$

In *Tollens' reaction* an aldehyde or ketone containing an α-hydrogen is treated with formaldehyde in the presence of $Ca(OH)_2$ or a similar base. The first step is a mixed aldol condensation (**6-40**), in which the α-carbon of the aldehyde or ketone adds to the carbonyl carbon of formaldehyde:



$$-\underset{|}{\mathrm{CH}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R}+\mathrm{H}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{H}\xrightarrow{\text{base}}-\overset{\overset{\overset{\overset{\mathrm{OH}}{|}}{\mathrm{H}-\mathrm{C}-\mathrm{H}}}{|}}{\underset{|}{\mathrm{C}}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R}$$

The reaction can be stopped at this point, but more often a second mole of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-glycol, in a crossed Cannizzaro reaction (**9-74**). If the aldehyde or ketone has several α-hydrogens, they can all be replaced. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:

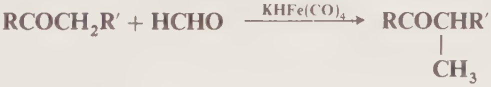


$$\mathrm{CH_3CHO}+4\mathrm{HCHO}\longrightarrow\mathrm{HOCH_2}-\overset{\overset{\mathrm{CH_2OH}}{|}}{\underset{\underset{\mathrm{CH_2OH}}{|}}{\mathrm{C}}}-\mathrm{CH_2OH}+\mathrm{HCOOH}$$

When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction is essentially a Knoevenagel reaction, though it is usually also called a Tollens' reaction:

$$\mathrm{CH_3NO_2}+\mathrm{HCHO}\xrightarrow{\mathrm{OH^-}}\mathrm{HOCH_2CH_2NO_2}$$

When a ketone of the type $RCOCH_3$ or $RCOCH_2R'$ is treated with formaldehyde and $KHFe(CO)_4$ in ethanol or water, a CH_3 group is introduced in the α position:[368]



$$\mathrm{RCOCH_2R'}+\mathrm{HCHO}\xrightarrow{\mathrm{KHFe(CO)_4}}\mathrm{RCO}\underset{\underset{\mathrm{CH_3}}{|}}{\mathrm{CH}}\mathrm{R'}$$

OS **I,** 425; **IV,** 907; **V,** 833.

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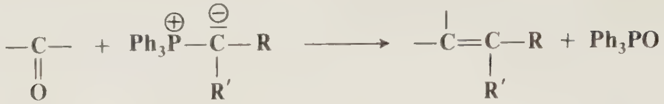
[366] Deyrup, *J. Org. Chem.* **34,** 2724 (1969).

[367] Sipos, Schöbel, and Baláspiri, *J. Chem. Soc. C* 1154 (1970); Sipos, Schöbel, and Sirokmán, *J. Chem. Soc., Perkin Trans. 2* 805 (1975).

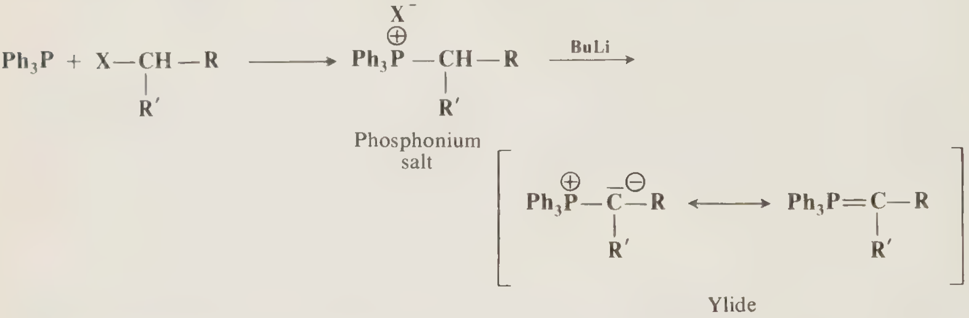
[368] Cainelli, Panunzio, and Umani-Ronchi, *Tetrahedron Lett.* 2491 (1973).

6-47 The Wittig Reaction



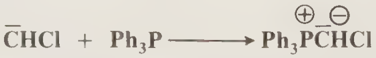
$$\underset{\overset{\|}{O}}{-C-} + Ph_3\overset{\oplus}{P}-\underset{R'}{\overset{\ominus}{C}}-R \longrightarrow -\overset{|}{C}=\underset{R'}{C}-R + Ph_3PO$$

In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylide* (also called a *phosphorane*) to give an olefin.[369] Phosphorus ylides, which are hybrids of two canonical forms, are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually prepared from the phosphine and an alkyl halide (reaction **0-46**):



$$Ph_3P + X-\underset{R'}{CH}-R \longrightarrow \overset{X^-}{\overset{\oplus}{Ph_3P}}-\underset{R'}{CH}-R \xrightarrow{BuLi} \left[Ph_3\overset{\oplus}{P}-\underset{R'}{\overset{\ominus}{C}}-R \longleftrightarrow Ph_3P=\underset{R'}{C}-R\right]$$

The overall sequence of three steps may be called the Wittig reaction, or only the final step.[370] Phosphonium salts are also prepared by addition of phosphines to Michael olefins (like reaction **5-9**) and in other ways. The phosphonium salts are most often converted to the ylides by treatment with a strong base such as butyllithium, sodium amide, sodium hydride, or a sodium alkoxide, though weaker bases may be used if the salt is acidic enough. For $(Ph_3P^+)_2CH_2$, sodium carbonate is a strong enough base.[371] Ethylene oxide has also been used as the base.[372] The conversion of phosphonium salts to ylides is apparently a simple acid-base reaction (**2-19**), but, at least with alkyllithiums, it must be more complicated than that, since, in addition to a simple proton abstraction, exchange of groups can occur. Thus, $Ph_3\overset{\oplus}{P}CH_3 \quad Br^-$ with methyllithium gave 26% *benzene*.[373] It is likely that an intermediate Ph_3PMe_2 was formed, which lost either methane or benzene to give an ylide. Phosphorus ylides can also be prepared by reaction **0-114** and by the addition of halocarbenes to phosphines in a Lewis acid-base reaction:



$$\overline{C}HCl + Ph_3P \longrightarrow Ph_3\overset{\oplus}{P}\overset{\ominus}{\underline{C}}HCl$$

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[369] For a monograph, see Johnson, "Ylid Chemistry," Academic Press, Inc., New York, 1966. For reviews, see Maercker, *Org. React.* **14**, 270–490 (1965); House, Ref. 124, pp. 682–709; Lowe, *Chem. Ind.* (*London*) 1070 1079 (1970); Bergelson and Shemyakin, in Patai, Ref. 276, pp. 295–340, *Angew. Chem. Int. Ed. Engl.* **3**, 250–260 (1964) [*Angew. Chem.* **76**, 113–123], *Newer Methods Prep. Org. Chem.* **5**, 154–175 (1968), *Pure Appl. Chem.* **9**, 271–283 (1964); Trippett, *Q. Rev., Chem. Soc.* **17**, 406–440 (1963), *Adv. Org. Chem.* **1**, 83–102 (1960), *Pure Appl. Chem.* **9**, 255–269 (1964); Schöllkopf, *Angew. Chem.* **71**, 260 (1959), *Newer Methods Prep. Org. Chem.* **3**, 111–150 (1964); Yanovskaya, *Russ. Chem. Rev.* **30**, 347–362 (1961). For related reviews, see Zbiral, *Synthesis* 775–797 (1974); Bestmann, *Bull. Soc. Chim. Fr.* 1619–1634 (1971), *Angew. Chem. Int. Ed. Engl.* **4**, 583–587, 645–660, 830–838 (1965) [*Angew. Chem.* **77**, 609–613, 651–666, 850–858], *Newer Methods Prep. Org. Chem.* **5**, 1–60 (1968); Horner, *Fortschr. Chem. Forsch.* **7**, 1–61 (1966). For a historical background, see Wittig, *Pure Appl. Chem.* **9**, 245–254 (1964).

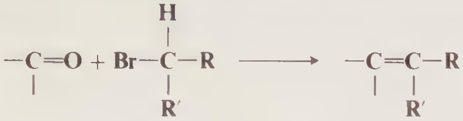
[370] When phosphonium *fluorides* are used, no base is necessary, as these react directly with the substrate to give the olefin: Schiemenz, Becker, and Stöckigt, *Chem. Ber.* **103**, 2077 (1970).

[371] Ramirez, Pilot, Desai, Smith, Hansen, and McKelvie, *J. Am. Chem. Soc.* **89**, 6273 (1967).

[372] Buddrus, *Angew. Chem. Int. Ed. Engl.* **7**, 536 (1968) [*Angew. Chem.* **80**, 535], *Chem. Ber.* **107**, 2050, 2062 (1974).

[373] Seyferth, Hughes, and Heeren, *J. Am. Chem. Soc.* **87**, 2847, 3467 (1965).

In the overall Wittig reaction, an olefin is formed from the aldehyde or ketone and an alkyl halide in which the halogen-bearing carbon contains at least one hydrogen:

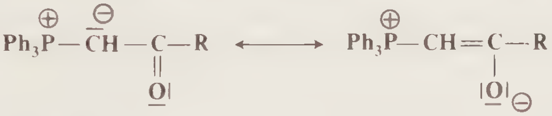


$$-\underset{|}{C}=O + Br-\overset{\overset{H}{|}}{\underset{\underset{R'}{|}}{C}}-R \longrightarrow -\underset{|}{C}=\underset{\underset{R'}{|}}{C}-R$$

This result is similar to that obtained in the Reformatsky reaction (**6-32**), but this is more general since no ester or other group is required to be α to the halogen. Another important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensations (**6-40** to **6-46**).

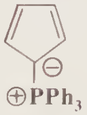
The reaction is very general. The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones); it may contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2, aromatic nitro or halo, acetal, or even ester groups. Although phosphorus ylides also react with esters (reaction **0-114**), that reaction is too slow to interfere.[374] Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the C=O carbon.

The phosphorus ylide may also contain double or triple bonds and certain functional groups. Simple ylides (R, R′ = hydrogen or alkyl) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and esters, so that the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, e.g., COR, CN, COOR, CHO, is present in the α position, the ylides are much more stable. The stability is increased because the charge on the carbon is spread by resonance:

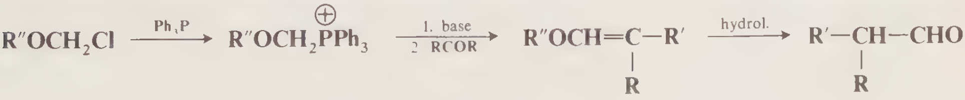


$$Ph_3\overset{\oplus}{P}-\overset{\ominus}{\bar{C}}H-\underset{\underset{\underline{O}|}{\|}}{C}-R \longleftrightarrow Ph_3\overset{\oplus}{P}-CH=\underset{\underset{|\underline{O}|^{\ominus}}{|}}{C}-R$$

These ylides react readily with aldehydes but slowly or not at all with ketones. In extreme cases, e.g., compound **72**, the ylide does not react with ketones *or* aldehydes. Besides these groups, the ylide may contain one or two α-halogens [these ylides can be prepared from halocarbenes and phosphines (p. 864) or in the normal manner][375] or an α-OR or α-OAr group. In the latter case



72



$$R''OCH_2Cl \xrightarrow{Ph_3P} R''OCH_2\overset{\oplus}{P}Ph_3 \xrightarrow[2.\ RCOR]{1.\ base} R''OCH=\underset{\underset{R}{|}}{C}-R' \xrightarrow{hydrol.} R'-\underset{\underset{R}{|}}{CH}-CHO$$

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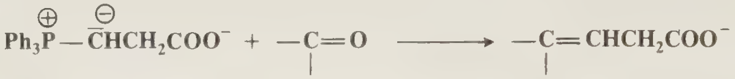
[374] Greenwald, Chaykovsky, and Corey, *J. Org. Chem.* **28,** 1128 (1963).

[375] Seyferth, Grim, and Read, *J. Am. Chem. Soc.* **82,** 1510 (1960), **83,** 1617 (1961); Seyferth, Heeren, Singh, Grim, and Hughes, *J. Organomet. Chem.* **5,** 267 (1966); Schlosser and Zimmermann, *Synthesis* 75 (1969); Burton and Greenlimb, *J. Fluorine Chem.* **3,** 447 (1974).

the product is a vinyl ether, which can be hydrolyzed (**0-7**) to an aldehyde,[376] so that this reaction is a means of achieving the conversion RCOR′ → RR′CHCHO. However, the ylide may not contain an α-nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in the β position, treatment with a base gives elimination, instead of the ylide:

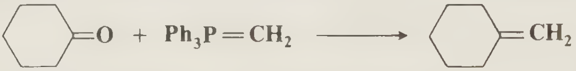
$$Ph_3\overset{\oplus}{P}CH_2CH_2Br \xrightarrow{\text{base}} Ph_3\overset{\oplus}{P}CH{=}CH_2$$

However, a β-COO⁻ group may be present, and the product is a β,γ-unsaturated acid:[377]

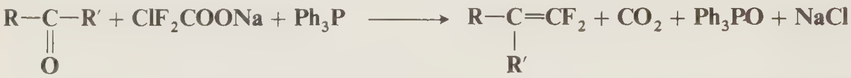


$$Ph_3\overset{\oplus}{P}-\overset{\ominus}{\bar{C}}HCH_2COO^- + -\underset{|}{C}{=}O \longrightarrow -\underset{|}{C}{=}CHCH_2COO^-$$

This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β-unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to olefins containing exocyclic double bonds, e.g.,[378]

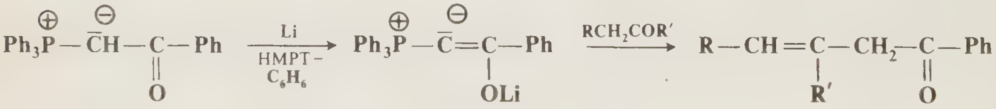


This is the only general method for the synthesis of these compounds. As indicated above, α,α′-dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare such compounds is to treat the carbonyl compound with a mixture of CBr_4 (or CCl_4) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph_3P to be used).[379] Aldehydes and ketones can be converted to 1,1-difluoroalkenes by treatment with a salt of chlorodifluoroacetic acid in the presence of triphenylphosphine:[380]



$$R-\underset{\underset{O}{\|}}{C}-R' + ClF_2COONa + Ph_3P \longrightarrow R-\underset{\underset{R'}{|}}{C}{=}CF_2 + CO_2 + Ph_3PO + NaCl$$

When the phosphorane **73** is treated with lithium in HMPT-benzene, a second proton is removed to give the enolate ylide **74**. This ylide reacts with ketones of the form RCH_2COR' to



$$Ph_3\overset{\oplus}{P}-\overset{\ominus}{\bar{C}}H-\underset{\underset{O}{\|}}{C}-Ph \xrightarrow[\text{HMPT}-C_6H_6]{\text{Li}} Ph_3\overset{\oplus}{P}-\overset{\ominus}{\bar{C}}{=}\underset{\underset{OLi}{|}}{C}-Ph \xrightarrow{RCH_2COR'} R-CH{=}\underset{\underset{R'}{|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-Ph$$

73 **74** **75**

give the nonconjugated β,γ-unsaturated ketones **75**.[381] As mentioned above, ylides of the type **73** are too unreactive to react with the ketones themselves, but if **73** did react directly with RCH_2COR', the normal Wittig product would be the α,β-unsaturated ketone $RCH_2CR'{=}CHCOPh$.

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[376] For example, see Levine, *J. Am. Chem. Soc.* **80,** 6150 (1958); Wittig, Böll, and Krück, *Chem. Ber.* **95,** 2514 (1962). For a similar example with a thioether, see Corey and Shulman, *J. Org. Chem.* **35,** 777 (1970); see also Corey and Märkl, *Tetrahedron Lett.* 3201 (1967).

[377] Corey, McCormick, and Swensen, *J. Am. Chem. Soc.* **86,** 1884 (1964).

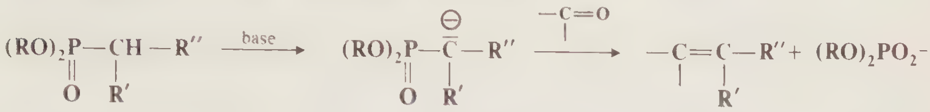
[378] Wittig and Schöllkopf, *Chem. Ber.* **87,** 1318 (1954).

[379] Rabinowitz and Marcus, *J. Am. Chem. Soc.* **84,** 1312 (1962); Ramirez, Desai, and McKelvie, *J. Am. Chem. Soc.* **84,** 1745 (1962); Raulet and Levas, *C. R. Acad. Sci., Ser. C* **270,** 1467 (1970); Corey and Fuchs, *Tetrahedron Lett.* 3769 (1972); Posner, Loomis, and Sawaya, *Tetrahedron Lett.* 1373 (1975).

[380] Fuqua, Duncan, and Silverstein, *J. Org. Chem.* **30,** 1027, 2543 (1965).

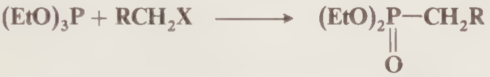
[381] Broquet, *Tetrahedron* **29,** 3595 (1973), **31,** 1331 (1975).

Ylides are usually prepared from triphenylphosphine, but other triarylphosphines,[382] trialkylphosphines,[383] and triphenylarsine have also been used. The Wittig reaction has also been carried out with other types of ylides, the most important being prepared from phosphonates:[384]



$$\underset{\text{O}}{\overset{\|}{(\text{RO})_2\text{P}}}-\underset{\text{R}'}{\overset{|}{\text{CH}}}-\text{R}'' \xrightarrow{\text{base}} \underset{\text{O}}{\overset{\|}{(\text{RO})_2\text{P}}}-\underset{\text{R}'}{\overset{\ominus}{\bar{\text{C}}}}-\text{R}'' \xrightarrow{-\overset{|}{\text{C}}=\text{O}} -\overset{|}{\text{C}}=\underset{\text{R}'}{\overset{|}{\text{C}}}-\text{R}'' + (\text{RO})_2\text{PO}_2^-$$

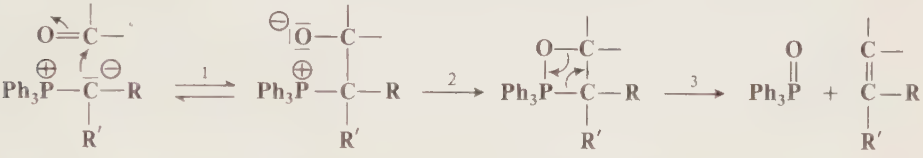
This method, sometimes called the *Horner-Emmons reaction*,[385] has several advantages over the use of phosphoranes. These ylides are more reactive than the corresponding phosphoranes, and when R′ is an electron-withdrawing group, these compounds often react with ketones which are inert to phosphoranes. In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph_3PO, which makes it easy to separate it from the olefin product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*:[386]



$$(\text{EtO})_3\text{P} + \text{RCH}_2\text{X} \longrightarrow \underset{\text{O}}{\overset{\|}{(\text{EtO})_2\text{P}}}-\text{CH}_2\text{R}$$

Ylides formed from $\text{Ar}_2\underset{\text{O}}{\overset{\|}{\text{P}}}\text{CHRR}'$, phosphonic acid bisamides $(\text{R}''_2\text{N})_2\text{POCHRR}'$,[387] and alkyl phosphonothionates $(\text{MeO})_2\text{PSCHRR}'$[388] share some of these advantages.

The mechanism of the key step of the Wittig reaction consists of at least two and perhaps three steps:



Step 1 may or may not be an equilibrium reaction. Steps 2 and 3 constitute an elimination of Ph_3PO (see reaction **7-21**) and may be simultaneous. Either step 1 or steps 2-3 may be rate-determining. Step 1 has been shown to be reversible for stable ylides (those containing COR, CN, etc., groups) by the preparation in another way of the betaine and the demonstration that the ylide can be prepared from it.[389] With unstable ylides it has been suggested[390] that steps 1 and 2 may be simultaneous[391] (so that the betaine is not an intermediate[392]). Evidence for this is that

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[382] Schiemenz and Thobe, *Chem. Ber.* **99**, 2663 (1966).

[383] For example, see Johnson and LaCount, *Tetrahedron* **9**, 130 (1960); Bestmann and Kratzer, *Chem. Ber.* **95**, 1894 (1962).

[384] Horner, Hoffmann, and Wippel, *Chem. Ber.* **91**, 61 (1958); Horner, Hoffmann, Wippel, and Klahre, *Chem. Ber.* **92**, 2499 (1959); Wadsworth and Emmons, *J. Am. Chem. Soc.* **83**, 1733 (1961).

[385] For reviews, see Dombrovskii and Dombrovskii, *Russ. Chem. Rev.* **35**, 733–741 (1966); Boutagy and Thomas, *Chem. Rev.* **74**, 87–99 (1974).

[386] For a review of the Arbuzov reaction, see Arbuzov, *Pure Appl. Chem.* **9**, 307–335 (1964).

[387] Corey and Kwiatkowski, *J. Am. Chem. Soc.* **90**, 6816 (1968); Corey and Cane, *J. Org. Chem.* **34**, 3053 (1969).

[388] Corey and Kwiatkowski, *J. Am. Chem. Soc.* **88**, 5654 (1966).

[389] Speziale and Bissing, *J. Am. Chem. Soc.* **85**, 3878 (1963). However, this interpretation has been challenged: see Nesmayanov, Binshtok, and Reutov, *Doklad. Chem.* **210**, 499 (1973).

[390] Vedejs and Snoble, *J. Am. Chem. Soc.* **95**, 5778 (1973).

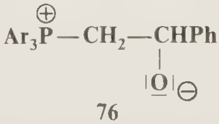
[391] Such a mechanism has been suggested for stable ylides as well: Nesmeyanov, Binshtok, and Reutov, Ref. 389.

[392] For kinetic evidence against a betaine intermediate, see Frøyen, *Acta Chem. Scand.* **26**, 2163 (1972).

^{31}P nmr spectra taken of the reaction mixture at low temperatures are compatible with an oxaphosphetane structure which persists for some time but not with a tetracoordinated phosphorus species. Since a betaine, an ylide, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution.[393] Under these conditions, steps 1 and 2 are obviously fast and step 3 rate-determining. According to any of these mechanisms, an optically active phosphonium salt $RR'R''\overset{\oplus}{P}CHR_2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide RR'R"PO. This has been shown to be the case.[394]

When ylides of the form $Ph_3P{=}CHR$ undergo the Wittig reaction in protic solvents, a different mechanism may compete with the one shown above, depending on the structure of the reactants and the reaction conditions. This mechanism involves protonation of the betaine and cleavage of the resulting β-hydroxy phosphonium salt.[395]

In reactions in which there is a betaine intermediate, we may examine the question of when step 1 is faster than steps 2-3 and vice versa. We have already seen that the ylide is increased in stability (and decreased in reactivity) by the presence of electron-withdrawing groups on the carbon. Another factor is the presence of electron-donating groups on the phosphorus. These groups stabilize the ylide canonical form (of the resonance hybrid) at the expense of the C=P form by decreasing the positive charge on the phosphorus. This increases the reactivity of the ylide and explains, for example, why trialkyl phosphorus ylides are more reactive than the triaryl variety. On the other hand, once the betaine is formed, these factors work in precisely the opposite direction. Electron-withdrawing groups on the carbon increase the reactivity of the betaine because they stabilize (by conjugation) the newly forming double bond; and electron-donating substituents on the phosphorus decrease the reactivity of the betaine since they decrease the positive charge on the phosphorus and make it less attractive to the negative oxygen. We see from all this that with ylides containing electron-donating groups on the phosphorus, the first step will be faster than the subsequent ones. In some cases, indeed, it has proved possible to isolate the betaine, an example being **76**.[396] However, if there are electron-withdrawing groups on the carbon, the first step will be slower than the subsequent ones and it should be much more difficult to isolate the betaine. Up to now, no such betaine has been isolated. We would also clearly not expect to be able to isolate a betaine in cases where steps 2 and 3 are simultaneous.



$$Ar_3\overset{\oplus}{P}{-}CH_2{-}\underset{\underset{\ominus}{|\underline{O}|}}{CHPh} \qquad Ar = p\text{-}MeOC_6H_4$$

76

These considerations make possible at least some conclusions about the stereochemistry of the reaction. If the betaine has two asymmetric carbons, there are two diastereomeric *dl* pairs. In cases where betaine formation is reversible, the thermodynamically more stable diastereomer will be predominantly formed before elimination (a syn process, in this case) occurs, and this diastereomer will normally give the trans olefin:

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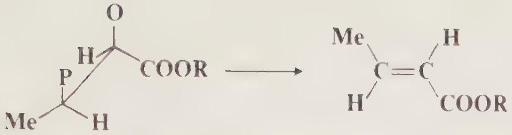
[393] In certain cases, oxaphosphetanes have been isolated: Birum and Matthews, *Chem. Commun.* 137 (1967); Mazhar-Ul-Haque, Caughlan, Ramirez, Pilot, and Smith, *J. Am. Chem. Soc.* **93**, 5229 (1971). See also Schlosser, Piskala, Tarchini, and Tuong, *Chimia* **29**, 341 (1975).

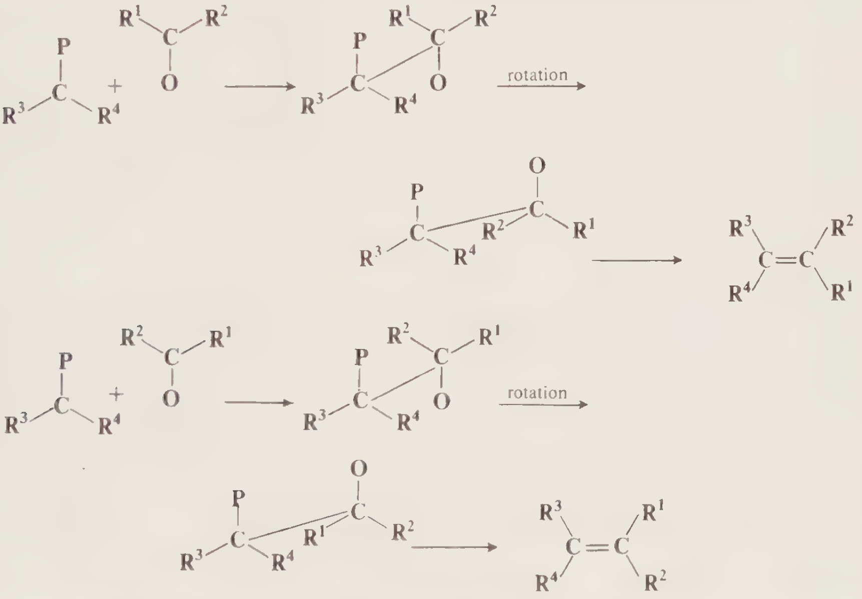
[394] McEwen, Kumli, Blade-Font, Zanger, and VanderWerf, *J. Am. Chem. Soc.* **86**, 2378 (1964).

[395] Schweizer, Crouse, Minami, and Wehman, *Chem. Commun.* 1000 (1971); Richards and Tebby, *J. Chem. Soc. C* 1059 (1971); Smith and Trippett, *J. Chem. Soc., Chem. Commun.* 191 (1972); Allen, Hutley, and Rich, *J. Chem. Soc., Perkin Trans. 2* 820 (1973); Allen, Heatley, Hutley, and Mellor, *Tetrahedron Lett.* 1787 (1974); Allen, Hutley, and Polasik, *J. Chem. Soc., Perkin Trans. 1* 619 (1975).

[396] Wittig, Weigmann, and Schlosser, *Chem. Ber.* **94**, 676 (1961).



Indeed it is generally found that ylides containing stabilizing groups or formed from trialkylphosphines give trans olefins.[397] However, ylides formed from triarylphosphines and not containing stabilizing groups often give cis or mixture of cis and trans olefins.[397] One explanation for this[390] is based on the suggestion, mentioned earlier, that in these cases steps 1 and 2 of the mechanism are simultaneous. If this is so, the reaction of the ylide with the carbonyl compound is a 2 + 2 cycloaddition, which in order to be concerted must adopt the $[_{\pi}2_s + _{\pi}2_a]$ pathway. As we have seen earlier (p. 780), this pathway leads to the formation of the more sterically crowded product, in this case the cis olefin. It is also possible to explain the formation of cis olefins and of cis-trans mixtures even in reactions in which there is a betaine intermediate if we assume that in cases where such products are formed, step 1 is irreversible. In such cases, which diastereomer forms is determined by the way the ylide and carbonyl compound line up. Once the betaine is formed, the stereochemistry of the olefin is determined by the fact that elimination is syn. The two possibilities can be shown:



The natural preference seems to be for the ylide and carbonyl compound to line up in such a way as to give the cis isomers ultimately, but the reasons for this are not clear.[398] It is also possible that cis isomers are not formed by the betaine pathway at all but only by the $[_{\pi}2_s + _{\pi}2_a]$ route.

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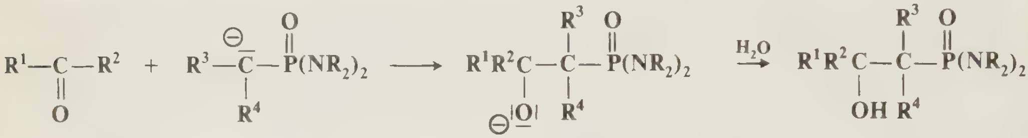
[397] See, for example, Ketcham, Jambotkar, and Martinelli, *J. Org. Chem.* **27**, 4666 (1962); House and Rasmusson, *J. Org. Chem.* **26**, 4278 (1961); Bestmann and Kratzer, ref. 383; Kucherov, Kovalev, Nazarova, and Yanovskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1405 (1960); Yanovskaya and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1252 (1964).

[398] For possible explanations, see Bergelson, Barsukov, and Shemyakin, *J. Gen. Chem. USSR* **38**, 810 (1968); Schneider, *Chem. Commun.* 785 (1969).

The cis-trans ratio of the product can often be changed by a change in solvent or by the addition of salts. It has been found possible to control the reaction so that either the cis or the trans olefin is the main product.[399]

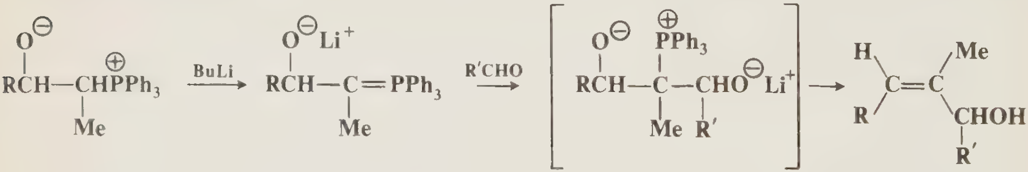
Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case the betaine (77) does not undergo spontaneous elimination



77 78

but when treated with water gives the β-hydroxyphosphonic acid bisamides **78**, which can be crystallized and then cleaved to $R^1R^2C{=}CR^3R^4$ by refluxing in benzene or toluene in the presence of silica gel.[387] **78** are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Cleavage of the two diastereomers gives the two isomeric olefins.

In reactions where the betaine intermediate is present in the solution, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylidenetriphenylphosphorane with heptanal at $-78°C$ gave the betaine **79**, which with butyllithium gave the ylide **80**. Treatment of this with an aldehyde R′CHO gave the intermediate **81**,

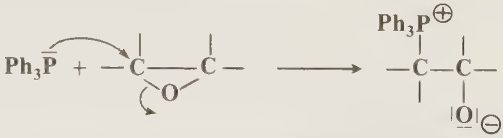


79 80 81 82

$R = n\text{-}C_6H_{13}$

which after workup gave **82**.[400] This reaction gives the unsaturated alcohols **82** stereoselectively. **80** also reacts with other electrophiles. For example, treatment of **80** with N-chlorosuccinimide or $PhICl_2$ gives the vinyl chloride $RCH{=}CMeCl$ stereoselectively, NCS giving the cis and $PhICl_2$ the trans isomer.[401] The use of Br_2 and $FClO_3$ gives the corresponding bromides and fluorides, respectively.[402] Reactions of **80** with electrophiles have been called *scoopy* reactions (α-*s*ubstitution plus *c*arbonyl *o*lefination via β-*o*xido *p*hosphorus *y*lides).[403]

The betaine can be formed in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (reaction **0-51**):



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[399] For reviews of the stereochemistry, see Reucroft and Sammes, *Q. Rev., Chem. Soc.* **25**, 135-169 (1971), pp. 137-148, 169; Schlosser, *Top. Stereochem.* **5**, 1-30 (1970). Also see Bergelson and Shemyakin, *Tetrahedron* **19**, 149 (1963); House, Jones, and Frank, *J. Org. Chem.* **29**, 3327 (1964); Wadsworth, Schupp, Seus, and Ford, *J. Org. Chem.* **30**, 680 (1965); Bergelson, Barsukov, and Shemyakin, *Tetrahedron* **23**, 2709 (1967).

[400] Corey and Yamamoto, *J. Am. Chem. Soc.* **92**, 226 (1970); Schlosser, Christmann, Piskala, and Coffinet, *Synthesis* 29 (1971); Schlosser and Coffinet, *Synthesis* 380 (1971), 575 (1972).

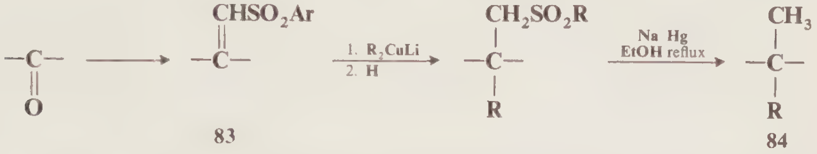
[401] Schlosser and Christmann, *Synthesis* 38 (1969); Corey, Shulman, and Yamamoto, *Tetrahedron Lett.* 447 (1970).

[402] Schlosser and Christmann, Ref. 401.

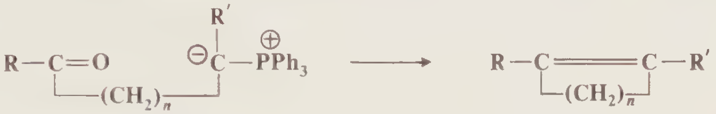
[403] Schlosser, Ref. 399, p. 22.

The betaine formed in this way, of course, can then be converted to the olefin.

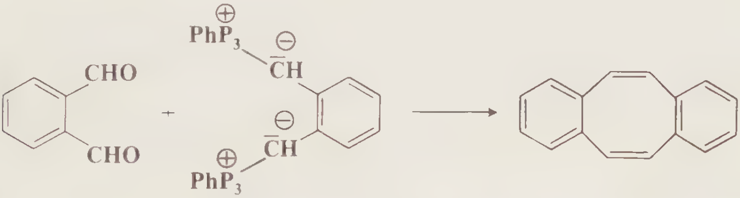
A method[404] for achieving the conversion $C{=}O \rightarrow CR_2$ (see also reactions **6-31** and **6-42**) begins with a Wittig or Horner-Emmons reaction to prepare the α,β-unsaturated aryl sulfones **83**. Treatment of **83** with a lithium dialkylcopper reagent (reaction **5-20**), followed by reduction of the sulfur linkage, gives the product **84**.



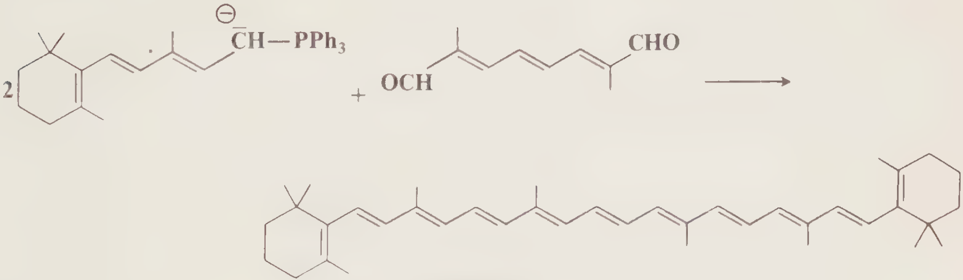
The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,[405] both by single ring closure



and double ring closure[405a]



The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways. One example out of many is the synthesis of β-carotene:[406]



β-Carotene

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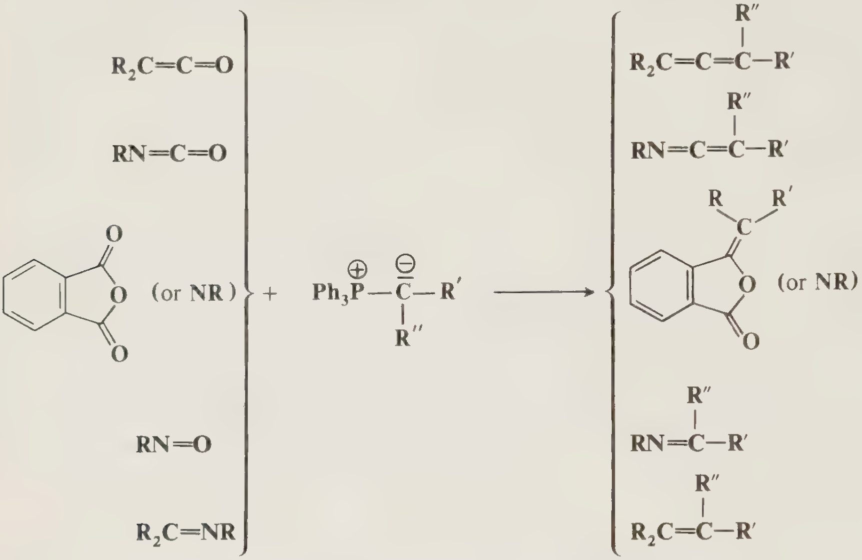
[404] Posner and Brunelle, *Tetrahedron Lett.* 935 (1973).

[405] See, for example, Wittig, Eggers, and Duffner, *Justus Liebigs Ann. Chem.* **619**, 10 (1958); Griffin and Witschard, *J. Org. Chem.* **27**, 3334 (1962), **29**, 1001 (1964); Griffin and Peters, *J. Org. Chem.* **28**, 1715 (1963); Schweizer, *J. Am. Chem. Soc.* **86**, 2744 (1964).

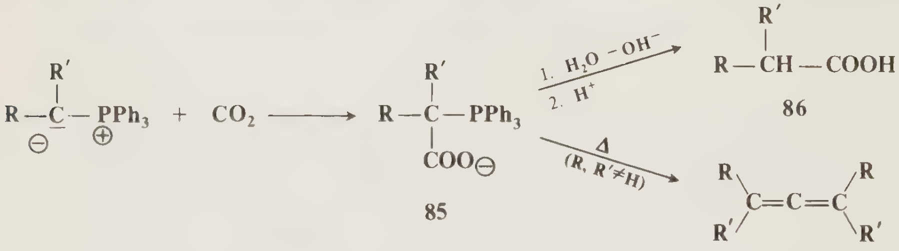
[405a] For a review of these double ring closures, see Vollhardt, *Synthesis* 765–780 (1975).

[406] Wittig and Pommer, German patent 954,247 (1956), *CA* **53**, 2279 (1959).

Phosphorus ylides also react in a similar manner with the C=O bonds of ketenes,[407] isocyanates,[408] and certain[409] anhydrides and imides (others give reaction **0-114**), the N=O of nitroso groups, and the C=N of imines:[410]


R₂C=C=O
RN=C=O
O
O (or NR)
O
RN=O
R₂C=NR
+
Ph₃P—C—R′
R″
R₂C=C=C—R′
R″
RN=C=C—R′
R″
R R′
C
O (or NR)
O
RN=C—R′
R″
R₂C=C—R′
R″

Phosphorus ylides react with carbon dioxide to give the isolable salts **85**,[411] which can be hydrolyzed to the carboxylic acids **86** (thus achieving the conversion RR′CHX → RR′CHCOOH)

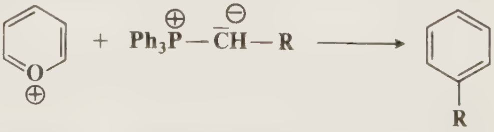

R′
R—C—PPh₃
+ CO₂
R′
R—C—PPh₃
COO
1. H₂O - OH⁻
2. H⁺
Δ
(R, R′≠H)
R′
R—CH—COOH
R
R
C=C=C
R′
R′

85

86

87

or (if neither R nor R′ is hydrogen) dimerized to the allenes **87**. Pyrilium salts react with ylides in the following manner:[412]



OS **V**, 361, 390, 499, 509, 547, 751, 949, 985; **53**, 104.

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[407] For example, see Aksnes and Frøyen, *Acta Chem. Scand.* **22**, 2347 (1968).

[408] For example, see Frøyen, *Acta Chem. Scand., Ser. B* **28**, 586 (1974).

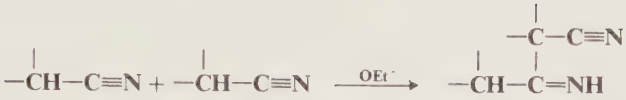
[409] For example, see Chopard, Hudson, and Searle, *Tetrahedron Lett.* 2357 (1965); Flitsch and Peters, *Tetrahedron Lett.* 1161 (1969); Gara, Massy-Westropp, and Reynolds, *Tetrahedron Lett.* 4171 (1969). For a review with respect to imides, see Flitsch and Schindler, *Synthesis* 685–700 (1975).

[410] Bestmann and Seng, *Tetrahedron* **21**, 1373 (1965).

[411] Bestmann, Denzel, and Salbaum, *Tetrahedron Lett.* 1275 (1974).

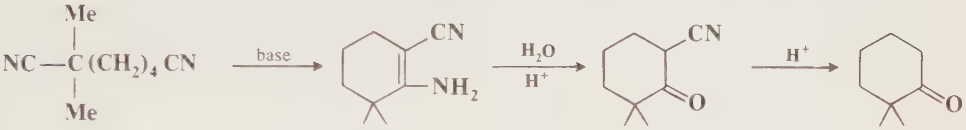
[412] Märkl, *Angew. Chem. Int. Ed. Engl.* **1**, 511 (1962) [*Angew. Chem.* **74**, 696].

6-48 The Thorpe Reaction



$$-\overset{|}{C}H-C\equiv N + -\overset{|}{C}H-C\equiv N \xrightarrow{OEt^-} -\overset{|}{C}H-\overset{\overset{|}{-C-C\equiv N}}{\overset{|}{C}}=NH$$

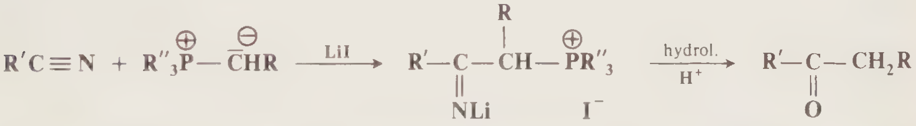
In the *Thorpe reaction*, the α-carbon of one nitrile molecule is added to the CN carbon of another, so that this reaction is analogous to the aldol condensation (**6-40**). The C=NH bond is, of course, hydrolyzable (reaction **6-2**), so that β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done internally, in which case it is called the *Thorpe-Ziegler reaction*.[413] This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings if high-dilution techniques are employed. The product in the Thorpe-Ziegler reaction is not the imine, but the tautomeric enamine, e.g., **88**; if desired this can be hydrolyzed to an α-cyano ketone (reaction **6-2**), which can in turn be hydrolyzed and decarboxylated (reactions **6-5**, **2-39**). Other active compounds can also be added to nitriles. In particular, CF_3CN adds compounds ZCH_2Z, in a Knoevenagel-type reaction.[414] See also reaction **6-49**.



88

OS **53**, 98.

6-49 The Reaction of Phosphoranes with Nitriles

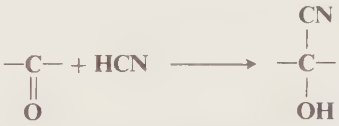


$$R'C\equiv N + R''_3\overset{\oplus}{P}-\overset{\ominus}{\overline{C}}HR \xrightarrow{LiI} R'-\underset{\underset{NLi}{\|}}{C}-\overset{\overset{R}{|}}{C}H-\overset{\oplus}{P}R''_3\quad I^- \xrightarrow[H^+]{hydrol.} R'-\underset{\underset{O}{\|}}{C}-CH_2R$$

Nitriles react with phosphoranes to give adducts which can be hydrolyzed to ketones,[415] in a reaction similar to **6-38**. The phosphoranes must be prepared from phosphonium iodides with organolithium compounds (see reaction **6-47**), or else LiI must be added to the solution. Both Li^+ and I^- are necessary for good yields. R′ may be alkyl or aryl.

J. Other Carbon Nucleophiles

6-50 The Formation of Cyanohydrins



$$-\underset{\underset{O}{\|}}{C}- + HCN \longrightarrow -\overset{\overset{CN}{|}}{\underset{\underset{OH}{|}}{C}}-$$

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[413] For a monograph, see Taylor and McKillop, "The Chemistry of Cyclic Enaminonitriles and *ortho*-Amino Nitriles," Interscience Publishers, New York, 1970. For a review, see Schaefer and Bloomfield, *Org. React.* **15**, 1-203 (1967).

[414] Josey, *J. Org. Chem.* **29**, 707 (1964).

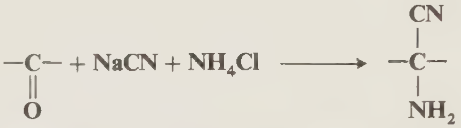
[415] Bladé-Font, McEwen, and VanderWerf, *J. Am. Chem. Soc.* **82**, 2646 (1960); Barnhardt and McEwen, *J. Am. Chem. Soc.* **89**, 7009 (1967).

The addition of HCN to aldehydes or ketones produces cyanohydrins.[416] This is an equilibrium reaction. For aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium is too far to the left. With aromatic aldehydes the benzoin condensation (reaction **6-56**) competes. With α,β-unsaturated aldehydes and ketones, 1,4 addition competes (reaction **5-28**). Ketones of low reactivity can be converted to cyanohydrins by treatment with diethylaluminum cyanide Et_2AlCN (see OS **52,** 96). Frequently it is the bisulfite addition product which is treated with CN^-, in which case the reaction is actually nucleophilic substitution. This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin in situ, without its isolation, to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani method* of extending the carbon chain of a sugar.

The addition is nucleophilic, and the actual nucleophile is CN^-, so that the reaction rate is increased by the addition of base.[417] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[418]

OS **I,** 336; **II,** 7, 29, 387; **III,** 436; **IV,** 58, 506; **52,** 96. For the reverse reaction, see OS **III,** 101.

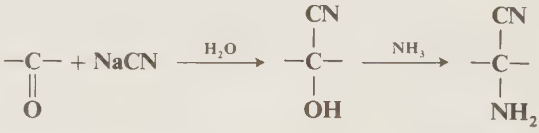
6-51 The Strecker Synthesis



$$-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}- + \mathrm{NaCN} + \mathrm{NH_4Cl} \longrightarrow -\overset{\overset{\mathrm{CN}}{|}}{\underset{\underset{\mathrm{NH_2}}{|}}{\mathrm{C}}}-$$

α-Amino nitriles can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis;* it is actually a special case of the Mannich reaction (**6-17**). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with NH_3 + HCN and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+, to obtain N-substituted and N,N-disubstituted α-amino nitriles. When *formaldehyde* is treated with NaCN and the salt of an amine, the reaction is known as *cyanomethylation* of the amine. Unlike reaction **6-50,** the Strecker synthesis is useful for aromatic as well as aliphatic ketones.

There are two possible pathways for the reaction. The cyanohydrin may be produced first, and a nucleophilic substitution (reaction **0-48**) may then follow:



$$-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}- + \mathrm{NaCN} \xrightarrow{\mathrm{H_2O}} -\overset{\overset{\mathrm{CN}}{|}}{\underset{\underset{\mathrm{OH}}{|}}{\mathrm{C}}}- \xrightarrow{\mathrm{NH_3}} -\overset{\overset{\mathrm{CN}}{|}}{\underset{\underset{\mathrm{NH_2}}{|}}{\mathrm{C}}}-$$

or ammonia (or the amine) may add first to give an imine (reaction **6-14**), to which NaCN adds (reaction **6-52**):[419]

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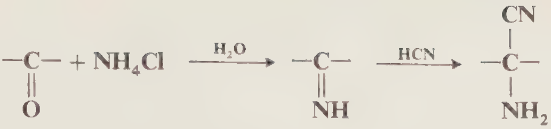
[416] For reviews, see Friedrich and Wallenfels, in Rappoport, Ref. 212, pp. 72–77; Mowry, *Chem. Rev.* **42,** 189–283 (1948); pp. 231–240.

[417] For a review, see Ogata and Kawasaki, in Zabicky, Ref. 17, pp. 21–32.

[418] Lapworth, *J. Chem. Soc.* **83,** 998 (1903).

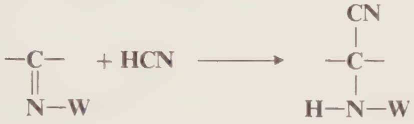
[419] For evidence that α-amino nitriles can be formed by this pathway, see Ogata and Kawasaki, *J. Chem. Soc. B* 325 (1971); Stanley, Beasley, and Mathison, *J. Org. Chem.* **37,** 3746 (1972); Walia, Bannore, Walia, and Guillot, *Chem. Lett.* 1005 (1974). For evidence for both pathways, see Taillades and Commeyras, *Tetrahedron* **30,** 2493 (1974).



$$\underset{\underset{\displaystyle O}{\|}}{-C-} + NH_4Cl \xrightarrow{H_2O} \underset{\underset{\displaystyle NH}{\|}}{-C-} \xrightarrow{HCN} \overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle NH_2}{|}}{-C-}}$$

OS **I**, 21, 355; **III**, 66, 84, 88, 275; **IV**, 274; **V**, 437.

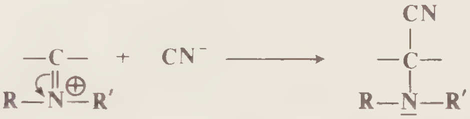
6-52 The Addition of HCN to C═N and C≡N Bonds



$$\underset{\underset{\displaystyle N-W}{\|}}{-C-} + HCN \longrightarrow \overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle H-N-W}{|}}{-C-}}$$

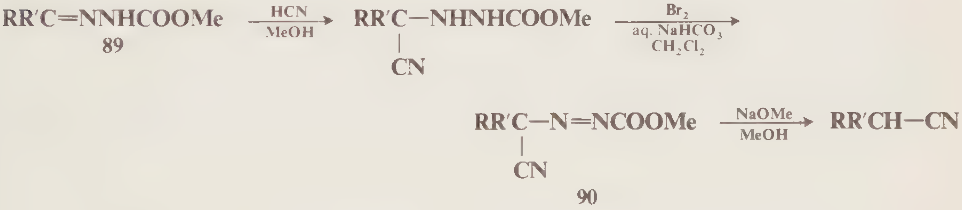
W = H, R, Ar, OH, NHAr, etc.

HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. CN^- can be added to iminium ions:[210]



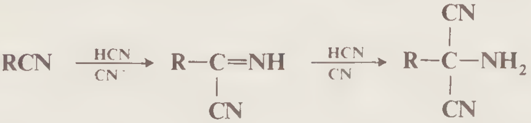
$$\underset{\underset{\displaystyle R-\overset{\oplus}{N}-R'}{\|}}{-C-} + CN^- \longrightarrow \overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle R-\underline{N}-R'}{|}}{-C-}}$$

The addition of HCN to carbomethoxyhydrazones **89**[420] provides an indirect method for achieving the conversion RR′CO → RR′CHCN.[421] The initial product is dehydrogenated with bromine (reaction **9-7**) to give a methyl dialkylcyanodiazenecarboxylate **90**, which with NaOMe in MeOH gives the nitrile:



$$\underset{\mathbf{89}}{RR'C{=}NNHCOOMe} \xrightarrow[MeOH]{HCN} \underset{\underset{\displaystyle CN}{|}}{RR'C}{-}NHNHCOOMe \xrightarrow[\substack{aq.\ NaHCO_3\\ CH_2Cl_2}]{Br_2} \underset{\mathbf{90}}{\underset{\underset{\displaystyle CN}{|}}{RR'C}{-}N{=}NCOOMe} \xrightarrow[MeOH]{NaOMe} RR'CH{-}CN$$

HCN can also be added to the C≡N bond to give iminonitriles or α-aminomalononitriles.[422]



$$RCN \xrightarrow[CN^-]{HCN} R{-}\underset{\underset{\displaystyle CN}{|}}{C}{=}NH \xrightarrow[CN^-]{HCN} R{-}\overset{\overset{\displaystyle CN}{|}}{\underset{\underset{\displaystyle CN}{|}}{C}}{-}NH_2$$

OS **V**, 344. See also OS **V**, 269.

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[420] Prepared by reaction **6-21**. See Rabjohn and Barnstorff, *J. Am. Chem. Soc.* **75**, 2259 (1953).

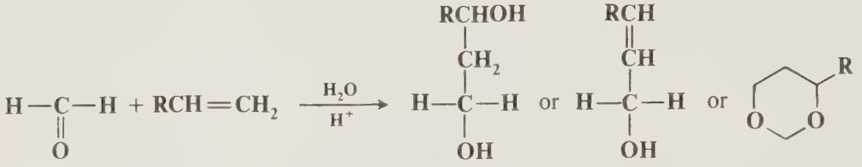
[421] Ziegler and Wender, *J. Am. Chem. Soc.* **93**, 4318 (1971). For another method of achieving this conversion, see Cacchi, Caglioti, and Paolucci, *Chem. Ind.* (*London*) 213 (1972).

[422] For an example, see Ferris and Sanchez, *Org. Synth.* **V**, 344.

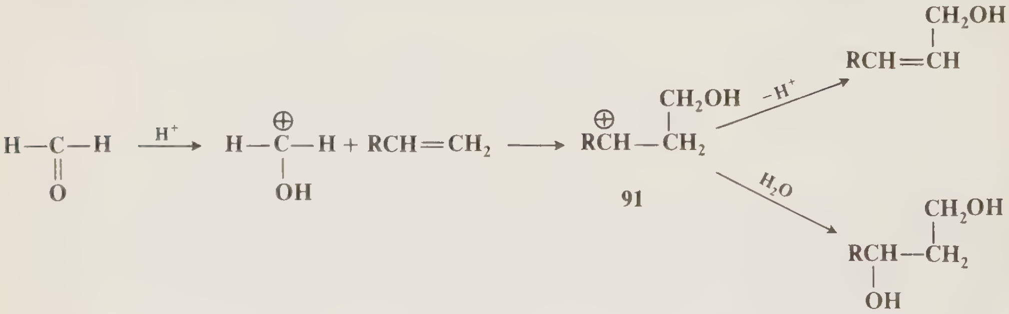
6-53 Addition of ArH to C=O, C=N, and C≡N Bonds

These reactions are discussed under aromatic substitution: **1-18, 1-23** to **1-28, 1-30,** and **1-31.**

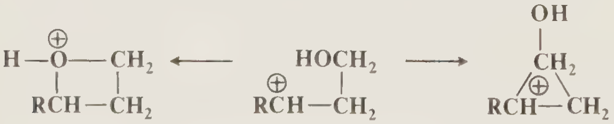
6-54 The Prins Reaction



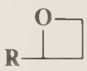
The addition of an olefin to formaldehyde in the presence of an acid[423] catalyst is called the *Prins reaction.*[424] Three main products are possible, and which one predominates depends on the olefin and the conditions. When the product is the 1,3-diol or the dioxane, the reaction involves addition to the C=C as well as to the C=O. The mechanism is one of electrophilic attack, on both double bonds. The acid first protonates the C=O, and the resulting carbonium ion attacks the C=C:



91 may undergo loss of H⁺ to give the olefin or may add water to give the diol.[425] It has been proposed that **91** is stabilized by neighboring-group attraction, with either the oxygen[426] or a carbon[427] stabilizing the charge (**92** and **93,** respectively). This stabilization is postulated to explain the fact that with 2-butenes[428] and with cyclohexenes the addition is anti. A backside



92 91 93



94

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[423] The Prins reaction has also been carried out with basic catalysts: Griengl and Sieber, *Monastsh. Chem.* **104,** 1008, 1027 (1973).

[424] For reviews, see Isagulyants, Khaimova, Melikyan, and Pokrovskaya, *Russ. Chem. Rev.* **37,** 17-25 (1968); Roberts, in Olah, "Friedel-Crafts and Related Reactions," vol. 2, pp. 1175-1210, Interscience Publishers, New York, 1963; Arundale and Mikeska, *Chem. Rev.* **51,** 505 (1952).

[425] Hellin, Davidson, and Coussemant, *Bull. Soc. Chim. Fr.* 1890, 3217 (1966).

[426] Blomquist and Wolinsky, *J. Am. Chem. Soc.* **79,** 6025 (1957); Schowen, Smissman, and Schowen, *J. Org. Chem.* **33,** 1873 (1968).

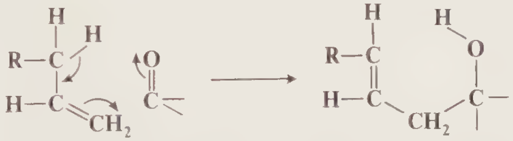
[427] Dolby, Lieske, Rosencrantz, and Schwarz, *J. Am. Chem. Soc.* **85,** 47 (1963); Dolby and Schwarz, *J. Org. Chem.* **28,** 1456 (1963); Safarov, Isagulyants, and Nigmatullin, *J. Org. Chem. USSR* **10,** 1378 (1974).

[428] Fremaux, Davidson, Hellin, and Coussemant, *Bull. Soc. Chim. Fr.* 4250 (1967).

attack of H_2O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **92** or **93**.[426, 427] Additional evidence for the intermediacy of **92** is the finding that oxetanes (**94**) subjected to the reaction conditions (which would protonate **94** to give **92**) give essentially the same product ratios as the corresponding alkenes.[429] An argument against the intermediacy of **92** and **93** is that not all alkenes show the anti stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.[430] Since addition to the C=C bond is electrophilic, the reactivity of the olefin increases with alkyl substitution and Markovnikov's rule is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde[431] (reaction **6-6**) or between **91** and formaldehyde, or even between the olefin and a formaldehyde dimer $HOCH_2$-$OCH_2{}^+$.[432]

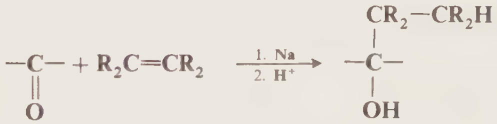
Lewis acids such as $SnCl_4$ also catalyze the reaction, in which case the species which adds to the olefins is $H_2\overset{\oplus}{C}-O-\overset{\ominus}{S}nCl_4$.[433] The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one.

The reaction has been performed with other aldehydes and even with ketones; without a catalyst, but with heat.[434] The aldehydes and ketones here are active ones, such as chloral and acetoacetic ester. The product in these cases is a β-hydroxy olefin, and a cyclic mechanism has been postulated:



This reaction is reversible, and suitable β-hydroxy olefins can be cleaved by heat (reaction **7-45**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 955), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too. Note that this reaction is an oxygen analog of the ene synthesis (**5-18**).

There is still another way in which olefins can be added to the C=O bond. If the two compounds are treated with sodium, there is addition accompanied by reduction:[435]



$$-\underset{\underset{O}{\|}}{C}- + R_2C{=}CR_2 \xrightarrow[2.\ H^+]{1.\ Na} -\overset{\overset{CR_2-CR_2H}{|}}{\underset{\underset{OH}{|}}{C}}-$$

[429] Meresz, Leung, and Denes, *Tetrahedron Lett.* 2797 (1972).

[430] For example, see LeBel, Liesemer, and Mehmedbasich, *J. Org. Chem.* **28,** 615 (1963); Portoghese and Smissman, *J. Org. Chem.* **27,** 719 (1962); Bernardi and Leone, *Tetrahedron Lett.* 499 (1964); Dolby, Wilkins, and Frey, *J. Org. Chem.* **31,** 1110 (1966); Wilkins and Marianelli, *Tetrahedron* **26,** 4131 (1970); Karpaty, Hellin, Davidson, and Coussemant, *Bull. Soc. Chim. Fr.* 1736 (1971); Coryn and Anteunis, *Bull. Soc. Chim. Belg.* **83,** 83 (1974).

[431] Ref. 425; Isagulyants, Isagulyants, Khairudinov, and Rakhmankulov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **22,** 1810 (1973); Sharf, Kheifets, and Freidlin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23,** 1681 (1974).

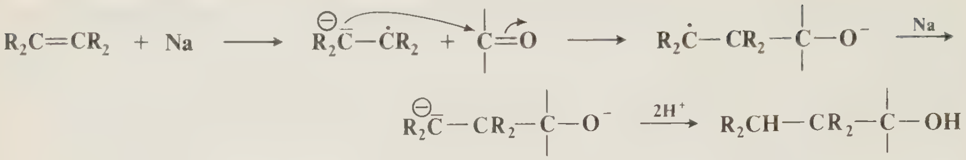
[432] Smissman, Schnettler, and Portoghese, *J. Org. Chem.* **30,** 797 (1965). See however, Gaillard, Hellin, and Coussemant, *Bull. Soc. Chim. Fr.* 3360 (1967); Dolby, Wilkins, and Rodia, *J. Org. Chem.* **33,** 4155 (1968).

[433] Yang, Yang, and Ross, *J. Am. Chem. Soc.* **81,** 133 (1959).

[434] Arnold and Veeravagu, *J. Am. Chem. Soc.* **82,** 5411 (1960); Klimova, Abramov, Antonova, and Arbuzov, *J. Org. Chem. USSR* **5,** 1308 (1969); Klimova, Antonova, and Arbuzov, *J. Org. Chem. USSR* **5,** 1312, 1315 (1969).

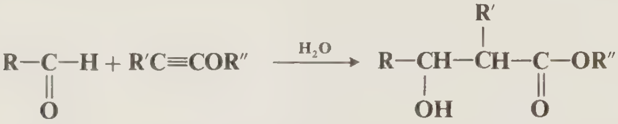
[435] Kochi, *J. Org. Chem.* **28,** 1960, 1969 (1963).

The mechanism probably involves a radical ion:



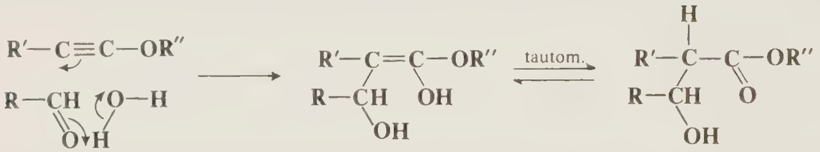
OS IV, 786.

6-55 The Addition of Triple-Bond Compounds

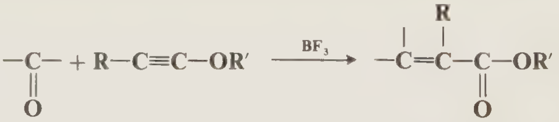


$$\mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}H + R'C{\equiv}COR''} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}\overset{\overset{\displaystyle R'}{|}}{CH}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OR''}$$

Aldehydes and water can be added to alkynyl ethers to give β-hydroxy esters.[436] The reaction is applicable to aldehydes only, but the yields rapidly diminish with chain length.[437] Formaldehyde is most commonly used. A cyclic mechanism has been suggested:

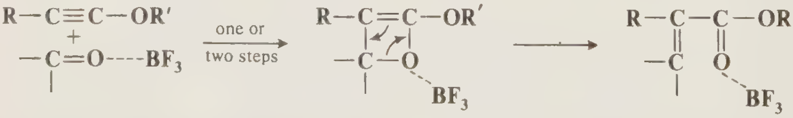


If the alkynyl ether is treated with a carbonyl compound in the absence of water but in the presence of BF_3, an α,β-unsaturated ester is produced:[438]



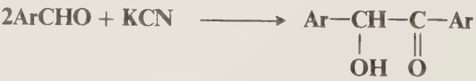
$$\mathrm{{-}\underset{\underset{\displaystyle O}{\|}}{C}{-} + R{-}C{\equiv}C{-}OR'} \xrightarrow{\mathrm{BF_3}} \mathrm{{-}\overset{|}{C}{=}\overset{\overset{\displaystyle R}{|}}{C}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}OR'}$$

This reaction is much more general, and the carbonyl compound may be an aldehyde, ketone, ester, or amide. A cyclic mechanism has also been proposed in this case:



In an analogous reaction, ynamines $\mathrm{RC{\equiv}CNR'_2}$ react with aldehydes or ketones to give α,β-unsaturated amides $\mathrm{{-}\underset{|}{C}{=}CRCONR'_2}$.[439]

6-56 The Benzoin Condensation



$$\mathrm{2ArCHO + KCN \longrightarrow Ar{-}\underset{\underset{\displaystyle OH}{|}}{CH}{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}Ar}$$

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[436] For a review, see Arens, *Adv. Org. Chem.* **2,** 117–212 (1960), pp. 174–178.

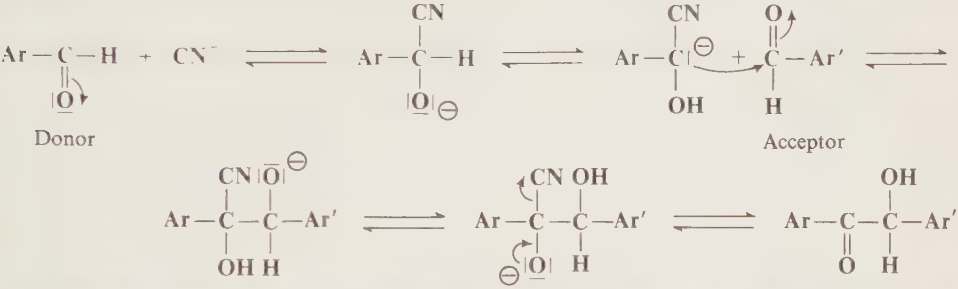
[437] Vieregge and Arens, *Recl. Trav. Chim. Pays-Bas* **78,** 921 (1959).

[438] Vieregge, Bos, and Arens, *Recl. Trav. Chim. Pays-Bas* **78,** 664 (1959); Krasnaya and Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 990 (1962), 96 (1965); Bos and Arens, *Recl. Trav. Chim. Pays-Bas* **83,** 845 (1963); Vieregge, Schmidt, Renema, Bos, and Arens, *Recl. Trav. Chim. Pays-Bas* **85,** 929 (1966).

[439] For example, see Fuks and Viehe, *Chem. Ber.* **103,** 564 (1970).

When certain aldehydes are treated with cyanide ion, *benzoins* are produced, in a reaction called the *benzoin condensation.* The condensation may be regarded as involving the addition of one molecule of aldehyde to the C═O group of another. The reaction can be accomplished only for aromatic aldehydes, though not for all of them,[440] and for glyoxals RCOCHO. The two molecules of aldehyde obviously perform different functions. The one which no longer has a C—H bond in the product is called the *donor* because it has "donated" its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions but is a better acceptor than it is a donor.

The following is the accepted mechanism,[441] which was originally proposed by Lapworth in 1903:[442]



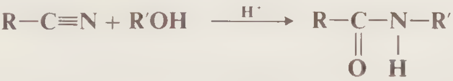
The reaction is reversible. The key step of the reaction, the loss of the aldehydic proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, CN^- is a highly specific catalyst for this reaction, because, almost uniquely,[443] it can perform three functions: (1) It acts as a nucleophile; (2) its electron-withdrawing ability permits loss of the aldehydic proton; and (3) having done this, it then acts as a leaving group.

OS **I,** 94.

Reactions in Which Carbon Adds to the Hetero Atom

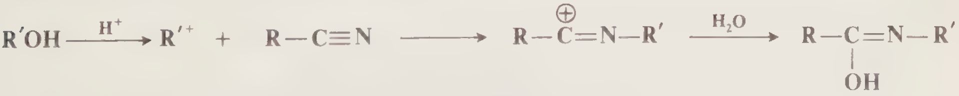
A. Oxygen Adding to the Carbon

6-57 The Ritter Reaction



$$R{-}C{\equiv}N + R'OH \xrightarrow{H^+} R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}\underset{\displaystyle H}{\underset{|}{N}}{-}R'$$

Alcohols can be added to nitriles in an entirely different manner from that of reaction **6-10.** In this reaction, the alcohol is converted by a strong acid to the carbonium ion, which adds to the negative nitrogen, water adding to the carbon:



$$R'OH \xrightarrow{H^+} R'^+ + R{-}C{\equiv}N \longrightarrow R{-}\overset{\oplus}{C}{=}N{-}R' \xrightarrow{H_2O} R{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}N{-}R'$$

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[440] For a review, see Ide and Buck, *Org. React.* **4,** 269-304 (1948).

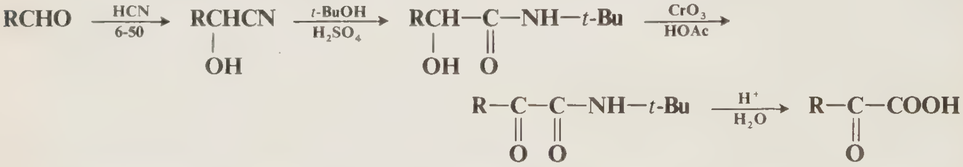
[441] For a discussion, see Kuebrich, Schowen, Wang, and Lupes, *J. Am. Chem. Soc.* **93,** 1214 (1971).

[442] Lapworth, *J. Chem. Soc.* **83,** 995 (1903), **85,** 1206 (1904).

[443] Certain thiazolium salts can also catalyze the reaction: see for example Ugai, Tanaka, and Dokawa, *J. Pharm. Soc. Jpn.* **63,** 296 (1943) [*CA* **45,** 5148]; Breslow, *J. Am. Chem. Soc.* **80,** 3719 (1958). Pyridine-2-carboxaldehyde and quinoline-2-carboxaldehyde undergo the reaction when dissolved in acetic acid in the absence of CN^-: Schaefer and Bertram, *J. Am. Chem. Soc.* **89,** 4121 (1967).

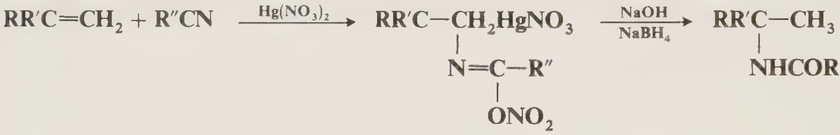
The immediate product tautomerizes to the N-alkyl amide. Only alcohols which give rise to fairly stable carbonium ions react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbonium ion need not be generated from an alcohol but may come from protonation of an olefin or from other sources, among them RCOOH + conc. $H_2SO_4 \rightarrow R^+$ (R in this case, tertiary only).[444] In any case, the reaction is called the *Ritter reaction.*[445] HCN also gives the reaction, the product being a formamide. Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions $R'OH \rightarrow R'NH_2$ (see reaction **0-48**) and alkene $\rightarrow R'NH_2$ (see reaction **5-9**) in those cases where R′ can form a relatively stable carbonium ion. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to alcohols which do not give stable carbonium ions (e.g., 1-decanol) by treating the alcohol with $Ph_2CCl^+ \ SbCl_6^-$ or a similar salt in the nitrile as solvent.[446]

α-Keto acids can be prepared from aldehydes with the aid of a Ritter reaction involving a cyanohydrin.[447]



$$RCHO \xrightarrow[6\text{-}50]{HCN} \underset{|\atop OH}{RCHCN} \xrightarrow[H_2SO_4]{t\text{-}BuOH} \underset{|\atop OH}{RCH}-\underset{\|\atop O}{C}-NH-t\text{-}Bu \xrightarrow[HOAc]{CrO_3} R-\underset{\|\atop O}{C}-\underset{\|\atop O}{C}-NH-t\text{-}Bu \xrightarrow[H_2O]{H^+} R-\underset{\|\atop O}{C}-COOH$$

Olefins of the form RCH=CHR′ and RR′C=CH_2 add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides which would be obtained by the Ritter reaction.[448] This method has the advantage of avoiding strong acids.

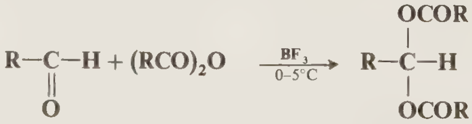


$$RR'C=CH_2 + R''CN \xrightarrow{Hg(NO_3)_2} \underset{\underset{\underset{|\atop ONO_2}{|}}{|\atop N=C-R''}}{RR'C}-CH_2HgNO_3 \xrightarrow[NaBH_4]{NaOH} \underset{|\atop NHCOR''}{RR'C}-CH_3$$

The Ritter reaction can be applied to cyanamides RNHCN to give ureas RNHCONHR′.[449]

OS **V**, 73, 471.

6-58 Acylation of Aldehydes and Ketones



$$R-\underset{\|\atop O}{C}-H + (RCO)_2O \xrightarrow[0\text{-}5°C]{BF_3} R-\overset{OCOR\atop |}{\underset{|\atop OCOR}{C}}-H$$

An acylal

---

[444] Haaf, *Chem. Ber.* **96,** 3359 (1963).

[445] Ritter and Minieri, *J. Am. Chem. Soc.* **70,** 4045 (1948). For reviews, see Krimen and Cota, *Org. React.* **17,** 213 325 (1969); Beckwith, in Zabicky, Ref. 46, pp. 125–130; Johnson and Madroñero, *Adv. Heterocycl. Chem.* **6,** 95–146 (1966); Zil'berman, *Russ. Chem. Rev.* **29,** 331–344 (1960), pp. 334–337.

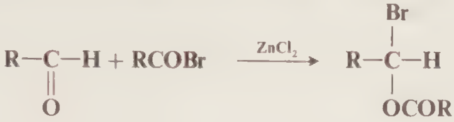
[446] Barton, Magnus, Garbarino, and Young, *J. Chem. Soc., Perkin Trans 1* 2101 (1974).

[447] Anatol and Medete, *Bull. Soc. Chim. Fr.* 189 (1972).

[448] Sokolov and Reutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 225 (1968); Beger and Vogel, *J. Prakt. Chem.* **311,** 737 (1969); Brown and Kurek, *J. Am. Chem. Soc.* **91,** 5647 (1969); Chow, Robson, and Wright, *Can. J. Chem.* **43,** 312 (1965).

[449] Anatol and Berecoechea, *Bull. Soc. Chim. Fr.* 395 (1975), *Synthesis* 111 (1975).

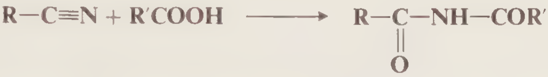
Aldehydes can be converted to acylals by treatment with an anhydride in the presence of BF_3. The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride. This compound does give acylals with ketones without a catalyst.[450] In a similar reaction, aldehydes and some ketones (though not acetone) add the elements of an acyl bromide when treated with the acyl bromide and $ZnCl_2$:[451]



$$R-\underset{\underset{\displaystyle O}{\|}}{C}-H + RCOBr \xrightarrow{ZnCl_2} R-\overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle OCOR}{|}}{C}}-H$$

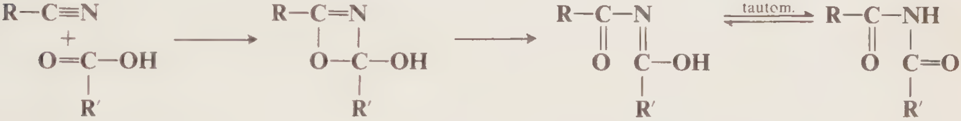
OS **IV**, 489.

6-59 The Addition of Acids to Nitriles



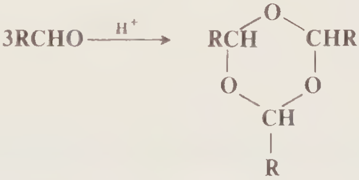
$$R-C\equiv N + R'COOH \longrightarrow R-\underset{\underset{\displaystyle O}{\|}}{C}-NH-COR'$$

Imides are the principal products when carboxylic acids are added to nitriles.[452] Several mechanisms have been proposed which more or less fit the data. In one of them the nitrogen is attacked directly by the carboxyl carbon, and in another the OH of the acid attacks the nitrile carbon and a migration of the acyl group follows. A more recently proposed mechanism is similar to the one proposed for reaction **6-55**:[453]



$$\begin{array}{c}R-C\equiv N\\+\\O=\underset{\underset{\displaystyle R'}{|}}{C}-OH\end{array} \longrightarrow \begin{array}{c}R-C=N\\ |\quad\;\;|\\ O-\underset{\underset{\displaystyle R'}{|}}{C}-OH\end{array} \longrightarrow R-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle \underset{\underset{\displaystyle R'}{|}}{C}-OH}{\|}}{N} \xrightleftharpoons{\text{tautom.}} R-\underset{\underset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle \underset{\underset{\displaystyle R'}{|}}{C}=O}{|}}{NH}$$

6-60 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.[454] The cyclic trimer of formaldehyde is called *trioxane*, and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers[455] or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases but may be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

[450] Libman, Sprecher, and Mazur, *Tetrahedron* **25**, 1679 (1969).

[451] Euranto and Kujanpää, *Acta Chem. Scand.* **15**, 1209 (1961).

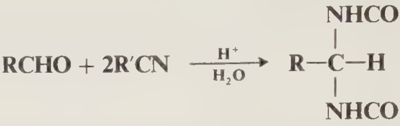
[452] For a review, see Zil'berman, Ref. 445, pp. 340–341.

[453] Durrell, Young, and Dresdner, *J. Org. Chem.* **28**, 831 (1963).

[454] For a review, see Bevington, *Q. Rev., Chem. Soc.* **6**, 141–156 (1952).

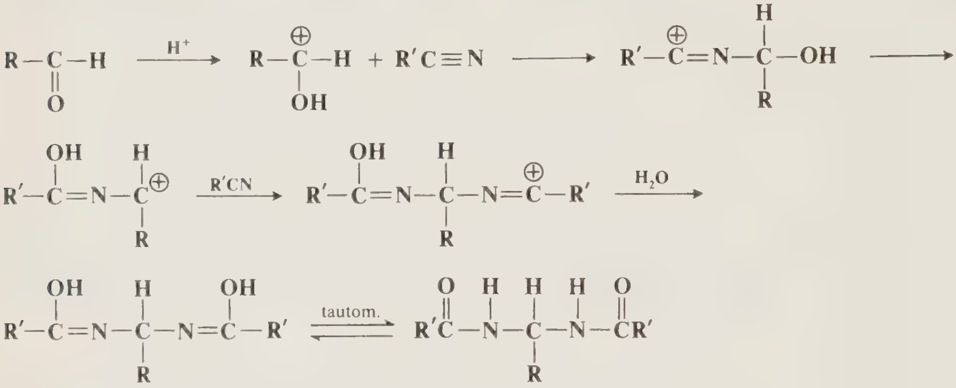
[455] Barón, *Nature* **192**, 258 (1961); Barón, Manderola, and Westerkamp, *Can. J. Chem.* **41**, 1893 (1963).

6-61 The Addition of Aldehydes to Nitriles



$$\mathrm{RCHO} + 2\mathrm{R'CN} \xrightarrow[\mathrm{H_2O}]{\mathrm{H^+}} \mathrm{R{-}\underset{\displaystyle NHCOR'}{\overset{\displaystyle NHCOR'}{C}}{-}H}$$

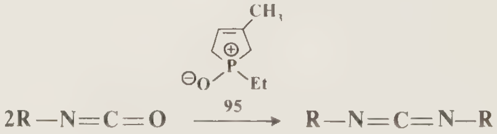
In the presence of acids, 2 moles of a nitrile add to 1 mole of aldehyde to give *amidals*.[456] The reaction is applicable only to aldehydes which do not contain an α-hydrogen. Apparently the mechanism is



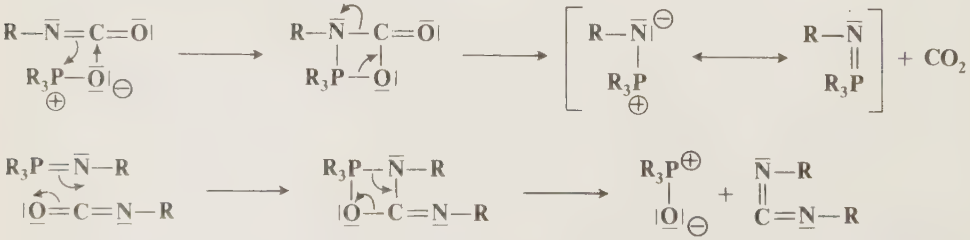
OS IV, 518.

B. Nitrogen Adding to the Carbon

6-62 The Addition of Isocyanates to Isocyanates



The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**95**) represents a useful method for the synthesis of carbodiimides in good yields.[457] The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $R_3\overset{\oplus}{P}-\overset{\ominus}{O}$):[458]



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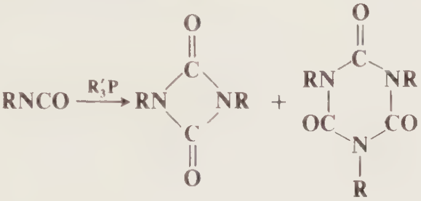
[456] For a review, see Zil'berman, Ref. 445, pp. 333–334.

[457] Campbell, Monagle, and Foldi, *J. Am. Chem. Soc.* **84,** 3673 (1962).

[458] Monagle, Campbell, and McShane, *J. Am. Chem. Soc.* **84,** 4288 (1962).

The first two steps together are rate-determining. According to this mechanism, one molecule of isocyanate undergoes addition to C=O and the other, addition to C=N. Evidence in favor of the mechanism is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from the phospholene oxide,[459] which is precisely what is predicted by this mechanism. Certain other catalysts are also effective.[460] When isocyanates are treated with phosphines (instead of phosphine oxides, as above), there is simple addition to give cyclic dimers and trimers:[461]



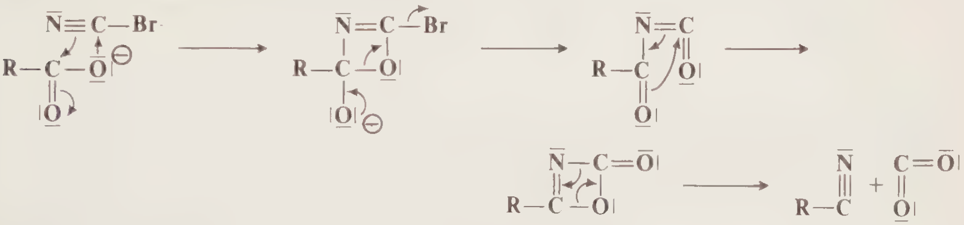
A number of other compounds also catalyze this cyclization.[462]

OS V, 501.

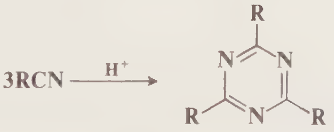
6-63 The Conversion of Acid Salts to Nitriles

$$RCOO^- + BrCN \xrightarrow{250\text{–}300^\circ C} RCN + CO_2$$

Salts of aliphatic or aromatic acids can be converted to the corresponding nitriles by heating with BrCN or ClCN. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile and not in the CO_2[463] and optical activity in R was retained.[464] The acyl isocyanate RCON=C=O could be isolated from the reaction mixture; hence the following mechanism was proposed:[463]



6-64 The Trimerization of Nitriles



Nitriles can be trimerized with various acids, bases, or other catalysts. HCl is most often used, and then the reaction is similar to reaction **6-60.** However, most nitriles with an α-hydrogen do not give the reaction. Mixed triazines can be obtained from mixtures of nitriles.[465] The mechanism with HCl may be as follows:

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[459] Monagle and Mengenhauser, *J. Org. Chem.* **31**, 2321 (1966).

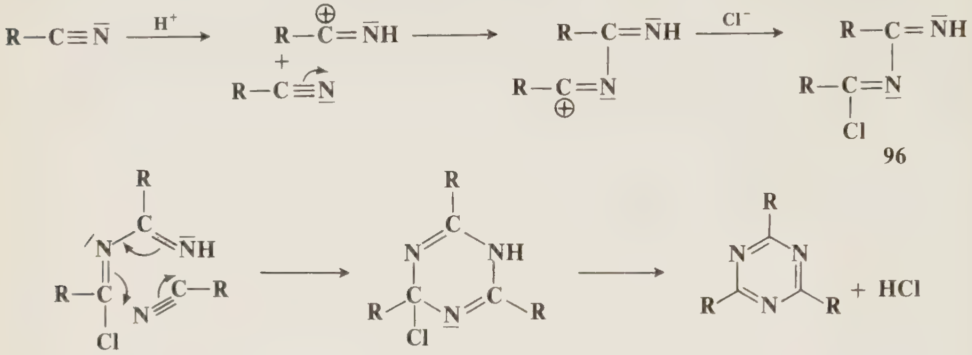
[460] Monagle, *J. Org. Chem.* **27**, 3851 (1962); Appleman and DeCarlo, *J. Org. Chem.* **32**, 1505 (1967); Ulrich, Tucker, and Sayıgh, *J. Org. Chem.* **32**, 1360 (1967), *Tetrahedron Lett.* 1731 (1967); Ostrogovich, Kerek, Buzás, and Doca, *Tetrahedron* **25**, 1875 (1969).

[461] For reviews, see Tiger, Sarynina, and Entelis, *Russ. Chem. Rev.* **41**, 774–785 (1972); Ulrich and Richter, *Newer Methods Prep. Org. Chem.* **6**, 280–315 (1971).

[462] For reviews of cycloaddition reactions of isocyanates and isothiocyanates, see Arbuzov and Zobova, *Synthesis* 461–476 (1974); Ulrich, "Cycloaddition Reactions of Heterocumulenes," pp. 122–126, Academic Press, Inc., New York, 1967. See also Ulrich, *Acc. Chem. Res.* **2**, 186–192 (1969).

[463] Douglas, Eccles, and Almond, *Can. J. Chem.* **31**, 1127 (1953); Douglas and Burditt, *Can. J. Chem.* **36**, 1256 (1958).

[464] Barltrop, Day, and Bigley, *J. Chem. Soc.* 3185 (1961).

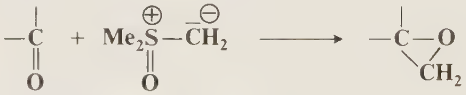


Intermediates of the type **96** have been isolated.

OS **III,** 71.

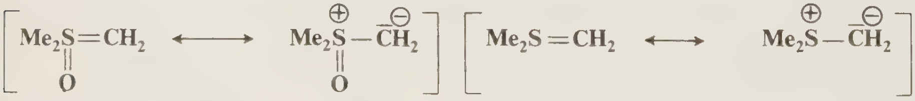
C. Carbon Adding to the Carbon. The reactions in this group (**6-65** to **6-70**) are cycloadditions.

6-65 The Formation of Epoxides from Aldehydes and Ketones



97

Aldehydes and ketones can be converted to epoxides[466] in good yields with the sulfur ylides dimethyloxosulfonium methylide (**97**) and dimethylsulfonium methylide (**98**).[467] For most purposes, **97** is the reagent of choice, because **98** is much less stable and ordinarily must be used as soon as it is formed, while **97** can be stored several days at room temperature. However, when diastereomeric epoxides can be formed, **98** usually attacks from the more hindered and **97** from the less hindered side. Thus, 4-*t*-butylcyclohexanone, treated with **97,** gave exclusively **100** while **98** gave mostly **99.**[468] Another difference in behavior between **97** and **98** is that with α,β-unsaturated ketones, **97** gives only cyclopropanes (reaction **5-53**), while **98** gives oxirane formation. Other



97 98

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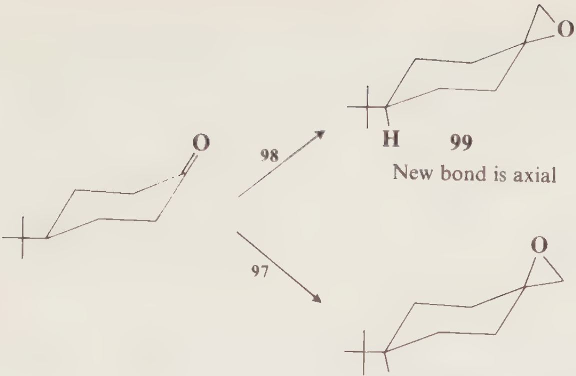
[465] Grundmann, Weisse, and Seide, *Justus Liebigs Ann. Chem.* **577,** 77 (1952); Grundmann, *Chem. Ber.* **97,** 3262 (1964).

[466] For a review, see Berti, *Top. Stereochem.* **7,** 93-251 (1973), pp. 218-232.

[467] For reviews, see House, Ref. 124, pp. 709-733; Durst, *Adv. Org. Chem.* **6,** 285 388 (1969), pp. 321-330; Johnson, Ref. 369, pp. 328 351. For a monograph on sulfur ylides, see Trost and Melvin, "Sulfur Ylides," Academic Press, Inc., New York, 1975.

[468] Corey and Chaykovsky, *J. Am. Chem. Soc.* **87,** 1353 (1965).

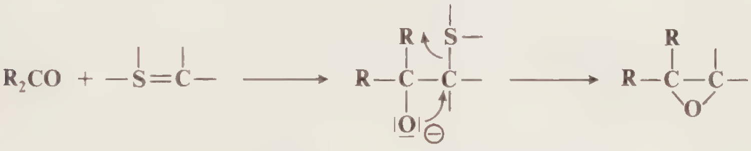


99 New bond is axial

100 New bond is equatorial

sulfur ylides have been used in an analogous manner, to transfer CHR or CR_2. Among these are $Me_2S{=}CHCOO^-$,[469] $Me_2S{=}CHPh$,[470] $Me_2S{=}CH{-}$vinyl,[471] and **117** on p. 795,[472] which transfer $CHCOO^-$, CHPh, CH—vinyl and CPh_2, respectively. Nitrogen-containing sulfur ylides, such as **118** on p. 795 and $Ph(Me_2N)SO{=}CH_2$, as well as carbanions like **120** on p. 795, have also been used.[473]

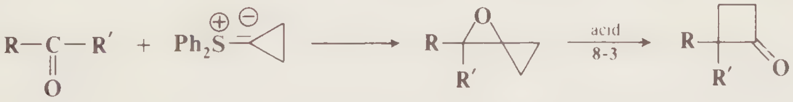
The generally accepted mechanism is



101

which is similar to that of the reaction of sulfur ylides with C=C double bonds (**5-53**).[474] The stereochemical difference in the behavior of **97** and **98** has been attributed to formation of the betaine **101** being reversible for **97** but not for the less stable **98**, so that the more hindered product is the result of kinetic control and the less hindered of thermodynamic control.[475]

The reaction of ketones with the ylide diphenylsulfoniumcyclopropylide (**102**) gives the oxaspiropentanes **103**, which, when treated with a proton or a Lewis acid, rearrange (reaction



102 **103** **104**

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[469] Adams, Hoffman, and Trost, *J. Org. Chem.* **35**, 1600 (1970).

[470] Yoshimine and Hatch, *J. Am. Chem. Soc.* **89**, 5831 (1967).

[471] Braun, Huber, and Kresze, *Tetrahedron Lett.* 4033 (1973).

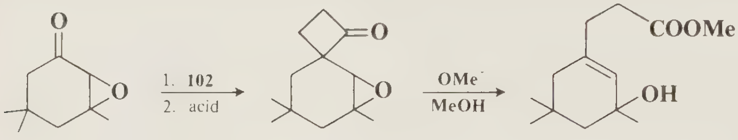
[472] Corey, Jautelat, and Oppolzer, *Tetrahedron Lett.* 2325 (1967).

[473] Johnson, Haake, and Schroeck, *J. Am. Chem. Soc.* **92**, 6594 (1970); Johnson, Kirchhoff, Reischer, and Katekar, *J. Am. Chem. Soc.* **95**, 4287 (1973); Johnson and Janiga, *J. Am. Chem. Soc.* **95**, 7692 (1973); Johnson, *Acc. Chem. Res.* **6**, 341–347 (1973).

[474] See for example, Townsend and Sharpless, *Tetrahedron Lett* 3313 (1972); Johnson, Schroeck, and Shanklin, *J. Am. Chem. Soc.* **95**, 7424 (1973).

[475] Johnson, Schroeck, and Shanklin, Ref. 474.

8-3) to the cyclobutanones **104**.[476] In some cases **103** is not isolated, but directly rearranges to **104**. The overall conversion of ketone to **104** is called *spiroannulation* (see reaction **6-42** for another way of accomplishing this conversion). When the reaction is applied to epoxy ketones, e.g., **105**, the cyclobutanone product **106** is easily cleaved by refluxing with NaOMe in MeOH

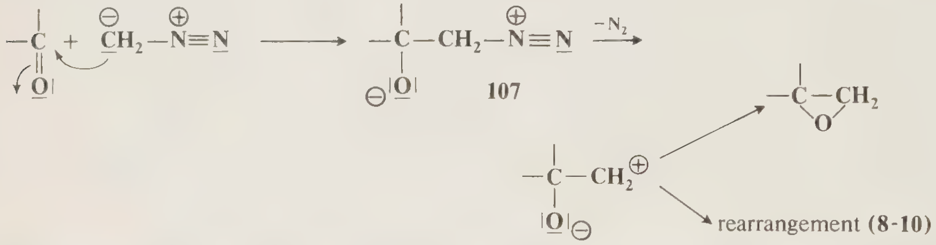


105 **106**

(similar to reaction **2-44**).[477] The net result of this method (called *secoalkylation*) is the addition of a $^-$C—C—COOR unit to the carbonyl group.

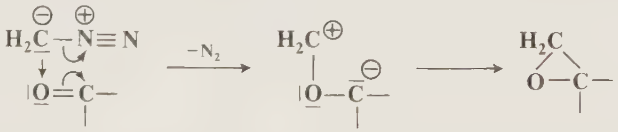
Phosphorus ylides do not give this reaction, but give reaction **6-47** instead.

Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,[478] most commonly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction **8-10**). The reaction can be carried out with many aldehydes, ketones, and quinones. A mechanism that accounts for both products is



107

Compound **107** or nitrogen-containing derivatives of it have sometimes been isolated. The last two steps leading to the epoxide (SN) may be concerted. It is also possible that another pathway exists,[479] which can lead only to the epoxide:



In one case, the conversion of a lactone C=O to the corresponding epoxide (with diazomethane) has been reported.[480]

Dihalocarbenes and carbenoids, which readily add to C=C bonds (reaction **5-53**), do not add to the C=O bonds of ordinary aldehydes and ketones, though addition to highly halogenated compounds, e.g., CCl_3CHO, CF_3COCF_3, to give the corresponding halogenated epoxides has been reported.[481]

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[476] Trost, *Acc. Chem. Res.* **7**, 85–92 (1974), *Top. Curr. Chem.* **41**, 1–29 (1973); Trost, LaRochelle and Bogdanowicz, *Tetrahedron Lett.* 3449 (1970); Trost and Bogdanowicz, *J. Am. Chem. Soc.* **93**, 3773 (1971), **95**, 2038, 5311 (1973); Bogdanowicz and Trost, *Tetrahedron Lett.* 887 (1972); Trost, Preckel, and Leichter, *J. Am. Chem. Soc.* **97**, 2224 (1975).

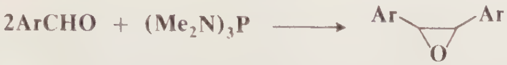
[477] Trost and Bogdanowicz, *J. Am. Chem. Soc.* **94**, 4777 (1972); Bogdanowicz, Ambelang, and Trost, *Tetrahedron Lett.* 923 (1973).

[478] For reviews, see Gutsche, *Org. React.* **8**, 364–429 (1954); Eistert, *Newer Methods Prep. Org. Chem.* **1**, 521–537 (1948).

[479] Bradley, Cowell, and Ledwith, *J. Chem. Soc.* 4334 (1964); Gutsche and Bowers, *J. Org. Chem.* **32**, 1203 (1967).

[480] Dean and Park, *J. Chem. Soc., Chem. Commun.* 162 (1974).

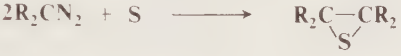
Symmetrical epoxides can be prepared by treatment of aromatic aldehydes with hexamethylphosphorus triamide.[482] It is likely that the betaine $(Me_2N)_2\overset{+}{P}CHRO^-$ is formed first and then attacks a second molecule of the aldehyde.



See also reaction **6-45**.

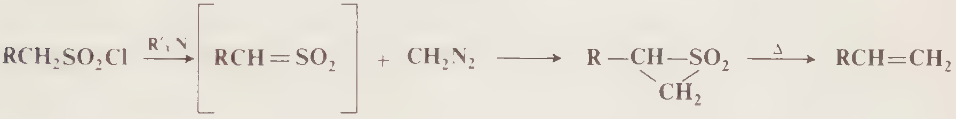
OS V, 755.

6-66 The Formation of Episulfides and Episulfones[483]



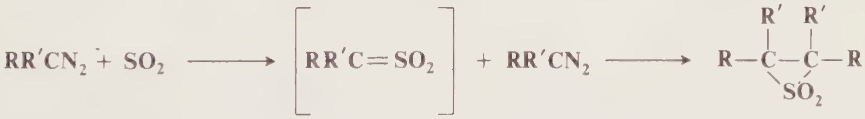
Diazoalkanes, treated with sulfur, give episulfides.[484] It is likely that $R_2C{=}S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in reaction **6-65**. Thioketones *do* react with diazoalkanes to give episulfides.[485] Thioketones have also been converted to episulfides with sulfur ylides.[468]

Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine) give episulfones (**109**).[486] The base removes HCl from the sulfonyl halide to produce



108 **109**

the highly reactive sulfene (**108**) (reaction **7-14**), which then adds CH_2. The episulfone can then be heated to give off SO_2 (reaction **7-23**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH{=}CH_2$.[487] In a related reaction, diazoalkanes, treated with sulfur dioxide, give the symmetrical episulfones **110**.



110

OS V, 231, 877.

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[481] Seyferth, Tronich, Smith, and Hopper, *J. Organomet. Chem.* **67,** 341 (1974).

[482] Mark, *J. Am. Chem. Soc.* **85,** 1884 (1963), *Org. Synth.* V, 358; Newman and Blum, *J. Am. Chem. Soc.* **86,** 5598 (1964).

[483] For a review, see Muller and Hamer, "1,2-Cycloaddition Reactions," pp. 57 86, Interscience Publishers, New York, 1967.

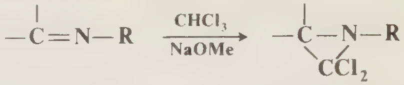
[484] Schönberg and Frese, *Chem. Ber.* **95,** 2810 (1962).

[485] For example, see Paquer and Vialle, *Bull. Soc. Chim. Fr.* 3327 (1969); Beiner, Lecadet, Paquer, Thuillier, and Vialle, *Bull. Soc. Chim. Fr.* 1979 (1973); Beiner, Lecadet, Paquer, and Thuillier, *Bull. Soc. Chim. Fr.* 1983 (1973).

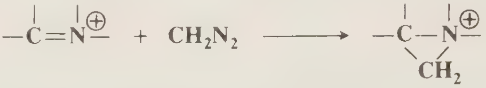
[486] Opitz and Fischer, *Angew. Chem. Int. Ed. Engl.* **4,** 70 (1965) [*Angew. Chem.* **77,** 41].

[487] For a review of this process, see Fischer, *Synthesis* 393–404 (1970).

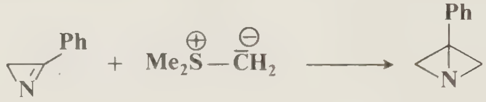
6-67 The Formation of Aziridines



There are a few reports in the literature of the preparation of aziridines by the addition of a divalent species to a C=N bond, analogous to reactions **6-65** and **6-66**.[488] In the example shown above[489] the attacking species is probably dichlorocarbene. Iminium ions[210] have been converted to quaternary aziridinium salts with diazomethane:[490]

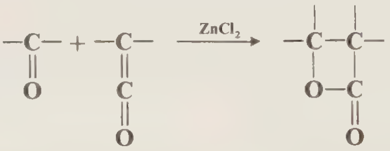


The reaction has also been performed with sulfur ylides.[468] An interesting example of the latter procedure is the reaction of 3-phenyl-2H-azirine with **98**, to give the azabicyclobutane **111**.[491]

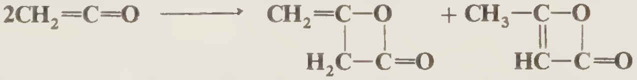


98 **111**

6-68 The Formation of β-Lactones and Oxetanes



Aldehydes, ketones, and quinones react with ketenes to give β-lactones, diphenylketene being used most often.[492] The reaction is catalyzed by Lewis acids, and without them most ketones do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. Ketene adds to another molecule of itself:



This dimerization is so rapid that ketene does not form β-lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases the major dimerization product is not the β-lactone, but a cyclobutenone (see p. 778). However, the proportion of ketene which dimerizes to β-lactone can be increased by the addition of catalysts such as triethylamine or triethyl phosphite $(EtO)_3P$.[493]

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[488] For reviews, see Kirmse, "Carbene Chemistry," 2d ed., pp. 412–414, Academic Press, Inc., New York, 1971; Anselme, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Ref. 31, pp. 300–305; Ref. 483, pp. 5–14, 32–38.

[489] Fields and Sandri, *Chem. Ind.* (*London*) 1216 (1959); see also Seyferth, Tronich, and Shih, *J. Org. Chem.* **39,** 158 (1974).

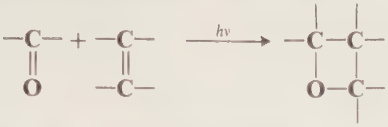
[490] Leonard, Jann, Paukstelis, and Steinhardt, *J. Org. Chem.* **28,** 1499 (1963).

[491] Hortmann and Robertson, *J. Am. Chem. Soc.* **89,** 5974 (1967).

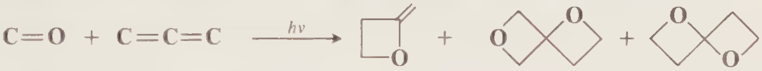
[492] For reviews, see Ref. 483, pp. 139–168; Ulrich, Ref. 462, pp. 39–45, 64–74; Lacey, *Adv. Org. Chem.* **2,** 213–263 (1960), pp. 226–228; Zaugg, *Org. React.* **8,** 305–363 (1954), pp. 313–315.

[493] Farnum, Johnson, Hess, Marshall, and Webster, *J. Am. Chem. Soc.* **87,** 5191 (1965); Elam, *J. Org. Chem.* **32,** 215 (1967).

Ordinary aldehydes and ketones can add to olefins, under the influence of uv light, to give

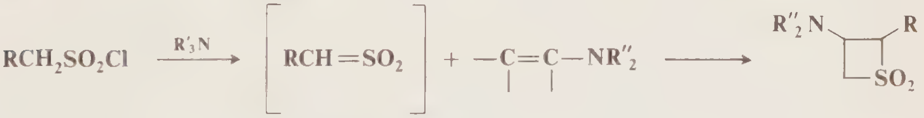


oxetanes. This reaction, called the *Paterno-Büchi reaction*,[494] is similar to the photochemical dimerization of olefins discussed at reaction **5-52.** In general, the mechanism consists of the addition of an excited state of the carbonyl compound to the ground state of the olefin, in many cases through the intermediacy of an exciplex[495] (p. 785). Both singlet (S_1)[496] and n,π^* triplet[497] states have been shown to add to olefins to give oxetanes. Yields in the Paterno-Büchi reaction are variable, ranging from very low to fairly high (80 to 90%). There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet-triplet photosensitization, see p. 219). In most cases quinones react normally with alkenes, giving oxetane products, but other α,β-unsaturated ketones usually give preferential cyclobutane formation (reaction **5-52**). Aldehydes and ketones also add photochemically to allenes, to give the corresponding alkylideneoxetanes and dioxaspiro compounds:[498]



OS **III,** 508; **V,** 456. For the reverse reaction, see OS **V,** 679.

6-69 The Formation of Thietane 1,1-Dioxides



Sulfene

The highly reactive sulfenes,[499] generated from sulfonyl chlorides (reaction **7-14**) add to enamines to give thietane 1,1-dioxides.[500] Yields are generally good. Other electron-rich olefins, e.g., vinyl ethers and ketene acetals $R_2C{=}C(OR')_2$, also react with sulfenes to give the corresponding thietane 1,1-dioxides.[501] The reaction has been extended to ynamines, to give the corresponding unsaturated four-membered heterocycles, called thietene 1,1-dioxides.[502]

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[494] For reviews, see Arnold, *Adv. Photochem.* **6,** 301–423 (1968); Chapman and Lenz, *Org. Photochem.* **1,** 283–321 (1967), pp. 283–294; Yang, *Pure Appl. Chem.* **9,** 591–596 (1964); Ref. 483, pp. 111–139.

[495] See for example Schore and Turro, *J. Am. Chem. Soc.* **97,** 2482 (1975).

[496] See for example, Turro, Wriede, Dalton, Arnold, and Glick, *J. Am. Chem. Soc.* **89,** 3950 (1967); Turro, *Pure Appl. Chem.* **27,** 679–705 (1971); Yang, *Photochem. Photobiol.* **7,** 767 (1968); Yang, Kimura, and Eisenhardt, *J. Am. Chem. Soc.* **95,** 5058 (1973); Singer, Davis, and Muralidharan, *J. Am. Chem. Soc.* **91,** 897 (1969); Barltrop and Carless, *J. Am. Chem. Soc.* **94,** 1951, 8761 (1972).

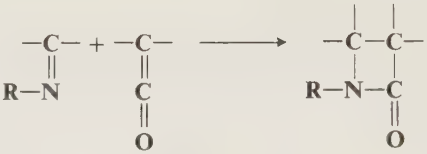
[497] Arnold, Hinman, and Glick, *Tetrahedron Lett.* 1425 (1964); Yang, Nussim, Jorgenson, and Murov, *Tetrahedron Lett.* 3657 (1964).

[498] Arnold and Glick, *Chem. Commun.* 813 (1966); Gotthardt, Steinmetz, and Hammond, *Chem. Commun.* 480 (1967), *J. Org. Chem.* **33,** 2774 (1968).

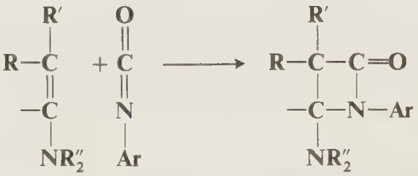
[499] For reviews of sulfenes, including their use in this reaction, see King, *Acc. Chem. Res.* **8,** 10–17 (1975); Nagai and Tokura, *Int. J. Sulfur Chem., Part B* 207–216 (1972); Truce and Liu, *Mech. React. Sulfur Compd.* **4,** 145–154 (1969); Opitz, *Angew. Chem. Int. Ed. Engl.* **6,** 107–123 (1967) [*Angew. Chem.* **79,** 161–177]; Wallace, *Q. Rev., Chem. Soc.* **20,** 67–74 (1966); Ref. 483, pp. 206–240; Ulrich, Ref. 462, pp. 286–305.

[500] For examples, see Stork and Borowitz, *J. Am. Chem. Soc.* **84,** 313 (1962); Opitz and Adolph, *Angew. Chem. Int. Ed. Engl.* **1,** 113 (1962) [*Angew. Chem.* **74,** 77]; Paquette, *J. Org. Chem.* **29,** 2851, 2854 (1964); Paquette and Rosen, *J. Am. Chem. Soc.* **89,** 4102 (1967); Siegl and Johnson, *J. Org. Chem.* **35,** 3657 (1970); Truce and Rach, *J. Org. Chem.* **39,** 1109 (1974).

6-70 The Formation of β-Lactams



Ketenes add to imines to give β-lactams.[503] The reaction is generally carried out with ketenes of the form $R_2C{=}C{=}O$. It has not been successfully applied to $RCH{=}C{=}O$, except when these are generated in situ by decomposition of a diazo ketone (the Wolff rearrangement, reaction **8-9**) in the presence of the enamine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. β-Lactams have also been prepared in the opposite manner: by the addition[462] of enamines to isocyanates:[504]



The reactive compound chlorosulfonyl isocyanate[505] $ClSO_2NCO$ forms β-lactams even with unactivated alkenes,[506] as well as with allenes,[507] conjugated dienes,[508] and cyclopropenes.[509]

OS V, 673.

Addition to Isonitriles[510]

Addition to $R-\overset{\oplus}{N}\equiv\overset{\ominus}{C}$ is not simply a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and in Chapter 15. In these additions the electrophile and the nucleophile *both add to the carbon*. No species adds to the nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons:

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[501] For example, see Truce and Norell, *J. Am. Chem. Soc.* **85**, 3231 (1963); Opitz, Rieth, and Walz, *Tetrahedron Lett.* 5269 (1966).

[502] Truce, Bavry, and Bailey, *Tetrahedron Lett.* 5651 (1968).

[503] For reviews of the formation of β-lactams by 2 + 2 cycloaddition reactions, see Mukerjee and Srivastava, *Synthesis* 327–346 (1973); Sheehan and Corey, *Org. React.* **9**, 388–408 (1957), pp. 395–399; Ref. 483, pp. 173–206; Anselme, Ref. 488, pp. 305–309; Ulrich, Ref. 462, pp. 75–83, 135–152.

[504] For example, see Perelman and Mizsak, *J. Am. Chem. Soc.* **84**, 4988 (1962); Opitz and Koch, *Angew. Chem. Int. Ed. Engl.* **2**, 152 (1963) [*Angew. Chem.* **75**, 167].

[505] For reviews of the reactions of this compound, see Rasmussen and Hassner, *Chem. Rev.* **76**, 389–408 (1976); Graf, *Angew. Chem. Int. Ed. Engl.* **7**, 172–182 (1968) [*Angew. Chem.* **80**, 179–189].

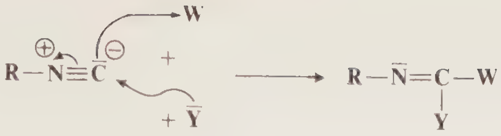
[506] Graf, *Justus Liebigs Ann. Chem.* **661**, 111 (1963); Bestian, *Pure Appl. Chem.* **27**, 611–634 (1971).

[507] Moriconi and Kelly, *J. Am. Chem. Soc.* **88**, 3657 (1966), *J. Org. Chem.* **33**, 3036 (1968); see also Martin, Carter, and Chitwood, *J. Org. Chem.* **36**, 2225 (1971).

[508] Moriconi and Meyer, *J. Org. Chem.* **36**, 2841 (1971); Malpass and Tweddle, *J. Chem. Soc., Chem. Commun.* 1247 (1972).

[509] Moriconi, Kelly, and Salomone, *J. Org. Chem.* **33**, 3448 (1968).

[510] For a monograph, see Ugi, "Isonitrile Chemistry," Academic Press, Inc., New York, 1971. For a review, see Hoffmann, Marquarding, Kliimann, and Ugi, in Rappoport, Ref. 212, pp. 853–883.

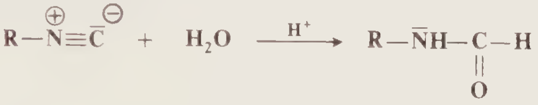


$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\overline{C}} + W + \overline{Y} \longrightarrow R-\overline{N}=\underset{\underset{Y}{|}}{C}-W$$

112

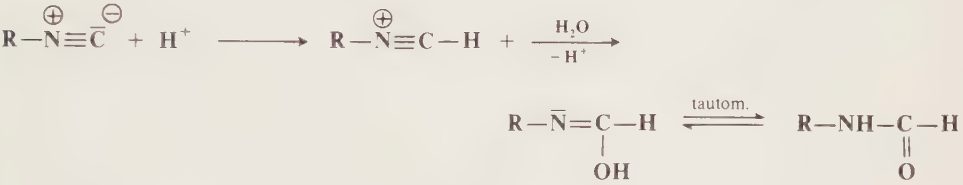
In most of the reactions considered below, **112** undergoes a further reaction, so that the product is of the form $R-\overline{N}H-\overset{|}{\underset{|}{C}}-$.

6-71 The Addition of Water to Isonitriles



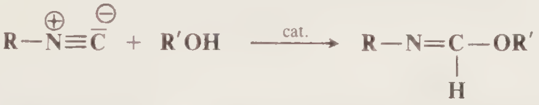
$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\overline{C}} + H_2O \xrightarrow{H^+} R-\overline{N}H-\underset{\underset{O}{\|}}{C}-H$$

Formamides can be prepared by the acid-catalyzed addition of water to isonitriles. The mechanism is probably[511]



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\overline{C}} + H^+ \longrightarrow R-\overset{\oplus}{N}\equiv C-H + \xrightarrow[-H^+]{H_2O} R-\overline{N}=\underset{\underset{OH}{|}}{C}-H \overset{\text{tautom.}}{\rightleftharpoons} R-NH-\underset{\underset{O}{\|}}{C}-H$$

6-72 The Addition of Alcohols, Mercaptans, Amines, or Azides to Isonitriles



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\overline{C}} + R'OH \xrightarrow{\text{cat.}} R-N=\underset{\underset{H}{|}}{C}-OR'$$

Isonitriles[512] are generally inert to alcohols in the absence of a catalyst, but the addition can be made to take place in high yields to give an alkyl formimidate by the use of certain catalysts, among them metallic copper and Cu(I) or Cu(II) oxides.[513] These compounds, as well as certain metallic salts, also catalyze the corresponding addition of primary and secondary amines, to give formamidines (respectively $RN=CHNHR'$ and $RN=CHNR'_2$).[514] In a similar manner, mercaptans give alkyl thioformamides $RN=CHSR'$.[515] Isonitriles react with azides $R'N_3$, in a reaction catalyzed with iron pentacarbonyl to give unsymmetrical carbodiimides $RN=C=NR'$.[516]

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[511] Drenth, *Recl. Trav. Chim. Pays-Bas* **81,** 319 (1962); Lim and Stein, *Can. J. Chem.* **49,** 2455 (1971).

[512] For a review of the reactions in this section, see Saegusa and Ito, in Ugi, Ref. 510, pp. 67–71.

[513] Saegusa, Ito, Kobayashi, Hirota, and Takeda, *Can. J. Chem.* **47,** 1217 (1969).

[514] Saegusa, Ito, Kobayashi, Hirota, and Yoshioka, *Tetrahedron Lett.* 6121 (1966), *Bull. Chem. Soc. Jpn.* **42,** 3310 (1969); Saegusa, Murase, and Ito, *Tetrahedron* **27,** 3795 (1971), *J. Org. Chem.* **36,** 2876 (1971).

[515] Saegusa, Kobayashi, Hirota, Okumura, and Ito, *Bull. Chem. Soc. Jpn.* **41,** 1638 (1968); Saegusa, Kobayashi, and Ito, *J. Org. Chem.* **35,** 2118 (1970).

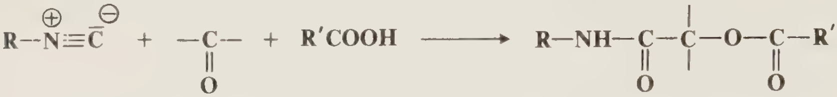
[516] Saegusa, Ito, and Shimiza, *J. Org. Chem.* **35,** 3995 (1970).

6-73 The Reduction of Isonitriles

$$R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{\bar{C}} \quad + \quad LiAlH_4 \longrightarrow R{-}NH{-}CH_3$$

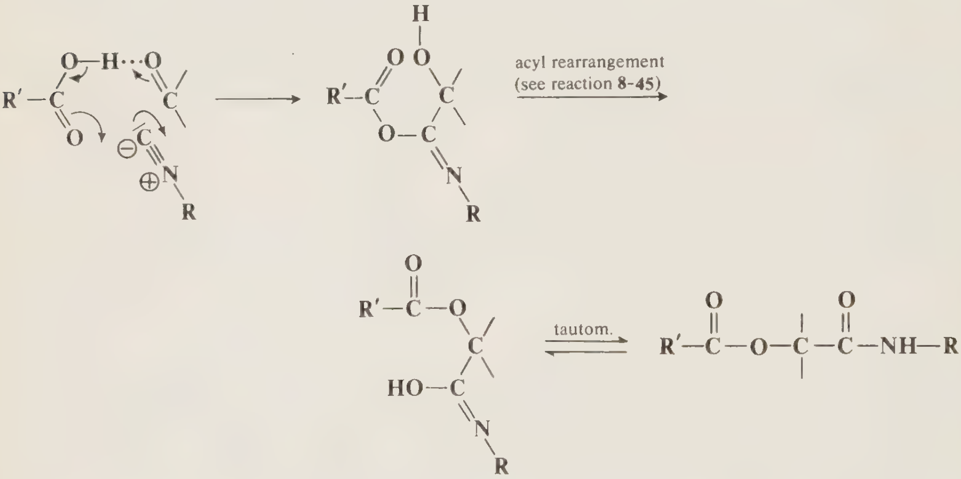
Isonitriles have been reduced to N-methylamines with lithium aluminum hydride as well as with other reducing agents.

6-74 The Passerini and Ugi Reactions[517]



$$R{-}\overset{\oplus}{N}{\equiv}\overset{\ominus}{\bar{C}} \quad + \quad -\underset{\underset{O}{\|}}{C}- \quad + \quad R'COOH \longrightarrow R{-}NH{-}\underset{\underset{O}{\|}}{C}{-}\overset{|}{\underset{|}{C}}{-}O{-}\underset{\underset{O}{\|}}{C}{-}R'$$

When an isonitrile is treated with a carboxylic acid and an aldehyde or ketone, an α-acyloxy amide is prepared. This is called the *Passerini reaction*, and the following mechanism has been postulated:



If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*, abbreviated 4 CC), the product is the corresponding bisamide $R'{-}\underset{\underset{O}{\|}}{C}{-}NH{-}\overset{|}{\underset{|}{C}}{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R$ (from NH_3) or $R'{-}\underset{\underset{O}{\|}}{C}{-}NR''{-}\overset{|}{\underset{|}{C}}{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R$ (from a primary amine $R''NH_2$). This product probably arises from a reaction between the carboxylic acid, the isonitrile, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. The use of an N-protected amino acid or peptide as the carboxylic acid component and/or the use of an isonitrile containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.[518] When a secondary amine R''_2NH is used, the initial addition product (**113**) cannot undergo an acyl rearrangement of the same type. In methanol the acyl group cleaves, and the product is an α-amino amide, while in chloroform the acyl group migrates to the *other* nitrogen

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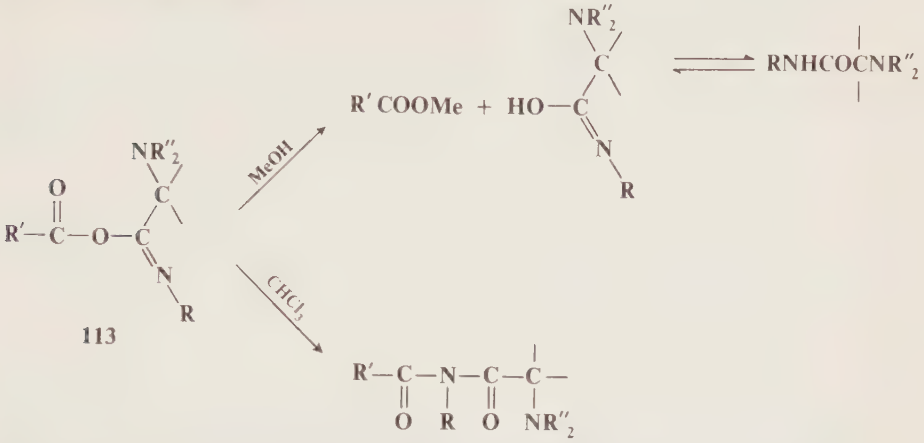
[517] For reviews, see Marquarding, Gokel, Hoffmann, and Ugi, Ref. 510, pp. 133–143; Gokel, Lüdke, and Ugi, Ref. 510, pp. 145–199, 252–254; Ugi, *Angew. Chem. Int. Ed. Engl.* **1**, 8–21 (1962) [*Angew. Chem.* **74**, 9–22], *Newer Methods Prep. Org. Chem.* **4**, 1–36 (1968).

[518] For reviews, see Gokel, Hoffmann, Kleimann, Klusacek, Lüdke, Marquarding, and Ugi, Ref. 510, pp. 201–215; Ugi, *Intra-Sci. Chem. Rep.* **5**, 229–261 (1971), *Rec. Chem. Prog.* **30**, 289–311 (1969).

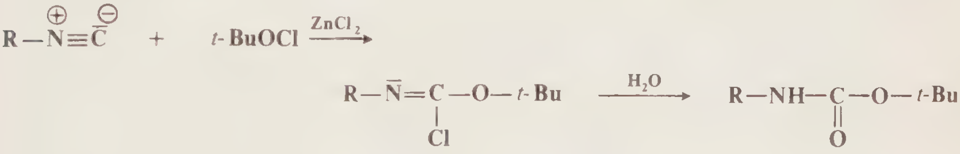


113

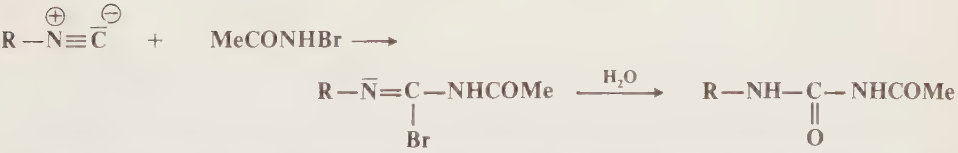
and the product is an imide containing a tertiary amine function. Intermediates corresponding to **113** have been isolated in certain cases where the carbonyl component is an aldehyde and the amine a primary amine.[519]

The Ugi reaction can also be carried out with an isonitrile, an aldehyde or ketone, and ammonia or an amine, but with some other YH substituting for the carboxylic acid, e.g., H_2O, HN_3, HNCO.

6-75 The Addition of O- and N-Halides to Isonitriles



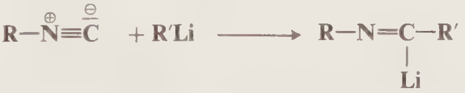
$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + t\text{-BuOCl} \xrightarrow{ZnCl_2} R-\bar{N}=\underset{Cl}{\underset{|}{C}}-O-t\text{-Bu} \xrightarrow{H_2O} R-NH-\underset{O}{\underset{\|}{C}}-O-t\text{-Bu}$$



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + \text{MeCONHBr} \longrightarrow R-\bar{N}=\underset{Br}{\underset{|}{C}}-\text{NHCOMe} \xrightarrow{H_2O} R-NH-\underset{O}{\underset{\|}{C}}-\text{NHCOMe}$$

Alkyl hypochlorites and N-halo amides add to isonitriles to give, after hydrolysis, carbamates and N-acylureas (ureides), respectively.[520]

6-76 The Formation of Metalated Aldimines



$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + R'Li \longrightarrow R-N=\underset{Li}{\underset{|}{C}}-R'$$

Isonitriles which do not contain an α-hydrogen react with alkyllithium compounds, as well as with

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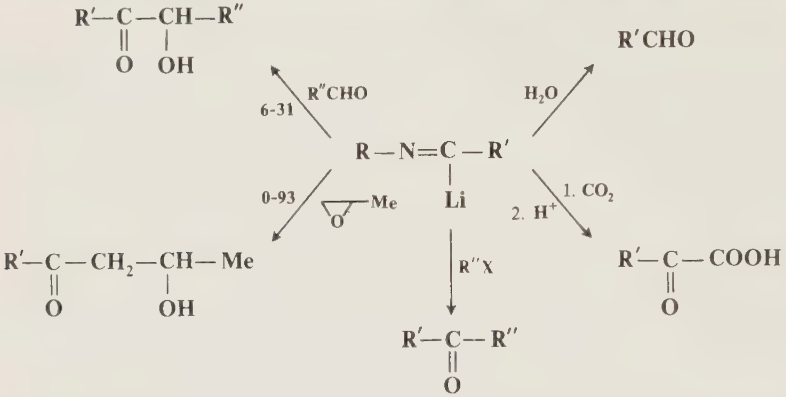
[519] Marquarding, *Angew. Chem. Int. Ed. Engl.* **12,** 79 (1973) [*Angew. Chem.* **85,** 92].

[520] Okano, Ito, Shono, and Oda, *Bull. Chem. Soc. Jpn.* **36,** 1314 (1963).

Grignard reagents, to give lithium (or magnesium) aldimines.[521] These metalated aldimines are versatile nucleophiles and react with various substrates as follows (see also reaction **8-28**):

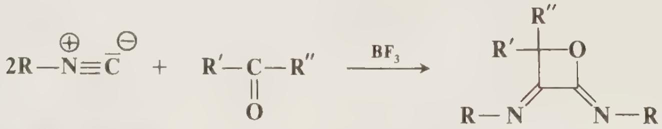


The reaction therefore constitutes a method for converting an organometallic compound R′M to an aldehyde R′CHO (see also reaction **2-31**), an α-keto acid, a ketone R′COR (see also reaction **2-31**), an α-hydroxy ketone, or a β-hydroxy ketone. In each case the C=N bond is hydrolyzed to a C=O bond (reaction **6-2**). In a reaction similar to **6-72**, aryl or α,β-unsaturated isonitriles can also be treated with active-hydrogen compounds (ZCH_2Z') in the presence of copper oxides or other copper catalysts, to give the corresponding enamines, formed by tautomerization of the initially formed aldimines.[522] Z and Z′ may be RCO, ROOC, NC, or Ph:

$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} + ZCH_2Z' \xrightarrow{\text{cat.}} ZZ'CH-CH=NR \xrightarrow{\text{tautom.}} ZZ'C=CH-NHR$$

OS **51,** 31.

6-77 The Formation of Four-membered Rings[523]



Isonitriles react with aldehydes and ketones in the presence of catalytic amounts[524] of BF_3 to give 2,3-diiminooxetanes.[525] These compounds can be treated with HCl to give the ring-opened compounds R′R″CClC(=NR)CONHR, which in turn can be hydrolyzed to β-chloro-α-keto amides R′R″CClCOCONHR.[526] Similar four-membered ring compounds have been prepared by reaction of isonitriles with C=N bonds[527] and with the C=C bonds of the electron-deficient olefin $(CF_3)_2C=C(CN)_2$.[528]

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[521] Niznik, Morrison, and Walborsky, *J. Org. Chem.* **39,** 600 (1974); Hirowatari and Walborsky, *J. Org. Chem.* **39,** 604 (1974).

[522] Saegusa, Murase, and Ito, *Synth. Commun.* **1,** 145 (1971).

[523] For a review, see Zeeh, *Synthesis* 65–73 (1969).

[524] If equimolar amounts of BF_3 are used, ring-opened products are obtained: Müller and Zeeh, *Justus Liebigs Ann. Chem.* **696,** 72 (1966); Zeeh and Müller, *Justus Liebigs Ann. Chem.* **715,** 47 (1968).

[525] Saegusa, Taka-Ishi, and Fujii, *J. Polym. Sci., Part B: Polym. Lett.* **5,** 785 (1967), *Tetrahedron* **24,** 3795 (1968); Zeeh, *Tetrahedron Lett.* 113 (1969); Kabbe, *Angew. Chem. Int. Ed. Engl.* **7,** 389 (1968) [*Angew. Chem.* **80,** 406], *Chem. Ber.* **102,** 1404 (1969).

[526] Kabbe, *Chem. Ber.* **102,** 1410 (1969).

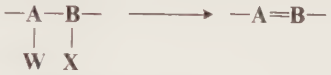
[527] Deyrup, Vestling, Hagan, and Yun, *Tetrahedron* **25,** 1467 (1969).

[528] Middleton, *J. Org. Chem.* **30,** 1402 (1965).

Seventeen

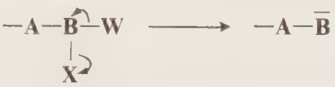
Eliminations

When two groups are lost from adjacent atoms so that a new double (or triple) bond is formed

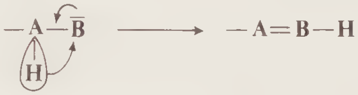


$$\underset{\displaystyle\text{W}}{-\text{A}}-\underset{\displaystyle\text{X}}{\text{B}}- \longrightarrow -\text{A}{=}\text{B}-$$

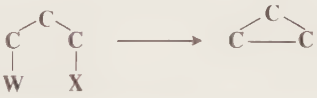
the reaction is called *β elimination*, with one atom called the α- and the other the β-atom. In an α elimination both groups are lost from the same atom, to give a carbene (or a nitrene):



This species may undergo a variety of reactions (see p. 182), but only when a hydrogen is present on A can a new double bond be formed, by a hydride shift:



In a γ elimination, a three-membered ring is formed:



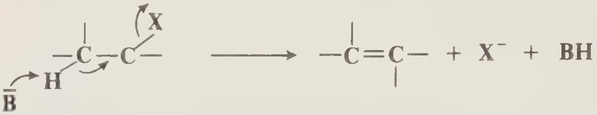
Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring (X—Y—Z → X—Z + Y). Such reactions are called *extrusion reactions*. This chapter discusses β elimination and (beginning on p. 956) extrusion reactions, except that β eliminations in which X and W are both hydrogen are oxidation reactions and are treated in Chapter 19.

MECHANISMS AND ORIENTATION

β elimination reactions may be divided into two types, with one type taking place largely in solution and the other (pyrolytic eliminations) mostly in the gas phase. In the reactions in solution one group leaves with its electrons, and the other without, the latter most often being hydrogen. In these cases we refer to the former group as the leaving group or nucleofuge. For pyrolytic eliminations there are two principle mechanisms, one a cyclic and the other a free-radical pathway. A few photochemical eliminations are also known (the most important is Norrish type II cleavage of ketones, discussed on p. 221), but these are not generally of synthetic importance[1] and will not be discussed further. In most β eliminations the new bonds are C=C or C≡C, and our discussion of mechanisms is largely confined to these cases.[2] Mechanisms in solution (E2, E1, E1cB) are discussed first.

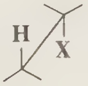
The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the two groups depart simultaneously, with the proton being pulled off by a base:

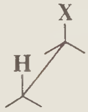


The mechanism thus takes place in one step and kinetically is second order: first order in substrate and first order in base. It is analogous to the SN2 mechanism (p. 266) and often competes with it. With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the SN2 mechanism, the leaving group may be positive or neutral, and the base may be negatively charged or neutral.

Among the evidence for the existence of the E2 mechanism are: (1) the reaction displays the proper second-order kinetics; and (2) when the leaving hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.[3] However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB p. 904). The most compelling evidence for the E2 mechanism is found in stereochemical studies.[4] As will be illustrated in the examples below, the E2 mechanism is stereospecific: the five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be trans to one another (A), with a dihedral angle of 180°, or



A



B

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[1] For synthetically useful examples of Norrish type II cleavage, see Neckers, Kellogg, Prins, and Schoustra, *J. Org. Chem.* **36,** 1838 (1971).

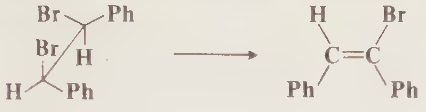
[2] For monographs on elimination mechanisms, see Saunders and Cockerill, "Mechanisms of Elimination Reactions," John Wiley & Sons, New York, 1973; Banthorpe, "Elimination Reactions," American Elsevier Publishing Company, Inc., New York, 1963. For reviews, see More O'Ferrall, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 2, pp. 609–675, John Wiley & Sons, New York, 1973; Cockerill, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 163–372, American Elsevier Publishing Company, Inc., New York, 1973; Saunders, *Acc. Chem. Res.* **9,** 19–25 (1976); Stirling, *Essays Chem.* **5,** 123–149 (1973); Bordwell, *Acc. Chem. Res.* **5,** 374–381 (1972); Fry, *Chem. Soc. Rev.* **1,** 163–210 (1972); LeBel, *Adv. Alicyclic Chem.* **3,** 195–290 (1971); Bunnett, *Survey Prog. Chem.* **5,** 53–93 (1969), *Angew. Chem. Int. Ed. Engl.* **1,** 225–235 (1962) [*Angew. Chem.* **74,** 731–741]; in Patai, "The Chemistry of Alkenes," vol. 1, Interscience Publishers, New York, 1964, the articles by Saunders, pp. 149–201 (eliminations in solution) and by Maccoll, pp. 203–240 (pyrolytic eliminations); Grigor'eva and Kucherov, *Russ. Chem. Rev.* **31,** 18–35 (1962); Köbrich, *Angew. Chem. Int. Ed. Engl.* **4,** 49–68 (1965), pp. 59–63 [*Angew. Chem.* **77,** 75–94] (for the formation of triple bonds).

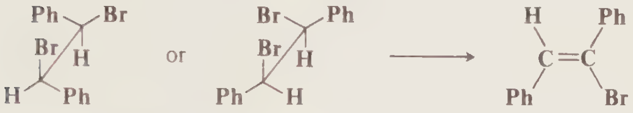
[3] See, for example, Saunders and Edison, *J. Am. Chem. Soc.* **82,** 138 (1960); Shiner and Smith, *J. Am. Chem. Soc.* **80,** 4095 (1958), **83,** 593 (1961). For a review of isotope effects in elimination reactions, see Fry, Ref. 2.

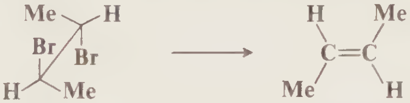
[4] For reviews, see Coke, *Sel. Org. Transform.* **2,** 269–307 (1972); Sicher, *Angew. Chem. Int. Ed. Engl.* **11,** 200–214 (1972) [*Angew. Chem.* **84,** 177–191], *Pure Appl. Chem.* **25,** 655–666 (1971); Saunders and Cockerill, Ref. 2, pp. 105–163; Cockerill, Ref. 2, pp. 217–235; More O'Ferrall, Ref. 2, pp. 630–640.

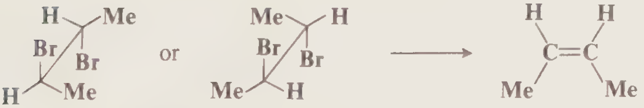
they may be cis (**B**), with a dihedral angle of 0°.[5] Conformation **A** is called *anti-periplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti elimination*. Conformation **B** is *syn-periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below) anti elimination is in most cases greatly favored over syn elimination, probably because **A** is a staggered conformation (p. 125) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. A few of the many known examples of predominant or exclusive anti elimination follow.

1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the trans olefin. This stereospecific result, which was obtained in 1904,[6] demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds which have a meso form. Anti elimination requires that an erythro *dl* pair (or either isomer) give the cis olefin, and the threo *dl* pair (or either isomer) give the trans isomer, and this has been found many times. Anti elimination has also been demonstrated in cases where the positive leaving group is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (reaction 7-27). In this case the meso compound gave the trans olefin and the *dl* pair the cis:[7]


meso cis


dl pair trans


meso trans


dl pair cis

2. In open-chain compounds the molecule can usually adopt that conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane, seven meso forms and a *dl* pair (see p. 118).

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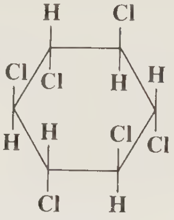
[5] DePuy, Morris, Smith, and Smat, *J. Am. Chem. Soc.* **87**, 2421 (1965).

[6] Pfeiffer, *Z. Phys. Chem.* **48**, 40 (1904).

[7] Winstein, Pressman, and Young, *J. Am. Chem. Soc.* **61**, 1645 (1939).

Four of the meso compounds and the *dl* pair (all that were then known) were subjected to elimination of HCl. Only one of these (**1**, called the β-isomer) has no Cl trans to an H. Of the other isomers, the fastest elimination rate was about 3 times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.[8] This result demonstrates that with these compounds anti elimination is greatly favored over syn elimination, though the latter must be taking place on **1**, very slowly, to be sure.



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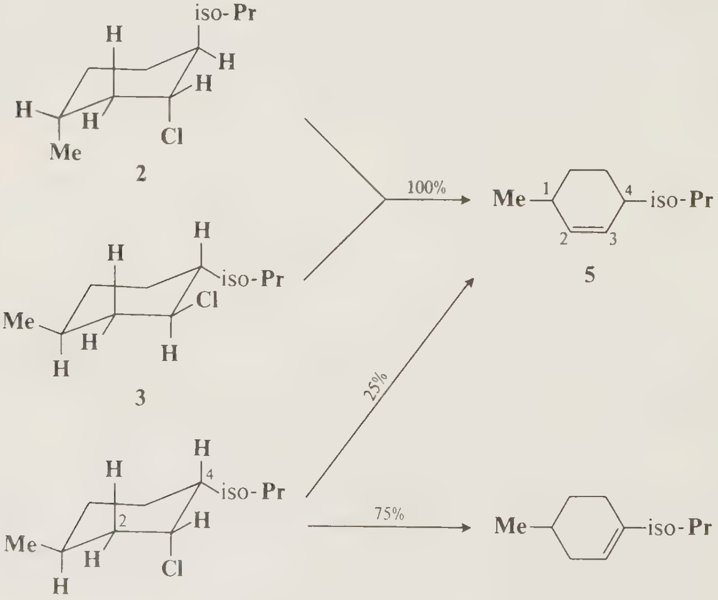
3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. However, there is an additional restriction. Adjacent trans groups on a six-membered ring may be diaxial or diequatorial (p. 129), and the molecule is generally free to adopt either conformation, though one may have a higher energy than the other. Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily interpretable on this basis. Menthyl chloride has two chair conformations, **2** and **3**. **3**, in which the three substituents are all equatorial, is the more stable. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial, and there are axial hydrogens on



2 **3** **4** **5** **6**

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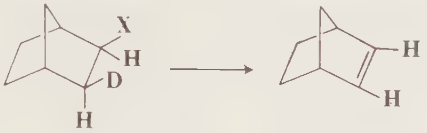
[8] Cristol, *J. Am. Chem. Soc.* **69**, 338 (1947); Cristol, Hause, and Meek, *J. Am. Chem. Soc.* **73**, 674 (1951).

both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination, and the olefin produced is predominantly **6** (**6** **5** ratio is about 3 : 1), in accord with Zaitsev's rule (p. 910). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination, and Zaitsev's rule is free to operate. However, for menthyl chloride, elimination is much slower, and the product is entirely the anti-Zaitsev **5**. It is slow because the unfavorable conformation **2** has to be achieved before elimination can take place, and the product is **5** because only on this side is there an axial hydrogen.[9]

4. That anti elimination also occurs in the formation of triple bonds is shown by elimination from *cis*- and *trans*-HOOC—CH=CCl—COOH. In this case the product in both cases is HOOCC≡CCOOH, but the trans isomer reacts about 50 times as fast as the cis compound.[10]

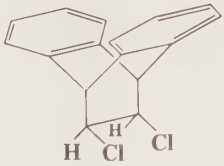
Some examples of syn elimination have been found in molecules where H and X could not achieve an anti-periplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.[11] Similar results were obtained with other leaving groups, and with bicyclo[2.2.2] compounds.[12] In these cases the exo X group cannot achieve a dihedral angle of 180° with the endo β-hydrogen because of the rigid structure of the molecule. The dihedral angle here is about 120°. These leaving groups prefer syn elimination, with a dihedral angle of about 0°, to anti elimination, with an angle of about 120°.



7

2. The molecule **8** is a particularly graphic example of the need for a planar transition state. In **8** each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups were not required, anti elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be about 120°, and elimination of HCl from **8** is much slower than from corresponding nonbridged compounds.[13] (Note that syn elimination from **8** is even less likely than anti elimination.) Syn elimination can take place from the trans isomer of **8** (dihedral angle about 0°), and this isomer reacted about 8 times faster than **8**.[13]



8

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[9] Hughes, Ingold, and Rose, *J. Chem. Soc.* 3839 (1953).

[10] Michael, *J. Prakt. Chem.* **52,** 308 (1895). See also Marchese, Naso, and Modena, *J. Chem. Soc. B* 958 (1968).

[11] Kwart, Takeshita, and Nyce, *J. Am. Chem. Soc.* **86,** 2606 (1964).

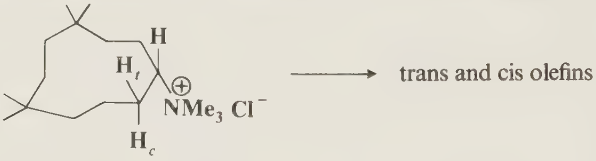
[12] For example, see Bird, Cookson, Hudec, and Williams, *J. Chem. Soc.* 410 (1963); Stille, Sonnenberg, and Kinstle, *J. Am. Chem. Soc.* **88,** 4922 (1966); Coke and Cooke, *J. Am. Chem. Soc.* **89,** 6701 (1967); DePuy, Naylor, and Beckman, *J. Org. Chem.* **35,** 2750 (1970); Brown and Liu, *J. Am. Chem. Soc.* **92,** 200 (1970); Sicher, Pánkova, Závada, Kniežo, and Orahovats, *Collect. Czech. Chem. Commun.* **36,** 3128 (1971).

[13] Cristol and Hause, *J. Am. Chem. Soc.* **74,** 2193 (1952).

The examples so far given illustrate two points. (1) Anti elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, anti elimination is greatly slowed or prevented entirely. (2) For the simple systems so far discussed syn elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

As noted in Chapter 4 (p. 145), six-membered rings are the only ones among rings of four to thirteen members in which strain-free anti-periplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cooke and Coke subjected cycloalkyltrimethylammonium hydroxides to elimination (reaction **7-6**) and found the following percentages of syn elimination with ring size: four-membered, 90%; five-membered, 46%; six-membered, 4%; seven-membered, 31 to 37%.[14] It should be noted that the NMe_3^+ group has a greater tendency to syn elimination than do other common leaving groups such as OTs, Cl, and Br.

Other examples of syn elimination have been found in medium-ring compounds, where both cis and trans olefins are possible (p. 115). As an illustration, we can look at experiments performed by Závada, Svoboda, and Sicher.[15] These workers subjected 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**) to elimination and obtained mostly *trans*- but also some *cis*-tetramethylcyclodecenes as products. (Note that *trans*-cyclodecenes, though stable, are less stable than the cis isomers.) In order to determine the stereochemistry of the reaction, they repeated the elimination, this time using deuterated substrates. They found that when **9** was deuterated in the trans position (H_t = D), there was a substantial isotope effect in the formation of *both* cis and trans olefins but when **9** was deuterated in the cis position (H_c = D), there was *no* isotope effect in the formation of either olefin. Since an isotope effect is expected for an E2 mechanism,[16] these results indicated that *only* the trans hydrogen (H_t) was lost, whether the product was the cis or the trans isomer.[17] This in turn means that *the cis isomer must have been formed by anti elimination and the trans isomer by syn elimination.* (Anti elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the C—H_t and C—NMe_3^+ bonds are syn-periplanar.) This remarkable result, called the *syn-anti dichotomy*, has also been demonstrated by other types of evidence.[18] The fact that syn elimination in this case predominates over anti (as indicated by the formation of trans isomer in greater amounts than cis) has been explained by conformational factors.[19] The syn-anti dichotomy has also been found in other medium-ring systems (8- to 12-



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[14] Cooke and Coke, *J. Am. Chem. Soc.* **90**, 5556 (1968). See also Coke, Smith and Britton, *J. Am. Chem. Soc.* **97**, 4323 (1975).

[15] Závada, Svoboda, and Sicher, *Tetrahedron Lett.* 1627 (1966), *Collect. Czech. Chem. Commun.* **33**, 4027 (1968).

[16] Other possible mechanisms, such as E1cB (p. 904) or α′,β elimination (p. 930), were ruled out in all these cases by other evidence.

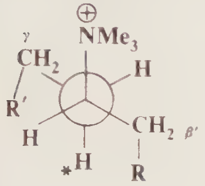
[17] This conclusion has been challenged by Coke, Ref. 4.

[18] Sicher, Závada, and Krupička, *Tetrahedron Lett.* 1619 (1966); Sicher and Závada, *Collect. Czech. Chem. Commun.* **32**, 2122 (1967); Závada and Sicher, *Collect. Czech. Chem. Commun.* **32**, 3701 (1967).

[19] For discussions, see Ref. 4.

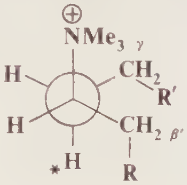
membered),[20] though the effect is greatest for 10-membered rings. With leaving groups,[21] the extent of this behavior decreases in the order $NMe_3^+ > OTs > Br > Cl$, which parallels steric requirements. When the leaving group is uncharged, syn elimination is favored by strong bases and by weakly ionizing solvents.[22]

Syn elimination and the syn-anti dichotomy have also been found in open-chain systems, though to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, about 67% of the reaction followed the syn-anti dichotomy.[23] The effects of leaving group, base strength, and solvents are similar. In general syn elimination in open-chain systems is only important in cases where substituents are found on both the β'- and the γ-carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors which cause these results are not completely understood, but the following conformational effects have been proposed as a partial explanation.[24] The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



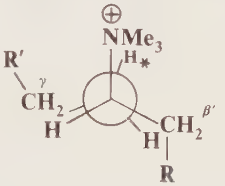
C

anti ⟶ trans



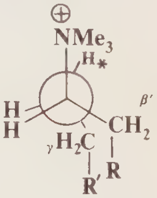
D

anti ⟶ cis



E

syn ⟶ trans



F

syn ⟶ cis

In order for an E2 mechanism to take place a base must approach the proton marked *. In **C** this proton is shielded on both sides by R and R′. In **D** the shielding is on only one side. Therefore, when anti elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti → trans route should be diminished more than the anti → cis route. When syn elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway, and syn elimination should generally give the trans isomer. In general, deviations from the syn-anti dichotomy are greater on the trans side than on the cis. Thus, trans olefins are formed partly or mainly by syn elimination, but cis olefins are formed entirely by anti elimination.

It was mentioned above that weakly ionizing solvents promote syn elimination when the leaving group is uncharged. This is probably caused by ion pairing, which is greatest in nonpolar solvents.[24a] Ion pairing can cause syn elimination with a neutral leaving group by means of the

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[20] For example, see Coke and Mourning, *J. Am. Chem. Soc.* **90,** 5561 (1968), where the experiment was performed on cyclooctyltrimethylammonium hydroxide, and *trans*-cyclooctene was formed by a 100% syn mechanism, and *cis*-cyclooctene by a 51% syn and 49% anti mechanism.

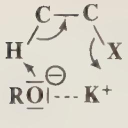
[21] For examples with other leaving groups, see Závada, Krupička, and Sicher, *Chem. Commun.* 66 (1967), *Collect. Czech. Chem. Commun.* **33,** 1393 (1968); Svobada, Závada, and Sicher, *Collect. Czech. Chem. Commun.* **32,** 2104 (1967), **33,** 1415 (1968), Sicher, Jan, and Schlosser, *Angew. Chem. Int. Ed. Engl.* **10,** 926 (1971) [*Angew. Chem.* **83,** 1012].

[22] See for example, Sicher and Závada, *Collect. Czech. Chem. Commun.* **33,** 1278 (1968).

[23] Bailey and Saunders, *Chem. Commun.* 1598 (1968), *J. Am. Chem. Soc.* **92,** 6904 (1970). For other examples of syn elimination and the syn-anti dichotomy in open-chain systems, see Pánková, Sicher, and Závada, *Chem. Commun.* 394 (1967); Závada, Pánková, and Sicher, *Chem. Commun.* 1145 (1968), *Collect. Czech. Chem. Commun.* **37,** 2414 (1972); Pánková, Vítek, Vašíčková, Řeřicha, and Zavada, *Collect. Czech. Chem. Commun.* **37,** 3456 (1972); Pánková and Závada, *Tetrahedron Lett.* 2237 (1973).

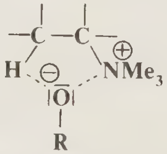
[24] Bailey and Saunders, Ref. 23; Bailey, Montgomery, Chodak, and Saunders, *J. Am. Chem. Soc.* **92,** 6911 (1970).

[24a] For a review of the effect of ion pairing in this reaction, see Bartsch, *Acc. Chem. Res.* **8,** 239–245 (1975).



G

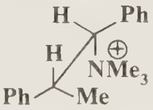
transition state shown in **G**. This effect was graphically illustrated by elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.[25] The ratio of syn to anti elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. But when the crown ether dicyclohexyl-18-crown-6 (p. 82) was added (this compound selectively removes K^+ from the *t*-BuO^- K^+ ion pair and thus leaves *t*-BuO^- as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.[26] However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti elimination.[27] In this case a relatively free base (e.g., PhO^-) can be attracted to the leaving group, putting it in a favorable position for attack on the syn β-hydrogen, while ion pairing would reduce this attraction.



We can conclude that anti elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion-pairing, and other factors cause syn elimination to intervene (and even predominate) in some cases.

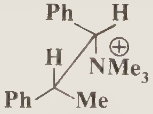
Eclipsing Effects in E2 Eliminations[28]

In the case of (1,2-diphenylpropyl)trimethylammonium ion, the threo *dl* pair (**10**) gave the trans olefin, and the erythro pair (**11**) gave the cis olefin, as expected for stereospecific anti elimination, but the threo pair reacted 57 times faster than the erythro (with OEt^- as the base).[29] For each isomer, the conformation necessary to achieve anti elimination is shown. In the threo isomer,



threo (one of the pair)

10



erythro (one of the pair)

11

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[25] Svoboda, Hapala, and Závada, *Tetrahedron Lett.* 265 (1972).

[26] For other examples of the effect of ion pairing, see Bayne and Snyder, *Tetrahedron Lett.* 571 (1971); Závada and Svoboda, *Tetrahedron Lett.* 23 (1972); Pánková, Svoboda, and Závada, *Tetrahedron Lett.* 2465 (1972); Svoboda and Závada, *Collect. Czech. Chem. Commun.* **37**, 3902 (1972); Bartsch and Wiegers, *Tetrahedron Lett.* 3819 (1972); Bartsch, Mintz, and Parlman, *J. Am. Chem. Soc.* **96**, 4249 (1974); Bartsch and Kayser, *J. Am. Chem. Soc.* **96**, 4346 (1974); Fiandanese, Marchese, Naso, and Sciacovelli, *J. Chem. Soc., Perkin Trans. 2* 1336 (1973); Borchardt, Swanson, and Saunders, *J. Am. Chem. Soc.* **96**, 3918 (1974); Mano, Sera, and Maruyama, *Bull. Chem. Soc. Jpn.* **47**, 1758 (1974).

[27] Borchardt and Saunders, *J. Am. Chem. Soc.* **96**, 3912 (1974).

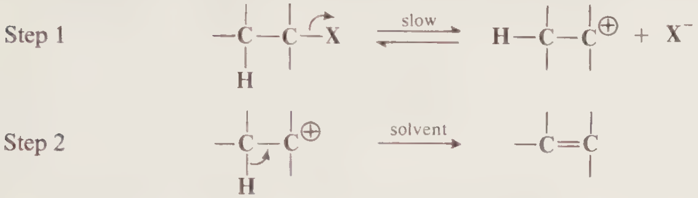
[28] For a discussion, see Cram, in Newman, "Steric Effects in Organic Chemistry," pp. 338–345, John Wiley & Sons, Inc., New York, 1956.

[29] Cram, Greene, and DePuy, *J. Am. Chem. Soc.* **78**, 790 (1956).

the β-phenyl group is completely staggered with respect to the other phenyl group, but in the erythro case the two phenyl groups are gauche. The latter is of course a higher-energy conformation than the former. Therefore, **10** can undergo elimination from its conformer of lowest energy, while **11** must adopt one of the higher-energy conformations, resulting in the lower rate. This type of effect is called an *eclipsing effect*. Note that eclipsing in the transition state, not in the ground state, is what matters.

The E1 Mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbonium ion which rapidly loses a β-proton to a base, usually the solvent:

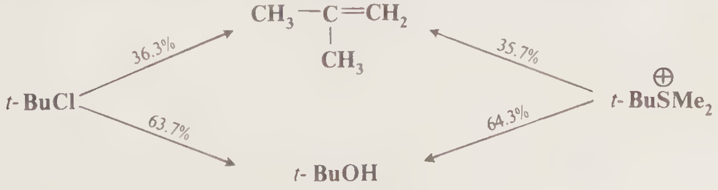


The E1 mechanism normally operates without an *added* base. Just as the E2 mechanism is analogous to and competes with the SN2, so is the E1 mechanism related to the SN1. In fact, the first step of the E1 is exactly the same as that of the SN1 mechanism. The second step differs in that the solvent pulls a proton from the β-carbon of the carbonium ion rather than attacking it at the positively charged carbon, as in the SN1 process. In a pure E1 reaction (that is, without ion pairs, etc.) the product should be completely nonstereospecific, since the carbonium ion is free to adopt its most stable conformation before giving up the proton.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (p. 201), but this point can be easily checked by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does.

2. If the reaction is performed on two molecules which differ only in the leaving group (for example, t-BuCl and $t\text{-Bu}\overset{\oplus}{\text{S}}\text{Me}_2$), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbonium ion is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases, since the nature of the leaving group does not affect the second step. This means that *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3°C in 80% aqueous ethanol, with the following results:[30]



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[30] Cooper, Hughes, Ingold, and MacNulty, *J. Chem. Soc.* 2038 (1948).

Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β-hydrogen compared to attack at a *neutral* chloride as for attack at the β-hydrogen compared to attack at a *positive* SMe_2 group.

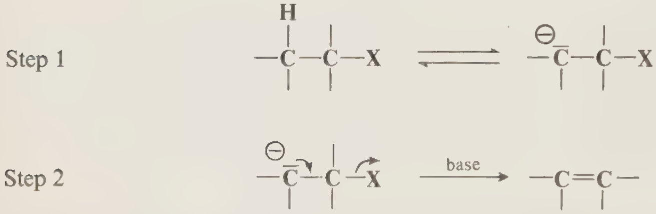
3. Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give olefins where a cis hydrogen must be removed, often in preference to the removal of a trans hydrogen. For example, menthyl chloride (**2**, p. 898), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable olefin (Zaitsev's rule, p. 910) is predominantly formed.

4. If carbonium ions are intermediates, we should expect rearrangements with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

It has been shown that E1 reactions can involve ion pairs, just as is true for SN1 reactions (p. 273).[31] This effect is naturally greatest for nondissociating solvents: it is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (p. 276) extends to elimination reactions too, and that the SN1, SN2, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least on occasion.[32]

The E1cB Mechanism[33]

In the E1 mechanism, X leaves first and then H. In the E2 mechanism the two groups leave at the same time. There is a third possibility: the H leaves first and then the X. This is a two-step process, called the *E1cB mechanism*, or the *carbanion mechanism*, since the intermediate is a carbanion:



The name E1cB comes from the fact that it is the conjugate base of the substrate which is giving up the leaving group (see the SN1cB mechanism, p. 330). We can distinguish three limiting cases: (1) The carbanion returns to starting material faster than it forms product; step 1 is reversible. (2) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case step 1 is essentially irreversible. (3) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here too, step 1 is essentially irreversible. Investigations of the reaction order are generally not very useful (except for case 3 which is first order) because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.[34] We would expect the greatest likelihood of finding the E1cB mechanism in substrates which have (a) a poor nucleofuge and (b) an acidic hydrogen, and most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism.

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[31] Cocivera and Winstein, *J. Am. Chem. Soc.* **85**, 1702 (1963); Smith and Goon, *J. Org. Chem.* **34**, 3127 (1969); Bunnett and Eck, *J. Org. Chem.* **36**, 897 (1971); Humski, Sendijarević, and Shiner, *J. Am. Chem. Soc.* **95**, 7722 (1973), **96**, 6187 (1974).

[32] Sneen and Robbins, *J. Am. Chem. Soc.* **91**, 3100 (1969); Sneen, *Acc. Chem. Res.* **6**, 46–53 (1973). See, however, McLennan, *J. Chem. Soc., Perkin Trans. 2* 1577 (1972).

[33] For reviews, see Hunter, *Intra-Sci. Chem. Rep.* 7(3), 19–26 (1973); McLennan, *Q. Rev., Chem. Soc.* **21**, 490–506 (1967).

1. The first step of the E1cB mechanism (case 1) involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, then recovered starting material should contain deuterium. This was found to be the case in the treatment of $Cl_2C{=}CHCl$ with NaOD to give $ClC{\equiv}CCl$. When the reaction was stopped before completion, there *was* deuterium in the recovered olefin.[35] A similar result was found for pentahaloethanes.[36] These substrates are relatively acidic. In both cases the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (p. 243). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $PhCH_2CH_2Br$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.[37] If this type of evidence is a guide, then it may be inferred that the E1cB mechanism (case 1) is quite rare, at least for eliminations yielding C=C double bonds. It has been pointed out[38] that even where deuterium exchange is taking place, the mechanism need not necessarily be E1cB since the exchange could be occurring without the carbanion necessarily being the species which loses the leaving group. Although this point is formally correct, it is difficult to see how it could happen in practice. A carbanion would be expected to lose the nucleofuge much more easily than the substrate.

2. We have predicted that the E1cB mechanism would be most likely to be found with substrates containing acidic hydrogens and poor leaving groups. Compounds of the type ZCH_2CH_2OPh, where Z is an electron-withdrawing group (e.g., NO_2, $SMe_2{}^+$, CN, COOR, etc.), belong to this category, because OPh is a very poor leaving group (p. 331). There is evidence to show that the mechanism here is indeed E1cB.[39] Isotope effects, measured for $MeSOCD_2CH_2OPh$ and $Me_2\overset{\oplus}{S}CD_2CH_2OPh$ with NaOD in D_2O, are about 0.7. This is compatible with an E1cB mechanism (case 1 or 3, though in this system case 1 is more likely) but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that k_H/k_D is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in this system is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^-. Note that elimination from substrates of the type $RCOCH_2CH_2Y$ is the reverse of Michael-type addition to C=C bonds. We have seen (p. 678) that such addition involves initial attack by a nucleophile Y and subsequent attack by a proton. Thus the initial loss of a proton from substrates of this type (that is, an E1cB mechanism) is in accord with the principle of microscopic reversibility.[40]

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[34] Case 2 cannot be distinguished from E2 by this means, because it has the identical rate law: Rate = k[substrate][B]. The rate law for case 1 is different: Rate = k[substrate][B] [BH], but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

[35] Houser, Bernstein, Miekka, and Angus, *J. Am. Chem. Soc.* **77**, 6201 (1955).

[36] Hine, Wiesboeck, and Ghirardelli, *J. Am. Chem. Soc.* **83**, 1219 (1961); Hine, Wiesboeck, and Ramsay, *J. Am. Chem. Soc.* **83**, 1222 (1961).

[37] Skell and Hauser, *J. Am. Chem. Soc.* **67**, 1661 (1945).

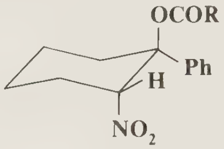
[38] Breslow, *Tetrahedron Lett.* 399 (1964).

[39] Crosby and Stirling, *J. Chem. Soc. B* 671, 679 (1970); Redman and Stirling, *Chem. Commun.* 633 (1970); Cann and Stirling, *J. Chem. Soc., Perkin Trans. 2* 820 (1974). For similar examples, see Fedor, *J. Am. Chem. Soc.* **91**, 908 (1969); More O'Ferrall and Slae, *J. Chem. Soc. B* 260 (1970); More O'Ferrall, *J. Chem. Soc. B* 268 (1970).

[40] Patai, Weinstein, and Rappoport, *J. Chem. Soc.* 1741 (1962).

It has been suggested that all base-initiated elimination reactions wherein the proton is activated by strong electron-withdrawing groups proceed by carbanion mechanisms.[41] It may also be recalled that benzyne formation (p. 589) can also occur by such a process.

3. Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is case 2. One way to make this distinction is to study the effect of a change in leaving group.[42] Such a change should have a large effect on the E2 reaction (because the C—X bond is broken in the rate-determining step) but not in case 2 of the E1cB mechanism. A change in leaving group in elimination from **12,** from R = Me to R = CH_2Br, resulted in only a threefold acceleration,[43] which is much less than expected for an E2 mechanism.[44] Note that in this substrate, carbanion formation is strongly favored because of the powerful electron-withdrawing nitro group.



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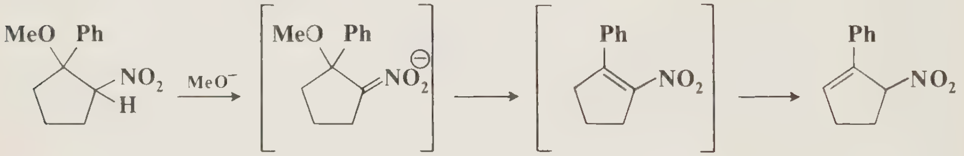
4. An example of an E1cB mechanism (case 3) has been found with the substrate **13,** which when treated with methoxide ion undergoes elimination to **15,** which is unstable under the reaction conditions and rearranges as shown.[45] Among the evidence for the proposed mechanism in this case were kinetic and isotope effect results, as well as the spectral detection of **14.**[46]



13 **14** **15**

5. In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes (most often case 1).

There is evidence that some E1cB mechanisms may involve carbanion ion pairs, e.g.,[47]

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[41] Bordwell, Vestling, and Yee, *J. Am. Chem. Soc.* **92,** 5950 (1970); Bordwell, Ref. 2.

[42] For a demonstration of case 2 by another method, see McLennan and Wong, *J. Chem. Soc., Perkin Trans. 2* 526, 1373 (1974).

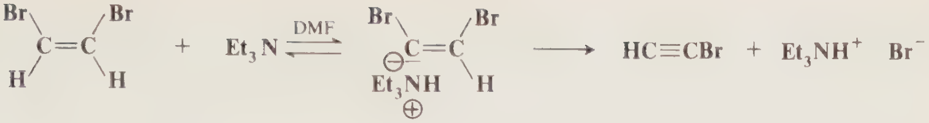
[43] Bordwell, Vestling, and Yee, Ref. 41.

[44] For other examples of the effect of leaving group on rate as evidence for E1cB mechanisms, see Cavestri and Fedor, *J. Am. Chem. Soc.* **92,** 4610 (1970); Fedor and Glave, *J. Am. Chem. Soc.* **93,** 985 (1971); Bordwell, Weinstock, and Sullivan, *J. Am. Chem. Soc.* **93,** 4728 (1971); Marshall, Thomas, and Stirling, *J. Chem. Soc., Chem. Commun.* 940 (1975).

[45] Bordwell, Yee, and Knipe, *J. Am. Chem. Soc.* **92,** 5945 (1970).

[46] For other examples of this mechanism, see Rappoport, *Tetrahedron Lett.* 3601 (1968); Berndt, *Angew. Chem. Int. Ed. Engl.* **8,** 613 (1969) [*Angew. Chem.* **81,** 567]; Hoz, Albeck, and Rappoport, *Tetrahedron Lett.* 3511 (1972); Albeck, Hoz, and Rappoport, *J. Chem. Soc., Perkin Trans. 2* 1248 (1972).

[47] Kwok, Lee, and Miller, *J. Am. Chem. Soc.* **91,** 468 (1969). See also Lord, Naan, and Hall, *J. Chem. Soc. B* 220 (1971); Rappoport and Shohamy, *J. Chem. Soc. B* 2060 (1971); Fiandanese, Marchese, and Naso, *J. Chem. Soc., Chem. Commun.* 250 (1972); Koch, Dahlberg, Toczko, and Solsky, *J. Am. Chem. Soc.* **95,** 2029 (1973); Hunter, Lin, McIntyre, Shearing, and Zvagulis, *J. Am. Chem. Soc.* **95,** 8327 (1973); Hunter and Shearing, *J. Am. Chem. Soc.* **95,** 8333 (1973); Ahlberg, *Chem. Scr.* **4,** 33 (1973); Ahlberg and Bengtsson, *Chem. Scr.* **6,** 45 (1974).



The E1-E2-E1cB Spectrum

In the three mechanisms so far considered the similarities are greater than the differences. In each case there is a leaving group which comes off with its pair of electrons and another group (usually hydrogen) which comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton comes off first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept may be expressed by the question: In the transition state, which bond (C—H or C—X) has undergone more cleavage?[48] Bunnett[2] has suggested that the words *paenecarbonium* and *paenecarbanion* be used to refer to E2 transition states near the E1 and E1cB extremes, respectively.

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.[49] For example, $CH_3CH_2\overset{\oplus}{N}Me_3$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $PhCH_2CH_2\overset{\oplus}{N}Me_3$ gave a corresponding value of 1.009.[50] It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C—N bond is not so greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that, in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with $\overset{\oplus}{S}R_2$ leaving groups, by the use of $^{32}S/^{34}S$ isotope effects.[51] The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,[52] although interpretation of these results is clouded by the fact that β-hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the β-hydrogen from the β-carbon to the base increases[53] (recall—p. 205—that isotope effects are greatest when the proton is half-transferred in the transition state) and by the possibility of secondary isotope effects (e.g., the presence of a β-deuterium or tritium may cause the leaving group to depart more slowly). Other isotope effect studies have involved labeled α- or β-carbon, labeled α-hydrogen, or labeled base.[49]

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[48] For discussions, see Saunders, *Acc. Chem. Res.* Ref. 2; Bunnett, Ref. 2; Saunders and Cockerill, Ref. 2, pp. 47–104; Bordwell, Ref. 2.

[49] For a review, see Fry, Ref. 2.

[50] Ayrey, Bourns, and Vyas, *Can. J. Chem.* **41**, 1759 (1963). Also see Simon and Müllhofer, *Chem. Ber.* **96**, 3167 (1963), **97**, 2202 (1964), *Pure Appl. Chem.* **8**, 379, 536 (1964); Smith and Bourns, *Can. J. Chem.* **48**, 125 (1970).

[51] Saunders and Zimmerman, *J. Am. Chem. Soc.* **86**, 3789 (1964); Saunders, Cockerill, Ašperger, Klasinc, and Stefanović, *J. Am. Chem. Soc.* **88**, 848 (1966); Cockerill and Saunders, *J. Am. Chem. Soc.* **89**, 4985 (1967).

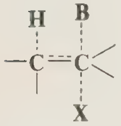
[52] For example, see Saunders and Edison, *J. Am. Chem. Soc.* **82**, 138 (1960); Hodnett and Sparapany, *Pure Appl. Chem.* **8**, 385, 537 (1964); Finley and Saunders, *J. Am. Chem. Soc.* **89**, 898 (1967); Ghanbarpour and Willi, *Justus Liebigs Ann. Chem.* 1295 (1975); Simon and Müllhofer, Ref. 50.

[53] For an example of this effect, see Cockerill, *J. Chem. Soc. B* 964 (1967).

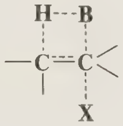
Another way to study the position of a given reaction on the spectrum involves the use of β-aryl substitution. Since a positive Hammett ρ value is an indication of a negatively charged transition state, the ρ value for substituted β-aryl groups should increase as a reaction moves from E1-like to E1cB-like along the spectrum. This has been shown to be the case in a number of studies;[54] for example, ρ values of $ArCH_2CH_2X$ increase as the leaving-group ability of X decreases. A typical set of ρ values was: X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+, 2.75; F, 3.12.[55] As we have seen, decreasing leaving-group ability correlates with increasing E1cB character.

The E2C Mechanism[56]

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases such as RO^- in ROH.[57] In order to explain these results Parker and coworkers have proposed[58] that there is a spectrum[59] of E2 transition states in which the base may interact in the transition state with the α-carbon as well as with the β-hydrogen. At one end of this spectrum is a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the carbon. The E2C mechanism is characterized by strong nucleophiles which are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. **16** represents a transition state which is between these extremes. Additional evidence[60] for the E2C mechanism is derived from Brönsted equation considerations (p. 235), from substrate effects, from isotope effects, and from the effects of solvents on rates.



E2C



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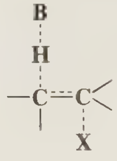
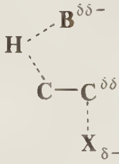


E2H



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However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.[61] McLennan has suggested that the transition state is that shown as **17**.[61a] An ion-pair mechanism has also been proposed.[62] Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists which is characterized by second-order attack by weak bases.[63] These reactions also have the following general characteristics:[64] (1) They are favored by good leaving groups; (2) they are favored by polar aprotic solvents; (3) the reactivity order is tertiary > secondary > primary, which is the opposite of the normal E2 order (p. 914); (4) the elimination is always anti (syn elimination is not found), but in cyclohexyl systems, a diequatorial anti elimination is about as favorable as a diaxial anti elimination (unlike the normal E2 reaction, p. 898); (5) they follow Zaitsev's rule (p. 910) where this does not conflict with the requirement for anti elimination.

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[54] Saunders, Bushman, and Cockerill, *J. Am. Chem. Soc.* **90**, 1775 (1968); Oae and Yano, *Tetrahedron* **24**, 5721 (1968); Yano and Oae, *Tetrahedron* **26**, 27, 67 (1970); Baker and Spillett, *J. Chem. Soc. B* 481 (1969); Banger, Cockerill, and Davies, *J. Chem. Soc. B* 498 (1971); Cockerill and Kendall, *J. Chem. Soc., Perkin Trans. 2* 1352 (1973); Blackwell, Buckley, Jolley, and MacGibbon, *J. Chem. Soc., Perkin Trans. 2* 169 (1973); Smith and Tsui, *J. Am. Chem. Soc.* **95**, 4760 (1973), *Can. J. Chem.* **52**, 749 (1974). See also Yoshida, Yano, and Oae, *Tetrahedron* **27**, 5343 (1971); Smith and Tsui, *Tetrahedron Lett.* 917 (1972); 61 (1973).

[55] DePuy and Froemsdorf, *J. Am. Chem. Soc.* **79**, 3710 (1957); DePuy and Bishop, *J. Am. Chem. Soc.* **82**, 2532, 2535 (1960).

[56] For reviews, see McLennan, *Tetrahedron* **31**, 2999–3010 (1975); Ford, *Acc. Chem. Res.* **6**, 410–415 (1973); Parker, *Chem. Technol.* 297–303 (1971).

[57] For example, see Winstein, Darwish, and Holness, *J. Am. Chem. Soc.* **78**, 2915 (1956); de la Mare and Vernon, *J. Chem. Soc.* 41 (1956); Eliel and Ro, *Tetrahedron* **2**, 353 (1958); Bunnett, Davis, and Tanida, *J. Am. Chem. Soc.* **84**, 1606 (1962); Kevill, Coppens, and Cromwell, *J. Am. Chem. Soc.* **86**, 1553 (1964); McLennan, *J. Chem. Soc. B* 705, 709 (1966); Hayami, Ono, and Kaji, *Tetrahedron Lett.* 2727 (1970), *Bull. Chem. Soc. Jpn.* **44**, 1628 (1971).

[58] Parker, Ruane, Biale, and Winstein, *Tetrahedron Lett.* 2113 (1968).

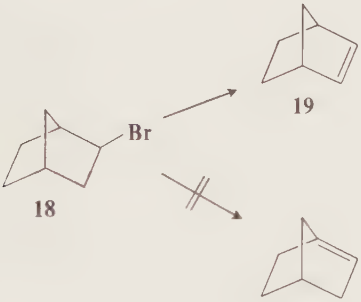
[59] This is apart from the E1-E2-E1cB spectrum.

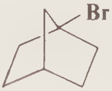
[60] Lloyd and Parker, *Tetrahedron Lett.* 5183 (1968), 5029 (1970); Cook, Parker, and Ruane, *Tetrahedron Lett.* 5715 (1968); Alexander, Ko, Parker, and Broxton, *J. Am. Chem. Soc.* **90**, 5049 (1968); Ko and Parker, *J. Am. Chem. Soc.* **90**, 6447 (1968); Parker, Ruane, Palmer, and Winstein, *J. Am. Chem. Soc.* **94**, 2228 (1972); Biale, Parker, Stevens, Takahashi, and Winstein, *J. Am. Chem. Soc.* **94**, 2235 (1972); Cook, Hutchinson, and Parker, *J. Org. Chem.* **39**, 3029 (1974); Cook, Hutchinson, MacLeod, and Parker, *J. Org. Chem.* **39**, 534 (1974).

Orientation of the Double Bond

With some substrates, a β-hydrogen is present on only one carbon, and (barring rearrangements) there is no doubt as to the identity of the product. For example, $PhCH_2CH_2Br$ can give only $PhCH{=}CH_2$. However, in many other cases two or three olefinic products are possible. In the simplest such case, a *sec*-butyl compound may give either 1-butene or 2-butene. There are a number of rules which enable us to predict, in many instances, which product will predominantly form.[65]

1. No matter what the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (Bredt's rule, see p. 147). This means, for example, not only that **18** gives only **19** and not **20** (indeed **20** is not a known compound), but also that **21** does not undergo elimination.





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[61] Eck and Bunnett, *J. Am. Chem. Soc.* **91,** 3099 (1969) [For a reply to this paper, see Cook and Parker, *Tetrahedron Lett.* 4901 (1969)]; Anderson, Ang, England, McCann, and McLennan, *Aust. J. Chem.* **22,** 1427 (1969); Bunnett and Baciocchi, *J. Org. Chem.* **32,** 11 (1967), **35,** 76 (1970); Jackson, McLennan, Short, and Wong, *J. Chem. Soc., Perkin Trans. 2* 2308 (1972); McLennan and Wong, *Tetrahedron Lett.* 881 (1970), *J. Chem. Soc., Perkin Trans. 2* 279 (1972), 1818 (1974); Bunnett and Eck, *J. Am. Chem. Soc.* **95,** 1897, 1900 (1973); Ford and Pietsek, *J. Am. Chem. Soc.* **97,** 2194 (1975); Loupy, *Bull. Soc. Chim. Fr.* 2662 (1975).

[61a] McLennan, Ref. 56.

[62] Ford, Ref. 56.

[63] For convenience, we will refer to this class of reactions as E2C reactions, though the actual mechanism is in dispute.

[64] Biale, Parker, Smith, Stevens, and Winstein, *J. Am. Chem. Soc.* **92,** 115 (1970); Biale, Cook, Lloyd, Parker, Stevens, Takahashi, and Winstein, *J. Am. Chem. Soc.* **93,** 4735 (1971); Lloyd and Parker, *Tetrahedron Lett.* 637 (1971); Lloyd, Muir, and Parker, *Tetrahedron Lett.* 3015 (1971); Beltrame, Biale, Lloyd, Parker, Ruane, and Winstein, *J. Am. Chem. Soc.* **94,** 2240 (1972); Beltrame, Ceccon, and Winstein, *J. Am. Chem. Soc.* **94,** 2315 (1972).

[65] For a review of orientation in cycloalkyl systems, see Hückel and Hanack, *Angew. Chem. Int. Ed. Engl.* **6,** 534–544 (1967) [*Angew. Chem.* **79,** 555–565].

2. No matter what the mechanism, if there is a double bond (C=C or C=O) already in the molecule which can be in conjugation with the new double bond, then the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see p. 913).

3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible olefins. In such cases *Zaitsev's rule*[66] *operates.* This rule states that *the double bond goes mainly toward the most highly substituted carbon.* That is, a *sec*-butyl compound gives more 2-butene than 1-butene, and 3-bromo-2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus Zaitsev's rule predicts that the olefin predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat-of-combustion data (see p. 26) it is known that olefin stability increases with alkyl substitution, though just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations Zaitsev's rule governs the orientation, whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $Me_2CHCHMe\overset{\oplus}{S}Me_2$ gave 91% of the Zaitsev product and 9% of the other.[67] However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.[68] This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. Thus, E1 elimination of 2,4,4-trimethyl-2-chloropentane ($Me_3CCH_2CMe_2Cl$) gives 81% $Me_3CCH_2CMe{=}CH_2$ and 19% $Me_3CCH{=}CMe_2$.[69] The latter is less stable than the former, because it has a methyl group cis to a *t*-butyl group. An even more striking example of this effect was found in the case of 1,2-diphenyl-2-X-propanes $PhMeCXCH_2Ph$, where E1 or E1-like eliminations were reported to give about 50% $CH_2{=}CPhCH_2Ph$, despite the fact that the double bond of the Zaitsev product (PhMeC=CHPh) is conjugated with two benzene rings.[70]

4. For the anti E2 mechanism a trans proton is necessary, and if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β-hydrogens are available on two or three carbons, two types of behavior are found, depending on substrate structure and on the nature of the leaving group. Some compounds follow Zaitsev's rule and give predominant formation of the most highly substituted olefin, but others follow *Hofmann's rule: the double bond goes mainly toward the least highly substituted carbon.* Though many exceptions are known, the following general statements can be made: In most cases, compounds containing uncharged leaving groups (those which come off as negative ions) follow Zaitsev's rule, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged leaving groups, e.g., NR_3^+, SR_2^+ (those which come off as neutral molecules) follow Hofmann's rule if the substrate is acyclic,[71] but Zaitsev's rule if the leaving group is attached to a six-membered ring.[72]

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[66] Often given the German spelling: Saytzeff.

[67] de la Mare, *Prog. Stereochem.* **1**, 112 (1954).

[68] Cram and Sahyun, *J. Am. Chem. Soc.* **85**, 1257 (1963); Silver, *J. Am. Chem. Soc.* **83**, 3482 (1961).

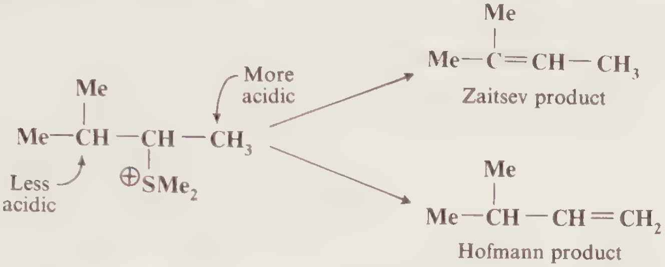
[69] Brown and Moritani, *J. Am. Chem. Soc.* **77**, 3607 (1955).

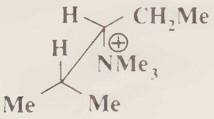
[70] Ho and Smith, *Tetrahedron* **26**, 4277 (1970).

[71] An example of an acyclic quaternary ammonium salt which follows Zaitsev's rule is found in Feit and Saunders, *J. Am. Chem. Soc.* **92**, 5615 (1970).

[72] For examples where Zaitsev's rule is followed with charged leaving groups in cyclohexyl systems, see Gent and McKenna, *J. Chem. Soc.* 137 (1959); Hughes and Wilby, *J. Chem. Soc.* 4094 (1960); Brownlee and Saunders, *Proc. Chem. Soc.* 314 (1961); Booth, Franklin, and Gidley, *J. Chem. Soc. C* 1891 (1968). For a discussion of the possible reasons for this, see Saunders and Cockerill, Ref. 2, pp. 192–193.

Much work has been devoted to searching for the reasons for the differences in orientation. Since Zaitsev orientation almost always gives the thermodynamically more stable isomer, what needs to be explained is why in some cases the less stable Hofmann product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these, by Hughes and Ingold,[73] is that Hofmann orientation is caused by the fact that the acidity of the β-hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $\text{Me}_2\text{CHCHMe}\overset{\oplus}{\text{S}}\text{Me}_2$ gives more of the Hofmann product, and it is the more acidic hydrogen which is removed by the base. Of course, the CH_3 hydrogens would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation of Hughes and Ingold is that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity more manifest than they are with the less electron-withdrawing neutral groups.[73] The explanation of Bunnett[74] is similar. According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more C—H bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1-like, C—X bond breaking is more important, and olefin stability determines the direction of the new double bond. On the other hand, the third explanation, by H. C. Brown, is completely different. In this picture, field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group, and a CHR_2 group is still less easily attacked. In addition, eclipsing effects are more important with increased substitution. For example, if we consider the case of $\text{Me}_2\text{CHCH}(\overset{\oplus}{\text{N}}\text{Me}_3)\text{CH}_2\text{Me}$, there is only one conformation (**22**) leading to Zaitsev elimination in which a hydrogen is trans to the leaving group, and this conformation is not the most stable one since there is a methyl group and not a hydrogen between the two bulky groups CH_2Me and $\overset{\oplus}{\text{N}}\text{Me}_3$. On the other hand, for Hofmann elimination there are two conformations with trans hydrogens (**23** and **24**), and one of these (**23**) is the most stable, since the $CHMe_2$ group is between two hydrogens. In molecules with a CH_3 group, the situation is still more favorable, since elimination can occur from any conformation,





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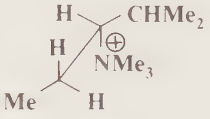

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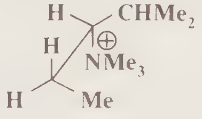

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[73] For summaries of this position, see Ingold, *Proc. Chem. Soc.* 265-274 (1962); Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* 4054 (1960); Banthorpe, Ref. 2, pp. 55–59.

[74] Bunnett, Ref. 2.

and none of them can be gauche. Of course, these steric considerations also apply when the leaving group is neutral, but, according to Brown, they are much less important here because the neutral groups are smaller, do not block access to the hydrogens so much, and make the energy difference between the favorable and unfavorable conformations much less. Brown was able to show that Hofmann elimination increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $CH_3CH_2CH_2CHXCH_3$ was as follows (X listed in order of increasing size): I, 30%; Br, 31%; OTs, 48%; $\overset{\oplus}{S}Me_2$, 87%; SO_2Me, 89%; $\overset{\oplus}{N}Me_3$, 98%.[75] Hofmann elimination was also shown to increase with increase in bulk of the substrate.[76] With large enough compounds, Hofmann orientation can be obtained even with halides, e.g., *t*-amyl bromide gave 89% of the Hofmann product. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.[77]

There is one series of results which is incompatible with the steric explanation: E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.[78] The same order was found for the four 2-halohexanes.[79] Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant Hofmann orientation. Another result which argues against the steric explanation is the effect of changing the nature of the base. Brown and coworkers reported that the proportion of Hofmann orientation increased with increasing size of the base,[80] but in these experiments the solvent and the strength of the base were also changed, so it was not really possible to say that base size alone was responsible for the increasing Hofmann orientation. An experiment in which the effective size of the base was kept constant while its basicity was increased (by using as bases a series of $XC_6H_4O^-$ ions) showed that the percentage of Hofmann elimination increased with increasing base strength, though the size of the base did not change.[81] These results are in accord with the explanation of Bunnett, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free-energy relationships between basicity and percentage of Hofmann elimination,[82] though certain very large bases (e.g., 2,6-di-*t*-butylphenoxide) did not obey the relationships, steric effects becoming important in these cases. Steric effects of the base can also become important in cases where the effective size of the base is increased by base association, when the leaving group is halogen or OTs.[83] Such base association effects are unimportant when the leaving group is NMe_3^+.[84]

5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that Hofmann orientation is greatly favored over Zaitsev.[85]

[75] Brown and Wheeler, *J. Am. Chem. Soc.* **78,** 2199 (1956).

[76] Brown, Moritani, and Nakagawa, *J. Am. Chem. Soc.* **78,** 2190 (1956); Brown and Moritani, *J. Am. Chem. Soc.* **78,** 2203 (1956); Bartsch, *J. Org. Chem.* **35,** 1334 (1970). See also Charton, *J. Am. Chem. Soc.* **97,** 6159 (1975).

[77] For example, see Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* 4054 (1960).

[78] Saunders, Fahrenholtz, Caress, Lowe, and Schreiber, *J. Am. Chem. Soc.* **87,** 3401 (1965). Similar results were obtained by Brown and Klimisch, *J. Am. Chem. Soc.* **88,** 1425 (1966).

[79] Bartsch and Bunnett, *J. Am. Chem. Soc.* **90,** 408 (1968).

[80] Brown, Moritani, and Okamoto, *J. Am. Chem. Soc.* **78,** 2193 (1956); Brown and Nakagawa, *J. Am. Chem. Soc.* **78,** 2197 (1956); Brown and Moritani, Ref. 76. See also Griffith, Meges, and Brown, *Chem. Commun.* 90 (1968); Acharya and Brown, *Chem. Commun.* 305 (1968).

[81] Froemsdorf and Robbins, *J. Am. Chem. Soc.* **89,** 1737 (1967). See also Froemsdorf, McCain, and Wilkison, *J. Am. Chem. Soc.* **87,** 3984 (1965); Froemsdorf, Dowd, and Leimer, *J. Am. Chem. Soc.* **88,** 2345 (1966); Bartsch, Kelly, and Pruss, *Tetrahedron Lett.* 3795 (1970); Feit, Breger, Capobianco, Cooke, and Gitlin, *J. Am. Chem. Soc.* **97,** 2477 (1975); Ref. 71.

[82] Bartsch, Pruss, Bushaw, and Wiegers, *J. Am. Chem. Soc.* **95,** 3405 (1973); Bartsch, Wiegers, and Guritz, *J. Am. Chem. Soc.* **96,** 430 (1974).

[83] Bartsch, Pruss, Cook, Buswell, Bushaw, and Wiegers, *J. Am. Chem. Soc.* **95,** 6745 (1973); Bartsch and Ingram, *J. Org. Chem.* **40,** 3138 (1975).

[84] Bartsch, *J. Org. Chem.* **38,** 846 (1973).

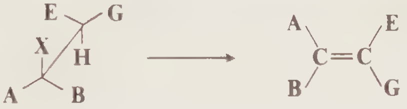
[85] Sicher, Svoboda, Pánková, and Závada, *Collect. Czech. Chem. Commun.* **36,** 3633 (1971); Bailey and Saunders, *J. Am. Chem. Soc.* **92,** 6904 (1970).

6. In the E1cB mechanism the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β-position, and that is where the double bond goes.

7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.[86] In some cases this can be put to preparative use. For example, the compound $PhCH_2CHOTs$-$CHMe_2$ gave about 98% $PhCH{=}CHCHMe_2$ under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case the double bond goes to the side with more hydrogens because on that side it will be able to conjugate with the benzene ring. However, with the weak base Bu_4N^+ Br^- in acetone the Zaitsev product $PhCH_2CH{=}CMe_2$ was formed in 90% yield.[87]

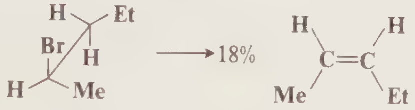
Steric Orientation of the Double Bond

When elimination takes place on a compound of the form CH_3—CABX or CHAB—CGGX, the new olefin does not have cis-trans isomerism, but for compounds of the form CHEG—CABX (E and G *not* H) (**25**) and CH_2E—CABX (**26**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **25** gives the isomer arising from trans orientation of X and H

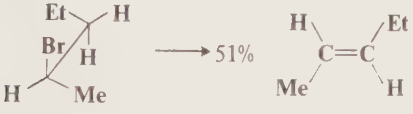


25

and, as we have seen before (p. 897), an erythro compound gives the cis olefin and a threo compound the trans. For **26** two conformations are possible for the transition state; these lead to different isomers, and often both are obtained. However, the one which predominates is often determined by the eclipsing effect (p. 902). For example, Zaitsev elimination from 2-bromopentane can occur as follows:



27



28

However, in **27** the ethyl group is between Br and Me, while in **28** it is between Br and H. This means that **28** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the Hofmann product).[88] These effects become larger with increasing size of A, B, and E.

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[86] For example, see Lloyd and Parker, *Tetrahedron Lett.* 637 (1971); Ono, *Bull. Chem. Soc. Jpn.* **44**, 1369 (1971); Bailey and Saunders, *J. Org. Chem.* **38**, 3363 (1973).

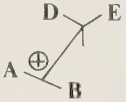
[87] Lloyd, Muir, and Parker, Ref. 64.

[88] Brown and Wheeler, *J. Am. Chem. Soc.* **78**, 2199 (1956).

However, eclipsing effects are not the only factors which affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all these effects are completely understood.[89]

For syn E2 elimination, we have seen (p. 901) that formation of the trans olefin should be greatly preferred to that of the cis isomer because of eclipsing effects. In accord with this, very high trans/cis ratios, higher than would be expected on the basis of olefin stabilities alone, have been found for syn elimination of the 5-decyltrimethylammonium ion.[90]

For E1 eliminations, if there is a free carbonium ion:



(**D** may be **H**)

then it is free to rotate, and no matter what the geometry of the original compound, the more stable situation is the one where the larger of the D-E pair is opposite the smaller of the A-B pair, and the corresponding olefin should form. If the carbonium ion is not completely free, then to that extent, E2-type products are formed. Also, if a suitable neighboring group is present, there may be a neighboring-group effect, and this may affect the proportions of cis and trans olefins.

REACTIVITY

In this section we examine the effects of changes in the substrate, base, leaving group, and medium on (1) overall reactivity, (2) E1 versus E2 versus E1cB, and (3) elimination versus substitution.

Effect of Substrate Structure

1. *Effect on overall activity.* We shall refer to the carbon containing the leaving group (X) as the α-carbon, and to the carbon which loses the proton (or other positive species) as the β-carbon. Groups attached to the α- or β-carbons can exert at least four kinds of influence:

a. They may stabilize or destabilize the incipient double bond (α- or β-groups may do this).

b. They may stabilize or destabilize an incipient carbanion, affecting the acidity of the proton (β-groups only).

c. They may stabilize or destabilize an incipient carbonium ion (α-groups only).

d. They may exert steric effects (e.g., eclipsing effects) (both α- and β-groups).

Effects a and d may apply in all three mechanisms, though steric effects are greatest for the E2 mechanism. Effect b does not apply in the E1 mechanism, and effect c does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rates by any mechanism, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the α position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO_2, CN, SR in the β position all increase the rate of E2 eliminations.

2. *Effect on E1 versus E2 versus E1cB.* α-Alkyl and α-aryl groups increase the extent of E1 elimination, since they stabilize the carbonium character of the transition state. That is, they shift the spectrum toward the E1 end. β-Alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β-aryl groups shift the mechanism the other way (toward E1cB), since they stabilize the carbanion. Indeed, as we have seen (p. 905), all

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[89] For discussions, see Bartsch and Bunnett, *J. Am. Chem. Soc.* **91**, 1376, 1382 (1969); Feit and Saunders, *J. Am. Chem. Soc.* **92**, 1630, 5615 (1970); Feit and Gitlin, *J. Chem. Soc., Chem. Commun.* 561 (1972); Alunni, Baciocchi, Ruzziconi, and Tingoli, *J. Org. Chem.* **39**, 3299 (1974); Saunders and Cockerill, Ref. 2, pp. 165–193.

[90] Sicher, Závada, and Pánková, *Chem. Commun.* 1147 (1968).

TABLE 1 The effect of α and β branching on the rate of E2 elimination and on the amount of olefin formed

The reactions were between the alkyl bromide and OEt^-. *The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β-branching series, cannot be compared because it has no β-hydrogen and cannot give an elimination product without rearrangement*

Substrate	Temperature, °C	Olefin, %	Rate × 10^5 of E2 reaction	Reference
CH_3CH_2Br	55	0.9	1.6	92
$(CH_3)_2CHBr$	25	80.3	0.237	93
$(CH_3)_3CBr$	25	97	4.17	94
$CH_3CH_2CH_2Br$	55	8.9	5.3	92
$CH_3\underset{CH_3}{C}HCH_2Br$	55	59.5	8.5	92

electron-withdrawing groups in the β position shift the mechanism toward E1cB.[91] α-Alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

3. *Effect on elimination versus substitution.* Under second-order conditions α branching increases elimination, to the point where tertiary substrates undergo few SN2 reactions, as we saw in Chapter 10. For example, Table 1 shows results on some simple alkyl bromides.[92–94] Similar results were obtained with $\overset{+}{S}Me_2$ as the leaving group.[95] Two reasons may be presented for this trend. One is statistical: as α branching increases, there are usually more hydrogens for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 versus SN1), though not so much, and usually the substitution product predominates. For example, solvolysis of *t*-butyl bromide gave only 19% elimination[94] (compare with Table 1). β branching also increases the amount of E2 elimination with respect to SN2 substitution (Table 1), not because elimination is faster but because the SN2 mechanism is so greatly slowed (p. 315). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.[96] However, E2 eliminations from compounds with charged leaving groups are slowed by β branching. This is related to Hofmann's rule (p. 910). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum but also increase the extent of elimination as opposed to substitution.

Effect of the Attacking Base

1. *Effect on E1 versus E2 versus E1cB.* In the E1 mechanism, an external base is generally not required: The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move

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[91] For a review of eliminations with COOH, COOR, $CONH_2$, and CN groups in the β position, see Butskus and Denis, *Russ. Chem. Rev.* **35**, 839 (1966).

[92] Dhar, Hughes, Ingold, and Masterman, *J. Chem. Soc.* 2055 (1948).

[93] Dhar, Hughes, and Ingold, *J. Chem. Soc.* 2058 (1948).

[94] Hughes, Ingold, and Maw, *J. Chem. Soc.* 2065 (1948).

[95] Hughes, Ingold, and Maw, *J. Chem. Soc.* 2072 (1948); Hughes, Ingold, Maw, and Woolf, *J. Chem. Soc.* 2077 (1948); Hughes, Ingold, and Woolf, *J. Chem. Soc.* 2084 (1948).

[96] Brown and Berneis, *J. Am. Chem. Soc.* **75**, 10 (1953).

toward the right of the E1-E2-E1cB spectrum (as we have written it).[97] However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction, p. 908). Normal E2 elimination has been accomplished with the following bases:[98] H_2O, NR_3, OH^-, OAc^-, OR^-, OAr^-, NH_2^-, CO_3^{2-}, $LiAlH_4$, I^-, CN^-, and organic bases. However, the only bases of preparative importance in the normal E2 reaction are OH^-, OR^-, and NH_2^-, usually in the conjugate acid as solvent. Weak bases which are effective in the E2C reaction are Cl^-, Br^-, F^-, OAc^-, and RS^-. These bases are often used in the form of their R_4N^+ salts.

2. *Effect on elimination versus substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favored, and E2 predominates over SN2. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the SN1 mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles though weak bases (p. 322). The use of these obviously favors substitution, except that, as we have seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the base CN^- that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (that is, the freer the base), the more substitution is favored at the expense of elimination.[99]

Effect of the Leaving Group

1. *Effect on reactivity.* The leaving groups in elimination reactions are similar to those in nucleophilic substitution. E2 eliminations have been performed with the following groups: NR_3^+, PR_3^+, SR_2^+, OHR^+, SO_2R, OSO_2R, OCOR, OOH, OOR, F, Cl, Br, I, and CN (*not* OH_2^+). E1 eliminations have been carried out with: NR_3^+, SR_2^+, OH_2^+, OHR^+, OSO_2R, OCOR, Cl, Br, I, and N_2^+.[100] However, the only important leaving groups for preparative purposes are OH_2^+ (always by E1) and Cl, Br, I, and NR_3^+ (usually by E2).

2. *Effect on E1 versus E2 versus E1cB.* Better leaving groups shift the mechanism toward the E1 end of the spectrum, since they make ionization easier. This effect has been studied in various ways. One way already mentioned was by a study of ρ values (p. 908). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β-hydrogen. The E2C reaction is favored by good leaving groups.

3. *Effect on elimination versus substitution.* As we have already seen (p. 903), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.[101] In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, though there is a slight increase in elimination in the order I > Br > Cl. When OTs is the leaving group, there is usually much more substitution. For example, n-$C_{18}H_{37}Br$ treated with t-BuOK gave 85% elimination, while n-$C_{18}H_{37}OTs$ gave, under the same conditions, 99% substitution.[102] On the other hand, positively charged leaving groups increase the amount of elimination.

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[97] For an example, see Alunni and Baciocchi, *Tetrahedron Lett.* 4665 (1973).

[98] This list is from Banthorpe, Ref. 2, p. 4.

[99] Loupy and Seyden-Penne, *Bull. Soc. Chim. Fr.* 2306 (1971).

[100] These lists are from Banthorpe, Ref. 2, pp. 4, 7.

[101] For example, see Skell and Hall, *J. Am. Chem. Soc.* **85,** 2851 (1963); Cocivera and Winstein, Ref. 31; Feit and Wright, *J. Chem. Soc., Chem. Commun.* 776 (1975). See, however, Cavazza, *Tetrahedron Lett,* 1031 (1975).

[102] Veeravagu, Arnold, and Eigenmann, *J. Am. Chem. Soc.* **86,** 3072 (1964).

Effect of the Medium

1. *Effect of solvent on E1 versus E2 versus E1cB.* With any reaction a more polar environment enhances the rate of mechanisms which involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing polarity of solvent and by increasing ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).

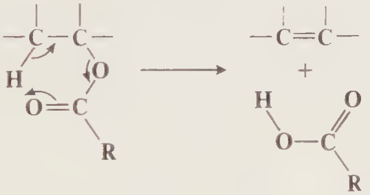
2. *Effect of solvent on elimination versus substitution.* Increasing polarity of solvent favors SN2 reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those on p. 332,[103] only partially explain this. In most solvents SN1 reactions are favored over E1. E1 reactions compete best in polar solvents which are poor nucleophiles.

3. *Effect of temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first order or second order.[104]

MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

Mechanisms[105]

A number of types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require a base (which may be the solvent) in one of the steps, and there is no base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One of these involves a cyclic transition state, which may be either four-, five-, or six-membered. Examples of each size are:



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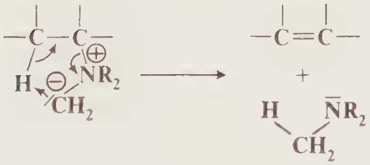

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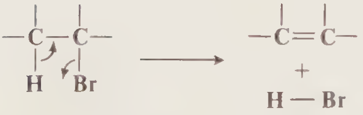

(7-13)

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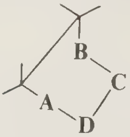
[103] Cooper, Dhar, Hughes, Ingold, MacNulty, and Woolf, *J. Chem. Soc.* 2043 (1948).

[104] Cooper, Hughes, Ingold, Maw, and MacNulty, *J. Chem. Soc.* 2049 (1948).

[105] For reviews, see Smith and Kelly, *Prog. Phys. Org. Chem.* **8,** 75–234 (1971), pp. 75–143, 207–234; in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 5, American Elsevier Publishing Company, Inc., New York, 1972, the articles by Swinbourne, pp. 149–233 (pp. 158–188) and by Richardson and O'Neal, pp. 381–565 (pp. 381–446); Maccoll, Ref. 2, *Adv. Phys. Org. Chem.* **3,** 91–122 (1965); DePuy and King, *Chem. Rev.* **60,** 431–445 (1960). For reviews of mechanisms in pyrolytic eliminations of halides, see Egger and Cocks, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 2, pp. 677–745, John Wiley & Sons, Inc., New York, 1973; Maccoll, *Chem. Rev.* **69,** 33–60 (1969).

In this mechanism, which is called the *Ei mechanism*, the two groups leave at about the same time and bond to each other as they are doing so. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered:

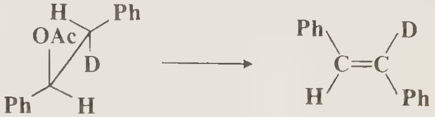


As in the case of the E2 mechanism, it is not necessary that the C—H and C—X bond be equally broken in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C—X bond breaking is a good deal more advanced than C—H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the Ei mechanism is:

1. The kinetics are first order, so that only one molecule of the substrate is involved in the reaction (that is, if one molecule attacked another, the kinetics would be second order in substrate).[106]

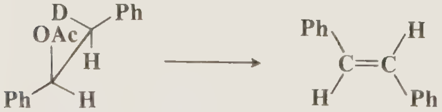
2. Free-radical inhibitors do not slow the reactions, so that no free-radical mechanism is involved.[107]

3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.[108] The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (1) an erythro isomer gives a trans olefin, and a threo gives a cis olefin; (2) the reaction takes place only when a cis β-hydrogen is available; and (3) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. We give here two examples of experimental evidence, neither of which exactly fits categories (1), (2), or (3). Elimination from the erythro (**29**) and threo (**30**) isomers of 1-acetoxy-2-deutero-1,2-diphenylethane gave in each case *trans*-stilbene, but the product from the erythro isomer retained 95% of the



(7-3)

erythro (one of the pair)
29



threo (one of the pair)
30

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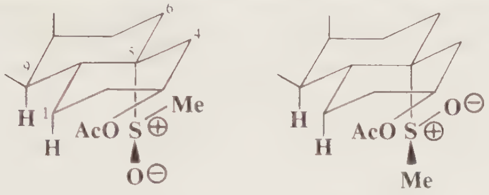
[106] O'Connor and Nace, *J. Am. Chem. Soc.* **75**, 2118 (1953).

[107] Barton, Head, and Williams, *J. Chem. Soc.* 1715 (1953).

[108] In a few instances anti or nonstereoselective elimination has been found; this behavior is generally ascribed to the intervention of other mechanisms. For example, see Bordwell and Landis, *J. Am. Chem. Soc.* **80**, 2450, 6383 (1958); Briggs and Djerassi, *J. Org. Chem.* **33**, 1625 (1968); Smissman, Li, and Creese, *J. Org. Chem.* **35**, 1352 (1970).

original deuterium, while the olefin obtained from the threo isomer retained only 26% of the deuterium.[109] In this case either the hydrogen or the deuterium could be cis to the acetoxy in either isomer, but the most favored conformations (shown) have the phenyls on opposite sides, and in these conformations **29** has a hydrogen nearest the acetoxy and **30** a deuterium. This is an eclipsing effect. The reason that 95% is not balanced by 5% (instead of 26%) is that there is an isotope effect. The other example involves a pair of steroid molecules. In 3β-acetoxy-(R)-5α-methylsulfinylcholestane (**31** shows rings A and B of this compound) and in 3β-acetoxy-(S)-5α-methylsulfinylcholestane (**32**: rings A and B), the *only* difference is the configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **31** gave only elimination to the 4-side (86% 4-ene), while **32** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).[110] Models show that interference from the 1- and 9-hydrogens causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is asymmetric, this means that in **31** the oxygen is near the 4-hydrogen, while in **32** it is near the 6 hydrogen. Both experiments are compatible only with syn elimination.



31 **32** **(7-13)**

4. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.[106]

Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C—X bond is cleaved to a much greater extent than the C—H bond; that is, there is a considerable amount of carbonium-ion character in the transition state. This is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the Woodward-Hoffmann rules (see the similar case of reaction **5-52**). Evidence for the carbonium-ion-like character of the transition state when halide is the leaving group is that relative rates are in the order I > Br > Cl[111] (see p. 325), and that the effects of substituents on reaction rates are in accord with such a transition state.[112] Rate ratios for pyrolysis of some alkyl bromides at 320°C were: ethyl bromide, 1; isopropyl bromide, 280; t-butyl bromide, 78,000. Also, α-phenylethyl bromide had about the same rate as t-butyl bromide. On the other hand, β-phenylethyl bromide was only slightly faster than ethyl bromide. This indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbonium ion was stabilized by α-alkyl and α-aryl substitution, while there was no incipient carbanion to be stabilized by β-aryl substitution. These substituent effects, as well as those for β-methyl, α- and β-halo, α-methoxy, and other groups, are very similar to the effects found for the SN1 mechanism and thus in very good accord with a carbonium-ion-like transition state. For chlorides the rate ratios were less,[113] and for esters much less,[114] though still in the same order, so that these reactions are closer to a pure Ei mechanism, though the transition states still have some carbonium-ion character. Other evidence for a greater initial C—O cleavage with esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ, showing carbonium-ion character at the 1 position.[115] Cleavage of xanthates (reaction **7-4**), cleavage of sulfoxides (**7-12**), the Cope reaction (**7-8**), and reaction **7-7** are probably very close to straight Ei mechanisms.

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[109] Curtin and Kellom, *J. Am. Chem. Soc.* **75,** 6011 (1953); also see Skell and Hall, *J. Am. Chem. Soc.* **86,** 1557 (1964).

[110] Jones and Saeed, *Proc. Chem. Soc.* 81 (1964). See also Goldberg and Sahli, *J. Org. Chem.* **32,** 2059 (1967).

[111] Maccoll, Ref. 2, pp. 215–216.

[112] For reviews of such studies, see Maccoll, Ref. 2, Ref. 105; Maccoll, in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 230–249. Butterworth Scientific Publications, London, 1959, also see Green, Maccoll, and Thomas, *J. Chem. Soc.* 184 (1960).

There has been speculation that in certain extreme cases, cleavage of the C—X bonds runs so much ahead of cleavage of the C—H bond that it could be said that a carbonium ion is involved. This type of mechanism is very like the E1 mechanism, except that in the gas phase, where nothing is available to solvate the negative ion, it would have to remain near the carbonium ion, so that the carbonium ion and the leaving group would form an ion pair. Evidence for this view is that rearrangements are sometimes found with esters[116] and with alkyl halides. For example, pyrolysis of neopentyl chloride gave 75% HCl (despite the fact that no direct elimination is possible) and a mixture of methylbutenes (which must arise from rearrangement).[117] Rearrangements have also been found on pyrolysis of bornyl and isobornyl chlorides.[118] However, the finding of such rearrangements is not conclusive evidence for the ion-pair mechanism because the rearrangements could also be caused by catalysis by the walls of the container, and there is evidence that this is indeed so.[119] Furthermore, there is evidence that actual ion pairs cannot be involved in most pyrolytic eliminations, even those with halide leaving groups. If ion pairs were involved, then, if the reaction of an optically active starting compound were stopped before it was completed, recovered starting material would show partial racemization, as is the case in the SN1 mechanism (p. 275). However, when this experiment was performed with (+)-2-chlorooctane, recovered starting material showed no racemization.[120] Additional evidence that ion pairs are not involved in ester eliminations is that when $CH_3CO^{18}OEt$ was partially pyrolyzed, recovered starting material showed only minor ^{18}O scrambling,[121] though if an ion pair were involved the two oxygens of the CH_3COO^- ion would become equivalent.[122]

The second type of pyrolysis mechanism is completely different from the Ei mechanism and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown:

$$\begin{array}{llcl}
\text{Initiation} & R_2CHCH_2X & \longrightarrow & R_2CHCH_2\cdot + X\cdot \\
\text{Propagation} & R_2CHCH_2X + X\cdot & \longrightarrow & R_2\underset{\bullet}{C}CH_2X + HX \\
 & R_2\underset{\bullet}{C}CH_2X & \longrightarrow & R_2C{=}CH_2 + X\cdot
\end{array}$$

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[113] Herndon, Sullivan, Henley, and Manion, *J. Am. Chem. Soc.* **86,** 5691 (1964), report a rate order for a series of chlorides that is not exactly the same as the SN1 rate order, but is similar. Also see Hoffmann and Maccoll, *J. Am. Chem. Soc.* **87,** 3774 (1965).

[114] For example, see Scheer, Kooyman, and Sixma, *Recl. Trav. Chim. Pays-Bas* **82,** 1123 (1963).

[115] Taylor, Smith, and Wetzel, *J. Am. Chem. Soc.* **84,** 4817 (1962); Smith, Jones, and Brown, *J. Org. Chem.* **28,** 403 (1963); Amin and Taylor, *J. Chem. Soc., Perkin Trans. 2* 1802 (1975). See also Lum and Smith, *Int. J. Chem. Kinet.* **1,** 401 (1969); Taylor, *J. Chem. Soc., Perkin Trans. 2* 165 (1972), 1025 (1975); Ottenbrite and Brockington, *J. Org. Chem.* **39,** 2463 (1974); de Burgh Norfolk and Taylor, *J. Chem. Soc., Perkin Trans. 2* 280 (1976).

[116] For example, see Emovon, *J. Chem. Soc. B* 588 (1966); Kwart and Hoster, *Chem. Commun.* 1155 (1967); Karabatsos and Krumel, *J. Am. Chem. Soc.* **91,** 3324 (1969).

[117] Maccoll and Swinbourne, *J. Chem. Soc.* 149 (1964); Shapiro and Swinbourne, *Can. J. Chem.* **46,** 1341 (1968).

[118] Bicknell and Maccoll, *Chem. Ind. (London)* 1912 (1961).

[119] For example, see Lewis and Newman, *J. Am. Chem. Soc.* **91,** 7455 (1969); Thies and Schick, *J. Am. Chem. Soc.* **96,** 456 (1974). See also Herndon and Manion, *Tetrahedron Lett.* 6327 (1968).

[120] Harding, Maccoll, and Ross, *Chem. Commun.* 289 (1967).

[121] Smith, Voorhees, and Kelly, *Chem. Commun.* 789 (1971). For a similar experiment on a carbamate, see Kwart and Slutsky, *J. Chem. Soc., Chem. Commun.* 552 (1972).

[122] For other evidence against ion pairs in these reactions, see Kwart and Waroblak, *J. Am. Chem. Soc.* **89,** 7145 (1967); Daly and Ziolkowski, *J. Chem. Soc., Chem. Commun.* 911 (1972). For evidence in favor of ion pairing in certain cases, see Ottenbrite, Brockington, and Rutherford, *J. Org. Chem.* **38,** 1186 (1973).

Termination (disproportionation)

$$2R_2\underset{\bullet}{C}CH_2X \longrightarrow R_2C{=}CH_2 + R_2CXCH_2X$$

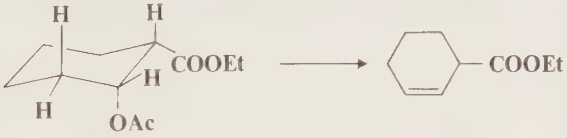
Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,[123] though they have been postulated in pyrolysis of certain esters too.[124] Much less is known about these mechanisms, and we shall not consider them further. Free-radical eliminations in solution are also known but are rare.[125]

Orientation in Pyrolytic Eliminations

As in the E1-E2-E1cB mechanistic spectrum, Bredt's rule applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible (p. 909). Apart from these considerations, the following statements can be made for Ei eliminations:

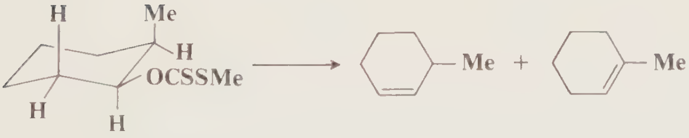
1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β-hydrogens available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55 to 62% 1-butene and 38 to 45% 2-butene,[126] which is close to the 3 : 2 distribution predicted by the number of hydrogens available.[127]

2. A cis β-hydrogen is required. Therefore in cyclic systems, if there is a cis hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be cis to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently cis to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, then it can form a transition state with a β-hydrogen which is either axial (hence cis) or equatorial (hence trans). Thus **33**, in which the leaving group is most likely axial, does not form a double bond in the direction of the carbethoxyl group, even though that would be conjugated, because there is no equatorial hydrogen on that side. Instead it gives 100% **34**.[128]



(7-3)

33 34



(7-4)

35

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[123] For example, see Barton and Howlett, *J. Chem. Soc.* 155, 165 (1949).

[124] For example, see Rummens, *Recl. Trav. Chim. Pays-Bas* **83**, 901 (1964); Louw and Kooyman, *Recl. Trav. Chim. Pays-Bas* **84**, 1511 (1965).

[125] For an example, see Kampmeier, Geer, Meskin, and D'Silva, *J. Am. Chem. Soc.* **88**, 1257 (1966); Kochi, Singleton, and Andrews, *Tetrahedron* **24**, 3503 (1968); Hepinstall and Kampmeier, *J. Am. Chem. Soc.* **95**, 1904 (1973).

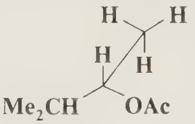
[126] Froemsdorf, Collins, Hammond, and DePuy, *J. Am. Chem. Soc.* **81**, 643 (1959); Haag and Pines, *J. Org. Chem.* **24**, 877 (1959).

[127] DePuy and King, Ref. 105, have tables showing the product distribution for many cases.

[128] Bailey and Baylouny, *J. Am. Chem. Soc.* **81**, 2126 (1959).

On the other hand, **35**, with an equatorial leaving group, gives about 50% of each olefin, even though, for elimination to the 1-ene, the leaving group must go off with a trans hydrogen.[129]

3. In open-chain systems, if there is a β-hydrogen, there is always a conformation in which it can be cis to the leaving group. However, there may be an eclipsing effect. For example, $Me_2CHCHMeOAc$ gave 80% $Me_2CHCH{=}CH_2$ and 20% $Me_2C{=}CHMe$.[126] Of the two transition states, the one which leads to the larger amount of olefin (**36**) is less eclipsed than the other (**37**). Of course this is a small effect, since a statistical distribution would give a 75 : 25 ratio, but it is probably real, since it is in the direction away from olefin stability (Zaitsev's rule) and the products from other acetates are in the same direction.



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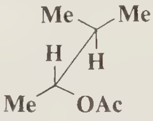


37

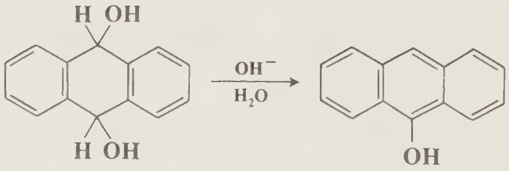
4. In some cases, especially with cyclic compounds, the more stable olefin forms and Zaitsev's rule applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even though a cis β-hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.[130]

1,4 Conjugate Eliminations

1,4 eliminations of the type

$$\mathrm{H{-}C{-}C{=}C{-}C{-}X} \longrightarrow \mathrm{C{=}C{-}C{=}C}$$

are much rarer than conjugate additions (Chapter 15), but some examples are known. One such is[131]



REACTIONS

First we shall consider reactions in which a C=C or a C≡C bond is formed. From a synthetic point of view, the most important reactions for the formation of double bonds are **7-1** (usually by an E1 mechanism), **7-6**, **7-13**, and **7-27** (usually by an E2 mechanism), and **7-3**, **7-4**, and **7-8** (usually by an Ei mechanism). The only synthetically important method for the formation of triple bonds is **7-13**. In the second section we treat reactions in which C≡N bonds and C=N bonds are formed, and then eliminations to give C=O bonds and diazoalkanes. Finally, we discuss extrusion reactions.

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[129] Botteron and Shulman, *J. Org. Chem.* **27**, 2007 (1962).

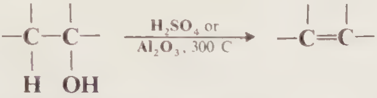
[130] Barton, Head, and Williams, *J. Chem. Soc.* 453 (1952); Bamkole and Maccoll, *J. Chem. Soc. B* 1159 (1970).

[131] Cristol, Barasch, and Tieman, *J. Am. Chem. Soc.* **77**, 583 (1955); Cristol, *Acc. Chem. Res.* **4**, 393–400 (1971).

Reactions in Which C=C and C≡C Bonds Are Formed

A. Reactions in Which Hydrogen Is Removed from One Side. In reactions **7-1** to **7-5** the other leaving atom is oxygen. In reactions **7-6** to **7-10** it is nitrogen. For reactions in which hydrogen is removed from both sides, see reactions **9-1** to **9-7.**

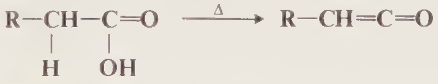
7-1 Dehydration of Alcohols



$$\underset{\mathrm{H}}{\overset{|}{\underset{|}{-\mathrm{C}}}}-\underset{\mathrm{OH}}{\overset{|}{\underset{|}{\mathrm{C}-}}} \xrightarrow[\mathrm{Al_2O_3},\ 300\ \mathrm{C}]{\mathrm{H_2SO_4}\ \text{or}} \overset{|}{-\mathrm{C}}=\overset{|}{\mathrm{C}-}$$

Dehydration of alcohols can be accomplished in several ways. H_2SO_4 and H_3PO_4 are common reagents, but in many cases these lead to rearrangement products and to ether formation (reaction **0-18**). If the alcohol can be evaporated, then vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.[132] Other metallic oxides (e.g., Cr_2O_3, TiO_2, WO_3) have also been used, as have been sulfides, other metallic salts, and zeolites. Another method of avoiding side reactions is the conversion of alcohols to esters, and the pyrolysis of these (reactions **7-3** to **7-5**). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with even a trace of acid that it sometimes happens even when the investigator desires otherwise. It may also be recalled that the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously (Chapter 16) because the new double bond can be in conjugation with one already there. Many other dehydrating agents have been used on occasion: P_2O_5, I_2, $ZnCl_2$, BF_3-etherate, dimethyl sulfoxide, $POCl_3$–pyridine, $KHSO_4$, KOH, the sulfurane $Ph_2S[OCPh(CF_3)_2]_2$,[133] and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPT.[134] With nearly all reagents, dehydration follows Zaitsev's rule. An exception involves the passage of hot alcohol vapors over thorium oxide at 350 to 450 C, under which conditions Hofmann's rule is followed,[135] and the mechanism is probably different.

Carboxylic acids can be dehydrated by pyrolysis, the product being a ketene:

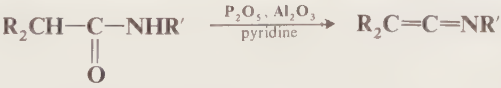


$$\mathrm{R}-\underset{\mathrm{H}}{\underset{|}{\mathrm{CH}}}-\underset{\mathrm{OH}}{\underset{|}{\mathrm{C}}}=\mathrm{O} \xrightarrow{\Delta} \mathrm{R-CH=C=O}$$

Ketene itself is commercially prepared in this manner. In a similar reaction, carbon suboxide is produced by heating malonic acid with P_2O_5:

$$\mathrm{HOOC-CH_2-COOH} \longrightarrow \mathrm{O=C=C=C=O}$$

Analogously, amides can be dehydrated with P_2O_5, pyridine, and Al_2O_3 to give ketenimines:[136]



$$\mathrm{R_2CH}-\underset{\mathrm{O}}{\underset{\|}{\mathrm{C}}}-\mathrm{NHR'} \xrightarrow[\text{pyridine}]{\mathrm{P_2O_5},\ \mathrm{Al_2O_3}} \mathrm{R_2C=C=NR'}$$

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[132] For example, see Spitzin, Michailenko, and Pirogowa, *J. Prakt. Chem.* [4] **25**, 160 (1964); Bertsch, Greiner, Kretzschmar, and Falk, *J. Prakt. Chem.* [4] **25**, 184 (1964).

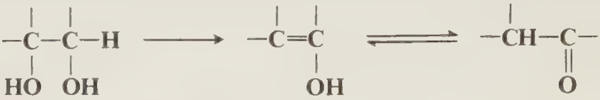
[133] Arhart and Martin, *J. Am. Chem. Soc.* **94**, 5003 (1972).

[134] Monson, *Tetrahedron Lett.* 567 (1971); Monson and Priest, *J. Org. Chem.* **36**, 3826 (1971); Lomas, Sagatys, and Dubois, *Tetrahedron Lett.* 165 (1972).

[135] Lundeen and Van Hoozer, *J. Am. Chem. Soc.* **85**, 2180 (1963), *J. Org. Chem.* **32**, 3386 (1967).

[136] Stevens and Singhal, *J. Org. Chem.* **29**, 34 (1964).

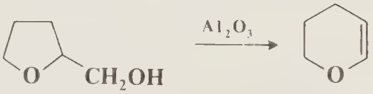
There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinyl alcohols do not exist, and *vic*-diols give either conjugated dienes or lose only 1 mole of water to give an aldehyde or ketone:



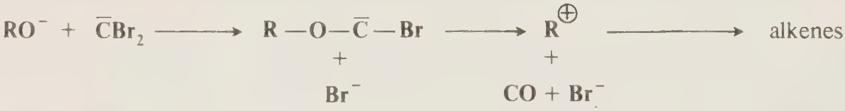
When proton acids catalyze alcohol dehydration, the mechanism is E1.[137] The principal process involves conversion of ROH to ROH_2^+ and cleavage of the latter to R^+ and H_2O (this process is not generally called E1cA, though it might be so called, by analogy to SN1cA, p. 325), though with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of *this* (illustrated for H_2SO_4):

$$\mathbf{ROH} \xrightarrow{H_2SO_4} \mathbf{ROSO_2OH} \longrightarrow \mathbf{R^+ + HSO_4^-}$$

Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (**5-2**), in accord with the principle of microscopic reversibility. With anhydrides, such as P_2O_5 or phthalic anhydride, as well as with some other reagents such as HMPT,[138] it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases the mechanism may be E1 or E2. The mechanism with Al_2O_3 and other solid catalysts has been studied extensively but is poorly understood.[139] It has been shown that not only is ethylene produced directly from ethanol (over Al_2O_3) but that some ethylene arises from diethyl ether formed as an intermediate.[140] In some cases, rearrangements occur even with Al_2O_3, for example,[141]



Dehydration of alcohols has also been accomplished by treating the *alkoxide* form of the alcohol with bromoform.[142] This reaction is called *deoxidation*. It is known that bromoform in basic solution gives rise to dibromocarbene, and the following mechanism is likely:



$$\mathbf{RO^- + \overline{C}Br_2} \longrightarrow \begin{array}{c}\mathbf{R{-}O{-}\overline{C}{-}Br}\\ +\\ \mathbf{Br^-}\end{array} \longrightarrow \begin{array}{c}\mathbf{R^{\oplus}}\\ +\\ \mathbf{CO + Br^-}\end{array} \longrightarrow \text{alkenes}$$

Note that the cleavage of the intermediate ROCBr is analogous to cleavage of RN_2^+ (p. 327), and the product distribution is similar.[143] Benzyl alkoxides (RR′CH—CArR″O⁻) undergo elimination when treated with $AlCl_3$.[144] Hofmann orientation is observed in this reaction.

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[137] For reviews of dehydration mechanisms, see Saunders and Cockerill, Ref. 2, pp. 221–274, 317–331; Banthorpe, Ref. 2, pp. 145–158; Knözinger, in Patai, "The Chemistry of the Hydroxyl Group," pt. 2, pp. 641–718, Interscience Publishers, New York, 1971.

[138] See for example, Kawanisi, Arimatsu, Yamaguchi, and Kimoto, *Chem. Lett.* 881 (1972).

[139] For reviews, see Pines, *Intra-Sci. Chem. Rep.* **6**(2), 1–42 (1972), pp. 17–21; Noller, Andréu, and Hunger, *Angew. Chem. Int. Ed. Engl.* **10,** 172–181 (1971) [*Angew. Chem.* **83,** 185–194]; Knözinger, *Angew. Chem. Int. Ed. Engl.* **7,** 791–805 (1968) [*Angew. Chem.* **80,** 778–792]; Pines and Manassen, *Adv. Catal.* **16,** 49–93 (1966); Ref. 137.

[140] Balaceanu and Jungers, *Bull. Soc. Chim. Belg.* **60,** 476 (1951); Balandin, Isaguliants, Popov, Derbentsev, and Vinogradov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 218 (1958).

[141] Sawyer and Andrus, *Org. Synth.* **III,** 276.

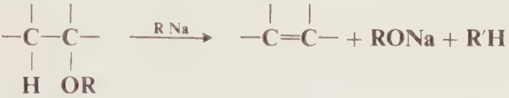
[142] Skell and Starer, *J. Am. Chem. Soc.* **81,** 4117 (1959).

[143] See for example Lee and Hahn, *Can. J. Chem.* **45,** 2129 (1967).

[144] Mead, Cum, and Uccella, *J. Chem. Soc., Chem. Commun.* 679 (1972).

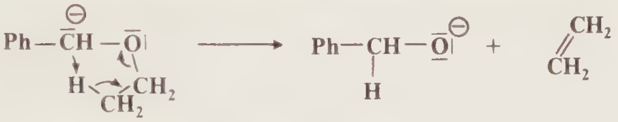
OS **I,** 15, 183, 226, 280, 345, 430, 473, 475; **II,** 12, 368, 408, 606; **III,** 22, 204, 237, 312, 313, 353, 560, 729, 786; **IV,** 130, 444, 771; **V,** 294; **50,** 66; **52,** 96. No attempt has been made to list olefin-forming dehydrations accompanying condensations or rearrangements.

7-2 Cleavage of Ethers to Olefins



$$\underset{\mathrm{H}\quad\mathrm{OR}}{-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-} \xrightarrow{\mathrm{R\,Na}} -\overset{|}{C}=\overset{|}{C}- + \mathrm{RONa} + \mathrm{R'H}$$

Olefins may be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium compounds or sodium amide,[145] though there are usually side reactions too. The reaction is aided by electron-withdrawing groups in the β-position, and, for example, $EtOCH_2$-$CH(COOEt)_2$ can be converted to $CH_2{=}C(COOEt)_2$ without any base at all, but simply on heating.[146] *t*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible for the elimination. In many cases the mechanism is probably E1cB, or on the E1cB side of the mechanistic spectrum, since the base required is so strong, but it has been shown (by the use of $PhCD_2OEt$) that $PhCH_2OEt$ reacts by the five-membered Ei mechanism:[147]

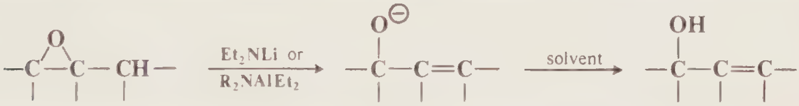


Still another possible mechanism involves carbene formation:

$$R_2CHOR' \xrightarrow{\text{base}} R_2\overset{\ominus}{\bar{C}}OR' \longrightarrow R_2\bar{C} + OR^-$$

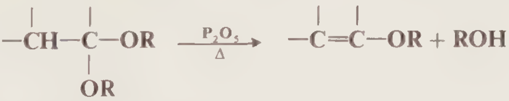
The carbene may then rearrange to an olefin (p. 183) or undergo any of the other carbene reactions. Most of the side reactions in base treatment of ethers arise from this pathway.

Epoxides can be converted to allylic alcohols by treatment with lithium diethylamide[148] or a



diethylaluminum dialkylamide,[149] though side reactions are possible. An alternative procedure is given in reaction **7-12.**

Ethers have also been converted to olefins and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to reaction **7-1**), but this is not a general reaction. However, acetals can be converted to vinyl ethers in this manner:



$$-\overset{|}{C}H-\overset{|}{\underset{\underset{\mathrm{OR}}{|}}{C}}-OR \xrightarrow[\Delta]{P_2O_5} -\overset{|}{C}=\overset{|}{C}-OR + ROH$$

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[145] For a review, see Köbrich, *Angew. Chem. Int. Ed. Engl.* **1,** 382–399 (1962), p. 389 [*Angew. Chem.* **74,** 453–465].

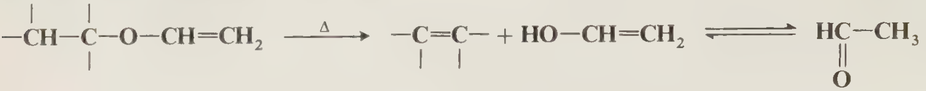
[146] Feely and Boekelheide, *Org. Synth.* **IV,** 298.

[147] Letsinger and Pollart, *J. Am. Chem. Soc.* **78,** 6079 (1956). See also Maercker and Demuth, *Angew. Chem. Int. Ed. Engl.* **12,** 75 (1973) [*Angew. Chem.* **85,** 90].

[148] See for example Cope, Brown, and Lee, *J. Am. Chem. Soc.* **80,** 2855 (1958); Crandall and Chang, *J. Org. Chem.* **32,** 435 (1967); Thummel and Rickborn, *J. Org. Chem.* **36,** 1365 (1971); Kissel and Rickborn, *J. Org. Chem.* **37,** 2060 (1972); Crandall and Crawley, *Org. Synth.* **53,** 17 (1973).

[149] Yasuda, Tanaka, Oshima, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **96,** 6513 (1974); Tanaka, Yasuda, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **97,** 3252 (1975).

Vinyl ethers can be pyrolyzed to olefins and aldehydes in a manner similar to that of reaction **7-3**:

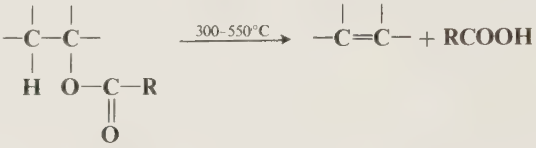


$$-\overset{|}{\mathrm{C}}\mathrm{H}-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{O}-\mathrm{CH}{=}\mathrm{CH_2} \xrightarrow{\Delta} -\underset{|}{\mathrm{C}}{=}\underset{|}{\mathrm{C}}- + \mathrm{HO}-\mathrm{CH}{=}\mathrm{CH_2} \rightleftharpoons \underset{\mathrm{O}}{\underset{\|}{\mathrm{HC}}}-\mathrm{CH_3}$$

The mechanism is probably similar to that of reaction **7-3**.

OS **IV**, 298, 404; **V**, 25, 642, 859, 1145; **53**, 17, 116; **54**, 19, 74, 77.

7-3 Pyrolysis of Esters of Carboxylic Acids



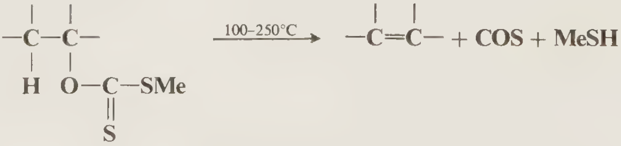
$$\begin{array}{l} -\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}- \\ \ \mathrm{H}\quad \mathrm{O}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{R} \end{array} \xrightarrow{300\text{–}550^\circ\mathrm{C}} -\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}- + \mathrm{RCOOH}$$

Esters in which the alkyl group has a β-hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an olefin.[150] No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing reaction **7-1**. The yields are excellent, and the workup is easy. Many olefins have been prepared in this manner. For higher olefins (above about C_{10}) a better method is to pyrolyze the *alcohol* in the presence of acetic anhydride.[151]

The mechanism is Ei (see p. 917). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for Ei reactions is available (it is not available for five- and six-membered lactones, but it is for larger rings). Amides give a similar reaction but require higher temperatures.

OS **III**, 30; **IV**, 746; **V**, 235.

7-4 The Chugaev Reaction



$$\begin{array}{l} -\overset{|}{\underset{|}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}- \\ \ \mathrm{H}\quad \mathrm{O}-\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{SMe} \end{array} \xrightarrow{100\text{–}250^\circ\mathrm{C}} -\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}- + \mathrm{COS} + \mathrm{MeSH}$$

Methyl xanthates are prepared by treatment of alcohols with NaOH and CS_2 to give RO—CS—SNa, followed by treatment of this with methyl iodide. Pyrolysis of the xanthate to give the olefin, COS, and the mercaptan is called the *Chugaev reaction*.[152] The reaction is thus, like reaction **7-3**, an indirect method of accomplishing reaction **7-1**. Elimination is easier with xanthates than with ordinary esters, and the temperatures required are lower, which is advantageous because possible isomerization of the resulting olefin is minimized. The Chugaev reaction is used even more often than reaction **7-3**. The mechanism is Ei, similar to that of reaction **7-3**. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ^{34}S and ^{13}C isotope effects, to show that it is the C=S sulfur:[153]

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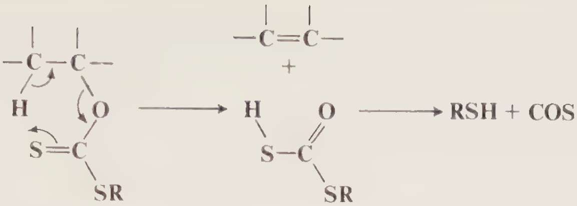
[150] For a review, see DePuy and King, Ref. 105, pp. 432–444.

[151] Aubrey, Barnatt, and Gerrard, *Chem. Ind.* (*London*) 681 (1965).

[152] For reviews, see DePuy and King, Ref. 105, pp. 444–448; Nace, *Org. React.* **12**, 57–100 (1962).

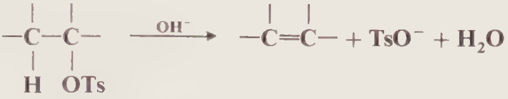
[153] Bader and Bourns, *Can. J. Chem.* **39**, 348 (1961).



The mechanism is thus exactly analogous to that of reaction **7-3**.

Similar reactions involve pyrolysis of O-alkyl dimethylthiocarbamates ROC(=S)NMe$_2$ to give olefins, COS, and Me$_2$NH,[154] and of O-alkyl imidates ROC(=NR′)R″ to give olefins and amides R″CONHR′.[155]

7-5 Decomposition of Other Esters

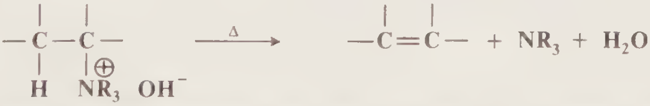


$$-\underset{\mathrm{H}}{\overset{|}{\underset{|}{C}}}-\underset{\mathrm{OTs}}{\overset{|}{\underset{|}{C}}}- \xrightarrow{\mathrm{OH^-}} -\overset{|}{C}=\overset{|}{C}- + \mathrm{TsO^-} + \mathrm{H_2O}$$

Several types of inorganic esters can be cleaved to olefins by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids. It has been shown that bis(tetra-*n*-butylammonium) oxalate $(\mathrm{Bu_4N^+})_2$ $(\mathrm{COO^-})_2$ is an excellent reagent for inducing tosylates to undergo elimination rather than substitution[156] (see p. 916). High yields of olefins are obtained by heating arylsulfonates in such solvents as dimethyl sulfoxide or HMPT.[157] Borates can be pyrolyzed similarly as in reaction **7-3**. Triethylammonium N-carbalkoxysulfamates derived from secondary or tertiary alcohols (prepared by $\mathrm{ROH} + \mathrm{MeOOC}\overset{-\ominus}{\mathrm{N}}\mathrm{SO_2}\overset{\oplus}{\mathrm{N}}\mathrm{Et_3} \rightarrow \mathrm{ROSO_2}\overset{-\ominus}{\mathrm{N}}\mathrm{COOMe}\quad \mathrm{HNEt_3}^+$) undergo syn elimination under mild conditions (30 to 70°C) to give good yields of alkenes.[158] Sodium N-carbalkoxysulfamates, prepared by treatment of the triethylammonium salts with NaH, can also be used.

OS **50**, 84.

7-6 Cleavage of Quaternary Ammonium Hydroxides



$$-\underset{\mathrm{H}}{\overset{|}{\underset{|}{C}}}-\underset{\mathrm{NR_3}\ \mathrm{OH^-}}{\overset{|}{\underset{|\oplus}{C}}}- \xrightarrow{\Delta} -\overset{|}{C}=\overset{|}{C}- + \mathrm{NR_3} + \mathrm{H_2O}$$

Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation*, or *Hofmann degradation*.[159] In the first step a primary, secondary, or tertiary amine is treated with enough methyl iodide to convert it to the quaternary ammonium iodide (reaction **0-46**). In the second step the iodide is converted to the hydroxide by treatment with

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[154] Newman and Hetzel, *J. Org. Chem.* **34**, 3604 (1969).

[155] Marullo, Smith, and Terapane, *Tetrahedron Lett.* 6279 (1966).

[156] Corey and Terashima, *Tetrahedron Lett.* 111 (1972).

[157] Nace, *J. Am. Chem. Soc.* **81**, 5428 (1959).

[158] Burgess, Penton, and Taylor, *J. Am. Chem. Soc.* **92**, 5224 (1970), *J. Org. Chem.* **38**, 26 (1973); Crabbé and León, *J. Org. Chem.* **35**, 2594 (1970).

[159] For reviews, see Bentley, in Bentley and Kirby, "Elucidation of Organic Structures by Physical and Chemical Methods," 2d ed. (vol. 4 of Weissberger, "Techniques of Chemistry"), pt. 2, pp. 255–289, John Wiley & Sons, Inc., New York, 1973; White and Woodcock, in Patai, "The Chemistry of the Amino Group," pp. 409-416, Interscience Publishers, New York, 1968; Cope and Trumbull, *Org. React.* **11**, 317–493 (1960).

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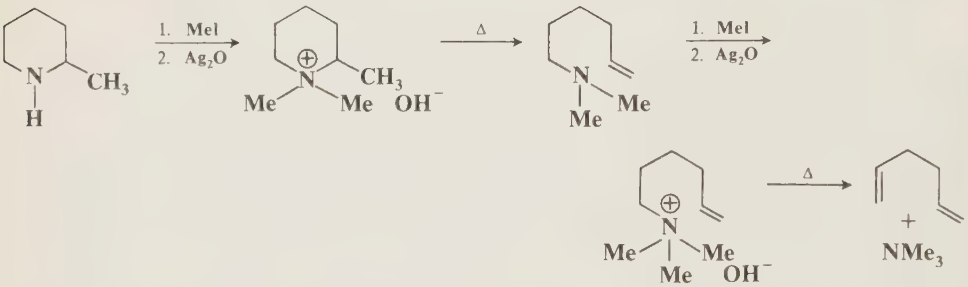
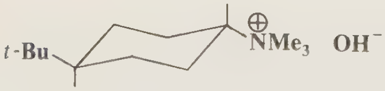
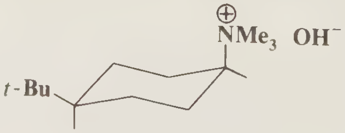
silver oxide. In the cleavage step an aqueous or alcoholic solution of the hydroxide is distilled, often under reduced pressure. The decomposition generally takes place at a temperature between 100 and 200°C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.[160] When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (OH^- or RO^-) is less solvated.[161] The reaction has not been used a great deal as a synthetic tool for synthesizing olefins, though some cyclic olefins are best prepared in this way. The principal importance of the method, especially in earlier years, has been for structural determination of unknown amines. The reaction has been extremely useful, especially in the alkaloid field. In many of these compounds the nitrogen is in a ring, or even at a ring junction, and in such cases the olefin still contains nitrogen and repetitions of the process are required to remove the nitrogen completely, for example,



A side reaction involving nucleophilic substitution to give an alcohol ($R_4N^+ \ OH^- \rightarrow ROH + R_3N$) generally accompanies the normal elimination reaction[162] but seldom causes trouble. However, when none of the four groups on the nitrogen has a β-hydrogen, then substitution is the only reaction possible. On heating $Me_4N^+ \ OH^-$ in water, methanol is obtained, though without a solvent the product is not methanol but dimethyl ether.[163] When a β-hydrogen *is* present, then substitution is enhanced at the expense of elimination if one of the R groups is aryl.[164] Substitution is also enhanced when the only β-hydrogens in the molecule are present in such positions that it is not possible (or not easily possible) for any of them to be in the anti-periplanar conformation with the nitrogen. For example, *trans*-4-*t*-butylcyclohexyltrimethylammonium hydroxide (**38**), in which the trimethylamino group is in the equatorial position (the axial position is of considerably higher energy, owing to the bulk of the two groups) and consequently cannot easily assume an anti-periplanar conformation with a β-hydrogen, gave 100% MeOH when subjected to heat, while the cis isomer, in which about 50% of the molecules exist



38



39

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[160] Archer, *J. Chem. Soc. C* 1327 (1971).

[161] Saunders and Cockerill, Ref. 2, pp. 4–5.

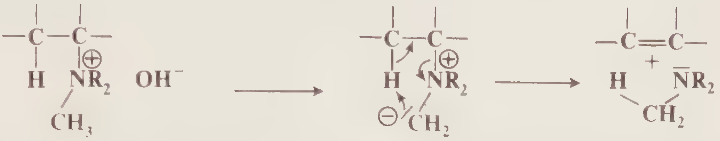
[162] Baumgarten, *J. Chem. Educ.* **45**, 122 (1968).

[163] Musker, *J. Am. Chem. Soc.* **86**, 960 (1964), *J. Chem. Educ.* **45**, 200 (1968); Musker and Stevens, *J. Am. Chem. Soc.* **90**, 3515 (1968); Tanaka, Dunning, and Carter, *J. Org. Chem.* **31**, 3431 (1966).

[164] Archer and Booth, *J. Chem. Soc.* 322 (1963); Bumgardner and Iwerks, *Chem. Commun.* 431 (1968).

in the conformation shown in **39**, gave 92% elimination and 8% substitution.[165] However, as we have seen (p. 900), syn elimination is also possible, and in some cases even preferred.[166]

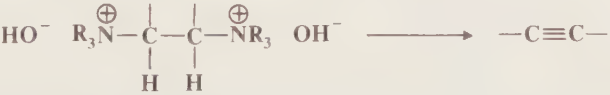
The mechanism is usually E2; Hofmann's rule is generally obeyed by acyclic, and Zaitsev's rule by cyclohexyl substrates (p. 910). In certain cases, where the molecule is highly hindered, a five-membered Ei mechanism, similar to that in reaction **7-7**, has been shown to operate. That is, the OH^- in these cases does not attract the β-hydrogen, but instead removes one of the methyl hydrogens:



The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β-carbon ($R_2CDCH_2NMe_3^+$ OH^-), then the fate of the deuterium indicates the mechanism. If the E2 mechanism is in operation, then the trimethylamine produced would contain no deuterium (which would be found only in the water). But if the mechanism is Ei, then the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+$ OH^-, the deuterium did appear in the amine, demonstrating an Ei mechanism for this case.[167] However, with simpler compounds, the mechanism is E2, as shown by the fact that here the amine was deuterium-free.[168] This is also true in the case of the *cis*-norbornyl compound **7** ($X = NMe_3^+$) (p. 899), where a maximum of 6% of the elimination takes place by the Ei mechanism.[169] The mechanism here is chiefly syn E2.

When the nitrogen bears more than one group possessing a β-hydrogen, which group cleaves? The Hofmann rule says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β-hydrogens cleaves more readily than any longer *n*-alkyl group, all of which have two β-hydrogens. "The β-hydrogen is removed most readily if it is located on a methyl group, next from RCH_2, and least readily from R_2CH."[170] In fact, the Hofmann rule as first stated[171] in 1851 applied only to which group cleaved, and not to the orientation within a group; the latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857–1860. Of course, the Hofmann rule (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2NMe_2Et^+$ OH^- gives mostly styrene instead of ethylene.

Triple bonds have been prepared by pyrolysis of 1,2-bis salts:[172]



$$HO^- \; R_3\overset{\oplus}{N}-\underset{H}{\overset{|}{C}}-\underset{H}{\overset{|}{C}}-\overset{\oplus}{N}R_3 \; OH^- \longrightarrow -C{\equiv}C-$$

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[165] Curtin, Stolow, and Maya, *J. Am. Chem. Soc.* **81**, 3330 (1959); Lamaty, Tapiero, and Wylde, *Bull. Soc. Chim. Fr.* 2039 (1968).

[166] For a review of the stereochemistry of this reaction, see Coke, Ref. 4.

[167] Cope and Mehta, *J. Am. Chem. Soc.* **85**, 1949 (1963). See also Baldwin, Banthorpe, Loudon, and Waller, *J. Chem. Soc. B* 509 (1967).

[168] Cope, LeBel, Moore, and Moore, *J. Am. Chem. Soc.* **83**, 3861 (1961).

[169] Coke and Cooke, *J. Am. Chem. Soc.* **89**, 6701 (1967).

[170] Cope and Trumbull, Ref. 159, p. 348.

[171] Hofmann, *Justus Liebigs Ann. Chem.* **78**, 253 (1851).

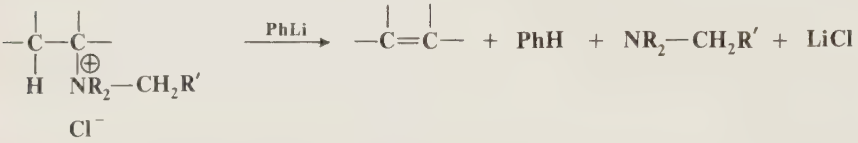
[172] For a review, see Franke, Ziegenbein, and Meister, *Angew. Chem.* **72**, 391–400 (1960), pp. 397–398.

If a double bond is β,γ to the amino group, it is possible to obtain 1,4 elimination, especially if there is a group Z (such as phenyl) which stabilizes the new double bond:[173]

$$HO^- \quad R_3\overset{\oplus}{N}-CH_2-CH=CH-CH_2-Z \longrightarrow CH_2=CH-CH=CH-Z$$

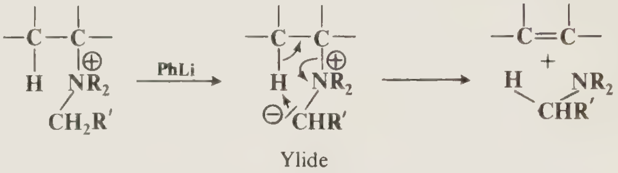
OS **IV,** 980; **V,** 315, 608; **55,** 3. Also see OS **V,** 621, 883; **53,** 13.

7-7 Cleavage of Quaternary Ammonium Salts with Strong Bases



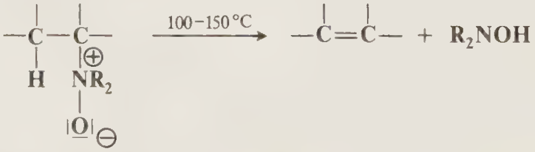
$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\overset{|\oplus}{NR_2-CH_2R'}}{C}}- \quad Cl^- \xrightarrow{PhLi} -\overset{|}{C}=\overset{|}{C}- + PhH + NR_2-CH_2R' + LiCl$$

When quaternary ammonium halides are treated with strong bases (e.g., PhLi, KNH_2 in liquid NH_3[174]), an elimination may occur which is similar in products, though not in mechanism, to reaction **7-6.**[175] This represents an alternative to reaction **7-6** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is Ei:



An α'-hydrogen is obviously necessary so that the ylide can be formed. This type of mechanism is called α',β elimination, since a β-hydrogen is removed by the α'-carbon. The mechanism has been confirmed by labeling experiments similar to those described at reaction **7-6,**[176] and by isolation of the intermediate ylides.[177] An important synthetic difference between this and most instances of reaction **7-6** is that syn elimination is observed here and anti elimination in reaction **7-6,** so that products of opposite configuration are formed when the olefin exhibits cis-trans isomerism.

7-8 Cleavage of Amine Oxides



$$-\underset{H}{\overset{|}{\underset{|}{C}}}-\overset{|}{\underset{\overset{|\oplus}{\underset{|\underline{O}|^{\ominus}}{NR_2}}}{C}}- \xrightarrow{100-150\,^\circ C} -\overset{|}{C}=\overset{|}{C}- + R_2NOH$$

Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* (not to be confused with the Cope *rearrangement*, reaction **8-37**). It is an alternative to reactions

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[173] Babayan, Indzhikyan, Grigoryan, and Minasyan, *J. Gen. Chem. USSR* **33,** 1720 (1963).

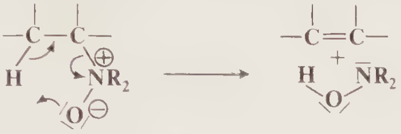
[174] Bach and Andrzejewski, *J. Am. Chem. Soc.* **93,** 7118 (1971); Bach, Bair, and Andrzejewski, *J. Am. Chem. Soc.* **94,** 8608 (1972), *J. Chem. Soc., Chem. Commun.* 819 (1974).

[175] For reviews, see Wittig, *Experientia* **14,** 393 (1958); Cope and Trumbull, Ref. 159, pp. 373–374.

[176] Weygand, Daniel, and Simon, *Chem. Ber.* **91,** 1691 (1958); Bach, Andrzejewski, and Bair, *J. Chem. Soc., Chem. Commun.* 820 (1974).

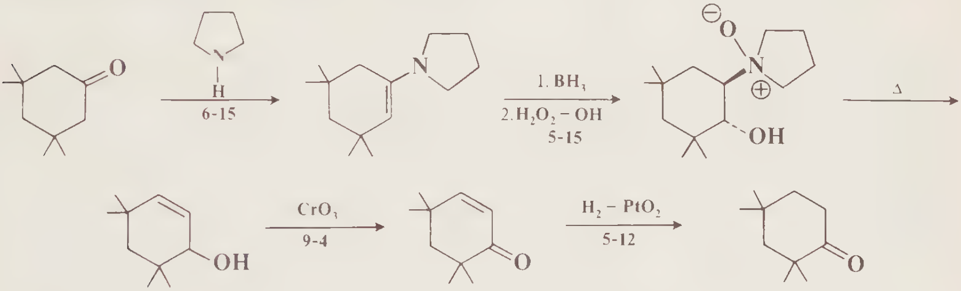
[177] Wittig and Polster, *Justus Liebigs Ann. Chem.* **612,** 102 (1958); Wittig and Burger, *Justus Liebigs Ann. Chem.* **632,** 85 (1960).

7-6 and **7-7**.[178] The reaction is usually performed with a mixture of amine and oxidizing agent (see reaction **9-29**) without isolation of the amine oxide. Because of the mild conditions side reactions are few, and the olefins do not usually rearrange. The reaction is thus very useful for the preparation of many olefins. However, it does not open 6-membered rings containing hetero nitrogen, though it does open rings of 5 and 7 to 10 members.[179] Rates of the reaction increase with increasing size of α- and β-substituents.[180] The reaction can be carried out at room temperature in dry dimethyl sulfoxide or tetrahydrofuran.[181] The elimination is a stereoselective syn process,[182] and the five-membered Ei mechanism operates:



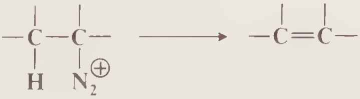
and all evidence indicates that the transition state must be planar. Deviations from planarity as in reaction **7-3** (see p. 918) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and because of the lack of rearrangement of the products, it is useful for the formation of trans cycloolefins (eight-membered and higher).

The Cope reaction has been used as a key step in a method of achieving the indirect migration of a carbonyl group, that is, the conversion of $RCOCH_2R'$ to RCH_2COR'. The method uses the following sequence of reactions,[183] illustrated for 3,3,5,5-tetramethylcyclohexanone (see also reaction **2-12**).



OS **IV**, 612.

7-9 Olefins from Aliphatic Diazonium Salts



The treatment of aliphatic amines with nitrous acid is not a useful method for the preparation of olefins any more than it is for the preparation of alcohols (reaction **0-5**), though some olefin is usually formed in such reactions.

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[178] For reviews, see Cope and Trumbull, Ref. 159, pp. 361–370; DePuy and King, Ref. 105, pp. 448–451.

[179] Cope and LeBel, *J. Am. Chem. Soc.* **82**, 4656 (1960); Cope, Ciganek, Howell, and Schweizer, *J. Am. Chem. Soc.* **82**, 4663 (1960).

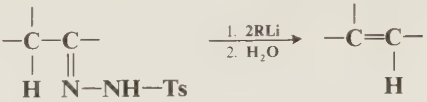
[180] Závada, Pánková, and Svoboda, *Collect. Czech. Chem. Commun.* **38**, 2102 (1973).

[181] Cram, Sahyun, and Knox, *J. Am. Chem. Soc.* **84**, 1734 (1962).

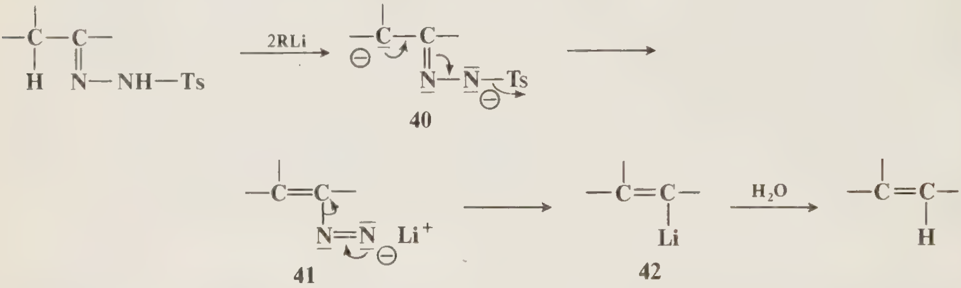
[182] See for example, Bach, Andrzejewski, and Dusold, *J. Org. Chem.* **38**, 1742 (1973).

[183] Barieux and Gore, *Bull. Soc. Chim. Fr.* 1649, 3978 (1971).

7-10 Decomposition of Toluene-*p*-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an olefin, the reaction being formally an elimination accompanied by a hydrogen shift.[183a] The reaction has been applied to tosylhydrazones of many aldehydes and ketones. Several mechanisms are possible,[184] depending on the base and the reaction conditions. The most useful method synthetically involves treatment of the substrate with at least two equivalents of an organolithium compound[185] (usually MeLi) in ether, hexane, or tetramethylenediamine.[186] This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted olefin. Tosylhydrazones of α,β-unsaturated ketones give conjugated dienes.[187] The mechanism has been formulated as:



Evidence for this mechanism is: (1) two equivalents of RLi are required; (2) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;[188] and (3) the intermediates **40**, **41**, and **42** have been trapped.[189]

The reaction also takes place with other bases (e.g., NaOMe,[190] LiH,[191] Na in ethylene glycol, NaH, $NaNH_2$[192]) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted olefin). The reaction with Na in ethylene glycol is called the *Bamford-Stevens reaction.*[193] For these reactions two mechanisms are possible, a carbenoid and a carbonium-ion mechanism.[194] The side reactions found are those expected of carbenes and carbonium ions. In general, the carbonium-ion mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**43**) which

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[183a] For a review, see Shapiro, *Org. React.* **23,** 405–507 (1976).

[184] For a review of the mechanism, see Casanova and Waegell, *Bull. Soc. Chim. Fr.* 922–932 (1975).

[185] Shapiro and Heath, *J. Am. Chem. Soc.* **89,** 5734 (1967); Kaufman, Cook, Shechter, Bayless, and Friedman, *J. Am. Chem. Soc.* **89,** 5736 (1967); Shapiro, *Tetrahedron Lett.* 345 (1968); Meinwald and Uno, *J. Am. Chem. Soc.* **90,** 800 (1968).

[186] Stemke and Bond, *Tetrahedron Lett.* 1815 (1975).

[187] Dauben, Lorber, Vietmeyer, Shapiro, Duncan, and Tomer, *J. Am. Chem. Soc.* **90,** 4762 (1968).

[188] Ref. 185; Shapiro and Hornaman, *J. Org. Chem.* **39,** 2302 (1974).

[189] Shapiro, Lipton, Kolonko, Buswell, and Capuano, *Tetrahedron Lett.* 1811 (1975); Ref. 186.

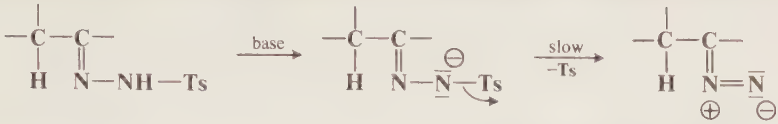
[190] Bartlett and Stevens, *J. Chem. Soc. C* 1964 (1967).

[191] Biellmann and Pète, *Bull. Soc. Chim. Fr.* 675 (1967).

[192] Kirmse, von Bülow, and Schepp, *Justus Liebigs Ann. Chem.* **691,** 41 (1966).

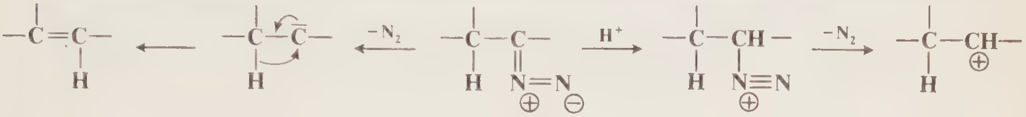
[193] Bamford and Stevens, *J. Chem. Soc.* 4735 (1952).

[194] Powell and Whiting, *Tetrahedron* **7,** 305 (1959), **12,** 168 (1961); DePuy and Froemsdorf, *J. Am. Chem. Soc.* **82,** 634 (1960); Bayless, Friedman, Cook, and Shechter, *J. Am. Chem. Soc.* **90,** 531 (1968); Nickon and Werstiuk, *J. Am. Chem. Soc.* **94,** 7081 (1972).



43

in some cases has been isolated.[195] In the absence of protic solvents **43** loses N_2, and hydrogen migrates, to give the olefin product. The migration of hydrogen may immediately follow, or be simultaneous with, the loss of N_2. In a protic solvent, **43** becomes protonated to give the diazonium



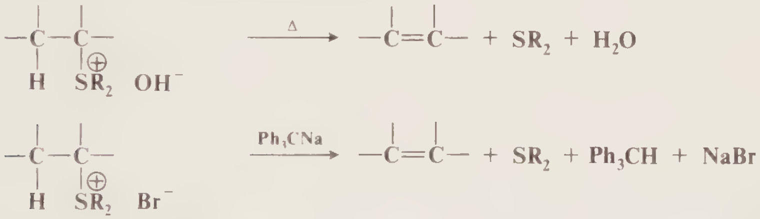
43 **44**

ion **44**, which loses N_2 to give the corresponding carbonium ion which may then undergo elimination (reaction **7-9**) or give other reactions characteristic of carbonium ions.

See also reaction **7-26**.

OS **51**, 66.

7-11 Cleavage of Sulfonium Compounds

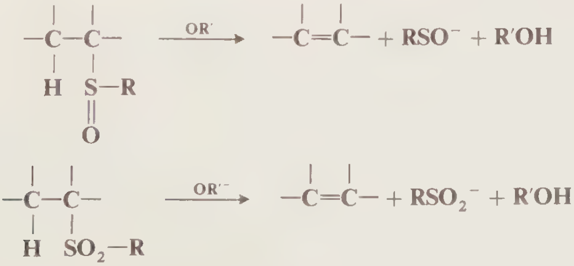


$$\underset{H}{\overset{|}{\underset{|}{-C}}}-\underset{SR_2}{\overset{|}{\underset{|\oplus}{C}}}-\;\; OH^- \xrightarrow{\Delta} -\overset{|}{C}=\overset{|}{C}- + SR_2 + H_2O$$

$$\underset{H}{\overset{|}{\underset{|}{-C}}}-\underset{SR_2}{\overset{|}{\underset{|\oplus}{C}}}-\;\; Br^- \xrightarrow{Ph_3CNa} -\overset{|}{C}=\overset{|}{C}- + SR_2 + Ph_3CH + NaBr$$

Sulfonium compounds undergo elimination similar to that of their ammonium counterparts (reactions **7-6** and **7-7**) in scope and in mechanism. The decomposition by heat of sulfonium hydroxides has been known for many years. The ylide reaction was discovered more recently.[196] Neither is important synthetically.

7-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones



$$\underset{H}{\overset{|}{\underset{|}{-C}}}-\underset{\substack{S-R \\ \| \\ O}}{\overset{|}{\underset{|}{C}}}- \xrightarrow{OR'} -\overset{|}{C}=\overset{|}{C}- + RSO^- + R'OH$$

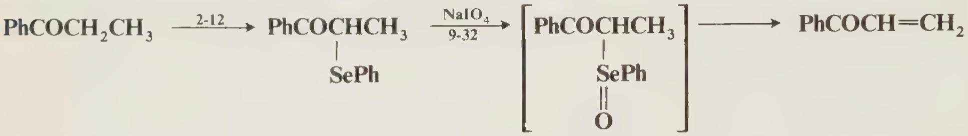
$$\underset{H}{\overset{|}{\underset{|}{-C}}}-\underset{SO_2-R}{\overset{|}{\underset{|}{C}}}- \xrightarrow{OR'^-} -\overset{|}{C}=\overset{|}{C}- + RSO_2^- + R'OH$$

---

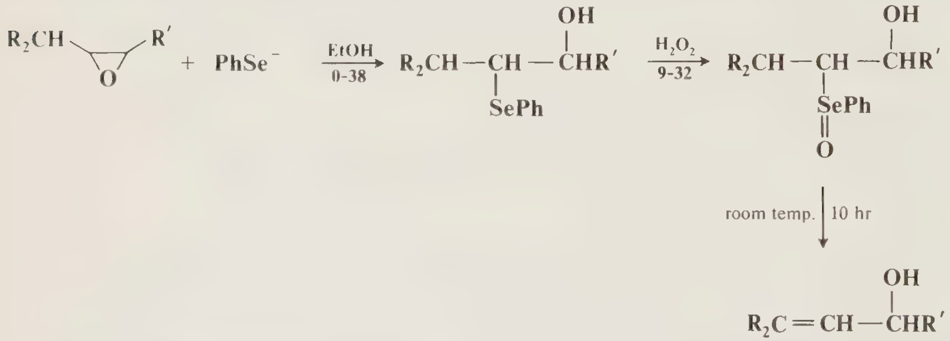
[195] For example, see Powell and Whiting, Ref. 194.

[196] Franzen and Mertz, *Chem. Ber.* **93**, 2819 (1960); Borchardt, Hargreaves, and Saunders, *Tetrahedron Lett.* 2307 (1972).

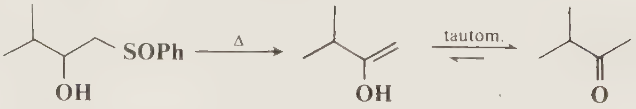
Sulfones and sulfoxides with a β-hydrogen undergo elimination on treatment with an alkoxide or, for sulfones, even with OH^-.[197] In mechanism, these reactions belong on the E1-E2-E1cB spectrum.[198] Although the leaving groups are uncharged, the orientation follows Hofmann's rule and not Zaitsev's. Sulfoxides (but not sulfones) also undergo elimination on pyrolysis at about 80°C in a manner analogous to reaction **7-8.** The mechanism is also analogous, being the five-membered Ei mechanism with syn elimination.[199] Selenoxides[200] and sulfinate esters $R_2CH{-}CHR{-}SO{-}OMe$[201] also undergo elimination by the Ei mechanism, the selenoxide reaction taking place at room temperature. Both the selenoxide[202] and sulfoxide[203] reactions have been used in a method for the conversion of ketones, aldehydes, and esters to their α,β-unsaturated derivatives (illustrated for the selenoxide). Because of the mildness of the procedure, this is probably the best means of accomplishing this conversion. The selenoxide reaction has been used in a procedure for the conversion of epoxides to allylic alcohols.[204]



$$\mathrm{PhCOCH_2CH_3} \xrightarrow{\text{2-12}} \underset{\mathrm{SePh}}{\underset{|}{\mathrm{PhCOCHCH_3}}} \xrightarrow[\text{9-32}]{\mathrm{NaIO_4}} \left[\underset{\underset{\mathrm{O}}{\Vert}}{\underset{\mathrm{SePh}}{\underset{|}{\mathrm{PhCOCHCH_3}}}}\right] \longrightarrow \mathrm{PhCOCH{=}CH_2}$$



See p. 429 for another application of the selenoxide reaction. Pyrolysis of β-hydroxy sulfoxides gives ketones,[204a] e.g.,



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[197] Hofmann, Wallace, Argabright, and Schriesheim, *Chem. Ind. (London)* 1234 (1963).

[198] Hofmann, Wallace, and Schriesheim, *J. Am. Chem. Soc.* **86,** 1561 (1964).

[199] Kingsbury and Cram, *J. Am. Chem. Soc.* **82,** 1810 (1960); Walling and Bollyky, *J. Org. Chem.* **29,** 2699 (1964); Entwhistle and Johnstone, *Chem. Commun.* 29 (1965); Emerson, Craig, and Potts, *J. Org. Chem.* **32,** 102 (1967); Kice and Campbell, *J. Org. Chem.* **32,** 1631 (1967).

[200] Jones, Mundy, and Whitehouse, *Chem. Commun.* 86 (1970); Sharpless, Young, and Lauer, *Tetrahedron Lett.* 1979 (1973); Sharpless and Young, *J. Org. Chem.* **40,** 947 (1975); Mitchell, *J. Chem. Soc., Chem. Commun.* 990 (1974). For a review, see Sharpless, Gordon, Lauer, Patrick, Singer, and Young, *Chem. Scr.* **8A,** 9–13 (1975).

[201] Jones and Higgins, *J. Chem. Soc. C* 81 (1970).

[202] Clive, *J. Chem. Soc., Chem. Commun.* 695 (1973); Reich, Reich, and Renga, *J. Am. Chem. Soc.* **95,** 5813 (1973); Reich, Renga, and Reich, *J. Org. Chem.* **39,** 2133 (1974), *J. Am. Chem. Soc.* **97,** 5434 (1975); Sharpless, Lauer, and Teranishi, *J. Am. Chem. Soc.* **95,** 6137 (1973); Grieco and Miyashita, *J. Org. Chem.* **39,** 120 (1974).

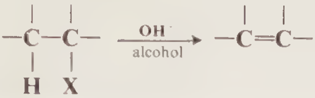
[203] Trost and Salzmann, *J. Am. Chem. Soc.* **95,** 6840 (1973). See also Trost, Conway, Strege, and Dietsche, *J. Am. Chem. Soc.* **96,** 7165 (1974); Trost and Bridges, *J. Org. Chem.* **40,** 2014 (1975); Trost and Leung, *Tetrahedron Lett.* 4197 (1975).

[204] Sharpless and Lauer, *J. Am. Chem. Soc.* **95,** 2697 (1973).

[204a] Nokami, Kunieda, and Kinoshita, *Tetrahedron Lett.* 2841 (1975).

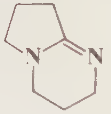
Sulfides and disulfides also undergo elimination when heated with KOH in the polar aprotic solvent HMPT.[205]

7-13 Dehydrohalogenation of Alkyl Halides

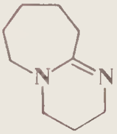


$$-\overset{|}{\underset{\substack{|\\ \mathrm{H}}}{\mathrm{C}}}-\overset{|}{\underset{\substack{|\\ \mathrm{X}}}{\mathrm{C}}}- \xrightarrow[\text{alcohol}]{\mathrm{OH}^-} -\overset{|}{\mathrm{C}}=\overset{|}{\mathrm{C}}-$$

The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides. Hot alcoholic KOH is the most frequently used base, though stronger bases (OR^-, NH_2^-, etc.) or weaker ones (e.g., amines) are used where warranted. The bicyclic amidines 1,5-diazabicyclo[3.4.0]nonene-5 (DBN)[206] and 1,5-diazabicyclo-[5.4.0]undecene-5 (DBU)[207] are good reagents for difficult cases.[208] As previously mentioned (p. 908), certain weak bases in polar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr–$LiCO_3$ in dimethylformamide.[209] Dehydrohalogenation has also been effected by heating of the alkyl halide in HMPT with no other reagent present.[210]



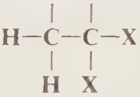
DBN



DBU

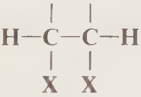
Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow Zaitsev's rule except for a few cases where steric effects are important (for an example, see p. 912). Eliminations of fluorides follow Hofmann's rule (p. 912).

This reaction is by far the most important way of introducing a triple bond into a molecule.[211] This may be accomplished with substrates of the types **45** to **47**. The most commonly used base for triple-bond formation is $NaNH_2$. This base causes 1-alkynes to predominate (where possible), because it forms the salt of the alkyne, shifting any equilibrium between 1- and 2-alkynes. When the base is OH^- or OR^-, the equilibrium tends to be shifted to the internal alkyne, which is



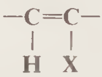
$$\mathrm{H}-\overset{|}{\underset{\substack{|\\ \mathrm{H}}}{\mathrm{C}}}-\overset{|}{\underset{\substack{|\\ \mathrm{X}}}{\mathrm{C}}}-\mathrm{X}$$

45



$$\mathrm{H}-\overset{|}{\underset{\substack{|\\ \mathrm{X}}}{\mathrm{C}}}-\overset{|}{\underset{\substack{|\\ \mathrm{X}}}{\mathrm{C}}}-\mathrm{H}$$

46



$$-\underset{\substack{|\\ \mathrm{H}}}{\mathrm{C}}=\underset{\substack{|\\ \mathrm{X}}}{\mathrm{C}}-$$

47

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[205] Wallace, Hofmann, and Schriesheim, *Chem. Ind. (London)* 1768 (1965).

[206] Truscheit and Eiter, *Justus Liebigs Ann. Chem.* **658,** 65 (1962); Eiter and Oediger, *Justus Liebigs Ann. Chem.* **682,** 62 (1965); Oediger, Kabbe, Möller, and Eiter, *Chem. Ber.* **99,** 2012 (1966); Vogel and Klärner, *Angew. Chem. Int. Ed. Engl.* **7,** 374 (1968) [*Angew. Chem.* **80,** 402].

[207] Oediger and Möller, *Angew. Chem. Int. Ed. Engl.* **6,** 76 (1967) [*Angew. Chem.* **79,** 53 (1967)].

[208] For a review of these reagents, see Oediger, Möller, and Eiter, *Synthesis* 591 (1972).

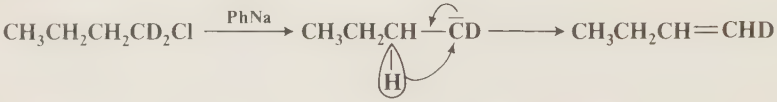
[209] For a discussion, see Fieser and Fieser, "Reagents for Organic Syntheses," vol. 1, pp. 606–609, John Wiley & Sons, Inc., New York, 1967.

[210] Hanna, *Tetrahedron Lett.* 2105 (1968); Monson, *Chem. Commun.* 113 (1971); Hutchins, Hutchins, and Milewski, *J. Org. Chem.* **37,** 4190 (1972).

[211] For reviews, see Köbrich and Buck, in Viehe, "Acetylenes," pp. 100–134, Marcel Dekker, Inc., New York, 1969; Jacobs, *Org. React.* **5,** 1–78 (1949), pp. 1–25; Ref. 172, pp. 391–397; Köbrich, Ref. 2, pp. 50–53.

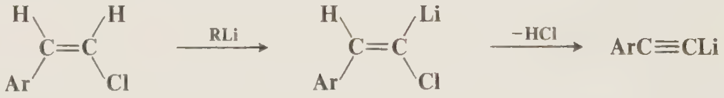
thermodynamically more stable. If another hydrogen is suitably located (for example, $-\overset{|}{C}H-CX_2-CH_2-$), then allene formation can compete, though alkynes are usually more stable.[212]

Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, though the E1 mechanism has been demonstrated in some cases. However, elimination of HX may also be accomplished by pyrolysis of the halide, in which case the mechanism is the Ei mechanism (p. 918), or in some instances the free-radical mechanism (p. 920). Pyrolysis is normally performed without a catalyst at about 400°C. The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst[213] (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2. It has been shown that when a very strong base is used in solution, an α-elimination mechanism through the carbene may compete with the normal E2 mechanism. This was shown by the treatment of $CH_3CH_2CH_2CD_2Cl$ with phenylsodium; the product contained $CH_3CH_2CH{=}CDH$, which arises from

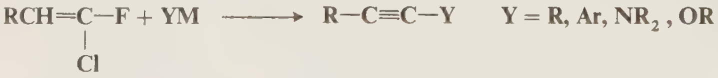


$$CH_3CH_2CH_2CD_2Cl \xrightarrow{PhNa} CH_3CH_2\underset{H}{CH}-\ddot{C}D \longrightarrow CH_3CH_2CH{=}CHD$$

and there was more of the former than of $CH_3CH_2CH{=}CD_2$, the normal E2 product.[214] Eliminations of vinyl halides to give triple bonds generally go by the E2 or E1cB mechanism. However, when the substrate is $ArCH{=}CHCl$ and the base RLi, a mechanism has been proposed in which the first step is hydrogen-lithium exchange (reaction **2-19**), followed by elimination of HCl.[215] This may be called an E2cB mechanism.



A combination elimination and substitution reaction has been used to synthesize alkynes. In this reaction a compound $RCH{=}CFCl$ is treated with YM, where M is a metal and Y may be alkyl, aryl, NR_2, or OR:

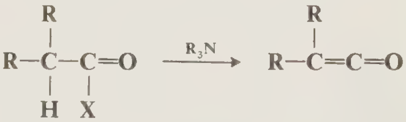


$$RCH{=}\underset{Cl}{\underset{|}{C}}-F + YM \longrightarrow R-C{\equiv}C-Y \qquad Y = R, Ar, NR_2, OR$$

Alkynes, ynamines, and acetylenic ethers can be prepared in this manner.[216]

OS **I,** 191, 205, 209, 438; **II,** 10, 17, 515; **III,** 125, 209, 270, 350, 506, 623, 731, 785; **IV,** 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; **V,** 285, 467, 514, 921; **51,** 115; **54,** 97; **55,** 12, 32, 86.

7-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides



$$R-\underset{H}{\underset{|}{\overset{R}{\overset{|}{C}}}}-\underset{X}{\underset{|}{C}}{=}O \xrightarrow{R_3N} R-\overset{R}{\overset{|}{C}}{=}C{=}O$$

---

[212] For a review of allene formation, see Taylor, *Chem. Rev.* **67,** 317–359 (1967), pp. 321–322.

[213] For a review, see Noller, Andréu, and Hunger, Ref. 139.

[214] Friedman and Berger, *J. Am. Chem. Soc.* **83,** 492, 500 (1961).

[215] Schlosser and Ladenberger, *Chem. Ber.* **100,** 3877, 3893, 3901 (1967); Schlosser and Zimmermann, *Chem. Ber.* **104,** 2885 (1971).

[216] Viehe, *Angew. Chem. Int. Ed. Engl.* **2,** 477 (1963) [*Angew. Chem.* **75,** 638]. For a review of ynamines, see Viehe, in Viehe, Ref. 211, pp. 861–912.

Ketenes can be prepared by treatment of acyl halides with tertiary amines.[217] The scope is broad, and most acyl halides possessing an α-hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, and not the ketene, is isolated. However, if it is desired to use a reactive ketene in a reaction with a given compound, the ketene may be generated in situ in the presence of the given compound.[218]

Closely related is the reaction of tertiary amines with sulfonyl halides which contain an α-hydrogen. In this case the initial product is the highly reactive sulfene, which cannot be isolated

$$RCH_2SO_2Cl \xrightarrow{R_3N} \underset{\text{Sulfene}}{[RCH{=}SO_2]} \longrightarrow RCH{=}CHR + \text{other products}$$

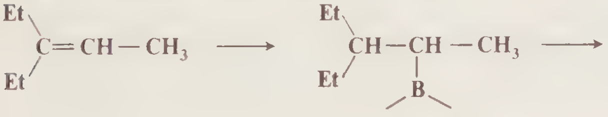
but reacts further to give various products, one of which may be the alkene which is the dimer of RCH.[219] Here too, reactions of sulfenes in situ are common (for example, see reactions **6-66**, **6-69**).

OS **IV**, 560; **V**, 294, 877; **52**, 36.

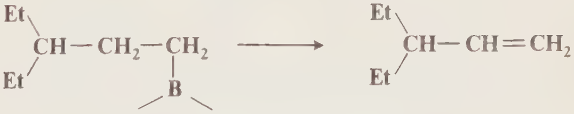
7-15 Elimination of Boranes

$$(R_2CH{-}CH_2)_3B + 3\ \text{1-decene} \rightleftharpoons 3R_2C{=}CH_2 + [CH_3(CH_2)_8CH_2]_3B$$

Trialkylboranes are formed from an olefin and BH_3 (reaction **5-15**). When the resulting borane is treated with another olefin, an exchange reaction occurs.[220] This is an equilibrium process which can be shifted by using a large excess of olefin, by using an unusually reactive olefin, or by using an olefin with a higher boiling point than the displaced olefin and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite that resulting from normal isomerization methods (reaction **2-2**). This cannot be accomplished simply by treatment of a borane such as **49** with an olefin, for elimination in this reaction follows Zaitsev's rule: It is in the direction of the most stable olefin, and the product would be **48** and not **51**. However, if it is desired to convert **48** to **51**, this can be accomplished by converting **48** to **49**, isomerizing **49** to **50** (reaction **8-14**), and then subjecting **50** to the exchange reaction with a higher-boiling olefin, e.g., 1-decene, whereupon **51** is produced. In the usual isomerizations (reaction **2-2**), **51** could be isomerized to **48**, but not the other way around. The reactions **49** → **50** and **50** → **51** proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (reaction **5-15**).



48 **49**



50 **51**

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[217] For a review, see Hanford and Sauer, *Org. React.* **3**, 108–140 (1946), pp. 124–126.

[218] For a review of this procedure, see Luknitskii and Vovsi, *Russ. Chem. Rev.* **38**, 487–494 (1969).

[219] For reviews of sulfenes, see Chapter 16, Ref. 499.

[220] Brown and Bhatt, *J. Am. Chem. Soc.* **88**, 1440 (1966); Brown, Bhatt, Munekata, and Zweifel, *J. Am. Chem. Soc.* **89**, 567 (1967).

A similar reaction, but irreversible, has been demonstrated for alkynes:[221]

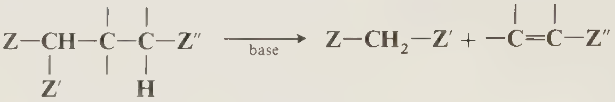
$$(\mathrm{R_2CH{-}CH_2})_3\mathrm{B} + \mathrm{R'C{\equiv}CR'} \longrightarrow 3\mathrm{R_2C{=}CH_2} + (\mathrm{R'CH{=}CR'})_3\mathrm{B}$$

7-16 Decarbonylation of Acyl Halides

$$\mathrm{RCH_2CH_2COCl} + \mathrm{RhCl(Ph_3P)_3} \xrightarrow{\Delta} \mathrm{RCH{=}CH_2} + \mathrm{HCl} + \mathrm{RhClCO(Ph_3P)_2}$$

Acyl halides containing an α-hydrogen are smoothly converted to olefins, with loss of HCl and CO, on heating with chlorotris(triphenylphosphine)rhodium, with metallic platinum, or with certain other catalysts.[222] See also reactions **4-41** and **9-14.**

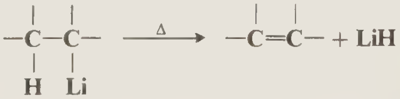
7-17 Reversal of the Michael Reaction



$$\mathrm{Z{-}}\underset{\displaystyle \mathrm{Z'}}{\underset{|}{\mathrm{CH}}}\mathrm{{-}}\underset{|}{\overset{|}{\mathrm{C}}}\mathrm{{-}}\underset{\displaystyle \mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}\mathrm{{-}Z''} \xrightarrow[\text{base}]{} \mathrm{Z{-}CH_2{-}Z'} + {-}\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}\mathrm{{-}Z''}$$

Olefins can be formed on base cleavage of Michael adducts. (See reaction **5-19.** Z is defined on p. 678.) In some cases cleavage occurs simply on heating, without basic catalysis.

7-18 Pyrolysis of Alkali-Metal Organometallic Compounds

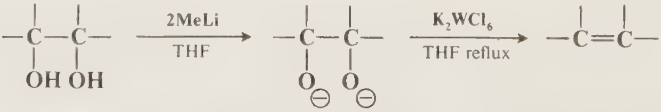


$${-}\underset{\displaystyle \mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-}\underset{\displaystyle \mathrm{Li}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-} \xrightarrow{\Delta} {-}\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}{-} + \mathrm{LiH}$$

Solid lithium hydride and an olefin can be obtained by heating alkyllithium compounds which contain a β-hydrogen.[223] With *sec*-BuLi the orientation followed Zaitsev's rule, although formation of *cis*-2-butene predominated over formation of the trans isomer.[224] The reaction has also been applied to alkylsodium and alkylpotassium compounds.[225] Grignard reagents gave olefins when thermally decomposed in nonsolvating solvents, e.g., cumene.[226]

B. Reactions in Which Neither Leaving Atom Is Hydrogen

7-19 Deoxygenation of Vicinal Diols



$${-}\underset{\displaystyle \mathrm{OH}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-}\underset{\displaystyle \mathrm{OH}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-} \xrightarrow[\text{THF}]{\text{2MeLi}} {-}\underset{\displaystyle \mathrm{O}^{\ominus}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-}\underset{\displaystyle \mathrm{O}^{\ominus}}{\underset{|}{\overset{|}{\mathrm{C}}}}{-} \xrightarrow[\text{THF reflux}]{\mathrm{K_2WCl_6}} {-}\overset{|}{\mathrm{C}}{=}\overset{|}{\mathrm{C}}{-}$$

vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide K_2WCl_6, or with certain other tungsten reagents, in refluxing tetrahydrofuran.[227] Tetrasubstituted diols react most rapidly. The elimination is largely, but not entirely, syn. Another method consists of treatment of the diol with PBr_3 in ether at low temperatures in the presence of CuBr, followed by addition of excess zinc powder.[149]

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[221] Hubert, *J. Chem. Soc.* 6669 (1965).

[222] Tsuji and Ohno, *J. Am. Chem. Soc.* **88,** 3452 (1966), **90,** 94, (1968); Ohno and Tsuji, *J. Am. Chem. Soc.* **90,** 99 (1968). For a review, see Tsuji and Ohno, *Synthesis* 157–169 (1969).

[223] Ziegler and Gellert, *Justus Liebigs Ann. Chem.* **567,** 179 (1950).

[224] Glaze, Lin, and Felton, *J. Org. Chem.* **30,** 1258 (1965).

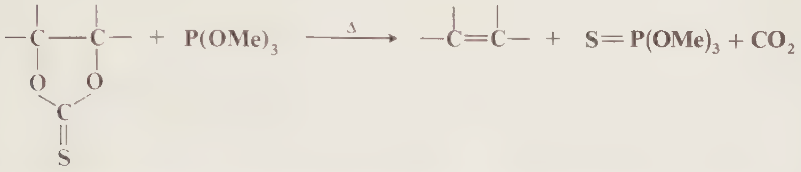
[225] For example, see Finnegan, *Chem. Ind. (London)* 895 (1962), *Tetrahedron Lett.* 851 (1963).

[226] Zakharkin, Okhlobystin, and Strunin, *J. Organomet. Chem.* **4,** 349 (1965); Lefrancois and Gault, *J. Organomet. Chem.* **16,** 7 (1969); Dymova, Grazhulene, Kuchinskii, and Kuznetsov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **20,** 1532 (1971).

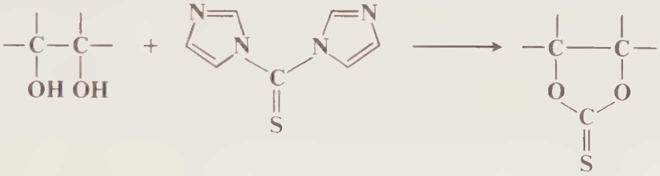
[227] Sharpless and Flood, *J. Chem. Soc., Chem. Commun.* 370 (1972); Sharpless, Umbreit, Nieh, and Flood, *J. Am. Chem. Soc.* **94,** 6538 (1972).

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene-sodium[228] and with NaI in dimethylformamide.[229] More often, *vic*-diols are deoxygenated through cyclic derivatives (reaction **7-20**).

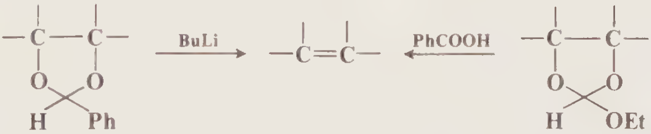
7-20 Cleavage of Cyclic Thionocarbonates



Cyclic thionocarbonates can be cleaved to olefins by heating with trimethyl phosphite[230] or other trivalent phosphorus compounds[231] or by treatment with bis(1,5-cyclooctadiene)nickel.[232] This is actually another method for removing *vic*-OH groups from a molecule, since the thionocarbonates can be prepared by the treatment of 1,2-glycols with N,N′-thiocarbonyldiimidazole:



The elimination is of course syn, so the product is sterically controlled, and olefins which are not sterically favored can be made in this way in high yield, for example, *cis*-$PhCH_2CH{=}CHCH_2Ph$.[233] Related reactions involve treatment of the benzaldehyde acetals (**52**) of 1,2-diols with butyllithium at room temperature,[234] and the heating of 2-ethoxy-1,3-dioxolanes (**53**) with benzoic acid.[235]



52 **53**

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[228] Carnahan and Closson, *Tetrahedron Lett.* 3447 (1972).

[229] Defaye, *Bull. Soc. Chim. Fr.* 2099 (1968).

[230] Corey and Winter, *J. Am. Chem. Soc.* **85,** 2677 (1963).

[231] Corey, *Pure Appl. Chem.* **14,** 19–37 (1967), pp. 32–33.

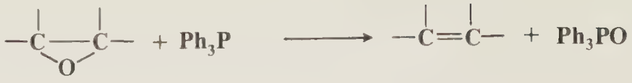
[232] Semmelhack and Stauffer, *Tetrahedron Lett.* 2667 (1973). For another method, see Vedejs and Wu, *J. Org. Chem.* **39,** 3641 (1974).

[233] Corey, Carey, and Winter, *J. Am. Chem. Soc.* **87,** 934 (1965).

[234] Hines, Peagram, Whitham, and Wright, *Chem. Commun.* 1593 (1968).

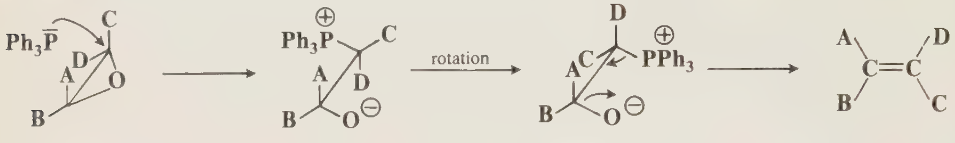
[235] Josan and Eastwood, *Aust. J. Chem.* **21,** 2013 (1968); Hiyama and Nozaki, *Bull. Chem. Soc. Jpn.* **46,** 2248 (1973). See also Eastwood, Harrington, Josan, and Pura, *Tetrahedron Lett.* 5223 (1970).

7-21 The Conversion of Epoxides to Olefins



$$-\overset{|}{C}\underset{O}{-}\overset{|}{C}- + Ph_3P \longrightarrow -\overset{|}{C}=\overset{|}{C}- + Ph_3PO$$

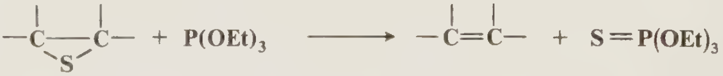
Epoxides can be converted to olefins by treatment with triphenylphosphine[236] or triethyl phosphite $P(OEt)_3$.[237] The first step of the mechanism is nucleophilic substitution (reaction **0-51**), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti; that is, if two groups A and C are cis in the epoxide, they will be trans in the olefin:



betaine

Alternatively, the epoxide can be treated with lithium diphenylphosphide Ph_2PLi, and the product quaternized with methyl iodide.[238] For another method of preparing the betaine, and hence olefins, see the Wittig reaction (**6-47**). Olefins have also been obtained from epoxides by reaction with a zinc-copper couple,[239] with atomic carbon,[240] with triphenylphosphine selenide–trifluoroacetic acid,[241] with sodium(cyclopentadienyl)dicarbonylferrate,[241a] with octacarbonyldicobalt,[242] with $TiCl_3$–$LiAlH_4$,[242a] with $K_2Fe(CO)_4$,[243] with Zn–$ZnCl_2$,[244] with $FeCl_3$–BuLi,[244a] with the tungsten reagents mentioned in reaction **7-19**,[227] and with NaI–NaOAc–Zn–AcOH.[245] The last-mentioned method is actually a variation of reaction **7-29**, since iodohydrins are intermediates.

7-22 The Conversion of Episulfides to Olefins



$$-\overset{|}{C}\underset{S}{-}\overset{|}{C}- + P(OEt)_3 \longrightarrow -\overset{|}{C}=\overset{|}{C}- + S{=}P(OEt)_3$$

Episulfides[246] can be converted to olefins in a reaction similar in appearance to reaction **7-21**.[247] However, in this case the elimination is syn, so that the mechanism cannot be the same as that of reaction **7-21**. The phosphite attacks not the carbon, but the sulfur. Among other reagents

[236] Wittig and Haag, *Chem. Ber.* **88,** 1654 (1955).

[237] Scott, *J. Org. Chem.* **22,** 1118 (1957).

[238] Vedejs and Fuchs, *J. Am. Chem. Soc.* **93,** 4070 (1971), **95,** 822 (1973).

[239] Kupchan and Maruyama, *J. Org. Chem.* **36,** 1187 (1971).

[240] Skell, Klabunde, Plonka, Roberts, and Williams-Smith, *J. Am. Chem. Soc.* **95,** 1547 (1973); Parker and Shevlin, *Tetrahedron Lett.* 2167 (1975).

[241] Clive and Denyer, *J. Chem. Soc., Chem. Commun.* 253 (1973).

[241a] Giering, Rosenblum, and Tancrede, *J. Am. Chem. Soc.* **94,** 7170 (1972); Rosenblum, Saidi, and Madhavarao, *Tetrahedron Lett.* 4009 (1975).

[242] Dowd and Kang, *J. Chem. Soc., Chem. Commun.* 384 (1974).

[242a] Mc Murry and Fleming, *J. Org. Chem.* **40,** 2555 (1975).

[243] Takegami, Watanabe, Mitsudo, Kanaya, and Masada, *Bull. Chem. Soc. Jpn.* **41,** 158 (1968).

[244] Miyano, Hida, and Hashimoto, *Bull. Chem. Soc. Jpn.* **42,** 746 (1969).

[244a] Fujisawa, Sugimoto, and Ohta, *Chem. Lett.* 883 (1975).

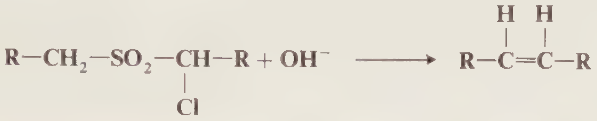
[245] Cornforth, Cornforth, and Mathew, *J. Chem. Soc.* 112 (1959).

[246] For a review of episulfides, see Goodman and Reist, in Kharasch and Meyers, "The Chemistry of Organic Sulfur Compounds," pp. 93–113, Pergamon Press, New York, 1966.

[247] Neureiter and Bordwell, *J. Am. Chem. Soc.* **81,** 578 (1959); Davis, *J. Org. Chem.* **23,** 1767 (1957).

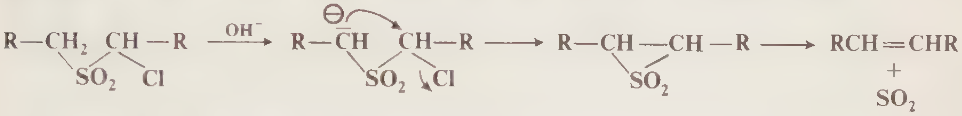
which convert episulfides to olefins are phenyllithium, lithium aluminum hydride[248] (this compound behaves quite differently with epoxides, see reaction **0-81**), and methyl iodide.[249] Episulfoxides can be converted to olefins and sulfur monoxide simply by heating.[250]

7-23 The Ramberg-Bäcklund Reaction



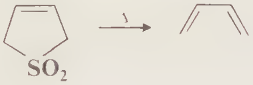
$$R{-}CH_2{-}SO_2{-}\underset{\displaystyle Cl}{\underset{|}{CH}}{-}R + OH^- \longrightarrow R{-}\overset{\displaystyle H}{\overset{|}{C}}{=}\overset{\displaystyle H}{\overset{|}{C}}{-}R$$

The reaction of an α-halo sulfone with a base to give an olefin is called the *Ramberg-Bäcklund reaction*.[251] The reaction is quite general for α-halo sulfones with an α′-hydrogen, despite the unreactivity of α-halo sulfones in normal SN2 reactions (p. 319). Halogen reactivity is in the order I > Br ≫ Cl. In general, mixtures of cis and trans isomers are obtained, but usually the less stable cis isomer predominates.[252] The mechanism involves formation of an episulfone and then elimination of SO_2. There is much evidence for this mechanism,[253] including the preparation

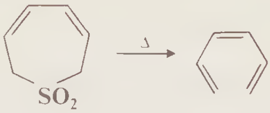


of episulfones in other ways and the demonstration that they give olefins under the reaction conditions faster than the corresponding α-halo sulfones.[254] Episulfones synthesized in other ways (e.g., reaction **6-66**) are reasonably stable compounds but eliminate SO_2 to give olefins when heated or when treated with base.

2,5-Dihydrothiophene-1,1-dioxides (**54**) and 2,7-dihydrothiepin-1,1-dioxides (**55**) undergo analogous 1,4 and 1,6 eliminations, respectively (see also reaction **7-50**). These are concerted reactions



54



55

and, as predicted by the Woodward-Hoffmann rules (p. 776), the former[255] is a suprafacial process and the latter[256] an antarafacial process. The rules also predict that elimination of SO_2 from episulfones cannot take place by a concerted mechanism (except antarafacially, which is

[248] Lightner and Djerassi, *Chem. Ind. (London)* 1236 (1962); Latif, Mishriky, and Zeid, *J. Prakt. Chem.* **312,** 421 (1970).

[249] Culvenor, Davies, and Heath, *J. Chem. Soc.* 282 (1949); Helmkamp and Pettitt, *J. Org. Chem.* **29,** 3258 (1964).

[250] Hartzell and Paige, *J. Am. Chem. Soc.* **88,** 2616 (1966), *J. Org. Chem.* **32,** 459 (1967).

[251] For reviews, see Rappe, in Patai, Ref. 2, pt. 2, pp. 1105–1110; Paquette, *Mech. Mol. Migr.* **1,** 121–156 (1968), *Acc. Chem. Res.* **1,** 209–216 (1968); Bordwell, *Acc. Chem. Res.* **3,** 281-290 (1970), pp. 285–286; in Janssen, "Organosulfur Chemistry," pp. 271–284, Interscience Publishers, New York, 1967.

[252] For a discussion of this, see Paquette and Wittenbrook, *J. Am. Chem. Soc.* **90,** 6783 (1968).

[253] See for example Bordwell and Cooper, *J. Am. Chem. Soc.* **73,** 5187 (1951); Paquette, *J. Am. Chem. Soc.* **86,** 4089 (1964); Neureiter, *J. Am. Chem. Soc.* **88,** 558 (1966); Bordwell, Doomes, and Corfield, *J. Am. Chem. Soc.* **92,** 2581 (1970); Bordwell and Wolfinger, *J. Org. Chem.* **39,** 2521 (1974); Bordwell and Doomes, *J. Org. Chem.* **39,** 2526, 2531 (1974).

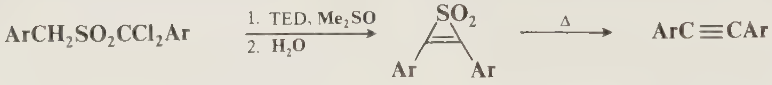
[254] Bordwell, Williams, Hoyt, and Jarvis, *J. Am. Chem. Soc.* **90,** 429 (1968); Bordwell and Williams, *J. Am. Chem. Soc.* **90,** 435 (1968).

[255] Mock, *J. Am. Chem. Soc.* **88,** 2857 (1966); McGregor and Lemal, *J. Am. Chem. Soc.* **88,** 2858 (1966).

[256] Mock, *J. Am. Chem. Soc.* **91,** 5682 (1969).

unlikely for such a small ring), and the evidence shows that this reaction occurs by a nonconcerted pathway.[257] The eliminations of SO_2 from **54** and **55** are examples of *cheletropic reactions*, which are defined as reactions in which two σ bonds which terminate at a single atom (in this case the sulfur atom) are made or broken in concert.[258]

α,α-Dichlorobenzyl sulfones (**56**) react with an excess of the base triethylenediamine in dimethyl sulfoxide at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**57**), which can be isolated.[259] Thermal decomposition of **57** gives the alkynes **58.** Alternatively, α,α-dichlorobenzyl sulfides $ArCH_2SCCl_2Ar$ can be converted to **58** by treatment with triphenylphosphine and *t*-BuOK in tetrahydrofuran.[260]



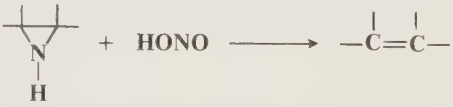
56 57 58

A Ramberg-Bäcklund–type reaction has been carried out on the α-halo *sulfides* $ArCHClSCH_2$-Ar, which react with *t*-BuOK and PPh_3 in refluxing tetrahydrofuran to give the alkenes $ArCH{=}CHAr$.[261] Another analogous reaction is treatment of α-bromo ketones $R_2CBrCOCHR_2$ with base and hydrogen peroxide to give olefins $R_2C{=}CR_2$.[262] This reaction involves a cyclopropanone intermediate (see the Favorskii rearrangement, reaction **8-8**) which loses CO on reaction with H_2O_2.

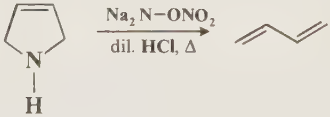
The Ramberg-Bäcklund reaction may be regarded as a type of extrusion reaction (see p. 956).

OS **V,** 877; **50,** 43, 65.

7-24 The Conversion of Aziridines to Olefins



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce olefins.[263] An N-nitroso compound is an intermediate (reaction **2-50**), and other reagents which produce such intermediates also give olefins. The reaction is stereospecific: Cis aziridines give cis olefins and trans aziridines give trans olefins.[264] 3-Pyrrolines give butadienes when treated with nitrohydroxylamine, in an analogous 1,4 elimination.[265] Aziridines carrying N-alkyl substituents can



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[257] Ref. 254. See also Vilsmaier, Tropitzsch, and Vostrowsky, *Tetrahedron Lett.* 3987 (1974).

[258] Woodward and Hoffmann, "The Conservation of Orbital Symmetry," pp. 152–163, Academic Press, Inc., New York, 1970.

[259] Philips, Swisher, Haidukewych, and Morales, *Chem. Commun.* 22 (1971).

[260] Mitchell, *J. Chem. Soc., Chem. Commun.* 955 (1973).

[261] Mitchell, *Tetrahedron Lett.* 4395 (1973).

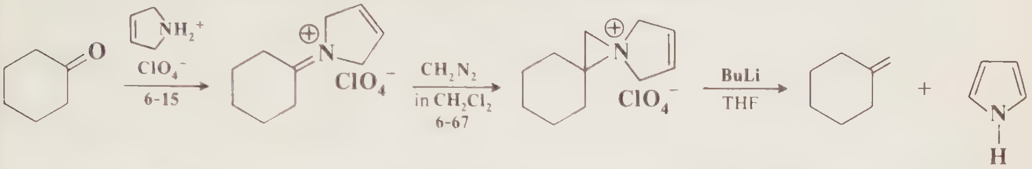
[262] Baldwin and Cardellina, *Chem. Commun.* 558 (1968).

[263] For a review, see Dermer and Ham, "Ethylenimine and other Aziridines," pp. 293–295, Academic Press, Inc., New York, 1969.

[264] Clark and Helmkamp, *J. Org. Chem.* **29,** 1316 (1964); Carlson and Lee, *Tetrahedron Lett.* 4001 (1969).

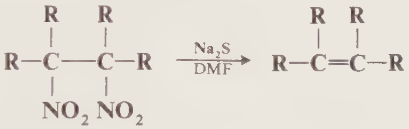
[265] Lemal and McGregor, *J. Am. Chem. Soc.* **88,** 1335 (1966).

be converted to olefins by treatment with ferrous iodide[266] or with *m*-chloroperbenzoic acid.[267] An N-oxide intermediate (reaction **9-29**) is presumably involved in the latter case. Conversion of aziridines to olefins has also been carried out photochemically.[268] An elimination reaction of aziridinium ions with butyllithium has been used as the key step in the conversion of cyclic ketones to the corresponding exo olefins, illustrated for cyclohexanol.[269]



Six-membered ring compounds with exocyclic double bonds are not easy to prepare by other methods.

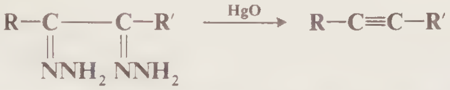
7-25 Conversion of Vicinal Dinitro Compounds to Olefins



$$\mathrm{R{-}\underset{NO_2}{\overset{R}{C}}{-}\underset{NO_2}{\overset{R}{C}}{-}R \xrightarrow[DMF]{Na_2S} R{-}\overset{R}{C}{=}\overset{R}{C}{-}R}$$

Tetrasubstituted *vic*-dinitro compounds are converted to olefins by treatment with sodium sulfide in dimethylformamide.[270] The olefins produced are free of isomers. A radical-ion mechanism has been suggested. *vic*-Dinitro compounds can be prepared by the reaction between an α,α-dinitro compound and the salt of a nitro paraffin (p. 421).

7-26 The Conversion of Dihydrazones to Alkynes

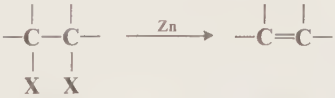


$$\mathrm{R{-}\underset{NNH_2}{\underset{\|}{C}}{-}\underset{NNH_2}{\underset{\|}{C}}{-}R' \xrightarrow{HgO} R{-}C{\equiv}C{-}R'}$$

1,2-Dihydrazones can be made to lose two moles of nitrogen to give alkynes by treatment with HgO, Ag_2O, or certain other reagents. R and R′ may be alkyl or aryl. Highly strained seven- and eight-membered cycloalkynes (see p. 147), as well as large cycloalkynes, have been obtained by this reaction.[271]

OS **IV,** 377. See also OS **55,** 73.

7-27 Dehalogenation of Vicinal Dihalides



$$\mathrm{{-}\underset{X}{\overset{|}{C}}{-}\underset{X}{\overset{|}{C}}{-} \xrightarrow{Zn} {-}\overset{|}{C}{=}\overset{|}{C}{-}}$$

Dehalogenation has been accomplished with many reagents, the most common being zinc, magnesium, and iodide ion. Among reagents used less frequently have been phenyllithium, phenylhydrazine, chromous chloride $CrCl_2$, naphthalene-sodium,[272] $Na\text{-}NH_3$,[273] $Na_2S_2O_3$ in dimethyl sulfoxide,[274] and lithium aluminum hydride.[275] Though the reaction gives good yields, it is not very useful because the best way to prepare *vic*-dihalides is by the addition of halogen to a double bond (reaction **5-30**). However, the two reactions are sometimes used to purify olefins. One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from $X{-}C{-}CX_2{-}C{-}X$ or $X{-}C{-}CX{=}C{-}$ systems.[276] Cumulenes have been obtained from 1,4 elimination:

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[266] Imamoto and Yukawa, *Chem. Lett.* 165 (1974).

[267] Heine, Myers, and Peltzer, *Angew. Chem. Int. Ed. Engl.* **9,** 374 (1970) [*Angew. Chem.* **82,** 395]. See also Hata and Watanabe, *Tetrahedron Lett.* 3827, 4659 (1972).

[268] Padwa and Hamilton, *J. Am. Chem. Soc.* **89,** 102 (1967).

[269] Hata and Watanabe, *J. Am. Chem. Soc.* **95,** 8450 (1973).

[270] Kornblum, Boyd, Pinnick, and Smith, *J. Am. Chem. Soc.* **93,** 4316 (1971).

[271] For example, see Blomquist and Liu, *J. Am. Chem. Soc.* **75,** 2153 (1953); Krebs and Kimling, *Tetrahedron Lett.* 761 (1970).

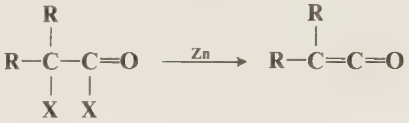
$$BrCH_2{-}C{\equiv}C{-}CH_2Br + Zn \longrightarrow CH_2{=}C{=}C{=}CH_2$$

Triple bonds can be prepared from $X{-}C{=}C{-}X$ or $X_2C{-}CX_2$ systems,[277] but availability considerations are even more extreme here.

The reaction can be carried out for any combination of halogens except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.[278] For different reagents, mechanisms involving carbonium ions, carbanions, and free-radical intermediates, as well as concerted mechanisms, have been proposed. The reaction with I^- was found to proceed with stereospecific anti orientation (p. 897); from this fact an E2 mechanism was assumed in this case, but more recent work[279] shows that the reaction is not completely stereospecific and the mechanism is more complicated. When the reagent is zinc, anti stereospecificity has been observed in some cases,[280] but not in others.[281]

OS **III,** 526, 531; **IV,** 195, 268; **V,** 22, 255, 393, 901; **50,** 21. Also see OS **IV,** 877, 914, 964.

7-28 Dehalogenation of α-Halo Acyl Halides

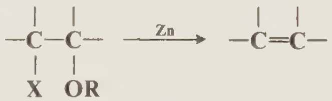


$$R_2C(X){-}C(X){=}O \xrightarrow{Zn} R_2C{=}C{=}O$$

Ketenes can be prepared by dehalogenation of α-halo acyl halides with zinc or with triphenylphosphine,[282] analogously to reaction **7-27.** The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.[282a]

OS **IV,** 348.

7-29 Elimination of a Halogen and a Hetero Group



$${-}\underset{X}{C}{-}\underset{OR}{C}{-} \xrightarrow{Zn} {-}C{=}C{-}$$

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[272] Scouten, Barton, Burgess, Story, and Garst, *Chem. Commun.* 78 (1969); Garst, Pacifici, Singleton, Ezzel, and Morris, *J. Am. Chem. Soc.* **97,** 5242 (1975).

[273] Allred, Beck, and Voorhees, *J. Org. Chem.* **39,** 1426 (1974).

[274] Ibne-Rasa, Tahir, and Rahman, *Chem. Ind.* (*London*) 232 (1973).

[275] For lists of reagents, see Gordon and Chang, *J. Org. Chem.* **38,** 3062 (1973); Mathai, Schug, and Miller, *J. Org. Chem.* **35,** 1733 (1970); King and Pews, *Can. J. Chem.* **42,** 1294 (1964).

[276] For a review, see Ref. 212, pp. 319–320.

[277] For a review, see Köbrich and Buck, in Viehe, Ref. 211, pp. 134–138.

[278] For a discussion, see Saunders and Cockerill, Ref. 2, pp. 332–368.

[279] Lee, Mathai, and Miller, *J. Am. Chem. Soc.* **92,** 4602 (1970); Mathai and Miller, *J. Org. Chem.* **35,** 3416 (1970). See also Nasielski and Guiette-Limbourg, *Bull. Soc. Chim. Belg.* **81,** 351 (1972).

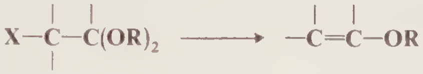
[280] For example, see House and Ro, *J. Am. Chem. Soc.* **80,** 182, (1958); Gordon and Hay, *J. Org. Chem.* **33,** 427 (1968).

[281] For example, see Stevens and Valicenti, *J. Am. Chem. Soc.* **87,** 838 (1965); Sicher, Havel, and Svoboda, *Tetrahedron Lett.* 4269 (1968).

[282] Darling and Kidwell, *J. Org. Chem.* **33,** 3974 (1968).

[282a] For a procedure which gives 60 to 65% yields when one R = H, see McCarney and Ward, *J. Chem. Soc., Perkin Trans. 1* 1600 (1975).

The elimination of OR and halogen from β-halo ethers is called the *Boord reaction.* It can be carried out with zinc, magnesium, or sodium. The yields are high and the reaction is of broad scope. β-Halo acetals yield vinyl ethers:

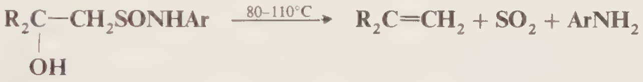


$$\mathrm{X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{C}(OR)_2 \longrightarrow {-}\overset{|}{C}{=}\overset{|}{C}{-}OR}$$

Besides β-halo ethers, the reaction can also be carried out on compounds of the formula $\mathrm{X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}Z}$, where X is halogen and Z is OCOR, OTs,[283] NR_2,[284] or SR.[285] Z may also be OH, but then X is limited to Br and I. Like reaction **7-28,** this method ensures that the new double bond will be in a specific position. The fact that magnesium causes elimination in these cases limits the preparation of Grignard reagents from these compounds. It has been shown that treatment of β-halo ethers and esters with zinc gives nonstereospecific elimination,[286] so that the mechanism was not E2. It was postulated that the mechanism is E1cB, because of the poor leaving-group ability of OR and OCOR. On the other hand, stereospecific syn elimination has been reported for the reaction of 1-bromo-2-methoxy-1,2-diphenylethane with butyllithium in nonpolar solvents.[287] Bromohydrins can be converted to olefins (elimination of Br, OH) in high yields by treatment with $LiAlH_4$–$TiCl_3$.[287a]

OS **III,** 698; **IV,** 748; **55,** 62.

7-30 Pyrolysis of Hydroxysulfinamides



$$\mathrm{R_2\underset{\underset{OH}{|}}{C}{-}CH_2SONHAr \xrightarrow{80\text{–}110°C} R_2C{=}CH_2 + SO_2 + ArNH_2}$$

It was mentioned at reaction **6-42** (p. 857) that β-hydroxysulfinamides, on heating, undergo a syn elimination to give alkenes, SO_2, and $ArNH_2$.[288] Two other eliminations of OH and a sulfur function are also mentioned at reaction **6-42.**[289]

Fragmentations

When carbon is the positive leaving group (the electrofuge) in an elimination reaction, the reaction is called *fragmentation.*[290] These processes occur on substrates of the form $\mathrm{W{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}X}$, where X is a normal nucleofuge (e.g., halogen, OH_2^+, OTs, NR_3, etc.) and W is a positive-carbon electrofuge. In most of the cases W is HO—C— or R_2N—C—, so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, e.g.,

---

[283] Cristol and Rademacher, *J. Am. Chem. Soc.* **81,** 1600 (1959). This reaction has also been accomplished with PhMgBr: Reeve, Brown, and Steckel, *J. Am. Chem. Soc.* **93,** 4607 (1971).

[284] Gurien, *J. Org. Chem.* **28,** 878 (1963).

[285] Amstutz, *J. Org. Chem.* **9,** 310 (1944).

[286] House and Ro, Ref. 280.

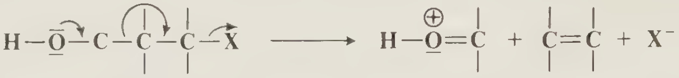
[287] Sugita, Nishimoto, and Ichikawa, *Chem. Lett.* 607 (1973).

[287a] Mc Murry and Hoz, *J. Org. Chem.* **40,** 3797 (1975).

[288] Corey and Durst, *J. Am. Chem. Soc.* **90,** 5548, 5553 (1968).

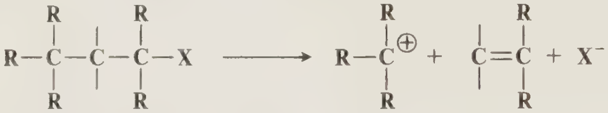
[289] For still others, see Kuwajima and Uchida, *Tetrahedron Lett.* 649 (1972); Kuwajima, Sato, and Kurata, *Tetrahedron Lett.* 737 (1972); Song, Shiono, and Mukaiyama, *Chem. Lett.* 1161 (1974); Watanabe, Shiono, and Mukaiyama, *Chem. Lett.* 871 (1975). See also Jung, Sharma, and Durst, *J. Am. Chem. Soc.* **95,** 3420 (1973).

[290] For reviews, see Grob, *Angew. Chem. Int. Ed. Engl.* **8,** 535–546 (1969) [*Angew. Chem.* **81,** 543–554], *Bull. Soc. Chim. Fr.* 1360–1365 (1960), in "Theoretical Organic Chemistry, The Kekulé Symposium," pp. 114–126, Butterworth Scientific Publications, London, 1959; Grob and Schiess, *Angew. Chem. Int. Ed. Engl.* **6,** 1–15 (1967) [*Angew. Chem.* **79,** 1–14].



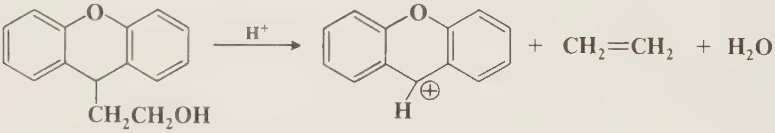
The mechanisms are mostly E1 or E2. We shall discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions **7-31** to **7-38** and **7-40** may be considered fragmentations. See also reactions **9-14** and **9-15.**

7-31 Fragmentation of γ-Branched Alcohols and Halides

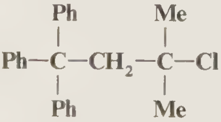


$$R-\underset{R}{\overset{R}{C}}-\overset{|}{\underset{|}{C}}-\underset{R}{\overset{R}{C}}-X \longrightarrow R-\underset{R}{\overset{R}{C}}{}^{\oplus} + \underset{|}{\overset{|}{C}}=\underset{R}{\overset{R}{C}} + X^-$$

When alkyl halides or alcohols with both α and γ branching are subjected to solvolysis, they undergo fragmentation to give an olefin and a carbonium ion. The carbonium ion then undergoes further elimination or substitution, depending on the conditions. This is of course an E1 process, with the first step being ionization of the halide or the protonated alcohol. This is another way of saying that carbonium ions of the form $R_3C-\overset{|}{\underset{|}{C}}-\overset{\oplus}{C}R_2$ find it easy to lose a relatively stable R_3C^+ carbonium ion rather than H^+. As expected for a carbonium-ion mechanism, these fragmentations occur to the greatest extent for tertiary substrates, to a smaller extent for secondary, and essentially not at all for primary substrates, even with γ branching, although they have been shown to occur for primary substrates when a very stable carbonium ion (the xanthyl cation) could be expelled:[291]

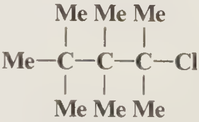


Even with apparently favorable substrates, fragmentation is not always observed. Thus, 2-methyl-4,4-triphenyl-2-chlorobutane (**59**) and 2,3,3,4,4-pentamethyl-2-chloropentane (**60**) gave no fragmentation products when solvolyzed in aqueous acetone.[292]



$$Ph-\underset{Ph}{\overset{Ph}{C}}-CH_2-\underset{Me}{\overset{Me}{C}}-Cl$$

59



$$Me-\underset{Me}{\overset{Me}{C}}-\underset{Me}{\overset{Me}{C}}-\underset{Me}{\overset{Me}{C}}-Cl$$

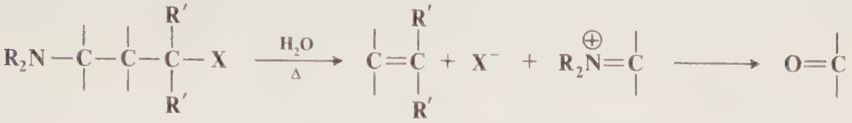
60

---

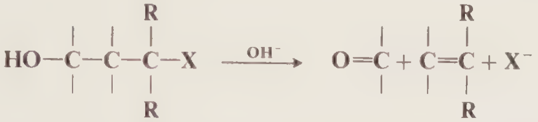
[291] Deno and Sachar, *J. Am. Chem. Soc.* **87**, 5120 (1965).

[292] Shiner and Meier, *J. Org. Chem.* **31**, 137 (1966). See, however, Dubois, Lomas, and Sagatys, *Tetrahedron Lett.* 1349 (1971).

7-32 Fragmentation of γ-Amino and γ-Hydroxy Halides

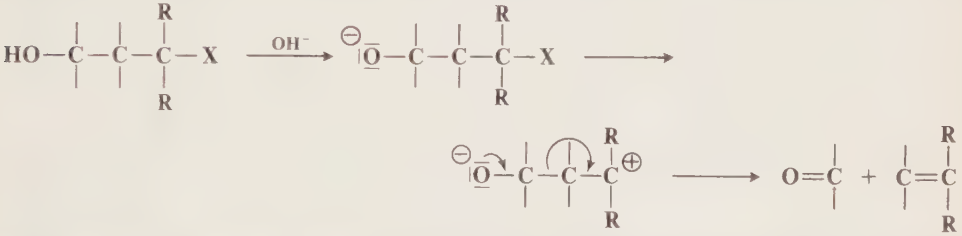


$$R_2N-C-C-CR'_2-X \xrightarrow[\Delta]{H_2O} C=CR'_2 + X^- + R_2\overset{\oplus}{N}=C \longrightarrow O=C$$



$$HO-C-C-CR_2-X \xrightarrow{OH^-} O=C + C=CR_2 + X^-$$

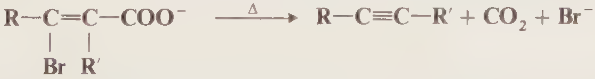
γ-Dialkylamino halides undergo fragmentation when heated with water, to give an olefin and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (reaction **6-2**).[293] γ-Hydroxy halides and tosylates are fragmented with base. In this instance the base does not play its usual role in elimination reactions but instead serves to remove a proton from the OH group, enabling the carbon leaving group to come off more easily:



The mechanism of these reactions is often E1, and the side reactions are similar to those in reaction **7-31.** However, in at least some cases, an E2 mechanism operates.[294] It has been shown that stereoisomers of cyclic γ-amino halides and tosylates in which the two leaving groups can assume an anti-periplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbonium ions.[295] In certain cases (electron-withdrawing groups in the β position, the use of poor nucleofuges such as ArCOO) an E1cB mechanism has been shown.[296]

γ-Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to OH_2^+ and this would convert NR_2 to NR_2H^+, which does not have the unshared pair necessary to form the double bond with the carbon.[297]

7-33 Fragmentation of β-Halo Acrylic Acid Salts



$$R-C(Br)=C(R')-COO^- \xrightarrow{\Delta} R-C\equiv C-R' + CO_2 + Br^-$$

---

[293] Grob and Ostermayer, *Helv. Chim. Acta* **45,** 1119 (1962); Grob, Ostermayer, and Raudenbusch, *Helv. Chim. Acta* **45,** 1672 (1962).

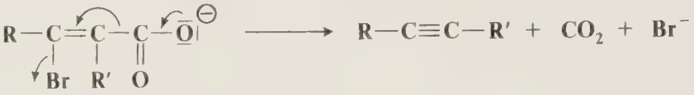
[294] Grob and Schwarz, *Helv. Chim. Acta* **47,** 1870 (1964); Brenneisen, Grob, Jackson, and Ohta, *Helv. Chim. Acta* **48,** 146 (1965); D'Arcy, Grob, Kaffenberger, and Krasnobajew, *Helv. Chim. Acta* **49,** 185 (1966).

[295] Bottini, Grob, Schumacher, and Zergenyi, *Helv. Chim. Acta* **49,** 2516 (1966); Burckhardt, Grob, and Kiefer, *Helv. Chim. Acta* **50,** 231 (1967); Grob, Kiefer, Lutz, and Wilkens, *Helv. Chim. Acta* **50,** 416 (1967); Geisel, Grob, and Wohl, *Helv. Chim. Acta* **52,** 2206 (1969). See also Gleiter, Stohrer, and Hoffmann, *Helv. Chim. Acta* **55,** 893 (1972).

[296] Grob, Unger, Weiler, and Weiss, *Helv. Chim. Acta* **55,** 501 (1972).

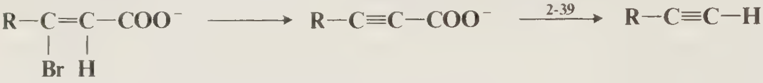
[297] Grob, Hoegerle, and Ohta, *Helv. Chim. Acta* **45,** 1823 (1962).

Salts of β-halo acrylic acids are dehalocarboxylated by heating, to give triple-bond compounds.[298] The elimination is anti, as shown by the fact that *trans*-MeCBr=CMeCOO⁻ reacts at 100°C while the cis isomer does not react. The mechanism is thus probably E2:[299]



$$\mathrm{R{-}\underset{Br}{\underset{|}{C}}{=}\underset{R'}{\underset{|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}O^{\ominus}} \longrightarrow \mathrm{R{-}C{\equiv}C{-}R' + CO_2 + Br^-}$$

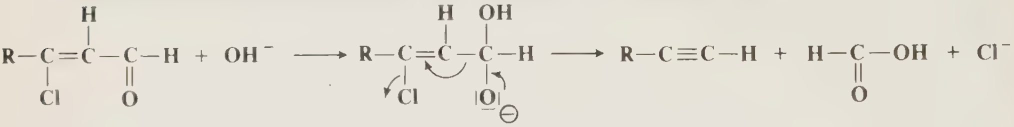
When R′ is hydrogen, then another mechanism is possible:



$$\mathrm{R{-}\underset{Br}{\underset{|}{C}}{=}\underset{H}{\underset{|}{C}}{-}COO^-} \longrightarrow \mathrm{R{-}C{\equiv}C{-}COO^-} \xrightarrow{\text{2-39}} \mathrm{R{-}C{\equiv}C{-}H}$$

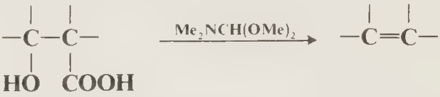
Other leaving groups (for example, OTs) may replace halogen.[300]

A similar cleavage may be effected by base treatment of β-chloroacroleins:[301]



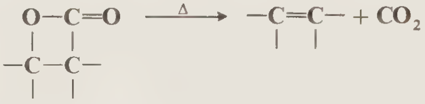
$$\mathrm{R{-}\underset{Cl}{\underset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}H + OH^-} \longrightarrow \mathrm{R{-}\underset{Cl}{\underset{|}{C}}{=}\overset{H}{\overset{|}{C}}{-}\overset{OH}{\overset{|}{\underset{O^{\ominus}}{\underset{|}{C}}}}{-}H} \longrightarrow \mathrm{R{-}C{\equiv}C{-}H + H{-}\underset{O}{\underset{\|}{C}}{-}OH + Cl^-}$$

7-34 Decarboxylation of β-Hydroxy Carboxylic Acids and of β-Lactones



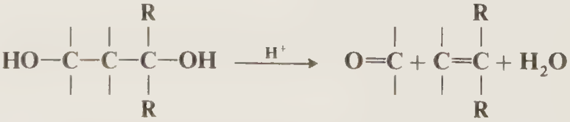
$$\mathrm{-\overset{|}{\underset{HO}{\underset{|}{C}}}-\overset{|}{\underset{COOH}{\underset{|}{C}}}-} \xrightarrow{\mathrm{Me_2NCH(OMe)_2}} \mathrm{-\overset{|}{C}{=}\overset{|}{C}-}$$

An OH and a COOH group can be eliminated from β-hydroxy carboxylic acids by refluxing with excess dimethylformamide dimethyl acetal.[302] Mono-, di-, tri-, and tetrasubstituted olefins have been prepared by this method in good yields. In a related procedure, β-lactones undergo thermal decarboxylation to give olefins in high yields. The reaction has been shown to be a stereospecific syn elimination.[303]



$$\begin{array}{c}\mathrm{O{-}C{=}O}\\ |\quad\;\; |\\ \mathrm{-C{-}C-}\\ |\quad\;\; |\end{array} \xrightarrow{\Delta} \mathrm{-\underset{|}{C}{=}\underset{|}{C}- + CO_2}$$

7-35 Fragmentation of 1,3-Diols



$$\mathrm{HO{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}\overset{R}{\overset{|}{\underset{R}{\underset{|}{C}}}}{-}OH} \xrightarrow{\mathrm{H^+}} \mathrm{O{=}\overset{|}{\underset{|}{C}} + \overset{|}{\underset{|}{C}}{=}\overset{R}{\overset{|}{\underset{R}{\underset{|}{C}}}} + H_2O}$$

---

[298] For a review of this and other fragmentations leading to C≡C bonds, see Köbrich and Buck, in Viehe, Ref. 211, pp. 143–150, 155–158.

[299] For example, see le Noble, Goitien, and Shurpik, *Tetrahedron Lett.* 895 (1969).

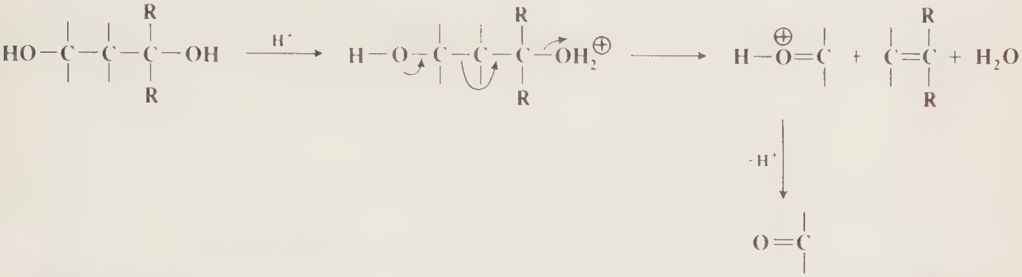
[300] For a review of the formation of alkynes from enol sulfonates and phosphates, see Cymerman Craig, Bergenthal, Fleming, and Harley-Mason, *Angew. Chem. Int. Ed. Engl.* **8**, 429–437 (1969) [*Angew. Chem.* **81**, 437–446].

[301] Bodendorf and Mayer, *Chem. Ber.* **98**, 3554 (1965).

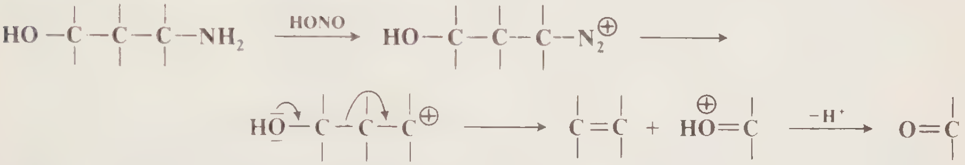
[302] Hara, Taguchi, Yamamoto, and Nozaki, *Tetrahedron Lett.* 1545 (1975).

[303] Noyce and Banitt, *J. Org. Chem.* **31**, 4043 (1966); Adam, Baeza, and Liu, *J. Am. Chem. Soc.* **94**, 2000 (1972); Krapcho and Jahngen, *J. Org. Chem.* **39**, 1322, 1650 (1974); Mageswaran and Sultanbawa, *J. Chem. Soc., Perkin Trans. 1* 884 (1976).

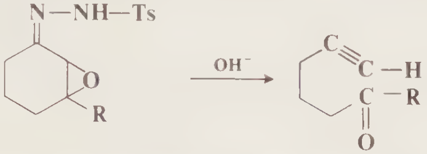
1,3-Diols in which at least one OH group is tertiary or is located on a carbon which has aryl substituents can be cleaved by acid treatment.[304] At least in some cases the mechanism seems to be E2 since anti elimination is found:[305]



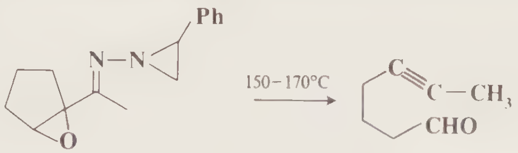
However, in other cases the mechanism is E1. Suitable β-hydroxy acids also give the reaction. As already mentioned (p. 947), γ-dialkylamino alcohols do not give fragmentation, but non-N-substituted γ-amino alcohols do give the reaction, when treated with nitrous acid, and give the same products as the corresponding 1,3-diol.[306] Here the mechanism is undoubtedly E1:



7-36 Fragmentation of α,β-Epoxy Hydrazones



Cyclic α,β-unsaturated ketones can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones.[307] The reaction can be applied to the formation of acetylenic aldehydes (R = H) by using the corresponding 2,4-dinitrotosylhydrazone derivatives.[308] Hydrazones (e.g., **61**) prepared from epoxy ketones and ring-substituted N-aminoaziridines



61

undergo similar fragmentation when heated.[309]

OS **55**, 52.

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[304] Zimmerman and English, *J. Am. Chem. Soc.* **76**, 2285, 2291, 2294 (1954).

[305] Maggio and English, *J. Am. Chem. Soc.* **83**, 968 (1961).

[306] English and Bliss, *J. Am. Chem. Soc.* **78**, 4057 (1956).

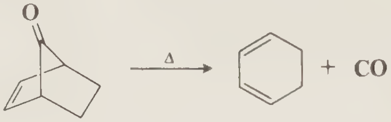
[307] Eschenmoser, Felix, and Ohloff, *Helv. Chim. Acta* **50**, 708 (1967); Tanabe, Crowe, Dehn, and Detre, *Tetrahedron Lett.* 3739 (1967); Tanabe, Crowe, and Dehn, *Tetrahedron Lett.* 3943 (1967).

[308] Corey and Sachdev, *J. Org. Chem.* **40**, 579 (1975).

[309] Felix, Müller, Horn, Joos, Schreiber, and Eschenmoser, *Helv. Chim. Acta* **55**, 1276 (1972).

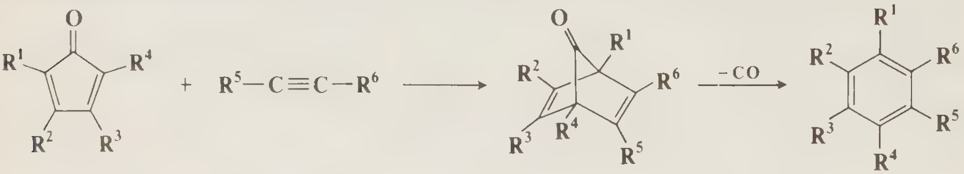
7-37 Reversal of the Diels-Alder reaction may be considered a fragmentation. See reaction **5-51.**

7-38 Elimination of CO and CO_2 from Bridged Bicyclic Compounds

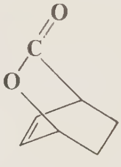


62

On heating, bicyclo[2.2.1]heptenones (**62**) usually lose CO to give cyclohexadienes,[310] in a type of reverse Diels-Alder reaction. Bicyclo[2.2.1]heptadienones (**63**) undergo the reaction so readily (because of the stability of the benzene ring produced) that they cannot generally be isolated. **62** and **63** can be prepared by Diels-Alder reactions between a cyclopentadienone and an alkyne or olefin, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.[311] Unsaturated bicyclic lactones of the type **64** can also undergo the reaction, losing CO_2. See also reaction **7-49.**



63

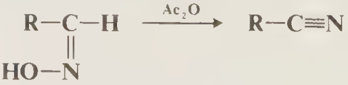


64

OS **III,** 807; **V,** 604, 1037.

Reactions in Which C≡N or C=N Bonds Are Formed

7-39 Dehydration of Aldoximes and Similar Compounds



$$\underset{\substack{\| \\ HO—N}}{R—C—H} \xrightarrow{Ac_2O} R—C≡N$$

Aldoximes can be dehydrated to nitriles[312] by many dehydrating agents, of which acetic anhydride is the most common. Reagents which are effective under mild conditions (room temperature) are diphenyl hydrogen phosphonate[313] $(PhO)_2PHO$, *p*-chlorophenyl chlorothionoformate[314] *p*-$ClC_6H_4OC(=S)Cl$, ethyl orthoformate and H^+,[315] 2,4,6-trichloro-*s*-triazine,[316] N,N′-carbonyldiimidazole[317] (p. 365), and dicyclohexylcarbodiimide in the presence of Et_3N and Cu(II) ions.[318] The reaction is most successful when the H and OH are trans. Various alkyl and acyl derivatives of aldoximes, for example, RCH=NOR, RCH=NOCOR, $RCH=NOSO_2Ar$, etc., also give nitriles, as do chlorimines RCH=NCl (the latter with base treatment)[319] and the cobalt complexes of imines[320] (see reaction **6-14**).

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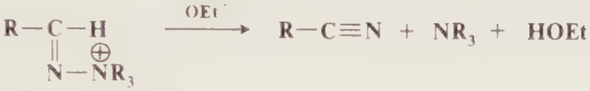
[310] For reviews, see Stark and Duke, Ref. 359, pp. 16–46; Allen, *Chem. Rev.* **62,** 653-664 (1962).

[311] For a review with many examples, see Ogliaruso, Romanelli, and Becker, *Chem. Rev.* **65,** 261-367 (1965), pp. 300–348.

[312] For a review, see Friedrich and Wallenfels, in Rappoport, "The Chemistry of the Cyano Group," pp. 92-96, Interscience Publishers, New York, 1970.

Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with OEt^-:[321]

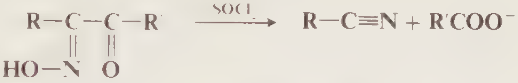


$$R-\underset{\underset{N-\overset{\oplus}{N}R_3}{\|}}{C}-H \xrightarrow{OEt^-} R-C{\equiv}N + NR_3 + HOEt$$

All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates, see reaction **6-23**.

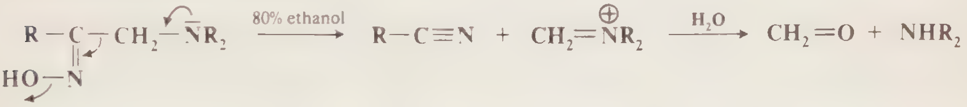
OS **II**, 622; **III**, 690.

7-40 The Conversion of Ketoximes to Nitriles



$$R-\underset{\underset{HO-N}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{SOCl_2} R-C{\equiv}N + R'COO^-$$

Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.[322] Among these are oximes of α-diketones (illustrated above), α-keto acids, α-dialkylamino ketones, α-hydroxy ketones, β-keto ethers, and similar compounds.[323] These are fragmentation reactions, analogous to reactions **7-32** and **7-35**. For example, α-dialkylamino ketoximes also give amines and aldehydes or ketones, in addition to nitriles:[324]



$$R-\underset{\underset{HO-N}{\|}}{C}-CH_2-NR_2 \xrightarrow{80\%\ ethanol} R-C{\equiv}N + CH_2{=}\overset{\oplus}{N}R_2 \xrightarrow{H_2O} CH_2{=}O + NHR_2$$

The reaction which normally occurs on treatment of a ketoxime with a Lewis or proton acid is the Beckmann rearrangement (reaction **8-21**), and fragmentations are considered side reactions, often called "abnormal" or "second-order" Beckmann rearrangements.[325] Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes[326] and, in cases where a particularly stable carbonium ion may be cleaved, may be the main reaction:[327]

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[313] Foley, *J. Org. Chem.* **34**, 2805 (1969).

[314] Clive, *Chem. Commun.* 1014 (1970).

[315] Rogić, Van Peppen, Klein, and Demmin, *J. Org. Chem.* **39**, 3424 (1974).

[316] Chakrabarti and Hotten, *J. Chem. Soc., Chem. Commun.* 1226 (1972).

[317] Foley and Dalton, *J. Chem. Soc., Chem. Commun.* 628 (1973).

[318] Vowinkel and Bartel, *Chem. Ber.* **107**, 1221 (1974). See also Ho, *Synth. Commun.* **3**, 101 (1973); Ho and Wong, *Synth. Commun.* **5**, 299 (1975).

[319] Hauser, Le Maistre, and Rainsford, *J. Am. Chem. Soc.* **57**, 1056 (1935).

[320] Rhee, Ryang, and Tsutsumi, *Tetrahedron Lett.* 3419 (1970).

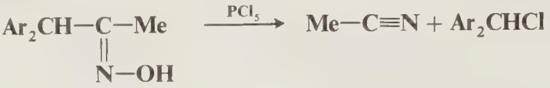
[321] Smith and Walker, *J. Org. Chem.* **27**, 4372 (1962); Grandberg, *J. Gen. Chem. USSR* **34**, 570 (1964); Grundon and Scott, *J. Chem. Soc.* 5674 (1964); Ioffe, and Zelenina, *J. Org. Chem. USSR* **4**, 1496 (1968). See also Smith, Albright, and Waring, *J. Org. Chem.* **31**, 4100 (1966).

[322] For reviews, see Conley and Ghosh, *Mech. Mol. Migr.* **4**, 197–308 (1971), pp. 197–251; McCarty, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," pp. 416–439, Interscience Publishers, New York, 1970; Casanova, in Rappoport, Ref. 312, pp. 915–932.

[323] For a more complete list and references, see Conley and Ghosh, Ref. 322.

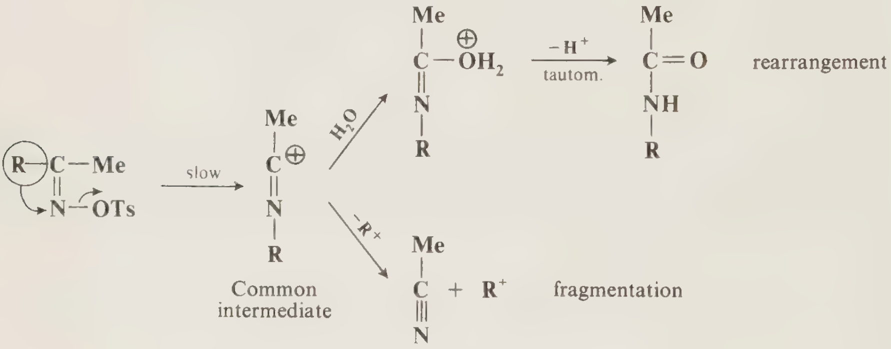
[324] Fischer, Grob, and Renk, *Helv. Chim. Acta* **45**, 2539 (1962); Fischer and Grob, *Helv. Chim. Acta* **46**, 936 (1963).

[325] See the discussion in Ferris, *J. Org. Chem.* **25**, 12 (1960).



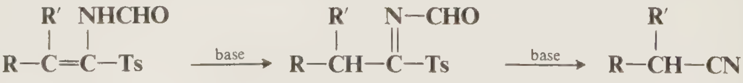
$$\mathrm{Ar_2CH{-}\underset{\underset{\displaystyle N{-}OH}{\|}}{C}{-}Me \xrightarrow{PCl_5} Me{-}C{\equiv}N + Ar_2CHCl}$$

There are indications that the mechanism at least in some cases first involves a rearrangement, and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates $\mathrm{R{-}\underset{\underset{\displaystyle NOTs}{\|}}{C}{-}Me}$ was not related to the solvolysis rate but *was* related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.[328] It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



However, in other cases the simple E1 or E2 mechanisms operate.[329] The fragmentation of certain ketoximes to nitriles has also been carried out with tetrakis(triphenylphosphine)palladium $Pd(PPh_3)_4$.[329a] In this case the other product is the aldehyde R′CHO.

The fragmentation of N-(1-tosyl-1-alkenyl)formamides (**65**) by refluxing with NaOMe in MeOH is a step in the conversion of a ketone to a nitrile,[330] since **65** can be prepared by treatment of



$$\underset{\textbf{65}}{\mathrm{R{-}\overset{\overset{\displaystyle R'}{|}}{C}{=}\overset{\overset{\displaystyle NHCHO}{|}}{C}{-}Ts}} \xrightarrow{\text{base}} \mathrm{R{-}\overset{\overset{\displaystyle R'}{|}}{C}H{-}\overset{\overset{\displaystyle N{-}CHO}{\|}}{C}{-}Ts} \xrightarrow{\text{base}} \mathrm{R{-}\overset{\overset{\displaystyle R'}{|}}{C}H{-}CN}$$

ketones with $TsCH_2NC$ (p. 858). The overall conversion is RR′C=O to RR′CHCN.

OS V, 266.

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[326] See for example Hill and Conley, *J. Am. Chem. Soc.* **82,** 645 (1960).

[327] Hassner and Nash, *Tetrahedron Lett.* 525 (1965).

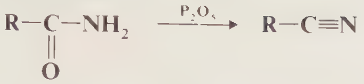
[328] Grob, Fischer, Raudenbusch, and Zergenyi, *Helv. Chim. Acta* **47,** 1003 (1964).

[329] Ahmad and Spenser, *Can. J. Chem.* **39,** 1340 (1961); Ferris, Johnson, and Gould, *J. Org. Chem.* **25,** 1813 (1960); Grob and Sieber, *Helv. Chim. Acta* **50,** 2520 (1967); Green and Pearson, *J. Chem. Soc. B* 593 (1969).

[329a] Maeda, Moritani, Hosokawa, and Murahashi, *J. Chem. Soc., Chem. Commun.* 689 (1975).

[330] Schöllkopf and Schröder, *Angew. Chem. Int. Ed. Engl.* **12,** 407 (1973) [*Angew. Chem.* **85,** 402].

7-41 Dehydration of Unsubstituted Amides



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}NH_2} \xrightarrow{\mathrm{P_2O_5}} \mathrm{R{-}C{\equiv}N}$$

Unsubstituted amides can be dehydrated to nitriles.[331] Phosphorus pentoxide is the most common dehydrating agent for this reaction, but many others, including $POCl_3$, PCl_5, CCl_4–Ph_3P,[332] $TiCl_4$–base,[333] $CHCl_3$-$PhCH_2NEt_3{}^+$ Cl^- base,[334] HMPT,[335] phosphorus tris(diethylamide) $P(NEt_2)_3$,[336] and $SOCl_2$, have also been used. It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent. The reaction may be formally looked on as a β-elimination from the enol form of the amide $\mathrm{R{-}\underset{\underset{OH}{|}}{C}{=}NH}$, in which case it is like reaction **7-39**, except that H and OH have changed places. In some cases, for example, with $SOCl_2$, the mechanism probably *is* through the enol form, with the dehydrating agent forming an ester with the OH group, for example, $\mathrm{R{-}\underset{\underset{OSOCl}{|}}{C}{=}NH}$, which undergoes elimination by the E1 or E2 mechanism.[337]

N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5. This reaction is called the *von Braun reaction* (not to be confused with the other von Braun reaction, **0-72**).

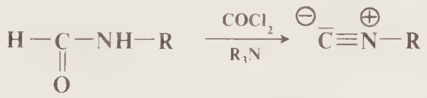
$$\mathrm{R'CONHR + PCl_5 \longrightarrow R'CN + RCl}$$

In a similar reaction, treatment of N-alkyl-substituted amides with chlorotris(triphenylphosphine)rhodium $RhCl(PPh_3)_3$ or certain other catalysts gives nitriles and the corresponding alcohols.[338] N-Sulfo chloride derivatives of amides (prepared by treatment of carboxylic acids or ketones with chlorosulfonyl isocyanate $ClSO_2NCO$) can be converted to nitriles by treatment with dimethylformamide[339] or with triethylamine.[340]

$$\mathrm{RCONHSO_2Cl} \xrightarrow[\mathrm{Et_3N}]{\mathrm{DMF\ or}} \mathrm{RCN}$$

OS **I,** 428; **II,** 379; **III,** 493, 535, 584, 646, 768; **IV,** 62, 144, 166, 172, 436, 486, 706; **50,** 18, 52.

7-42 Conversion of N-Alkylformamides to Isonitriles



$$\mathrm{H{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R} \xrightarrow[\mathrm{R_3N}]{\mathrm{COCl_2}} \overset{\ominus}{\underline{C}}{\equiv}\overset{\oplus}{N}{-}R$$

Isonitriles can be prepared by elimination of water from N-alkylformamides with phosgene and a tertiary amine.[341] Other reagents, among them TsCl in quinoline, $POCl_3$ in pyridine, chlorodimethylformiminium chloride[342] $Me_2N{=}CHCl^+\ Cl^-$, $Ph_3P\text{–}CCl_4\text{–}Et_3N$,[343] and $Ph_3PBr_2\text{–}Et_3N$,[344] have also been employed.

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[331] For reviews, see Bieron and Dinan, in Zabicky, "The Chemistry of Amides," pp. 274–283, Interscience Publishers, New York, 1970; Friedrich and Wallenfels, Ref. 312, pp. 96–103.

[332] Yamamoto and Sugasawa, *Tetrahedron Lett.* 4383 (1970); Appel, Kleinstück, and Ziehn, *Chem. Ber.* **104,** 1030 (1971).

[333] Lehnert, *Tetrahedron Lett.* 1501 (1971).

[334] Saraie, Ishiguro, Kawashima, and Morita, *Tetrahedron Lett.* 2121 (1973).

[335] Monson and Priest, *Can. J. Chem.* **49,** 2897 (1971).

[336] Sodeyama, Kodomari, and Itabashi, *Chem. Lett.* 577 (1973).

[337] Rickborn and Jensen, *J. Org. Chem.* **27,** 4608 (1962).

[338] Blum, Fisher, and Greener, *Tetrahedron* **29,** 1073 (1973).

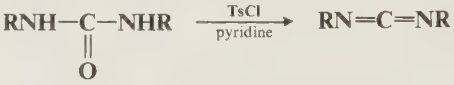
[339] Lohaus, *Chem. Ber.* **100,** 2719 (1967); Rasmussen and Hassner, *Synthesis* 682 (1973).

[340] Vorbrüggen, *Tetrahedron Lett.* 1631 (1968).

[341] For reviews, see Hoffmann, Gokel, Marquarding, and Ugi, in Ugi, "Isonitrile Chemistry," pp. 10–17, Academic Press, Inc., New York, 1971; Ugi, Fetzer, Eholzer, Knupfer, and Offermann, *Angew. Chem. Int. Ed. Engl.* **4,** 472–484 (1965) [*Angew. Chem.* **77,** 492–504], *Newer Methods Prep. Org. Chem.* **4,** 37–66 (1968); Sandler and Karo, "Organic Functional Group Preparations," vol. 3, pp. 188–200, Academic Press, Inc., New York, 1972.

OS **V**, 300, 772; **51**, 31.

7-43 Dehydration of N,N′-Disubstituted Ureas and Thioureas



$$RNH\text{—}\underset{\underset{O}{\|}}{C}\text{—}NHR \xrightarrow[\text{pyridine}]{\text{TsCl}} RN{=}C{=}NR$$

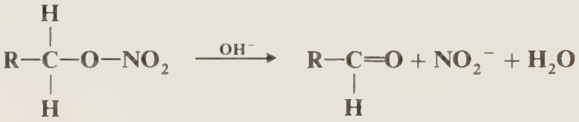
Carbodiimides[345] can be prepared by the dehydration of N,N′-disubstituted ureas with various dehydrating agents, among which are TsCl in pyridine, $POCl_3$, PCl_5, P_2O_5–pyridine, and $Ph_3PBr_2\text{–}Et_3N$.[344] H_2S can be removed from the corresponding thioureas by treatment with HgO, NaOCl, phosgene,[346] or diethyl azodicarboxylate–triphenylphosphine.[347]

OS **V**, 555.

Reactions in Which C=O Bonds Are Formed

Many elimination reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions. Also see reactions **2-39** to **2-41** and **4-42.**

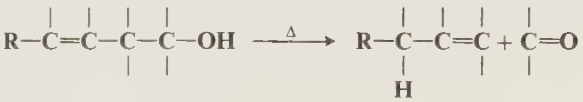
7-44 Alkaline Hydrolysis of Nitrates



$$R\text{—}\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}\text{—}O\text{—}NO_2 \xrightarrow{OH^-} R\text{—}\underset{\underset{H}{|}}{C}{=}O + NO_2^- + H_2O$$

Nitrates of primary or secondary alcohols can be hydrolyzed with base to give aldehydes or ketones,[348] but other reactions compete: hydrolysis to the alcohol (reaction **0-4**) and elimination to the olefin (reaction **7-5**). Compounds in which R is aryl give the highest yields. The mechanism is E2[349] (often expressed as Eco2 when applied to this reaction, to indicate that a C=O bond is being formed). This is an indirect method of oxidation of alcohols to aldehydes or ketones. (See reaction **9-4.**)

7-45 Pyrolysis of β-Hydroxy Olefins



$$R\text{—}\overset{|}{C}{=}\overset{|}{C}\text{—}\underset{|}{\overset{|}{C}}\text{—}\underset{|}{\overset{|}{C}}\text{—}OH \xrightarrow{\Delta} R\text{—}\underset{\underset{H}{|}}{\overset{|}{C}}\text{—}\overset{|}{C}{=}\underset{|}{\overset{|}{C}} + \underset{|}{\overset{|}{C}}{=}O$$

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[342] Walborsky and Niznik, *J. Org. Chem.* **37**, 187 (1972).

[343] Appel, Kleinstück, and Ziehn, *Angew. Chem. Int. Ed. Engl.* **10**, 132 (1971) [*Angew. Chem.* **83**, 143].

[344] Bestmann, Lienert, and Mott, *Justus Liebigs Ann. Chem.* **718**, 24 (1968).

[345] For reviews of the reactions in this section, see Sandler and Karo, Ref. 341, vol. 2, pp. 212–219 (1971); Bocharov, *Russ. Chem. Rev.* **34**, 212–219 (1965).

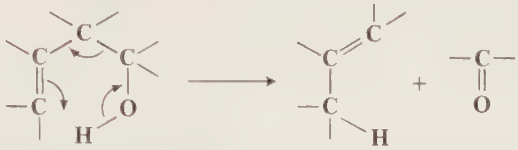
[346] Ulrich and Sayigh, *Angew. Chem. Int. Ed. Engl.* **5**, 704–712 (1966) [*Angew. Chem.* **78**, 761–769], *Newer Methods Prep. Org. Chem.* **6**, 223–242 (1971).

[347] Mitsunobu, Kato, and Tomari, *Tetrahedron* **26**, 5731 (1970). See also Appel, Kleinstück, and Ziehn, *Chem. Ber.* **104**, 1335 (1971).

[348] Boschan, Merrow, and Van Dolah, *Chem. Rev.* **55**, 485-510 (1955).

[349] Buncel and Bourns, *Can. J. Chem.* **38**, 2457 (1960); Smith and Bourns, *Can. J. Chem.* **44**, 2553 (1966); Smith, Pollock, and Bourns, *Can. J. Chem.* **53**, 1319 (1975).

β-Hydroxy olefins are cleaved when pyrolyzed to give olefins and aldehydes or ketones.[350] Olefins produced in this way are quite pure, since there are no side reactions. The mechanism has been shown to be Ei, primarily by observations that the kinetics are first order[351] and that, for ROD, the deuterium appeared in the allylic position of the new olefin.[352]

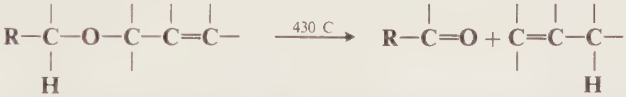


An example of this reaction is the pyrolysis of ricinoleic acid

$$CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7COOH \rightarrow CH_3(CH_2)_5CHO + CH_2{=}CH(CH_2)_8COOH$$

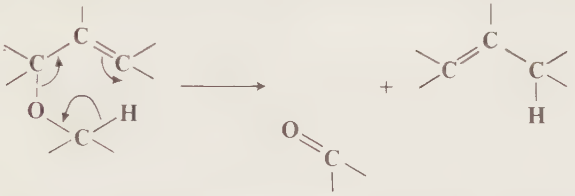
β-Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.[353] The mechanism is the same despite the linear geometry of the triple bonds.

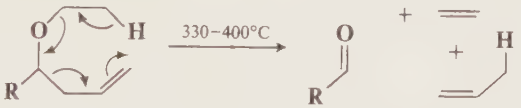
7-46 Pyrolysis of Allyl Ethers



$$\mathrm{R{-}\underset{H}{\overset{|}{C}}{-}O{-}\underset{|}{\overset{|}{C}}{-}\overset{|}{C}{=}\overset{|}{C}{-}} \xrightarrow{430\ \mathrm{C}} \mathrm{R{-}\overset{|}{C}{=}O + \underset{|}{\overset{|}{C}}{=}\overset{|}{C}{-}\underset{H}{\overset{|}{C}}{-}}$$

Pyrolysis of allyl ethers which contain at least one α-hydrogen gives olefins and aldehydes or ketones. The reaction is closely related to reaction **7-45**, and the mechanism is also Ei, though not exactly analogous.[354] Note that this mechanism is the reverse of that of the ene synthesis (**5-18**). Homoallylic ethers can be pyrolytically cleaved via an eight-membered cyclic transition state to give an aldehyde and two alkenes.[355]





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[350] Arnold and Smolinsky, *J. Am. Chem. Soc.* **81,** 6443 (1959). For a review, see Marvell and Whalley, in Patai, Ref. 137, pt. 2, pp. 729–734.

[351] Smith and Yates, *J. Chem. Soc.* 7242 (1965); Smith and Voorhees, *J. Org. Chem.* **35,** 2182 (1970); Voorhees and Smith, *J. Org. Chem.* **36,** 1755 (1971).

[352] Arnold and Smolinsky, *J. Org. Chem.* **25,** 128 (1960); Smith and Taylor, *Chem. Ind.* (*London*) 949 (1961).

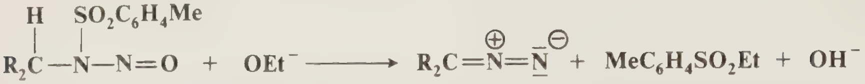
[353] Viola, MacMillan, Proverb, and Yates, *J. Am. Chem. Soc.* **93,** 6967 (1971); Viola, Proverb, Yates, and Larrahondo, *J. Am. Chem. Soc.* **95,** 3609 (1973).

[354] Cookson and Wallis, *J. Chem. Soc. B* 1245 (1966); Kwart, Sarner, and Slutsky, *J. Am. Chem. Soc.* **95,** 5234 (1973); Kwart, Slutsky, and Sarner, *J. Am. Chem. Soc.* **95,** 5242 (1973); Egger and Vitins, *Int. J. Chem. Kinet.* **6,** 429 (1974).

[355] Viola, Madhavan, Proverb, Yates, and Larrahondo, *J. Chem. Soc., Chem. Commun.* 842 (1974).

Reactions in Which N=N Bonds Are Formed

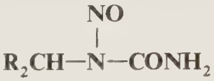
7-47 Eliminations to Give Diazoalkanes



$$R_2\overset{H}{C}-\overset{SO_2C_6H_4Me}{N}-N=O + OEt^- \longrightarrow R_2C=\overset{\oplus}{N}=\overset{\ominus}{\underline{N}} + MeC_6H_4SO_2Et + OH^-$$

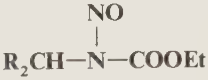
Various N-nitroso-N-alkyl compounds undergo elimination to give diazoalkanes.[356] One of the most convenient methods for the preparation of diazomethane involves base treatment of N-nitroso-N-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).[357] However, other compounds commonly used are (base treatment is required in all cases):

N-Nitroso-N-alkylureas



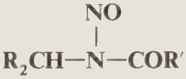
$$R_2CH-\overset{NO}{N}-CONH_2$$

N-Nitroso-N-alkylcarbamates



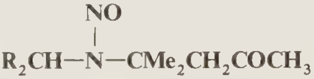
$$R_2CH-\overset{NO}{N}-COOEt$$

N-Nitroso-N-alkyl amides



$$R_2CH-\overset{NO}{N}-COR'$$

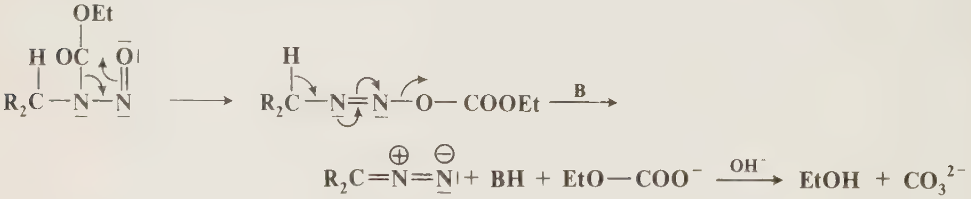
N-Nitroso-N-alkyl-4-amino-4-methyl-2-pentanones



$$R_2CH-\overset{NO}{N}-CMe_2CH_2COCH_3$$

All these compounds can be used to prepare diazomethane, though the sulfonamide, which is commercially available, is most satisfactory. (N-Nitroso-N-methylcarbamate and N-nitroso-N-methylurea give good yields, but are highly irritating and carcinogenic.[358]) For higher diazoalkanes the preferred substrates are nitrosoalkylcarbamates.

Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS **II**, 165; **III**, 119, 244; **IV**, 225, 250; **V**, 351.

Extrusion Reactions

We consider an *extrusion reaction*[359] to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z. Reactions **4-41**, **4-42**, **7-23**, and part of **9-54** also fit this definition. Reaction **7-38**

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[356] For discussions, see Cowell and Ledwith, *Q. Rev., Chem. Soc.* **24**, 119–167 (1970), pp. 126–131; Sandler and Karo, Ref. 341, vol. 1, pp. 389–397 (1968); Smith, "Open-chain Nitrogen Compounds," vol. 2, especially pp. 257–258, 474–475, W. A. Benjamin, Inc., New York, 1966; Gutsche, *Org. React.* **8**, 364–429 (1954), pp. 389–390.

[357] de Boer and Backer, *Org. Synth.* **IV**, 225, 250.

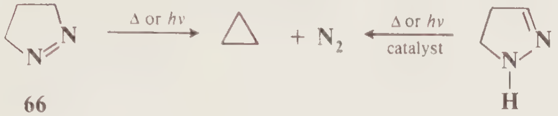
[358] Searle, *Chem. Br.* **6**, 5–10 (1970).

[359] For a monograph, see Stark and Duke, "Extrusion Reactions," Pergamon Press, Oxford, 1967.

$$\mathrm{X{-}Y{-}Z} \longrightarrow \mathrm{X{-}Z} + \mathrm{Y}$$

does not fit the definition but is often also classified as an extrusion reaction.

7-48 Extrusion of N_2 from Pyrazolines, Pyrazoles, and Triazolines



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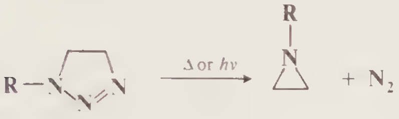

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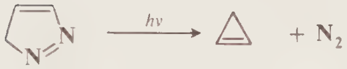
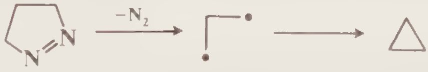


69

1-Pyrazolines (**66**) can be converted to cyclopropanes and N_2 on photolysis[360] or pyrolysis.[361] The tautomeric 2-pyrazolines (**67**), which are more stable than **66**, also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **67** to **66**.[362] In the absence of such catalysts, **67** do not react.[363] In a similar manner, triazolines (**68**) are converted to aziridines.[364] Side reactions are frequent with both **66** and **68**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **66** and **68**. 3*H*-Pyrazoles (**69**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,[365] though in other cases other types of products are obtained.

There is much evidence that the mechanism of the 1-pyrazoline reactions generally involves diradicals,[366] though the mode of formation and detailed structure (e.g., singlet versus triplet) of



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[360] Van Auken and Rinehart, *J. Am. Chem. Soc.* **84,** 3736 (1962).

[361] For a review of the reactions in this section, see Ref. 359, pp. 116–151. For a review of the formation and fragmentation of cyclic azo compounds, see Mackenzie, in Patai, "The Chemistry of the Hydrazo, Azo, and Azoxy Groups," pt. 1, pp. 329–442, John Wiley & Sons, New York, 1975.

[362] For example, see Jones, Sanderfer, and Baarda, *J. Org. Chem.* **32,** 1367 (1967).

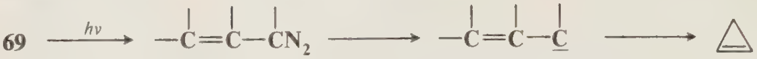
[363] McGreer, Wai, and Carmichael, *Can. J. Chem.* **38,** 2410 (1960); Kocsis, Ferrini, Arigoni, and Jeger, *Helv. Chim. Acta* **43,** 2178 (1960).

[364] For a review, see Scheiner, *Sel. Org. Transform.* **1,** 327–362 (1970).

[365] Closs and Böll, *J. Am. Chem. Soc.* **85,** 3904 (1963), *Angew. Chem. Int. Ed. Engl.* **2,** 399 (1963) [*Angew. Chem.* **75,** 640]; Ege, *Tetrahedron Lett.* 1667 (1963); Closs, Kaplan, and Bendall, *J. Am. Chem. Soc.* **89,** 3376 (1967); Closs, Böll, Heyn, and Dev, *J. Am. Chem. Soc.* **90,** 173 (1968); Franck-Neumann and Buchecker, *Tetrahedron Lett.* 15 (1969); Pincock, Morchat, and Arnold, *J. Am. Chem. Soc.* **95,** 7536 (1973).

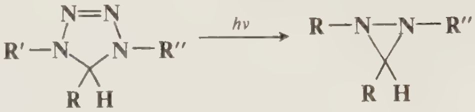
[366] For example, see Crawford and Erickson, *J. Am. Chem. Soc.* **89,** 3907 (1967); Al-Sader and Crawford, *Can. J. Chem.* **46,** 3301 (1968); Moore, Mishra, and Crawford, *Can. J. Chem.* **46,** 3305 (1968); Allred and Smith, *J. Am. Chem. Soc.* **91,** 6766 (1969); White, Condit, and Bergman, *J. Am. Chem. Soc.* **94,** 1348, 7931 (1972); Nowacki, Do, and Dorer, *J. Chem. Soc., Chem. Commun.* 273 (1972); Klunder and Carr, *J. Am. Chem. Soc.* **95,** 7386 (1973); Neuman and Ertley, *J. Am. Chem. Soc.* **97,** 3130 (1975); Clarke, Wendling, and Bergman, *J. Am. Chem. Soc.* **97,** 5638 (1975).

these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles have been postulated to proceed through a diazo compound which loses N_2 to give a vinylcarbene.[367]



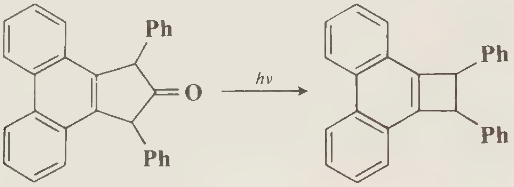
$$\mathbf{69} \xrightarrow{h\nu} -\overset{|}{C}=\overset{|}{C}-\overset{|}{C}N_2 \longrightarrow -\overset{|}{C}=\overset{|}{C}-\overset{|}{\underline{C}} \longrightarrow \triangle$$

Δ^2-Tetrazolines can be photolyzed to diaziridines.[368]



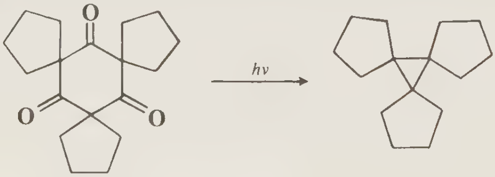
OS V, 96, 929.

7-49 Extrusion of CO or CO_2



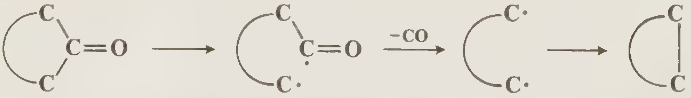
70 **71**

Though the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.[369] In the example above, the tetracyclic ketone **70** was photolyzed to give the diphenylphenanthro(*l*)cyclobutene compound **71.**[370] Another example is formation of trispiro-[4.0.4.0.4.0]pentadecane by extrusion of three moles of CO from the triene **72.**[371]



72

The mechanism probably involves a Norrish type I cleavage (p. 221), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO_2 on heating or on irradiation, examples being pyrolysis of 7-chloro-6,8-dimethyl-1,4,5-benzoxadiazepin-2-one (**73**) to give the corresponding indazole **74**,[372]

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[367] Closs, Böll, Heyn, and Dev, Ref. 365; Pincock, Morchat, and Arnold, Ref. 365.

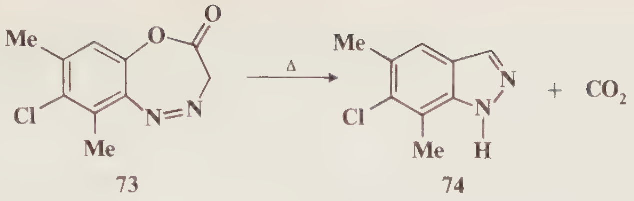
[368] Akiyama, Kitamura, Isida, and Kawanisi, *Chem. Lett.* 185 (1974).

[369] For reviews of the reactions in this section, see Redmore and Gutsche, *Adv. Alicyclic Chem.* **3**, 1–138 (1971), pp. 91–107; Ref. 359, pp. 47–71; Quinkert, *Pure Appl. Chem.* **9**, 607–621 (1964); Srinivasan, *Adv. Photochem.* **1**, 83–113 (1963).

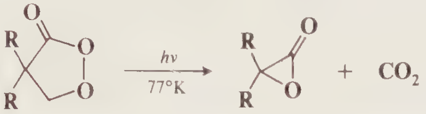
[370] Cava and Mangold, *Tetrahedron Lett.* 1751 (1964).

[371] Krapcho and Waller, *Tetrahedron Lett.* 3521 (1970).

[372] Ried and Dietrich, *Angew. Chem. Int. Ed. Engl.* **2**, 323 (1963) [*Angew. Chem.* **75**, 476]; Ried and Wagner, *Justus Liebigs Ann. Chem.* **681**, 45 (1965).

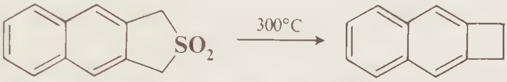

Me
Cl
Me
O
O
N=N
Δ
Me
Cl
Me
N
N
H
+ CO_2
73
74

and the formation of α-lactones by photolysis of 1,2-dioxolane-3,5-diones.[373]

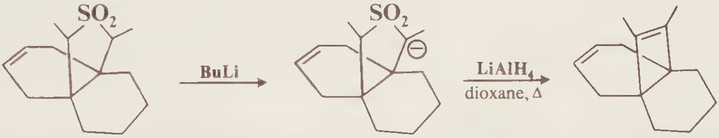

O
R
O
O
R
hν
77°K
R
O
R
O
+ CO_2

Decarboxylation of *β*-lactones (see reaction **7-34**) may be regarded as a degenerate example of this reaction. See also reactions **7-38** and **7-53.**

7-50 Extrusion of SO_2

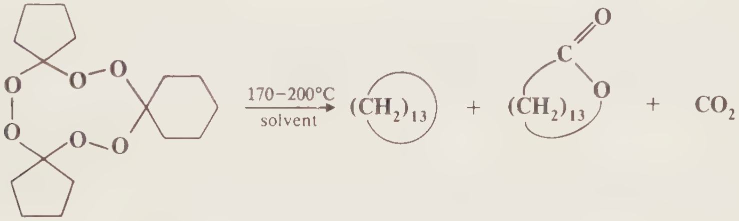


In a reaction similar to **7-49,** certain cyclic sulfones extrude SO_2 on heating to give ring-contracted products.[374] Like **7-49,** this is not a general reaction, but it can be useful in certain cases, for example, in the preparation of naphtho(*b*)cyclobutene shown above.[375] In a different kind of reaction, five-membered cyclic sulfones can be converted to cyclobutenes by treatment with butyllithium followed by $LiAlH_4$,[376] e.g.,


SO_2
BuLi
SO_2
⊖
$LiAlH_4$
dioxane, Δ

This method is most successful when both the α and α′ positions of the sulfone bear alkyl substituents. See also reaction **7-23.**

7-51 The Story Synthesis


O
O—O
O
O
O—O
170–200°C
solvent
$(CH_2)_{13}$
+
O
C
O
$(CH_2)_{13}$
+ CO_2

75

When cycloalkylidene peroxides (e.g., **75**) are heated in an inert solvent (e.g., decane), extrusion of CO_2 takes place, and the products are the cycloalkane containing three carbon atoms less than the starting peroxide, and the lactone containing two carbon atoms less.[377] The reaction is called the *Story synthesis*.[378] The two products are formed in comparable yields, usually about 15 to 25% each. Although the yields are not high, the reaction is useful because there are not many other ways to prepare large rings. The same products are obtained by photolysis, but yields are generally lower. The reaction is versatile, having been used to prepare rings of every size from 8 to 33 members. The method is also applicable to dimeric cycloalkylidene peroxides, in which case the cycloalkane and lactone products result from loss of two molecules and one molecule of CO_2, respectively, e.g.,

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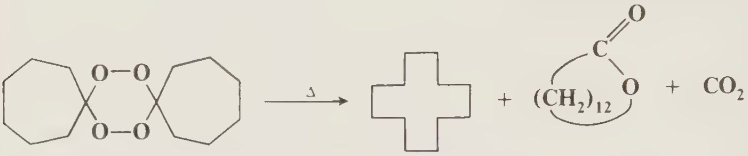
[373] Chapman, Wojtkowski, Adam, Rodriquez, and Rucktäschel, *J. Am. Chem. Soc.* **94,** 1365 (1972).

[374] For reviews of extrusions of SO_2, see Ref. 359, pp. 72–90; Kice, Ref. 246, pp. 115–136.

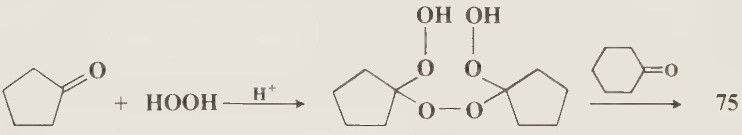
[375] Cava and Shirley, *J. Am. Chem. Soc.* **82,** 654 (1960).

[376] Photis and Paquette, *J. Am. Chem. Soc.* **96,** 4715 (1974).



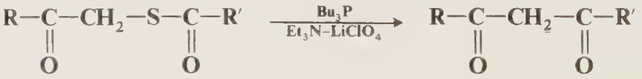
Dimeric and trimeric cycloalkylidene peroxides containing certain ring substituents (e.g., Me, *t*-Bu, OMe) also give the reaction.[379]

Both dimeric and trimeric cycloalkylidene peroxides can be synthesized by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution,[380] or in the presence of an ion-exchange resin.[381] The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.[382] Mixed trimeric peroxides (e.g., **75**) can be prepared[383] by formation of 1,1′-dihydroperoxycycloalkyl peroxides (e.g., **76**) and treatment of these with cyclic ketones.



76

7-52 Formation of β-Dicarbonyl Compounds by Extrusion of Sulfur



$$R-\underset{\underset{O}{\|}}{C}-CH_2-S-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[Et_3N-LiClO_4]{Bu_3P} R-\underset{\underset{O}{\|}}{C}-CH_2-\underset{\underset{O}{\|}}{C}-R'$$

Thioesters containing a β-keto group in the alkyl portion can be converted to β-diketones by treatment with a tertiary phosphine under basic conditions.[384] The starting thioesters can be prepared by the reaction between a thiol acid and an α-halo ketone (similar to reaction **0-26**).

OS **55**, 127.

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[377] Story, Denson, Bishop, Clark, and Farine, *J. Am. Chem. Soc.* **90**, 817 (1968); Sanderson and Story, *J. Org. Chem.* **39**, 3463 (1974); Sanderson, Story, and Paul, *J. Org. Chem.* **40**, 691 (1975).

[378] For a review, see Story and Busch, *Adv. Org. Chem.* **8**, 67–95 (1972), pp. 79–94.

[379] Sanderson, Paul, Story, Denson, and Alford, *Synthesis* 159 (1975); Sanderson, Paul, and Story, *Synthesis* 275 (1975).

[380] Kharasch and Sosnovsky, *J. Org. Chem.* **23**, 1322 (1958); Ledaal, *Acta Chem. Scand.* **21**, 1656 (1967).

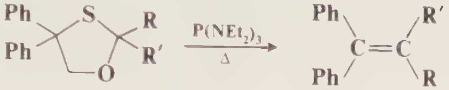
[381] Sanderson and Zeiler, *Synthesis* 125 (1975).

[382] Story, Lee, Bishop, Denson, and Busch, *J. Org. Chem.* **35**, 3059 (1970).

[383] Sanderson and Zeiler, *Synthesis* 388 (1975); Paul, Story, Busch, and Sanderson, *J. Org. Chem.* **41**, 1283 (1976). See also Busch and Story, *Synthesis* 181 (1970).

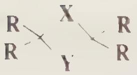
[384] Roth, Dubs, Götschi, and Eschenmoser, *Helv. Chim. Acta* **54**, 710 (1971).

7-53 Olefin Synthesis by Twofold Extrusion

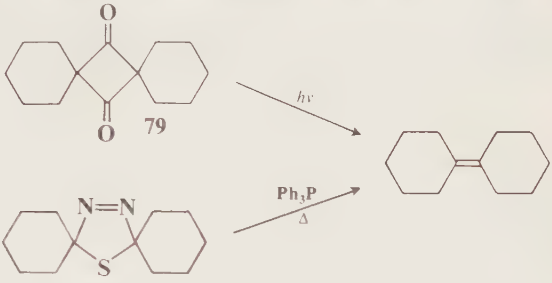


77

4,4-Diphenyloxathiolan-5-ones (**77**) give good yields of the corresponding olefins when heated with tris(diethylamino)phosphine.[385] This reaction is an example of a general type: olefin synthesis by twofold extrusion of X and Y from a molecule of the type **78.** Other examples



78



79

80

are photolysis of 1,4-diones[386] (e.g., **79**) and treatment with Ph_3P of the azo sulfide **80.**[387] **77** can be prepared by the condensation of thiobenzilic acid $Ph_2C(SH)COOH$ with aldehydes or ketones.

OS **V,** 297.

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[385] Barton and Willis, *J. Chem. Soc., Perkin Trans. 1* 305 (1972).

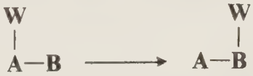
[386] Turro, Leermakers, Wilson, Neckers, Byers, and Vesley, *J. Am. Chem. Soc.* **87,** 2613 (1965).

[387] Barton, Smith, and Willis, *Chem. Commun.* 1226 (1970); Barton, Guziec, and Shahak, *J. Chem. Soc., Perkin Trans. 1* 1794 (1974). See also Buter, Wassenaar, and Kellogg, *J. Org. Chem.* **37,** 4045 (1972); Bee, Beeby, Everett, and Garratt, *J. Org. Chem.* **40,** 2212 (1975).

Eighteen

Rearrangements

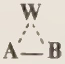
In a rearrangement reaction a group moves from one atom to another in the same molecule.[1] Most are migrations from an atom to an adjacent one (called 1,2 shifts)



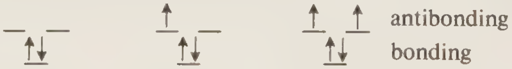
$$\overset{W}{A}-B \longrightarrow A-\overset{W}{B}$$

but some are over longer distances. The migrating group (W) may move with its electron pair (these may be called *nucleophilic* or *anionotropic* rearrangements; the migrating group may be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (free-radical rearrangements). The atom A is called the *migration origin*, and B is the *migration terminus*. However, there are some rearrangements which do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (reactions **8-32** to **8-45**).

As we shall see, nucleophilic 1,2 shifts are much more common than electrophilic or free-radical 1,2 shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. We represent the transition state or intermediate for all three cases by **1**, in which the two-electron A—W bond overlaps with the orbital on atom B, which contains zero, one, and two electrons, in the cases of nucleophilic, free-radical, and electrophilic migration, respectively.



1



Nucleophilic Free radical Electrophilic

The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those on p. 53 (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital, and **1** is a low-energy transition state; but in a free-radical or electrophilic migration, there are, respectively, three or four electrons which must be accommodated, and antibonding orbitals must be occupied. It is not surprising therefore that, when 1,2 electrophilic or free-radical shifts are found, the migrating group W is usually aryl or some other group which can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see **37** on p. 976).

In any rearrangement we may in principle distinguish between two possible modes of reaction: In one of these the group W becomes completely detached from A and may end up on the

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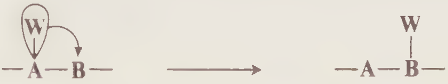
[1] For monographs, see Stevens and Watts, "Selected Molecular Rearrangements," Van Nostrand Reinhold Company, London, 1973; Mayo, "Molecular Rearrangements," 2 vols., Interscience Publishers, New York, 1963. For a review of many of these rearrangements, see Collins and Eastham, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 761–821, Interscience Publishers, New York, 1966. See also the series *Mechanisms of Molecular Migrations*.

B-atom of a different molecule (*intermolecular* rearrangement), and in the other W goes from A to B in the *same* molecule (*intramolecular* rearrangement), in which case there must be some continuing tie holding W to the A—B system, preventing it from coming completely free. Strictly speaking, only the intramolecular type fits our definition of a rearrangement, but the general practice, which is followed here, is to include under the title "rearrangement" all net rearrangements whether they are inter- or intramolecular. It is usually not difficult to tell whether a given rearrangement is intramolecular or not. The most common method involves the use of *crossover* experiments. In this type of experiment, rearrangement is carried out on a mixture of W—A—B and V—A—C, where V is closely related to W (say, methyl versus ethyl) and B to C. In an intramolecular process only A—B—W and A—C—V are recovered, but if the reaction is intermolecular, then not only will these two be found, but also A—B—V and A—C—W.

MECHANISMS

Nucleophilic Rearrangements[2]

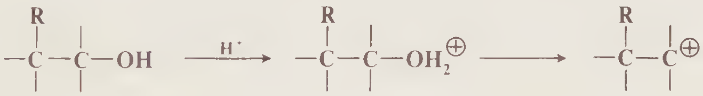
Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:



$$\overset{W}{-A-B-} \longrightarrow -A-\overset{\overset{W}{|}}{B}-$$

This process is sometimes called the Whitmore 1,2 shift.[3] Since the migrating group carries the electron pair with it, the migration terminus B must be an atom with only six electrons in its outer shell (an open sextet). The first step therefore is creation of a system with an open sextet. Such a system can arise in various ways, but two of these are the most important:

1. *Formation of a carbonium ion.* Carbonium ions can be formed in a number of ways (see p. 159), but one of the most common methods when a rearrangement is desired is the acid treatment of an alcohol:

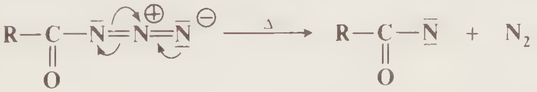


$$-\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{|}{C}}-OH \xrightarrow{H^+} -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{|}{C}}-OH_2^{\oplus} \longrightarrow -\underset{|}{\overset{\overset{R}{|}}{C}}-\underset{|}{\overset{|}{C}}^{\oplus}$$

2

These two steps are of course the same as the first two steps of the SN1cA or the E1 reactions of alcohols.

2. *Formation of a nitrene.* The decomposition of acyl azides is one of several ways in which nitrenes are formed (see p. 185):



$$R-\underset{\overset{\|}{O}}{C}-\bar{N}=\overset{\oplus}{N}=\bar{N}^{\ominus} \xrightarrow{\Delta} R-\underset{\overset{\|}{O}}{C}-\bar{N} + N_2$$

3

After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step this atom acquires an octet. In the case of carbonium ions, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of a hydrogen (rearrangement with elimination).

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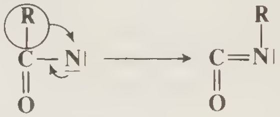
[2] For a review, see Wheland, "Advanced Organic Chemistry," 3d ed., pp. 550–619, John Wiley & Sons, Inc., New York, 1960.

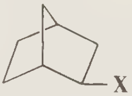
[3] It was first postulated by Whitmore, *J. Am. Chem. Soc.* **54**, 3274 (1932).

Though we have presented this mechanism as taking place in three steps, and some reactions do take place in this way, in many cases two or all three steps are actually simultaneous. For instance, in the nitrene example above, as the R migrates, an electron pair from the nitrogen moves into the C—N bond to give a stable isocyanate:



In this example, the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the "third" step involves more than just a simple motion of a pair of electrons. Similarly, there are reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species such as **2** or **3**. In these instances it may be said that R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as **2** or **3** actually form, or whether the steps are simultaneous (see, for example, the discussions on pp. 966, 1003), but the difference between the two possibilities is often subtle, and the question is not always easily answered.

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbonium ions: SN1 conditions, Friedel-Crafts alkylation, etc. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,[4] so that the first step is carbonium-ion formation. The same compound under SN2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbonium ion leads only to rearrangement. Carbonium ions usually rearrange to more stable carbonium ions. Thus the direction of rearrangement is usually primary → secondary → tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **4**) type systems are especially prone to carbonium-ion rearrangement reactions.



4

We have previously mentioned (p. 152) that stable tertiary carbonium ions can be obtained, in solution, at very low temperatures. Nmr studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an equilibrium mixture of structures.[5] For example, the *t*-pentyl cation (**5**)[6] equilibrates as follows:[7]

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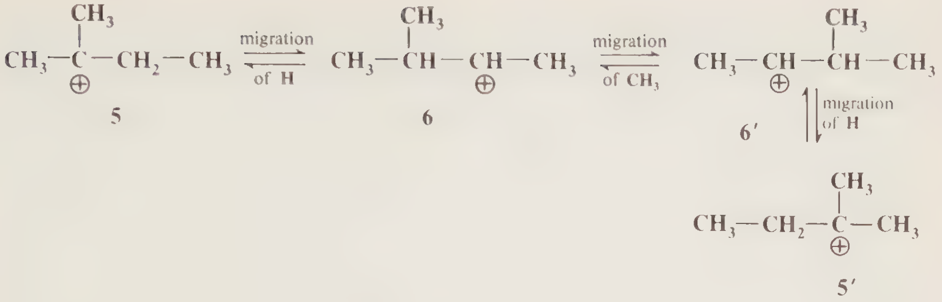
[4] Dostrovsky and Hughes, *J. Chem. Soc.* 166 (1946).

[5] For reviews, see Brouwer and Hogeveen, *Prog. Phys. Org. Chem.* **9**, 179–240 (1972), pp. 203–237; Olah and Olah, in Olah and Schleyer, "Carbonium Ions," vol. 2, pp. 751–760, 766–778, Interscience Publishers, New York, 1970.

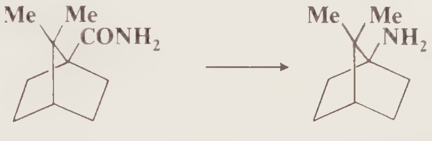
[6] Brouwer, *Recl. Trav. Chim. Pays-Bas* **87**, 210 (1968); Saunders and Hagen, *J. Am. Chem. Soc.* **90**, 2436 (1968).

[7] Carbonium ions which rearrange to give products of identical structure (e.g., **5** ⇌ **5′**, **6** ⇌ **6′**, or **89** or **90** on p. 302) are called *degenerate carbonium ions*. Many examples are known. For reviews, see Leone, Barborak, and Schleyer, in Olah and Schleyer, Ref. 5, vol. 4, pp. 1837–1939 (1973); Leone and Schleyer, *Angew. Chem. Int. Ed. Engl.* **9**, 860–890 (1970) [*Angew. Chem.* **82**, 889–919].



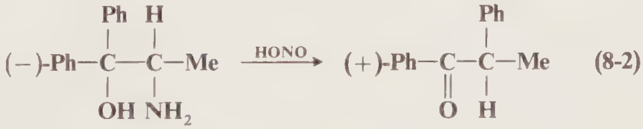
The Actual Nature of the Migration

Most nucleophilic 1,2 shifts are intramolecular: W does not become free but always remains connected in some way to the substrate. Apart from the evidence from crossover experiments, the strongest evidence is that, when the group W is chiral, the configuration is *retained* in the product. For example (+)-PhCHMeCOOH was converted to (−)-PhCHMeNH_2 by the Curtius (**8-18**), Hofmann (**8-17**), Lossen (**8-19**), and Schmidt (**8-20**) reactions.[8] In these reactions the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.[9] Another experiment demonstrating retention was the easy conversion of **7** to **8**.[10]



7 **8**

Neither inversion nor racemization could take place at a bridgehead. There is much other evidence that retention of configuration usually occurs in W, and inversion never.[11] However, this is not the state of affairs at A and B. In many reactions, of course, the structure of W—A—B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. Thus the following conversion proceeded with inversion at B:[12]



$$(-)\text{-Ph}-\underset{\text{OH}}{\overset{\text{Ph}}{\text{C}}}-\underset{\text{NH}_2}{\overset{\text{H}}{\text{C}}}-\text{Me} \xrightarrow{\text{HONO}} (+)\text{-Ph}-\underset{\text{O}}{\overset{\text{Ph}}{\overset{\|}{\text{C}}}}-\underset{\text{H}}{\text{C}}-\text{Me} \qquad (8\text{-}2)$$

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[8] Arcus and Kenyon, *J. Chem. Soc.* 916 (1939); Kenyon and Young, *J. Chem. Soc.* 263 (1941); Campbell and Kenyon, *J. Chem. Soc.* 25 (1946).

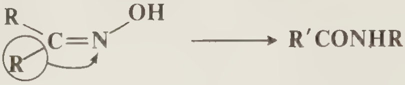
[9] For retention of migrating group configuration in the Wagner-Meerwein and pinacol rearrangements, see Beggs and Meyers, *J. Chem. Soc. B* 930 (1970); Kirmse and Gruber, *Chem. Ber.* **106,** 1365 (1973); Kirmse, Gruber, and Knist, *Chem. Ber.* **106,** 1376 (1973); Shono, Fujita, and Kumai, *Tetrahedron Lett.* 3123 (1973).

[10] Bartlett and Knox, *J. Am. Chem. Soc.* **61,** 3184 (1939).

[11] See Cram, in Newman, "Steric Effects in Organic Chemistry," pp. 251–254, John Wiley & Sons, Inc., New York, 1956; Ref. 2, pp. 597–604.

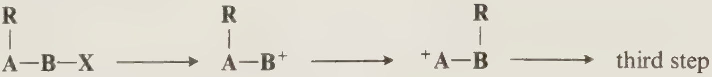
[12] Bernstein and Whitmore, *J. Am. Chem. Soc.* **61,** 1324 (1939).

and inversion at A has been shown in other cases.[13] However, in many other cases, racemization occurs at A or B or both.[14] It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most Beckmann rearrangements (reaction **8-21**), only the group trans (usually called *anti*) to the hydroxyl group migrates:



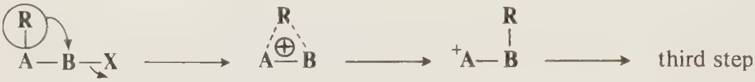
showing inversion at B, though no optical activity is involved.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First we shall look at the migration terminus B. If racemization is found at B, then it is probable that the first step takes place before the second, and that a carbonium-ion carbon (or other sextet atom) is present at B:



$$\begin{array}{l}R\\|\\A{-}B{-}X\end{array} \longrightarrow \begin{array}{l}R\\|\\A{-}B^+\end{array} \longrightarrow \begin{array}{r}R\\|\\{}^+A{-}B\end{array} \longrightarrow \text{third step}$$

With respect to B this is an SN1-type process. If inversion occurs at B, then it is likely that the first two steps are concerted, that a carbonium ion is *not* an intermediate, and that the process is SN2-like:



9

In this case participation by R assists in removal of X in the same way that neighboring groups do (p. 279). Indeed, R *is* a neighboring group here, and the only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken. In either case, the anchimeric assistance results in an increased rate of reaction. Of course, for such a process to take place, R must be in a favorable geometrical position (R and X anti-periplanar; see for example, p. 329). **9** may be a true intermediate or only a transition state, depending on what migrates. In certain cases of the SN1-type process, it is possible for migration to take place with net retention of configuration at the migrating terminus because of conformational effects in the carbonium ion.[15]

Cram[11] presents a full discussion of these points, but we summarize a few conclusions here:

1. The SN1-type process occurs mostly when B is a tertiary atom or has one aryl group and at least one other alkyl or aryl group. In other cases, the SN2-type process is more likely. Inversion of configuration (which indicates an SN2-type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[16] On the other hand, there is other evidence that neopentyl systems undergo rearrangement by a carbonium-ion (SN1-type) mechanism.[17]

[13] For example, see Meerwein and van Emster, *Ber.* **53,** 1815 (1920), **55,** 2500 (1922); Meerwein and Gérard, *Justus Liebigs Ann. Chem.* **435,** 174 (1923).

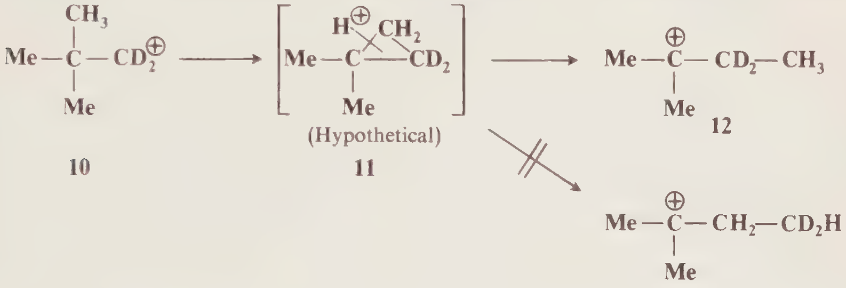
[14] For example, see Winstein and Morse, *J. Am. Chem. Soc.* **74,** 1133 (1952).

[15] Benjamin and Collins, *J. Am. Chem. Soc.* **83,** 3662 (1961); Collins, Staum, and Benjamin, *J. Org. Chem.* **27,** 3525 (1962); Collins and Benjamin, *J. Org. Chem.* **37,** 4358 (1972).

[16] Sanderson and Mosher, *J. Am. Chem. Soc.* **88,** 4185 (1966); Mosher, *Tetrahedron* **30,** 1733 (1974). See also Guthrie, *J. Am. Chem. Soc.* **89,** 6718 (1967); Solladié, Muskatirovic, and Mosher, *Chem. Commun.* 809 (1968); Liggero, Sustmann, and Schleyer, *J. Am. Chem. Soc.* **91,** 4571 (1969).

[17] Nordlander, Jindal, Schleyer, Fort, Harper, and Nicholas, *J. Am. Chem. Soc.* **88,** 4475 (1966).

2. The question as to whether **9** is an intermediate or a transition state has been much debated. When R is aryl or vinyl, then **9** is probably an intermediate, and the migrating group lends anchimeric assistance[18] (see p. 293 for resonance stabilization of this intermediate when R is aryl). When R is alkyl, **9** is a protonated cyclopropane (edge- or corner-protonated; see p. 693). There is much evidence that in simple migrations of a methyl group, the bulk of the products formed do not arise from protonated cyclopropane *intermediates*. Evidence for this statement has already been given (p. 300). Further evidence was obtained from experiments involving labeling. Rearrangement of the neopentyl cation labeled with deuterium in the 1 position (**10**) gave only *t*-pentyl products with the label in the 3 position (derived from **12**), though if **11** were an intermediate, the cyclopropane ring could just as well cleave the other way to give *t*-pentyl derivatives labeled in the 4 position (derived from **13**).[19]



10 **11** **12** **13**

Another experiment which led to the same conclusion was the generation, in several ways, of $Me_3C^{13}CH_2^+$. In this case the only *t*-pentyl products isolated were labeled in C-3, that is, $Me_2\overset{\oplus}{C}-{}^{13}CH_2CH_3$ derivatives; no derivatives of $Me_2\overset{\oplus}{C}-CH_2{}^{13}CH_3$ were found.[20] Though the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl systems, a small part of the product can in fact arise from such intermediates.[21] Among this evidence is the isolation of 10 to 15% cyclopropanes (mentioned on p. 300). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CD_2CH_2^+$, $CH_3CH_2CD_2^+$, $CH_3CH_2{}^{14}CH_2^+$), where isotopic distribution in the products indicated that a small amount (about 5%) of the product had to be formed from protonated cyclopropane intermediates, e.g.,[22]

$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D-CHD-OH$$

$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D-CHD-OH$$

$$CH_3CH_2{}^{14}CH_2NH_2 \xrightarrow{HONO} \sim 2\%\ {}^{14}CH_3CH_2CH_2OH + \sim 2\%\ CH_3{}^{14}CH_2CH_2OH$$

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[18] For an opposing view, see Kirmse and Feyen, *Chem. Ber.* **108**, 71 (1975); Kirmse, Plath, and Schaffrodt, *Chem. Ber.* **108**, 79 (1975).

[19] Skell, Starer, and Krapcho, *J. Am. Chem. Soc.* **82**, 5257 (1960).

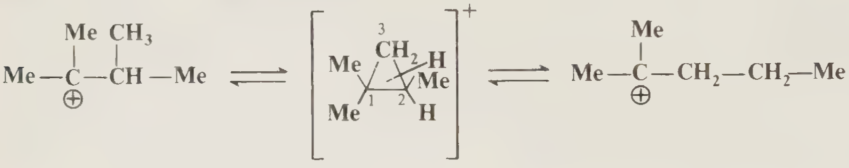
[20] Karabatsos and Graham, *J. Am. Chem. Soc.* **82**, 5250 (1960); Karabatsos, Orzech, and Meyerson, *J. Am. Chem. Soc.* **86**, 1994 (1964).

[21] For reviews, see Saunders, Vogel, Hagen, and Rosenfeld, *Acc. Chem. Res.* **6**, 53–59 (1973); Lee, *Prog. Phys. Org. Chem.* **7**, 129–187 (1970); Collins, *Chem. Rev.* **69**, 543–550 (1969).

[22] Lee, Kruger, and Wong, *J. Am. Chem. Soc.* **87**, 3985 (1965); Lee and Kruger, *J. Am. Chem. Soc.* **87**, 3986 (1965), *Tetrahedron* **23**, 2539 (1967); Karabatsos, Orzech, and Meyerson, *J. Am. Chem. Soc.* **87**, 4394 (1965); Lee and Wan, *J. Am. Chem. Soc.* **91**, 6416 (1969); Karabatsos, Orzech, Fry, and Meyerson, *J. Am. Chem. Soc.* **92**, 606 (1970).

Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[23] However, protonated cyclopropane intermediates accounted for less than 1% of the products from diazotization of labeled isobutylamine[24] and from formolysis of labeled 1-propyl tosylate.[25]

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in super-acid solution, the dimethylisopropylcarbonium ion (**14**) is in equilibrium with the dimethyl-*n*-propylcarbonium ion (**16**). It is not

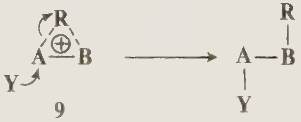


14 **15** **16**

possible for these to interconvert solely by 1,2 alkyl or hydride shifts unless primary carbonium ions (which are highly unlikely) are intermediates. However, the reaction can be explained[26] by postulating that (in the forward reaction) it is the 1,2 bond of the intermediate or transition state **15** that opens up rather than the 2,3 bond, which is the one which would open if the reaction were a normal 1,2 shift of a methyl group. In this case opening of the 1,2 bond produces a tertiary cation, while opening of the 2,3 bond would give a secondary cation. (In the reaction **16** → **14**, it is of course the 1,3 bond which opens.)

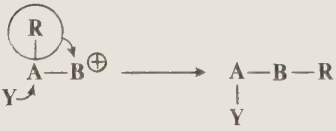
3. There has been much discussion of H as migrating group. There is no conclusive evidence for the viewpoint that **9** in this case is a true intermediate or that it is not, though both positions have been argued (see p. 301).

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an SN2-type process at the beginning of the migration. This may or may not be accompanied by an SN2 process at the migration terminus B:



9

inversion at A and B



inversion at A only

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[23] Lee, Cessna, Ko, and Vassie, *J. Am. Chem. Soc.* **95**, 5688 (1973). See also Lee and Chwang, *Can J. Chem.* **48**, 1025 (1970); Lee and Law, *Can. J. Chem.* **49**, 2746 (1971).

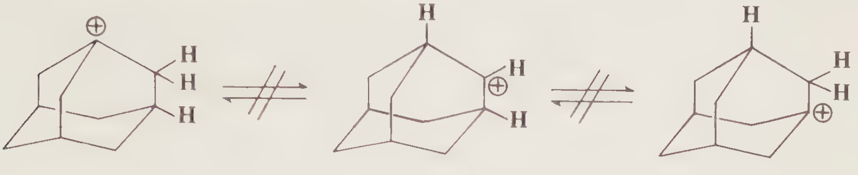
[24] Karabatsos, Hsi, and Meyerson, *J. Am. Chem. Soc.* **92**, 621 (1970). See also Karabatsos, Mount, Rickter, and Meyerson, *J. Am. Chem. Soc.* **92**, 1248 (1970); Karabatsos, Anand, Rickter, and Meyerson, *J. Am. Chem. Soc.* **92**, 1254 (1970).

[25] Lee and Kruger, *Can. J. Chem.* **44**, 2343 (1966); Shatkina, Lovtsova, and Reutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 2616 (1967); Karabatsos, Fry, and Meyerson, *J. Am. Chem. Soc.* **92**, 614 (1970).

[26] Brouwer and Oelderik, *Recl. Trav. Chim. Pays-Bas* **87**, 721 (1968); Saunders, Jaffe, and Vogel, *J. Am. Chem. Soc.* **93**, 2558 (1971); Saunders and Vogel, *J. Am. Chem. Soc.* **93**, 2559, 2561 (1971). See also Brouwer, *Recl. Trav. Chim. Pays-Bas* **87**, 1435 (1968); Kramer, *J. Am. Chem. Soc.* **91**, 4819 (1969), **92**, 4344 (1970).

In some cases it has been found that, when H is the migrating species, the configuration at A may be *retained*.[27]

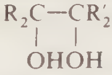
There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**17**) does not equilibrate intramolecularly even at temperatures up to 130°C,[28] though open-chain (e.g., $\mathbf{5} \rightleftharpoons \mathbf{5'}$) and cyclic tertiary carbonium ions undergo such equilibration at 0°C or below. On the basis of this and other evidence it has been concluded that for a 1,2 shift of hydrogen or methyl to proceed as smoothly as possible, the vacant *p* orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,[28] which is not possible for **17**.



17 **17′**

Migratory Aptitudes[29]

In many reactions there is no question about which group migrates. For example, in the Hofmann, Curtius, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The Beckmann rearrangement (reaction **8-21**) provides an example. As we have seen, only the group trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 902), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[30] However, in some reactions, especially the Wagner-Meerwein (**8-1**) and the pinacol (**8-2**) rearrangements, the molecule may contain several groups which, geometrically at least, have approximately equal chances of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the pinacol rearrangement there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on *the other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form  $\underset{\mathrm{OH}}{R_2\overset{|}{C}}-\underset{\mathrm{OH}}{\overset{|}{C}R'_2}$, since the only thing that determines migratory aptitude is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH which leaves is the one whose loss gives rise to the more stable carbonium ion. Thus 1,1-diphenylethanediol (**18**) gives diphenylacetaldehyde (**19**) and not phenylacetophenone

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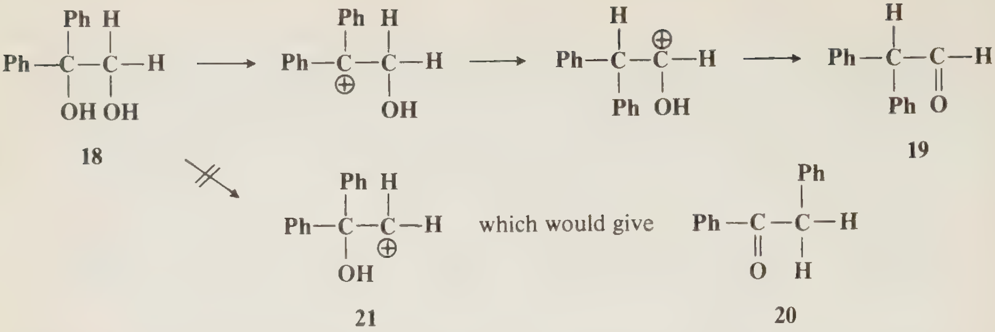
[27] Winstein and Holness, *J. Am. Chem. Soc.* **77,** 5562 (1955); Cram and Tadanier, *J. Am. Chem. Soc.* **81,** 2737 (1959); Bundel', Pankratova, Gordin, and Reutov, *Doklad. Chem.* **199,** 700 (1971); Kirmse and Gruber, *Chem. Ber.* **104,** 1783 (1971); Kirmse and Arold, *Chem. Ber.* **104,** 1800 (1971); Kirmse, Feyen, Gruber, and Kapmeyer, *Chem. Ber.* **108,** 1839 (1975).

[28] Brouwer and Hogeveen, *Recl. Trav. Chim. Pays-Bas* **89,** 211 (1970), Majerski, Schleyer, and Wolf, *J. Am. Chem. Soc.* **92,** 5731 (1970).

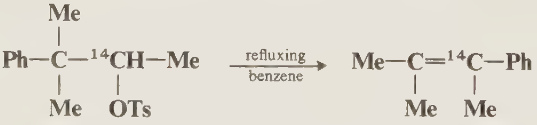
[29] For a discussion, see Ref. 2, pp. 573–597.

[30] For a discussion, see Cram, Ref. 11, pp. 270–276. For an interesting example, see Nickon and Weglein, *J. Am. Chem. Soc.* **97,** 1271 (1975).



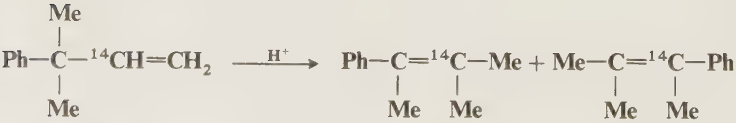
(**20**). Obviously, it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because **21** is not formed. As we have already seen, carbonium-ion stability is enhanced by groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (for an example, see the reaction of **43**, p. 983).

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $\mathrm{RR'\underset{OH}{C}{-}\underset{OH}{C}RR'}$, since the same carbonium ion is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R′ is possible. On closer inspection, however, we can see that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R′ migrates is determined not only by the relative inherent migrating abilities of R and R′ but also by whether the group which does *not* migrate is better at stabilizing the positive charge which will now be found at the migration origin.[31] Thus, migration of R gives rise to the cation $\mathrm{R'\overset{\oplus}{C}(OH)CR_2R'}$, while migration of R′ gives the cation $\mathrm{R\overset{\oplus}{C}(OH)CRR'_2}$, and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R′ not because it actually has a lower inherent migrating tendency, but because it is much better at stabilizing the positive charge. In addition to this factor, migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the nucleofuge. An example of this effect is the finding that in the decomposition of the tosylate **22** only the phenyl group migrates, while in acid treatment of the



$$\mathrm{Ph{-}\overset{\displaystyle Me}{\underset{\displaystyle Me}{C}}{-}\underset{\displaystyle OTs}{^{14}CH}{-}Me} \xrightarrow[\text{benzene}]{\text{refluxing}} \mathrm{Me{-}\underset{\displaystyle Me}{C}{=}\underset{\displaystyle Me}{^{14}C}{-}Ph}$$

22



$$\mathrm{Ph{-}\overset{\displaystyle Me}{\underset{\displaystyle Me}{C}}{-}{^{14}CH}{=}CH_2} \xrightarrow{\mathrm{H^+}} \mathrm{Ph{-}\underset{\displaystyle Me}{C}{=}\underset{\displaystyle Me}{^{14}C}{-}Me} + \mathrm{Me{-}\underset{\displaystyle Me}{C}{=}\underset{\displaystyle Me}{^{14}C}{-}Ph}$$

23

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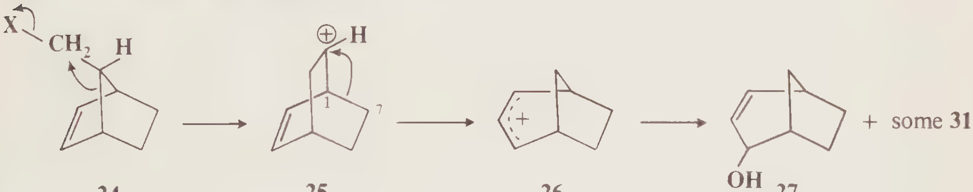
[31] For example, see Howells and Warren, *J. Chem. Soc., Perkin Trans. 2* 1645 (1973); McCall, Townsend, and Bonner, *J. Am. Chem. Soc.* **97**, 2743 (1975).

corresponding alkene **23**, there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).[32] Both **22** and **23** give the same carbonium ion, and the differing results must be caused by the fact that in **22** the phenyl group can assist the leaving group, while no such process is possible for **23**. This example clearly illustrates the difference between migration to a relatively free carbonium-ion terminus and one that proceeds with the migrating group lending anchimeric assistance.

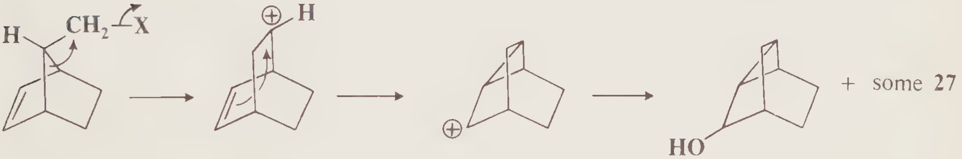
It is not surprising therefore that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases migration of hydrogen is preferred to aryl migration; in other cases migration of alkyl is preferred to that of hydrogen. Mixtures are often found, and the isomer which predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.[33] However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups by Bachmann and Ferguson:[34] *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is, with respect to the benzene ring.

Memory Effects[35]

Solvolysis of the endo bicyclic compound **24** (X = ONs[36] or Br) gave mostly the bicyclic allylic alcohol **27**, along with a smaller amount of the tricyclic alcohol **31**; while solvolysis of the exo



24 **25** **26** **27**



28 **29** **30** **31**

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[32] Grimaud and Laurent, *Bull. Soc. Chim. Fr.* 3599 (1967).

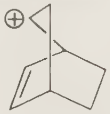
[33] For examples, see Cram and Knight, *J. Am. Chem. Soc.* **74**, 5839 (1952); Stiles and Mayer, *J. Am. Chem. Soc.* **81**, 1497 (1959); Heidke and Saunders, *J. Am. Chem. Soc.* **88**, 5816 (1966); Dubois and Bauer, *J. Am. Chem. Soc.* **90**, 4510, 4511 (1968); Bundel', Levina, and Reutov, *J. Org. Chem. USSR* **6**, 1 (1970); Pilkington and Waring, *Tetrahedron Lett.* 4345 (1973).

[34] Bachmann and Ferguson, *J. Am. Chem. Soc.* **56**, 2081 (1934).

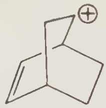
[35] For a review, see Berson, *Angew. Chem. Int. Ed. Engl.* **7**, 779–791 (1968) [*Angew. Chem.* **80**, 765–777].

[36] Ns = nosylate, see p. 326.

isomers **28** gave mostly **31,** with smaller amounts of **27.**[37] Thus the two isomers gave entirely different ratios of products, though the carbonium ion initially formed (**25** or **29**) seems to be the same for each. In the case of **25,** a second rearrangement (a shift of the 1,7 bond) follows, while with **29** it is an intramolecular addition of the carbonium-ion carbon to the double bond which follows. It seems as if **25** and **29** "remember" how they were formed before they go on to give the second step. Such effects are called *memory effects,* and other such cases are also known.[38] The causes of these effects are not well understood, though there has been much discussion. One possible cause is differential solvation of the apparently identical ions **25** and **29.** Other possibilities are: (1) that the ions have geometrical structures which are twisted in opposite senses (e.g., a twisted **29** might have its positive carbon closer to the double bond than a twisted **25**); (2) that ion pairing is responsible;[38a] and (3) that nonclassical carbonium ions are involved.[39] One possibility that has been ruled out is that the steps **24** → **25** → **26** and **28** → **29** → **30** are concerted, so that **25** and **29** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **24** gives not only **27,** but also some **31;** and **28** gives not only **31,** but also some **28.** This means that some of the **25** and **29** ions interconvert, a phenomenon known as *leakage.*



Twisted **29**



Twisted **25**

Longer Nucleophilic Rearrangements

The question as to whether a group can migrate with its electron pair from A to C in W—A—B—C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way,[40] the evidence is that such migration is extremely rare, if it occurs at all. One experiment which demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation $Me_3CCH_2CH_2^+$. If 1,3 methyl migrations are possible, this cation would appear to be a favorable substrate for them, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation $Me_2\overset{\oplus}{C}CH_2CH_2CH_3$, while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2 hydride migration.[41] 1,3 Migration of bromine (but not chlorine) has been reported.[42]

However, most of the debate over the possibility of 1,3 migrations has concerned not methyl or bromine but 1,3 hydride shifts.[43] There is no doubt that *apparent* 1,3 hydride shifts take place

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[37] Berson, Poonian, and Libbey, *J. Am. Chem. Soc.* **91,** 5567 (1969); Berson, Donald, and Libbey, *J. Am. Chem. Soc.* **91,** 5580 (1969); Berson, Wege, Clarke, and Bergman, *J. Am. Chem. Soc.* **91,** 5594 (1969); Berson, Bergman, Clarke, and Wege, *J. Am. Chem. Soc.* **91,** 5601 (1969).

[38] For examples of memory effects in other systems, see Berson, Gajewski, and Donald, *J. Am. Chem. Soc.* **91,** 5550 (1969); Berson, McKenna, and Junge, *J. Am. Chem. Soc.* **93,** 1296 (1971); Berson and Foley, *J. Am. Chem. Soc.* **93,** 1297 (1971); Berson, Luibrand, Kundu, and Morris, *J. Am. Chem. Soc.* **93,** 3075 (1971); Collins, *Acc. Chem. Res.* **4,** 315–322 (1971); Collins, Glover, Eckart, Raaen, Benjamin, and Benjaminov, *J. Am. Chem. Soc.* **94,** 899 (1972); Svensson, *Chem. Scr.* **6,** 22 (1974).

[38a] See Collins, *Chem. Soc. Rev.* **4,** 251–262 (1975).

[39] See for example, Seybold, Vogel, Saunders, and Wiberg, *J. Am. Chem. Soc.* **95,** 2045 (1973).

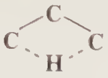
[40] For example, see Carlin and Moores, *J. Am. Chem. Soc.* **81,** 1259 (1959).

[41] Skell and Reichenbacher, *J. Am. Chem. Soc.* **90,** 2309 (1968).

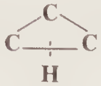
[42] Reineke and McCarthy, *J. Am. Chem. Soc.* **92,** 6376 (1970); Reutov, Smolina, Polevaya, Gopius, and Betaneli, *Doklad. Chem.* **197,** 290 (1971); Smolina, Gopius, Gruzdneva, and Reutov, *Doklad. Chem.* **209,** 280 (1973).

[43] For reviews, see Fry and Karabatsos, in Olah and Schleyer, Ref. 5, vol. 2, pp. 527–566; Reutov, *Pure Appl. Chem.* **7,** 203–227 (1963).

(many instances have been found), but the question is whether they are truly direct hydride shifts or whether they occur by another mechanism. There are at least two ways in which indirect 1,3 hydride shifts can take place: (1) by successive 1,2 shifts or (2) through the intervention of protonated cyclopropanes (see p. 968). A direct 1,3 shift would have the transition state **A**, while the transition state for a 1,3 shift involving a protonated cyclopropane intermediate would resemble

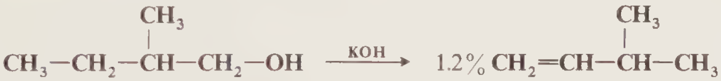


A



B

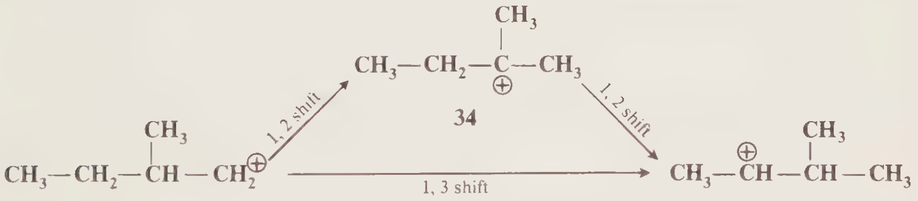
B. The evidence is that most reported 1,3 hydride shifts are actually the result of successive 1,2 migrations,[44] but that in some cases small amounts of products cannot be accounted for in this way. For example, the reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of olefins, nearly all of which could have arisen from simple elimination or 1,2 shifts of hydride or alkyl. However, 1.2% of the product was 3-methyl-1-butene (**32**):[45]



$$CH_3{-}CH_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_2{-}OH \xrightarrow{KOH} 1.2\%\ CH_2{=}CH{-}\overset{\displaystyle CH_3}{\overset{|}{C}H}{-}CH_3$$

32

Hypothetically, **32** could have arisen from a 1,3 shift (direct or through a protonated cyclopropane) or from two successive 1,2 shifts:



33 **35**

However, the same reaction applied to 2-methyl-2-butanol gave no **32**, which demonstrated that **35** was not formed from **34**. The conclusion was thus made that **35** was formed directly from **33**. This experiment does not answer the question as to whether **35** was formed by a direct shift or through a protonated cyclopropane, but from other evidence[46] it appears that 1,3 hydride shifts that do not result from successive 1,2 migrations usually take place through protonated cyclopropane intermediates (which, as we saw on p. 967, account for only a small percentage of the product in any case). However, there is evidence that direct 1,3 hydride shifts by way of **A** may take place in super-acid solutions.[47]

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[44] For example, see Bundel', Levina, Krzhizhevskii, and Reutov, *Doklad. Chem.* **181,** 583 (1968); Bundel', Levina, Prokhorenko, and Reutov, *Doklad. Chem.* **188,** 732 (1969); Fărcaşiu, Kascheres, and Schwartz, *J. Am. Chem. Soc.* **94,** 180 (1972).

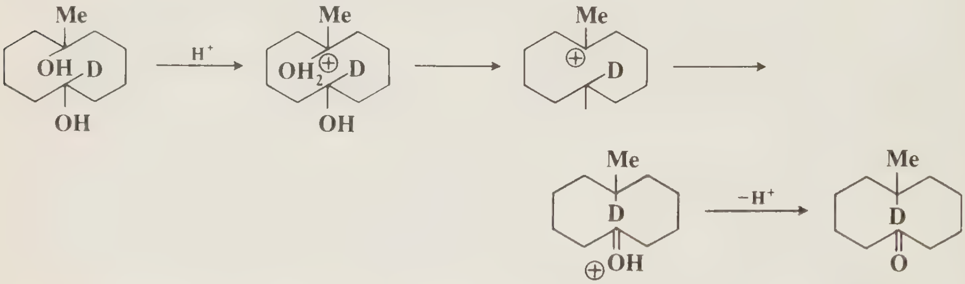
[45] Skell and Maxwell, *J. Am. Chem. Soc.* **84,** 3963 (1962). See also Skell and Starer, *J. Am. Chem. Soc.* **84,** 3962 (1962).

[46] For example, see Brouwer and van Doorn, *Recl. Trav. Chim. Pays-Bas* **88,** 573 (1969); Dupuy, Goldsmith, and Hudson, *J. Chem. Soc., Perkin Trans. 2* 74 (1973); Hudson, Koplick, and Poulton, *Tetrahedron Lett.* 1449 (1975); Fry and Karabatsos, Ref. 43.

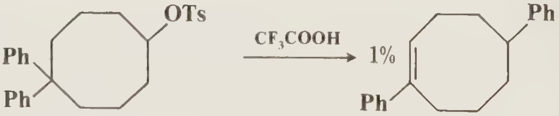
[47] Saunders and Stofko, *J. Am. Chem. Soc.* **95,** 252 (1973).

Even longer hydride shifts have been reported. $CH_3(CH_2)_5CH{=}CH_2$, when treated with peroxytrifluoroacetic acid (reaction **5-39**), gave mostly the unrearranged product, 1,2-octanediol. But small amounts of the 1,3-, 1,4-, 1,5-, 1,6-, and 1,7-diols were also obtained.[48] These products could have arisen from successive 1,2 shifts, but the ratio of the yields obtained makes it unlikely. It has been reported that the ion $Me_2CHCH_2CH_2\overset{\oplus}{C}HOH$ undergoes a 1,4 hydride shift to give the ion $Me_2\overset{\oplus}{C}CH_2CH_2CH_2OH$.[49]

Although direct nucleophilic rearrangements over distances greater than 1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8 to 11 members. Many such transannular rearrangements are known.[50] Several examples are given on p. 146. We look at the mechanism of one of these:[51]

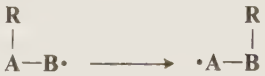


It is noteworthy that the *methyl* group does not migrate in this system. It is generally true that alkyl groups do not undergo transannular migration. In most cases it is hydride which undergoes this type of migration, though a small amount of phenyl migration has also been shown:[52]



Free-Radical Rearrangements[53]

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned on p. 962. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



$$\overset{\displaystyle R}{\underset{}{A}}\!-\!B\cdot \longrightarrow \cdot A\!-\!\overset{\displaystyle R}{B}$$

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[48] Cope, Fleckenstein, Moon, and Petree, *J. Am. Chem. Soc.* **85**, 3752 (1963).

[49] Brouwer and Kiffen, *Recl. Trav. Chim. Pays-Bas* **92**, 906 (1973). For other 1,4 and 1,5 shifts, see Ref. 47.

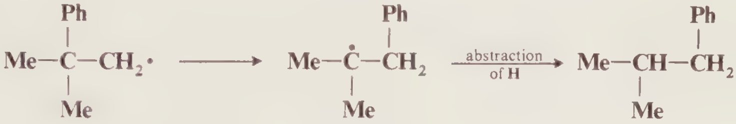
[50] For reviews, see Prelog and Traynham, in Mayo, Ref. 1, vol. 1, pp. 593–615; Cope, Martin, and McKervey. *Q. Rev., Chem. Soc.* **20**, 119–152 (1966). For many references, see Blomquist and Buck, *J. Am. Chem. Soc.* **81**, 672 (1951).

[51] Prelog and Küng, *Helv. Chim. Acta* **39**, 1394 (1956).

[52] Cope, Burton, and Caspar, *J. Am. Chem. Soc.* **84**, 4855 (1962).

[53] For reviews, see Wilt, in Kochi, "Free Radicals," vol. 1, pp. 333–501, John Wiley & Sons, Inc., New York, 1973; Stepukhovich and Babayan, *Russ. Chem. Rev.* **41**, 750 (1972); Nonhebel and Walton, "Free-Radical Chemistry," pp. 498–552, Cambridge University Press, London, 1974; Huyser, "Free-Radical Chain Reactions," pp. 235–255, Interscience Publishers, New York, 1970; Freidlina, *Adv. Free-Radical Chem.* **1**, 211–278 (1965); Fish, *Q. Rev., Chem. Soc.* **18**, 243–269 (1964); Pryor, "Free Radicals," pp. 266–284, McGraw-Hill Book Company, New York, 1966; Freidlina, Kost, and Khorlina, *Russ. Chem. Rev.* **31**, 1–18 (1962); Walling, in Mayo, Ref. 1, pp. 407–455.

Finally, the new free radical must stabilize itself by a further reaction. The order of radical stability leads us to predict that here too, as with carbonium-ion rearrangements, any migrations should be in the order primary → secondary → tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (reaction **4-41**). In this manner it was found that neophyl radicals *do* undergo rearrangement. Thus, $PhCMe_2CH_2CHO$ treated with di-*t*-butyl peroxide gave about equal amounts of the normal product $PhCMe_2CH_3$ and the product arising from migration of phenyl:[54]



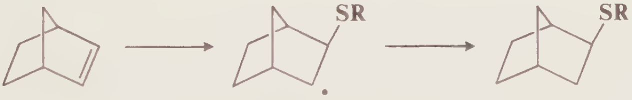
$$\mathrm{Me{-}\overset{Ph}{\underset{Me}{C}}{-}CH_2\cdot} \longrightarrow \mathrm{Me{-}\underset{Me}{\dot{C}}{-}\overset{Ph}{CH_2}} \xrightarrow[\text{of H}]{\text{abstraction}} \mathrm{Me{-}\underset{Me}{CH}{-}\overset{Ph}{CH_2}}$$

Many other cases of aryl free-radical migration have also been found.[55]

It is noteworthy that the extent of migration is much less than with the corresponding carbonium ions: Thus in the example given there was only about 50% migration, whereas the carbonium ion would have given much more. Also noteworthy is that there was no migration of the methyl group. In general it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed,[56] even in substrates where the corresponding carbonium ions undergo facile rearrangement.[57] Another type of migration which is very common for carbonium ions, but which is not observed for free radicals, is 1,2 migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

1. 3,3-Dimethylpentanal ($EtCMe_2CH_2CHO$) gave no rearranged products on decarbonylation.[58]

2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **36** is an intermediate, and the corresponding carbonium ion cannot be formed without rearrangement.[59]



36

3. It was shown[60] that no rearrangement of isobutyl radical to *t*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

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[54] Winstein and Seubold, *J. Am. Chem. Soc.* **69,** 2916 (1947); Seubold, *J. Am. Chem. Soc.* **75,** 2532 (1953). For the observation of this rearrangement by esr, see Hamilton and Fischer, *Helv. Chim. Acta* **56,** 795 (1973).

[55] For example, see Curtin and Hurwitz, *J. Am. Chem. Soc.* **74,** 5381 (1952); Wilt and Philip, *J. Org. Chem.* **24,** 441 (1959), **25,** 891 (1960); Pines and Pillai, *J. Am. Chem. Soc.* **82,** 2921 (1960); Pines and Goetschel, *J. Am. Chem. Soc.* **87,** 4207 (1965); Cote and Vittimberga, *J. Am. Chem. Soc.* **93,** 276 (1971).

[56] Formal migration of alkyl has been observed, but by an elimination-addition mechanism: Berson, Olsen, and Walia, *J. Am. Chem. Soc.* **84,** 3337 (1962).

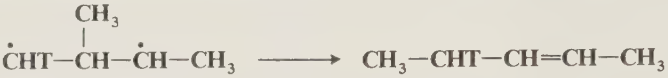
[57] For a summary of unsuccessful attempts, see Slaugh, Magoon, and Guinn, *J. Org. Chem.* **28,** 2643 (1963).

[58] Seubold, *J. Am. Chem. Soc.* **76,** 3732 (1954).

[59] Cristol and Brindell, *J. Am. Chem. Soc.* **76,** 5699 (1954).

[60] Brown and Russell, *J. Am. Chem. Soc.* **74,** 3995 (1952). See also Desai, Nechvatel, and Tedder, *J. Chem. Soc. B* 386 (1970).

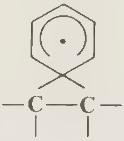
However, 1,2 migration of alkyl groups has been shown to occur in certain *diradicals*.[61] For example, the following rearrangement has been established by tritium labeling.[62]



$$\dot{C}HT-\overset{CH_3}{\overset{|}{C}H}-\dot{C}H-CH_3 \longrightarrow CH_3-CHT-CH=CH-CH_3$$

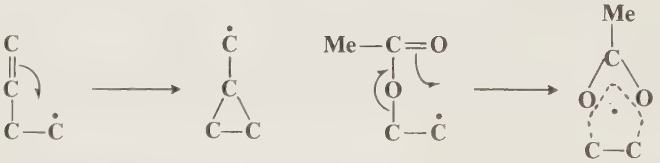
In this case the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

The fact that aryl groups migrate, but generally alkyl groups and hydrogen do not, leads to the proposition that **37**, in which the odd electron is not found in the three-membered ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **37** is a transition state and not an intermediate. Among the evidence is the failure to observe **37** by esr,[63] a technique which can detect free radicals with extremely short lifetimes (p. 170).[64]



37

Besides aryl, vinyl,[65] and acetoxy groups[66] also migrate. Vinyl groups migrate by way of a cyclopropylcarbinyl radical intermediate,[67] while the migration of acetoxy groups involves the five-membered transition state shown.[68] In addition, migration has been observed for chloro (and to a much lesser extent bromo) groups. For example in the reaction of $Cl_3CCH=CH_2$ with bromine under the influence of peroxides, the products were 47% $Cl_3CCHBrCH_2Br$ (the normal addition product) and 53% $BrCCl_2CHClCH_2Br$, which arose by rearrangement:



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[61] For a review, see Freidlina and Terent'ev, *Russ. Chem. Rev.* **43,** 129–139 (1974).

[62] McKnight and Rowland, *J. Am. Chem. Soc.* **88,** 3179 (1966). For other examples, see Greene, Adam, and Knudsen, *J. Org. Chem.* **31,** 2087 (1966); Adam, Cheng, Wilkerson, and Zaidi, *J. Am. Chem. Soc.* **91,** 2111 (1969); Gajewski and Burka, *J. Am. Chem. Soc.* **94,** 8857, 8860, 8865 (1972); Adam and Aponte, *J. Am. Chem. Soc.* **93,** 4300 (1971).

[63] Kochi and Krusic, *J. Am. Chem. Soc.* **91,** 3940 (1969); Edge and Kochi, *J. Am. Chem. Soc.* **94,** 7695 (1972).

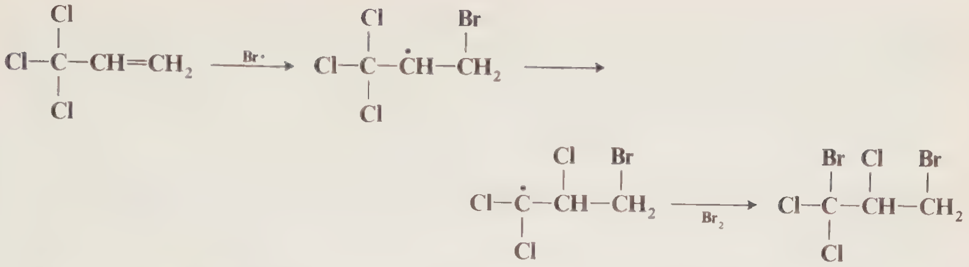
[64] For other evidence, see Martin, *J. Am. Chem. Soc.* **84,** 1986 (1962); Rüchardt and Hecht, *Tetrahedron Lett.* 957 (1962), *Chem. Ber.* **98,** 2460, 2471 (1965); Rüchardt and Trautwein, *Chem. Ber.* **98,** 2478 (1965).

[65] For example, see Slaugh, Mullineaux, and Raley, *J. Am. Chem. Soc.* **85,** 3180 (1963); Slaugh *J. Am. Chem. Soc.* **87,** 1522 (1965).

[66] Surzur and Teissier, *C. R. Acad. Sci., Ser. C* **264,** 1981 (1967); *Bull. Soc. Chim. Fr.* 3060 (1970); Tanner and Law, *J. Am. Chem. Soc.* **91,** 7535 (1969); Julia and Lorne, *C. R. Acad. Sci., Ser. C* **273,** 174 (1971); Lewis, Miller, and Winstein, *J. Org. Chem.* **37,** 1478 (1972).

[67] For evidence for this species, see Montgomery, Matt, and Webster, *J. Am. Chem. Soc.* **89,** 923 (1967); Montgomery and Matt, *J. Am. Chem. Soc.* **89,** 934, 6556 (1967).

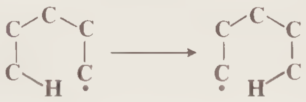
[68] Beckwith and Tindal, *Aust. J. Chem.* **24,** 2099 (1971); Beckwith and Thomas, *J. Chem. Soc., Perkin Trans. 2* 861 (1973).



In this particular case the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and coworkers have extensively studied reactions of this sort.[69] It has been shown that the 1,2 migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.[70] Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

In summary then, 1,2 free-radical migrations are less prevalent than the analogous carbonium-ion processes and are important only for aryl, vinyl, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[71]

Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known. The most common are 1,5 shifts, but 1,6 and longer shifts have also been found. The possibility of 1,3 hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for C---H---C in the transition state is linear, and this geometry cannot be achieved in a 1,3 shift. 1,4 shifts are definitely known, but still not very common. These long shifts may be regarded as internal abstractions of hydrogen (for reactions involving them, see **4-7** and **8-46**):



Transannular shifts of hydrogen atoms have also been observed.[72] A few shifts longer than 1,2 have been noted for aryl, but not for alkyl or halogen groups.

Electrophilic Rearrangements[73]

Rearrangements in which a group migrates without its electrons are much rarer than the two kinds previously considered, but the general principles are the same. There is first created a carbanion (or other negative ion), and the actual rearrangement step involves migration of a group without its electrons:

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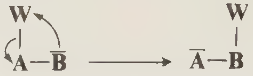
[69] For reviews, see Nesmeyanov, Freidlina, Kost, and Khorlina, *Tetrahedron* **16,** 94–105 (1961); Freidlina, Kost, and Khorlina, Ref. 53, pp. 6–11; Freidlina, Ref. 53, pp. 231–249.

[70] See for example, Skell, Pavlis, Lewis, and Shea, *J. Am. Chem. Soc.* **95,** 6735 (1973); Chen, Tang, Montgomery, and Kochi, *J. Am. Chem. Soc.* **96,** 2201 (1974).

[71] Slaugh and Raley, *J. Am. Chem. Soc.* **82,** 1259 (1960); Bonner and Mango, *J. Org. Chem.* **29,** 29 (1964); Dannenberg and Dill, *Tetrahedron Lett.* 1571 (1972).

[72] Heusler and Kalvoda, *Tetrahedron Lett.* 1001 (1963); Cope, Bly, Martin, and Petterson, *J. Am. Chem. Soc.* **87,** 3111 (1965); Fisch and Ourisson, *Chem. Commun.* 407 (1965); Traynham and Couvillon, *J. Am. Chem. Soc.* **89,** 3205 (1967).

[73] For reviews, see Jensen and Rickborn, "Electrophilic Substitution of Organomercurials," pp. 21–30, McGraw-Hill Book Company, New York, 1968; Cram, "Fundamentals of Carbanion Chemistry," pp. 223–243, Academic Press, Inc., New York, 1965.



The product of the rearrangement may be stable or may react further, depending on its nature (see also pp. 982–983).

REACTIONS

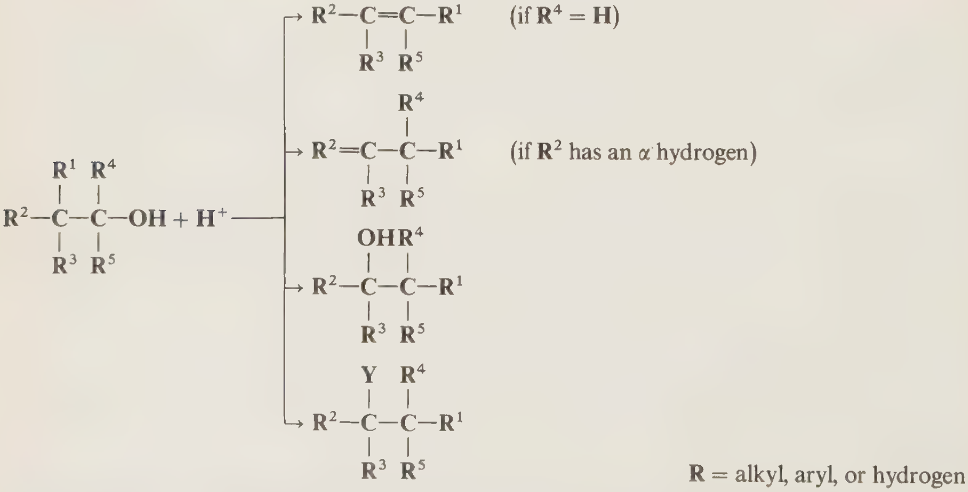
The reactions in this chapter are classified into three main groups. 1,2 Shifts are considered first. Within this group, reactions are classified according to (1) the identity of the substrate atoms A and B and (2) the nature of the migrating group W. In the second group are the cyclic rearrangements. The third group consists of rearrangements which cannot be fitted into either of the first two categories.

Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are reactions **1-34** to **1-40**, **1-44**, **3-26** to **3-29**, and, partially, **1-41**, **1-47**, and **1-48**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. 303, p. 528, and reaction **2-2**). Two other reactions which may be regarded as rearrangements are the Willgerodt reaction (**9-76**) and the decomposition of tertiary hypochlorites (**4-42**).

1,2 Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

8-1 Wagner-Meerwein and Related Reactions

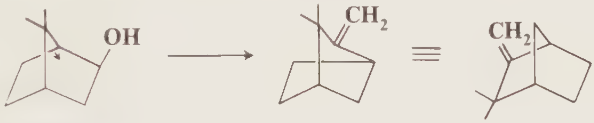


When alcohols are treated with acids, simple substitution (e.g., reaction **0-67**) or elimination (reaction **7-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β-carbon, some or all of the product is rearranged.

These rearrangements are called *Wagner-Meerwein rearrangements*.[74] As pointed out previously (p. 963), the carbonium ion which is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss of a hydrogen β to it, so that the rearrangement product is usually an olefin. The proton lost may be R^4 (if this is a hydrogen) or an α-proton from R^2 (if it has one). If there is a choice of protons, Zaitsev's rule (p. 910) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton.[75] Less often, the new carbonium ion stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water which is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present, which we have called Y. Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under SN2 conditions substitution is extremely slow,[76] and under SN1 conditions carbonium ions are formed which rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, though, as we have seen (p. 975), neophyl systems undergo rearrangement as well as substitution.

Wagner-Meerwein rearrangements were first discovered in the bicyclic terpenes, and most of the early development of this reaction was with these compounds.[77] For this reason they are often illustrated with an example from the terpenes, e.g.,

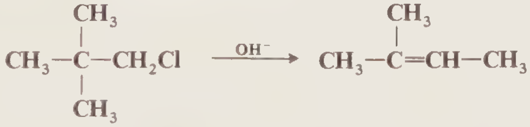
Example *a*



Isoborneol Camphene

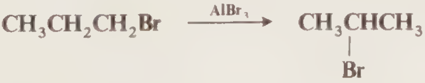
However, they may be illustrated in simpler systems:

Example *b*



$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2Cl \xrightarrow{OH^-} CH_3-\overset{CH_3}{C}=CH-CH_3$$

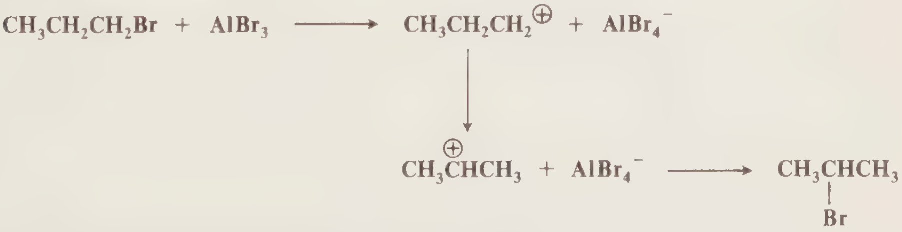
Example *c*



$$CH_3CH_2CH_2Br \xrightarrow{AlBr_3} CH_3\underset{Br}{CH}CH_3$$

These examples illustrate the following points:

1. Hydride ion may migrate. In example *c*, it was hydride that shifted, and not bromide:



$$CH_3CH_2CH_2Br + AlBr_3 \longrightarrow CH_3CH_2CH_2^{\oplus} + AlBr_4^-$$

$$\downarrow$$

$$CH_3\overset{\oplus}{C}HCH_3 + AlBr_4^- \longrightarrow CH_3\underset{Br}{CH}CH_3$$

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[74] For a review, see Pocker, in Mayo, Ref. 1, vol. 1, pp. 6–15.

[75] For example, see Grob, Hoegerle, and Ohta, *Helv. Chim. Acta* **45**, 1823 (1962).

[76] See however, Chapter 10, Ref. 228.

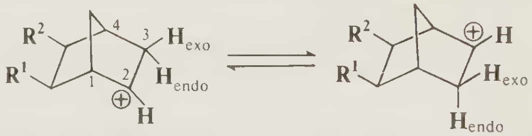
[77] For a review of rearrangements of bicyclic systems, see Berson, in Mayo, Ref. 1, pp. 111-231. For reviews of the Wagner-Meerwein rearrangement applied to natural products, see Mayo, Ref. 1, as follows: King and Mayo, pp. 813–840 (terpenes); Warnhoff, pp. 842–879 (alkaloids); Wendler, pp. 1020–1028 (steroids). For a review concerning pinanes, see Banthorpe and Whittaker, *Q. Rev., Chem. Soc.* **20**, 373–387 (1966).

2. The leaving group does not have to be H_2O, but it may be any departing species whose loss creates a carbonium ion, including N_2 from aliphatic diazonium ions[78] (see the section on leaving groups in nucleophilic substitution, p. 325). Also rearrangement may follow when the carbonium ion is created by addition of a proton or other positive species to a double bond. Even alkanes give rearrangements when heated with Lewis acids, provided there is some species present initially to form a carbonium ion from the alkane.

3. Example *c* illustrates that the last step may be substitution instead of elimination.

4. Example *b* illustrates that the new double bond is formed in accord with Zaitsev's rule.

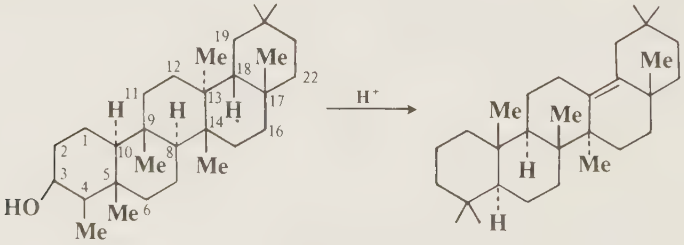
2-Norbornyl cations, besides displaying the 1,2 shifts of a CH_2 group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2 shifts). These 3,2 shifts usually take place from the exo side;[79] that is, the 3-exo hydrogen migrates to the 2-exo position.[80] This stereoselectivity is analogous to the behavior we have previously seen for norbornyl systems, namely, that nucleophiles attack norbornyl cations from the exo side (p. 295), and that addition to norbornenes is also usually from the exo direction (p. 690).



The direction of rearrangement is usually in the direction of the most stable carbonium ion (or free radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found, and often the product is a mixture corresponding to an equilibrium mixture of the possible carbonium ions. The favored direction may be counter to carbonium-ion stability if the new carbonium ion can stabilize itself more easily than the original one.

The term "Wagner-Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and in **8-2.** Others use it only when an alcohol is converted to a rearranged olefin. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

Sometimes several of these rearrangements occur in one molecule either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid



38 39

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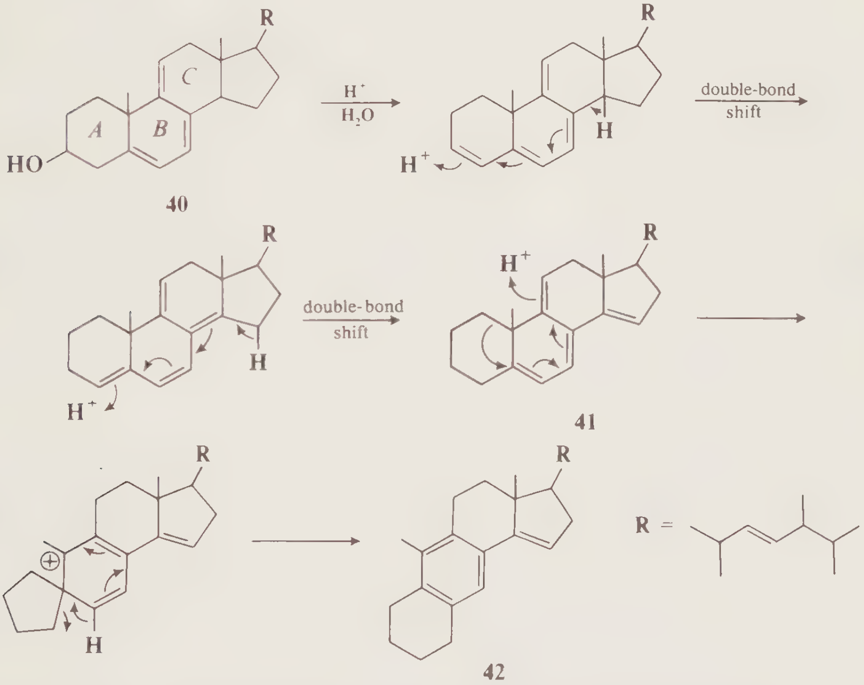
[78] For reviews of rearrangements arising from diazotization of aliphatic amines, see, in Patai, "The Chemistry of the Amino Group," Interscience Publishers, New York, 1968, the articles by White and Woodcock, pp. 407–497 (pp. 473–483) and by Banthorpe, pp. 585–667 (pp. 586–612).

[79] For example, see Kleinfelter and Schleyer, *J. Am. Chem. Soc.* **83,** 2329 (1961); Collins, Cheema, Werth, and Benjamin, *J. Am. Chem. Soc.* **86,** 4913 (1964); Berson, Hammons, McRowe, Bergman, Remanick, and Houston, *J. Am. Chem. Soc.* **89,** 2590 (1967).

[80] For examples of 3,2 endo shifts, see Bushell and Wilder, *J. Am. Chem. Soc.* **89,** 5721 (1967); Wilder and Hsieh, *J. Org. Chem.* **36,** 2552 (1971).

ketone found in cork. Reduction gives 3β-friedelanol (**38**). When this compound is treated with acid, 13(18)-oleanene (**39**) is formed.[81] In this case *seven* 1,2 shifts take place. On removal of H_2O from position 3 to leave a positive charge, the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give the 13(18)-ene. Until the elimination, each time a positive charge is formed, migration of a hydride or a methyl moves in to fill it, leaving another positive charge, which must be filled in its turn. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **39**) moves above the plane, and a group below the plane (dashed line) moves below it. It is probable that the seven shifts are not all concerted, though some of them may be, for intermediate products can be isolated.[82] As an illustration of point 2 (p. 980), it may be mentioned that friedelene, derived from dehydration of **38**, also gives **39** on treatment with acid.[83]

An interesting Wagner-Meerwein rearrangement is found in the steroid series. The *A-B-C* rings of a steroid are changed from an angular (phenanthrene-like) arrangement to a linear (anthracene-like) one. This is called the *anthrasteroid rearrangement*, and it may be illustrated for dehydroergosterol (**40**):



The product is anthraergostapentaene (**42**). The intermediate **41** has been isolated.

It was mentioned above that even alkanes undergo Wagner-Meerwein rearrangements if treated with Lewis acids and a small amount of initiator. An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.[84] It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid such as $AlCl_3$. If the substrate contains more than 10 carbons, alkyl-substituted adamantanes are produced. Some examples are

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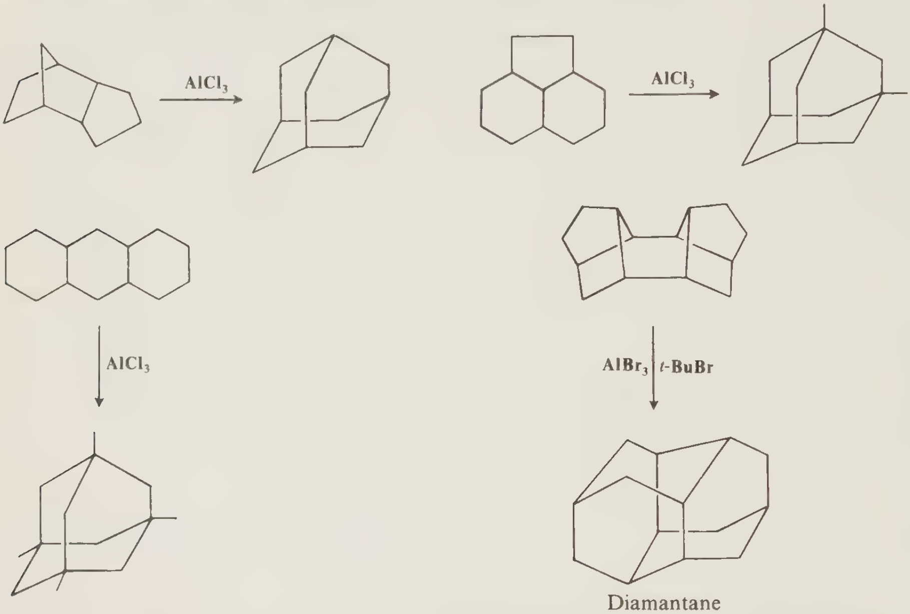
[81] Corey and Ursprung, *J. Am. Chem. Soc.* **78**, 5041 (1956).

[82] For a discussion, see Whitlock and Olson, *J. Am. Chem. Soc.* **92**, 5383 (1970).

[83] Dutler, Jeger, and Ruzicka, *Helv. Chim. Acta* **38**, 1268 (1955); Brownlie, Spring, Stevenson, and Strachan, *J. Chem. Soc.* 2419 (1956); Coates, *Tetrahedron Lett.* 4143 (1967).



Diamantane

If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[85] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. Best yields are obtained by the use of "sludge" catalysts[86] (i.e., a mixture of AlX_3 and *t*-butyl bromide or *sec*-butyl bromide) or by passing the substrate in the gas phase through a tube containing a chlorinated platinum-alumina catalyst.[87] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2 shifts, the exact pathways are not easy to unravel because of their complexity.[88] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[89]

As already indicated, the mechanism of the Wagner-Meerwein rearrangement is usually nucleophilic. Free-radical rearrangements are also known (see the mechanism section of this chapter), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic) have also been found.[73] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[90] The intermediate is $Ph_3C\bar{C}H_2^{\ominus}$, and the phenyl moves without its electron pair. There is evidence that the reaction involves a tight ion pair.[91] Only aryl and not alkyl groups migrate by the electrophilic mechanism (p. 962), and a transition state analogous to **37** is likely.[92] An apparently similar migration of a benzyl group has been shown not to be an electrophilic migration, but to proceed through an elimination-addition mechanism.[93]

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[84] For reviews, see McKervey, *Chem. Soc. Rev.* **3**, 479–512 (1974); Engler and Schleyer, *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **5**, 253–260 (1973); Bingham and Schleyer, *Fortschr. Chem. Forsch.* **18**, 1–102 (1971), pp. 3–23; Fort and Schleyer, *Chem. Rev.* **64**, 277–300 (1964); pp. 280–283.

[85] See Gund, Osawa, Williams, and Schleyer, *J. Org. Chem.* **39**, 2979 (1974).

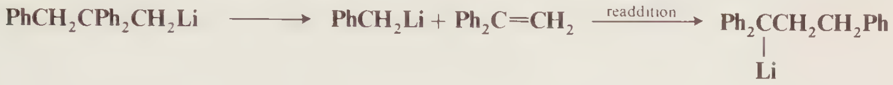
[86] Schneider, Warren, and Janoski, *J. Org. Chem.* **31**, 1617 (1966); Williams, Schleyer, Gleicher, and Rodewald, *J. Am. Chem. Soc.* **88**, 3862 (1966); Robinson and Tarratt, *Tetrahedron Lett.* 5 (1968).

[87] Johnston, McKervey, and Rooney, *J. Am. Chem. Soc.* **93**, 2798 (1971).

[88] See for example Engler, Farcasiu, Sevin, Cense, and Schleyer, *J. Am. Chem. Soc.* **95**, 5769 (1973).

[89] Majerski, Liggero, Schleyer, and Wolf, *Chem. Commun.* 1596 (1970).

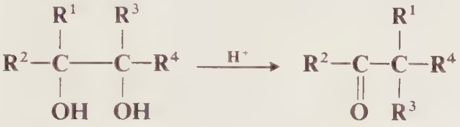
[90] Grovenstein, *J. Am. Chem. Soc.* **79**, 4985 (1957); Zimmerman and Smentowski, *J. Am. Chem. Soc.* **79**, 5455 (1957); Grovenstein and Williams, *J. Am. Chem. Soc.* **83**, 412 (1961); Zimmerman and Zweig, *J. Am. Chem. Soc.* **83**, 1196 (1961). See also Crimmins, Murphy, and Hauser, *J. Org. Chem.* **31**, 4273 (1966); Grovenstein and Cheng, *J. Am. Chem. Soc.* **94**, 4971 (1972).



$$\mathrm{PhCH_2CPh_2CH_2Li} \longrightarrow \mathrm{PhCH_2Li + Ph_2C{=}CH_2} \xrightarrow{\text{readdition}} \mathrm{Ph_2\underset{\underset{\displaystyle Li}{|}}{C}CH_2CH_2Ph}$$

OS **V**, 16, 194; **53**, 30.

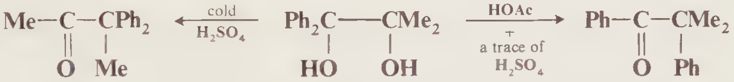
8-2 The Pinacol Rearrangement



$$\mathrm{R^2{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle R^1}{|}}{C}}{-}\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle R^3}{|}}{C}}{-}R^4} \xrightarrow{H^+} \mathrm{R^2{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle R^3}{|}}{\overset{\overset{\displaystyle R^1}{|}}{C}}{-}R^4}$$

R = alkyl, aryl, or hydrogen

When *vic*-diols are treated with acids, they can be rearranged to give aldehydes or ketones, though elimination without rearrangement can also be accomplished. This reaction is called the *pinacol*, or the *pinacol-pinacolone rearrangement;* the reaction gets its name from the typical compound pinacol $Me_2COHCOHMe_2$, which is rearranged to pinacolone Me_3CCOCH_3.[94] The reaction has been accomplished many times, with alkyl, aryl, and hydrogen as migrating groups. In most cases each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see p. 969 for a discussion of migratory aptitudes). Mixtures are often produced, and which group preferentially migrates may depend on the reaction conditions as well as on the nature of the substrate. Thus the action of cold, concentrated sulfuric acid on **43** produces mainly the ketone **44** (methyl



$$\underset{\mathbf{44}}{\mathrm{Me{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle Me}{|}}{C}Ph_2}} \xleftarrow[\mathrm{H_2SO_4}]{\text{cold}} \underset{\mathbf{43}}{\mathrm{Ph_2\underset{\underset{\displaystyle HO}{|}}{C}{-}\underset{\underset{\displaystyle OH}{|}}{C}Me_2}} \xrightarrow[\substack{\text{a trace of}\\ \mathrm{H_2SO_4}}]{\mathrm{HOAc}\ +} \underset{\mathbf{45}}{\mathrm{Ph{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle Ph}{|}}{C}Me_2}}$$

44 **43** **45**

migration), while treatment of **43** with acetic acid containing a trace of sulfuric acid gives mostly **45** (phenyl migration).[95] If at least one R group is hydrogen, then aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (reaction **8-4**).

The mechanism involves a simple Whitmore 1,2 shift. The ion **46** (where all four R groups are Me) has been trapped by the addition of tetrahydrothiophene.[96] It may seem odd that a migration

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[91] Grovenstein and Williamson, *J. Am. Chem. Soc.* **97**, 646 (1975).

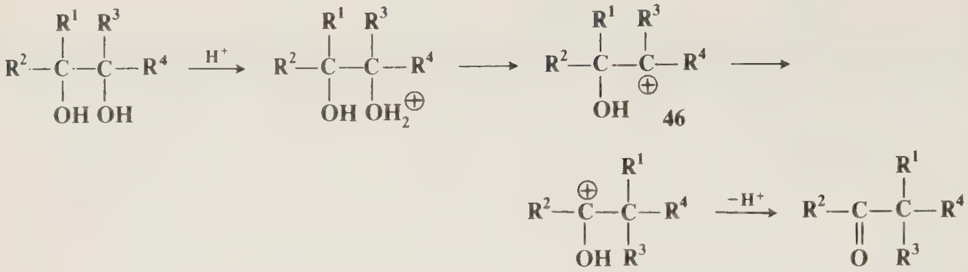
[92] Grovenstein and Wentworth, *J. Am. Chem. Soc.* **89**, 2348 (1967). See, however, Eisch and Kovacs, *J. Organomet. Chem.* **25**, C33 (1970), for evidence that free radicals intervene.

[93] Grovenstein and Wentworth, *J. Am. Chem. Soc.* **89**, 1852 (1967).

[94] For ,reviews, see Collins and Eastham, Ref. 1, pp. 762–771; Pocker, in Mayo, Ref. 1, pp. 15 25; Collins. *Q. Rev., Chem. Soc.* **14**, 357–377 (1960).

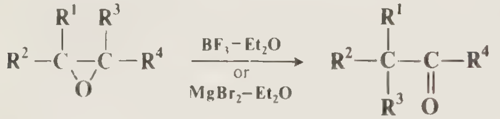
[95] Ramart-Lucas and Salmon-Legagneur, *C. R. Acad. Sci.* **188**, 1301 (1928).

[96] Bosshard, Baumann, and Schetty, *Helv. Chim. Acta* **53**, 1271 (1970).


46

takes place when the positive charge is already at a tertiary position, but carbonium ions stabilized by an oxygen atom are even more stable than tertiary alkyl cations (p. 156). There is also the driving force supplied by the fact that the new carbonium ion can immediately stabilize itself by losing a proton.

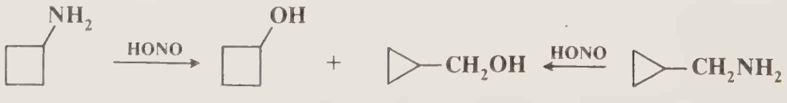
It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β-amino alcohols, which rearrange on treatment with nitrous acid (this is called the *semipinacol* rearrangement), iodohydrins, for which the reagent is mercuric oxide or silver nitrate, and allylic alcohols, which can rearrange on treatment with a strong acid which protonates the double bond. A similar rearrangement is given by epoxides, when treated with acidic[97] reagents such as BF_3-etherate or $MgBr_2$-etherate, or sometimes by heat alone.[98] It has been shown that epoxides are intermediates


R = alkyl, aryl, or hydrogen

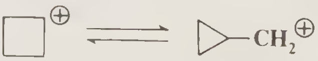
in the pinacol rearrangements of certain glycols.[99] Among the evidence for the mechanism given is that $Me_2COHCOHMe_2$, $Me_2COHCNH_2Me_2$, and $Me_2COHCClMe_2$ gave the reaction at different rates (as expected) but yielded the *same mixture* of two products—pinacol and pinacolone—indicating a common intermediate.[100]

OS **I,** 462; **II,** 73, 408; **III,** 312; **IV,** 375, 957; **V,** 326, 647.

8-3 Expansion and Contraction of Rings



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring which is one carbon smaller than the original.



Note that this change involves conversion of a secondary to a primary carbonium ion. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring expansion can take place.[101] The new carbonium ion, and the old one, may then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is really a special case of reaction **8-1.** Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbonium ion is formed by diazotization of the amine, the reaction is called the *Demyanov rearrangement*,[102] but of course similar products are formed when the carbonium ion is generated in other ways. The expansion reaction has been performed on rings of C_3 to C_8,[103] but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. The contraction reaction has been applied to four-membered rings, and to rings of C_6 to C_8, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved. Strain is apparently much less of a factor in the cyclobutyl-cyclopropylmethyl interconversion (for a discussion of this interconversion, see p. 298).

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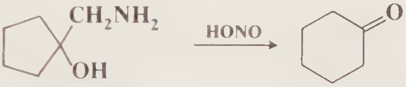
[97] Epoxides can also be rearranged with basic catalysts, though the products are usually different. For a review, see Yandovskii and Ershov, *Russ. Chem. Rev.* **41,** 403-410 (1972).

[98] For a review, see Parker and Isaacs, *Chem. Rev.* **59,** 737-799 (1959), pp. 772-778.

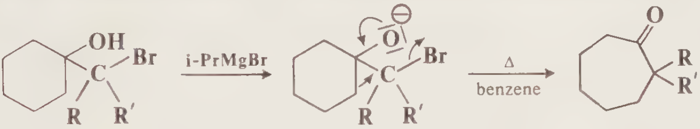
[99] See for example, Matsumoto, *Tetrahedron* **24,** 6851 (1968); Pocker and Ronald, *J. Am. Chem. Soc.* **92,** 3385 (1970), *J. Org. Chem.* **35,** 3362 (1970); Tamura and Moriyoshi, *Bull. Chem. Soc. Jpn.* **47,** 2942 (1974).

[100] Pocker, *Chem. Ind.* (*London*) 332 (1959).

Ring expansions of certain hydroxyamines, e.g.,

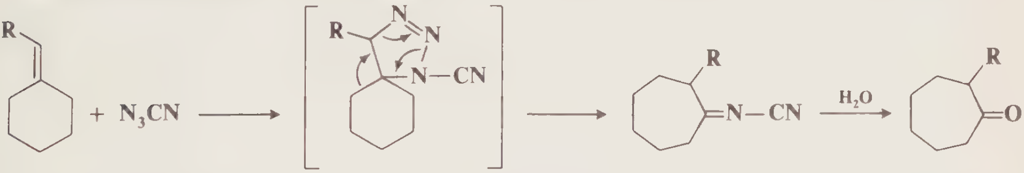


are analogous to the semipinacol rearrangement (**8-2**). This reaction is called the *Tiffeneu-Demyanov ring expansion.* These have been performed on rings of C_4 to C_8, and the yields are better than for the simple Demyanov ring expansion. A similar reaction has been used to expand rings of from five to eight members.[104] In this case, a cyclic bromohydrin of the form **47** is



47 **48**

treated with a Grignard reagent which, acting as a base, removes the OH proton to give the alkoxide **48.** Refluxing of **48** brings about the ring enlargement. The reaction has been accomplished for **47** in which at least one R group is phenyl or methyl,[105] but fails when both R groups are hydrogen.[106] A related ring expansion involves treatment of an exocyclic olefin (which



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[101] For a monograph on ring expansions, see Gutsche and Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, Inc., New York, 1968. For a review of ring contractions, see Redmore and Gutsche, *Adv. Alicyclic Chem.* **3,** 1–138 (1971). For a review of ring expansions in spirane systems, see Dolbier, *Mech. Mol. Migr.* **3,** 1-66 (1971). For a review of expansions and contractions of three- and four-membered rings, see Conia and Robson, *Angew. Chem. Int. Ed. Engl.* **14,** 473–485 (1975) [*Angew. Chem.* **87,** 505–516].

[102] For a review, see Smith and Baer, *Org. React.* **11,** 157–188 (1960).

[103] For a review concerning three- and four-membered rings, see Breslow, in Mayo, Ref. vol. 1, pp. 233–294.

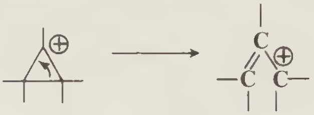
[104] Sisti, *Tetrahedron Lett.* 5327 (1967), *J. Org. Chem.* **33,** 453 (1968). See also Sisti and Vitale, *J. Org. Chem.* **37,** 4090 (1972).

[105] Sisti, *J. Org. Chem.* **35,** 2670 (1970), *Tetrahedron Lett.* 3305 (1970); Sisti and Meyers, *J. Org. Chem.* **38,** 4431 (1973); Sisti and Rusch, *J. Org. Chem.* **39,** 1182 (1974).

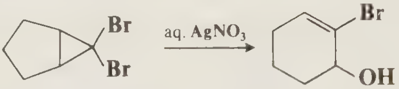
[106] Sisti, *J. Org. Chem.* **33,** 3953 (1968).

can be prepared by reaction **6-47**) with cyanogen azide.[107] The azide adds to the double bond in a 1,3 dipolar addition (**5-50**) to give a triazolidine intermediate which undergoes ring expansion. The cyanamide product is easily hydrolyzed to a cyclic ketone.

A positive charge generated on a three-membered ring gives "contraction" to an allylic cation.

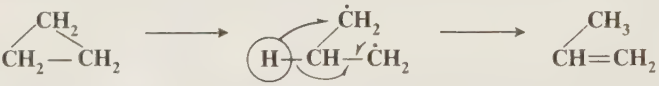


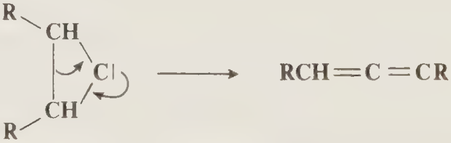
We have previously seen (p. 321) that this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being[108]

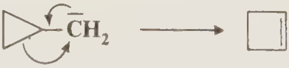


The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see p. 1034).

Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (1) On pyrolysis, cyclopropanes may undergo "contraction" to propenes.[109] In the simplest case, cyclopropane gives propene when heated to 400 to 500°C. The mechanism is generally regarded[110] as involving a diradical intermediate[111] (recall that free-radical 1,2 migration is possible for diradicals, p. 976). (2) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in this way.[112] In contrast, the generation of a carbene or carbenoid at a cyclopropylmethyl carbon gives ring expansion.[113]







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[107] Mc Murry and Coppolino, *J. Org. Chem.* **38,** 2821 (1973).

[108] Skell and Sandler, *J. Am. Chem. Soc.* **80,** 2024 (1958).

[109] For reviews, see Bergman, in Kochi, Ref. 53, vol. 1, pp. 191–237; Frey, *Adv. Phys. Org. Chem.* **4,** 147–193 (1966), pp. 148–170; Breslow, in Mayo, Ref. 1, pp. 234–245.

[110] For evidence that diradical intermediates may not be involved, at least in some cases, see Fields, Haszeldine, and Peter, *Chem. Commun.* 1081 (1967); Parry and Robinson, *Chem. Commun.* 1083 (1967); Holbrook and Parry, *J. Chem. Soc. B* 1019 (1970); Clifford and Holbrook, *J. Chem. Soc., Perkin Trans. 2* 1972 (1972); Baldwin and Grayston, *J. Am. Chem. Soc.* **96,** 1629, 1630 (1974).

[111] We have seen before that such diradicals can close up to give cyclopropanes (reaction **7-48**). Therefore, pyrolysis of cyclopropanes can produce not only propenes but also isomerized (cis → trans or optically active → inactive) cyclopropanes. See for example Berson and Balquist, *J. Am. Chem. Soc.* **90,** 7343 (1968); Carter and Bergman, *J. Am. Chem. Soc.* **90,** 7344 (1968); Bergman and Carter, *J. Am. Chem. Soc.* **91,** 7411 (1969).

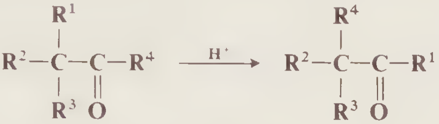
[112] For a review, see Kirmse, "Carbene Chemistry," 2d ed., pp. 462–467, Academic Press, Inc., New York, 1971.

[113] For a review, see Gutsche and Redmore, Ref. 101, pp. 111–117.

Formation of cyclobutenes also takes place when cyclopropylmethyl bromides and tosylates are treated with *t*-BuOK in dimethyl sulfoxide, but in this case the mechanism does not involve a carbene or carbenoid pathway.[114]

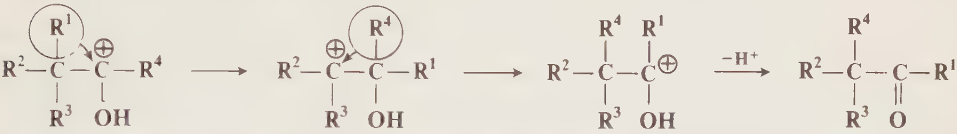
OS **III,** 276; **IV,** 221, 957; **V,** 306, 320; **51,** 60.

8-4 Acid-catalyzed Rearrangements of Aldehydes and Ketones

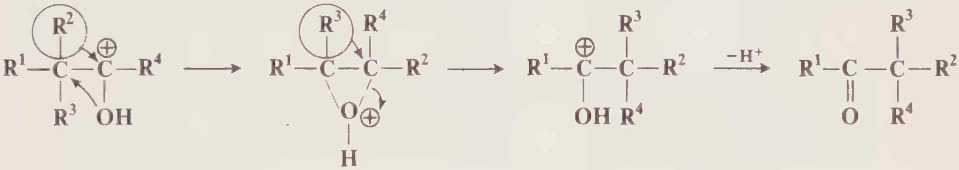


$$R^2-\underset{R^3}{\overset{R^1}{\overset{|}{\underset{|}{C}}}}-\underset{O}{\underset{\|}{C}}-R^4 \xrightarrow{H^+} R^2-\underset{R^3}{\overset{R^4}{\overset{|}{\underset{|}{C}}}}-\underset{O}{\underset{\|}{C}}-R^1$$

Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[115] R^2, R^3, and R^4 may be alkyl or hydrogen. Aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($R^1 = H$) has so far been reported. There are two mechanisms,[116] each beginning with protonation of the oxygen and each involving two migrations. In one mechanism the migrations are in opposite directions:[117]



In the other pathway the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate[118] is one possibility:[119]



If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, then the first pathway predicts that the product will contain all the ^{14}C in the C=O carbon, while in the second pathway the label will be in the α-carbon (demonstrating migration of oxygen). The results of such experiments[120] have shown that in some cases only the C=O carbon was labeled, in other cases only the α-carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α-hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the *α-ketol rearrangement*).

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[114] Dolbier and Alonso, *J. Chem. Soc., Chem. Commun.* 394 (1973).

[115] For reviews, see Fry, *Mech. Mol. Migr.* **4,** 113–196 (1971); Collins and Eastham, in Patai, Ref. 1, pp. 771–790.

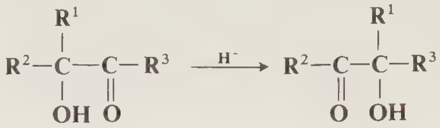
[116] Favorskii and Chilingaren, *C. R. Acad. Sci.* **182,** 221 (1926).

[117] Raaen and Collins, *J. Am. Chem. Soc.* **80,** 1409 (1958); Kendrick, Benjamin, and Collins, *J. Am. Chem. Soc.* **80,** 4057 (1958); Rothrock and Fry, *J. Am. Chem. Soc.* **80,** 4349 (1958); Collins and Bowman, *J. Am. Chem. Soc.* **81,** 3614 (1959).

[118] Zook, Smith, and Greene, *J. Am. Chem. Soc.* **79,** 4436 (1957).

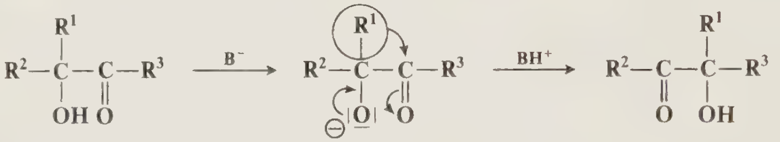
[119] Some such pathway is necessary to account for the migration of oxygen which is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2 shift of an OH group.

[120] See for example, Barton and Porter, *J. Chem. Soc.* 2483 (1956); Fry, Carrick, and Adams, *J. Am. Chem. Soc.* **80,** 4743 (1958); Fry and Corkern, *J. Am. Chem. Soc.* **89,** 5894 (1967); Oka and Fry, *J. Org. Chem.* **35,** 2801 (1970); Remizova and Zalesskaya, *J. Gen. Chem. USSR* **34,** 1398 (1964); Zalesskaya and Remizova, *J. Gen. Chem. USSR* **35,** 29 (1965).

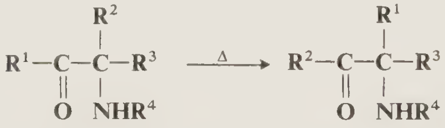


$$R^2-\underset{\displaystyle OH}{\overset{\displaystyle R^1}{C}}-\underset{\displaystyle \| \atop O}{C}-R^3 \xrightarrow{H^-} R^2-\underset{\displaystyle \| \atop O}{C}-\underset{\displaystyle OH}{\overset{\displaystyle R^1}{C}}-R^3$$

The α-ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.



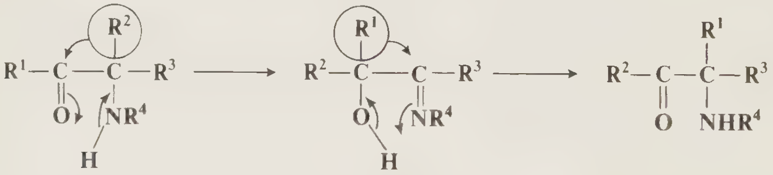
8-5 Thermal Rearrangement of Amino Ketones



$$R^1-\underset{\displaystyle \| \atop O}{C}-\underset{\displaystyle NHR^4}{\overset{\displaystyle R^2}{C}}-R^3 \xrightarrow{\Delta} R^2-\underset{\displaystyle \| \atop O}{C}-\underset{\displaystyle NHR^4}{\overset{\displaystyle R^1}{C}}-R^3$$

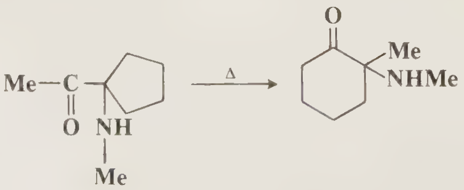
R = alkyl, aryl

When heated, ketones containing an α secondary amino group may undergo a rearrangement,[121] similar in appearance to reaction **8-4**, in which two R groups "change places."[122] R may be alkyl or aryl. The mechanism is different from that of reaction **8-4**, though it also involves two migrations in opposite directions. In this case the 1,2 migrations of R are accompanied by 1,4 migration of hydrogen between O and N:



49

The mechanism predicts that when heated, α-hydroxy imines (**49**) in which the OH group is tertiary should rearrange to α-amino ketones, and this has been found to be the case. The reaction has been used for ring enlargement, e.g.,[123]



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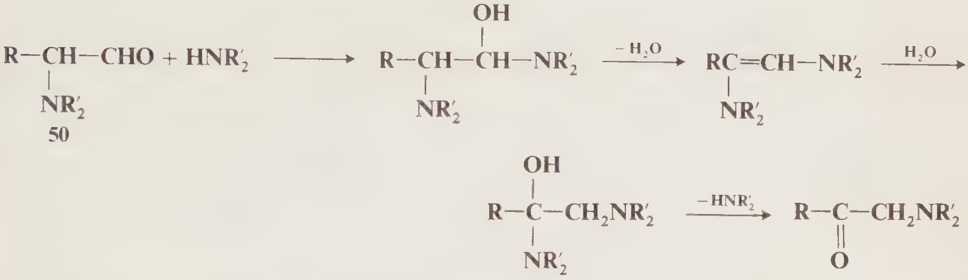
[121] For a review of amino ketone rearrangements, see Stevens, Pillai, Munk, and Taylor, *Mech. Mol. Migr.* **3**, 271–296 (1971).

[122] Stevens, Elliot, Winch, and Klundt, *J. Am. Chem. Soc.* **84**, 2272 (1962); Stevens, Elliott, and Winch, *J. Am. Chem. Soc.* **85**, 1464 (1963).

[123] Stevens, Klundt, Munk, and Pillai, *J. Org. Chem.* **30**, 2967 (1965).

Unbranched aldehydes containing an α tertiary amino group (**50**) rearrange spontaneously to α-amino ketones.[124] The mechanism is quite different from that of the ketone reaction given

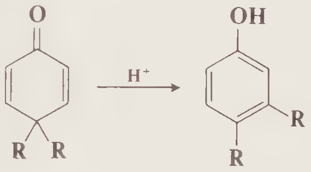


$$\underset{\substack{|\\ NR'_2}}{R-CH}-CHO + HNR'_2 \longrightarrow R-\underset{\substack{|\\ NR'_2}}{CH}-\overset{\substack{OH\\ |}}{CH}-NR'_2 \xrightarrow{-H_2O} R\underset{\substack{|\\ NR'_2}}{C}=CH-NR'_2 \xrightarrow{H_2O} R-\underset{\substack{|\\ NR'_2}}{\overset{\substack{OH\\ |}}{C}}-CH_2NR'_2 \xrightarrow{-HNR'_2} R-\underset{\substack{\|\\ O}}{C}-CH_2NR'_2$$

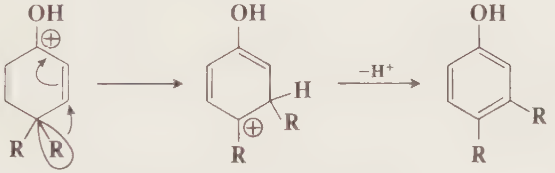
50

above and involves an elimination-addition sequence. The R'_2NH needed to initiate the reaction is probably formed by the reaction of **50** with small amounts of water present.[125]

8-6 The Dienone-Phenol Rearrangement



Compounds in which a cyclohexadienone has two alkyl groups in the 4 position undergo, on acid treatment, migration of one of these groups to a position allylic to the hydroxy group generated by protonation of the oxygen:



51 52

The driving force in the overall reaction (the *dienone-phenol rearrangement*) is of course creation of an aromatic system.[126] The anthrasteroid rearrangement (p. 981) is closely related. It may be noted that ions **51** and **52** are arenium ions (p. 454), the same as those generated by attack of an electrophile on a phenol.[127] Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol-dienone rearrangement*) takes place, though without an actual migration.[128] An example is

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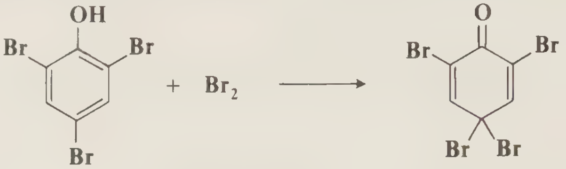
[124] Kirrmann, Duhamel, and Duhamel, *Bull. Soc. Chim. Fr.* 1732 (1966); Duhamel, Duhamel, and Jarry, *Bull. Soc. Chim. Fr.* 1797 (1970).

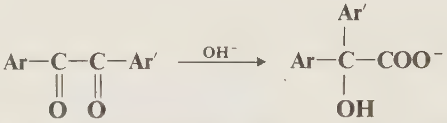
[125] Duhamel and Duhamel, *Bull. Soc. Chim. Fr.* 1999 (1969).

[126] For reviews, see Perkins and Ward, *Mech. Mol. Migr.* **4**, 55–112 (1971), pp. 90–103; Miller, *Mech. Mol. Migr.* **1**, 247–313 (1968); Shine, "Aromatic Rearrangements," pp. 55–68, American Elsevier Publishing Company, New York, 1967; Waring, *Adv. Alicyclic Chem.* **1**, 129–256 (1966), pp. 207–223. For a review of other rearrangements of cyclohexadienones, see Miller, *Acc. Chem. Res.* **8**, 245–256 (1975).

[127] For evidence that these ions are indeed intermediates in this rearrangement, see Vitullo, *J. Org. Chem.* **34**, 224 (1969), *J. Org. Chem.* **35**, 3976 (1970); Vitullo and Grossman, *J. Am. Chem. Soc.* **94**, 3844 (1972).

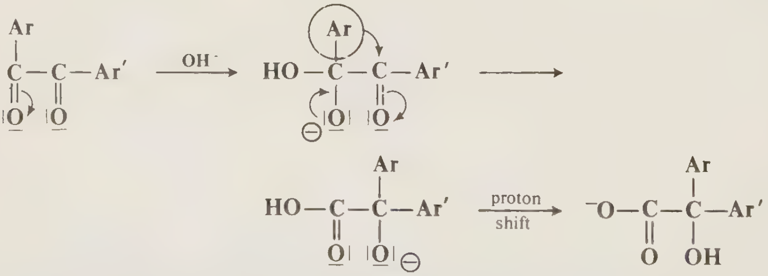


8-7 The Benzil–Benzilic Acid Rearrangement



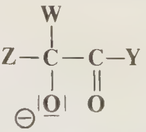
$$\text{Ar}-\underset{\substack{\|\\ \text{O}}}{\text{C}}-\underset{\substack{\|\\ \text{O}}}{\text{C}}-\text{Ar}' \xrightarrow{\text{OH}^-} \text{Ar}-\overset{\substack{\text{Ar}'\\ |}}{\underset{\substack{|\\ \text{OH}}}{\text{C}}}-\text{COO}^-$$

When treated with base, α-diketones rearrange to give the salts of α-hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is PhCOCOPh; benzilic acid is $Ph_2COHCOOH$).[129] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones and to α-keto aldehydes. The use of alkoxide ion instead of OH^- gives the corresponding ester directly,[130] though alkoxide ions which are readily oxidized (such as OEt^- or $OCHMe_2^-$) are not useful here since they reduce the benzil to a benzoin. Aroxide ions (OAr^-) are not strong enough bases for the reaction. The mechanism is similar to the rearrangements in reactions **8-1** to **8-4**, but there is a difference: The migrating group does not move to a carbon with an open sextet. The carbon has an octet but can still accept a group with its pair of electrons by releasing a π pair of electrons from the C=O bond to the oxygen. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (p. 308) and of many additions to the C=O bond (Chapter 16):



The mechanism has been intensively studied, and there is much evidence for it.[129] The reaction is irreversible.

There are other related reactions in which an intermediate of the form



$$\text{Z}-\overset{\substack{\text{W}\\ |}}{\underset{\substack{|\\ \ominus|\underline{\text{O}}|}}{\text{C}}}-\underset{\substack{\|\\ \text{O}}}{\text{C}}-\text{Y}$$

53

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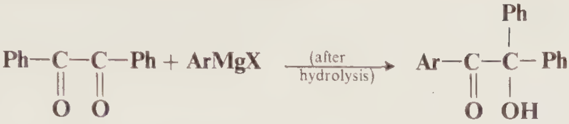
[128] For a review, see Ershov, Volod'kin, and Bogdanov, *Russ. Chem. Rev.* **32,** 75–93 (1963).

[129] For a review, see Selman and Eastham, *Q. Rev., Chem. Soc.* **14,** 221–235 (1960).

[130] Doering and Urban, *J. Am. Chem. Soc.* **78,** 5938 (1956).

is formed and then rearrangement follows. An example is

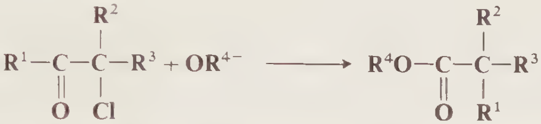


$$\text{Ph}-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\text{Ph}+\text{ArMgX}\xrightarrow[\text{hydrolysis)}]{\text{(after}}\text{Ar}-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\underset{\underset{\displaystyle \text{OH}}{|}}{\overset{\overset{\displaystyle \text{Ph}}{|}}{\text{C}}}-\text{Ph}$$

In the intermediate **53**, for the benzilic acid rearrangement, Z = OH, W and Y = R, Ar, or H; for the benzilic ester case, Z = OR, W and Y = R or Ar; for the Grignard example shown, Z, W, and Y all = Ar. In other cases, W and Z may be ArNH, ArCO, RCO, etc., and Y may be OH, RCO, etc. The base-catalyzed α-ketol rearrangement (reaction **8-4**) also belongs to this group of reactions, with W and Z = R or Ar; Y = R, Ar, or H.

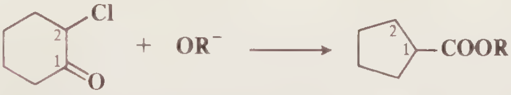
OS **I,** 89.

8-8 The Favorskii Rearrangement



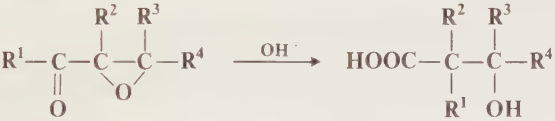
$$\text{R}^1-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\underset{\underset{\displaystyle \text{Cl}}{|}}{\overset{\overset{\displaystyle \text{R}^2}{|}}{\text{C}}}-\text{R}^3+\text{OR}^{4-}\longrightarrow \text{R}^4\text{O}-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\underset{\underset{\displaystyle \text{R}^1}{|}}{\overset{\overset{\displaystyle \text{R}^2}{|}}{\text{C}}}-\text{R}^3$$

The reaction of α-halo ketones (chloro, bromo, or iodo)[131] with alkoxide ions to give rearranged esters is called the *Favorskii rearrangement.*[132] The use of hydroxide ions or amines as bases leads to the free acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction:



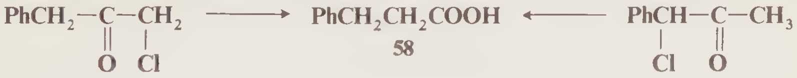
54 **55**

The reaction has also been carried out on α-hydroxy ketones[133] and on α,β-epoxy ketones:[134]



The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.

Through the years the mechanism of the Favorskii rearrangement has been the subject of much investigation, and at least five different mechanisms have been proposed. However, the finding[135] that **56** and **57** *both* give **58** (this behavior is typical) shows that any mechanism where



$$\text{PhCH}_2-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\underset{\underset{\displaystyle \text{Cl}}{|}}{\text{CH}_2}\longrightarrow \text{PhCH}_2\text{CH}_2\text{COOH}\longleftarrow \text{PhCH}\underset{\underset{\displaystyle \text{Cl}}{|}}{}-\underset{\underset{\displaystyle \text{O}}{\|}}{\text{C}}-\text{CH}_3$$

56 **58** **57**

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[131] Nace and Olsen, *J. Org. Chem.* **32,** 3438 (1967).

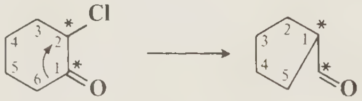
[132] For reviews, see Rappe, in Patai, "The Chemistry of the Carbon-Halogen Bond," pt. 2, pp. 1084–1101, John Wiley & Sons, Inc., New York, 1973; Redmore and Gutsche, Ref. 101, pp. 46–69; Akhrem, Ustynyuk and Titov, *Russ. Chem. Rev.* **39,** 732–746 (1970); Kende, *Org. React.* **11,** 261–316 (1960).

[133] Craig, Dinner, and Mulligan, *J. Org. Chem.* **37,** 3539 (1972).

[134] See for example, House and Gilmore, *J. Am. Chem. Soc.* **83,** 3972 (1961); Mouk, Patel, and Reusch, *Tetrahedron* **31,** 13 (1975).

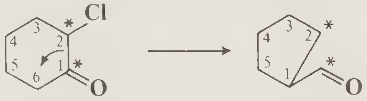
[135] McPhee and Klingsberg, *J. Am. Chem. Soc.* **66,** 1132 (1944); Bordwell, Scamehorn, and Springer, *J. Am. Chem. Soc.* **91,** 2087 (1969).

the halogen leaves and R^1 takes its place is invalid, since in such a case **56** would be expected to give **58** (with $PhCH_2$ migrating), but **57** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **57**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **54**, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **55**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[136] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so that the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, then the other half of the radioactivity would be only on C-1 of the product:



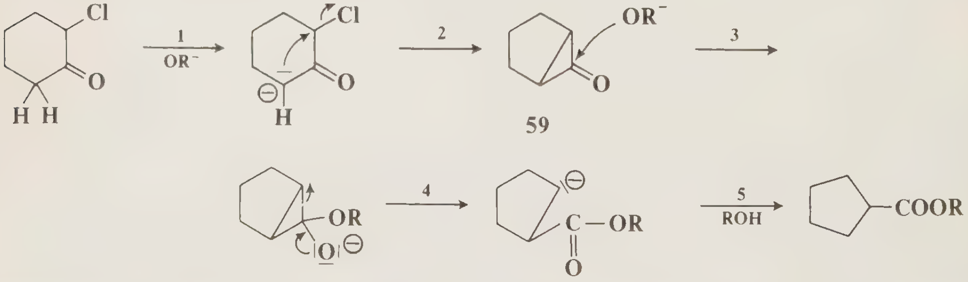
54

On the other hand, if the migration had gone the other way—if the C-2 carbon had migrated to C-6—then this half of the radioactivity would be found solely on C-2 of the product:



54

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations occurred*, and with equal probability. Since C-2 and C-6 of **54** are not equivalent, this means that there must be a symmetrical intermediate. The type of intermediate which best fits the circumstances is a cyclopropanone,[137] and the mechanism is formulated:



59

A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **54** had the same isotopic distribution as the starting **54**.

For the general case the mechanism is (replacing R^1 of our former symbolism with CHR^5R^6, since it is obvious that for this mechanism an α-hydrogen is required on the nonhalogenated side of the carbonyl):

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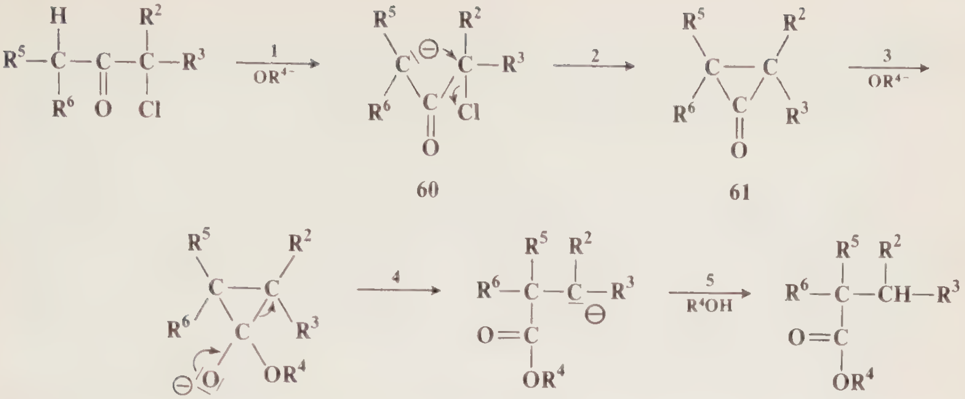
[136] Loftfield, *J. Am. Chem. Soc.* **73**, 4707 (1951).

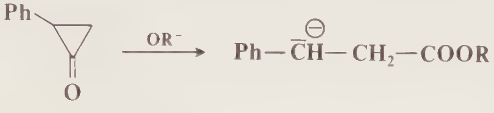
[137] Although cyclopropanones are very reactive compounds, several of them have been isolated. For reviews of cyclopropanone chemistry, see Wasserman, Clark, and Turley, *Top. Curr. Chem.* **47**, 73–156 (1974); Turro, *Acc. Chem. Res.* **2**, 25–32 (1969).



60

61

59 is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C. In the general case, **61** is not symmetrical and should open on the side which gives the more stable carbanion.[138] This accounts for the fact that **56** and **57** give the same product. The intermediate in both cases is **62**, which



62

always opens to give the carbanion stabilized by resonance. Though the cyclopropanone intermediate (**61**) has not been isolated, it has been trapped;[139] and cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[140] The question of the exact timing of the steps involved has been much investigated. One possibility is that proton loss takes place simultaneously with formation of the cyclopropane; that is, that steps 1 and 2 are concerted. However, after an extensive study, Bordwell and coworkers have concluded that these steps are not concerted, and that the carbanion **60** is an intermediate.[141] In some cases step 2 is rate-determining,[142] and in other cases step 1 (proton removal).[143] Another question involves step 2. Does the Cl^- leave before the ring closes (SN1), or is attack by the carbanionic carbon simultaneous with the departure of the Cl^- (SN2)? Evidence for an SN2 mechanism at least in some cases is the fact that the diastereomers **63** and **64** reacted stereospecifically to give, respectively, **65** and **66** when treated with NaOMe in an ether solvent.[144]

[138] Factors other than carbanion stability (including steric factors) may also be important in determining which side of an unsymmetrical **61** is preferentially opened. See for example, Rappe and Knutsson, *Acta Chem. Scand.* **21,** 2205 (1967); Rappe, Knutsson, Turro, and Gagosian, *J. Am. Chem. Soc.* **92,** 2032 (1970).

[139] Fort, *J. Am. Chem. Soc.* **84,** 4979 (1962); Cookson and Nye, *Proc. Chem. Soc.* 129 (1963); Breslow, Posner, and Krebs, *J. Am. Chem. Soc.* **85,** 234 (1963); Baldwin and Cardellina, *Chem. Commun.* 558 (1968).

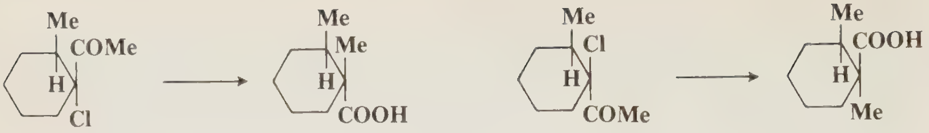
[140] Turro and Hammond, *J. Am. Chem. Soc.* **87,** 3258 (1965); Hammond and Turro, *J. Am. Chem. Soc.* **88,** 2880 (1966); Crandall and Machleder, *J. Org. Chem.* **90,** 7347 (1968); Turro, Gagosian, Rappe, and Knutsson, *Chem. Commun.* 270 (1969); Wharton and Fritzberg, *J. Org. Chem.* **37,** 1899 (1972).

[141] Bordwell, *Acc. Chem. Res.* **3,** 281–290 (1970); Bordwell, Frame, Scamehorn, Strong, and Meyerson, *J. Am. Chem. Soc.* **89,** 6704 (1967). See also McGrath, *Tetrahedron* **32,** 377 (1976).

[142] See for example, Rappe and Knutsson, *Acta Chem. Scand.* **22,** 2910 (1968); Bordwell and Scamehorn, *J. Am. Chem. Soc.* **90,** 6751 (1968); Bordwell, Scamehorn, and Springer, Ref. 135.

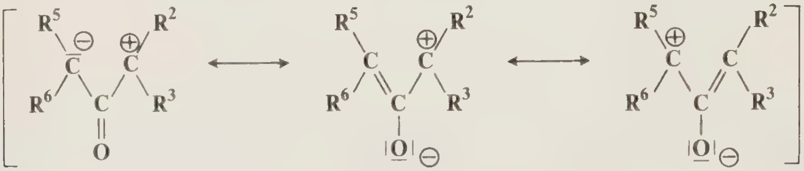
[143] See for example Bordwell and Carlson, *J. Am. Chem. Soc.* **92,** 3370, 3377 (1970); Bordwell and Scamehorn, *J. Am. Chem. Soc.* **93,** 3410 (1971).

[144] Stork and Borowitz, *J. Am. Chem. Soc.* **82,** 4307 (1960); House and Gilmore, *J. Am. Chem. Soc.* **83,** 3980 (1961). See also Smissman, Lemke, and Kristiansen, *J. Am. Chem. Soc.* **88,** 334 (1966).



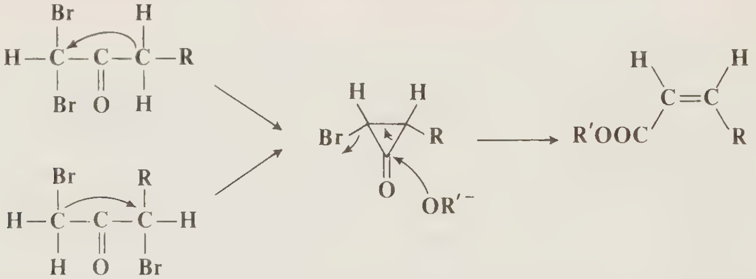
63 **65** **64** **66**

This result demonstrates that inversion of configuration has taken place at the carbon attached to the chlorine, as required by the SN2 mechanism. However, the same reaction in methanol is not stereospecific,[145] and an SN1 mechanism (which requires a dipolar intermediate **67**[146]) may take place in such cases.[147]

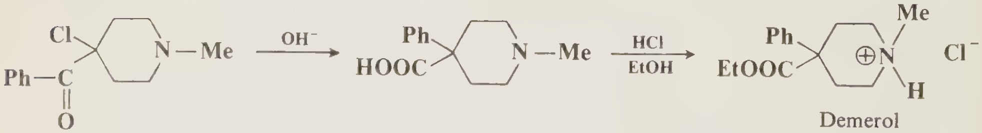


67

When the Favorskii rearrangement is applied to α,α-dihalo ketones containing an α′-hydrogen[148] or to α,α′-dihalo ketones containing an α-hydrogen,[149] the product is an α,β-unsaturated ester. In either case the same cyclopropanone is formed. Ring opening is different here, involving simultaneous elimination of halide ion:



The mechanism discussed is in accord with all the facts when the halo ketone contains an α-hydrogen on the other side of the carbonyl group. However, ketones which do not have a hydrogen there also rearrange to give the same type of product. This is usually called the *quasi-Favorskii rearrangement*. An example is found in the preparation of Demerol:[150]



Demerol

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[145] House and Gilmore, Ref. 144. See also House and Richey, *J. Org. Chem.* **32,** 2151 (1967); Engel, Roy, Capitaine, Bilodeau, McPherson-Foucar, and Lachance, *Can. J. Chem.* **48,** 361 (1970).

[146] Aston and Newkirk, *J. Am. Chem. Soc.* **73,** 3900 (1951); Burr and Dewar, *J. Chem. Soc.* 1201 (1954); Fort, *J. Am. Chem. Soc.* **84,** 2620, 2625 (1962).

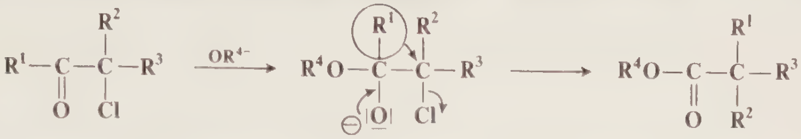
[147] There is also other evidence for the intermediacy of **67.** See Bordwell and Scamehorn, Ref. 143; Bordwell and Strong, *J. Org. Chem.* **38,** 579 (1973); Paquette, Meisinger, and Wingard, *J. Am. Chem. Soc.* **95,** 2230 (1973).

[148] Kennedy, McCorkindale, Raphael, Scott, and Zwanenburg, *Proc. Chem. Soc.* 148 (1964).

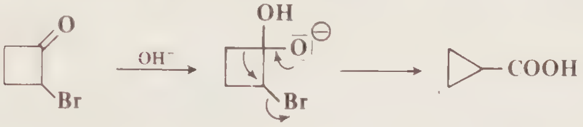
[149] Rappe and Adeström, *Acta Chem. Scand.* **19,** 383 (1965); Rappe, *Acta Chem. Scand.* **20,** 862 (1966); Rappe, *Acta Chem. Scand.* **17,** 2766 (1963).

[150] Smissman and Hite, *J. Am. Chem. Soc.* **81,** 1201 (1959).

The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The mechanism which is generally accepted (called the *semibenzilic mechanism*[151]) is a base-catalyzed pinacol rearrangement-type mechanism similar to that of reaction **8-7.** This mechanism



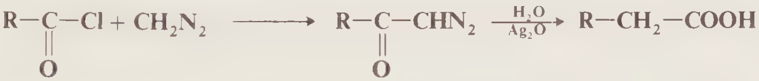
requires inversion at the migration terminus, and this has been found.[152] It has been shown that even where there *is* an appropriately situated α-hydrogen, the semibenzilic mechanism may still operate. One such example is the ring contraction of α-halocyclobutanones[153] (for these



substrates, boiling water may be all that is necessary; a stronger base is not always required). The semibenzilic mechanism has been shown for these compounds by experiments involving deuterium labeling, as well as by other experiments.[154] In at least one case it has been shown that an α-halo ketone with an α′-hydrogen can give the Favorskii reaction by either the cyclopropanone or the semibenzilic mechanism, depending on the experimental conditions.[155]

OS **IV,** 594; **53,** 123.

8-9 The Arndt-Eistert Synthesis



$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}Cl + CH_2N_2 \longrightarrow R{-}\underset{\underset{O}{\|}}{C}{-}CHN_2 \xrightarrow[Ag_2O]{H_2O} R{-}CH_2{-}COOH}$$

In the *Arndt-Eistert synthesis* an acyl halide is converted to a carboxylic acid with one additional carbon.[156] The first step of this process is reaction **0-116.** The actual rearrangement occurs in the second step on treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*. It is the best method of increasing a carbon chain by one if a *carboxylic acid* is available (reactions **0-103** and **6-35** begin with alkyl halides). If an alcohol R′OH is used instead of water, the ester RCH_2COOR' is isolated directly. Similarly, ammonia gives the amide. Other catalysts are sometimes used, e.g., colloidal platinum, copper, etc., but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all. The photolysis method often gives better results than the silver catalysis method. Of course diazo ketones prepared in any other way also give the rearrangement. The reaction is of wide scope. R may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., reactions **0-6** and **0-28**). Sometimes the reaction is performed with other diazoalkanes (that is, $R'CHN_2$) to give RCHR′COOH. The reaction has been used for ring contraction of cyclic diazo ketones;[157] e.g.,[158]

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[151] Tchoubar and Sackur, *C. R. Acad. Sci.* **208,** 1020 (1939).

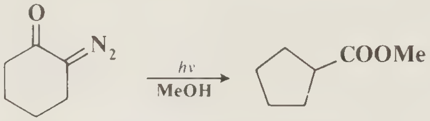
[152] Baudry, Bégué, and Charpentier-Morize, *Bull. Soc. Chim. Fr.* 1416 (1971), *Tetrahedron Lett.* 2147 (1970).

[153] For a review of cyclobutane ring contractions not involving carbonium ions, see Conia and Salaun, *Acc. Chem. Res.* **5,** 33–40 (1972).

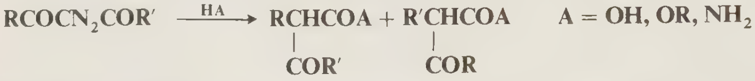
[154] Conia and Salaun, *Tetrahedron Lett.* 1175 (1963), *Bull. Soc. Chim. Fr.* 1957 (1964); Salaun, Garnier, and Conia, *Tetrahedron* **29,** 2895 (1973); Rappe and Knutsson, *Acta Chem. Scand.* **21,** 163 (1967).

[155] Warnhoff, Wong, and Tai, *J. Am. Chem. Soc.* **90,** 514 (1968).

[156] For reviews, see Meier and Zeller, *Angew. Chem. Int. Ed. Engl.* **14,** 32–43 (1975) [*Angew. Chem.* **87,** 52–63]; Kirmse, Ref. 112, pp. 475–493; Rodina and Korobitsyna, *Russ. Chem. Rev.* **36,** 260–272 (1967); Weygand and Bestmann, *Angew. Chem.* **72,** 535–554 (1960), *Newer Methods Prep. Org. Chem.* **3,** 451–508 (1964); Smith, in Mayo, Ref. 1, pp. 528–550, 558–564; Eistert, *Newer Methods Prep. Org. Chem.* **1,** 513–570 (1948); Bachmann and Struve, *Org. React.* **1,** 38–62 (1942).

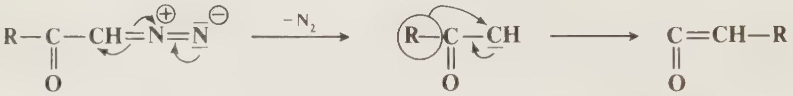


Unsymmetrical diacyldiazomethanes (prepared as in reaction **2-9**) can rearrange to give two isomeric products:[159]



$$RCOCN_2COR' \xrightarrow{HA} \underset{\displaystyle COR'}{RCHCOA} + \underset{\displaystyle COR}{R'CHCOA} \qquad A = OH, OR, NH_2$$

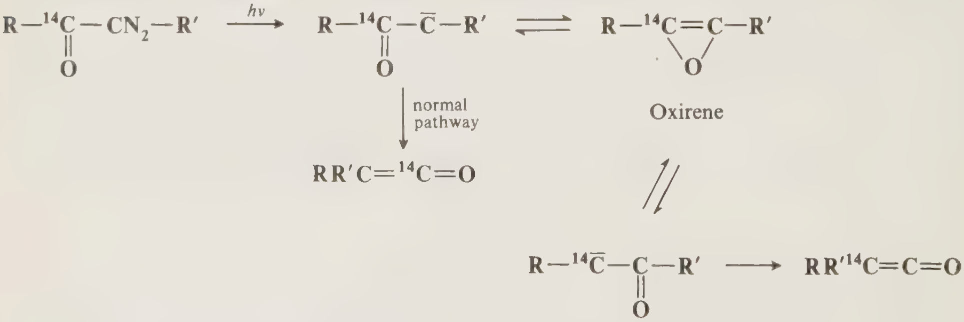
The mechanism is generally regarded to involve formation of a carbene. It is the divalent carbon which has the open sextet and to which the migrating group brings its electron pair:



$$R-\underset{\displaystyle O}{\overset{\|}{C}}-CH{=}\overset{\oplus}{N}{=}\overset{\ominus}{N} \xrightarrow{-N_2} R-\underset{\displaystyle O}{\overset{\|}{C}}-\ddot{C}H \longrightarrow \underset{\displaystyle O}{\overset{\|}{C}}{=}CH-R$$

The actual product of the reaction is thus the ketene, which then reacts with water (reaction **5-2**), an alcohol (reaction **5-5**), or ammonia or an amine (reaction **5-9**). Particularly stable ketenes (for example, $Ph_2C{=}C{=}O$) have been isolated, and others have been trapped in other ways (e.g., as β-lactams,[160] reaction **6-70**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the Curtius rearrangement (reaction **8-18**). Although the mechanism as shown above involves a free carbene, and there is much evidence to support this,[161] it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the Wolff rearrangement is carried out photochemically, the mechanism is basically the same, but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene-carbene rearrangement, through an oxirene intermediate. This was shown by ^{14}C labeling



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[157] For a review, see Redmore and Gutsche, Ref. 101, pp. 125–136.

[158] Korobitsyna, Rodina, and Sushko, *J. Org. Chem. USSR* **4**, 165 (1968); Jones and Ando, *J. Am. Chem. Soc.* **90**, 2200 (1968).

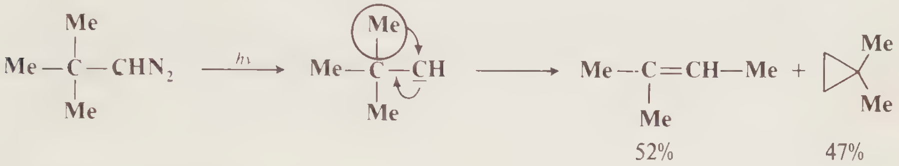
[159] Heyes and Holt, *J. Chem. Soc., Perkin Trans. 1* 1206 (1973).

[160] Kirmse and Horner, *Chem. Ber.* **89**, 2759 (1956); also see Horner and Spietschka, *Chem. Ber.* **89**, 2765 (1956).

[161] For a summary of evidence on both sides of the question, see Kirmse, Ref. 112, pp. 476–480.

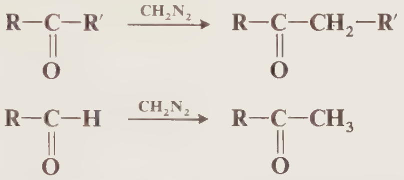
experiments, where diazo ketones labeled in the carbonyl group gave rise to ketenes which bore the label at both C=C carbons.[162] In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when R′ = H. The oxirene pathway is not found in the thermal Wolff rearrangement. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.[163]

Other 1,2 alkyl migrations to a carbene or carbenoid terminus are also known,[164] e.g.,[165]



OS **III**, 356; **50**, 77; **52**, 53.

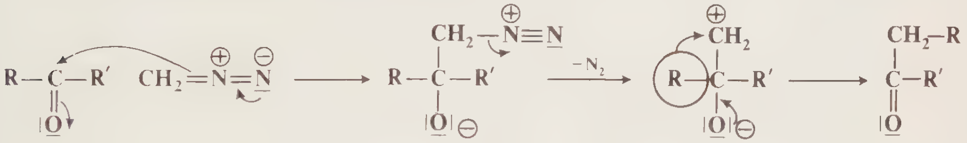
8-10 Homologization of Aldehydes and Ketones



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{CH_2N_2} R-\underset{\underset{O}{\|}}{C}-CH_2-R'$$

$$R-\underset{\underset{O}{\|}}{C}-H \xrightarrow{CH_2N_2} R-\underset{\underset{O}{\|}}{C}-CH_3$$

Aldehydes and ketones can be converted to their homologs with diazomethane.[166] Formation of the epoxide (reaction **6-65**) is a side reaction. Although this reaction appears superficially to be similar to the insertion of carbenes into C—H bonds (reaction **2-18**), the mechanism is quite different, and this reaction is a true rearrangement. No free carbene is involved. The first step is an addition to the C=O bond of the aldehyde or ketone:



68 **69**

The betaine **68** can sometimes be isolated. As shown on p. 886, **69** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.[166] It may be noted that this mechanism is essentially the same as in the apparent "insertions" of oxygen (reaction **8-23**) and nitrogen (reaction **8-20**) into ketones. Although the mechanism normally does not involve a free carbene, it has been shown that free carbene does give similar products. Thus, acetone, treated with carbene, gave methyl ethyl ketone (undoubtedly by insertion into the C—H bond) and 1,1-dimethylethylene oxide.[167]

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[162] Csizmadia, Font, and Strausz, *J. Am. Chem. Soc.* **90,** 7360 (1968); Frater and Strausz, *J. Am. Chem. Soc.* **92,** 6654 (1970); Fenwick, Frater, Ogi, and Strausz, *J. Am. Chem. Soc.* **95,** 124 (1973); Zeller, Meier, Kolshorn, and Müller, *Chem. Ber.* **105,** 1875 (1972). See also Thornton, Gosavi, and Strausz, *J. Am. Chem. Soc.* **92,** 1768 (1970); Russell and Rowland, *J. Am. Chem. Soc.* **92,** 7508 (1970); Majerski and Redvanly, *J. Chem. Soc., Chem. Commun.* 694 (1972).

[163] Csizmadia, Gunning, Gosavi, and Strausz, *J. Am. Chem. Soc.* **95,** 133 (1973).

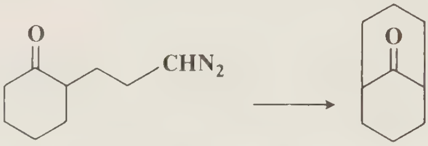
[164] For a review, see Kirmse, Ref. 112, pp. 457–462.

[165] Kirmse and Horn, *Chem. Ber.* **100,** 2698 (1967).

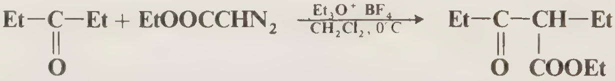
[166] For reviews, see Gutsche, *Org. React.* **8,** 364–429 (1954); Eistert, Ref. 156, pp. 521–537.

[167] Bradley and Ledwith, *J. Chem. Soc.* 3480 (1963).

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of boron trifluoride[168] or aluminum chloride[169] increases the yield of ketone.[170] Cyclic ketones, three-membered[171] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[172] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[173] An interesting example is the preparation of bicyclic compounds from alicyclic compounds with a diazo group in the side chain, e.g.,[174]



Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[175] e.g.,

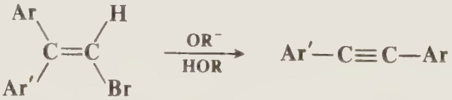


$$\underset{\text{O}}{\overset{}{\text{Et}-\underset{\Vert}{\text{C}}-\text{Et}}} + \text{EtOOCCHN}_2 \xrightarrow[\text{CH}_2\text{Cl}_2,\ 0^\circ\text{C}]{\text{Et}_3\text{O}^+\ \text{BF}_4^-} \text{Et}-\underset{\underset{\text{O}}{\Vert}}{\text{C}}-\underset{\underset{\text{COOEt}}{|}}{\text{CH}}-\text{Et}$$

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[176]

OS IV, 225, 780.

8-11 The Fritsch-Buttenberg-Wiechell Rearrangement



The rearrangement of 1,1-diaryl-2-haloethylenes to diarylacetylenes with strong bases[177] is called the *Fritsch-Buttenberg-Wiechell rearrangement*.[178] Alkoxide ions, sodium amide, and alkyl- and aryllithiums have been used as bases. The order of halide reactivity is $Br > I \gg Cl$.[179] There are two main side reactions, which may predominate. One of these is simple nucleophilic substitution of the halide by the base (for example, $Ar_2C{=}CHBr + OEt \rightarrow Ar_2C{=}CHOEt$), and the other, which occurs with alkyl- and aryllithiums, is halogen-metal interchange (reaction **2-38**). In the latter case the olefin goes to $Ar_2C{=}CHLi$, which may be converted to $Ar_2C{=}CHCOOH$ with CO_2 or to $Ar_2C{=}CH_2$ with water. The reaction has also been applied to compounds of the type $ArRC{=}CHBr$ and $(R'_2C{=}CH)RC{=}CHCl$,[180] but $R_2C{=}CHBr$ do not generally give the rearrangement. Ketene aminals of the form $(R_2N)_2C{=}CHCl$ can be similarly converted to ynediamines $R_2NC{\equiv}CNR_2$.[181]

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[168] House, Grubbs, and Gannon, *J. Am. Chem. Soc.* **82,** 4099 (1960).

[169] Müller and Heischkeil, *Tetrahedron Lett.* 2809 (1964).

[170] For a review of homologizations catalyzed by Lewis acids, see Müller, Kessler, and Zeeh, *Fortschr. Chem. Forsch.* 7, 128–171 (1966), pp. 137–150.

[171] For example, see Turro and Gagosian, *J. Am. Chem. Soc.* **92,** 2036 (1970).

[172] For a review, see Gutsche and Redmore, Ref. 101, pp. 81–98.

[173] For example, see Smith, *J. Org. Chem.* **25,** 453 (1960); Warner, Walsh, and Smith, *J. Chem. Soc.* 1232 (1962).

[174] Gutsche and Bailey, *J. Org. Chem.* **28,** 607 (1963); Bailey, Bowers, and Gutsche, *J. Org. Chem.* **28,** 610 (1963); Gutsche and Zandstra, *J. Org. Chem.* **39,** 324 (1974).

[175] Mock and Hartman, *J. Am. Chem. Soc.* **92,** 5767 (1970).

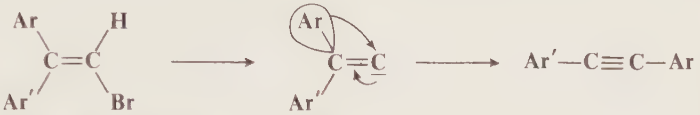
[176] Liu and Majumdar, *Synth. Commun.* **5,** 125 (1975).

[177] For reviews, see Köbrich and Buck, in Viehe, "Acetylenes," pp. 117–122, 131–134, Marcel Dekker, Inc., New York, 1969; Köbrich, *Angew. Chem. Int. Ed. Engl.* **4,** 49–68 (1965); pp. 63–67 [*Angew. Chem.* **77,** 75–94].

[178] Fritsch, *Justus Liebigs Ann. Chem.* **279,** 319 (1894); Buttenberg, *Justus Liebigs Ann. Chem.* **279,** 327 (1894); Wiechell, *Justus Liebigs Ann. Chem.* **279,** 337 (1894).

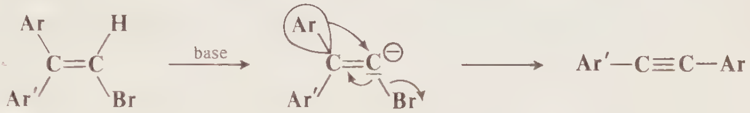
[179] Pritchard and Bothner-By, *J. Phys. Chem.* **64,** 1271 (1960).

In this rearrangement, a hydrogen and a halogen are removed from the same carbon on treatment with a base, and it is tempting to assume that a carbene intermediate is involved here (see p. 181):



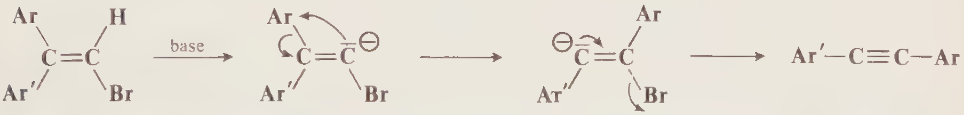
However, a major piece of evidence against this mechanism is that the reaction is stereoselective: The predominant migrating group is the one trans to the halogen. This was determined by the use of two different aryl groups and the labeling of one of the ethylenic carbons with ^{14}C.[182] A free carbene should be symmetrical, and it should not matter which group migrates.[183] Other evidence against the carbene mechanism is that products of carbene insertion or addition are not found. If we reject the carbene mechanism, there are still two major possibilities.[184] The aryl group may migrate with (mechanism *a*) or without (mechanism *b*) its electrons:

Mechanism *a*



70

Mechanism *b*



Although we have shown these mechanisms with two and three steps, respectively, it is also possible that two or three of the steps are concerted. The principal way of distinguishing between mechanisms *a* and *b* is the study of the effects of substituents on the migrating group. In mechanism *a* the reaction with respect to the migrating group is electrophilic aromatic substitution, with a transition state in which the ring is positively charged. Electron-donating substituents in the ortho or para position should aid the migration, and withdrawing substituents should hinder it. In mechanism *b* the reaction is nucleophilic aromatic substitution, with a negatively charged transition state, and the effect of substituents should be just the opposite. The results are in accord with mechanism *a*.[185] The question remains as to whether it is a one-step or two-step process. There is evidence that, at least in some cases, there is a two-step mechanism: the intermediate **70** has been isolated as the lithium compound and on heating gave the diarylacetylene;[186] and hydrogen-deuterium exchange has been shown.[179] However, it may be that in other cases the two steps are concerted. The fact that the reaction is stereoselective does not *require* that the reaction be concerted, since vinyl carbanions can hold their configurations (p. 165).

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[180] Fienemann and Köbrich, *Chem. Ber.* **107**, 2797 (1974).

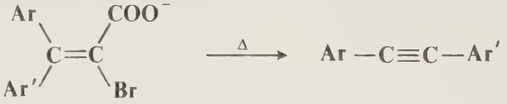
[181] Delavarenne and Viehe, *Chem. Ber.* **103**, 1209 (1970).

[182] Curtin, Flynn, and Nystrom, *J. Am. Chem. Soc.* **80**, 4599 (1958); Bothner-By, *J. Am. Chem. Soc.* **77**, 3293 (1955).

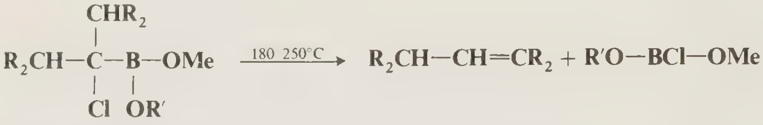
[183] It has been shown [Tadros, Sakla, Ishak, and Armanious, *J. Chem. Soc.* 4218 (1963)] that the reaction of 1-phenyl-1-*p*-anisyl-2-bromoethylene with sodium glycoxide in boiling ethylene glycol is not stereoselective, the anisyl group preferentially migrating, whether cis or trans. It may be that the mechanism in this case is different or, more simply, that here the olefin isomerizes before migration takes place.

[184] An *intermolecular* mechanism was ruled out by crossover experiments and by the fact that a substituent on a migrating ring is found in the same position in the product.

A similar rearrangement has been carried out on salts of 3,3-diaryl-2-halopropenoic acids:[187]



8-12 Rearrangement of α-Chloroboronic Acids



$$R_2CH-\underset{Cl}{\overset{CHR_2}{C}}-\underset{OR'}{B}-OMe \xrightarrow{180\text{–}250^\circ C} R_2CH-CH{=}CR_2 + R'O-BCl-OMe$$

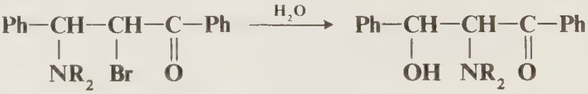
71

When α-chloroboronic esters (**71**) are heated at 180 to 250°C, loss of B and Cl takes place, accompanied by 1,2 migration of hydrogen (in some cases, alkyl), to give high yields of the corresponding alkenes.[188] The R groups may be the same or different. **71** can be prepared starting from alkenes, by the following route,[189] so that the overall reaction is a method for the dimerization of alkenes with the addition of an extra carbon atom.

$$\text{alkene} \xrightarrow[5\text{-}15]{H_2BCl,\ Et_2O} (R_2CH)_2BCl \xrightarrow{R'OH} (R_2CH)_2BOR' \xrightarrow[Et_3COLi]{Cl_2CHOMe} \mathbf{71}$$

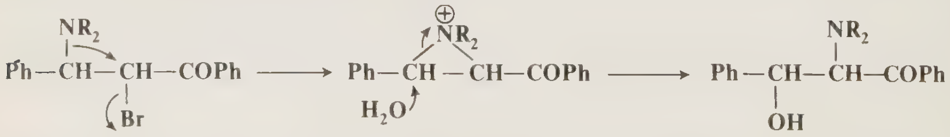
B. Carbon-to-Carbon Migrations of Other Groups

8-13 Migrations of Halogen, Hydroxyl, Amino, etc.



$$Ph-\underset{NR_2}{CH}-\underset{Br}{CH}-\underset{O}{\overset{}{C}}-Ph \xrightarrow{H_2O} Ph-\underset{OH}{CH}-\underset{NR_2}{CH}-\underset{O}{C}-Ph$$

When a nucleophilic substitution is carried out on a substrate which has a neighboring group (p. 279) on the adjacent carbon, then if the cyclic intermediate is opened on the opposite side, the result is migration of the neighboring group. In the example shown above (NR_2 = morpholino)[190] the reaction took place as follows:



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[185] Köbrich and Trapp, *Z. Naturforsch.* **18,** 1125 (1963), *Chem. Ber.* **99,** 680 (1966); Jones and Damico, *J. Am. Chem. Soc.* **85,** 2273 (1963); Köbrich, Trapp, and Hornke, *Tetrahedron Lett.* 1131 (1964), *Chem. Ber.* **100,** 961 (1967).

[186] Köbrich and Trapp, Ref. 185.

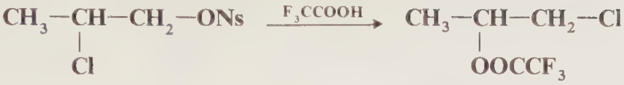
[187] Köbrich and Fröhlich, *Chem. Ber.* **98,** 3637 (1965); Köbrich, Reitz, and Schumacher, *Chem. Ber.* **105,** 1674 (1972).

[188] Katz, Carlson, and Brown, *J. Org. Chem.* **39,** 2817 (1974). See also Brown, Katz, and Carlson, *J. Org. Chem.* **40,** 813 (1975).

[189] Carlson, Katz, and Brown, *J. Organomet. Chem.* **67,** C39 (1974).

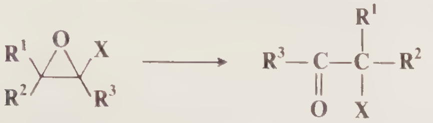
[190] Southwick and Walsh, *J. Am. Chem. Soc.* **77,** 405 (1955).

Another example is[191] (ONs = nosylate, see p. 326):



$$CH_3-\underset{\displaystyle Cl}{CH}-CH_2-ONs \xrightarrow{F_3CCOOH} CH_3-\underset{\displaystyle OOCCF_3}{CH}-CH_2-Cl$$

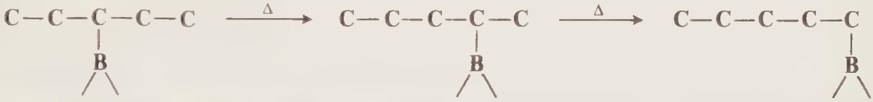
α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[192] These substrates are very prone to rearrange, and often do so on standing without



X=F, Cl, Br, or OCOR

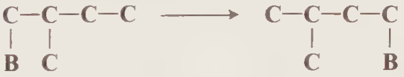
a catalyst, though in some cases an acid catalyst is necessary. The reaction is essentially the same as the rearrangement of epoxides shown in reaction **8-2**, except that in this case halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups -alkyl, aryl, or hydrogen -to migrate instead, and mixtures are sometimes obtained).

8-14 Migration of Boron



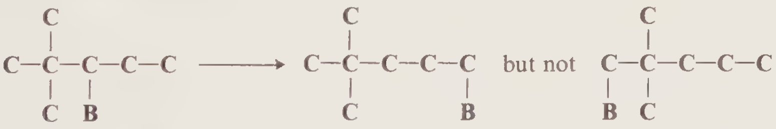
$$C-C-\underset{\underset{\wedge}{B}}{C}-C-C \xrightarrow{\Delta} C-C-C-\underset{\underset{\wedge}{B}}{C}-C \xrightarrow{\Delta} C-C-C-C-\underset{\underset{\wedge}{B}}{C}$$

When a nonterminal borane is heated at temperatures ranging from 100 to 200°C, the boron moves toward the end of the chain.[193] The reaction is catalyzed by small amounts of borane or other species containing B—H bonds. The boron can move past a branch, e.g.,



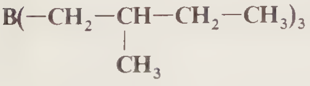
$$\underset{B}{C}-\underset{C}{C}-C-C \longrightarrow C-\underset{C}{C}-C-\underset{B}{C}$$

but not past a double branch, e.g.,



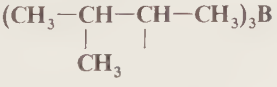
$$C-\underset{C}{\overset{C}{C}}-\underset{B}{C}-C-C \longrightarrow C-\underset{C}{\overset{C}{C}}-C-C-\underset{B}{C} \quad \text{but not} \quad C-\underset{B}{\overset{C}{C}}-\underset{C}{C}-C-C$$

The reaction is an equilibrium: **72**, **73**, and **74** each gave a mixture containing about 40% **72**, 1% **73**, and 59% **74**. The migration can go quite a long distance. Thus $(C_{11}H_{23}CHC_{11}H_{23})_3B$



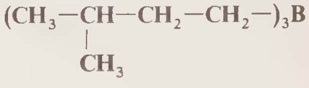
$$B(-CH_2-\underset{CH_3}{CH}-CH_2-CH_3)_3$$

72



$$(CH_3-\underset{CH_3}{CH}-\underset{|}{CH}-CH_3)_3B$$

73



$$(CH_3-\underset{CH_3}{CH}-CH_2-CH_2-)_3B$$

74

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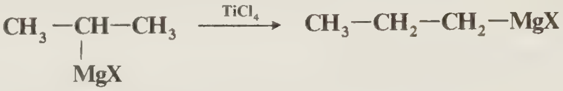
[191] For a review of Cl migrations, see Peterson, *Acc. Chem. Res.* **4**, 407-413 (1971). For examples of Br migration, see Gudkova, Uteniyazov, and Reutov, *Doklad. Chem.* **214**, 70 (1974); Smolina, Gopius, Us, Shchekut'eva, and Reutov, *Doklad. Chem.* **216**, 427 (1974), *J. Org. Chem. USSR* **10**, 908 (1974); Smolina, Medvedev, Ignatov, and Reutov, *J. Org. Chem. USSR* **10**, 1337 (1974).

[192] For a review, see McDonald, *Mech. Mol. Migr.* **3**, 67-107 (1971).

[193] Brown, "Hydroboration," pp. 136-149, W. A. Benjamin, Inc., New York, 1962; Brown and Zweifel, *J. Am. Chem. Soc.* **88**, 1433 (1966).

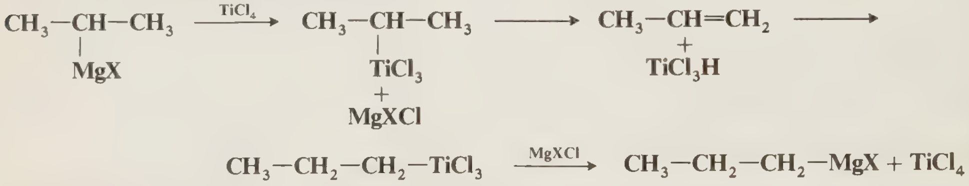
was completely converted to $(C_{23}H_{47})_3B$, involving a migration of 11 positions.[194] If the boron is on a cycloalkyl ring, it can move around the ring; if an alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.[195] The reaction is useful for the migration of double bonds in a controlled way (see reaction **2-2**). The mechanism may involve elimination-addition (see reactions **7-15** and **5-15**).[196]

8-15 Rearrangement of Grignard Reagents



$$\mathrm{CH_3-\underset{\displaystyle MgX}{\underset{|}{CH}}-CH_3 \xrightarrow{TiCl_4} CH_3-CH_2-CH_2-MgX}$$

The MgX of Grignard reagents[197] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[198] The mechanism proposed consists of metal exchange (reaction **2-34**), elimination-addition, and metal exchange:

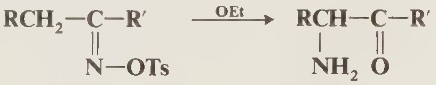


$$\mathrm{CH_3-\underset{\displaystyle MgX}{\underset{|}{CH}}-CH_3 \xrightarrow{TiCl_4} CH_3-\underset{\displaystyle TiCl_3 \atop {+ \atop MgXCl}}{\underset{|}{CH}}-CH_3 \longrightarrow \underset{TiCl_3H}{\overset{CH_3-CH=CH_2}{+}} \longrightarrow}$$

$$\mathrm{CH_3-CH_2-CH_2-TiCl_3 \xrightarrow{MgXCl} CH_3-CH_2-CH_2-MgX + TiCl_4}$$

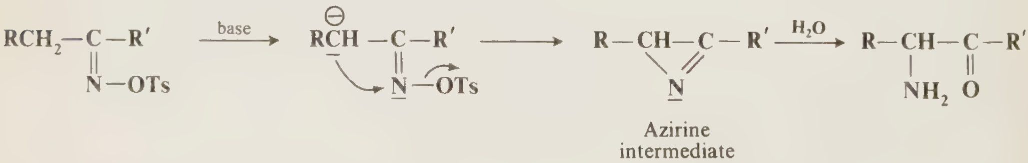
The addition step is similar to reaction **5-15** or **5-16** and follows Markovnikov's rule, so that the positive titanium goes to the terminal carbon.

8-16 The Neber Rearrangement



$$\mathrm{RCH_2-\underset{\displaystyle N-OTs}{\underset{\|}{C}}-R' \xrightarrow{OEt} R\underset{\displaystyle NH_2}{\underset{|}{CH}}-\underset{\displaystyle O}{\underset{\|}{C}}-R'}$$

α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base such as ethoxide ion or pyridine.[199] This is called the *Neber rearrangement*. R is usually aryl, though the reaction has been carried out with R = alkyl or hydrogen. R′ may be alkyl or aryl but not hydrogen. The Beckmann rearrangement (reaction **8-21**) and the abnormal Beckmann reaction (elimination to the nitrile, reaction **7-40**) may be side reactions, though these generally occur in acid media. A similar rearrangement is given by N,N-dichloroamines of the type $RCH_2CH(NCl_2)R'$, where the product is also $RCH(NH_2)COR'$.[200] The mechanism of the Neber rearrangement is as follows:[201]



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[194] Logan, *J. Org. Chem.* **26,** 3657 (1961).

[195] Brown and Zweifel, *J. Am. Chem. Soc.* **89,** 561 (1967).

[196] For evidence against this mechanism, see Mikhailov, Kuimova, and Shagova, *Doklad. Chem.* **179,** 361 (1968).

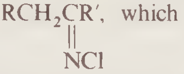
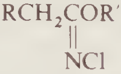
[197] For a review of rearrangements in organomagnesium chemistry, see Hill, *J. Organomet. Chem.* **91,** 123 271 (1975).

[198] Cooper and Finkbeiner, *J. Org. Chem.* **27,** 1493 (1962); Fell, Asinger, and Sulzbach, *Chem. Ber.* **103,** 3830 (1970).

[199] For reviews, see Conley and Ghosh, *Mech. Mol. Migr.* **4,** 197-308 (1971), pp. 289–304; O'Brien, *Chem. Rev.* **64,** 81-89 (1964).

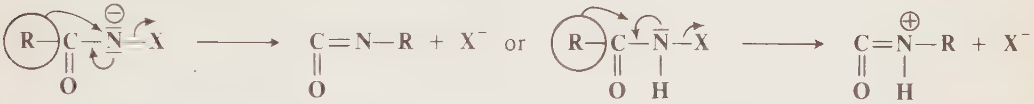
[200] Baumgarten and Petersen, *J. Am. Chem. Soc.* **82,** 459 (1960), and references cited therein.

[201] Cram and Hatch, *J. Am. Chem. Soc.* **75,** 33 (1953); Hatch and Cram, *J. Am. Chem. Soc.* **75,** 38 (1953).

The best evidence for this mechanism is that the azirine intermediate has been isolated.[202] In contrast to the Beckmann rearrangement, this one is sterically indiscriminate:[203] both a syn and an anti ketoxime give the same product. Where there are two possible C—H groups to which the nitrogen can migrate, the more acidic proton is lost. The mechanism as shown above consists of three steps, the last being hydrolysis of an imine (reaction **6-2**). However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to give  $RCH_2\underset{\underset{NCl}{\|}}{C}R'$, which then behaves analogously.[204] N-Chloroimines prepared in other ways also give the reaction.[205] Analogously, N-chloroimino esters  $RCH_2\underset{\underset{NCl}{\|}}{C}OR'$ give α-amino ortho esters $RCH(NH_2)C(OR')_3$,[206] or α-amino esters $RCH(NH_2)COOR'$,[207] each of which can be hydrolyzed to α-amino acids.

OS **V**, 909.

C. Carbon-to-Nitrogen Migrations of R and Ar. The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (p. 964). Reactions **8-17** to **8-20** are used to prepare amines from acid derivatives. Reactions **8-20** and **8-21** are used to prepare amines from ketones. The mechanisms of reactions **8-17, 8-18, 8-19,** and **8-20** (with carboxylic acids) are very similar and follow one of two patterns:



Some of the evidence[208] is: (1) Configuration is retained in R (p. 965); (2) the kinetics are first order; (3) intramolecular rearrangement is shown by labeling; and (4) no rearrangement occurs *within* the migrating group, e.g., a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene[209] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.[210] It is likely that both possibilities can exist, depending on the substrate and reaction conditions, and that there is a spectrum of mechanisms.

8-17 The Hofmann Rearrangement

$$RCONH_2 + NaOBr \longrightarrow R{-}N{=}C{=}O \xrightarrow{\text{hydrol.}} RNH_2$$

In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give a primary amine which has one carbon fewer than the starting amide.[211] The actual product of the reaction is the isocyanate, but this compound is seldom isolated since it is usually hydrolyzed under the reaction conditions. R may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.[212] Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (reaction **6-8**), which is easily isolated or can be hydrolyzed to the amine. Side reactions when NaOH is the base are formation of ureas RNHCONHR and acylureas RCONHCONHR by addition, respectively, of RNH_2 and $RCONH_2$ to RNCO (reaction **6-18**). If acylureas are desired, they can be made the main products by using only half the usual quantities of Br_2 and NaOH. Another side product, though only from primary R, is the nitrile derived from oxidation of RNH_2 (reaction **9-6**). Imides react to give amino acids; e.g., phthalimide gives *o*-aminobenzoic acid. α-Hydroxy and α-halo amides give aldehydes and ketones by way of the unstable α-hydroxy- or α-haloamines. However, a side product with an α-halo amide is a *gem*-dihalide. Ureas analogously give hydrazines. This reaction is sometimes called the *Hofmann degradation*, but this name is easily confused with reaction **7-6.**

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[202] Neber and Burgard, *Justus Liebigs Ann. Chem.* **493**, 281 (1932); Parcell, *Chem. Ind.* (*London*) 1396 (1963); Ref. 201.

[203] House and Berkowitz, *J. Org. Chem.* **28**, 2271 (1963).

[204] For example, see Oae and Furukawa, *Bull. Chem. Soc. Jpn.* **38**, 62 (1965); Nakai, Furukawa, and Oae, *Bull. Chem. Soc. Jpn.* **42**, 2917 (1969).

[205] Baumgarten, Petersen, and Wolf, *J. Org. Chem.* **28**, 2369 (1963).

[206] Graham, *Tetrahedron Lett.* 2223 (1969).

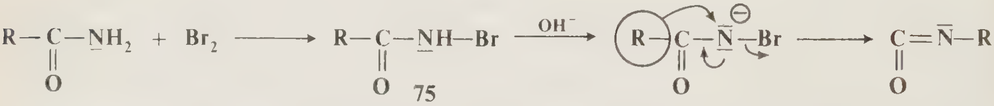
[207] Baumgarten, Dirks, Petersen, and Zey, *J. Org. Chem.* **31**, 3708 (1966).

[208] For a discussion of this mechanism and of the evidence for it, see Smith, in Mayo, Ref. 1, vol. 1, pp. 528–550.

[209] For a review of rearrangements involving nitrene intermediates, see Boyer, *Mech. Mol. Migr.* **2**, 267–318 (1969). See also Ref. 217.

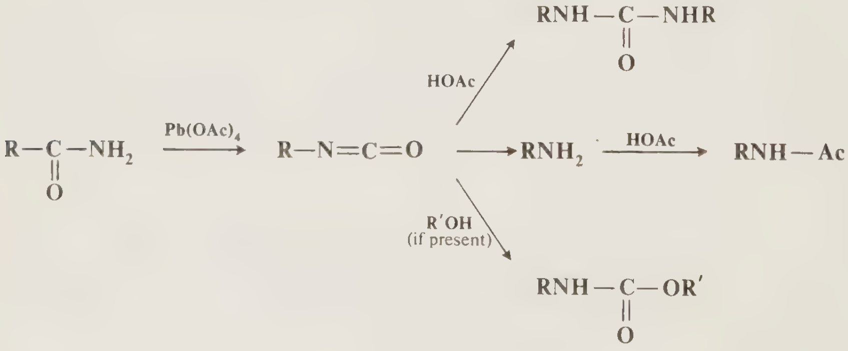
[210] The question is discussed by Lwowski, in Lwowski, "Nitrenes," pp. 217–221, Interscience Publishers, New York, 1970.

The mechanism follows the pattern outlined on p. 1003:



The first step is an example of reaction **2-54,** and the intermediate N-halo amides (**75**) have been isolated. In the second step, **75** loses a proton to the base. **75** is acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.[213]

A similar reaction can be effected by the treatment of amides with lead tetraacetate.[214] In this case the initial isocyanate and the amine formed from it react with the acetic acid liberated from the lead tetraacetate to give, respectively, ureas and amides. If the reaction is carried out in the presence of an alcohol, carbamates are formed (reaction **6-8**).



OS **II,** 19, 44, 462; **IV,** 45.

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[211] For a review, see Wallis and Lane, *Org. React.* **3,** 267–306 (1946).

[212] For an example of the use of this method at low temperatures, see Radlick and Brown, *Synthesis* 290 (1974).

[213] See for example Imamoto, Tsuno, and Yukawa, *Bull. Chem. Soc. Jpn.* **44,** 1632, 1639, 1644 (1971); Imamoto, Kim, Tsuno, and Yukawa, *Bull. Chem. Soc. Jpn.* **44,** 2776 (1971).

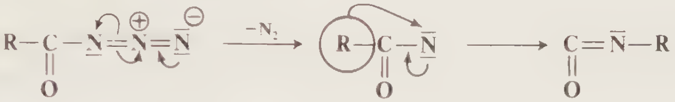
[214] Acott and Beckwith, *Chem. Commun.* 161 (1965); Baumgarten and Staklis, *J. Am. Chem. Soc.* **87,** 1141 (1965); Acott, Beckwith, Hassanali, and Redmond, *Tetrahedron Lett.* 4039 (1965); Acott, Beckwith, and Hassanali, *Aust. J. Chem.* **21,** 185, 197 (1968); Baumgarten, Smith, and Staklis, *J. Org. Chem.* **40,** 3554 (1975).

8-18 The Curtius Rearrangement

$$RCON_3 \xrightarrow{\Delta} R{-}N{=}C{=}O$$

The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.[215] The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in reaction **8-17.** This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in reaction **0-63** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to reaction **2-49**). The Curtius rearrangement is catalyzed by Lewis or protic acids, but these are usually not necessary for good results.

The mechanism is similar to that in reaction **8-17:**

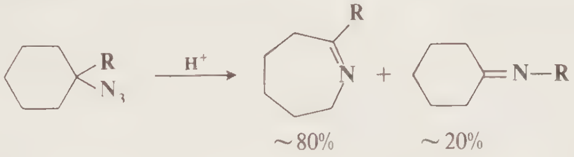


Also note the exact analogy between this reaction and reaction **8-9.** However, in this case, there is no evidence for a free nitrene, and it is probable that the steps are concerted.[216]

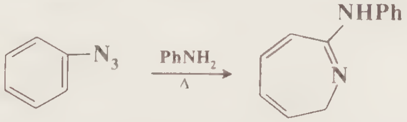
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:[217]

$$R_3CN_3 \xrightarrow{\Delta} R_2C{=}NR$$

The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $R_2C{=}NH$. The mechanism is essentially the same as that of the Curtius rearrangement. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.[218] The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, though the acid may hydrolyze the imine (reaction **6-2**). Cycloalkyl azides give ring expansion.[219]



Aryl azides also give ring expansion on heating, e.g.,[220]



OS **III,** 846; **IV,** 819; **V,** 273; **51,** 48. Also see OS **55,** 32.

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[215] For reviews, see Banthorpe, in Patai, "The Chemistry of the Azido Group," pp. 397–405, Interscience Publishers, New York, 1971; Smith, *Org. React.* **3,** 337–449 (1946).

[216] See for example, Lwowski, *Angew. Chem. Int. Ed. Engl.* **6,** 897–906 (1967) [*Angew. Chem.* **79,** 922–931]; Linke, Tissue, and Lwowski, *J. Am. Chem. Soc.* **89,** 6308 (1967); Smalley and Bingham, *J. Chem. Soc. C* 2481 (1969).

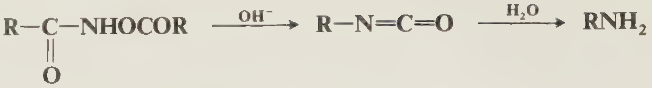
[217] For reviews, see Stevens and Watts, Ref. 1, pp. 45–52; Smith, in Mayo, Ref. 1, vol. 1, pp. 462–479. For reviews of the formation of nitrenes from alkyl and aryl azides, see, in Lwowski, Ref. 210, the chapters by Lewis and Saunders, 47–97, pp. 47–78 and by Smith, 99–162.

[218] Abramovitch and Kyba, *J. Am. Chem. Soc.* **96,** 480 (1974).

[219] Smith and Lakritz, cited in Smith, in Mayo, Ref. 1, vol. 1, p. 474.

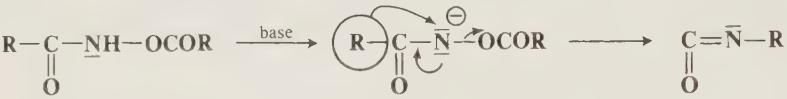
[220] Huisgen, Vossius, and Appl, *Chem. Ber.* **91,** 1, 12 (1958).

8-19 The Lossen Rearrangement



$$R-\underset{\underset{O}{\|}}{C}-NHOCOR \xrightarrow{OH^-} R-N=C=O \xrightarrow{H_2O} RNH_2$$

The O-acyl derivatives of hydroxamic acids[221] give isocyanates when treated with bases, or sometimes even just on heating,[222] in a reaction known as the *Lossen rearrangement*. The mechanism is similar to that of reactions **8-17** and **8-18:**



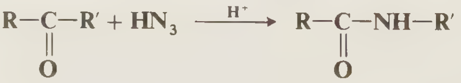
This reaction is performed much less often than reactions **8-17, 8-18,** or **8-20** because hydroxamic acids are not readily available. The reaction can be carried out under particularly mild conditions by treatment of a hydroxamic acid with 1-benzyl-3-dimethylaminopropylcarbodiimide, which is water-soluble.[223] It is possible to convert ArCOOH to $ArNH_2$ in one step by heating the acid with nitromethane in polyphosphoric acid. The hydroxamic acid is an intermediate, and this is actually a Lossen rearrangement.[224]

8-20 The Schmidt Reaction

$$RCOOH + HN_3 \xrightarrow{H^+} R-N=C=O \xrightarrow{H_2O} RNH_2$$

There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and olefins.[225] The most common is the reaction with carboxylic acids, illustrated above. Sulfuric acid is the most common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over reactions **8-17** and **8-18** that it is just one step (in practice, not in mechanism) from the acid to the amine, but conditions are more drastic.[226] Under the acid conditions employed, the isocyanate is virtually never isolated, though this has been accomplished.[227]

The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, thus converting a ketone into an amide:[228]



$$R-\underset{\underset{O}{\|}}{C}-R' + HN_3 \xrightarrow{H^+} R-\underset{\underset{O}{\|}}{C}-NH-R'$$

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[221] For a review of hydroxamic acids, see Bauer and Exner, *Angew. Chem. Int. Ed. Engl.* **13**, 376–384 (1974) [*Angew. Chem.* **86**, 419–428].

[222] For a review, see Yale, *Chem. Rev.* **33**, 209 (1943).

[223] Hoare, Olson, and Koshland, *J. Am. Chem. Soc.* **90**, 1638 (1968). For another variation, see Bittner, Grinberg, and Kartoon, *Tetrahedron Lett.* 1965 (1974).

[224] Bachman and Goldmacher, *J. Org. Chem.* **29**, 2576 (1964).

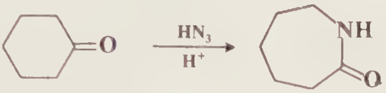
[225] For reviews, see Banthorpe, Ref. 215, pp. 405–434; Wolff, *Org. React.* **3**, 307–336 (1946).

[226] For a comparison of reactions **8-17** to **8-20** as methods for converting an acid to an amine, see Smith, Ref. 215, pp. 363–366.

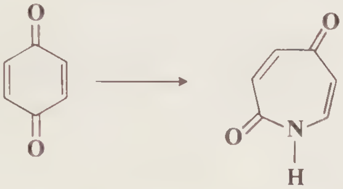
[227] Rutherford and Newman, *J. Am. Chem. Soc.* **79**, 213 (1957).

[228] For reviews, see Koldobskii, Tereshchenko, Gerasimova, and Bagal, *Russ. Chem. Rev.* **40**, 835–846 (1971); Beckwith, in Zabicky, "The Chemistry of Amides," pp. 137–145, Interscience Publishers, New York, 1970; Smith, in Mayo, Ref. 1, vol. 1, pp. 507–527.

Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones or carboxylic acids or alcohols—that these functions may be present in the same molecule without interference. Cyclic ketones give lactams:



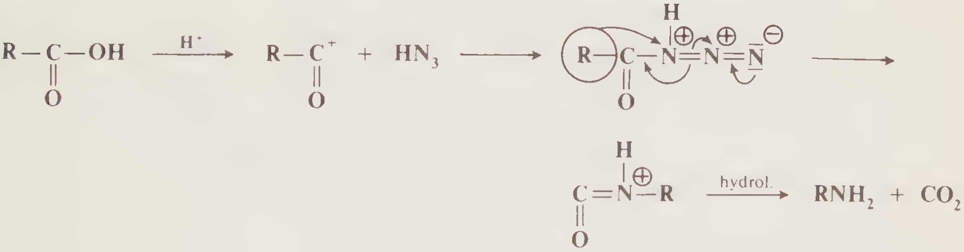
and quinones give 1*H*,2*H*,5*H*,-2,5-azepindiones:[229]



With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[230] The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (reaction **6-23**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives reaction **7-40.** Aromatic aldehydes and ketones containing an *o*-hydroxy group give *o*-hydroxy aromatic amides when treated with NaOH and monochloroamine NH_2Cl.[231]

Alcohols and olefins react with HN_3 to give alkyl azides, which in the course of reaction rearrange in the same way as discussed in reaction **8-18.**[217]

The mechanism with carboxylic acids is similar to that of reaction **8-18,** except that it is the protonated azide which undergoes the rearrangement:



The first step is the same as that of the AAC1 mechanism (p. 351), which explains why good results are obtained with hindered substrates. The mechanism with ketones is[232]

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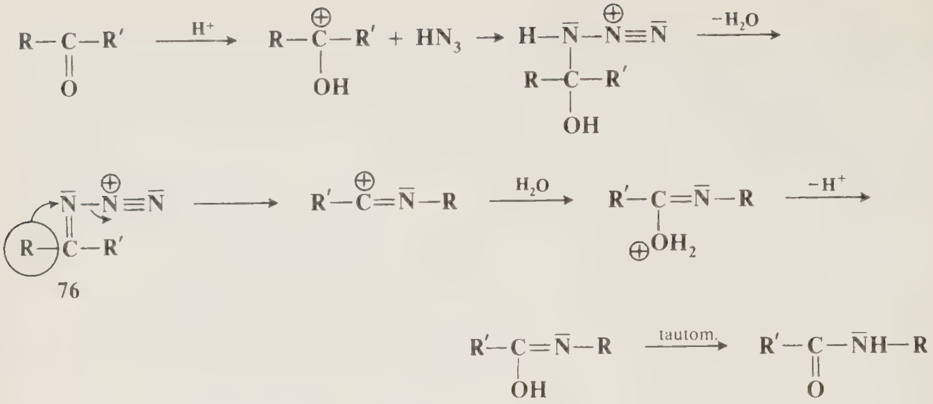
[229] For a review, see Moore and Wikholm, in Patai, "The Chemistry of the Quinonoid Compounds," pt. 1, pp. 446–449, John Wiley & Sons, Inc., New York, 1974.

[230] Exceptions to this statement have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in ortho and para positions: Bhalerao and Thyagarajan, *Can. J. Chem.* **46,** 3367 (1968); Tomita, Minami, and Uyeo, *J. Chem. Soc. C* 183 (1969).

[231] Crochet and Kovacic, *J. Chem. Soc., Chem. Commun.* 716 (1973).

[232] Smith, *J. Am. Chem. Soc.* **70,** 320 (1948); Smith and Antoniades, *Tetrahedron* **9,** 210 (1960).

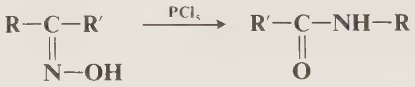


76

Note the similarity of this mechanism to those of "insertion" of CH_2 (reaction **8-10**) and of O (reaction **8-23**). The three reactions are essentially analogous, both in products and in mechanism.[233] Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (reaction **8-21**).

OS **V**, 408. See also OS **V**, 623.

8-21 The Beckmann Rearrangement



$$\underset{\displaystyle \underset{\text{N—OH}}{\|}}{\text{R—C—R}'} \xrightarrow{PCl_5} \underset{\displaystyle \underset{\text{O}}{\|}}{\text{R}'\text{—C—NH—R}}$$

When oximes are treated with PCl_5, concentrated H_2SO_4, or a number of other reagents, they rearrange to substituted amides, in a reaction called the *Beckmann rearrangement*.[234] Among the reagents used have been concentrated H_2SO_4, PCl_5 and ether, formic acid, liquid SO_2, PPh_3-CCl_4,[235] HMPT,[236] P_2O_5-methanesulfonic acid,[237] HCl-HOAc-Ac_2O, and polyphosphoric acid.[238] The group which migrates is generally the one trans to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the cis group migrates and that with others, especially where R and R′ are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the cis group actually undergoes migration. In most cases the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[239] The scope of the reaction is quite broad. R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates*, so that the reaction is not generally a means of converting aldoximes to unsubstituted amides $RCONH_2$. This conversion can be accomplished, though, by treatment of the aldoxime with nickel acetate under neutral conditions[240] or by heating the aldoxime for 60 hr at 100°C after it has been adsorbed onto silica gel.[241] As in the case of the Schmidt rearrangement, when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group which preferentially migrates. The oximes of cyclic ketones give ring enlargement,[242] e.g.,

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[233] For evidence for this mechanism, see Koldobskii, Enin, Naumov, Ostrovskii, Tereshchenko, and Bagal, *J. Org. Chem. USSR* **8**, 242 (1972); Ostrovskii, Enin, and Koldobskii, *J. Org. Chem. USSR* **9**, 827 (1973); Ostrovskii, Koshtaleva, Shirokova, Koldobskii, and Gidaspov, *J. Org. Chem. USSR* **10**, 2365 (1974); Ref. 228.

[234] For reviews, see McCarty, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," pp. 408–439, Interscience Publishers, New York, 1970; Donaruma and Heldt, *Org. React.* **11**, 1–156 (1960); Smith, in Mayo, Ref. 1, vol. 1, pp. 483–507.

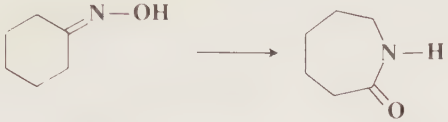
[235] Waters, Wakabayashi, and Fields, *Org. Prep. Proced. Int.* **6**, 53 (1974).

[236] Monson and Broline, *Can. J. Chem.* **51**, 942 (1973).

[237] Eaton, Carlson, and Lee, *J. Org. Chem.* **38**, 4071 (1973).

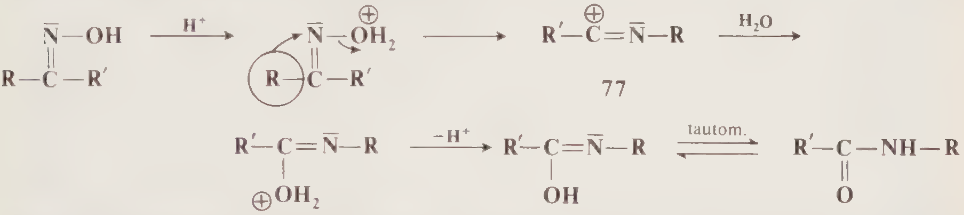
[238] For reviews of Beckmann rearrangements with polyphosphoric acid, see Beckwith, in Zabicky, Ref. 228, pp. 131–137; Uhlig and Snyder, *Adv. Org. Chem.* **1**, 35–81 (1960), pp. 65–68; Popp and McEwen, *Chem. Rev.* **58**, 321–401 (1958), pp. 370–374.

[239] Lansbury and Mancuso, *Tetrahedron Lett.* 2445 (1965), have shown that some Beckmann rearrangements are *authentically* nonstereospecific.

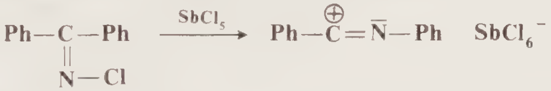


Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, reaction **7-40**).

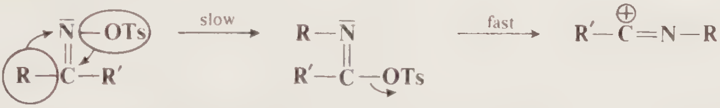
In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group. After that, the mechanism follows a course analogous to that for the Schmidt reaction of ketones (**8-20**) from the formation of **76** on:[243]



The other reagents convert OH to an ester leaving group (for example, $OPCl_4$ from PCl_5 and OSO_2OH from concentrated H_2SO_4[244]). Alternatively, the attack on **77** can be by the leaving group, if different from H_2O. An intermediate of the form **77** has been isolated by Grob and coworkers from treatment of the N-chloroimine of benzophenone



and found to have a linear geometry.[245] These workers also showed that the rate of solvolysis of the oxime tosylate from cyclohexanone was about the same (actually a little greater) as that from diethyl ketone, even though the intermediate **77** from the cyclic compound cannot be linear. They thus concluded that, in this case at least, **77** cannot be formed in the rate-determining step, and that it is formed in this manner:[246]



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[240] Field, Hughmark, Shumaker, and Marshall, *J. Am. Chem. Soc.* **83,** 1983 (1961). See also Leusink, Meerbeek, and Noltes, *Recl. Trav. Chim. Pays-Bas* **95,** 123 (1976).

[241] Chattopadhyaya and Rama Rao, *Tetrahedron* **30,** 2899 (1974).

[242] For a review of such ring enlargements, see Vinnik and Zarakhani, *Russ. Chem. Rev.* **36,** 51–64 (1967).

[243] For summaries of the considerable evidence for this mechanism, see Ref. 234: Donaruma and Heldt, pp. 5–14; Smith, pp. 488–493.

[244] Gregory, Moodie, and Schofield, *J. Chem. Soc. B* 338 (1970); Yukawa and Ando, *Chem. Commun.* 1601 (1971).

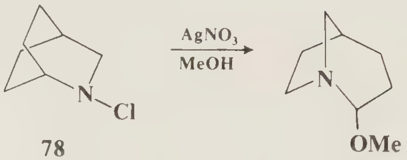
[245] Grob, Fischer, Raudenbusch, and Zergenyi, *Helv. Chim. Acta* **47,** 1003 (1964).

[246] For another example of intramolecular migration of the nucleofuge, see Kukhtenko, *J. Org. Chem. USSR* **7,** 327 (1971).

The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a Ritter reaction (**6-57**).[247] Beckmann rearrangements have also been carried out photochemically.[248]

OS **II,** 76, 371.

8-22 Stieglitz and Related Rearrangements



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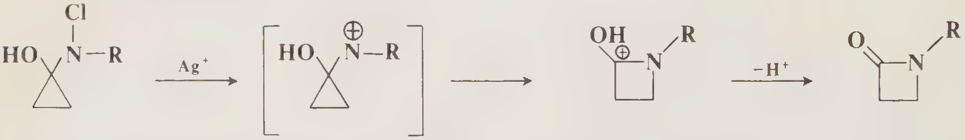
Besides the reactions discussed at **8-17** to **8-21**, a number of other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic N-haloamines, for example N-chloro-2-azabicyclo[2.2.2]octane (**78**), undergo rearrangement when solvolyzed in the presence of silver nitrate.[249] This reaction is similar to the Wagner-Meerwein rearrangement (**8-1**) and is initiated by the silver-catalyzed departure of the chloride ion. A nitrenium-ion-type transition state (p. 186) is undoubtedly involved.[250] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **8-3.**[251] An example is the conversion of 1-(N-chloroamino)cyclopropanols to β-lactams.[252]



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl N-haloamines and hydroxylamines. These reactions are similar to the rearrangements of alkyl

$$\mathrm{Ar_3CNHX} \xrightarrow{\text{base}} \mathrm{Ar_2C{=}NAr}$$

$$\mathrm{Ar_3CNHOH} \xrightarrow{\mathrm{PCl_5}} \mathrm{Ar_2C{=}NAr}$$

azides (reaction **8-18**), and the name Stieglitz rearrangement is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate.[253]

$$\mathrm{Ar_3CNH_2} \xrightarrow{\mathrm{Pb(OAc)_4}} \mathrm{Ar_2C{=}NAr}$$

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[247] Hill, Conley, and Chortyk, *J. Am. Chem. Soc.* **87**, 5646 (1965); Palmere, Conley, and Rabinowitz, *J. Org. Chem.* **37**, 4095 (1972).

[248] For example, see Amin and Mayo, *Tetrahedron Lett.* 1585 (1963); Izawa, Mayo, and Tabata, *Can. J. Chem.* **47**, 51 (1969); Taylor, Douek, and Just, *Tetrahedron Lett.* 4143 (1966); Cunningham, Ng Lim, and Just, *Can. J. Chem.* **49**, 2891 (1971); Suginome and Takahashi, *Tetrahedron Lett.* 5119 (1970), *Bull. Chem. Soc. Jpn.* **48**, 576 (1975).

[249] Gassman and Fox, *J. Am. Chem. Soc.* **89,** 338 (1967). See also Gassman and Cryberg, *J. Am. Chem. Soc.* **91,** 2047 (1969); Fleury, Biehler, and Desbois, *Tetrahedron Lett.* 4091 (1969).

[250] For C → N rearrangements induced by AlCl$_3$, see Kovacic, Lowery, and Roskos, *Tetrahedron* **26,** 529 (1970); Kovacic, Liu, Levi, and Roskos, *J. Am. Chem. Soc.* **93,** 5801 (1971); Kling, Nazareno, and Kovacic, *J. Am. Chem. Soc.* **94,** 2157 (1972); Kling, White, and Kovacic, *J. Am. Chem. Soc.* **94,** 7416 (1972).

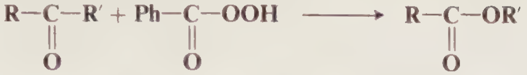
[251] Gassman and Carrasquillo, *Tetrahedron Lett.* 109 (1971).

[252] Wasserman, Adickes, and Espejo de Ochoa, *J. Am. Chem. Soc.* **93,** 5586 (1971); Wasserman, Glazer, and Hearn, *Tetrahedron Lett.* 4855 (1973).

[253] Sisti, *Chem. Commun.* 1272 (1968); Sisti and Milstein, *J. Org. Chem.* **39,** 3932 (1974).

D. Carbon-to-Oxygen Migrations of R and Ar

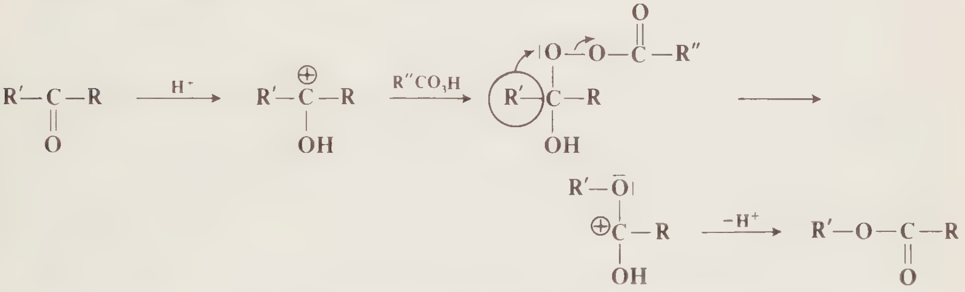
8-23 The Baeyer-Villiger Rearrangement



$$R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}R' + Ph{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OOH \longrightarrow R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OR'$$

The treatment of ketones with peracids such as perbenzoic or peracetic acid, or with other peroxy compounds in the presence of acid catalysts, gives esters by "insertion" of oxygen. The reaction is called the *Baeyer-Villiger rearrangement*.[254] A particularly good reagent is peroxytrifluoroacetic acid. Reactions with this reagent are rapid and clean, giving high yields of product, though it is often necessary to add a buffer such as Na_2HPO_4 to prevent transesterification of the product with trifluoroacetic acid. The reaction is often applied to cyclic ketones to give lactones. For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[255] with BF_3–H_2O_2,[256] and with $K_2S_2O_8$–H_2SO_4.[257] For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone R′COMe to produce an alcohol or phenol R′OH (by hydrolysis of the ester R′OCOMe). Diaryl ketones give the reaction but are seldom used preparatively. The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents. Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides. With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing reaction **4-6.** Migration of the other group would give formates, but this seldom happens, though in some cases aryl aldehydes have been converted to formates[258] (see also the Dakin reaction in **9-13**).

The mechanism[259] is similar to those of the analogous reactions with hydrazoic acid (reaction **8-20** with ketones) and with diazomethane (reaction **8-9**):



One important piece of evidence for this mechanism was that benzophenone-^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxyl oxygen.[260] Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,[261] demonstrating that migration of Ar is concerted with departure of OCOR″.[262] (It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.)

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[254] For reviews, see House, "Modern Synthetic Reactions," 2d ed., pp. 321–329, W. A. Benjamin, Inc., New York, 1972; Lewis, in Augustine, "Oxidation," vol. 1, pp. 237–244, Marcel Dekker, Inc., New York, 1969; Lee and Uff, *Q. Rev., Chem. Soc.* **21,** 429–457 (1967), pp. 449–453; Hassall, *Org. React.* **9,** 73–106 (1957); Smith, in Mayo, Ref. 1, vol. 1, pp. 577–589.

[255] Emmons and Lucas, *J. Am. Chem. Soc.* **77,** 2287 (1955).

[256] McClure and Williams, *J. Org. Chem.* **27,** 24 (1962).

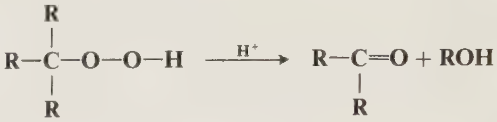
[257] Deno, Billups, Kramer, and Lastomirsky, *J. Org. Chem.* **35,** 3080 (1970).

[258] For example, see Godfrey, Sargent, and Elix, *J. Chem. Soc., Perkin Trans. 1* 1353 (1974).

[259] Proposed by Criegee, *Justus Liebigs Ann. Chem.* **560,** 127 (1948).

[260] Doering and Dorfman, *J. Am. Chem. Soc.* **75,** 5595 (1953). For summaries of the other evidence, see Ref. 254: Hassall, pp. 74–76; Smith, pp. 578–584.

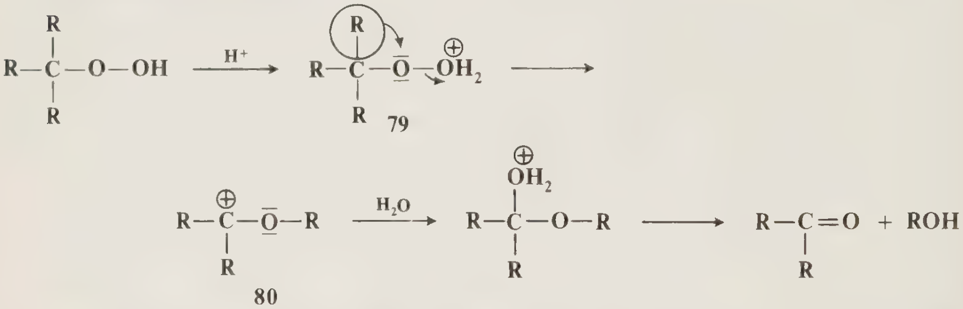
8-24 Rearrangement of Hydroperoxides



$$R_3C{-}O{-}O{-}H \xrightarrow{H^+} R_2C{=}O + ROH$$

Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[263] The reaction has also been applied to peroxy esters $R_3COOCOR'$, but less often. When aryl and alkyl groups are both present, migration of aryl dominates. Among alkyl groups the migratory order is tertiary R > secondary R > Pr ≈ H > Et ≫ Me.[257] It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolog ($RCH_2OOH \rightarrow CH_2{=}O + ROH$).[257]

The mechanism is as follows:

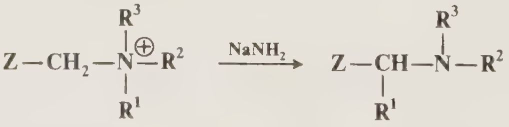


The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbonium-ion intermediates (**80**, R = alkyl) have been isolated in super-acid solution, at low temperatures, and their structures proved by nmr.[264] The protonated hydroperoxides (**79**) could not be observed in these solutions, evidently reacting immediately on formation.

OS V, 818.

E. Nitrogen-to-Carbon and Oxygen-to-Carbon Migration

8-25 The Stevens Rearrangement



$$Z{-}CH_2{-}\overset{\oplus}{N}R^1R^2R^3 \xrightarrow{NaNH_2} Z{-}CH(R^1){-}NR^2R^3$$

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[261] Palmer and Fry, *J. Am. Chem. Soc.* **92,** 2580 (1970). See also Mitsuhashi, Miyadera, and Simamura, *Chem. Commun.* 1301 (1970). For secondary isotope-effect studies, see Winnik, Stoute, and Fitzgerald, *J. Am. Chem. Soc.* **96,** 1977 (1974).

[262] In some cases the rate-determining step has been shown to be the addition of peracid to the substrate [see for example, Ogata and Sawacki, *J. Org. Chem.* **37,** 2953 (1972)]. Even in these cases it is still highly probable that migration is concerted with departure of the nucleofuge.

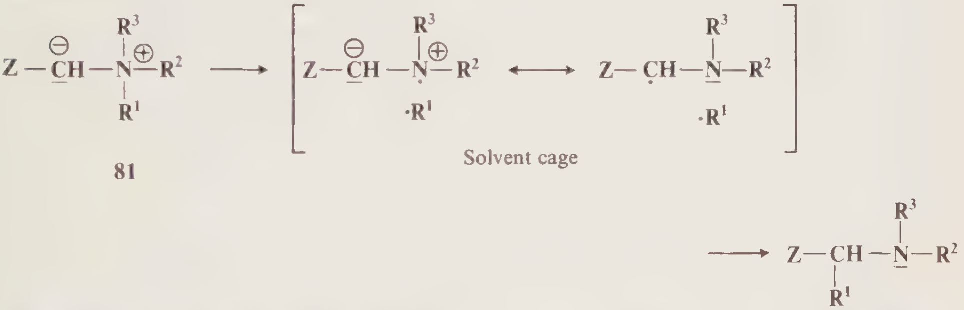
[263] For a review, see Lee and Uff, Ref. 254, pp. 445–449.

[264] Sheldon and van Doorn, *Tetrahedron Lett.* 1021 (1973).

In the *Stevens rearrangement* a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (such as NaOR or $NaNH_2$) to give a rearranged tertiary amine. Z is a group such as RCO, ROOC, phenyl, etc.[265] The most common migrating groups are allyl, benzyl, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center.[266] When an allyl group migrates, it may or may not involve an allylic rearrangement within the migrating group (see reaction **8-40**), depending on the substrate and reaction conditions. In a few cases the reaction has been applied to compounds without a Z group, but stronger bases are required and yields are often low.[267]

The mechanism has been the subject of much study.[268] That the rearrangement is intramolecular was shown by crossover experiments, by ^{14}C labeling,[269] and by the fact that retention of configuration is found at R.[270] The first step is loss of the acidic proton to give the ylide **81**, which has been isolated.[271] The finding[272] that CIDNP spectra[273] (p. 171) could be obtained in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical-pair mechanism was proposed.[274]

Mechanism *a*



81

The radicals do not drift apart because they are held together by the solvent cage.[274a] According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R^1 does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R^1R^1) have been isolated,[275] which would be expected if some $\cdot R^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.[276] It is possible that another mechanism (*b*) similar to mechanism *a*, but involving ion pairs in a solvent cage instead of radical pairs, operates in some cases. For a number of years it was generally believed that the Stevens rearrangement takes place by a one-step electrophilic migration (mechanism *c*), but doubt was cast on this pathway by the following result: Optically active **82** rearranged to **83** (with the benzyl and not the allyl migrating) and **84** (by a 1,4 shift). The benzyl group retained its configuration in **83**, as expected, but also in **84**.[277] If the benzyl group were migrating without its electrons (mechanism *c*), then it would have to move over this long distance either as a relatively free carbonium ion (and be racemized) or in an SNi′ process (p. 305) (and be inverted):

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[265] For reviews of the Stevens rearrangement, see Lepley and Giumanini, *Mech. Mol. Migr.* **3**, 297–440 (1971); Pine, *Org. React.* **18**, 403–464 (1970). For reviews of the Stevens and of the closely related Wittig rearrangement (**8-26**), see Stevens and Watts, Ref. 1, pp. 81–116; Wilt, in Kochi, Ref. 53, pp. 448–458; Iwai, *Mech. Mol. Migr.* **2**, 73–116 (1969), pp. 105–113; Stevens, *Prog. Org. Chem.* **7**, 48–74 (1968); Zimmerman, in Mayo, Ref. 1, vol. 1, pp. 345–406.

[266] Migration of aryl is rare, but has been reported: Heaney and Ward, *Chem. Commun.* 810 (1969); Truce and Heuring, *Chem. Commun.* 1499 (1969).

[267] For example, see Adams, Liu, and Kovacic, *Tetrahedron Lett.* 427 (1974); Fry, Adlington, Badger, and McCullough, *Tetrahedron Lett.* 429 (1974).

[268] For example, see Pine, *J. Chem. Educ.* **48**, 99–102 (1971).

[269] Stevens, *J. Chem. Soc.* 2107 (1930); Johnstone and Stevens, *J. Chem. Soc.* 4487 (1955).

[270] Brewster and Kline, *J. Am. Chem. Soc.* **74**, 5179 (1952); Schöllkopf, Ludwig, Ostermann, and Patsch, *Tetrahedron Lett.* 3415 (1969).

[271] Jemison, Mageswaran, Ollis, Potter, Pretty, Sutherland, and Thebtaranonth, *Chem. Commun.* 1201 (1970).

[272] Lepley, *J. Am. Chem. Soc.* **91**, 1237 (1969), *Chem. Commun.* 1460 (1969); Lepley, Becker, and Giumanini, *J. Org. Chem.* **36**, 1222 (1971); Baldwin and Brown, *J. Am. Chem. Soc.* **91**, 3646 (1969); Jemison and Morris, *Chem. Commun.* 1226 (1969); Ref. 271; Schöllkopf, Ludwig, Ostermann, and Patsch, Ref. 270.

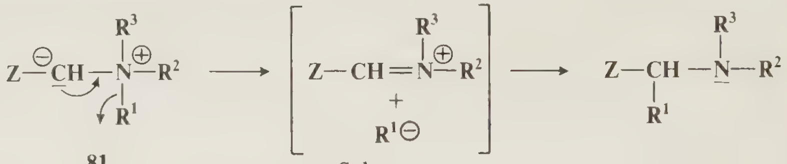
[273] For a review of the application of CIDNP to rearrangement reactions, see Lepley, in Lepley and Closs, "Chemically Induced Magnetic Polarization," pp. 323–384, John Wiley & Sons, Inc., New York, 1973.

[274] Suggested by Schöllkopf and Ludwig, *Chem. Ber.* **101**, 2224 (1968).

[274a] It has been suggested that either the radicals combine exceptionally rapidly, or there are dual pathways involving both radical and concerted processes: Ollis, Rey, Sutherland, and Closs, *J. Chem. Soc., Chem. Commun.* 543 (1975); Dolling, Closs, Cohen, and Ollis, *J. Chem. Soc., Chem. Commun.* 545 (1975).

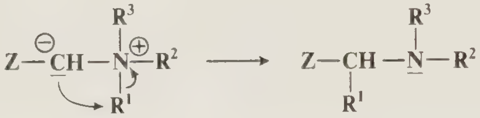
[275] Schöllkopf, Ludwig, Ostermann, and Patsch, Ref. 270; Hennion and Shoemaker, *J. Am. Chem. Soc.* **92**, 1769 (1970).

Mechanism *b*

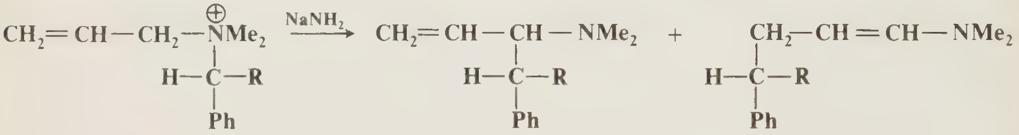


81

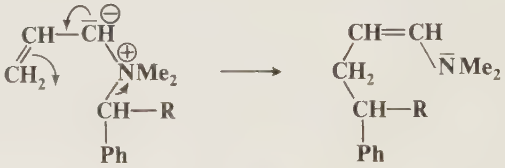
Mechanism *c*



81



82 **83** **84**



In neither case would there be retention. Therefore, the 1,4 shift appears to operate by mechanism *a* or *b*. If the 1,4 shift operates by mechanism *a* or *b*, it is unlikely that the 1,2 shift has a different mechanism. An additional argument against mechanism *c* is that the principle of orbital symmetry conservation requires that a concerted migration of this type take place with inversion at R′.[278] A migration with retention is forbidden (see p. 1042). Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism (mechanism *c*).[279] However, in the case where the migrating group is allylic a concerted mechanism can also operate (reaction **8-40**). An interesting finding which is compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 89) gave optically active product:[280]

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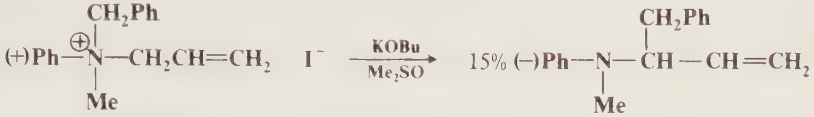
[276] See for example, Pine, Catto, and Yamagishi, *J. Org. Chem.* **35**, 3663 (1970).

[277] Jenny and Druey, *Angew. Chem. Int. Ed. Engl.* **1**, 155 (1962) [*Angew. Chem.* **74**, 152].

[278] Woodward and Hoffmann, "The Conservation of Orbital Symmetry," p. 131, Academic Press, Inc., New York, 1970.

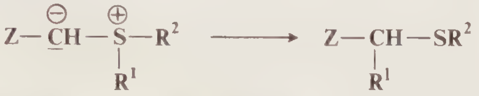
[279] It has been argued that the rearrangement takes place by a concerted mechanism, in violation of the orbital symmetry rules: Dewar and Ramsden, *J. Chem. Soc., Perkin Trans. 1* 1839 (1974).



$$(+)\mathrm{Ph}-\overset{\mathrm{CH_2Ph}}{\underset{\mathrm{Me}}{\overset{\oplus|}{\mathrm{N}}}}-\mathrm{CH_2CH{=}CH_2}\quad \mathrm{I^-}\ \xrightarrow[\mathrm{Me_2SO}]{\mathrm{KOBu}}\ 15\%\ (-)\mathrm{Ph}-\underset{\mathrm{Me}}{\mathrm{N}}-\overset{\mathrm{CH_2Ph}}{\mathrm{CH}}-\mathrm{CH{=}CH_2}$$

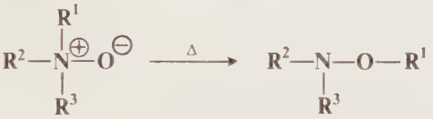
The Sommelet-Hauser rearrangement competes when Z is an aryl group (see reaction **3-27**). Hofmann elimination competes when one of the R groups contains a β-hydrogen atom (reactions **7-6**, **7-7**).

Sulfur ylides containing a Z-group give an analogous rearrangement, often also referred to as a Stevens rearrangement.[281] In this case too, there is much evidence (including CIDNP) that a



$$\mathrm{Z}-\overset{\ominus}{\underline{\mathrm{C}}\mathrm{H}}-\underset{\mathrm{R^1}}{\overset{\oplus}{\mathrm{S}}}-\mathrm{R^2}\ \longrightarrow\ \mathrm{Z}-\underset{\mathrm{R^1}}{\mathrm{CH}}-\mathrm{SR^2}$$

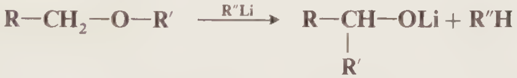
radical-pair cage mechanism is operating,[282] except that when the migrating group is allyl, the mechanism may be different (see reaction **8-40**). Another reaction with a similar mechanism[283] is the *Meisenheimer rearrangement*,[284] in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines. The migrating group R^1 is almost always allylic or benzilic.



$$\mathrm{R^2}-\overset{\mathrm{R^1}}{\underset{\mathrm{R^3}}{\overset{\oplus}{\mathrm{N}}}}-\mathrm{O}^{\ominus}\ \xrightarrow{\Delta}\ \mathrm{R^2}-\underset{\mathrm{R^3}}{\mathrm{N}}-\mathrm{O}-\mathrm{R^1}$$

R^2 and R^3 may be alkyl or aryl, but if one of the R groups contains a β-hydrogen, the Cope elimination reaction (**7-8**) often competes.

8-26 The Wittig Rearrangement



$$\mathrm{R-CH_2-O-R'}\ \xrightarrow{\mathrm{R''Li}}\ \mathrm{R}-\underset{\mathrm{R'}}{\mathrm{CH}}-\mathrm{OLi}+\mathrm{R''H}$$

The rearrangement of ethers with alkyllithiums is called the *Wittig rearrangement* (not to be confused with the Wittig reaction, **6-47**) and is similar to reaction **8-25**.[265] However, a stronger base is required (e.g., phenyllithium or sodium amide). R and R′ may be alkyl, aryl, or vinyl.[285] Also, one of the hydrogens may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allyl, benzyl > ethyl > methyl >

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[280] Hill and Chan, *J. Am. Chem. Soc.* **88**, 866 (1966).

[281] For a review, see Olsen and Currie, in Patai, "The Chemistry of the Thiol Group," pt. 2, pp. 561–566, John Wiley & Sons, Inc., New York, 1974.

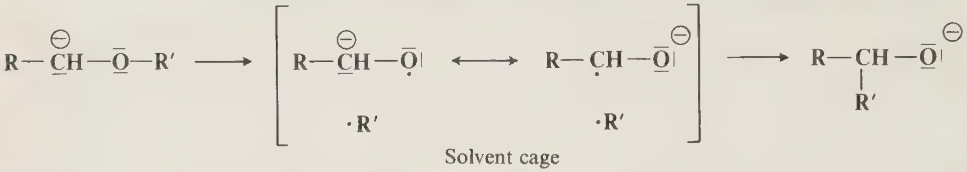
[282] See for example, Baldwin, Erickson, Hackler, and Scott, *Chem. Commun.* 576 (1970); Schöllkopf, Schossig, and Ostermann, *Justus Liebigs Ann. Chem.* **737**, 158 (1970); Iwamura, Iwamura, Nishida, Yoshida, and Nakayama, *Tetrahedron Lett.* 63 (1971).

[283] For sòme of the evidence, see Schöllkopf and Ludwig, *Chem. Ber.* **101**, 2224 (1968); Ostermann and Schöllkopf, *Justus Liebigs Ann. Chem.* **737**, 170 (1970); Lorand, Grant, Samuel, O'Connell, and Zaro, *Tetrahedron Lett.* 4087 (1969).

[284] For a review, see Johnstone, *Mech. Mol. Migr.* **2**, 249–266 (1969).

[285] For migration of vinyl, see Rautenstrauch, Büchi, and Wüest, *J. Am. Chem. Soc.* **96**, 2576 (1974).

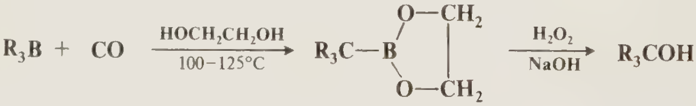
phenyl.[286] The following radical-pair mechanism[287] (similar to mechanism *a* of reaction **8-25**) is likely, after removal of the proton by the base. One of the radicals in the radical pair is a ketyl



radical. Among the evidence for this mechanism is: (1) The rearrangement is largely intramolecular; (2) migratory aptitudes are in the order of free-radical stabilities, and not of carbanion stabilities[288] (which rules out an ion-pair mechanism similar to mechanism *b* of reaction **8-25**); (3) aldehydes are obtained as side products;[289] (4) partial racemization of **R**′ has been observed[290] (the remainder of the product retained its configuration); (5) crossover products have been detected;[291] and (6) when ketyl radicals and R′· radicals from different precursors were brought together, similar products resulted.[292] However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.[293] Most of the above investigations were carried out with systems where R′ is alkyl, but a radical-pair mechanism has also been suggested for the case where R′ is aryl.[294] When R′ is allylic a concerted mechanism may operate (reaction **8-40**).

F. Boron-to-Carbon Migrations.[295] For another reaction involving boron-to-carbon migration, see reaction **0-101.**

8-27 Conversion of Boranes to Tertiary Alcohols



85

Trialkylboranes (which can be prepared from olefins by reaction **5-15**) react with carbon monoxide[296] at 100 to 125°C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes **85**, which are easily oxidized (reaction **2-26**) to tertiary alcohols.[297] The R groups may be primary, secondary, or tertiary, and may be the same or different,[298] though a general method for the preparation of trialkylboranes with all three groups different is not yet available. Yields are high, and the reaction is quite useful, especially for the preparation of sterically hindered alcohols such as tricyclohexylcarbinol and tri-2-norbornylcarbinol, which are difficult to prepare by reaction **6-31.** Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.[299] The

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[286] Wittig, *Angew. Chem.* **66**, 10 (1954).

[287] For a review of the mechanism, see Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **9**, 763–773 (1970) [*Angew. Chem.* **82**, 795–805].

[288] Lansbury, Pattison, Sidler, and Bieber, *J. Am. Chem. Soc.* **88**, 78 (1966); Schäfer, Schöllkopf, and Walter, *Tetrahedron Lett.* 2809 (1968).

[289] For example, see Hauser and Kantor, *J. Am. Chem. Soc.* **73**, 1437 (1951); Cast, Stevens, and Holmes, *J. Chem. Soc.* 3521 (1960).

[290] Schöllkopf and Fabian, *Justus Liebigs Ann. Chem.* **642**, 1 (1961); Schöllkopf and Schäfer, *Justus Liebigs Ann. Chem.* **663**, 22 (1963).

[291] Lansbury and Pattison, *J. Org. Chem.* **27**, 1933 (1962), *J. Am. Chem. Soc.* **84**, 4295 (1962).

[292] Garst and Smith, *J. Am. Chem. Soc.* **95**, 6870 (1973).

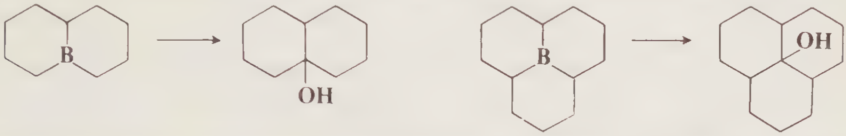
[293] Garst and Smith, *J. Am. Chem. Soc.* **98**, 1526 (1976).

[294] Eisch, Kovacs, and Rhee, *J. Organomet. Chem.* **65**, 289 (1974).

[295] For reviews, see Cragg, "Organoboranes in Organic Synthesis," pp. 249–300, Marcel Dekker, Inc., New York, 1973; Paetzold and Grundke, *Synthesis* 635–660 (1973).

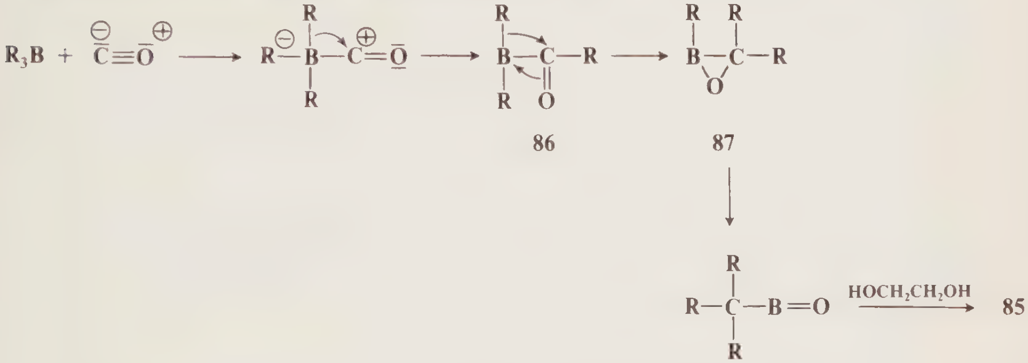
[296] For discussions of the reactions of boranes with CO, see Negishi, *Intra-Sci. Chem. Rep.* **7**(1), 81–94 (1973); Brown, "Boranes in Organic Chemistry," pp. 343–371, Cornell University Press, Ithaca, N.Y., 1972, *Acc. Chem. Res.* **2**, 65–72 (1969).

[297] Hillman, *J. Am. Chem. Soc.* **84**, 4715 (1962), **85**, 982 (1963); Brown and Rathke, *J. Am. Chem. Soc.* **89**, 2737 (1967); Puzitskii, Pirozhkov, Ryabova, Pastukhova, and Eidus, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **21**, 1939 (1972), **22**, 1760 (1973).



preparation of such heterocyclic boranes was discussed in reaction **5-15.** The overall conversion of a diene or triene to a cyclic alcohol has been described by H. C. Brown as "stitching" with boron, and "riveting" with carbon.

Though the mechanism has not been investigated thoroughly, it has been shown to be intramolecular, by the failure to find crossover products when mixtures of boranes are used.[300] The following scheme, involving three boron-to-carbon migrations, has been suggested.



86 **87**

88

The purpose of the ethylene glycol is to intercept the boronic anhydride **88,** which otherwise forms polymers which are difficult to oxidize. As we shall see in reactions **8-28** and **8-29,** it is possible to stop the reaction after only one or two migrations have taken place.

There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (1) treatment with α,α-dichloromethyl methyl ether and the base lithium triethyl-

Method 1 $$R_3B + CHCl_2OMe \xrightarrow[\text{2. } H_2O_2-NaOH]{\text{1. } LiOCEt_3-THF} R_3COH$$

Method 2 $$R_3B + CN^- \xrightarrow{\text{THF}} \underset{\textbf{89}}{R_3\overset{\ominus}{B}-CN} \xrightarrow[\text{2. } NaOH-H_2O_2]{\text{1. excess } (CF_3CO)_2O} R_3COH$$

---

[298] Brown, Negishi, and Gupta, *J. Am. Chem. Soc.* **92,** 6648 (1970); Brown and Gupta, *J. Am. Chem. Soc.* **93,** 1818 (1971); Negishi and Brown, *Synthesis* 197 (1972).

[299] Brown and Negishi, *J. Am. Chem. Soc.* **89,** 5478 (1967), **91,** 1224 (1969); Knights and Brown, *J. Am. Chem. Soc.* **90,** 5283 (1968); Brown and Dickason, *J. Am. Chem. Soc.* **91,** 1226 (1969).

[300] Brown and Rathke, *J. Am. Chem. Soc.* **89,** 4528 (1967).

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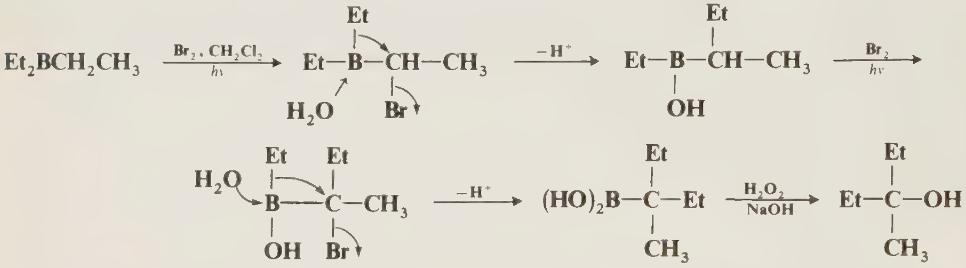
carboxide,[301] and (2) treatment with a suspension of sodium cyanide in tetrahydrofuran followed by reaction of the resulting trialkylcyanoborate **89** with an excess (more than 2 moles) of trifluoroacetic anhydride.[302] All the above migrations take place with retention of configuration at the migrating carbon.

Another method converts a trialkylborane to a tertiary alcohol in which only two of the R groups are derived from the borane. In this method the borane is treated with a 1-lithio-1,1-bis(phenylthio)alkane, then with $HgCl_2$, and the product finally oxidized.[303] This method can be

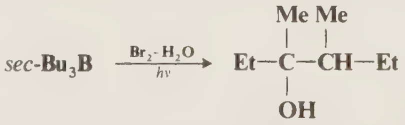
$$R_3B + R'\overset{\ominus}{\bar{C}}(SPh)_2 \longrightarrow R_3\overset{\ominus}{B}-CR'(SPh)_2 \longrightarrow R_2B-CRR'SPh \xrightarrow[2.\ H_2O_2-OH^-]{1.\ HgCl_2} R_2R'COH$$

adapted to the preparation of secondary alcohols R_2CHOH ($R' = H$) if three equivalents of $HgCl_2$ are used.[303a]

A different kind of borane-to-tertiary-alcohol conversion involves treatment of a tri-*n*-alkylborane with 2 moles of bromine or N-bromosuccinimide in the presence of water and light, followed by oxidation.[304] In this reaction, illustrated for triethylborane, bromination steps (reaction **4-1**)

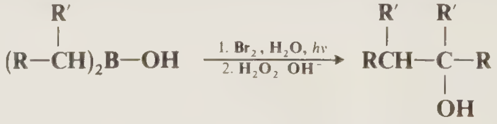


are followed by migration steps. Tri-*sec*-alkylboranes give corresponding products, but in lower yields. However, when tri-*sec*-alkylboranes are treated with only 1 mole of Br_2, in the presence of water and light, only one migration takes place and the product is a tertiary alcohol derived from two alkyl groups.[305]



$$sec\text{-}Bu_3B \xrightarrow[h\nu]{Br_2\text{-}H_2O} Et-\underset{OH}{\overset{Me}{C}}-\overset{Me}{CH}-Et$$

Extension of this reaction to boranes of the form RR′R″B, where R″ is thexyl, permits combination of R and R′, since thexyl neither can be α-brominated, nor does it migrate.[306] Alternatively, tertiary alcohols derived from one migration can also be prepared by starting with dialkylborinic acids.[307]



$$(R-\overset{R'}{CH})_2B-OH \xrightarrow[2.\ H_2O_2\ OH^-]{1.\ Br_2,\ H_2O,\ h\nu} R\overset{R'}{CH}-\underset{OH}{\overset{R'}{C}}-R$$

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[301] Brown and Carlson, *J. Org. Chem.* **38**, 2422 (1973); Brown, Katz, and Carlson, *J. Org. Chem.* **38**, 3968 (1973).

[302] Pelter, Hutchings, and Smith, *J. Chem. Soc., Chem. Commun.* 186 (1973); Pelter, Hutchings, Rowe, and Smith, *J. Chem. Soc., Perkin Trans. 1* 138 (1975); Pelter, Hutchings, Smith, and Williams, *J. Chem. Soc., Perkin Trans. 1* 145 (1975); Pelter, *Chem. Ind. (London)* 206–209 (1973), *Intra-Sci. Chem. Rep.* 7(1), 73–79 (1973).

[303] Hughes, Pelter, and Smith, *J. Chem. Soc., Chem. Commun.* 863 (1974).

[303a] Hughes, Pelter, Smith, Negishi, and Yoshida, *Tetrahedron Lett.* 87 (1976).

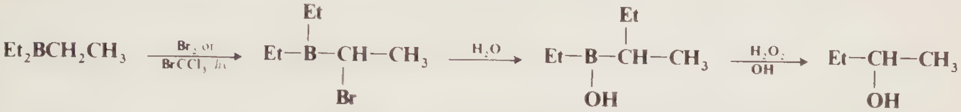
[304] Lane and Brown, *J. Am. Chem. Soc.* **93**, 1025 (1971); Brown and Yamamoto, *Synthesis* 699 (1972).

[305] Lane and Brown, Ref. 304; Yamamoto and Brown, *J. Chem. Soc., Chem. Commun.* 801 (1973), *J. Org. Chem.* **39**, 861 (1974).

[306] Brown, Yamamoto, and Lane, *Synthesis* 304 (1972).

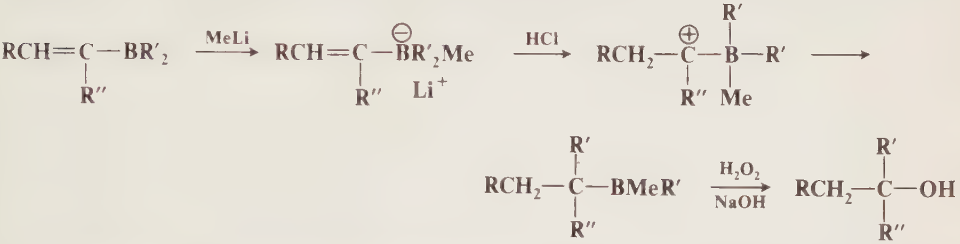
[307] Brown and Lane, *Synthesis* 303 (1972).

When tri-*n*-alkylboranes are treated with 1 mole of Br_2, or with bromotrichloromethane, under the influence of light, in the absence of water, the α-bromoboranes can be isolated.[308] Treatment of these with nucleophiles,[309] such as H_2O or pyridine, followed by oxidation, produces secondary alcohols.



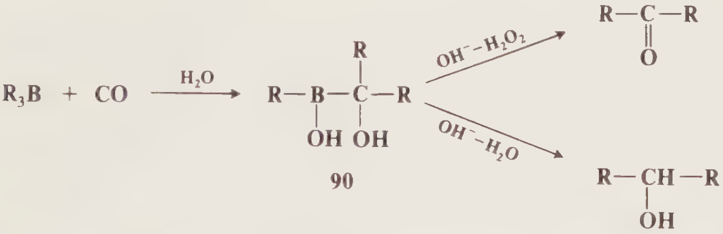
$$\mathrm{Et_2BCH_2CH_3} \xrightarrow[\mathrm{BrCCl_3},\ h\nu]{\mathrm{Br_2\ or}} \mathrm{Et{-}\overset{Et}{B}{-}\underset{Br}{CH}{-}CH_3} \xrightarrow{\mathrm{H_2O}} \mathrm{Et{-}\underset{OH}{B}{-}\overset{Et}{CH}{-}CH_3} \xrightarrow[\mathrm{OH^-}]{\mathrm{H_2O_2}} \mathrm{Et{-}\underset{OH}{CH}{-}CH_3}$$

Secondary and tertiary alcohols can also be prepared from vinyldialkylboranes (R″ = alkyl or hydrogen; prepared by addition of R_2BH to alkynes, reaction **5-15**), by treatment with methyllithium followed by HCl, and oxidation of the product.[310] This migration proceeds with retention of configuration in R′.



$$\mathrm{RCH{=}\underset{R''}{C}{-}BR'_2} \xrightarrow{\mathrm{MeLi}} \mathrm{RCH{=}\underset{R''}{C}{-}\overset{\ominus}{B}R'_2Me\ \ Li^+} \xrightarrow{\mathrm{HCl}} \mathrm{RCH_2{-}\underset{R''}{\overset{\oplus}{C}}{-}\underset{Me}{\overset{R'}{B}}{-}R'} \longrightarrow \mathrm{RCH_2{-}\underset{R''}{\overset{R'}{C}}{-}BMeR'} \xrightarrow[\mathrm{NaOH}]{\mathrm{H_2O_2}} \mathrm{RCH_2{-}\underset{R''}{\overset{R'}{C}}{-}OH}$$

8-28 Conversion of Boranes to Secondary Alcohols or Ketones



$$\mathrm{R_3B + CO} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}\underset{OH}{B}{-}\underset{OH}{\overset{R}{C}}{-}R} \quad \begin{cases} \xrightarrow{\mathrm{OH^-{-}H_2O_2}} \mathrm{R{-}\underset{\|\atop O}{C}{-}R} \\ \xrightarrow{\mathrm{OH^-{-}H_2O}} \mathrm{R{-}\underset{OH}{CH}{-}R} \end{cases}$$

90

If the reaction between trialkylboranes and carbon monoxide (**8-27**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.[311] Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,[312] though if they are in the α or β position relative to the boron atom, difficulties may be encountered. The reaction has been extended to the formation of unsymmetrical ketones by use of a borane of the form $R_2R'B$, where one of the groups migrates much less readily than the other (migratory aptitudes are in the order primary > secondary > tertiary). For example, *n*-alkyldicyclohexylboranes gave good yields of alkyl cyclohexyl ketones.[300] When R′ is thexyl, it is always the other two groups which migrate, so the product from a borane RR′R″ (R″ = thexyl) is the ketone RCOR′.[313] However, the thexyl reaction suffers from the disadvantage that carbonylation of boranes containing a thexyl group requires CO pressures of 70 atm. Cyclic thexylboranes give cyclic ketones,[314] e.g.,

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[308] Brown and Yamamoto, *J. Am. Chem. Soc.* **93,** 2796 (1971), *Chem. Commun.* 1535 (1971); Brown and DeLue, *J. Am. Chem. Soc.* **96,** 311 (1974).

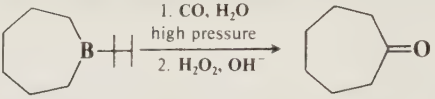
[309] This conversion can also be induced by electrophiles, such as $AlCl_3$: Brown and Yamamoto, *J. Chem. Soc., Chem. Commun.* 71 (1972).

[310] Zweifel and Fisher, *Synthesis* 339 (1974). See also Zweifel, Fisher, and Horng, *Synthesis* 37 (1973).

[311] Brown and Rathke, *J. Am. Chem. Soc.* **89,** 2738 (1967).

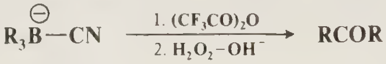
[312] Brown, Kabalka, and Rathke, *J. Am. Chem. Soc.* **89,** 4530 (1967).

[313] Brown and Negishi, *J. Am. Chem. Soc.* **89,** 5285 (1967); Negishi and Brown, *Synthesis* 196 (1972).



The reaction follows the mechanism shown in reaction **8-27** until formation of the borepoxide **87.** In the presence of water the third boron → carbon migration does not take place, because the water hydrolyzes **87** to the diol **90.**

Trialkylboranes can also be converted to ketones by the cyanoborate procedure, mentioned in reaction **8-27.** In this case the procedure is similar, but use of an equimolar amount of trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[315] By this procedure thexylboranes RR′R″B (R″ = thexyl) can be converted to unsymmetrical ketones RCOR′ without the use of high pressures. Like the carbon monoxide procedure, this method tolerates the presence of various functional groups in R. Another method involves the treatment of borinic acid esters (which can be prepared by treatment of dialkylchloroboranes with alcohols) with α,α-dichloromethyl methyl ether and lithium triethylcarboxide.[316] This method does not waste an R group

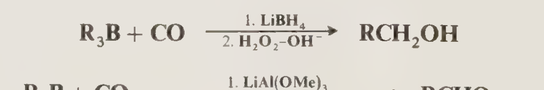


$$R_3\overset{\ominus}{B}\text{—CN} \xrightarrow[\text{2. } H_2O_2\text{–}OH^-]{\text{1. } (CF_3CO)_2O} RCOR$$

89

$$R_2BCl + R'OH \longrightarrow R_2BOR' \xrightarrow[\text{2. } H_2O_2\text{-}OH^-]{\text{1. } CHCl_2OMe,\ LiOCEt_3 \quad THF,\ 25°C} R_2CO$$

and is carried out under mild conditions. In still another procedure ketones are prepared by the reaction between dialkylchloroboranes and lithium aldimines[317] (which can be prepared by reaction **6-76**).



$$R_2BCl + R''\text{—N=}\underset{\displaystyle Li}{\underset{|}{C}}\text{—}R' \xrightarrow[\text{2. } H_2O_2\text{-}OH^-]{\text{1. HCN or PhCHO}} R\text{—}\underset{\displaystyle O}{\underset{\|}{C}}\text{—}R'$$

For another conversion of trialkylboranes to ketones, see reaction **8-31.** For other conversions of boranes to secondary alcohols, see reaction **8-27.**

8-29 Conversion of Boranes to Primary Alcohols or Aldehydes

$$R_3B + CO \xrightarrow[\text{2. } H_2O_2\text{-}OH^-]{\text{1. } LiBH_4} RCH_2OH$$

$$R_3B + CO \xrightarrow[\text{2. } H_2O_2\text{-}NaH_2PO_4\text{-}Na_2HPO_4]{\text{1. } LiAl(OMe)_3} RCHO$$

When the reaction between a trialkylborane and carbon monoxide (**8-27**) is carried out in the presence of a reducing agent such as lithium borohydride or lithium trimethoxyaluminum hydride, the reducing agent intercepts the intermediate **86,** so that only one boron-to-carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[318] This procedure wastes two of the three R groups, but this problem can be avoided by the use of B-alkyl-9-BBN derivatives (p. 432). Since only the 9-alkyl group migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[319] When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*t*-butoxyaluminum hydride, other functional groups (e.g., CN and ester) may be present in the alkyl group without being reduced.[320]

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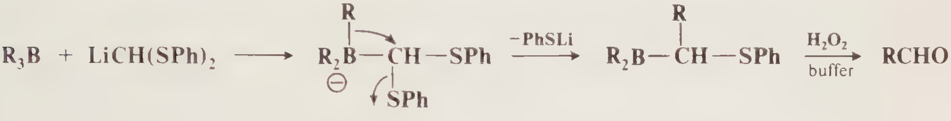
[314] Brown and Negishi, *J. Am. Chem. Soc.* **89,** 5477 (1967), *Chem. Commun.* 594 (1968).

[315] Pelter, Smith, Hutchings, and Rowe, *J. Chem. Soc., Perkin Trans. 1,* 129 (1975); Ref. 302. See also Pelter, Hutchings, and Smith, *J. Chem. Soc., Perkin Trans. 1* 142 (1975).

[316] Carlson and Brown, *J. Am. Chem. Soc.* **95,** 6876 (1973), *Synthesis* 776 (1973).

[317] Yamamoto, Kondo, and Moritani, *Tetrahedron Lett.* 793 (1974); *Bull. Chem. Soc. Jpn.* **48,** 3682 (1975).

Another preparation of aldehydes utilizes α-lithiated thioacetals **91**, which react with trialkyl-

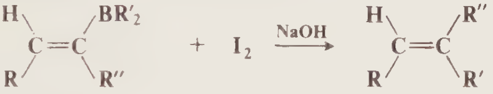


$$R_3B + LiCH(SPh)_2 \longrightarrow R_2\overset{\ominus}{B}(R)-CH(SPh)-SPh\ Li^+ \xrightarrow{-PhSLi} R_2B-CH(R)-SPh \xrightarrow[\text{buffer}]{H_2O_2} RCHO$$

91 **92**

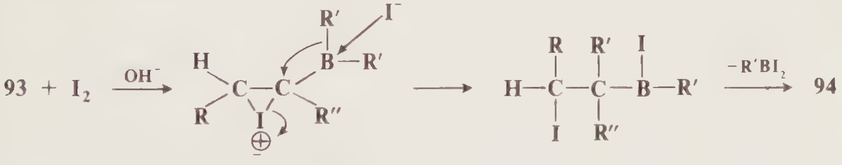
boranes to give, after migration of R, the boranes **92**, which are oxidized to aldehydes with hydrogen peroxide.[321] The method can be adapted to the preparation of ketones by the use of $LiCR'(SPh)_2$ instead of **91**.

8-30 Conversion of Vinylboranes to Alkenes



93 94

The reaction between trialkylboranes and iodine to give alkyl iodides was discussed at reaction **2-28.** When the substrate contains a vinyl group, the reaction takes a different course, with one of the R′ groups migrating to the carbon, to give alkenes **94.**[322] The reaction is stereospecific in two senses: (1) If the groups R and R″ are cis in the starting compound, they will be trans in the product. (2) There is retention of configuration within the migrating group R′.[323] Since vinylboranes can be prepared from alkynes (**5-15**), this is a method for the addition of R′ and H to a triple bond. If R″ = H, the product is a cis alkene. The mechanism is believed to be



When R′ is vinyl, the product is a conjugated diene.[324]

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[318] Brown and Rathke, *J. Am. Chem. Soc.* **89,** 2740 (1967); Brown, Coleman, and Rathke, *J. Am. Chem. Soc.* **90,** 499 (1968).

[319] Brown, Knights, and Coleman, *J. Am. Chem. Soc.* **91,** 2144 (1969).

[320] Brown and Coleman, *J. Am. Chem. Soc.* **91,** 4606 (1969).

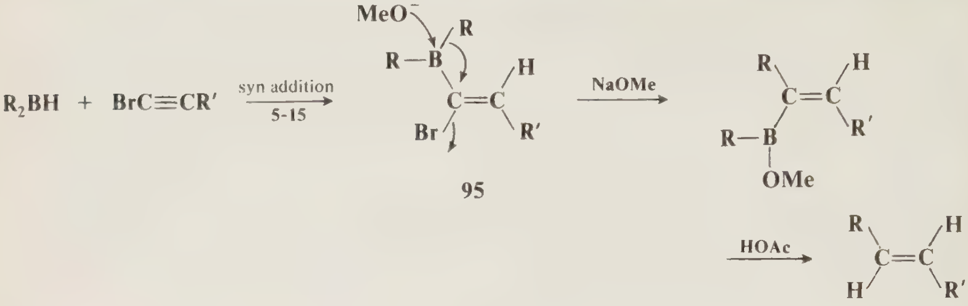
[321] Yamamoto, Shiono, and Mukaiyama, *Chem. Lett.* 961 (1973); See also Negishi, Yoshida, Silveira, and Chiou, *J. Org. Chem.* **40,** 814 (1975).

[322] Zweifel, Arzoumanian, and Whitney, *J. Am. Chem. Soc.* **89,** 3652 (1967); Zweifel and Fischer, *Synthesis* 376 (1975). See also Negishi, Lew, and Yoshida, *J. Org. Chem.* **39,** 2321 (1974).

[323] Zweifel, Fisher, Snow, and Whitney, *J. Am. Chem. Soc.* **93,** 6309 (1971).

[324] Zweifel, Polston, and Whitney, *J. Am. Chem. Soc.* **90,** 6243 (1968); Brown and Ravindran, *J. Org. Chem.* **38,** 1617 (1973).

In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halovinylborane (**95**). Treatment of this with NaOMe gives the rearrangement shown, and protonolysis

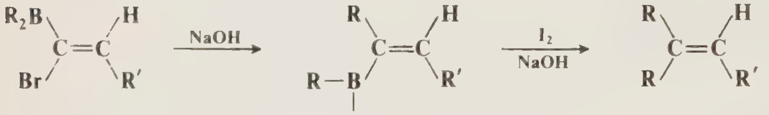


95

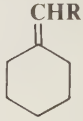
96

of the product produces the trans alkene **96**.[323] If R is a vinyl group the product is a 1,3-diene.[325] If one of the groups is thexyl, then the other one migrates.[326] This extends the scope of the synthesis, since dialkylboranes where one R group is thexyl are easily prepared.

A combination of both of the procedures described above results in the preparation of trisubstituted olefins.[327] The entire conversion of haloalkyne to **97** can be carried out in one reaction



95 **97**



98

vessel, without isolation of intermediates. If R_2BH is a heterocyclic borane, the product is an exocyclic olefin, e.g., **98.**

Trans alkenes **96** can also be obtained by treatment of **93** (R″ = H) with cyanogen bromide or cyanogen iodide in CH_2Cl_2.[328]

8-31 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides

$$R'_3B + RC{\equiv}CLi \longrightarrow \underset{\textbf{99}}{RC{\equiv}C{-}\overset{\ominus}{B}R'_3,\ Li^+} \xrightarrow{I_2} RC{\equiv}CR'$$

A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate **99** with iodine.[329] R′ may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **0-102.** R may be alkyl, aryl, or hydrogen, though in the last-mentioned case satisfactory yields are obtained only if lithium acetylide–ethylenediamine is used as the starting compound.[330] When the starting compound is $ClC\equiv CLi$, the Cl is also replaced and the product is the symmetrical alkyne $RC\equiv CR$.[331] The reaction is similar to the one mentioned in **8-30**, in that iodine causes a migration of R′ from boron to carbon, but the mechanism of the migration step may be different. Methanesulfinyl chloride MeSOCl has been used instead of iodine, but yields are lower.[332] The reaction may be adapted to the preparation of alkenes by treatment of **99** with a carboxylic acid

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[325] Negishi and Yoshida, *J. Chem. Soc., Chem. Commun.* 606 (1973).

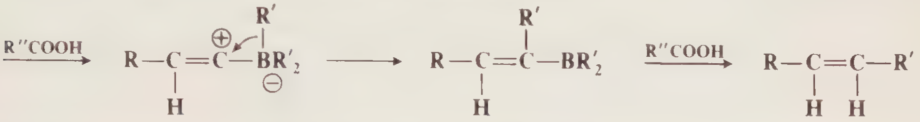
[326] Corey and Ravindranathan, *J. Am. Chem. Soc.* **94,** 4013 (1972); Negishi, Katz, and Brown, *Synthesis* 555 (1972).

[327] Zweifel and Fisher, *Synthesis* 557 (1972). For another procedure, see Pelter, Subrahmanyam, Laub, Gould, and Harrison, *Tetrahedron Lett.* 1633 (1975).

[328] Zweifel, Fisher, Snow, and Whitney, *J. Am. Chem. Soc.* **94,** 6560 (1972).

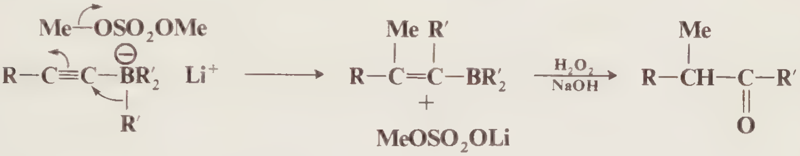
[329] Suzuki, Miyaura, Abiko, Itoh, Brown, Sinclair, and Midland, *J. Am. Chem. Soc.* **95,** 3080 (1973).

[330] Midland, Sinclair, and Brown, *J. Org. Chem.* **39,** 731 (1974).

99


such as propionic acid.[333] This reaction is partially stereoselective, with mostly cis alkene generally produced.

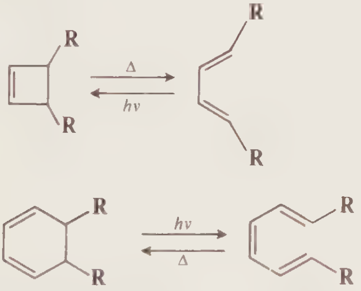
Treatment of **99** with an electrophile, such as methyl sulfate, allyl bromide, or triethyloxonium borofluoride, followed by oxidation of the resulting vinylborane gives a ketone (illustrated for methyl sulfate):[334]



Non-1,2 Rearrangements

A. Electrocyclic Rearrangements

8-32 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes



Cyclobutenes and 1,3-dienes can be interconverted by treatment with uv light or with heat. The thermal reaction is generally not reversible (though exceptions[335] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200°C.

[331] Yamada, Miyaura, Itoh, and Suzuki, *Tetrahedron Lett.* 1961 (1975).

[332] Naruse, Utimoto, and Nozaki, *Tetrahedron Lett.* 1847 (1973).

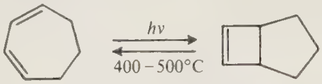
[333] Pelter, Harrison, and Kirkpatrick, *J. Chem. Soc., Chem. Commun.* 544 (1973); Miyaura, Yoshinari, Itoh, and Suzuki, *Tetrahedron Lett.* 2961 (1974); Pelter, Gould, and Harrison, *Tetrahedron Lett.* 3327 (1975).

[334] Pelter, Harrison, and Kirkpatrick, Ref. 333. See also Pelter, Harrison, and Kirkpatrick, *Tetrahedron Lett.* 4491 (1973); Utimòto, Furubayashi, and Nozaki, *Chem. Lett.* 397 (1975).

[335] For example, see Shumate, Neuman, and Fonken, *J. Am. Chem. Soc.* **87**, 3996 (1965); Gil-Av and Herling, *Tetrahedron Lett.* 1 (1967); Doorakian and Freedman, *J. Am. Chem. Soc.* **90**, 3582 (1968); Brune and Schwab, *Tetrahedron* **25**, 4375 (1969).

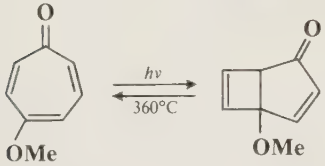
The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wavelengths used.[336] In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally, and the ring-opening process photochemically, though exceptions are known in both directions.

Some examples are



100

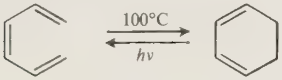
Ref. 337

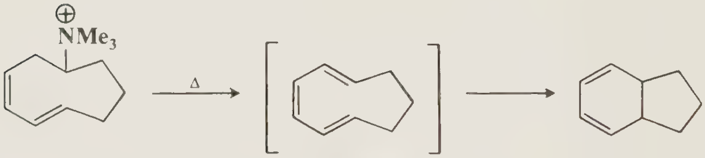


4-Methoxytropone

101

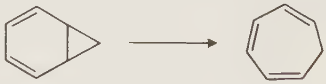
Ref. 338





Not isolated

Note that in the second example the tropone is a 1,3,5-triene, but in this case reacts as a 1,3-diene (see p. 1032). An interesting example of a 1,3-cyclohexadiene-1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.[339] Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see p. 1045) that they cannot generally be isolated, though some exceptions are known[340] (see also p. 792).



Norcaradiene

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[336] For examples of photochemical conversion of a cyclobutene to a 1,3-diene, see Scherer, *J. Am. Chem. Soc.* **90,** 7352 (1968); Saltiel and Lim, *J. Am. Chem. Soc.* **91,** 5404 (1969).

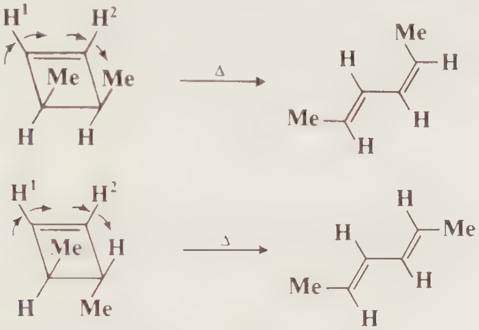
[337] Dauben and Cargill, *Tetrahedron* **12,** 186 (1961); Chapman, Pasto, Borden, and Griswold, *J. Am. Chem. Soc.* **84,** 1220 (1962).

[338] Chapman and Pasto, *J. Am. Chem. Soc.* **80,** 6685 (1958), **82,** 3642 (1960). For a review of the photochemistry of tropolones, see Koch, *Adv. Alicyclic Chem.* **1,** 257–281 (1966).

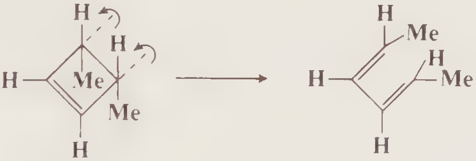
[339] For reviews of the norcaradiene-cycloheptatriene interconversion, and of the analogous benzene oxide–oxepin interconversion, see, respectively, Maier, *Angew. Chem. Int. Ed. Engl.* **6,** 402–413 (1967) [*Angew. Chem.* **79,** 446–458]; Vogel and Günther, *Angew. Chem. Int. Ed. Engl.* **6,** 385–401 (1967) [*Angew. Chem.* **79,** 429–446]; Vogel, *Pure Appl. Chem.* **20,** 237–262 (1969).

[340] See Chapter 15, Refs. 745 and 746.

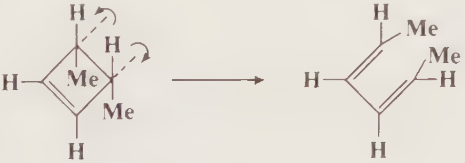
These reactions, called *electrocyclic rearrangements*,[341] take place by pericyclic mechanisms. The evidence for this comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis,trans*-2,4-hexadiene, while the trans isomer gave only the trans-trans diene:[342]



This is evidence for a four-membered cyclic transition state and arises from *conrotatory* motion of the C-1 and C-2 hydrogens. That is, as H¹ moves up, H² moves down. It is called conrotatory because they both move clockwise (or both counterclockwise). The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise. Another way to look at this is to observe the motions of the methyl groups and of the C-3 and C-4 hydrogens. In conrotatory motion they rotate in the same direction (and the cis isomer gives the cis-trans diene):[343]



On the other hand, in a disrotatory motion, in which they moved in opposite ways, the cis isomer would have given the cis-cis diene (shown), or the trans-trans diene:



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[341] For reviews, see Gilchrist and Storr, "Organic Reactions and Orbital Symmetry," pp. 48–72, Cambridge University Press, New York, 1972; DeWolfe, in Bamford and Tipper, "Comprehensive Chemical Kinetics," vol. 9, pp. 461–470, American Elsevier Publishing Company, New York, 1973; Crowley and Mazzocchi, in Zabicky, "The Chemistry of Alkenes," vol. 2, pp. 284–297, Interscience Publishers, New York, 1970; Criegee, *Angew. Chem. Int. Ed. Engl.* **7**, 559–565 (1968) [*Angew. Chem.* **80**, 585–591]; Vollmer and Servis, *J. Chem. Educ.* **45**, 214–220 (1968).

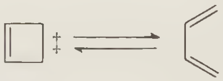
[342] Winter, *Tetrahedron Lett.* 1207 (1965). Also see Vogel, *Justus Liebigs Ann. Chem.* **615**, 14 (1958); Criegee and Noll, *Justus Liebigs Ann. Chem.* **627**, 1 (1959).

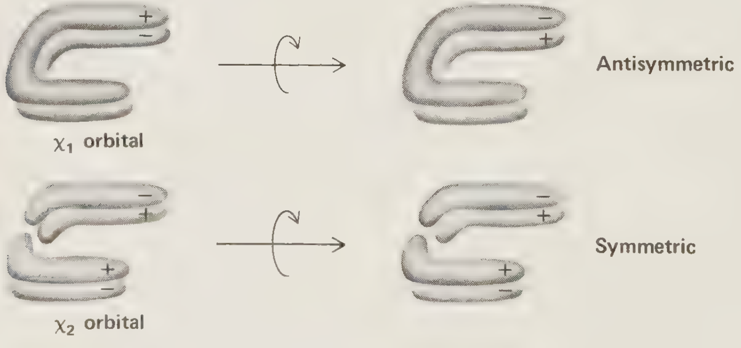
[343] This picture is from Woodward and Hoffmann, *J. Am. Chem. Soc.* **87**, 395 (1965), who coined the terms conrotatory and disrotatory.

If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse reaction is also conrotatory. In contrast, the photochemical cyclobutene-1,3-diene interconversion is *disrotatory* in either direction. On the other hand, the cyclohexadiene-1,3,5-triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Chapter 15 (p. 767).[344] As in the case of cycloaddition reactions, we may use the correlation diagram or the orbital frontier approach.[345]

The Correlation Diagram Method

Let us consider the cyclobutene-1,3-diene interconversion. The orbitals to be correlated are the four π orbitals of the diene (p. 33) and the two π and the two σ orbitals (marked ‡) of the cyclobutane. First we examine the case where the reaction proceeds in a conrotatory manner. As in Chapter 15, we draw the orbitals involved and examine each one to see if it is symmetric or antisymmetric. However, in this case it is not possible to use a *plane of symmetry* as our symmetry element, because no plane of symmetry is present throughout the course of the reaction.[346] An alternating axis of symmetry is present, however, and we may use this instead. The procedure in using such an axis is to rotate the entire orbital through 180°. If it then coincides with itself, it is symmetric. If all signs are changed, it is antisymmetric. For example, if the χ_1 orbital of a 1,3-diene is rotated through 180° (turned upside down) the signs are inverted, so it is antisymmetric with respect to this operation (the same orbital would be symmetric with respect to a plane





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[344] Woodward and Hoffmann, Ref. 343. Also see Longuet-Higgins and Abrahamson, *J. Am. Chem. Soc.* **87,** 2045 (1965); Fukui, *Tetrahedron Lett.* 2009 (1965).

[345] For reviews, see Woodward and Hoffmann, Ref. 278, pp. 38–64; Fukui and Fujimoto, *Mech. Mol. Migr.* **2,** 117–189 (1969). See also Chapter 15, Ref. 614.

[346] A plane of symmetry is present before the reaction begins and after it is over, but not during the reaction. Examine the σ and σ^* orbitals in Figure 1. The curved arrows show the direction in which the orbitals must move in a conrotatory process. It may be seen that the plane of symmetry present in the cyclobutene disappears soon after the reaction begins.

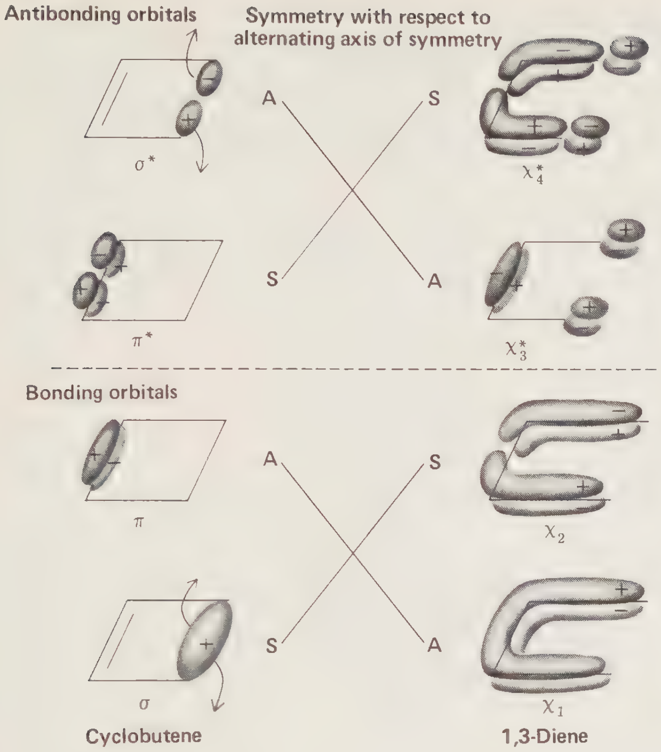

Figure 1 Correlation diagram for a conrotatory cyclobutene-1,3-diene interconversion.

of symmetry, but that does not concern us here). On the other hand, if the same operation is performed on the χ_2 orbital no change in sign is observed, and this orbital is symmetric with respect to an alternating axis of symmetry. Performing the same operation on all eight of our orbitals gives the correlation diagram shown in Figure 1. As the diagram shows, the conrotatory reaction is thermally allowed in both directions because only the two lower orbitals are occupied, and no occupied orbital is forced to move from a bonding to an antibonding condition.

Now let us examine the disrotatory reaction. In this case, a plane of symmetry is present throughout the course of the reaction (see the arrows on the σ and σ^* orbitals in Figure 2), and we can easily construct the correlation diagram shown in Figure 2. Again, only the lower two orbitals are occupied. Because this reaction requires an occupied bonding orbital to be converted to an antibonding orbital, it is thermally forbidden in either direction.[347] For the photochemical reactions, these predictions are reversed. In this case, whether we start with the cyclobutene or with the 1,3-diene, initial promotion of an electron means that *three* orbitals are occupied in the starting compound, so that the conrotatory process (Figure 1) is now forbidden in either direction (because it requires an increase in energy of either the π^* or the χ_3^* orbital, depending on the

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[347] For discussions of the difference in energy between the allowed and forbidden pathways, see van der Lugt and Oosterhoff, *J. Am. Chem. Soc.* **91,** 6042 (1969); Stephenson and Brauman, *Acc. Chem. Res.* **7,** 65–71 (1974). See also Kikuchi, *Bull. Chem. Soc. Jpn.* **47,** 1551 (1974).

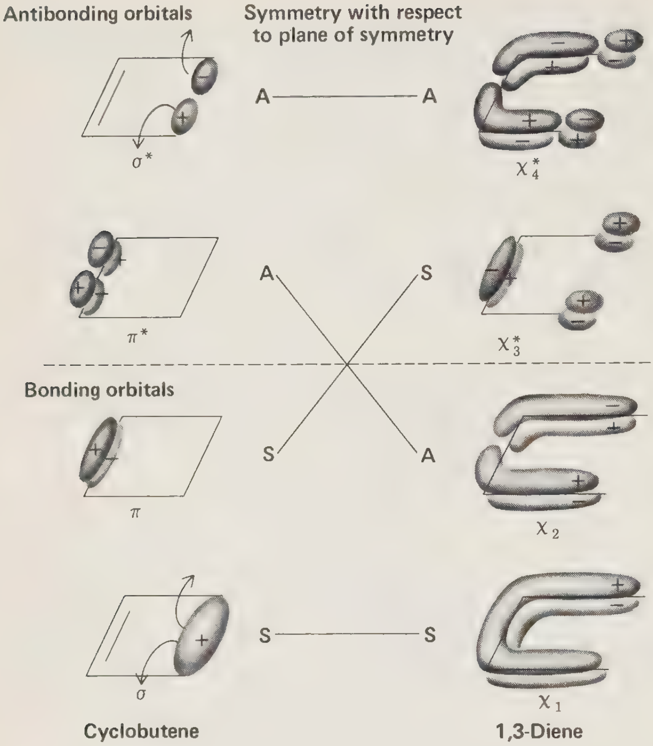
Antibonding orbitals
Symmetry with respect to plane of symmetry
A
A
σ^*
χ_4^*
A
S
π^*
χ_3^*
Bonding orbitals
S
A
π
χ_2
S
S
σ
χ_1
Cyclobutene
1,3-Diene

Figure 2 Correlation diagram for a disrotatory cyclobutene-1,3-diene interconversion.

direction), and the disrotatory process (Figure 2) is now allowed (because there is essentially no change in orbital energies). We can therefore see why, in either direction, the thermal reaction follows the conrotatory pathway, and the photochemical reaction, the disrotatory pathway.

The Frontier Orbital Method[348]

As applied to these reactions, the frontier orbital method may be expressed: *A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product*. In the case of cyclobutenes, the highest occupied π orbital of the product in the thermal reaction is the χ_2 orbital (Figure 3). Therefore, in a thermal process, the cyclobutene

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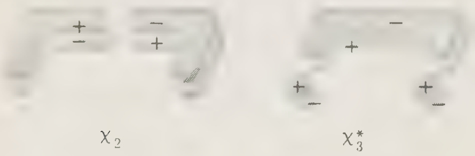
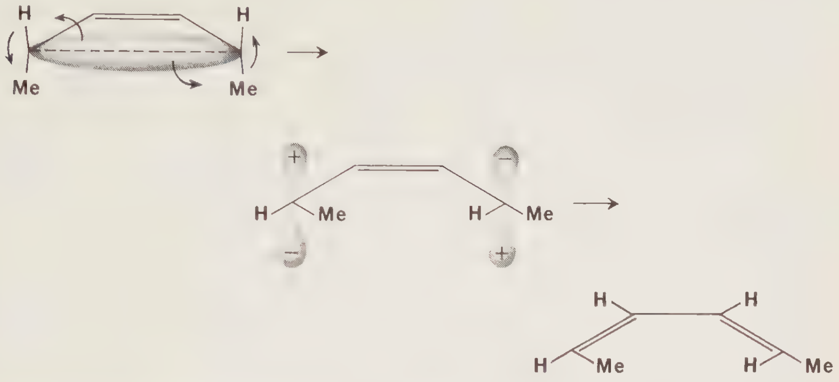
[348] See Chapter 15, Ref. 619.

Figure 3 Symmetries of the χ_2 and χ_3* orbitals of a conjugated diene.

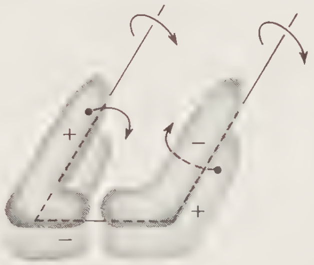


must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion:



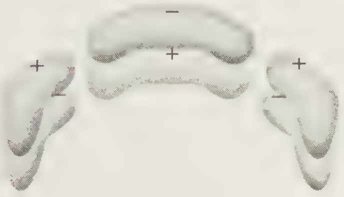
On the other hand, in the photochemical process, the highest occupied π orbital of the product is now the χ_3 orbital (Figure 3), and in order for the p orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

We may also look at this reaction from the opposite direction (ring closing). For this direction the rule is that *those lobes of orbitals which overlap (in the highest occupied molecular orbital) must be of the same sign.* For thermal cyclization of butadienes, this requires conrotatory motion:

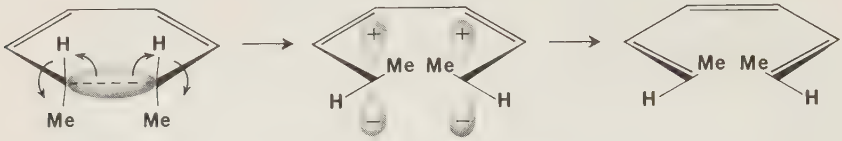


In the photochemical process the highest occupied orbital is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

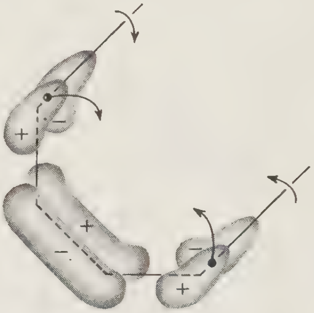
Both the correlation diagram and the frontier orbital methods can also be applied to the cyclohexadiene-1,3,5-triene reaction; in either case the result predicted is that for the thermal process only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for a 1,3,5-triene, the symmetry of the highest occupied molecular orbital is



In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:

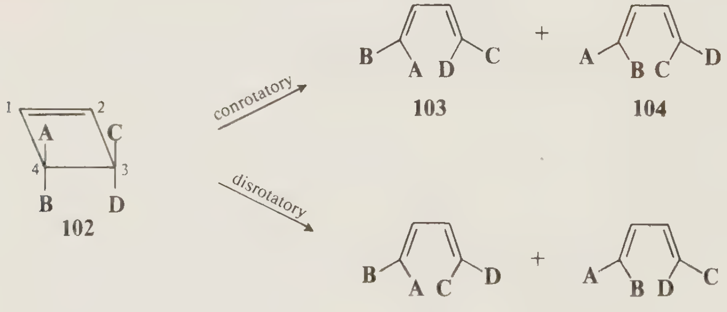


Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals which overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the most general case, there are four possible products which can arise from a given cyclobutene or cyclohexadiene, two from the conrotatory and two from the disrotatory pathway. For example, conrotatory ring opening of **102** gives either **103** or **104**, while disrotatory opening gives either **105** or **106**. The orbital symmetry rules tell us when a given reaction will operate by the conrotatory and when by the disrotatory mode, but they do not say which of the two possible conrotatory or disrotatory pathways will be followed. It is often possible, however, to make such predictions on steric grounds. For example, in the opening of **102** by the disrotatory pathway, **105** arises when groups A and C swing in toward each other (clockwise motion around C-4, counterclockwise around C-3), while **106** is formed when groups B and D swing in, and A and C swing out (clockwise motion around C-3; counterclockwise around C-4). We therefore predict that when A



102 **103** **104** **105** **106**

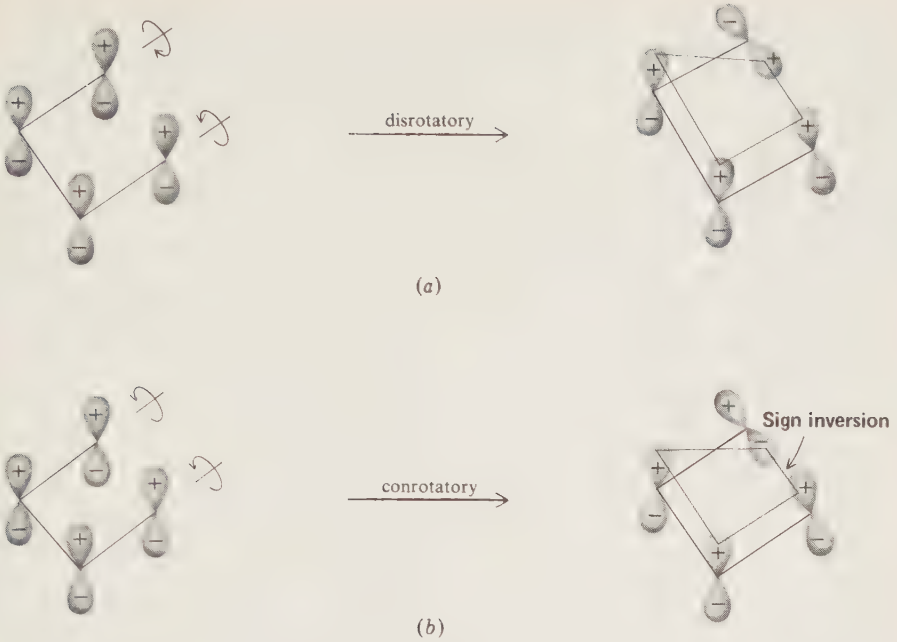


Figure 4 The 1,3-diene-cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversions. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (for example, another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversions, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

and C are larger than B and D, the predominant or exclusive product will be **106,** rather than **105.** Predictions of this kind have largely been borne out.[349]

It is possible to relate the orbital symmetry rules to the Hückel aromaticity rule discussed in Chapter 2. Hückel's rule, which states that a cyclic system of electrons will be aromatic (hence stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle we are not concerned with ground states, but with transition states. In the present method[350] we do not examine the molecular orbitals themselves, but rather the *p* orbitals before they overlap to form the molecular orbitals. Figure 4 shows such a set of *p* orbitals (called a *basis set*) for a 1,3-diene. It is seen that disrotatory ring closing (Figure 4*a*) results in overlap of plus lobes only, while in conrotatory closing (Figure 4*b*) there is one overlap of a plus with a minus lobe. In the first case we have zero sign inversions, while in the second there is one sign inversion. For such pericyclic reactions, if there are *zero or an even number* of sign inversions, we call it a *Hückel system.* If there is an *odd number* of sign inversions, we call it a *Möbius system* (note the similarity to the Möbius strip, which is a mathematical surface, shown in Figure 5). The orbital symmetry rules may then be stated:[350] *A thermal peri-*

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[349] For example, see Baldwin and Krueger, *J. Am. Chem. Soc.* **91,** 6444 (1969); Spangler and Hennis, *J. Chem. Soc., Chem. Commun.* 24 (1972).

[350] Zimmerman, *J. Am. Chem. Soc.* **88,** 1564, 1566 (1966), *Acc. Chem. Res.* **4,** 272–280 (1971); Jefford and Burger, *Chimia* **25,** 297–307 (1971).

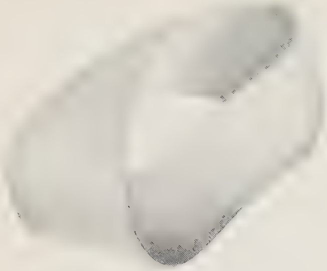
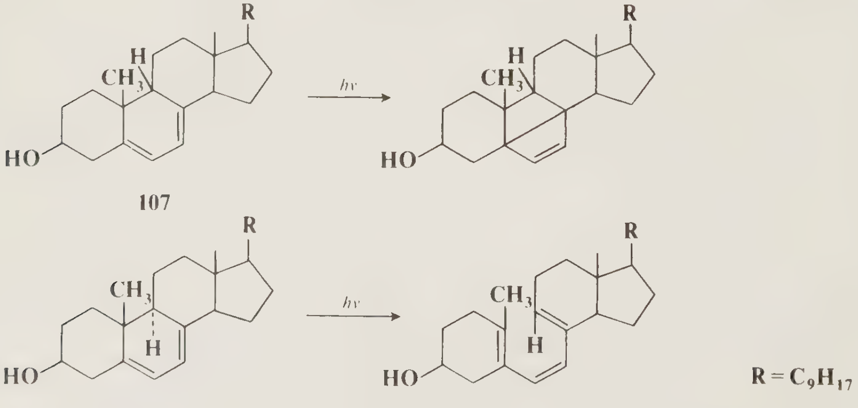


Figure 5 A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

cyclic reaction involving a Hückel system is allowed only if the total number of electrons is $4n + 2$. *A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is* $4n$. For photochemical reactions, these rules are reversed. Thus the thermal cyclobutene-1,3-diene interconversion, which has four electrons, is allowed to proceed only if the transition state has an odd number of inversions (Möbius). As shown in Figure 4, this requires a conrotatory path for this system. In contrast, the photochemical process requires a Hückel system, and hence a disrotatory path. Diagrams similar to those in Figure 4 may be drawn for the cyclohexadiene-1,3,5-triene interconversion. For this case also, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are involved here, the thermal reaction follows the Hückel pathway and the photochemical reaction the Möbius pathway. The Hückel-Möbius approach has the advantage over the correlation diagram approach that it is not necessary to determine the symmetries of the orbitals, which permits it to be applied to transition states with no symmetry (see p. 773).

Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.[351] An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer **107** (or of the other syn isomer, not shown) leads to the corre-



107

108 **109**

$R = C_9H_{17}$

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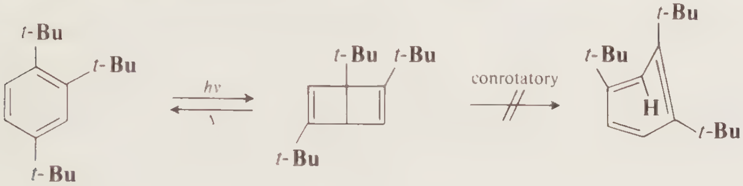
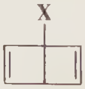
[351] For a discussion of the factors favoring either direction, see Dauben, Kellogg, Seeman, Vietmeyer, and Wendschuh, *Pure Appl. Chem.* **33**, 197–215 (1973).

sponding cyclobutene,[352] while photolysis of the anti isomers (one of them is **108**) gives the ring-opened 1,3,5-triene **109.** This difference in behavior is at first sight remarkable, but is easily explained by the orbital symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **107** were to proceed by this pathway, the product would be the triene **109,** but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **108** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (p. 118) but are very strained. Stable *trans*-cyclohexenes are unknown (p. 147). Thus, **107** and **108** give the products they do owing to a combination of orbital symmetry rules and steric influences. Note that **100** and **101** (p. 1024) can be opened thermally, though high temperatures are required. The orbital symmetry rules require concerted thermal ring opening in these systems to be conrotatory, but this is impossible here for similar reasons. It is possible that a diradical mechanism is operating, though it has been suggested that concerted disrotatory pathways are allowed in these cases.[353]

The 1,3-diene-cyclobutene interconversion can even be applied to benzene rings. For example,[354] photolysis of 1,2,4-tri-*t*-butylbenzene (**110**) gives 1,2,5-tri-*t*-butyl[2.2.0]hexadiene (**111,** a Dewar benzene).[355] The reaction owes its success to the fact that once **111** is formed it cannot, under the conditions used, revert to **110** by either a thermal or a photochemical route. The orbital symmetry rules prohibit thermal conversion of **111** to **110** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **111** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**112**), which is of course too strained to exist. **111** cannot revert to **110** by a photochemical pathway either, because light of the frequency used to excite **110** would not be absorbed by **111.** This is thus another example of a molecule which owes its stability to the orbital symmetry rules (see p. 787). Pyrolysis of **111** does give **110,** probably by a diradical mechanism.[356] Dewar benzenes bearing a chlorine or bromine in the 1 position (**113,** X = Cl or F) are converted to the corresponding benzenes much more rapidly.[357] This has been attributed to stabilization by the electron-withdrawing halogen of the disrotatory transition state.[357]



110 **111** **112**



113

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[352] Dauben and Fonken, *J. Am. Chem. Soc.* **81,** 4060 (1959). This was the first reported example of the conversion of a 1,3-diene to a cyclobutene.

[353] Branton, Frey, Montague, and Stevens, *Trans. Faraday Soc.* **62,** 659 (1966); Frey, Metcalfe, and Brown, *J. Chem. Soc. B* 1586 (1970).

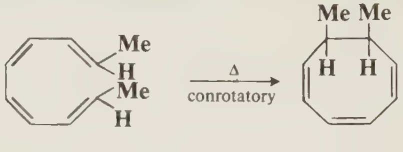
[354] Unsubstituted Dewar benzene has been obtained, along with other photoproducts, by photolysis of benzene: Ward and Wishnok, *J. Am. Chem. Soc.* **90,** 1085 (1968); Bryce-Smith, Gilbert, and Robinson, *Angew. Chem. Int. Ed. Engl.* **10,** 745 (1971) [*Angew. Chem.* **83,** 803]. For other examples, see Arnett and Bollinger, *Tetrahedron Lett.* 3803 (1964); Camaggi, Gozzo, and Cevidalli, *Chem. Commun.* 313 (1966); Haller, *J. Am. Chem. Soc.* **88,** 2070 (1966), *J. Chem. Phys.* **47,** 1117 (1967); Barlow, Haszeldine, and Hubbard, *Chem. Commun.* 202 (1969); Lemal, Staros, and Austel, *J. Am. Chem. Soc.* **91,** 3373 (1969).

[355] van Tamelen and Pappas, *J. Am. Chem. Soc.* **84,** 3789 (1962); Wilzbach and Kaplan, *J. Am. Chem. Soc.* **87,** 4004 (1965); van Tamelen, Pappas, and Kirk, *J. Am. Chem. Soc.* **93,** 6092 (1971); van Tamelen, *Acc. Chem. Res.* **5,** 186–192 (1972). As mentioned on p. 787 (Ref. 704) Dewar benzenes can be photolyzed further to give prismanes.

[356] See for example, Oth, *Recl. Trav. Chim. Pays-Bas* **87,** 1185 (1968); Adam and Chang, *Int. J. Chem. Kinet.* **1,** 487 (1969); Lechtken, Breslow, Schmidt, and Turro, *J. Am. Chem. Soc.* **95,** 3025 (1973).

[357] Breslow, Napierski, and Schmidt, *J. Am. Chem. Soc.* **94,** 5906 (1972).

A number of electrocyclic reactions have been carried out with systems of other sizes, for example, conversion of the 1,3,5,7-octatetraene **114** to the cyclooctatriene **115**.[358] The stereochemistry of these reactions can be predicted in a similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n + 2$ (where n is any integer including zero).

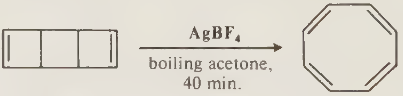


114 **115**

	Thermal reaction	**Photochemical reaction**
$4n$	conrotatory	disrotatory
$4n + 2$	disrotatory	conrotatory

Although the orbital symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (p. 775) that they only say what is allowed and what is forbidden, but the fact that a reaction is allowed does not necessarily mean that that reaction takes place, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.[359]

As was the case for 2 + 2 cycloaddition reactions (**5-52**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[360] An example is the silver ion–catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**116**) to cyclooctatetraene.[360a] This conversion is very slow thermally (that is, without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally. There is evidence that in reactions such as this, the metallic ion coordinates with the π electrons, in effect removing them from the transition state, so that the allowed process is now disrotatory instead of conrotatory.[361]



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The ring opening of cyclopropyl cations (pp. 321, 986) is an electrocyclic reaction and is governed by the orbital symmetry rules.[362] For this case we may invoke the rule that the σ bond opens in such a way that the resulting p orbitals have the symmetry of the highest occupied orbital of the product, in this case an allylic cation. We may recall that an allylic system has three molecular orbitals (p. 34). For the cation, with only two electrons, the highest occupied of these is the one of lowest energy (**A**). Thus, the cyclopropyl cation must undergo a disrotatory

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[358] Marvell and Seubert, *J. Am. Chem. Soc.* **89**, 3377 (1967); Huisgen, Dahmen, and Huber, *J. Am. Chem. Soc.* **89**, 7130 (1967), *Tetrahedron Lett.* 1461 (1969); Dahmen and Huber, *Tetrahedron Lett.* 1465 (1969).

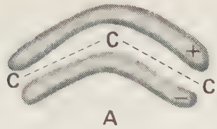
[359] For a discussion, see Baldwin, Andrist, and Pinschmidt, *Acc. Chem. Res.* **5**, 402–406 (1972).

[360] For a review, see Pettit, Sugahara, Wristers, and Merk, *Discuss. Faraday Soc.* **47**, 71–78 (1969). See also Chapter 15, Ref. 694.

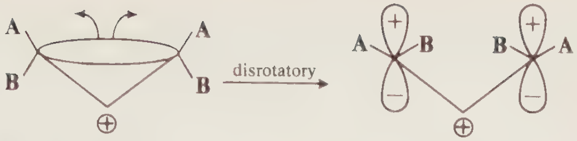
[360a] Merk and Pettit, *J. Am. Chem. Soc.* **89**, 4788 (1967).

[361] Slegeir, Case, McKennis, and Pettit, *J. Am. Chem. Soc.* **96**, 287 (1974).

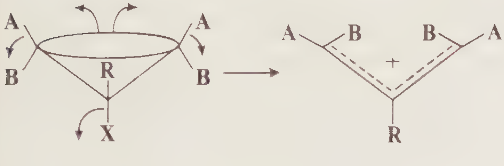
[362] For discussions, see DePuy, *Acc. Chem. Res.* **1**, 33–41 (1968); Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **7**, 588–598 (1968) [*Angew. Chem.* **80**, 603–613].



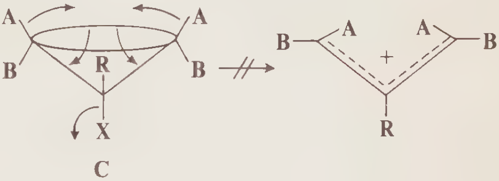
A



ring opening in order to maintain the symmetry. (Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory, since in this case it is the next orbital of the allylic system which is the highest occupied, and this has the opposite symmetry.[363]) However, it is very difficult (perhaps impossible) to generate a free cyclopropyl cation (p. 250), and it is likely that in most (perhaps all) cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This of course means that the σ bond provides anchimeric assistance to the removal of the leaving group (an SN2-type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital symmetry rules require that the ring opening be disrotatory but, as we have seen, there are two disrotatory pathways, and the rules do not tell us which is preferred. But the fact that the σ orbital provides assistance from the back side means that the two substituents which are trans to the leaving group must move *outward* and not inward.[364] Thus, the disrotatory pathway which is followed is the one shown in **B**, and not the one shown in **C**, because

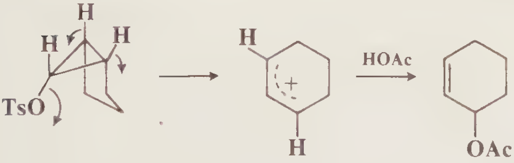


B



C

the former puts the electrons of the σ bond on the side opposite that of the leaving group.[365] Strong confirmation of this picture[366] comes from acetolysis of *endo*- (**117**) and *exo*-bicyclo[3,1,0]-hexyl-6-tosylate (**118**). The groups trans to the tosylate must move outward. For **117** this means



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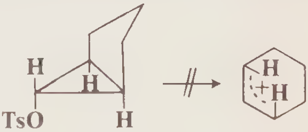

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[363] For evidence that this is so, see Newcomb and Ford, *J. Am. Chem. Soc.* **96,** 2968 (1974).

[364] This statement was first proposed by DePuy, Schnack, Hausser, and Wiedemann, *J. Am. Chem. Soc.* **87,** 4006 (1965).

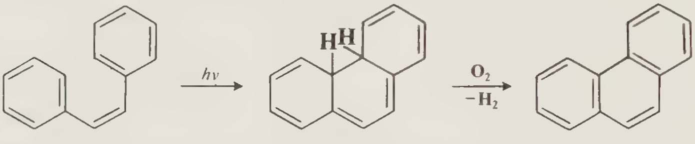
[365] It has been suggested that the pathway shown in C is possible in certain cases: Hausser and Grubber, *J. Org. Chem.* **37,** 2648 (1972); Hausser and Uchic, *J. Org. Chem.* **37,** 4087 (1972).

[366] There is much other evidence. For example, see Jefford and Medary, *Tetrahedron Lett.* 2069 (1966); Jefford, Yen, and Medary, *Tetrahedron Lett.* 6317 (1966); Jefford and Wojnarowski, *Tetrahedron Lett.* 199 (1968); Jefford and Hill, *Tetrahedron Lett.* 1957 (1969); Schleyer, Van Dine, Schöllkopf, and Paust, *J. Am. Chem. Soc.* **88,** 2868 (1966); Schleyer, Sliwinski, Van Dine, Schöllkopf, Paust, and Fellenberger, *J. Am. Chem. Soc.* **94,** 125 (1972); Sliwinski, Su, and Schleyer, *J. Am. Chem. Soc.* **94,** 133 (1972); Sandler, *J. Org. Chem.* **32,** 3876 (1967); Ghosez, Laroche, and Slinckx, *Tetrahedron Lett.* 2767 (1967); Ghosez, Slinckx, Glineur, Hoet, and Laroche, *Tetrahedron Lett.* 2773 (1967); Parham and Sperley, *J. Org. Chem.* **32,** 924, 926 (1967); Parham and Yong, *J. Org. Chem.* **33,** 3947 (1968); Baird and Reese, *Tetrahedron Lett.* 2117 (1969); Baird, Lindsay, and Reese, *J. Chem. Soc. C* 1173 (1969); Reese and Shaw, *J. Am. Chem. Soc.* **92,** 2566 (1970).

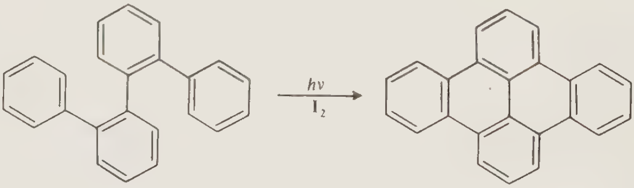
that the two hydrogens can go outside the framework of the six-membered ring, but for **118** they are forced to go inside. Consequently, it is not surprising that the rate ratio for solvolysis of **117**/**118** was found to be greater than 2.5 × 10^6, and that at 150°C **118** did not solvolyze at all.[367] This evidence is kinetic. Unlike the cases of the cyclobutene-1,3-diene and cyclohexadiene-1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in super acids, where it is possible to keep the cations intact and to study their structures by nmr, that in all cases studied the cation which is predicted by these rules is in fact formed.[368] In another product study, it was shown that when the nucleophile is the same as the leaving group (isomerization of cyclopropyl chlorides to allyl chlorides), it reenters from the same side from which it departed.[369]

OS **V,** 235, 277, 467; **50,** 24, 36; **55,** 15, 86.

8-33 Conversion of Stilbenes to Phenanthrenes



Stilbenes can be converted to phenanthrenes by irradiation with uv light in the presence of an oxidizing agent such as dissolved molecular oxygen, $FeCl_3$, or iodine.[370] The reaction is a photochemically allowed conrotatory[371] conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated in one case.[371a] The use of substrates containing hetero atoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems. The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the cis isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, e.g.,[372]



though not all such systems give the reaction.[373]

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[367] Schöllkopf, Fellenberger, Patsch, Schleyer, Su, and Van Dine, *Tetrahedron Lett.* 3639 (1967).

[368] Schleyer, Su, Saunders, and Rosenfeld, *J. Am. Chem. Soc.* **91,** 5174 (1969).

[369] Fleming and Thomas, *Tetrahedron* **28,** 4989 (1972).

[370] For reviews, see Bryce-Smith and Gilbert, *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **3,** 121–131 (1973); Blackburn and Timmons, *Q. Rev., Chem. Soc.* **23,** 482–503 (1969); Stermitz, *Org. Photochem.* **1,** 247–282 (1967).

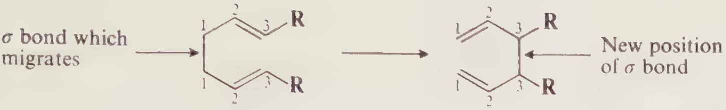
[371] Cuppen and Laarhoven, *J. Am. Chem. Soc.* **94,** 5914 (1972).

[371a] Doyle, Benson, and Filipescu, *J. Am. Chem. Soc.* **98,** 3262 (1976).

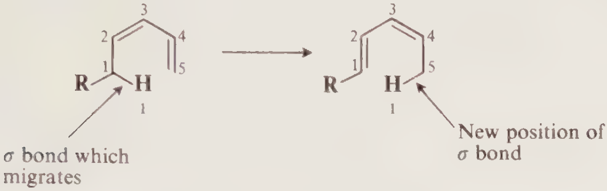
[372] Sato, Shimada, and Hata, *Bull. Chem. Soc. Jpn.* **44,** 2484 (1971).

[373] For a discussion, and lists of photocyclizing and nonphotocyclizing compounds, see Laarhoven, Cuppen, and Nivard, *Recl. Trav. Chim. Pays-Bas* **87,** 687 (1968).

B. Sigmatropic Rearrangements. A sigmatropic rearrangement is defined[374] as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



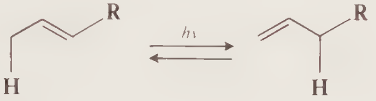
Reaction **8-37**
A [3,3] sigmatropic rearrangement



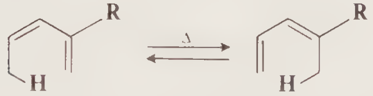
Reaction **8-34**
A [1,5] sigmatropic rearrangement

The *order* of a sigmatropic rearrangement is expressed by two numbers set in brackets: [*i,j*]. These numbers can be determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has migrated from C-1 to C-3, so the order is [3,3]. In the second example the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

8-34 [1,*j*] Sigmatropic Migrations of Hydrogen



[1,3]



[1,5]

Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,[375] though the reaction is subject to geometrical conditions. Pericyclic mechanisms are involved, and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by means of which any sigmatropic rearrangement can take place, which we illustrate for the case of a [1,5] sigmatropic rearrangement,[376] starting with a substrate of the form **119**, where the migration origin is an asymmetric carbon atom, and U ≠ V. In one of the two pathways, the hydrogen moves along the top or

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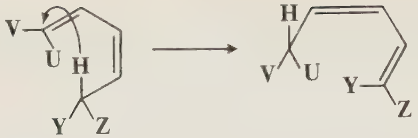
[374] Woodward and Hoffmann, Ref. 278; p. 114.

[375] For reviews, see Spangler, *Chem. Rev.* **76**, 187–217 (1976); DeWolfe, in Bamford and Tipper, Ref. 341, pp. 474–480; Woodward and Hoffmann, Ref. 278, pp. 114–140; Hansen and Schmid, *Chimia* **24**, 89–99 (1970); Roth, *Chimia* **20**, 229–236 (1966).

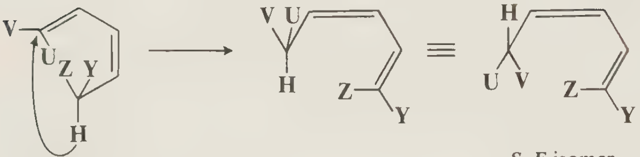
[376] Note that a [1,5] sigmatropic rearrangement of hydrogen is also an internal ene synthesis (reaction **5-18**).



119

R, *Z* isomer

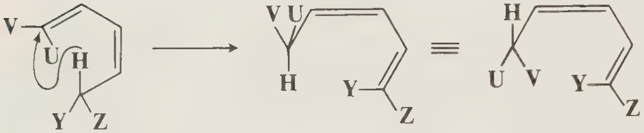
suprafacial



119

S, *E* isomer

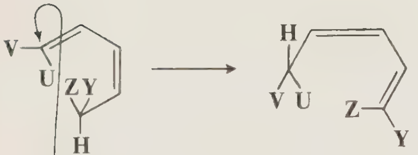
suprafacial



119

S, *Z* isomer

antarafacial



R, *E* isomer

119

antarafacial

bottom face of the π system. This is called *suprafacial migration.* In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **119** can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the *R,Z* isomer, or it can rotate 180° and move across the bottom of the π system to give the *S,E* isomer.[377] The antarafacial migration can similarly lead to two diastereomers, in this case the *S,Z* and *R,E* isomers.

In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital symmetry rules; the other is forbidden. To analyze this situation we cannot use correlation diagrams, because there is no element of symmetry present throughout the course of the reaction (a plane of symmetry may be present in the transition state, but not before or after). Therefore we will use a modified frontier orbital approach.[378] We will imagine that in the transition state the migrating H atom breaks away from the rest of the system, which we may treat as if it were a free radical. Note that this is not what actually takes place; we merely imagine it in order to be able to analyze the process. In a [1,3] sigmatropic rearrangement the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (p. 34) has three π orbitals, but the only one which concerns us here is the highest occupied orbital which, in a thermal

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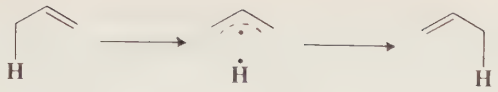
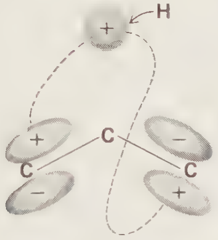
[377] Since we are using the arbitrary designations U, V, Y, and Z, we have been arbitrary in which isomer to call *R,Z* and which to call *S,E*.

[378] See Woodward and Hoffmann, Ref. 278, pp. 114–140.

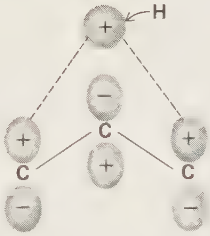


Imaginary
transition state
for a [1,3]
sigmatropic
rearrangement

rearrangement, is **D**. The electron of the hydrogen atom is of course in a 1*s* orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is that *the H must move from a plus to a plus or from a minus to a minus lobe, of the highest occupied molecular orbital; it cannot move to a lobe of opposite sign.*[379] Obviously, the only way this can happen in a thermal [1,3] sigmatropic rearrangement is if the migration is antarafacial. Consequently, the rule predicts that antarafacial thermal [1,3] sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the highest occupied π orbital; the suprafacial pathway is now allowed, and the antarafacial pathway forbidden.



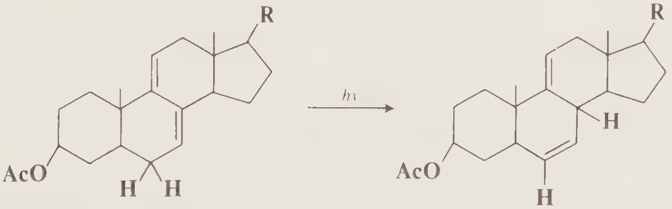
D



E

A similar analysis of [1,5] sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered *j*, we may say that [1,*j*] suprafacial migrations are allowed thermally when *j* is of the form $4n + 1$, and photochemically when *j* has the form $4n - 1$; the opposite is true for antarafacial migrations.

The actual reported results bear out this analysis. Thus a thermal [1,3] migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3] sigmatropic migrations of hydrogen are unknown. On the other hand, the photochemical pathway allows suprafacial [1,3] shifts, and a few such reactions are known, an example being[380]



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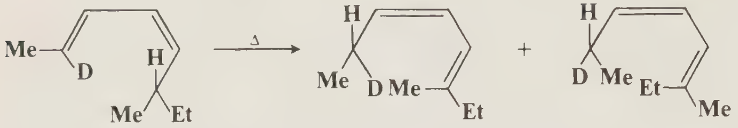
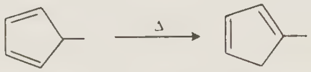
[379] This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.

[380] Dauben and Wipke, *Pure Appl. Chem.* **9**, 539–553 (1964), p. 546. For another example, see Kropp, Fravel, and Fields, *J. Am. Chem. Soc.* **98**, 840 (1976).

The situation is reversed for [1,5] hydrogen shifts. In this case the thermal rearrangements, being suprafacial, are quite common, while photochemical rearrangements are rare.[381] Examples of the thermal reaction are



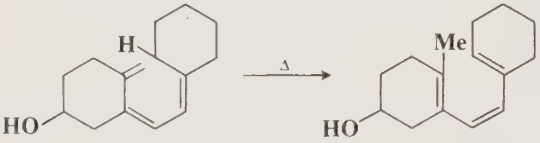
Ref. 382

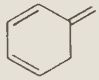


Ref. 383

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed.

With respect to [1,7] hydrogen shifts, the orbital symmetry rules predict that the thermal reaction must be antarafacial. Unlike the case of [1,3] shifts, the transition state is not too greatly strained, and such rearrangements have been reported, e.g.,[384]



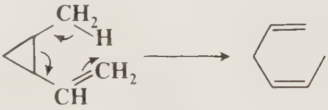


120

Photochemical [1,7] shifts are suprafacial, and not surprisingly, many of these have been observed.[385]

The orbital symmetry rules also help us to explain, as on pp. 787 and 1033, the unexpected stability of certain compounds. Thus, **120** could, by a thermal [1,3] sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet **120** has been prepared and is stable at dry ice temperature and in dilute solutions.[386]

Analogs of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, for example:[387]



A homodienyl [1,5] shift

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[381] For examples of photochemical [1,5] antarafacial reactions, see Kiefer and Tanna, *J. Am. Chem. Soc.* **91,** 4478 (1969); Kiefer and Fukunaga, *Tetrahedron Lett.* 993 (1969); Dauben, Poulter, and Suter, *J. Am. Chem. Soc.* **92,** 7408 (1970).

[382] Roth, König, and Stein, *Chem. Ber.* **103,** 426 (1970).

[383] McLean and Haynes, *Tetrahedron* **21,** 2329 (1965).

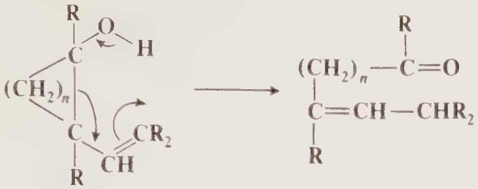
[384] Schlatmann, Pot, and Havinga, *Recl. Trav. Chim. Pays-Bas* **83,** 1173 (1964).

[385] See Murray and Kaplan, *J. Am. Chem. Soc.* **88,** 3527 (1966); ter Borg and Kloosterziel, *Recl. Trav. Chim. Pays-Bas* **88,** 266 (1969); Tezuka, Kimura, Sato, and Mukai, *Bull. Chem. Soc. Jpn.* **43,** 1120 (1970).

[386] Bailey and Baylouny, *J. Org. Chem.* **27,** 3476 (1962).

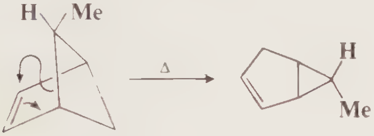
[387] Ellis and Frey, *Proc. Chem. Soc.* 221 (1964); Frey and Solly, *Int. J. Chem. Kinet,* **1,** 473 (1969); Roth and König, *Justus Liebigs Ann. Chem.* **688,** 28 (1965); Ohloff, *Tetrahedron Lett.* 3795 (1965); Jorgenson and Thacher, *Tetrahedron Lett.* 4651 (1969); Corey, Yamamoto, Herron, and Achiwa, *J. Am. Chem. Soc.* **92,** 6635 (1970). See also Crandall and Watkins, *Tetrahedron Lett.* 1717 (1967).

The reverse reaction has also been reported.[388] 2-Vinylcycloalkanols[389] undergo an analogous reaction, as do cyclopropyl ketones (see p. 1052 for this reaction).

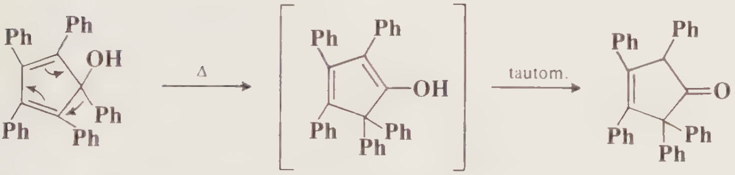


Simple nucleophilic, electrophilic, and free-radical 1,2 shifts may also be regarded as sigmatropic rearrangements (in this case [1,2] rearrangements). We have already (p. 962) applied similar principles to such rearrangements to show that nucleophilic 1,2 shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair.

8-35 [1,*j*] Sigmatropic Migrations of Carbon



[1,3] migration of alkyl[390]



[1,5] migration of phenyl[391]

Sigmatropic migrations of alkyl or aryl groups[391a] are less common than the corresponding hydrogen migrations.[392] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1*s* orbital which has only one lobe, a carbon free radical has its odd electron in a *p* orbital which has *two lobes of opposite sign*. Therefore, if we draw the imaginary transition states for this case (see p. 1039), we see that in a thermal suprafacial [1,5] process (**F**), symmetry can be conserved only if the migrating carbon moves in such a way that the lobe which was originally attached to the π system remains attached to the π system. This can

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[388] Roth and König, *Justus Liebigs Ann. Chem.* **688,** 28 (1965). Also see Grimme, *Chem. Ber.* **98,** 756 (1965).

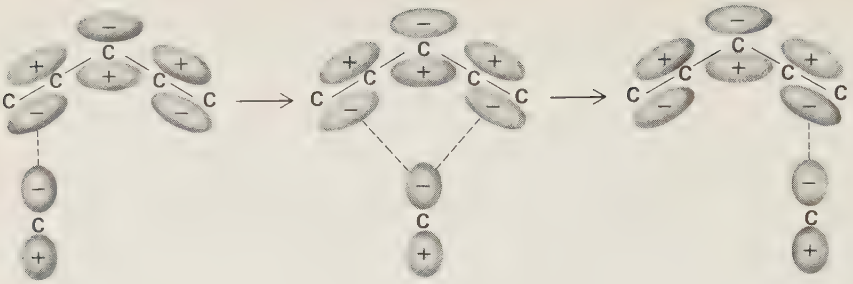
[389] Arnold and Smolinsky, *J. Am. Chem. Soc.* **82,** 4918 (1960); Leriverend and Conia, *Tetrahedron Lett.* 2681 (1969); Conia and Barnier, *Tetrahedron Lett.* 2679 (1969).

[390] Roth and Friedrich, *Tetrahedron Lett.* 2607 (1969).

[391] Youssef and Ogliaruso, *J. Org. Chem.* **37,** 2601 (1972).

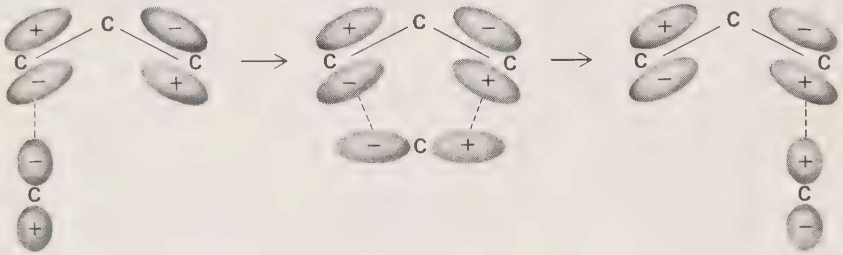
[391a] For a review, see Spangler, Ref. 375.

[392] It has been shown that methyl and phenyl have lower migratory aptitudes than hydrogen in thermal sigmatropic rearrangements: Shen, McEwen, and Wolf, *Tetrahedron Lett.* 827 (1969); Miller, Greisinger, and Boyer, *J. Am. Chem. Soc.* **91,** 1578 (1969).



F

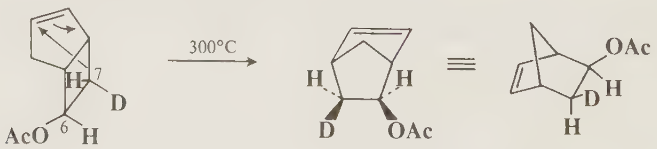
happen only if configuration is *retained within the migrating group.* On the other hand, a thermal suprafacial [1,3] migration (**G**) *can* take place if the migrating carbon switches lobes. If the migrating



G

carbon was originally bonded by its minus lobe, it must now use its plus lobe to form the new C—C bond. Thus configuration in the migrating group will be *inverted.* From these considerations we predict that suprafacial [1,j] sigmatropic rearrangements in which carbon is the migrating group are always allowed, both thermally and photochemically, but that thermal [1,3] migrations will proceed with inversion, and thermal [1,5] migrations with retention of configuration within the migrating group. More generally, we may say that suprafacial [1,j] migrations of carbon in systems where $j = 4n - 1$ proceed with inversion thermally and retention photochemically, while systems where $j = 4n + 1$ show the opposite behavior. Where antarafacial migrations take place, all these predictions are of course reversed.

The first laboratory test of these predictions was the pyrolysis of deuterated *endo*-bicyclo[3.2.0]-hept-2-en-6-yl acetate (**121**), which gave the *exo*-deuterio-*exo*-norbornyl acetate **122**.[393] Thus, as



121 **122**

predicted by the orbital symmetry rules, this thermal suprafacial [1,3] sigmatropic reaction took place with complete inversion at C-7. Similar results have been obtained in a number of other cases.[394] However, because rotation of the C-7 carbon is required to be clockwise, the pathway leading to inversion can be blocked by the introduction into **121** of an endo methyl group at C-7, in which case the reaction takes place with predominant retention.[395] It has been suggested that an orbital-symmetry-forbidden concerted reaction takes place in these cases.[396] Photochemical suprafacial [1,3] migrations of carbon have been shown to proceed with retention, as predicted.[397]

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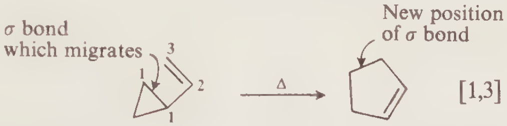
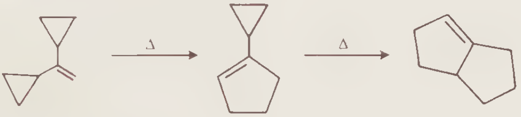
[393] Berson and Nelson, *J. Am. Chem. Soc.* **89**, 5503 (1967); Berson, *Acc. Chem. Res.* **1**, 152–160 (1968).

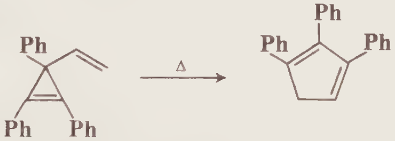
[1,3] antarafacial migrations of carbon are predicted by the orbital symmetry rules to take place with retention at the migrating carbon if thermal, and inversion if photochemical. Despite the seeming geometrical barrier to such reactions, instances of both these processes have been reported.[398] The prediction that thermal suprafacial [1,5] migrations of carbon take place with retention has also been confirmed.[399]

8-36 Conversion of Vinylcyclopropanes to Cyclopentenes

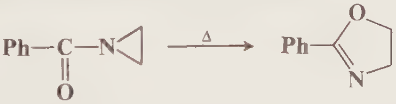


The thermal expansion of a vinylcyclopropane to a cyclopentene ring[400] is a special case of a [1,3] sigmatropic migration of carbon, though it can also be considered an internal $[_\pi2 + {}_\sigma2]$ cycloaddition reaction (see reaction **5-52**). The reaction has been carried out on many vinylcyclopropanes bearing various substituents in the ring or on the vinyl group and has been extended to 1,1-dicyclopropylethene[401] and to vinylcyclopropenes.[402]





Various heterocyclic analogs are also known, for example:[403]



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[394] See Ref. 390; Berson, *Acc. Chem. Res.* **5**, 406–414 (1972); Bampfield, Brook, and Hunt, *J. Chem. Soc., Chem. Commun.* 146 (1976); Franzus, Scheinbaum, Waters, and Bowlin, *J. Am. Chem. Soc.* **98**, 1241 (1976).

[395] Berson and Nelson, *J. Am. Chem. Soc.* **92**, 1096 (1970); Berson and Holder, *J. Am. Chem. Soc.* **95**, 2037 (1973); Berson, Ref. 394. See also Cookson and Kemp, *Chem. Commun.* 385 (1971); Krow and Reilly, *J. Am. Chem. Soc.* **97**, 3837 (1975).

[396] Berson, Ref. 394.

[397] Cookson, Hudec, and Sharma, *Chem. Commun.* 107, 108 (1971).

[398] Baldwin and Fleming, *J. Am. Chem. Soc.* **94**, 2140 (1972); Zimmerman and Epling, *J. Am. Chem. Soc.* **94**, 3647 (1972). See also Berson, Miyashi, and Jones, *J. Am. Chem. Soc.* **96**, 3468 (1974).

[399] Boersma, de Haan, Kloosterziel, and van de Ven, *Chem. Commun.* 1168 (1970).

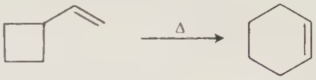
[400] For reviews, see DeWolfe, in Bamford and Tipper, Ref. 341, pp. 470–474; Gutsche and Redmore, Ref. 101, pp. 163–170; Frey, *Adv. Phys. Org. Chem.* **4**, 147–193 (1966), pp. 155–163, 175–176.

[401] Ketley, *Tetrahedron Lett.* 1687 (1964); Branton and Frey, *J. Chem. Soc. A* 1342 (1966).

[402] Small and Breslow, cited in Breslow, in Mayo, Ref. 1, vol. 1, p. 236.

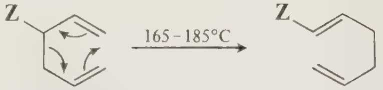
[403] For reviews of ring expansions of aziridines, see Heine, *Mech. Mol. Migr.* **3**, 145–176 (1971); Dermer and Ham, "Ethylenimine and Other Aziridines," pp. 282–290, Academic Press, Inc., New York, 1969.

Vinylcyclobutenes can be similarly converted to cyclohexenes,[404] but larger ring compounds do not generally give the reaction.[405]



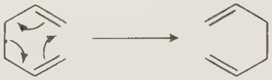
The mechanisms of these ring expansions are not certain. Both concerted[406] and diradical[407] pathways have been proposed, and it is possible that both pathways operate, in different systems.

8-37 The Cope Rearrangement

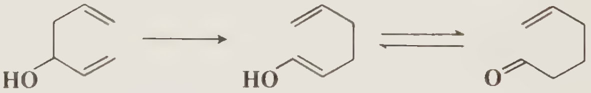


Z = **Ph**, **RCO**, etc.

When 1,5-dienes are heated, they isomerize, in a [3,3] sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, **7-8**).[408] When the diene is symmetrical about the 3,4 bond, we have the unusual situation where a reaction gives a product which is identical with the starting material:[409]



Therefore, a Cope rearrangement can be detected only when the diene is not symmetrical about this bond. Any 1,5-diene gives the rearrangement; for example, 3-methyl-1,5-hexadiene heated to 300°C gives 1,5-heptadiene.[410] However, the reaction takes place more easily (lower temperature required) when there is a group on the 3- or 4-carbon with which the new double bond can conjugate. The reaction is obviously reversible and produces an equilibrium mixture of the two 1,5-dienes, which is richer in the thermodynamically more stable isomer. However, the reaction cannot be reversed for 3-hydroxy-1,5-dienes, because the product tautomerizes to the ketone or aldehyde:



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[404] Overberger and Borchert, *J. Am. Chem. Soc.* **82,** 1007 (1960); Vogel, Palm, and Ott, cited in Vogel, *Angew. Chem.* **72,** 4–26 (1960), p. 21.

[405] For an exception, see Thies, *J. Am. Chem. Soc.* **94,** 7074 (1972).

[406] For evidence favoring the diradical mechanism, see Willcott and Cargle, *J. Am. Chem. Soc.* **89,** 723 (1967); Doering and Schmidt, *Tetrahedron* **27,** 2005 (1971); Roth and Schmidt, *Tetrahedron Lett.* 3639 (1971); Simpson and Richey, *Tetrahedron Lett.* 2545 (1973); Gilbert and Higley, *Tetrahedron Lett.* 2075 (1973); Caramella, Huisgen, and Schmolke, *J. Am. Chem. Soc.* **96,** 2997, 2999 (1974); Mazzocchi and Tamburin, *J. Am. Chem. Soc.* **97,** 555 (1975). A "continuous diradical transition state" has also been proposed: Doering and Sachdev, *J. Am. Chem. Soc.* **96,** 1168 (1974), **97,** 5512 (1975).

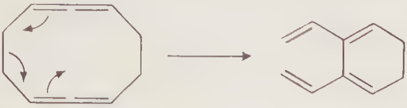
[407] For evidence favoring the concerted mechanism, see Shields, Billups, and Lepley, *J. Am. Chem. Soc.* **90,** 4749 (1968); Berson and Dervan, *J. Am. Chem. Soc.* **95,** 267, 269 (1973); Billups, Leavell, Lewis, and Vanderpool, *J. Am. Chem. Soc.* **95,** 8096 (1973).

[408] For reviews, see Rhoads and Raulins, *Org. React.* **22,** 1–252 (1975); Smith and Kelly, *Prog. Phys. Org. Chem.* **8,** 75–234 (1971), pp. 153–201; DeWolfe, in Bamford and Tipper, Ref. 341, pp. 455–461; Vogel, *Angew. Chem. Int. Ed. Engl.* **2,** 1–11 (1963) [*Angew. Chem.* **74,** 829–839 (1962)]: Doering and Roth, *Angew. Chem. Int. Ed. Engl.* **2,** 115–122 (1963) [*Angew. Chem.* **75,** 27–35]; Rhoads, in Mayo, Ref. 1, vol. 1, pp. 684–706.

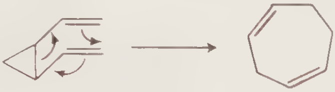
[409] Note that the same holds true for [1,*j*] sigmatropic reactions of symmetrical substrates (reactions **8-34, 8-35**).

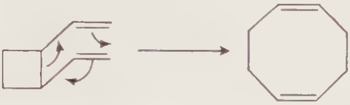
[410] Levy and Cope, *J. Am. Chem. Soc.* **66,** 1684 (1944).

This has been called the *oxy-Cope rearrangement*.[411] The 1,5-diene system may be inside a ring, or it may be part of an allenic system (this example illustrates both of these situations):[412]

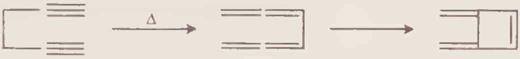


but the reaction does not take place when one of the double bonds is part of an aromatic system, e.g., 4-phenyl-1-butene. When the two double bonds are in vinyl groups attached to adjacent ring positions, then the product is a ring which is four carbons larger. This has been applied to divinylcyclopropanes and cyclobutanes:[413]





Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated at room temperature,[414] though exceptions are known.[415] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes.[416] A rate-determining Cope rearrangement is



followed by a very rapid electrocyclic (**8-32**) reaction.

The interconversion of 1,3,5-trienes and cyclohexadienes (in reaction **8-32**) is very similar to the Cope rearrangement, though in the case of reaction **8-32** the 3,4 bond goes from a double bond to a single bond rather than from a single bond to no bond.

As we have indicated with our arrows, the mechanism of the Cope rearrangement is a simple six-centered pericyclic process. Since the mechanism is so simple, it has been possible to study some rather subtle points, among them the question of whether the six-membered transition state is in the boat or the chair form. For the case of 3,4-dimethyl-1,5-hexadiene it was demonstrated conclusively that the transition state is in the chair form. This was shown by the stereospecific nature of the reaction: The meso isomer gave the cis-trans product, while the *dl* compound gave the trans-trans diene.[417] Now if the transition state is in the chair form (taking the meso isomer, for example), one methyl must be "axial" and the other "equatorial" and the product must be the cis-trans olefin:

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[411] Berson and Jones, *J. Am. Chem. Soc.* **86,** 5017, 5019 (1964); Viola and Levasseur, *J. Am. Chem. Soc.* **87,** 1150 (1965); Viola, Iorio, Chen, Glover, Nayak, and Kocienski, *J. Am. Chem. Soc.* **89,** 3462 (1967); Berson and Walsh, *J. Am. Chem. Soc.* **90,** 4729 (1968); Viola, Padilla, Lennox, Hecht, and Proverb, *J. Chem. Soc., Chem. Commun.* 491 (1974); For a review, see Marvell and Whalley, in Patai, "The Chemistry of the Hydroxyl Group," pt. 2, pp. 738–743, Interscience Publishers, New York, 1971.

[412] Harris, *Tetrahedron Lett.* 1359 (1965).

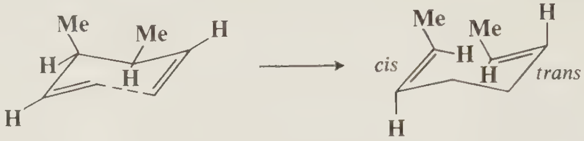
[413] Vogel, Ott, and Gajek, *Justus Liebigs Ann. Chem.* **644,** 172 (1961).

[414] Unsubstituted *cis*-1,2-divinylcyclopropane is fairly stable at −20°C: Brown, Golding, and Stofko, *J. Chem. Soc., Chem. Commun.* 319 (1973); Schneider and Rebell, *J. Chem. Soc., Chem. Commun.* 283 (1975).

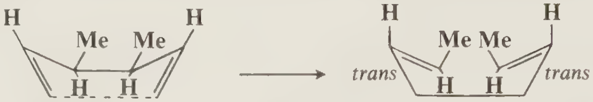
[415] See for example, Brown, *Chem. Commun.* 226 (1965); Schönleber, *Chem. Ber.* **102,** 1789 (1969); Bolesov, Ii-hsein, and Levina, *J. Org. Chem. USSR* **6,** 1791 (1970); Baldwin and Ullenius, *J. Am. Chem. Soc.* **96,** 1542 (1974).

[416] For a review, see Huntsman, *Intra-Sci. Chem. Rep.* **6,** 151–159 (1972).

[417] Doering and Roth, *Tetrahedron* **18,** 67 (1962). See also Hill and Gilman, *Chem. Commun.* 619 (1967); Goldstein and DeCamp, *J. Am. Chem. Soc.* **96,** 7356 (1974); Hansen and Schmid, *Tetrahedron* **30,** 1959 (1974).

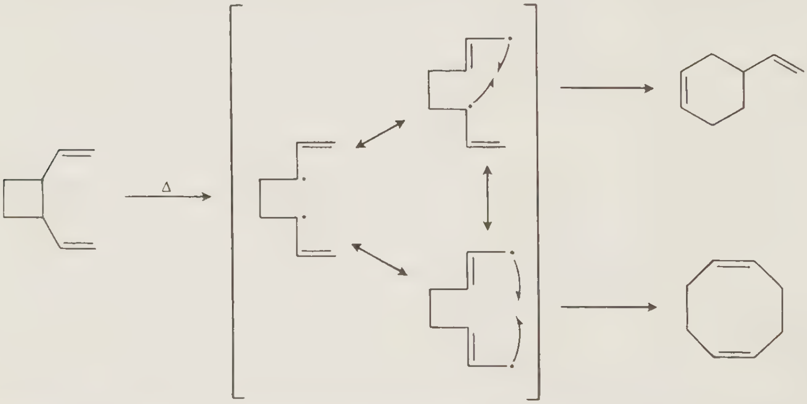


There are two possible boat forms for the transition state of the meso isomer. One of these leads to a trans-trans product:



and the other to a cis-cis olefin. For the *dl* pair the predictions are just the opposite: There is just one boat form, and it leads to the cis-trans olefin, while one chair form ("diaxial" methyls) leads to the cis-cis product and the other ("diequatorial" methyls) predicts the trans-trans product. Thus the nature of the products obtained demonstrates that the transition state is a chair and not a boat.[418] However, 3,4-dimethyl-1,5-hexadiene is free to assume either the chair or boat (it prefers the chair), but other compounds are not so free. Thus 1,2-divinylcyclopropane (p. 1045) can react *only* in the boat form, demonstrating that such reactions are not impossible.

Not all Cope rearrangements proceed by the cyclic six-centered mechanism. Thus *cis*-1,2-divinylcyclobutane (p. 1045) rearranges smoothly to 1,5-cyclooctadiene, since the geometry is favorable. The trans isomer also gives this product, but the main product is 4-vinylcyclohexene (resulting from reaction **8-36**). This reaction can be rationalized as proceeding by a diradical mechanism,[419] though it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.[420]



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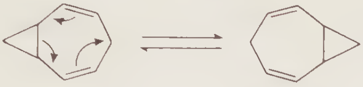
[418] Preference for the chair transition state is a consequence of orbital symmetry relationships: Hoffmann and Woodward, *J. Am. Chem. Soc.* **87**, 4389 (1965); Fukui and Fujimoto, *Tetrahedron Lett.* 251 (1966).

[419] Hammond and De Boer, *J. Am. Chem. Soc.* **86**, 899 (1964); Trecker and Henry, *J. Am. Chem. Soc.* **86**, 902 (1964). Also see Gibson and Pettit, *J. Am. Chem. Soc.* **87**, 2620 (1965); Berson and Dervan, Ref. 407; Dolbier and Mancini, *Tetrahedron Lett.* 2141 (1975).

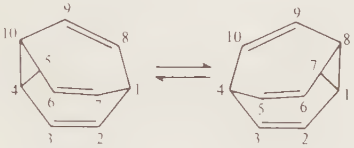
[420] See for example, Berson and Dervan, *J. Am. Chem. Soc.* **94**, 8949 (1972). For a similar result in the 1,2-divinylcyclopropane series, see Baldwin and Ullenius, Ref. 415.

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[421] In this pathway, the 1,6 bond is formed before the 3,4 bond breaks.

It was pointed out earlier that a Cope rearrangement of 1,5-hexadiene gives 1,5-hexadiene. This type of rearrangement, in which the product is equivalent to the starting compound, is called a *degenerate Cope rearrangement*. Another molecule which undergoes a degenerate Cope rearrangement is bicyclo[5.1.0]octadiene (**123**).[422] At room temperature the nmr spectrum of this compound is in accord with the structure shown. At 180°C it can be converted by a Cope reaction to a compound equivalent to itself. The interesting thing is that at 180°C the nmr spectrum shows that what exists is an equilibrium mixture of the two structures. That is, at this temperature the molecule rapidly (faster than 10^3 times per second) changes back and forth between the two structures. This is called *valence tautomerism* and is quite distinct from resonance, even though only electrons shift.[423] The positions of the nuclei are not the same in the two structures. Molecules like **123** which exhibit valence tautomerism (in this case at 180°C) are said to have *fluxional* structures. It may be recalled that *cis*-1,2-divinylcyclopropane does not exist at room temperature because it rapidly rearranges to 1,4-cycloheptadiene (p. 1045), but in **123** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds in which this situation holds are also known. Of these, *bullvalene* (**124**) is especially interesting. The Cope rearrangement shown changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7.



123 **123**



124

Any of these could then undergo several Cope rearrangements. In all there are 10!/3, or more than 1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons which are adjacent. Since each of these tautomers is equivalent to all the others, this has been called an infinitely degenerate Cope rearrangement. Bullvalene has been synthesized and its proton nmr spectrum determined.[424] At −25°C there are two peaks with an area ratio of 6 : 4. This is in accord with a single nontautomeric structure. The six are the vinyl protons and the four are the allylic ones. But at 100°C the compound shows only one nmr peak, indicating that we have here a truly unique situation where the compound rapidly interchanges its structure among 1.2 million equivalent forms.[425]

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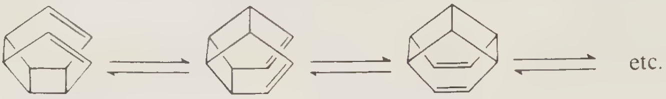
[421] Doering, Toscano, and Beasley, *Tetrahedron* **27**, 5299 (1971); Dewar and Wade, *J. Am. Chem. Soc.* **95**, 290 (1973); Gajewski, Hoffman, and Shih, *J. Am. Chem. Soc.* **96**, 3705 (1974).

[422] Doering and Roth, *Tetrahedron* **19**, 715 (1963).

[423] For reviews of valence tautomerizations, see Decock-Le Révérend and Goudmand, *Bull. Soc. Chim. Fr.* 389–407 (1973); Gajewski, *Mech. Mol. Migr.* **4**, 1–53 (1971), pp. 32–49; Paquette, *Angew. Chem. Int. Ed. Engl.* **10**, 11–20 (1971) [*Angew. Chem.* **83**, 11–20]; Domareva-Mandel'shtam and D'yakonov, *Russ. Chem. Rev.* **35**, 559–568 (1966); Schröder, Oth, and Merényi, *Angew. Chem. Int. Ed. Engl.* **4**, 752–761 (1965) [*Angew. Chem.* **77**, 774–784].

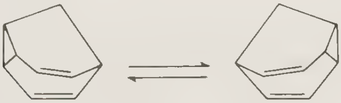
[424] Schröder, *Angew. Chem. Int. Ed. Engl.* **2**, 481 (1963) [*Angew. Chem.* **75**, 722], *Chem. Ber.* **97**, 3140 (1964); Merényi, Oth, and Schröder, *Chem. Ber.* **97**, 3150 (1964). See also Doering et al., Ref. 428. For a review of bullvalenes, see Schröder and Oth, *Angew. Chem. Int. Ed. Engl.* **6**, 414–423 (1967) [*Angew. Chem.* **79**, 458–467].

The ^{13}C nmr spectrum of bullvalene also shows only one peak at 100°C.[426] Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is



125

hypostrophene (**125**).[427] In the case of the compound *barbaralane* (**126**) (bullvalene in which one CH=CH has been replaced by a CH_2):



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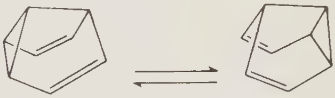

127

there are only two equivalent tautomers.[428] However, nmr spectra indicate that even at room temperature a rapid interchange of both tautomers is present, though by about −100°C this has slowed to the point where the spectrum is in accord with a single structure. Corresponding behavior, both at 25°C and at −100°C, is exhibited by substituted barbaralanes in which the CH_2 group has been replaced by CHOH, CHCl, CO, and $C(SR)_2$.[429] In the case of *semibullvalene* (**127**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at −110°C.[430] **127** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.[431]

The molecules taking part in a valence tautomerization need not be equivalent. Thus, nmr spectra indicate that a true valence tautomerization exists at room temperature between the cycloheptatriene **128** and the norcaradiene **129**.[432] In this case one isomer (**129**) has the *cis*-1,2-divinyl-

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[425] A number of azabullvalenes (**124** containing heterocyclic nitrogen) have been synthesized, and these too have fluxional structures when heated, though with fewer tautomeric forms than bullvalene itself: Paquette and Barton, *J. Am. Chem. Soc.* **89**, 5480 (1967); Paquette, Barton, and Whipple, *J. Am. Chem. Soc.* **89**, 5481 (1967); Wegener, *Tetrahedron Lett.* 4985 (1967); Paquette, Malpass, Krow, and Barton, *J. Am. Chem. Soc.* **91**, 5296 (1969).

[426] Oth, Müllen, Gilles, and Schröder, *Helv. Chim. Acta* **57**, 1415 (1974); Nakanishi and Yamamoto, *Tetrahedron Lett.* 1803 (1974); Günther and Ulmen, *Tetrahedron* **30**, 3781 (1974).

[427] McKennis, Brener, Ward, and Pettit, *J. Am. Chem. Soc.* **93**, 4957 (1971); Paquette, Davis, and James, *Tetrahedron Lett.* 1615 (1974).

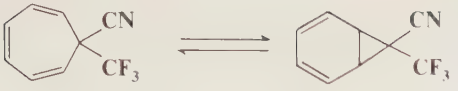
[428] Barbaralane was synthesized by Biethan, Klusacek, and Musso, *Angew. Chem. Int. Ed. Engl.* **6**, 176 (1967) [*Angew. Chem.* **79**, 152]; by Tsuruta, Kurabayashi, and Mukai, *Tetrahedron Lett.* 3775 (1965); and by Doering, Ferrier, Fossel, Hartenstein, Jones, Klumpp, Rubin, and Saunders, *Tetrahedron* **23**, 3943 (1967).

[429] Lambert, *Tetrahedron Lett.* 1901 (1963); Doering et al., Ref. 428; Barborak, Chari, and Schleyer, *J. Am. Chem. Soc.* **93**, 5275 (1971).

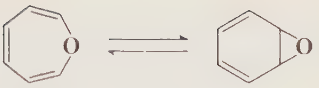
[430] Zimmerman and Grunewald, *J. Am. Chem. Soc.* **88**, 183 (1966); Meinwald and Schmidt, *J. Am. Chem. Soc.* **91**, 5877 (1969); Zimmerman, Robbins, and Schantl, *J. Am. Chem. Soc.* **91**, 5878 (1969); Zimmerman, Binkley, Givens, Grunewald, and Sherwin, *J. Am. Chem. Soc.* **91**, 3316 (1969). See also Criegee and Askani, *Angew. Chem. Int. Ed. Engl.* **7**, 537 (1968) [*Angew. Chem.* **80**, 531].

[431] Cheng, Anet, Mioduski, and Meinwald, *J. Am. Chem. Soc.* **96**, 2887 (1974).

[432] Ciganek, *J. Am. Chem. Soc.* **87**, 1149 (1965). For other examples of norcaradiene-cycloheptatriene valence tautomerizations, see Görlitz and Günther, *Tetrahedron* **25**, 4467 (1969); Reich, Ciganek, and Roberts, *J. Am. Chem. Soc.* **92**, 5166 (1970); Hall and Roberts, *J. Am. Chem. Soc.* **93**, 2203 (1971); Ciganek, *J. Am. Chem. Soc.* **93**, 2207 (1971); Günther, Tunggal, Regitz, Scherer, and Keller, *Angew. Chem. Int. Ed. Engl.* **10**, 563 (1971) [*Angew. Chem.* **83**, 585]; Dürr and Kober, *Chem. Ber.* **106**, 1565 (1973); Betz and Daub, *Chem. Ber.* **107**, 2095 (1974).



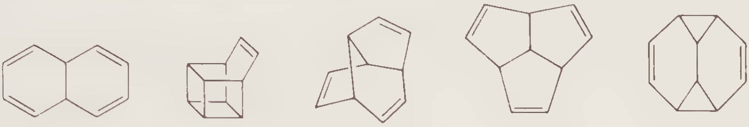
128 **129**



Oxepin Benzene oxide

cyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide and oxepin exist in a tautomeric equilibrium at room temperature.[339]

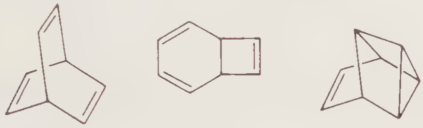
Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[433] Many other members of this group are known, including **130** to **134** and the [10]annulenes (p. 60). All these compounds represent positions



130 Basketene **131** **132** **133** **134**

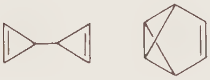
Some of the $(\mathbf{CH})_{10}$ compounds

of minimum energy on the $(CH)_{10}$ energy surface, and many of them have been interconverted by electrocyclic or Cope rearrangements. Similar groups of $(CH)_n$ compounds exist for other even-numbered values of n.[433] For example, there are 20 possible $(CH)_8$ compounds,[434] including semibullvalene (**127**), cubane (p. 143), cuneane (p. 143), cyclooctatetraene (p. 59), **135** to **137**; and five possible $(CH)_6$ compounds, all of which are known: benzene, prismane (p. 143), Dewar benzene (p. 1033), bicyclopropenyl (**138**), and benzvalene (**139**).



Barrelene **135** **136** **137**

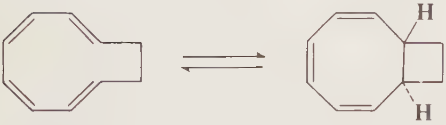
Some $(\mathbf{CH})_8$ compounds



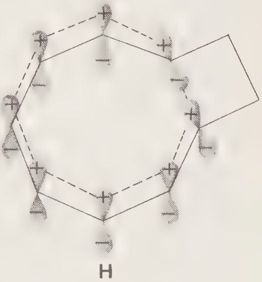
138 **139**

Two $(\mathbf{CH})_6$ compounds

An interesting example of a valence tautomerization was reported for the molecules (*E*,*Z*,*Z*,*E*)-1,3,5,7-cyclodecatetraene (**140**) and *trans*-bicyclo[6.2.0]deca-2,4,6-triene (**141**), which rapidly interconvert at temperatures above 50°C[435] (an electrocyclic reaction, **8-32**). The transition state for



140 **141**



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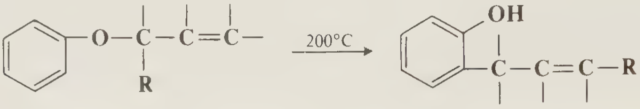
[433] For reviews of rearrangements and interconversions of $(CH)_n$ compounds, see Scott and Jones, *Chem. Rev.* **72**, 181–202 (1972); Balaban, *Rev. Roum. Chim.* **11**, 1097–1116 (1966).

[434] The structures of all possible $(CH)_n$ compounds, for $n = 4, 6, 8$, and 10, are shown in Balaban, Ref. 433.

[435] Staley and Henry, *J. Am. Chem. Soc.* **92**, 7612 (1970); **93**, 1294 (1971).

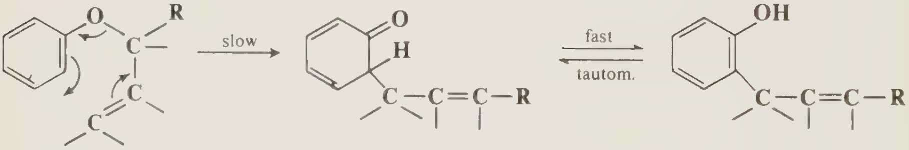
this interconversion (**H**) consists of eight electrons connected in a Möbius array (that is, with one sign inversion, see p. 1031). Since the number of electrons is of the form 4*n*, the Möbius is the only allowed pathway for a thermal reaction (p. 1032).

8-38 The Claisen Rearrangement



Allyl aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[436] If both ortho positions are filled, the allyl group migrates to the para position (this is often called the *para-Claisen rearrangement*). Sometimes some para product is obtained even if one or both ortho positions are free,[437] though in general it may be said that, when one or both ortho positions are open, the product is the *o*-allylphenol and that, when both ortho positions are blocked, the product is the para compound. There is no reaction when the para and both ortho positions are filled. Migration to the meta position has not been observed. In the ortho migration the allyl group always undergoes an allylic shift. That is, as shown above, a substituent α to the oxygen is now γ to the ring (and vice versa). On the other hand, in the para migration there is never an allylic shift: the allyl group is found exactly as it was in the original ether. Propargyl groups (that is, groups with a triple bond in the appropriate position) do not generally give the reaction.

The mechanism is a concerted pericyclic [3,3] sigmatropic rearrangement and accounts for all these facts. For the ortho rearrangement:



Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for the para) has been demonstrated by ^{14}C labeling, even when no substituents are present. Studies of the transition-state geometry have shown that, like the Cope rearrangement, the Claisen rearrangement prefers a chair-like transition state.[438] When the ortho positions have no hydrogen, a second [3,3] sigmatropic migration (a Cope reaction) follows:

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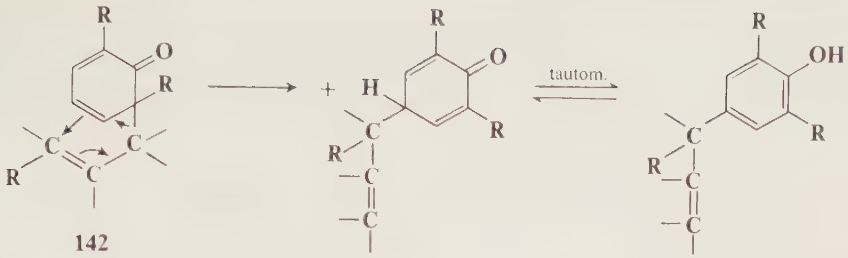
[436] For reviews, see Rhoads and Raulins, Ref. 408; Shine, "Aromatic Rearrangements," pp. 89–120, American Elsevier Publishing Company, New York, 1969, *MTP Int. Rev. Sci.: Org. Chem. Ser. One* **3**, 72–78 (1973); Smith and Kelly, *Prog. Phys. Org. Chem.* **8**, 75–234 (1971), pp. 153–201; Hansen and Schmid, *Chimia* **24**, 89–99 (1970), *Chem. Br.* **5**, 111–116 (1969); Jefferson and Scheinemann, *Q. Rev., Chem. Soc.* **22**, 391–421 (1968); Thyagarajan, *Adv. Heterocycl. Chem.* **8**, 143–163 (1967); Dalrymple, Kruger, and White, in Patai, "The Chemistry of the Ether Linkage," pp. 635–660, Interscience Publishers, New York, 1967; Rhoads, in Mayo, Ref. 1, vol. 1, pp. 660–684; Tarbell, *Org. React.* 2, 1–48 (1944).

[437] Borgulya, Hansen, Barner, and Schmid, *Helv. Chim. Acta* **46**, 2444 (1963); Scheinmann, Barner, and Schmid, *Helv. Chim. Acta* **51**, 1603 (1968).

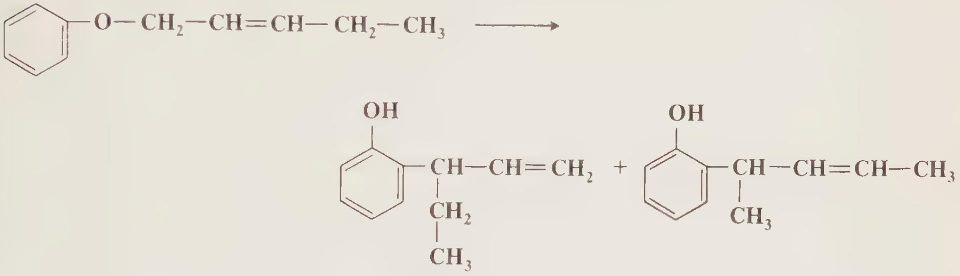
[438] Vittorelli, Winkler, Hansen, and Schmid, *Helv. Chim. Acta* **51**, 1457 (1968); Fráter, Habich, Hansen, and Schmid, *Helv. Chim. Acta* **52**, 335 (1969).


R
O
R
C
C
C
R
+ H
C
R
C
C
O
R
tautom.
R
OH
R
C
R
C
C

142

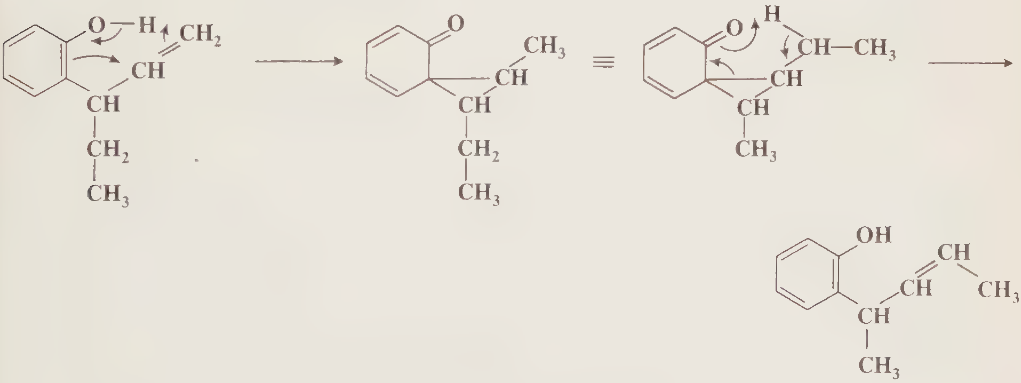
and the group is restored to its original structure. Intermediates of structure **142** have been trapped by means of a Diels-Alder reaction.[439]

Ethers with an alkyl group in the γ position ($ArO{-}C{-}C{=}C{-}R$ systems) sometimes give abnormal products, with the β-carbon becoming attached to the ring:[440]


O—CH₂—CH=CH—CH₂—CH₃
OH
CH—CH=CH₂
CH₂
CH₃
+
OH
CH—CH=CH—CH₃
CH₃

Normal product Abnormal product

It has been established that these abnormal products do not arise directly from the starting ether but are formed by a further rearrangement of the normal product:[441]


O—H
CH₂
CH
CH
CH₂
CH₃
O
CH₃
CH
CH
CH₂
CH₃
≡
O
H
CH—CH₃
CH
CH
CH₃
OH
CH
CH
CH₃
CH
CH₃

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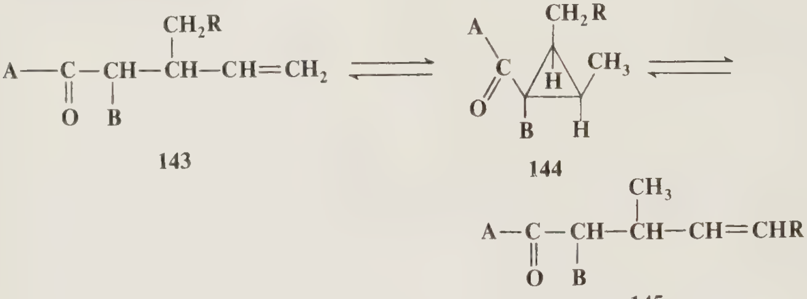
[439] Conroy and Firestone, *J. Am. Chem. Soc.* **75**, 2530 (1953).

[440] For reviews of these abnormal Claisen rearrangements, see Hansen, *Mech. Mol. Migr.* **3**, 177-236 (1971); Marvell and Whalley, in Patai, Ref. 411, pt. 2, pp. 743-750.

[441] Marvell, Anderson, and Ong, *J. Org. Chem.* **27**, 1109 (1962); Habich, Barner, Roberts, and Schmid, *Helv. Chim. Acta* **45**, 1943 (1962); Lauer and Johnson, *J. Org. Chem.* **28**, 2913 (1963); Habich, Barner, Philipsborn, and Schmid, *Helv. Chim. Acta* **48**, 1297 (1965); Fráter and Schmid, *Helv. Chim. Acta* **49**, 1957 (1966); Marvell and Schatz, *Tetrahedron Lett.* 67 (1967).

This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5] *sigmatropic hydrogen shift* (see p. 1040), and a [1,5] *homosigmatropic rearrangement*, involves a shift of three electron pairs over *seven* atoms. It has been found that this "abnormal" Claisen rearrangement is general and can interconvert the enol forms of systems of the types **143** and **145** through the cyclopropane intermediate **144**.[442]



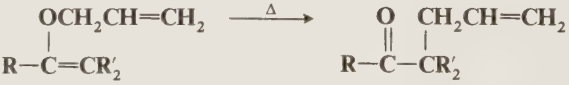
$$\underset{\mathbf{143}}{\text{A}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{B}}{|}}{\text{CH}}-\overset{\overset{\text{CH}_2\text{R}}{|}}{\text{CH}}-\text{CH}{=}\text{CH}_2} \rightleftharpoons \mathbf{144} \rightleftharpoons \underset{\mathbf{145}}{\text{A}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\underset{\text{B}}{|}}{\text{CH}}-\overset{\overset{\text{CH}_3}{|}}{\text{CH}}-\text{CH}{=}\text{CHR}}$$

143 **144** **145**

A = **H** , **R** , **Ar**, **OR** , etc.
B = **H**, **R** , **Ar** , **COR** , **COAr** , **COOR** , etc.

Since the Claisen rearrangement mechanism does not involve ions, it should not be greatly dependent on the presence or absence of substituent groups on the ring. This is the case. Electron-donating groups increase the rate, and electron-withdrawing groups decrease it, but the effect is small, with the *p*-amino compound reacting only about 10 to 20 times faster than the *p*-nitro compound.[443] However, solvent effects are greater: Rates varied over a 300-fold range when the reaction was run in 17 different solvents.[444] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[445] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ or BF_3 is sometimes used.[446] In this case it may become a Friedel-Crafts reaction, with the mechanism no longer cyclic,[447] and ortho, meta, and para products may be obtained.

Allyl ethers of enols (allyl vinyl ethers) also undergo the Claisen rearrangement; in fact it was discovered with these compounds first:[448]



$$\text{R}-\overset{\overset{\text{OCH}_2\text{CH}{=}\text{CH}_2}{|}}{\text{C}}{=}\text{CR}'_2 \xrightarrow{\Delta} \text{R}-\overset{\overset{\text{O}}{\|}}{\text{C}}-\overset{\overset{\text{CH}_2\text{CH}{=}\text{CH}_2}{|}}{\text{CR}'_2}$$

In these cases of course the final tautomerization does not take place even when R′ = H, since there is no aromaticity to restore, and ketones are more stable than enols. The mechanism is similar to that with allyl aryl ethers. One experiment which demonstrated this was the conversion of optically active **146** to **147** which was still optically active.[449] This is another example of asymmetric induction (p. 107):

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[442] Roberts, Landolt, Greene, and Heyer, *J. Am. Chem. Soc.* **89**, 1404 (1967); Roberts and Watson, *J. Org. Chem.* **34**, 4191 (1969); Watson, Irvine, and Roberts, *J. Am. Chem. Soc.* **95**, 3348 (1973).

[443] Goering and Jacobson, *J. Am. Chem. Soc.* **80**, 3277 (1958); White, Gwynn, Schlitt, Girard, and Fife, *J. Am. Chem. Soc.* **80**, 3271 (1958); White and Fife, *J. Am. Chem. Soc.* **83**, 3846 (1961); White, Slater, and Fife, *J. Org. Chem.* **26**, 627 (1961); White and Slater, *J. Org. Chem.* **27**, 2908 (1962).

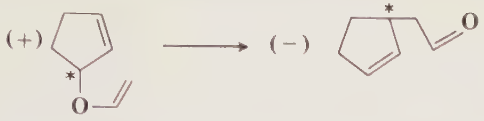
[444] White and Wolfarth, *J. Org. Chem.* **35**, 2196 (1970). See also Miller and Scrimgeour, *J. Chem. Soc., Perkin Trans. 2* 1137 (1973).

[445] Svanholm and Parker, *J. Chem. Soc., Perkin Trans 2* 169 (1974).

[446] For example, see Borgulya, Madeja, Fahrni, Hansen, Schmid, and Barner, *Helv. Chim. Acta* **56**, 14 (1973).

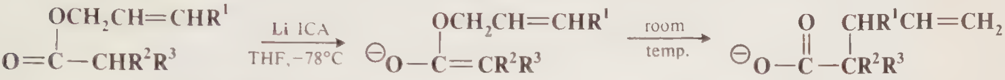
[447] For example, crossover experiments have demonstrated that the $ZnCl_2$-catalyzed reaction is intermolecular: Yagodin, Bunina-Krivorukova, and Bal'yan, *J. Org. Chem. USSR* **7**, 1491 (1971).

[448] Claisen, *Ber.* **45**, 3157 (1912).

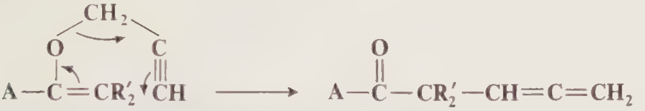


146 **147**

It is possible to treat ketones with allyl alcohol and an acid catalyst to give γ,δ-unsaturated ketones directly, presumably by initial formation of the vinyl ethers, and then Claisen rearrangement.[450] In an analogous procedure, the enolates of allylic esters [formed by treatment of the esters with lithium isopropylcyclohexylamide (ICA)] rearrange to γ,δ-unsaturated acids.[451]



A number of expected analogs of the Claisen rearrangement are known,[452] e.g., rearrangement of $ArNHCH_2CH{=}CH_2$,[453] of N-allyl enamines $R_2C{=}CRNRCR_2CR{=}CR_2$,[454] and of $RC(OCH_2CH{=}CH_2){=}NR$.[455] Propargyl vinyl compounds give allenic aldehydes, ketones, esters, or amides:[456]



A = H, R, OR, NR$_2$

Under strenuous conditions (potassium *t*-butoxide in *t*-butyl alcohol at 350°C for 24 hr) the reaction has even been extended to a carbon analog: a mixture of 1-phenylbutenes was placed in equilibrium with a mixture of 1-(*o*-tolyl)propenes.[457] The conversion of allyl aryl thioethers $ArSCH_2CH{=}CH_2$ to *o*-allylthiophenols (the thio-Claisen rearrangement) is not feasible, because the latter are not stable[458] but react to give bicyclic compounds.[459] However, many allyl vinyl sulfides do give the rearrangement,[460] and this has been used in a synthesis of γ,δ-unsaturated

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[449] Hill and Edwards, *Tetrahedron Lett.* 3239 (1964).

[450] Lorette, *J. Org. Chem.* **26,** 4855 (1961). See also Saucy and Marbet, *Helv. Chim. Acta* **50,** 2091 (1967); Marbet and Saucy, *Helv. Chim. Acta* **50,** 2095 (1967); Thomas, *J. Am. Chem. Soc.* **91,** 3281 (1969); Johnson, Werthemann, Bartlett, Brocksom, Li, Faulkner, and Petersen, *J. Am. Chem. Soc.* **92,** 741 (1970).

[451] Ireland and Mueller, *J. Am. Chem. Soc.* **94,** 5897 (1972). See also Baldwin and Walker, *J. Chem. Soc., Chem. Commun.* 117 (1973).

[452] For a review of [3,3] sigmatropic rearrangements with hetero atoms present, see Winterfeldt, *Fortschr. Chem. Forsch.* **16,** 75–102 (1970).

[453] Marcinkiewicz, Green, and Mamalis, *Tetrahedron,* **14,** 208 (1961); Inada, Ikado, and Okazaki, *Chem. Lett.* 1213 (1973); Schmid, Hansen, and Schmid, *Helv. Chim. Acta* **56,** 105 (1973); Jolidon and Hansen, *Chimia* **30,** 21, 23 (1976).

[454] Ficini and Barbara, *Tetrahedron Lett.* 6425 (1966); Hill and Gilman, *Tetrahedron Lett.* 1421 (1967); Hill and Newkome, *Tetrahedron Lett.* 5059 (1968); Ireland and Willard, *J. Org. Chem.* **39,** 421 (1974).

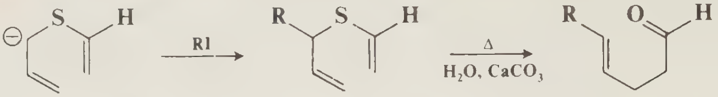
[455] For examples, see Synerholm, Gilman, Morgan, and Hill, *J. Org. Chem.* **33,** 1111 (1968); Black, Eastwood, Okraglik, Poynton, Wade, and Welker, *Aust. J. Chem.* **25,** 1483 (1972); Overman, *J. Am. Chem. Soc.* **96,** 597 (1974).

[456] Black and Landor, *J. Chem. Soc.* 6784 (1965); Saucy and Marbet, *Helv. Chim. Acta* **50,** 1158 (1967); Ficini, Lumbroso-Bader, and Pouliquen, *Tetrahedron Lett.* 4139 (1968); Crandall and Tindell, *Chem. Commun.* 1411 (1970); Black, Fomum, Landor, and Landor, *J. Chem. Soc., Perkin Trans. 1* 1349 (1973).

[457] Doering and Bragole, *Tetrahedron* **22,** 385 (1966).

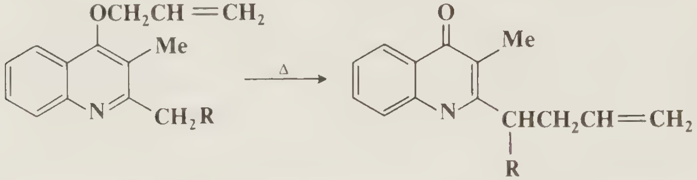
[458] They have been trapped: see for example, Mortensen, Hedegaard, and Lawesson, *Tetrahedron* **27,** 3831 (1971); Kwart and Schwartz, *J. Org. Chem.* **39,** 1575 (1974).

[459] Kwart and Hackett, *J. Am. Chem. Soc.* **84,** 1754 (1962); Kwart and Evans, *J. Org. Chem.* **31,** 413 (1966); Meyers, Rinaldi, and Banoli, *J. Org. Chem.* **28,** 2440 (1963); Makisumi, *Tetrahedron Lett.* 6399 (1966); Kwart and Cohen, *J. Org. Chem.* **32,** 3135 (1967), *Chem. Commun.* 319 (1968); Makisumi and Murabayashi, *Tetrahedron Lett.* 1971, 2449 (1969); Makisumi and Sasatani, *Tetrahedron Lett.* 1975 (1969).



aldehydes.[461] A similar reaction has been applied to enolates of dithio esters.[462]

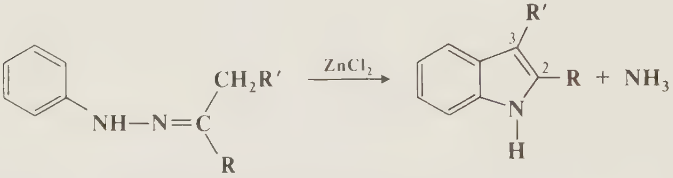
In some cases rearrangement has been shown to go to the α-position of a meta side chain:[463]



The mechanism of this process is the same as that of the para-Claisen rearrangement.

OS **III,** 418; **V,** 25; **53,** 116; **54,** 71, 74, 77.

8-39 The Fischer Indole Synthesis



When arylhydrazones of aldehydes or ketones are treated with a catalyst, elimination of ammonia takes place and an indole is formed, in a reaction called the *Fischer indole synthesis.*[464] Zinc chloride is the catalyst most frequently employed, but dozens of others, including other metal halides, proton and Lewis acids, and certain transition metals have also been used. Arylhydrazones are easily prepared by the treatment of aldehydes or ketones with phenylhydrazine (reaction **6-21**) or by aliphatic diazonium coupling (reaction **2-7**). However, it is not necessary to isolate the arylhydrazone. The arylhydrazine can be treated with a mixture of the aldehyde or ketone and the catalyst, and this is now common practice. In order to obtain an indole, the aldehyde or ketone must be of the form $RCOCH_2R'$ (R = alkyl, aryl, or hydrogen). When R is hydrogen or methyl, then this group is always found at the 2 position of the indole, and R′ at the 3 position. When the aldehyde or ketone is of the form $CH_3COCHR'_2$ ($R' \neq$ hydrogen), then the product is

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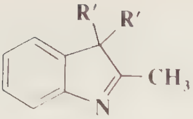
[460] Schuijl and Brandsma, *Recl. Trav. Chim. Pays-Bas* **87,** 929 (1968), **88,** 1201 (1969); Corey and Shulman, *J. Am. Chem. Soc.* **92,** 5522 (1970); Sasaki, Kojima, and Ohta, *J. Chem. Soc. C* 196 (1971); Kondo and Ojima, *Chem. Commun.* 62 (1972); Meijer and Brandsma, *Recl. Trav. Chim. Pays-Bas* **91,** 578 (1972); Meijer, Vermeer, Bos, and Brandsma, *Recl. Trav. Chim. Pays-Bas* **93,** 26 (1974); Hartke and Gölz, *Chem. Ber.* **107,** 566 (1974).

[461] Oshima, Takahashi, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **95,** 2693 (1973). See also Brandsma and Verkruijsse, *Recl. Trav. Chim. Pays-Bas* **93,** 319 (1974).

[462] Takahashi, Oshima, Yamamoto, and Nozaki, *J. Am. Chem. Soc.* **95,** 5803 (1973).

[463] Makisumi, *J. Org. Chem.* 30, 1989 (1965).

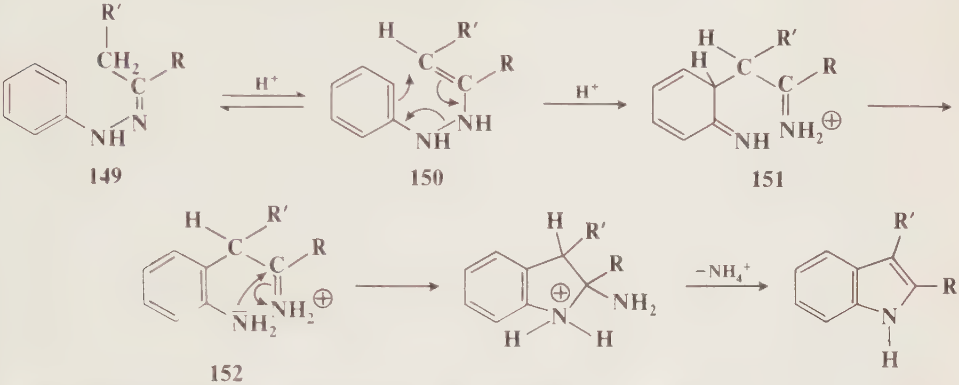
[464] For reviews, see Grandberg and Sorokin, *Russ. Chem. Rev.* **43,** 115–128 (1974); Shine, "Aromatic Rearrangements," Ref. 436, pp. 190–207, *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **3,** 85–89 (1973); Sundberg, "The Chemistry of Indoles," pp. 142 163, Academic Press, Inc., New York, 1970; Robinson, *Chem. Rev.* **69,** 227–250 (1969), **63,** 373–401 (1963).



148

usually **148**, though exceptions are known.[465] For compounds of the form $RCH_2COCHR'_2$, a mixture of both types is obtained.

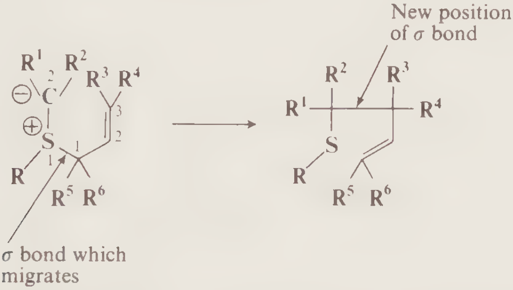
At first glance the reaction does not seem to be a rearrangement. However, the key step of the mechanism is a [3,3] sigmatropic rearrangement:[466]



There is much evidence for this mechanism, for example, (1) the isolation of **152**,[467] (2) the isolation of side products which could only have come from **151**,[468] and (3) ^{15}N labeling experiments which showed that it was the nitrogen farther from the ring which was eliminated as ammonia.[469] The main function of the catalyst seems to be to speed the conversion of **149** to **150**. The reaction can be performed without a catalyst.

OS **III**, 725; **IV**, 884. Also see OS **IV**, 657.

8-40 [2,3] Sigmatropic Rearrangements



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[465] For example, see Buu-Hoï, Jacquignon, and Périn-Roussel, *Bull. Soc. Chim. Fr.* 2849 (1965); Lyle and Skarlos, *Chem. Commun.* 644 (1966); Illy and Funderburk, *J. Org. Chem.* **33**, 4283 (1968).

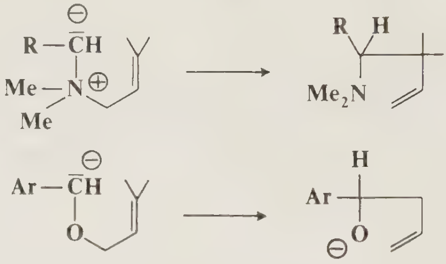
[466] This mechanism was proposed by Robinson and Robinson, *J. Chem. Soc.* **113**, 639 (1918).

[467] Southwick, McGrew, Engel, Milliman, and Owellen, *J. Org. Chem.* **28**, 3058 (1963); Southwick, Vida, Fitzgerald, and Lee, *J. Org. Chem.* **33**, 2051 (1968); Forrest and Chen, *J. Chem. Soc., Chem. Commun.* 1067 (1972).

[468] Robinson and Brown, *Can. J. Chem.* **42**, 1940 (1964); Bajwa and Brown, *Can. J. Chem.* **46**, 1927, 3105 (1968), **47**, 785 (1969), **48**, 2293 (1970).

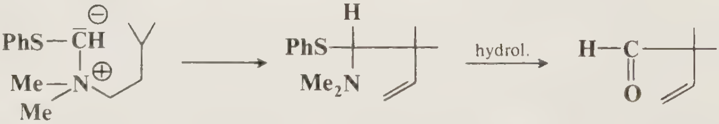
[469] Clausius and Weisser, *Helv. Chim. Acta* **35**, 400 (1952).

Sulfur ylides bearing an allylic group are converted on heating to unsaturated sulfides.[470] This is a concerted [2,3] sigmatropic rearrangement and has also been demonstrated for the analogous cases of nitrogen ylides[471] and the conjugate bases of allylic ethers,[472] as well as certain other systems.[473] It has even been extended to all-carbon systems.[474]



Since the reactions involve migration of an allylic group from a sulfur, nitrogen, or oxygen atom to an adjacent negatively charged carbon atom, they are special cases of the Stevens or Wittig rearrangements (reactions **8-25, 8-26**). However, in this case the migrating group *must* be allylic (in reactions **8-25** and **8-26** other groups may also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (1) the radical-ion or ion-pair mechanisms (**8-25, 8-26**) and (2) the concerted pericyclic [2,3] sigmatropic rearrangement. These can easily be told apart, since the latter always involves an allylic shift (as in the Claisen rearrangement), while the former pathway does not. Of course, migration of groups other than allylic can take place only by the radical-ion or ion-pair mechanisms, because the orbital symmetry rules forbid a concerted mechanism for 1,2 shifts.

If an OR or SR group is attached to the negative carbon, the reaction becomes a method for the preparation of β,γ-unsaturated aldehydes, because the product is easily hydrolyzed.[475]



Another [2,3] sigmatropic rearrangement converts allylic sulfoxides to allylically rearranged alcohols by treatment with a thiophilic reagent such as trimethyl phosphite.[476] In this case the

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[470] For example, see Blackburn, Ollis, Plackett, Smith, and Sutherland, *Chem. Commun.* 186 (1968); Trost and LaRochelle, *Tetrahedron Lett.* 3327 (1968); Baldwin, Hackler, and Kelly, *Chem. Commun.* 537, 538, 1083 (1968); Bates and Feld, *Tetrahedron Lett.* 417 (1968); Kirmse and Kapps, *Chem. Ber.* **101,** 994, 1004 (1968); Biellmann and Ducep, *Tetrahedron Lett.* 33 (1971); Rautenstrauch, *Helv. Chim. Acta* **54,** 739 (1971); Grieco, Meyers, and Finkelhor, *J. Org. Chem.* **39,** 119 (1974); Kreiser and Wurziger, *Tetrahedron Lett.* 1669 (1975).

[471] For example, see Jemison and Ollis, *Chem. Commun.* 294 (1969); Rautenstrauch, *Helv. Chim. Acta* **55,** 2233 (1972); Mageswaran, Ollis, Sutherland, and Thebtaranonth, *J. Chem. Soc., Chem. Commun.* 651 (1973); Ollis, Sutherland, and Thebtaranonth, *J. Chem. Soc., Chem. Commun.* 657 (1973); Mander and Turner, *J. Org. Chem.* **38,** 2915 (1973).

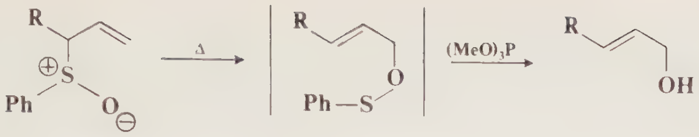
[472] Makisumi and Notzumoto, *Tetrahedron Lett.* 6393 (1966); Schöllkopf and Fellenberger, *Justus Liebigs Ann. Chem.* **698,** 80 (1966); Schöllkopf, Fellenberger, and Rizk, *Justus Liebigs Ann. Chem.* **734,** 106 (1970); Rautenstrauch, *Chem. Commun.* 4 (1970); Baldwin and Patrick, *J. Am. Chem. Soc.* **93,** 3556 (1971); Cazes and Julia, *Tetrahedron Lett.* 2077 (1974); Thomas and Dubini, *Helv. Chim. Acta* **57,** 2084 (1974).

[473] See for example Baldwin, Brown, and Cordell, *Chem. Commun.* 31 (1970); Baldwin, Brown, and Höfle, *J. Am. Chem. Soc.* **93,** 788 (1971); Yamamoto, Oda, and Inouye, *J. Chem. Soc., Chem. Commun.* 848 (1973); Ranganathan, Ranganathan, Sidhu, and Mehrotra, *Tetrahedron Lett.* 3577 (1973).

[474] Baldwin and Urban, *Chem. Commun.* 165 (1970).

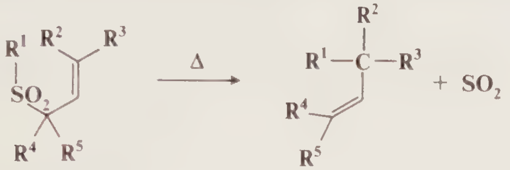
[475] Huynh, Julia, Lorne, and Michelot, *Bull. Soc. Chim. Fr.* 4057 (1972).

[476] Bickart, Carson, Jacobus, Miller, and Mislow, *J. Am. Chem. Soc.* **90,** 4869 (1968); Tang and Mislow, *J. Am. Chem. Soc.* **92,** 2100 (1970); Grieco, *J. Chem. Soc., Chem. Commun.* 702 (1972); Evans and Andrews, *Acc. Chem. Res.* **7,** 147–155 (1974).



migration is from sulfur to oxygen. [2,3] oxygen-to-sulfur migrations are also known.[477] The Sommelet-Hauser rearrangement (**3-27**) is also a [2,3] sigmatropic rearrangement.

In a closely related reaction, allylic sulfones on heating rearrange with simultaneous loss of SO_2 to give alkenes.[478]



C. Other Cyclic Rearrangements

8-41 Metathesis of Olefins

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6,\ EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When olefins are treated with certain catalysts (most often tungsten or molybdenum complexes), they are converted to other olefins in a reaction in which the alkylidene groups ($R^1R^2C{=}$) have become interchanged by a process schematically illustrated by the equation:

$$\begin{array}{c} R^1R^2C{=}CR^1R^2 \\ + \\ R^3R^4C{=}CR^3R^4 \end{array} \rightleftharpoons \begin{array}{ccc} R^1R^2C & + & CR^1R^2 \\ \| & & \| \\ R^3R^4C & & CR^3R^4 \end{array}$$

The reaction has been variously called *metathesis*, *dismutation*, and *disproportionation* of olefins.[479] In the example shown above, 2-pentene (either cis- trans, or a cis-trans mixture) is converted to a mixture of about 50% 2-pentene, 25% 2-butene, and 25% 3-hexene. The reaction is an equilibrium, and the same mixture can be obtained by starting with equimolar quantities of 2-butene and 3-hexene.[480] In general, the reaction can be applied to a single unsymmetrical olefin, giving a mixture of itself and two other olefins, or to a mixture of two olefins, in which case the number of different molecules in the product depends on the symmetry of the reactants. As in the case above, a mixture of $R^1R^2C{=}CR^1R^2$ and $R^3R^4C{=}CR^3R^4$ gives rise to only one new olefin ($R^1R^2C{=}CR^3R^4$), while in the most general case, a mixture of $R^1R^2C{=}CR^3R^4$ and $R^5R^6C{=}CR^7R^8$ gives a mixture of 10 olefins: the original 2 plus 8 new ones. With simple alkenes the proportions of products are generally statistical,[481] which limits the synthetic utility of the reaction, since the yield of any one product is low. However, in some cases one alkene may be more or less thermodynamically stable than the rest, so that the proportions are not statistical. Furthermore, it may be possible to shift the equilibrium. For example, 2-methyl-1-butene gives rise to ethylene and 3,4-dimethyl-3-hexene. By allowing the gaseous ethylene to escape, the yield of 3,4-dimethyl-3-hexene can be raised to 95%.[482] As expected for an equilibrium process, both cis and trans alkenes are produced, with the more stable trans isomers usually predominating.[483]

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[477] Braverman and Mechoulam, *Isr. J. Chem.* **5**, 71 (1967); Braverman and Stabinsky, *Chem. Commun.* 270 (1967); Rautenstrauch, *Chem. Commun.* 526 (1970); Smith and Stirling, *J. Chem. Soc. C* 1530 (1971).

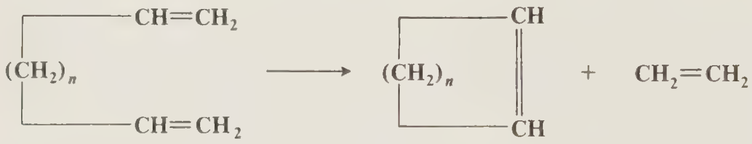
[478] Hendrickson and Bergeron, *Tetrahedron Lett.* 3609 (1973).

[479] For reviews, see Haines and Leigh, *Chem. Soc. Rev.* **4**, 155–188 (1975); Hocks, *Bull. Soc. Chim. Fr.* 1893-1903 (1975); Mol and Moulijn, *Adv. Catal.* **24**, 131–171 (1975); Hughes, *Chem. Technol.* 486–495 (1975); *Organomet. Chem. Synth.* **1**, 341–374 (1972); Calderon, *Acc. Chem. Res.* **5**, 127–132 (1972); Banks, *Fortschr. Chem. Forsch.* **25**, 39–69 (1972); Khidekel', Shebaldova, and Kalechits, *Russ. Chem. Rev.* **40**, 669–678 (1971); Bailey, *Catal. Rev.* **3**, 37–60 (1969).

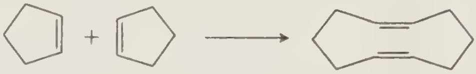
[480] Calderon, Chen, and Scott, *Tetrahedron Lett.* 3327 (1967); Wang and Menapace, *J. Org. Chem.* **33**, 3794 (1968); Hughes, *J. Am. Chem. Soc.* **92**, 532 (1970).

[481] Calderon, Ofstead, Ward, Judy, and Scott, *J. Am. Chem. Soc.* **90**, 4133 (1968).

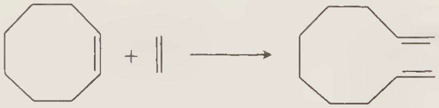
Many catalysts, both homogeneous[484] and heterogeneous,[485] have been used for this reaction. Some of the former[486] are WCl_6–EtOH–$EtAlCl_2$,[481] $MoCl_2(NO)_2(Ph_3P)_2$–$EtAlCl_2$,[487] WCl_6–BuLi,[488] and WCl_6–$LiAlH_4$,[489] while among the latter are oxides of Mo, W, and Re deposited on alumina or silica gel.[490] In general, the former group are more useful for synthetic purposes. By choice of the proper catalyst, the reaction has been applied to terminal and internal alkenes, straight chain or branched. The effect of substitution on the ease of reaction is $CH_2\!= \; > RCH_2CH\!= \; > R_2CHCH\!= \; > R_2C\!=$. Dienes may react intermolecularly or intramolecularly,[491] e.g.,



Cyclic olefins give dimeric dienes,[492] e.g.,



However, the products can then react with additional monomers and with each other, so that polymers are generally produced, and the cyclic dienes are obtained only in low yield. The reaction between a cyclic and a linear olefin can give a ring-opened diene:[493]



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[482] Knoche, Ger. Pat. (Offen.) 2024835 (1970) [*Chem. Abstr.* **74,** 44118b (1971)]. See also Chevalier, Sinou, and Descotes, *Bull. Soc. Chim. Fr.* 2254 (1976).

[483] For an exception, see Hughes, *Chem. Commun.* 431 (1969).

[484] First reported by Calderon, Chen, and Scott, Ref. 480.

[485] First reported by Banks and Bailey, *Ind. Eng. Chem., Prod. Res. Dev.* **3,** 170 (1964).

[486] For a lengthy list, see Hughes, *Organomet. Chem. Synth.* Ref. 479, pp. 362–368.

[487] Zuech, Hughes, Kubicek, and Kittleman, *J. Am. Chem. Soc.* **92,** 528 (1970); Hughes, Ref. 480.

[488] Wang and Menapace, Ref. 480.

[489] Chatt, Haines, and Leigh, *J. Chem. Soc., Chem. Commun.* 1202 (1972); Matlin and Sammes, *J. Chem. Soc., Chem. Commun.* 174 (1973).

[490] For a list of heterogeneous catalysts, see Banks, Ref. 479, pp. 41–46.

[490a] For an explanation for this order, see McGinnis, Katz, and Hurwitz, *J. Am. Chem. Soc.* **98,** 605 (1976); Casey, Tuinistra, and Saeman, *J. Am. Chem. Soc.* **98,** 608 (1976).

[491] Kroll and Doyle, *Chem. Commun.* 839 (1971); Zuech et al., Ref. 487.

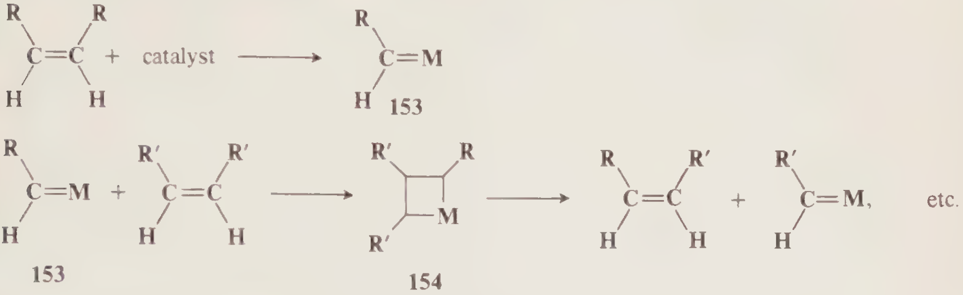
[492] Calderon, Ofstead, and Judy, *J. Polym. Sci., Part A-1* **5,** 2209 (1967); Wasserman, Ben-Efraim, and Wolovsky, *J. Am. Chem. Soc.* **90,** 3286 (1968); Wolovsky and Nir, *Synthesis* 134 (1972).

[493] Wasserman, Ben-Efraim, and Wolovsky, Ref. 492; Ray and Crain, Fr. Pat. 1511381 (1968) [*Chem. Abstr.* **70,** 114580q (1969)]; Mango, U.S. Pat. 3424811 (1969) [*Chem. Abstr.* **70,** 106042a (1969)]; Rossi, Diversi, Lucherini, and Porri, *Tetrahedron Lett.* 879 (1974); Lal and Smith, *J. Org. Chem.* **40,** 775 (1975).

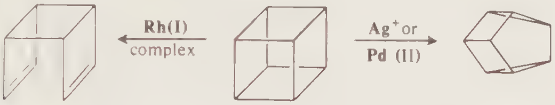
When the catalyst is supported tungsten oxide, the reaction can be applied to triple bonds:[494]

$$2RC{\equiv}CR' \rightleftharpoons RC{\equiv}CR + R'C{\equiv}CR'$$

The mechanism is not completely understood.[495] Several mechanisms have been suggested,[496] but the most likely is a chain process involving the intervention of a metal-carbene (**153**) and a four-membered ring containing a metal (**154**).[497]

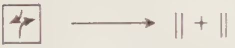


8-42 Metal-ion-catalyzed σ-Bond Rearrangements

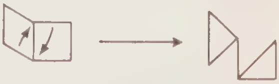


155 Cubane Cuneane

Many highly strained cage molecules undergo rearrangement when treated with metallic ions such as Ag^+, Rh(I), or Pd(II).[498] The bond rearrangements observed can be formally classified into two main types: (1) 2 + 2 ring openings of cyclobutanes and (2) conversion of a bicyclo-[3.3.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type (see above). Treatment with Rh(I) complexes converts cubane to tricyclo[$4.2.0.0^{2,5}$]octa-3,7-diene (**155**),[499] an example of type 1, while Ag^+ or Pd(II) causes the second type of reaction, producing cuneane.[500] Other examples are:



Type 1



Type 2

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[494] Pennella, Banks, and Bailey, *Chem. Commun.* 1548 (1968).

[495] For a discussion, see Cardin, Çetinkaya, Doyle, and Lappert, *Chem. Soc. Rev.* **2**, 99–144 (1973), pp. 139–144.

[496] For example, see Ref. 481; Calderon, Ref. 479; Lewandos and Pettit, *J. Am. Chem. Soc.* **93**, 7087 (1971), *Tetrahedron Lett.* 789 (1971); O'Neill and Rooney, *J. Chem. Soc., Chem. Commun.* 104 (1972); Levissales, Rudler, and Villemin, *J. Organomet. Chem.* **87**, C7 (1975). See also Gassman and Johnson, *J. Am. Chem. Soc.* **98**, 861 (1976).

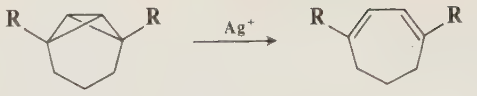
[497] Katz and McGinnis, *J. Am. Chem. Soc.* **97**, 1592 (1975); Grubbs, Burk, and Carr, *J. Am. Chem. Soc.* **97**, 3265 (1975); Mocella, Busch, and Muetterties, *J. Am. Chem. Soc.* **98**, 1283 (1976); Katz and Rothchild, *J. Am. Chem. Soc.* **98**, 2519 (1976); Grubbs, Carr, Hoppin, and Burk, *J. Am. Chem. Soc.* **98**, 3478 (1976).

[498] For reviews, see Cardin et al., Ref. 495, pp. 132–139; Paquette, *Synthesis* 347–357 (1975), *Acc. Chem. Res.* **4**, 280–287 (1971); *MTP Int. Rev. Sci.: Org. Chem. Ser. One* **5**, 127–158 (1973).

[499] Cassar, Eaton, and Halpern, *J. Am. Chem. Soc.* **92**, 3515 (1970).

[500] Cassar, Eaton, and Halpern, *J. Am. Chem. Soc.* **92**, 6336 (1970).

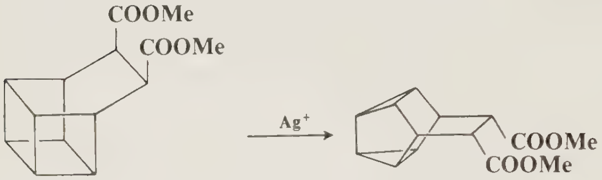
Type 1



156 **157**

Ref. 501

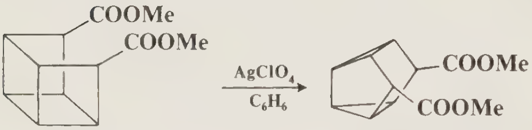
Type 2



158

Ref. 502

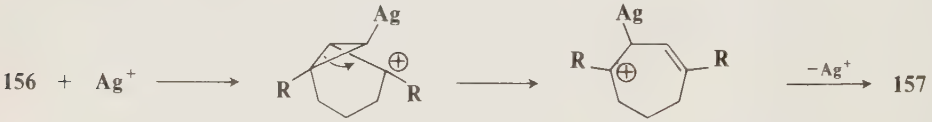
Type 2



Ref. 503

158 is the 9,10-dicarbomethoxy derivative of *snoutane* (pentacyclo[3.3.2.0^{2,4}.0^{3,7}.0^{6,8}]decane).

The mechanisms of these reactions are not completely understood, though relief of strain undoubtedly supplies the driving force. The reactions are thermally forbidden by the orbital symmetry rules, and the role of the catalyst is to provide low-energy pathways so that the reactions can take place. The type-1 reactions are the reverse of the catalyzed 2 + 2 ring closures discussed at reaction **5-52.** The following mechanism, in which Ag$^+$ attacks one of the edge bonds, has been suggested for the conversion of **156** to **157**:[504]



Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[505] For example, treatment of **159** with AgBF$_4$,[506] (C$_6$F$_5$Cu)$_4$,[507] or [(π-allyl)PdCl]$_2$[508] gives a mixture of **160** and **161** result-

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[501] Paquette, Allen, and Henzel, *J. Am. Chem. Soc.* **92,** 7002 (1970); Gassman and Atkins, *J. Am. Chem. Soc.* **93,** 4579 (1971), **94,** 7748 (1972); Sakai, Westberg, Yamaguchi, and Masamune, *J. Am. Chem. Soc.* **93,** 4611 (1972); Paquette, Wilson, Henzel, and Allen, *J. Am. Chem. Soc.* **94,** 7761 (1972); Paquette, Wilson, and Henzel, *J. Am. Chem. Soc.* **94,** 7771 (1972).

[502] See for example, Furstoss and Lehn, *Bull. Soc. Chim. Fr.* 2497 (1966); Paquette and Stowell, *J. Am. Chem. Soc.* **92,** 2584 (1970), **93,** 2459 (1971); Dauben, Buzzolini, Schallhorn, and Whalen, *Tetrahedron Lett.* 787 (1970); Dauben and Kielbania, *J. Am. Chem. Soc.* **93,** 7345 (1971); Paquette, Beckley, and Farnham, *J. Am. Chem. Soc.* **97,** 1089 (1975).

[503] Paquette, Beckley, and McCreadie, *Tetrahedron Lett.* 775 (1971); Dauben, Schallhorn, and Whalen, *J. Am. Chem. Soc.* **93,** 1446 (1971).

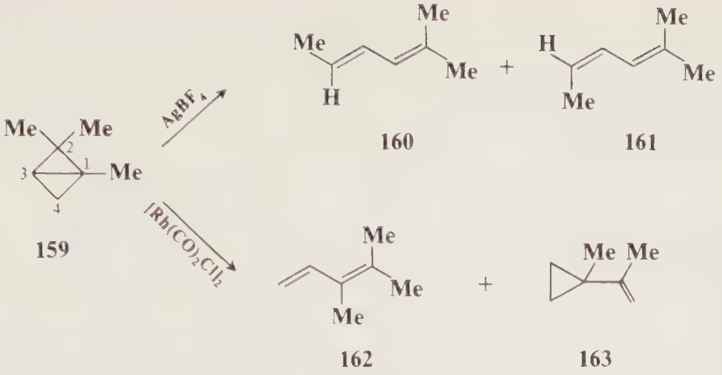
[504] Gassman and Atkins, Ref. 501; Sakai et al., Ref. 501.

[505] **156** can also be cleaved in this manner, giving a 3-methylenecyclohexene. See for example Gassman and Atkins, *J. Am. Chem. Soc.* **93,** 1042 (1971); Dauben and Kielbania, *J. Am. Chem. Soc.* **94,** 3669 (1972); Gassman and Reitz, *J. Am. Chem. Soc.* **95,** 3057 (1973); Paquette and Zon, *J. Am. Chem. Soc.* **96,** 203, 224 (1974); Zon and Paquette, *J. Am. Chem. Soc.* **96,** 215 (1974).

[506] Paquette, Henzel, and Wilson, *J. Am. Chem. Soc.* **93,** 2335 (1971).

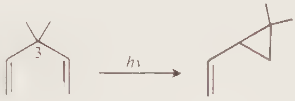
[507] Gassman and Williams, *Tetrahedron Lett.* 1409 (1971).

[508] Gassman, Meyer, and Williams, *Chem. Commun.* 842 (1971).

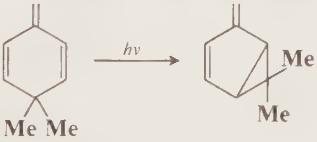


ing from a formal cleavage of the $C_1—C_3$ and $C_1—C_2$ bonds (note that a hydride shift has taken place). The use of $[Rh(CO)_2Cl]_2$,[509] $[Ru(CO)_3Cl_2]_2$,[509] or $Pd(PhCN)_2Cl_2$[508] cleaves **159** in a different way, giving **162** and **163.** Although **162** could formally have arisen from a 2 + 2 ring opening with the $C_1—C_3$ bond intact, isotopic labeling has shown that this is not the case, at least for the rhodium complex. It was the $C_1—C_3$ and $C_2—C_3$ bonds which cleaved in this case.[509]

8-43 The Di-π-methane Rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3[510] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement.*[511] An interesting example is conversion of 1-methylene-4,4-dimethyl-2,5-cyclohexadiene to 2-methylene-6,6-dimethylbicyclo-[3.1.0]-3-hexene.[512] For most[513] 1,4-dienes it is only the singlet excited states which give the



reaction; triplet states generally take other pathways. For unsymmetrical dienes, the reaction is regiospecific: The more conjugated double bond is the one which is converted to the cyclopropane ring. Thus **166** gave **167** and not **168.**[514] The mechanism may be described by the di-

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[509] Gassman and Williams, *J. Am. Chem. Soc.* **92,** 7631 (1970).

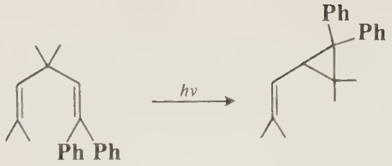
[510] Zimmerman and Pincock, *J. Am. Chem. Soc.* **95,** 2957 (1973).

[511] For a review, see Hixson, Mariano, and Zimmerman, *Chem. Rev.* **73,** 531-551 (1973).

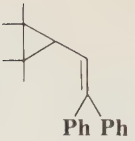
[512] Zimmerman, Hackett, Juers, McCall, and Schröder, *J. Am. Chem. Soc.* **93,** 3653 (1971).

[513] However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, p. 1049, which is converted to semi-bullvalene) give the di-π-methane rearrangement only from triplet states.

[514] Zimmerman and Pratt, *J. Am. Chem. Soc.* **92,** 6259, 6267 (1970); Zimmerman and Baum, *J. Am. Chem. Soc.* **93,** 3646 (1971). See also Zimmerman and Cotter, *J. Am. Chem. Soc.* **96,** 7445 (1974).

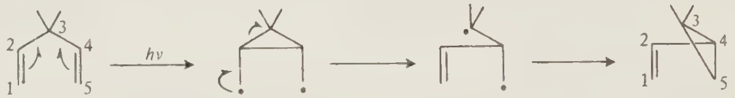


166 **167**



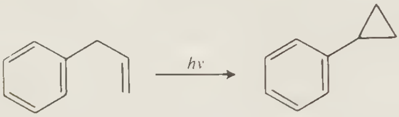
168
Not formed

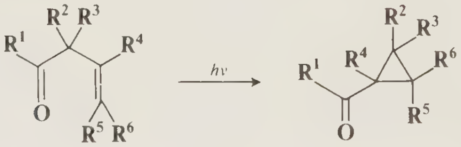
radical pathway given[515] (the C-3 substituents act to stabilize the radical), though the species



shown are not necessarily intermediates, but may be transition states. It has been shown, for the case of certain substituted substrates, that configuration is retained at C-1 and C-5 and inverted at C-3.[516]

The reaction has been extended to allylbenzenes[517] (in this case C-3 substituents are not required) and to β,γ-unsaturated ketones[518] (the latter reaction, which is called the oxa-di-π-methane rearrangement, occurs only from the triplet state).





When photolyzed, 2,5-cyclohexadienones can undergo a number of different reactions, one of which is formally the same as the di-π-methane rearrangement.[519] In this reaction, photolysis of the substrate **169** gives a bicyclo[3.1.0]hex-2-enone **174**.[520] Though the reaction is formally the same (note the conversion of **164** to **165** above), the mechanism is different from that of the di-π-methane rearrangement, because irradiation of a ketone can cause an $n \rightarrow \pi^*$ transition, which is of course not possible for a diene lacking a carbonyl group. The mechanism[520] in this case has been formulated as proceeding through the excited triplet states **171** and **172.** In step 1, the

[515] See Zimmerman, Werthemann, and Kamm, *J. Am. Chem. Soc.* **96**, 439 (1974); Zimmerman and Little, *J. Am. Chem. Soc.* **96**, 5143 (1974); Zimmerman, Boettcher, Buehler, and Keck, *J. Am. Chem. Soc.* **97**, 5635 (1975).

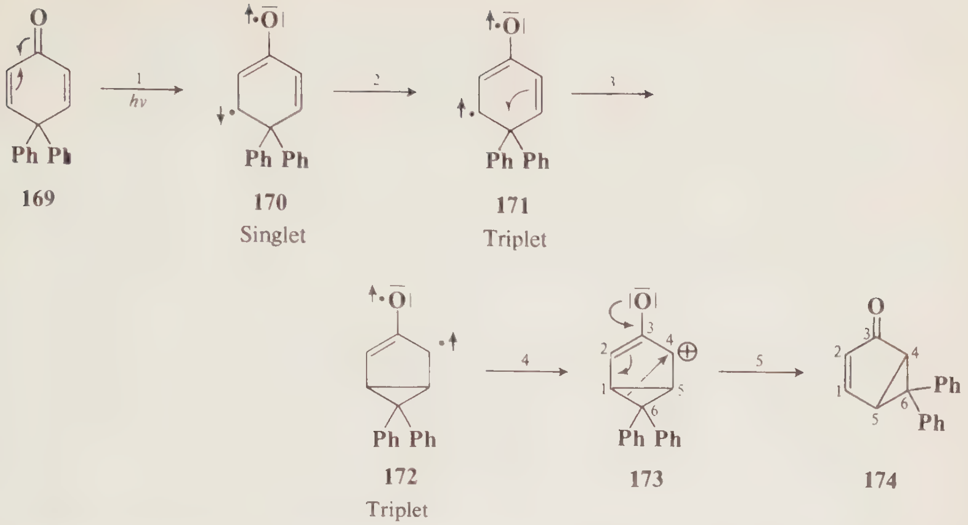
[516] Zimmerman, Robbins, McKelvey, Samuel, and Sousa, *J. Am. Chem. Soc.* **96**, 4630 (1974).

[517] For example, see Griffin, Covell, Petterson, Dodson, and Klose, *J. Am. Chem. Soc.* **87**, 1410 (1965); Hixson, *J. Am. Chem. Soc.* **94**, 2507 (1972); Cookson, Ferreira, and Salisbury, *J. Chem. Soc., Chem. Commun.* 665 (1974).

[518] For example, see Tenney, Boykin, and Lutz, *J. Am. Chem. Soc.* **88**, 1835 (1966); Dauben, Kellogg, Seeman, and Spitzer, *J. Am. Chem. Soc.* **92**, 1786 (1970); Seeman and Ziffer, *Tetrahedron Lett.* 4413 (1973).

[519] For reviews of the photochemistry of 2,5-cyclohexadienones and related compounds, see Zimmerman, *Angew. Chem. Int. Ed. Engl.* **8**, 1-11 (1969) [*Angew. Chem.* **81**, 45-55], *Adv. Photochem.* **1**, 183-208 (1963); Kropp, *Org. Photochem.* **1**, 1-90 (1967); Schaffner, *Adv. Photochem.* **4**, 81-112 (1966); Turro, "Molecular Photochemistry," pp. 162-169, W. A. Benjamin, Inc., New York, 1965; Chapman, *Adv. Photochem.* **1**, 323-420 (1963), pp. 330-344.

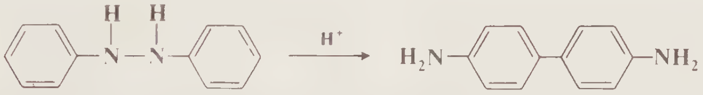
[520] Zimmerman and Schuster, *J. Am. Chem. Soc.* **83**, 4486 (1961); Zimmerman and Swenton, *J. Am. Chem. Soc.* **86**, 1436 (1964); Patel and Schuster, *J. Am. Chem. Soc.* **90**, 5137 (1968); Schuster and Patel, *J. Am. Chem. Soc.* **90**, 5145 (1968).



molecule undergoes an $n \rightarrow \pi^*$ excitation to the singlet species **170** which crosses to the triplet **171**. Step 3 is a rearrangement from one excited state to another. Step 4 is a $\pi^* \rightarrow n$ electron demotion (an intersystem crossing from $T_1 \rightarrow S_0$, see p. 218). The conversion of **173** to **174** actually consists of two 1,2 alkyl migrations (a one-step process would be a 1,3 migration of alkyl to a carbonium-ion center, see p. 972): The old $C_6—C_5$ bond becomes the new $C_6—C_4$ bond, and the old $C_6—C_1$ bond becomes the new $C_6—C_5$ bond.[521] This double-migration process is called the *slither mechanism*, as opposed to the single 1,3 migration, which in this case would be the *pivot mechanism*.

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[522]

8-44 The Benzidine Rearrangement



When hydrazobenzene is treated with acids, it rearranges to give about 70% 4,4′-diaminobiphenyl (benzidine) and about 30% 2,4′-diaminobiphenyl (**175**). This reaction is called the *benzidine rearrangement* and is general for N,N′-diarylhydrazines.[523] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced. These are the 2,4′-diaminobiaryl (**175**), already referred to, the 2,2′-diaminobiaryl (**176**), and the *o*- and *p*-arylaminoanilines (**177**

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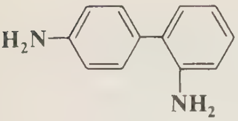
[521] Zimmerman, Crumrine, Döpp, and Huyffer, *J. Am. Chem. Soc.* **91**, 434 (1969).

[522] For reviews, see Quinkert, *Angew. Chem. Int. Ed. Engl.* **11**, 1072–1087 (1972) [*Angew. Chem.* **84**, 1157–1173]; Kropp, Ref. 519; Chapman, Ref. 519, pp. 344–351.

[523] For reviews, see Williams, in Bamford and Tipper, Ref. 341, vol. 13, pp. 437–448 (1972), Shine, *Mech. Mol. Migr.* **2**, 191–247 (1969), "Aromatic Rearrangements," Ref. 436, pp. 126–179; *MTP Int. Rev. Sci.: Org. Chem., Ser. One* **3**, 79–85 (1973); Banthorpe, *Top. Carbocyclic Chem.* **1**, 1–62 (1969); Lukashevich, *Russ. Chem. Rev.* **36**, 895–902 (1967); Cox and Buncel, in Patai, "The Chemistry of the Hydrazo, Azo, and Azoxy Groups," pt. 2, pp. 775–807, John Wiley & Sons, Inc., New York, 1975.



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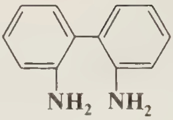

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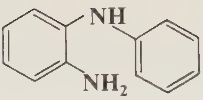

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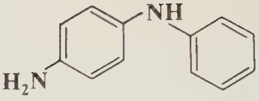

178

and **178**), called *semidines*. The 2,2′-diaminobiaryl and the *p*-semidine are formed less often and in smaller amounts than the other two side products. Usually, the 4,4′-diaminobiaryl predominates, except when one or both of the para positions of the diarylhydrazine are occupied. However, the 4,4′-diamine may still be produced, even if the para positions are occupied. If SO_3H, COOH, or Cl (but not R, Ar, or NR_2) is present in the para position, it may be ejected. With dinaphthylhydrazines, the major products are not the 4,4′-diaminobinaphthyls, but the 2,2′ isomers. Another side reaction is disproportionation to $ArNH_2$ and ArN═NAr. For example, p,p'-PhC_6H_4NH-NHC_6H_4Ph gives 88% disproportionation products at 25°C.[524]

The mechanism has been exhaustively studied, and several mechanisms have been proposed. At one time it was believed that NHAr broke away from ArNHNHAr and then became attached to the para position to give the semidine (**178**), which then went on to product. The fact that semidines could be isolated lent this argument support, as did the fact that this would be analogous to the rearrangements considered in Chapter 11 (reactions **1-36** to **1-40**). However, this theory was killed when it was discovered that semidines could not be converted to benzidines under the reaction conditions. Cleavage into two independent pieces (either ions or free radicals) has been ruled out by many types of crossover experiments, which always show that the two rings of the starting material are in the product; that is, ArNHNHAr′ gives no molecules (of any of the five products) containing two Ar groups or two Ar′ groups, and mixtures of ArNHNHAr and Ar′NHNHAr′ give no molecules containing both Ar and Ar′. An important discovery was the fact that although the reaction is always first order in substrate, it may be either first[525] or second[526] order in $[H^+]$. The generalized rate law is (S = substrate):

$$\frac{-d(S)}{dt} = k_2[S][H^+] + k_3[S][H^+]^2$$

However, the values of k_2 and k_3 are such that with some substrates the reaction is entirely first order in $[H^+]$, while with others it is entirely second order in $[H^+]$, regardless of the acidity. With still other substrates, the reaction is first order in $[H^+]$ at low acidities and second order at higher acidities. With the latter substrates fractional orders can often be observed,[527] because at intermediate acidities both processes take place simultaneously. These kinetic results seem to indicate that the actual reacting species can be either the monoprotonated substrate $\mathrm{ArNH\overset{\oplus}{N}H_2Ar}$ or the diprotonated $\mathrm{Ar\overset{\oplus}{N}H_2\overset{\oplus}{N}H_2Ar}$. A mechanism which accounts for most of the known facts was devised by Banthorpe, Hughes, and Ingold. This mechanism, called the "polar-transition-state" mechanism, has the electrons moving around a ring, with the rings linking up in the 2,2′, 4,4′, or 2,4′ manner. These intermediates can go to product, they can convert from one to another (shown for the 2,2′ → the 4,4′), or they can go to semidine (shown for 2,2′ → the *o*-semidine):

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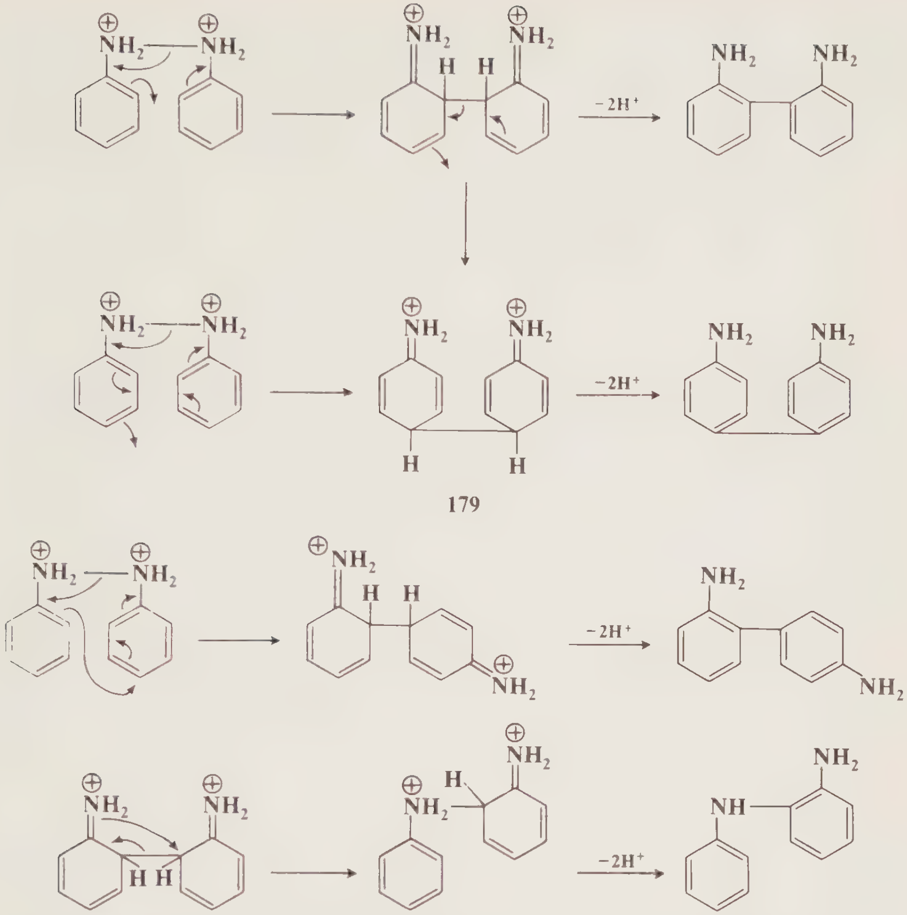
[524] Shine and Stanley, *J. Org. Chem.* **32,** 905 (1967).

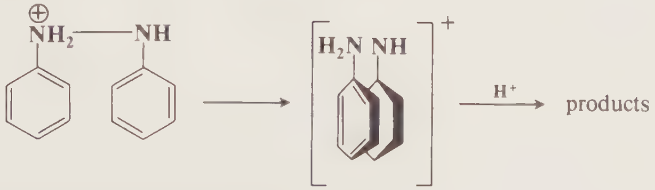
[525] Banthorpe, Hughes, and Ingold, *J. Chem. Soc.* 2386, 2402, 2407, 2413, 2418, 2429 (1962); Shine and Chamness, *J. Org. Chem.* **28,** 1232 (1963); Banthorpe and Cooper, *J. Chem. Soc. B* 605 (1968); Banthorpe, Cooper, and Ingold, *J. Chem. Soc. B* 609 (1968); Banthorpe and O'Sullivan, *J. Chem. Soc. B* 627 (1968).

[526] Hammond and Shine, *J. Am. Chem. Soc.* **72,** 220 (1950); Banthorpe and O'Sullivan, *J. Chem. Soc. B* 615 (1968); Banthorpe and Cooper, *J. Chem. Soc. B* 618 (1968); Banthorpe, Cooper, and O'Sullivan, *J. Chem. Soc. B* 2054 (1971).

[527] Carlin and Odioso, *J. Am. Chem. Soc.* **76,** 100 (1954); Banthorpe, Ingold, and Roy, *J. Chem. Soc. B* 64 (1968); Banthorpe, Ingold, and O'Sullivan, *J. Chem. Soc. B* 624 (1968).



The diion **179** was obtained as a stable species in super-acid solution at −78°C by treatment of hydrazobenzene with FSO_3H-SO_2 (SO_2ClF).[528] Though the mechanism shown above begins with the diprotonated substrate, the polar-transition-state mechanism can also account for the reaction with monoprotonated substrate. Another mechanism, called the "π-complex mechanism," was proposed by Dewar;[529] it envisions cleavage of the monoprotonated substrate into two parts which are held together by a π-orbital overlap between a filled orbital of the benzene-type ring and an empty orbital of the other.[530]



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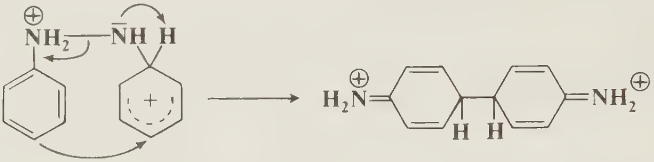
[528] Olah, Dunne, Kelly, and Mo, *J. Am. Chem. Soc.* **94**, 7438 (1972).

[529] Dewar, in Mayo, Ref. 1, vol. 1, pp. 323–344.

[530] For a criticism of this proposal, see Banthorpe, *Chem. Rev.* **70**, 295–322 (1970), pp. 315–317, 322.

Since the rings are held together at the centers, it is easy to see how they can rotate to form the various products. In this view the role of the second proton is to attack the complex in the rate-determining step.

Another proposal is that the second proton protonates one of the ring carbons (in the ipso position) and that the mechanism is simply an electrophilic substitution (shown for formation of the 4,4′-diaminobiphenyl, but the other products can be similarly rationalized).[531] A radical cation mechanism has also been proposed.[532] Complicating matters further was the discovery that the rearrangement can proceed without any acid at all, merely on heating.[533] Photochemical benzidine rearrangements are also known.[534]



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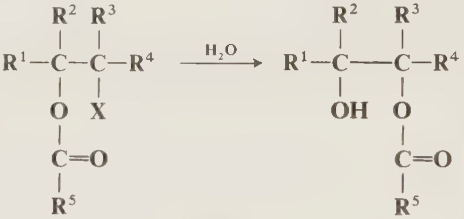
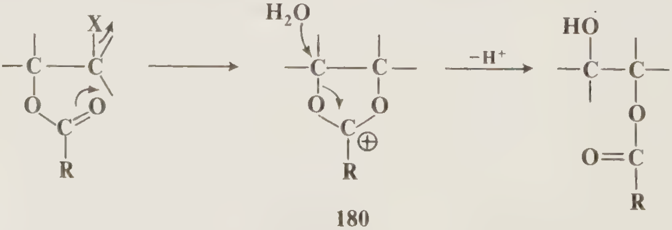
Despite the immense amount of work done on this unique reaction, it seems that much more needs to be done before a mechanism is established on which all can agree.

8-45 Acyl Rearrangements



There are two basic kinds of acyl rearrangements. One of these, illustrated above, involves migration of an acyloxy group to a position formerly occupied by a leaving group, and the replacement of the acyloxy group by a nucleophile. The reaction is similar in appearance to reaction **8-13**, but the mechanism is not entirely the same. The acyloxy group does replace the leaving group in an SN2 process and is replaced in turn by another SN2 process (as in reaction **8-13**), but it is not the alkyl oxygen which attacks, but the acyl oxygen; that is, the transition state is five-membered and not three-membered:



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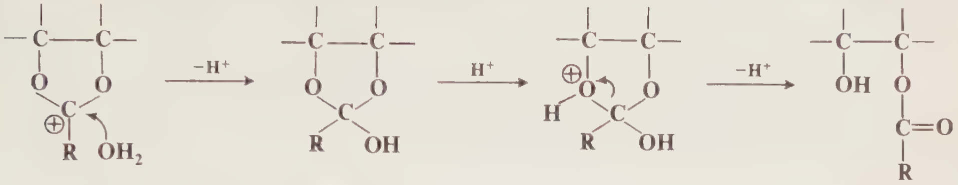
[531] Allan, *Tetrahedron Lett.* 4225 (1971), *Monatsh. Chem.* **106**, 429 (1975); Olah et al., Ref. 528. For a criticism of this proposal, see Banthorpe, *Tetrahedron Lett.* 2707 (1972).

[532] For example, see Svanholm, Bechgaard, Hammerich, and Parker, *Tetrahedron Lett.* 3675 (1972).

[533] Shine and Trisler, *J. Am. Chem. Soc.* **82**, 4054 (1960); Banthorpe and Hughes, *J. Chem. Soc.* 2849, 2860 (1964); Banthorpe, *J. Chem. Soc.* 2854 (1964).

[534] See for example, Cheng and Shine, *J. Org. Chem.* **39**, 2835 (1974).

180 can be opened in two ways: (1) attack by the nucleophile at the position which is more favorable, the reaction thus becoming either a nucleophilic substitution by the neighboring-group mechanism or a rearrangement (this path is shown above), or (2) attack at the *carbonyl* carbon:



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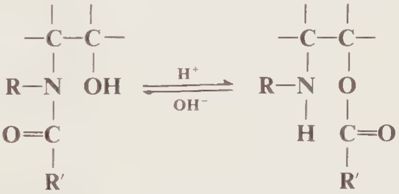
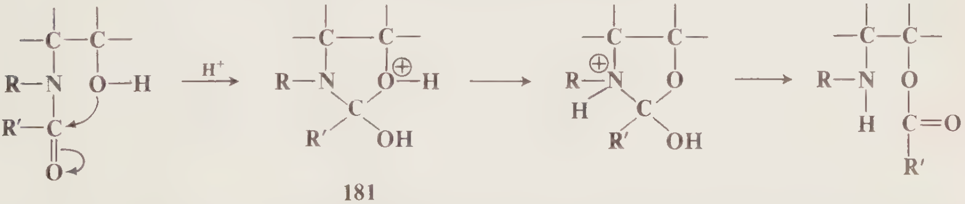
Of course, ring opening in the other direction gives the substitution and not the rearrangement product. When the nucleophile is water, then rearrangement by path 1 or by path 2 gives the same product, and similarly for substitution. The paths may be told apart by the difference in stereochemical consequences. For rearrangement, path 1 requires inversion at both carbons, while path 2 requires retention at the migration origin (C-1) and inversion at the terminus (C-2). Substitution by path 1 involves retention at both carbons, while path 2 predicts retention at C-1 and inversion at C-2. The leaving group may be halo, OTs, OH_2^+, or any other good SN leaving group. Besides water, the nucleophile may be ROH or RCOOH, in which case OR or OCOR appears in the product instead of OH. However, with these nucleophiles the reaction proceeds only by path 1, or if it does take path 2, then the reaction stops at the ortho ester stage (**181**, with OR or OCOR instead of OH). Analogous reactions have been carried out with nitrogen or sulfur replacing one or both of the acyloxy oxygens.

In the second type of acyl rearrangement,[535] there is a 1,4 or longer migration of an acyl (RCO) or an acyloxy (ROCO) group from one hetero atom to another, e.g.,



This type of reaction is undergone by N- and O-acylated amino alcohols and conceivably by monoacylated 1,2-diamines and 1,2-glycols and the sulfur analogs of these compounds, though not many of these possibilities have been examined. The mechanism is



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In this particular case, nitrogen-to-oxygen migration can be accomplished with acids (which stabilize the amine as the salt) and the reverse oxygen-to-nitrogen migration with bases. The stereochemistry must involve retention at both carbons.[536] These reactions are actually internal examples of alcoholysis of amides (p. 367) and of acylation of amines by esters (reaction **0-57**). Transannular rearrangements of this type have also been reported.

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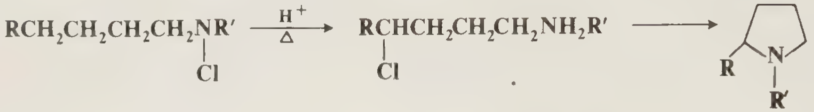
[535] For a review, see Pavlova and Rachinskii, *Russ. Chem. Rev.* 37, 587–602 (1968).

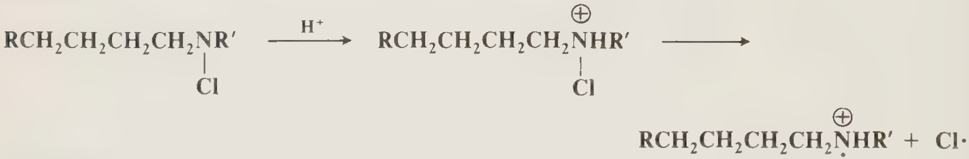
There are no *Organic Syntheses* references, but see OS V, 650 for a related reaction.

8-46 The Hofmann-Löffler and Related Reactions



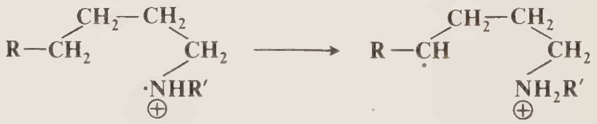
A common feature of the reactions in this section[537] is that they serve to introduce functionality at a position remote from functional groups already present. As such they have proved very useful in synthesizing many compounds, especially in the steroid field (see also reactions **9-3** and **9-16**). When N-haloamines in which one alkyl group has a hydrogen in the 4 or 5 position are heated with sulfuric acid, pyrrolidines or piperidines are formed, in a reaction known as the *Hofmann-Löffler reaction* (also called the *Hofmann-Löffler-Freytag reaction*).[538] R′ is normally alkyl, but the reaction has been extended to R′ = H by use of concentrated sulfuric acid solution and ferrous salts.[539] The first step of the reaction is a rearrangement, with the halogen migrating from the nitrogen to the 4 or 5 position of the alkyl group. It is possible to isolate the resulting haloamine salt, but usually this is not done, and the second step, the ring closure (reaction **0-46**), takes place. Though the reaction is most often induced by heat, this is not necessary, and irradiation and chemical initiators (e.g., peroxides) have been used instead. The mechanism is of a free-radical type, with the main step involving an internal hydrogen abstraction.[540]

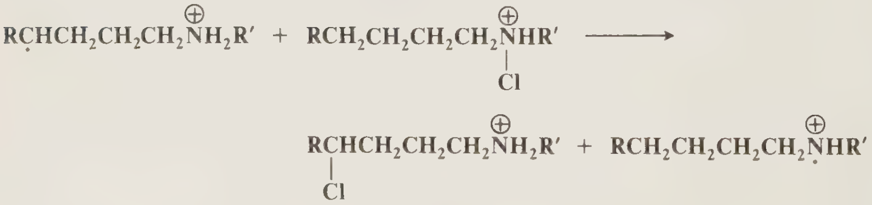
Initiation



$$RCH_2CH_2CH_2CH_2\underset{\underset{\displaystyle Cl}{|}}{N}R' \xrightarrow{H^+} RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\underset{\displaystyle Cl}{|}}{N}}HR' \longrightarrow RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\bullet}{N}}HR' + Cl\cdot$$

Propagation





$$R\underset{\bullet}{C}HCH_2CH_2CH_2\overset{\oplus}{N}H_2R' + RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\underset{\displaystyle Cl}{|}}{N}}HR' \longrightarrow R\underset{\underset{\displaystyle Cl}{|}}{C}HCH_2CH_2CH_2\overset{\oplus}{N}H_2R' + RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\bullet}{N}}HR'$$

etc.

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[536] Confirmation that this reaction gives retention at the migration terminus while the other type of acyl rearrangement gives inversion was obtained by ^{18}O labeling: Welsh, *J. Org. Chem.* **32,** 119 (1967).

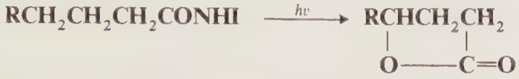
[537] For a review of the reactions in this section, see Carruthers, "Some Modern Methods of Organic Synthesis," pp. 172–197, Cambridge University Press, London, 1971.

[538] For reviews, see Sosnovsky and Rawlinson, *Adv. Free-Radical Chem.* **4,** 203–284 (1972), pp. 249–259; Deno, *Methods Free-Radical Chem.* **3,** 135–154 (1972), pp. 136–143; Wolff, *Chem. Rev.* **63,** 55–64 (1963).

[539] Schmitz and Murawski, *Chem. Ber.* **99,** 1493 (1966).

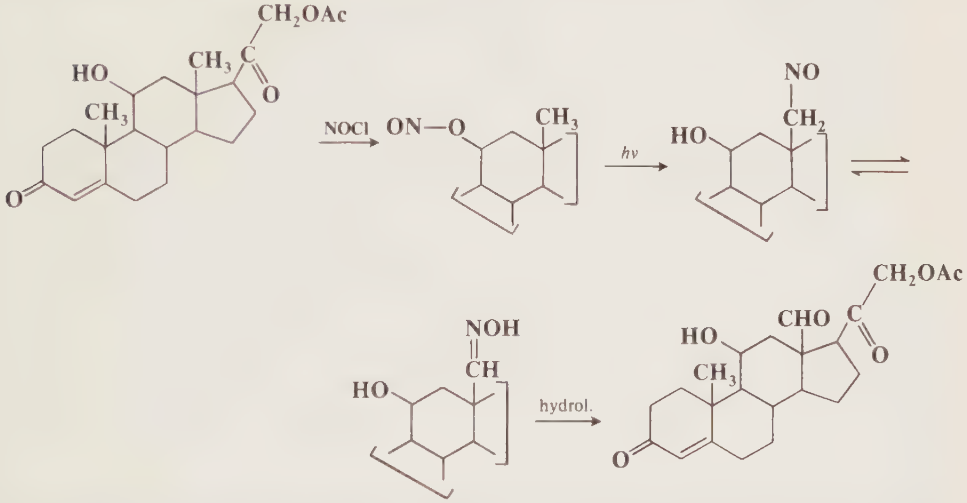
[540] Wawzonek and Thelan, *J. Am. Chem. Soc.* **72,** 2118 (1950).

A similar reaction has been carried out on N-halo amides, which give γ-lactones:[541]

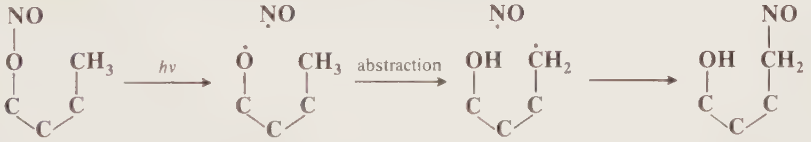


$$\mathrm{RCH_2CH_2CH_2CONHI} \xrightarrow{h\nu} \begin{array}{l}\mathrm{RCHCH_2CH_2} \\ \;\;|\qquad\;\;\; | \\ \;\mathrm{O}\text{——}\mathrm{C{=}O}\end{array}$$

Another related reaction is the *Barton reaction*,[542] by means of which a methyl group in the δ position to an OH group can be oxidized to a CHO group. The alcohol is first converted to the nitrite ester. Photolysis of the nitrite results in conversion of the nitrite group to the OH group, and nitrosation of the methyl group. Hydrolysis of the oxime tautomer gives the aldehyde, e.g.,[543]



This reaction takes place only when the methyl group is in a favorable steric position. The mechanism is similar to that of the Hofmann-Löffler reaction.[544]



This is one of the few known methods for effecting substitution at an angular methyl group. Not only $\mathrm{CH_3}$ groups but also alkyl groups of the form $\mathrm{RCH_2}$ and $\mathrm{R_2CH}$ can give the Barton reaction if the geometry of the system is favorable. An $\mathrm{RCH_2}$ group is converted to the oxime R(C=NOH)[545] (which is hydrolyzable to a ketone) or to a nitroso dimer, while an $\mathrm{R_2CH}$ group gives a nitroso compound $\mathrm{R_2C(NO)}$. With very few exceptions, the only carbons which become nitrosated are those in the position δ to the original OH group, indicating that a six-membered transition state is necessary for the hydrogen abstraction.

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[541] Barton, Beckwith, and Goosen, *J. Chem. Soc.* 181 (1965); Petterson and Wambsgans, *J. Am. Chem. Soc.* **86**, 1648 (1964); Neale, Marcus, and Schepers, *J. Am. Chem. Soc.* **88**, 3051 (1966). For a review of N-halo amide rearrangements, see Neale, *Synthesis* 1–15 (1971).

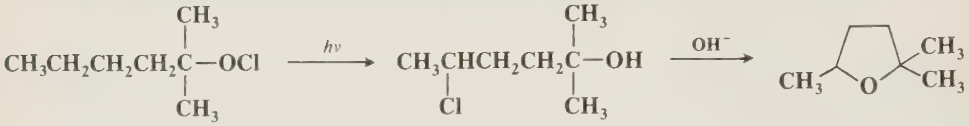
[542] For reviews, see Hesse, *Adv. Free-Radical Chem.* **3**, 83–137 (1969); Barton, *Pure Appl. Chem.* **16**, 1–15 (1968); Akhtar, *Adv. Photochem.* **2**, 263–304 (1964).

[543] Barton and Beaton, *J. Am. Chem. Soc.* **83**, 4083 (1961). Also see Barton, Beaton, Geller, and Pechet, *J. Am. Chem. Soc.* **82**, 2640 (1960).

[544] Kabasakalian and Townley, *J. Am. Chem. Soc.* **84**, 2711 (1962); Akhtar, Barton, and Sammes, *J. Am. Chem. Soc.* **87**, 4601 (1965).

[545] For an example, see Reimann and Sarre, *Can. J. Chem.* **49**, 344 (1971).

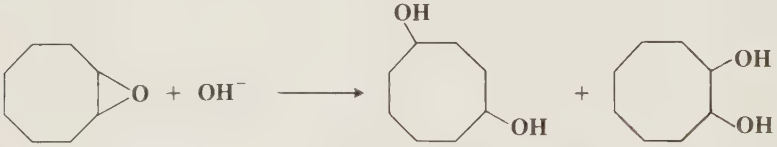
Another reaction with a similar mechanism is the photolytic conversion of tertiary hypohalites to δ-chloro alcohols, which can then be cyclized to tetrahydrofurans.[546]



OS III, 159.

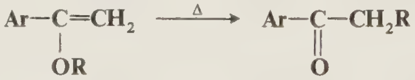
D. Noncyclic Rearrangements

8-47 Hydride Shifts



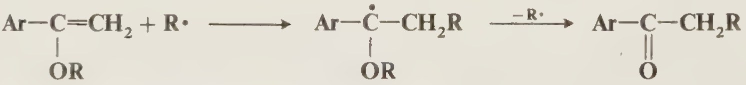
The above is a typical example of a transannular hydride shift. The 1,2-glycol is formed by a normal epoxide hydrolysis reaction (**0-8**). For a discussion of 1,3 and longer hydride shifts, see p. 972.

8-48 Rearrangement of Enol Ethers and Tosylates



$$\mathrm{Ar{-}\underset{\substack{|\\ OR}}{C}{=}CH_2} \xrightarrow{\Delta} \mathrm{Ar{-}\underset{\substack{\|\\ O}}{C}{-}CH_2R}$$

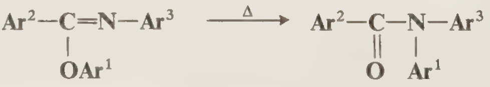
When vinyl ethers of the form $\mathrm{ArC(OR){=}CH_2}$ are heated, they rearrange to ketones. This is a 1,3 shift of R from O to C.[547] It is an intermolecular process and involves free radicals.[548] After some type of initiation step, the propagation steps are



$$\mathrm{Ar{-}\underset{\substack{|\\ OR}}{C}{=}CH_2 + R\cdot} \longrightarrow \mathrm{Ar{-}\underset{\substack{|\\ OR}}{\dot{C}}{-}CH_2R} \xrightarrow{-\mathrm{R}\cdot} \mathrm{Ar{-}\underset{\substack{\|\\ O}}{C}{-}CH_2R}$$

In a reaction with a similar mechanism, enol tosylates $\mathrm{RC(OTs){=}CHR'}$ are converted by heat or photolytically to α-tosyl ketones $\mathrm{RCOCHR'Ts}$.[549]

8-49 The Chapman Rearrangement



$$\mathrm{Ar^2{-}\underset{\substack{|\\ OAr^1}}{C}{=}N{-}Ar^3} \xrightarrow{\Delta} \mathrm{Ar^2{-}\underset{\substack{\|\\ O}}{C}{-}\underset{\substack{|\\ Ar^1}}{N}{-}Ar^3}$$

In the *Chapman rearrangement*, N,N-diaryl amides are formed when aryl imino esters are heated.

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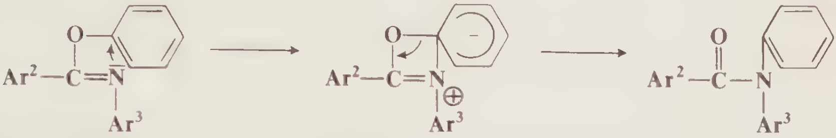
[546] Greene, Savitz, Lau, Osterholtz, and Smith, *J. Am. Chem. Soc.* **83**, 2196 (1961); Walling and Padwa, *J. Am. Chem. Soc.* **83**, 2207 (1961). See also Akhtar and Barton, *J. Am. Chem. Soc.* **83**, 2213 (1961). For a review for the case of hypobromites, see Brun and Waegell, *Tetrahedron* **32**, 517–527 (1976).

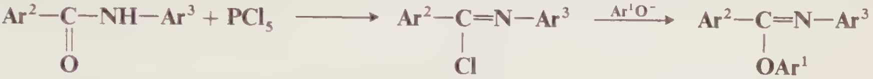
[547] For a review of 1,3 migrations of R, see Landis, *Mech. Mol. Migr.* **2**, 43–63 (1969).

[548] Wiberg, Kintner, and Motell, *J. Am. Chem. Soc.* **85**, 450 (1963), and references cited therein.

[549] Frydman and Mazur, *J. Am. Chem. Soc.* **92**, 3203 (1970).

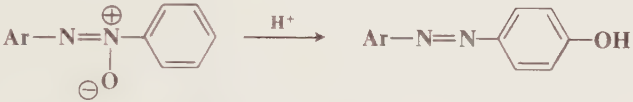
The reaction is similar in appearance to reaction **8-48**.[550] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[551] though the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, for example, alkyl, halo, OR, CN, COOR, etc. Aryl migrates best when it contains electron-withdrawing groups. On the other hand, electron-withdrawing groups in Ar^2 or Ar^3 decrease the reactivity. The products may be hydrolyzed to diarylamines, and this is a method for preparing these compounds. The mechanism is different from that of reaction **8-48** and probably involves an intramolecular[552] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift. Imino esters can be prepared from N-aryl amides by reaction with PCl_5, followed by treatment of the resulting imino chloride with an aroxide ion.[553] Imino esters with any or all of the three groups being alkyl also rearrange, but they require catalysis by H_2SO_4 or a trace of methyl iodide or methyl sulfate.[547] The mechanism is different, however, involving an intermolecular process. This is also true for derivatives of formamide (Ar^2 = H).





$$Ar^2-\underset{\underset{O}{\|}}{C}-NH-Ar^3 + PCl_5 \longrightarrow Ar^2-\underset{\underset{Cl}{|}}{C}=N-Ar^3 \xrightarrow{Ar^1O^-} Ar^2-\underset{\underset{OAr^1}{|}}{C}=N-Ar^3$$

8-50 The Wallach Rearrangement



182 **183**

The conversion of azoxy compounds, on acid treatment, to *p*-hydroxy azo compounds (or sometimes the *o*-hydroxy isomers[554]) is called the *Wallach rearrangement*.[555] Although the mechanism[556] is not completely settled, the following facts are known: (1) The para rearrangement is intermolecular.[557] (2) When the reaction was carried out with an azoxy compound in which the N—O nitrogen was labeled with ^{15}N, *both* nitrogens of the product carried the label equally,[558] demonstrating that the oxygen did not have a preference for migration to either the near or the far ring. This shows that there is a symmetrical intermediate. (3) Kinetic studies show that two protons are normally required for the reaction.[559] The following mechanism,[560] involving the symmetrical intermediate **185**, has been proposed to explain the facts.[561]

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[550] For reviews, see Schulenberg and Archer, *Org. React.* **14**, 1–51 (1965); McCarty, in Patai, Ref. 234, pp. 439-447, McCarty and Garner, in Patai, "The Chemistry of Amidines and Imidates," pp. 189–240, John Wiley & Sons, Inc., New York, 1975.

[551] Wheeler, Roman, Santiago, and Quiles, *Can. J. Chem.* **47**, 503 (1969).

[552] For evidence for the intramolecular character of the reaction, see Wiberg and Rowland, *J. Am. Chem. Soc.* **77**, 2205 (1955); Wheeler, Roman, and Rosado, *J. Org. Chem.* **34**, 966 (1969).

[553] For a review of the formation and reactions of imino chlorides, see Bonnett, in Patai, Ref. 234, pp. 597–662.

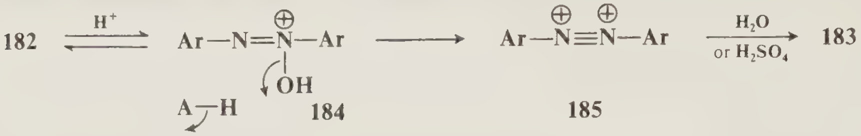
[554] For example, see Dolenko and Buncel, *Can. J. Chem.* **52**, 623 (1974); Yamamoto, Nishigaki, Imagawa, Umezu, and Matsuura, *Chem. Lett.* 261 (1976).

[555] For reviews, see Buncel, *Mech. Mol. Migr.* **1**, 61–119 (1968); Shine, "Aromatic Rearrangements," Ref. 436, pp. 272–284, 357–359; Cox and Buncel, Ref. 523, pp. 808–837.

[556] For a review, see Buncel, *Acc. Chem. Res.* **8**, 132–139 (1975).

[557] See for example, Oae, Fukumoto, and Yamagami, *Bull. Chem. Soc. Jpn.* **36**, 601 (1963).

[558] Shemyakin, Maimind, and Vaichunaite, *Chem. Ind. (London)* 755 (1958), *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 808 (1960). Also see Behr and Hendley, *J. Org. Chem.* **31**, 2715 (1966).



It has proved possible to obtain **184** and **185** as stable acids in super-acid solutions.[528] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[562]

When other nucleophiles are used, it may be possible to obtain *o*- or *p*-substituted azo compounds as products. For example, azoxybenzene reacts with aryl sulfonyl chlorides $ArSO_2Cl$ to give *o*- and *p*-arenesulfonyloxaazobenzenes $PhN{=}NC_6H_4OSO_2Ar$.[563]

A photochemical Wallach rearrangement is also known: The product is the *o*-hydroxy azo compound, the OH group is found in the farther ring, and the rearrangement is intramolecular.[564]

[559] Buncel and Lawton, *Chem. Ind.* (*London*) 1835 (1963); Hahn, Lee, and Jaffé, *J. Am. Chem. Soc.* **89,** 4975 (1967); Cox, *J. Am. Chem. Soc.* **96,** 1059 (1974).

[560] Buncel and Lawton, *Can. J. Chem.* **43,** 862 (1965); Buncel and Strachan, *Can. J. Chem.* **48,** 377 (1970); Cox, Ref. 559.

[561] For other proposed mechanisms, see Shemyakin, Maimind, and Agadzhanyan, *Chem. Ind.* (*London*) 1223 (1961); Shemyakin, Agadzhanyan, Maimind, and Kudryavtsev, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1216 (1963); Hahn, Lee, and Jaffé, Ref. 559; Duffey and Hendley, *J. Org. Chem.* **33,** 1918 (1968); Hendley and Duffey, *J. Org. Chem.* **35,** 3579 (1970).

[562] Cox, Dolenko, and Buncel, *J. Chem. Soc., Perkin Trans. 2* 471 (1975); Cox and Buncel, *J. Am. Chem. Soc.* **97,** 1871 (1975).

[563] Oae, Maeda, Kozuka, and Nakai, *Bull. Chem. Soc. Jpn.* **44,** 2495 (1971). For other examples, see Stevens, *J. Org. Chem.* **33,** 2667 (1968); Oae and Maeda, *Tetrahedron* **28,** 2127 (1972).

[564] For discussions of the mechanism of the photochemical reaction, see Goon, Murray, Schoch, and Bunce, *Can. J. Chem.* **51,** 3827 (1973); Squire and Jaffé, *J. Am. Chem. Soc.* **95,** 8188 (1973).

Nineteen

Oxidations and Reductions

First we must examine what we mean when we speak of oxidation and reduction. Inorganic chemists define oxidation in two ways: loss of electrons and increase in oxidation number. In organic chemistry, these definitions, while still technically correct, are not easy to apply. While electrons are directly transferred in some organic oxidations and reductions (see p. 1075), the mechanisms of most of these reactions do not involve a direct electron transfer. As for oxidation number, while this is easy to apply in some cases, e.g., the oxidation number of carbon in CH_4 is -4, in most cases attempts to apply the concept lead to fractional values or to apparent absurdities. Thus, carbon in propane has an oxidation number of -2.67 and in butane of -2.5, though organic chemists seldom think of these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them (for example, the two carbons in acetic acid are obviously in different oxidation states), but for this a whole set of arbitrary assumptions would be required, since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. There would seem little to be gained by such a procedure. What organic chemists have done—though more by custom than by any formal agreement—is to set up a series of functional groups, in a qualitative way, arranged in order of increasing oxidation state, and then to define oxidation as *the conversion of a functional group in a molecule from one category to a higher one*. Reduction is the opposite. For the simple functional groups this series is shown in Table 1.[1] It should be noted that this classification applies only to a single carbon atom or to two adjacent carbon atoms. Thus 1,3-dichloropropane is in the same oxidation state as chloromethane, but 1,2-dichloropropane is in a higher one. Obviously, such distinctions are somewhat arbitrary, and if we attempt to carry them too far, we shall find ourselves painted into a corner. Nevertheless the basic idea will serve us well. It should be noted that conversion of any compound to another in the same category is not an oxidation or a reduction. Most oxidations in organic chemistry involve a gain of oxygen and or a loss of hydrogen. The reverse is true for reductions.

Of course, there is no oxidation without a concurrent reduction. However, we classify reactions as oxidations or reductions depending on whether the *organic compound* is oxidized or reduced. In some cases both the oxidant and reductant are organic, and we will consider those reactions separately.

MECHANISMS

It must be noted that our definition of oxidation has nothing to do with mechanism. Thus the conversions of bromomethane to methanol with KOH (reaction **0-1**) and to methane with $LiAlH_4$ (reaction **0-77**) have the same SN2 mechanisms, but one is a reduction (according to our

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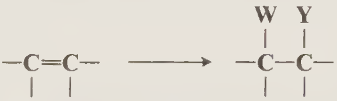
[1] For more extensive tables, with subclassifications, see Soloveichik and Krakauer, *J. Chem. Educ.* **43**, 532–535 (1966).

TABLE 1 Categories of simple functional groups arranged according to oxidation state

Oxidation is the conversion of a functional group in a molecule to a higher category; reduction is conversion to a lower one. Conversions within a category are neither oxidations nor reductions. The numbers given at the bottom are only approximations

RH	$-\overset{\vert}{C}=\overset{\vert}{C}-$ ROH RCl RNH_2 etc.	$-C\equiv C-$ $R-\underset{\overset{\Vert}{O}}{C}-R$ $-\underset{\underset{Cl}{\vert}}{\overset{\vert}{C}}-Cl$ $-\underset{\underset{Cl}{\vert}}{\overset{\vert}{C}}-\underset{\underset{Cl}{\vert}}{\overset{\vert}{C}}-$ $-\underset{\underset{OH}{\vert}}{\overset{\vert}{C}}-\underset{\underset{OH}{\vert}}{\overset{\vert}{C}}-$ etc.	$R-\underset{\overset{\Vert}{O}}{C}-OH$ $R-\underset{\overset{\Vert}{O}}{C}-NH_2$ $-\underset{\underset{Cl}{\vert}}{\overset{\overset{Cl}{\vert}}{C}}-Cl$ etc.	CO_2 CCl_4
		Approximate oxidation number		
−4	−2	0	+2	+4

definition), and the other is not. It is impractical to consider the mechanisms of oxidation and reduction reactions in broad categories in this chapter as we have done for the reactions considered in Chapters 10 to 18.[2] The main reason is that the mechanisms are too diverse, and this in turn is because the bond changes are too different. For example, in Chapter 15, all the reactions involved the following bond change (with respect to the substrate):



$$-\underset{|}{C}=\underset{|}{C}- \longrightarrow -\underset{|}{\overset{\overset{W}{|}}{C}}-\underset{|}{\overset{\overset{Y}{|}}{C}}-$$

and a relatively few mechanisms covered all the reactions. But for oxidations and reductions the bond changes are far more diverse. Another reason is that the mechanism of a given oxidation or reduction reaction often varies greatly with the oxidizing or reducing agent employed. Very often the mechanism has been studied intensively for only one or a few of many possible agents. A third reason is closely related: As a class, less work has been done on the mechanisms of oxidation-reduction reactions than on the reactions covered in previous chapters. However, in recent years the pace in the area has been increasing rapidly, and it is likely that before long this reason will no longer apply.

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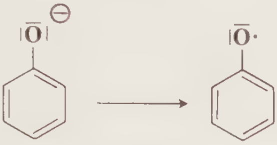
[2] For monographs on oxidation mechanisms, see "Oxidation in Organic Chemistry," Academic Press, New York, pt. A [Wiberg (ed.)], 1965; pt. B [Trahanovsky (ed.)], 1973; Waters, "Mechanisms of Oxidation of Organic Compounds," John Wiley & Sons, Inc., New York, 1964; Stewart, "Oxidation Mechanisms," W. A. Benjamin, Inc., New York, 1964. For a review, see Wiberg, *Surv. Prog. Chem.* **1**, 211–248 (1963).

Though we therefore do not cover oxidation and reduction mechanisms in the same way as we have covered other mechanisms, it is still possible to list a few broad mechanistic categories. In doing this, we follow the scheme of Wiberg.[3]

1. *Direct electron transfer.* We have already met a few reactions in which the reduction is actually a direct gain of electrons or the oxidation a direct loss of them. An example is the Birch reduction (reaction **5-13**), where sodium directly transfers an electron to an aromatic ring. An example from this chapter is found in the bimolecular reduction of ketones (reaction **9-67**), where again it is a metal which supplies the electrons. This kind of mechanism is found largely in three types of reaction:[4] (a) the oxidation or reduction of a free radical (oxidation to a positive or reduction to a negative ion), (b) the oxidation of a negative ion or the reduction of a positive ion to a comparatively stable free radical, and (c) electrolytic oxidations or reductions (an example being the Kolbe reaction, **4-38**). An important example of the second type is oxidation of amines and phenolate ions:



These reactions occur easily because of the relative stability of the radicals involved.[5]

2. *Hydride transfer.*[6] In some reactions a hydride ion is transferred to or from the substrate. The reduction of epoxides with $LiAlH_4$ is an example (reaction **0-81**). Another is the Cannizzaro reaction (**9-74**), in which one organic species transfers a hydride ion to another and is itself oxidized, while the other is reduced. Reactions in which a carbonium ion abstracts a hydride ion belong in this category:[7]

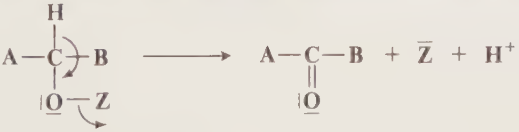
$$\mathbf{R^+ + R'H \longrightarrow RH + R'^+}$$

3. *Hydrogen-atom transfer.* Many oxidation and reduction reactions are free-radical substitutions and involve the transfer of a hydrogen atom. For example, one of the two main propagation steps of reaction **4-1** involves abstraction of hydrogen:

$$\mathbf{RH + Cl\cdot \longrightarrow R\cdot + HCl}$$

This is the case for many of the reactions of Chapter 14.

4. *Formation of ester intermediates.* A number of oxidations involve the formation of an ester intermediate (usually of an inorganic acid), and then the cleavage of this intermediate:



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[3] Wiberg, *Surv. Prog. Chem.* **1,** 211–248 (1963).

[4] Littler and Sayce, *J. Chem. Soc.* 2545 (1964).

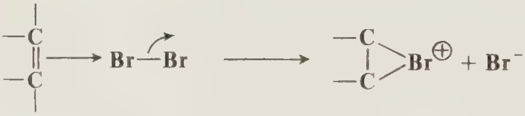
[5] For a review of the oxidation of phenols, see Mihailović and Čeković, in Patai, "The Chemistry of the Hydroxyl Group," pt. 1, pp. 505–592, Interscience Publishers, New York, 1971.

[6] For reviews, see Deno, Peterson, and Saines, *Chem. Rev.* **60,** 7–14 (1960); Kursanov and Parnes, *Russ. Chem. Rev.* **30,** 598–602 (1961).

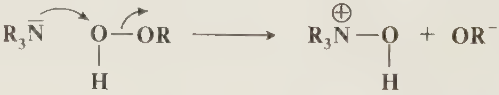
[7] For a review of these reactions, see Nenitzescu, in Olah and Schleyer, "Carbonium Ions," vol. 2, pp. 463–520, Interscience Publishers, New York, 1970.

Z is usually CrO_3H, MnO_3, or a similar inorganic acid moiety. One example of this mechanism was seen in reaction **4-6**, where A was an alkyl or aryl group, B was OH, and Z was CrO_3H. Another is the oxidation of a secondary alcohol to a ketone (reaction **9-4**), where A and B are alkyl or aryl groups and Z is also CrO_3H. In the lead tetraacetate oxidation of glycols (reaction **9-8**) the mechanism also follows this pattern, but the positive leaving group is carbon instead of hydrogen. It should be noted that the cleavage shown is actually an example of an E2 elimination mechanism. Reaction **7-44** is another example.

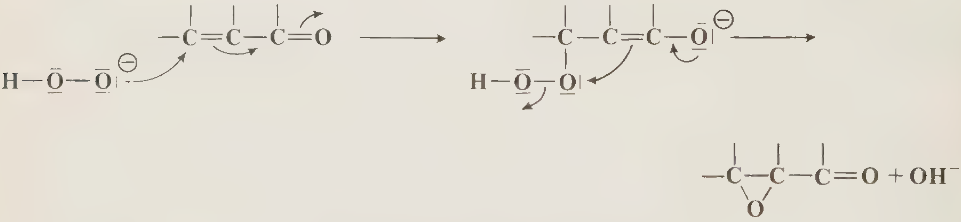
5. *Displacement mechanisms.* In these reactions the organic substrate uses its electrons to cause displacement on an electrophilic oxidizing agent. One example is the addition of bromine to an olefin (reaction **5-30**).



An example from this chapter is found in reaction **9-29**:



6. *Addition-elimination mechanisms.* In the reaction between α,β-unsaturated ketones and alkaline peroxide (reaction **5-40**), the oxidizing agent adds to the substrate, and then part of it is lost:



In this case the oxygen of the oxidizing agent was in oxidation state −1 and the OH^- departed with its oxygen in the −2 state, so it was reduced and the substrate oxidized. There are several reactions which follow this pattern of addition of an oxidizing agent and the loss of part of the agent, usually in a different oxidation state. Another example is the oxidation of ketones with SeO_2 (reaction **9-16**). This reaction is also an example of category 4, since it involves formation and E2 cleavage of an ester. This example shows that these six categories are not mutually exclusive.

REACTIONS

In this chapter, the reactions are classified by the type of bond change occurring to the organic substrate, in conformity with our practice in the other chapters. This means that there is no discussion in any one place of the use of a particular oxidizing or reducing agent, e.g., acid dichromate or $LiAlH_4$ (except for a discussion of selectivity of reducing agents, p. 1116). Some oxidizing or reducing agents are fairly specific in their action, attacking only one or a few types of substrate. Others, like acid dichromate, permanganate, $LiAlH_4$, and catalytic hydrogenation, are much more versatile.[8]

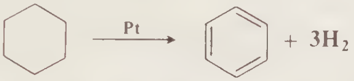
When an oxidation or a reduction could be considered in a previous chapter, this was done. For example, the catalytic hydrogenation of olefins is a reduction, but it is also an addition to the C=C bond and was treated in Chapter 15. In this chapter are discussed only those reactions which do not fit into the nine categories of Chapters 10 to 18. An exception to this rule was made for reactions which involve elimination of hydrogen (**9-1** to **9-7**), which were not treated in Chapter 17 because the mechanisms generally differ from those in that chapter.

Oxidations[9]

The reactions in this section are classified into groups depending on the type of bond change involved. These groups are: eliminations of hydrogen, reactions involving cleavage of carbon-carbon bonds, reactions involving replacement of hydrogen by oxygen, reactions in which oxygen is added to the substrate, and oxidative coupling.

A. Eliminations of Hydrogen

9-1 Aromatization of Six-membered Rings



Six-membered alicyclic rings can be aromatized in a number of ways.[10] Aromatization is accomplished most easily if there are already one or two double bonds in the ring or if the ring is fused to an aromatic ring. The reaction can also be applied to heterocyclic five- and six-membered rings. Many groups may be present on the ring without interference, and even *gem*-dialkyl substitution does not always prevent the reaction: In such cases one alkyl group often migrates or is eliminated. However, more drastic conditions are usually required for this. In some cases OH and COOH groups are lost from the ring. Cyclic ketones are converted to phenols. Seven-membered and larger rings are often isomerized to six-membered aromatic rings, though this is not the case for partially hydrogenated azulene systems (which are frequently found in nature); these are converted to azulenes.

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[8] For reviews of certain oxidizing agents, see George and Balachandran, *Chem. Rev.* **75,** 491–519 (1975) (nickel peroxide); Fatiadi, *Synthesis* 229–272 (1974) (HIO_4); Sklarz, *Q. Rev., Chem. Soc.* **21,** 3–28 (1967) (HIO_4); Courtney and Swansborough, *Rev. Pure Appl. Chem.* **22,** 47–54 (1972) (ruthenium tetraoxide); Ho, *Synthesis,* 347–354 (1973) (ceric ion); Aylward, *Q. Rev., Chem. Soc.* **25,** 407–429 (1971) (lead tetraacetate); Meth-Cohn and Suschitzky, *Chem. Ind.* (*London*) 443–450 (1969) (MnO_2), Korshunov and Vereshchagin, *Russ. Chem. Rev.* **35,** 942–957 (1966) (MnO_2); Weinberg and Weinberg, *Chem. Rev.* **68,** 449–523 (1968) (electrochemical oxidation); Ladbury and Cullis, *Chem. Rev.* **58,** 403–438 (1958), pp. 425–431 (permanganate); Thyagarajan, *Chem. Rev.* **58,** 439–460 (1958) (ferricyanide); Fatiadi, *Synthesis* 65–104, 133–167 (1976) (MnO_2); Waters, *Q. Rev., Chem. Soc.* **12,** 277–300 (1958) (chromic acid and permanganate); Bailey, *Chem. Rev.* **58,** 925–1010 (1958) (ozone); Criegee, *Angew. Chem.* **70,** 173–179 (1958), *Newer Methods Prep. Org. Chem.* **2,** 367–388 (1963) (lead tetraacetate). For reviews of the behavior of certain reducing agents, see Winterfeldt, *Synthesis* 617–630 (1975) (diisobutylaluminum hydride and triisobutylaluminum); Hückel, *Fortschr. Chem. Forsch.* **6,** 197–250 (1966) (metals in ammonia or amines); Rausch, McEwen, and Kleinberg, *Chem. Rev.* **57,** 417–437 (1957) (unipositive magnesium); Popp and Schultz, *Chem. Rev.* **62,** 19–40 (1962) (cathodic reductions); and Jackman, *Adv. Org. Chem.* **2,** 329–366 (1960) (reductions in which the hydrogen comes from an organic molecule). For a review of reduction methods in general, see Candlin and Rennie, in Bentley and Kirby, "Elucidation of Chemical Structures by Physical and Chemical Methods" (vol. 4 of Weissberger, "Techniques of Chemistry"), 2d ed. pt. 2, pp. 77–135, John Wiley & Sons, Inc., New York, 1973. For a treatise on reductions with metal hydrides, see Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956. Also see House, "Modern Synthetic Reactions," 2d ed., W. A. Benjamin, Inc., New York, 1972; Ref. 9.

[9] For books on oxidation reactions, see Chinn, "Selection of Oxidants in Synthesis," Marcel Dekker, Inc., New York, 1971; Augustine and Trecker, "Oxidation," 2 vols., Marcel Dekker, Inc., New York, 1969, 1971. See also Ref. 2.

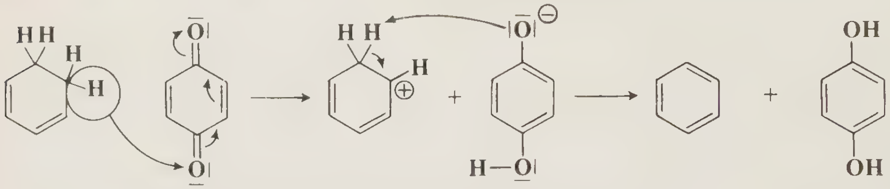
[10] For reviews, see Valenta, in Bentley and Kirby, Ref. 8, pp. 1–76; House, Ref. 8, pp. 34–44; Plattner, *Newer Methods Prep. Org. Chem.* **1,** 21–59 (1948).

There are three types of reagents most frequently used to effect aromatization.

1. Hydrogenation catalysts[11] such as platinum, palladium, nickel, etc. In this case the reaction is the reverse of double-bond hydrogenation (reactions **5-12** and **5-13**), and presumably the mechanism is also the reverse of that one, though not much is known. The substrate is heated with the catalyst at about 300 to 350°C. The reactions can often be carried out under milder conditions if a hydrogen acceptor, such as maleic acid, cyclohexene, or benzene, is present to remove hydrogen as it is formed. The acceptor is reduced to the saturated compound. It has been reported that dehydrogenation of 1-methylcyclohexene-1-^{13}C over an alumina catalyst gave toluene with the label partially scrambled throughout the aromatic ring.[12]

2. The elements sulfur and selenium, which combine with the hydrogen evolved to give, respectively, H_2S and H_2Se. Little is known about this mechanism either.[13]

3. Quinones,[14] which become reduced to the corresponding hydroquinones. Two important quinones often used for aromatizations are chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[15] The latter is more reactive and may be used in cases where the substrate is difficult to dehydrogenate. The mechanism involves a transfer of hydride to the quinone oxygen, followed by the transfer of a proton to the phenolate ion:[16]



Other reagents which have been used are atmospheric oxygen, MnO_2,[17] SeO_2, BuLi-N,N,N′,N′-tetramethylethylenediamine,[18] Ph_3COH in CF_3COOH,[19] and activated charcoal.[20] The last-mentioned reagent also dehydrogenates cyclopentanes to cyclopentadienes. In some instances the hydrogen is not released as H_2 or transferred to an external oxidizing agent but instead serves to reduce another molecule of substrate. This is a disproportionation reaction and may be illustrated by the conversion of cyclohexene to cyclohexane and benzene.

Aromatization reactions have been particularly important in the proof of structure of many cyclic natural products, especially steroids and terpenes. Diels-Alder adducts (which must contain at least one double bond) are also frequently aromatized.[21]

OS **II,** 214, 423; **III,** 310, 358, 729, 807; **IV,** 536; **54, 11.** Also see OS **III,** 329.

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[11] For a review, see Rylander, "Organic Syntheses with Noble Metal Catalysts," pp. 1–59, Academic Press, Inc., New York, 1973.

[12] Marshall, Miiller, and Ihrig, *Tetrahedron Lett.* 3491 (1973).

[13] House and Orchin, *J. Am. Chem. Soc.* **82,** 639 (1960); Silverwood and Orchin, *J. Org. Chem.* **27,** 3401 (1962).

[14] For reviews, see Becker, in Patai, "The Chemistry of the Quinonoid Compounds," pt. 1, pp. 335–423, John Wiley & Sons, Inc., New York, 1974; Jackman, *Adv. Org. Chem.* **2,** 329–366 (1960).

[15] For a review of DDQ, see Walker and Hiebert, *Chem. Rev.* **67,** 153–195 (1967).

[16] Barnard and Jackman, *J. Chem. Soc.* 3110 (1960); Braude, Jackman, Linstead, and Shannon, *J. Chem. Soc.* 3116 (1960); Braude, Jackman, Linstead, and Lowe, *J. Chem. Soc.* 3123, 3133 (1960); Trost, *J. Am. Chem. Soc.* **89,** 1847 (1967); Ref. 14. See also Stoos and Roček, *J. Am. Chem. Soc.* **94,** 2719 (1972); Müller, *Helv. Chim. Acta* **56,** 1243 (1973).

[17] See for example, Leffingwell and Bluhm, *Chem. Commun.* 1151 (1969).

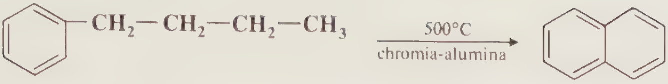
[18] Harvey, Nazareno, and Cho, *J. Am. Chem. Soc.* **95,** 2376 (1973); Harvey and Cho, *J. Am. Chem. Soc.* **96,** 2434 (1974).

[19] Fu and Harvey, *Tetrahedron Lett.* 3217 (1974).

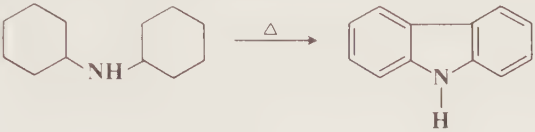
[20] Shuikin and Naryschkina, *J. Prakt. Chem.* [4] **13,** 183 (1961).

[21] For a review of the aromatization of Diels-Alder adducts, see Skvarchenko, *Russ. Chem. Rev.* **32,** 571–589 (1963).

9-2 Cyclodehydrogenation

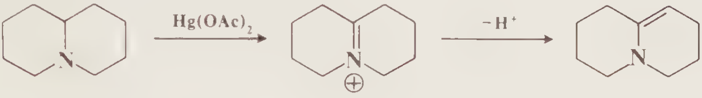


Many aliphatic chains of at least six carbons have been pyrolyzed over chromia-alumina catalysts to yield aromatic compounds.[22] Where structural features permit (as in the reaction illustrated above), bicyclic and polycyclic compounds can be formed. Many heterocyclic aromatic compounds have also been made in this way. In some cases the chains are unsaturated and the only loss of hydrogen is from ring closure, but in other cases ring closure and aromatization (reaction **9-1**) take place concurrently. The majority of rings formed in this reaction are six-membered, but five-membered rings can also be formed, an example being[23]



The mechanism of these reactions is complex.[24]

9-3 Dehydrogenations Yielding Carbon-Carbon Bonds



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Dehydrogenation of an aliphatic compound to give a double bond in a specific location is not usually a feasible process, though industrially mixtures of olefins are obtained in this way from mixtures of alkanes (generally by heating with chromia-alumina catalysts). There are, however, some notable exceptions, and it is not surprising that these generally involve cases where the new double bond can be in conjugation with a double bond or with an unshared pair of electrons already present. One example is the synthesis developed by Leonard and coworkers[25] in which tertiary amines give enamines when treated with mercuric acetate[26] (see the example above). In this case the initial product is the iminium ion **1** which loses a proton to give the enamine. In another example, the oxidizing agent SeO_2 can in certain cases convert a carbonyl compound to an α,β-unsaturated carbonyl compound by removing H_2[27] (though this reagent more often gives reaction **9-16**). This reaction has been most often applied in the steroid series, an example being[28]

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[22] For reviews, see Skarchenko, *Russ. Chem. Rev.* **40,** 997–1013 (1971); Rozengart and Kazanskii, *Russ. Chem. Rev.* **40,** 715–732 (1971); Hansch, *Chem. Rev.* **53,** 353–396 (1953); and Pines and Goetschel, *J. Org. Chem.* **30,** 3530 (1965).

[23] Zelinskii, Titz, and Gaverdovskaya, *Ber.* **59,** 2590 (1926).

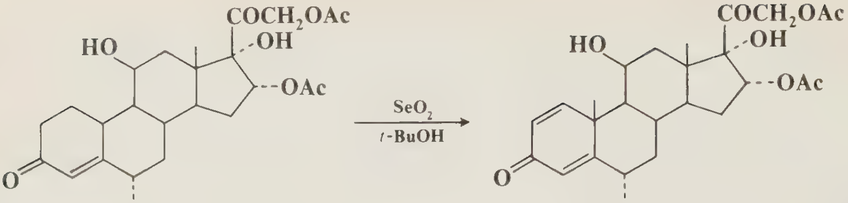
[24] For details, see Pines and Dembinski, *J. Org. Chem.* **30,** 3537 (1965); Pines, Goetschel, and Dembinski, *J. Org. Chem.* **30,** 3540 (1965); Goetschel and Pines, *J. Org. Chem.* **30,** 3544 (1965); Pines and Goetschel, *J. Org. Chem.* **30,** 3548 (1965); Davis and Venuto, *J. Org. Chem.* **36,** 337 (1971); Pines, *Intra-Sci. Chem. Rep.* **6**(2), 1–42 (1972), pp. 21–25; Csicsery, *Intra-Sci. Chem. Rep.* **6**(2), 43–63 (1972).

[25] For example, see Leonard, Hay, Fulmer, and Gash, *J. Am. Chem. Soc.* **77,** 439 (1955); Leonard and Musker, *J. Am. Chem. Soc.* **81,** 5631 (1959), **82,** 5148 (1960); Leonard and Sauers, *J. Am. Chem. Soc.* **79,** 6210 (1957), *J. Org. Chem.* **21,** 1187 (1956).

[26] For reviews, see Haynes, in Cook, "Enamines," pp. 68–81, Marcel Dekker, Inc., New York, 1969; Lee, in Augustine, Ref. 9, vol. 1, pp. 102–107; Szmuszkovicz, *Adv. Org. Chem.* **4,** 1–113 (1963), pp. 12–16.

[27] For reviews, see Jerussi, *Sel. Org. Transform.* **1,** 301–326 (1970), pp. 315–321; Trachtenberg, in Augustine, Ref. 9, pp. 166–174.

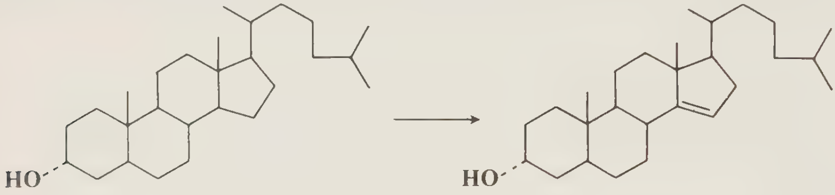
[28] Bernstein and Littell, *J. Am. Chem. Soc.* **82,** 1235 (1960).



Similarly, SeO_2 has been used to dehydrogenate 1,4-diketones[29] ($RCOCH_2CH_2COR \rightarrow RCOCH{=}CHCOR$) and 1,2-diarylalkanes ($ArCH_2CH_2Ar \rightarrow ArCH{=}CHAr$). These conversions can also be carried out by certain quinones, most notably DDQ (see reaction **9-1**).[15] Simple aldehydes and ketones have been dehydrogenated (e.g., cyclopentanone → cyclopentenone) by $PdCl_2$[30] and by oxygen in the presence of a group VIII metal such as Pd(II) and a cocatalyst such as Cu(II) or a quinone.[31] (For an indirect method for the dehydrogenation of simple aldehydes, ketones, and esters, see reaction **7-12.**)

An entirely different approach to specific dehydrogenation has been reported by R. Breslow[32] and by J. E. Baldwin.[33] By means of this approach it was possible, for example, to convert 3α-cholestanol (**2**) to 5α-cholest-14-en-3α-ol (**3**), thus *introducing a double bond at a specific site remote from any functional group*. This was accomplished by conversion of **2** to the ester **4**, followed by irradiation of **4**, which gave 55% **6** which was then hydrolyzed to **3**. The radiation excites the benzophenone portion of **4** (p. 223), which then abstracts hydrogen from the 14 position to give the diradical **5** which undergoes another internal abstraction to give **6.** In other cases, diradicals like **5** may close to a macrocyclic lactone (reaction **9-16**). In an alternate approach,[34] a 9(11) double bond was introduced into a steroid nucleus by conversion of the *m*-iodo ester 7 to the radical **8** (for example, by treatment with $PhICl_2$ and uv light), which abstracts hydrogen regiospecifically from the 9 position, resulting in chlorination at that position. Dehydrohalogenation of **9** gives the 9(11)-unsaturated steroid **10.** In contrast, use of the para isomer of 7 results in chlorination at the 14 position, and loss of HCl gives the 14-unsaturated steroid. These reactions are among the very few ways to introduce functionality at a specific site remote from any functional group (see also **9-16**).

OS V, 428.



2 **3**

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[29] For example, see Barnes and Barton, *J. Chem. Soc.* 1419 (1953).

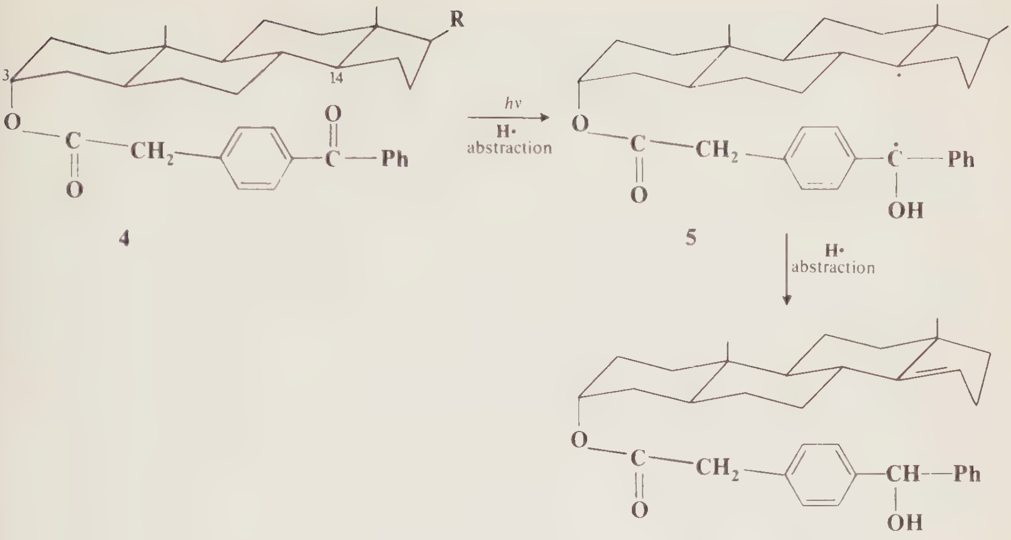
[30] Bierling, Kirschke, Oberender, and Schulz, *J. Prakt. Chem.* **314,** 170 (1972); Kirschke, Müller, and Timm, *J. Prakt. Chem.* **317,** 807 (1975).

[31] Theissen, *J. Org. Chem.* **36,** 752 (1971).

[32] Breslow and Baldwin, *J. Am. Chem. Soc.* **92,** 732 (1970); Breslow and Kalicky, *J. Am. Chem. Soc.* **93,** 3540 (1971); Breslow, Baldwin, Flechtner, Kalicky, Liu, and Washburn, *J. Am. Chem. Soc.* **95,** 3251 (1973); Breslow, *Chem. Soc. Rev.* **1,** 553–580 (1972); Wife, Prezant, and Breslow, *Tetrahedron Lett.* 517 (1976).

[33] Baldwin, Bhatnagar, and Harper, *Chem. Commun.* 659 (1970).

[34] Breslow, Corcoran, Dale, Liu, and Kalicky, *J. Am. Chem. Soc.* **96,** 1973 (1974); Breslow, Corcoran, and Snider, *J. Am. Chem. Soc.* **96,** 6791 (1974); Breslow, Snider, and Corcoran, *J. Am. Chem. Soc.* **96,** 6792 (1974). See also Snider, Corcoran, and Breslow, *J. Am. Chem. Soc.* **97,** 6580 (1975); Corcoran, *Tetrahedron Lett.* 317 (1976); Breslow, Wife, and Prezant, *Tetrahedron Lett.* 1925 (1976).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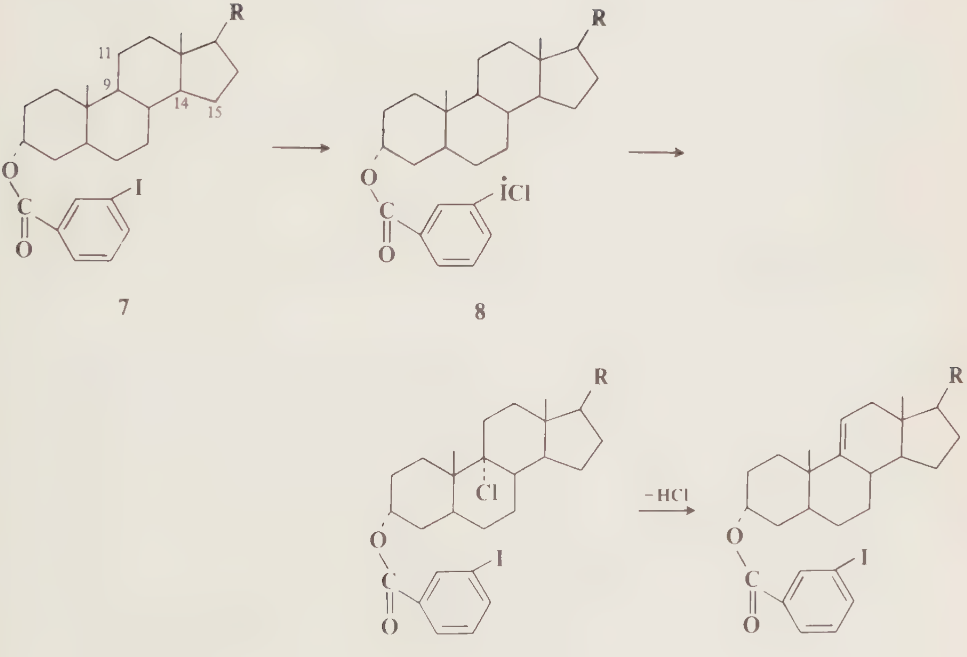
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ICl
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−HCl

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8

9

10

9-4 Oxidation or Dehydrogenation of Alcohols to Aldehydes and Ketones

$$\mathrm{RCH_2OH} \xrightarrow[\text{chromite}]{\text{copper}} \mathrm{RCHO}$$

$$\mathrm{RCHOHR'} \xrightarrow[\mathrm{H_2SO_4}]{\mathrm{K_2Cr_2O_7}} \mathrm{RCOR'}$$

Primary alcohols can be converted to aldehydes, and secondary alcohols to ketones, in four main ways:[35]

1. *With strong oxidizing agents.*[36] Secondary alcohols are easily oxidized to ketones by acid dichromate[37] at room temperature or slightly above. Though this is the most common reagent, many other strong oxidizing agents (for example, $KMnO_4$, Br_2, MnO_2, ruthenium tetroxide,[38] etc.) have also been employed. A solution of chromic acid and sulfuric acid in water is known as the *Jones reagent.*[39] When secondary alcohols are dissolved in acetone,[40] titration with the Jones reagent oxidizes them to ketones rapidly and in high yield without disturbing any double or triple bonds which may be present (see reaction **9-11**), and without epimerizing an adjacent asymmetric center.[41] The Jones reagent also oxidizes primary allylic alcohols to the corresponding aldehydes.[42] MnO_2 is also a fairly specific reagent for OH groups and is often used to oxidize allylic alcohols to α,β-unsaturated aldehydes or ketones. For acid-sensitive compounds a CrO_3-pyridine complex can be used.[43] Most of these oxidizing agents have also been used to convert primary alcohols to aldehydes, but precautions must be taken so that the aldehyde is not further oxidized to the acid (reaction **9-22**).[44] One way to halt oxidation is by evaporation of the aldehyde as it is formed. The following are among the oxidizing agents which have been used to convert at least some primary alcohols to aldehydes: dimethyl sulfoxide (see reaction **9-20**), ceric ammonium nitrate,[45] dipyridine Cr(VI) oxide,[46] $Na_2Cr_2O_7$ in water,[47] pyridine-dichromate,[48] $Na_2Cr_2O_7$–H_2SO_4 in dimethyl sulfoxide,[49] CrO_3-dimethylpyrazole complex,[50] pyridinium chlorochromate,[50a] Ag_2CO_3-on-celite,[51] hot nitric acid in aqueous glyme,[52] iodosobenzene PhIO,[53]

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[35] For a review, see Cullis and Fish, in Patai, "The Chemistry of the Carbonyl Group," vol. 1, pp. 129–157, Interscience Publishers, New York, 1966.

[36] For thorough discussions, see Lee, Ref. 26, pp. 56–81, and (with respect to chromium and manganese reagents) House, Ref. 8, pp. 257–273.

[37] Various forms of H_2CrO_4 and of CrO_3 are used for this reaction. For discussions, see Fieser and Fieser, "Reagents for Organic Synthesis," vol. 1, pp. 142-147, 1059–1064, vol. 2, pp. 70–75, John Wiley & Sons, Inc., New York, 1967, 1969.

[38] For a review, see Lee and van den Engh, in Trahanovsky, Ref. 1, pp. 197–222.

[39] Bowden, Heilbron, Jones, and Weedon, *J. Chem. Soc.* **39** (1946); Bowers, Halsall, Jones, and Lemin, *J. Chem. Soc.* 2548 (1953).

[40] Saturated secondary alcohols also give nonepimerized ketones in good yield when ether is used instead of acetone: Brown, Garg, and Liu, *J. Org. Chem.* **36,** 387 (1971).

[41] For example, see Djerassi, Hart, and Warawa, *J. Am. Chem. Soc.* **86,** 78 (1964).

[42] Harding, May, and Dick, *J. Org. Chem.* **40,** 1664 (1975).

[43] Poos, Arth, Beyler, and Sarett, *J. Am. Chem. Soc.* **75,** 422 (1953).

[44] Though ketones are much less susceptible to further oxidation than aldehydes, such oxidation is possible (reaction **9-9**) and care must be taken to avoid it, usually by controlling the temperature and/or the oxidizing agent.

[45] Trahanovsky and Young, *J. Chem. Soc.* 5777 (1965); Young and Trahanovsky, *J. Org. Chem.* **32,** 2349 (1967); Trahanovsky, Young, and Brown, *J. Org. Chem.* **32,** 3865 (1967).

[46] Collins, Hess, and Frank, *Tetrahedron Lett.* 3363 (1968); Ratcliffe and Rodehorst, *J. Org. Chem.* **35,** 4000 (1970); Stensiö, *Acta Chem. Scand.* **25,** 1125 (1971); Collins and Hess, *Org. Synth.* **52,** 5 (1972); Sharpless and Akashi, *J. Am. Chem. Soc.* **97,** 5927 (1975).

[47] Lee and Spitzer, *J. Org. Chem.* **35,** 3589 (1970).

[48] Coates and Corrigan, *Chem. Ind. (London)* 1594 (1969).

[49] Rao and Filler, *J. Org. Chem.* **39,** 3304 (1974).

[50] Corey and Fleet, *Tetrahedron Lett.* 4499 (1973).

[50a] Corey and Suggs, *Tetrahedron Lett.* 2647 (1975).

[51] Fetizon and Golfier, *C. R. Acad. Sci., Ser. C* **267,** 900 (1968); Kakis, Fetizon, Douchkine, Golfier, Mourgues, and Prange, *J. Org. Chem.* **39,** 523 (1974).

[52] McKillop and Ford, *Synth. Commun.* **2,** 307 (1972).

[53] Takaya, Enyo, and Imoto, *Bull. Chem. Soc. Jpn.* **41,** 1032 (1968).

silver(II) picolinate,[54] and $Pb(OAc)_4$-pyridine.[55] Most of these reagents also oxidize secondary alcohols to ketones. Reagents which can be used specifically to oxidize a secondary OH group in the presence of a primary OH group are Cl_2-pyridine[56] and Ag_2CO_3-on-celite.[57]

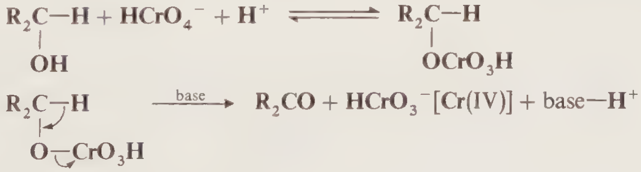
2. *By catalytic dehydrogenation.*[58] For the conversion of primary alcohols to aldehydes, dehydrogenation catalysts have the advantage over strong oxidizing agents that further oxidation to the acid is prevented. Copper chromite is the agent most often used, but other catalysts, e.g., silver and copper, have also been employed. Many ketones have also been prepared in this manner. Catalytic dehydrogenation is more often used industrially than as a laboratory method. However, a convenient laboratory procedure using copper oxide has been reported.[59]

3. *The Oppenauer oxidation.* When a ketone in the presence of base is used as the oxidizing agent (it is reduced to a secondary alcohol), the reaction is known as the *Oppenauer oxidation.*[60] This is the reverse of the Meerwein-Ponndorf-Verley reaction (**6-27**), and the mechanism is also the reverse. The ketones most commonly used are acetone, methyl ethyl ketone, and cyclohexanone. The most common base is aluminum *t*-butoxide. The chief advantage of the method is its high selectivity. Though the method is most often used for the preparation of ketones, it has also been used to prepare aldehydes.

4. *With* N-*bromosuccinimide or related compounds.* These compounds are selective oxidizing agents and often oxidize OH groups without disturbing other oxidizable groups.[61] N-Bromosuccinimide does not oxidize aliphatic primary alcohols, but N-chlorosuccinimide does. With these reagents it is often possible to oxidize only one of several OH groups which may be present in a molecule. The reactions readily proceed in the dark, so that the mechanism is not of the free-radical type, but involves attack by positive halogen.

Primary and secondary alcohols can also be oxidized, indirectly, through their esters (see reaction **9-20**). In some cases, isolation of the ester is not required, and the alcohol can then be oxidized to the aldehyde or ketone in one step. Alkoxide ions can be oxidized to aldehydes or ketones in good yield by photooxidation with O_2[62] (singlet O_2 is the oxidizing agent here; see reactions **4-8, 5-41**).

The mechanism of oxidation with acid dichromate has been intensively studied.[63] The currently accepted mechanism is essentially that proposed by Westheimer.[64] The first two steps constitute an example of category 4 (p. 1075).



$$\underset{\displaystyle OH}{R_2C{-}H} + HCrO_4^- + H^+ \rightleftharpoons \underset{\displaystyle OCrO_3H}{R_2C{-}H}$$

$$\underset{\displaystyle O{-}CrO_3H}{R_2C{-}H} \xrightarrow{\text{base}} R_2CO + HCrO_3^-[Cr(IV)] + \text{base}{-}H^+$$

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[54] Lee and Clarke, *Tetrahedron Lett.* 415 (1967).

[55] Partch, *Tetrahedron Lett.* 3071 (1964); Partch and Monthony, *Tetrahedron Lett.* 4427 (1967).

[56] Wicha and Zarecki, *Tetrahedron Lett.* 3059 (1974).

[57] Fetizon, Golfier, and Louis, *Chem. Commun.* 1102 (1969).

[58] For a review, see Heyns and Paulsen, *Angew. Chem.* **69**, 600–608 (1957), *Newer Methods Prep. Org. Chem.* **2**, 303–335 (1963).

[59] Sheikh and Eadon, *Tetrahedron Lett.* 257 (1972).

[60] For reviews, see Djerassi, *Org. React.* **6**, 207–272 (1951); Bersin, *Newer Methods Prep. Org. Chem.* **1**, 125–158 (1948), pp. 143 158.

[61] For a review, see Filler, *Chem. Rev.* **63**, 21–43 (1963), pp. 22–28.

[62] Wasserman and Van Verth, *J. Am. Chem. Soc.* **96**, 585 (1974).

[63] Wiberg, in Wiberg, Ref. 2, pp. 142–170; Venkatasubramanian, *J. Sci. Ind. Res.* **22**, 397–400 (1963); Waters, Ref. 2, pp. 49–71; Stewart, Ref. 2, pp. 37–48.

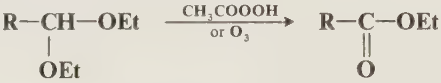
[64] Westheimer, *Chem. Rev.* **45**, 419–451 (1949), p. 434; Holloway, Cohen, and Westheimer, *J. Am. Chem. Soc.* **73**, 65 (1951).

$$R_2CHOH + Cr(IV) \longrightarrow R_2\dot{C}OH + Cr(III)$$
$$R_2\dot{C}OH + Cr(VI) \longrightarrow R_2CO + Cr(V)$$
$$R_2CHOH + Cr(V) \longrightarrow R_2CO + Cr(III)$$

The base in the second step may be water, though it is also possible[65] that in some cases no external base is involved, and that the proton is transferred directly to one of the CrO_3H oxygens, in which case the Cr(IV) species produced would be H_2CrO_3. Part of the evidence for this mechanism was the isotope effect of about 6 found on use of MeCDOHMe, showing that the α-hydrogen is removed in the rate-determining step.[66] Note that, as in reaction **4-6,** the substrate is oxidized by three different oxidation states of chromium.[67]

With other oxidizing agents, mechanisms are less clear. It seems certain that some oxidizing agents operate by a hydride-shift mechanism,[68] for example, dehydrogenation with triphenylmethyl cation[69] and the Oppenauer oxidation, and some by a free-radical mechanism, for example, oxidation with $S_2O_8^{2-}$ [70] and with VO_2^+.[71] A summary of many proposed mechanisms is given by Littler.[72]

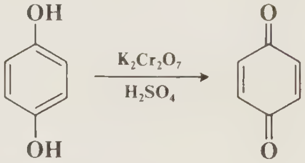
Secondary alkyl ethers can be oxidized to ketones by bromine (e.g., $Me_2CHOCHMe_2 + Br_2 \rightarrow Me_2CO$).[73] Primary alkyl ethers give carboxylic acids (reaction **9-22**). Acetals can be oxidized to esters with peracetic acid[74] or with ozone.[75]



$$R{-}\underset{\displaystyle OEt}{\underset{|}{CH}}{-}OEt \xrightarrow[\text{or } O_3]{CH_3COOOH} R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}OEt$$

OS **I,** 87, 211, 241, 340; **II,** 139, 541; **III,** 37, 207; **IV,** 189, 192, 195, 467, 813, 838; **V,** 242, 310, 324, 692, 852, 866; **52,** 5; **55,** 84. Also see OS **IV,** 283.

9-5 Oxidation of Phenols and Aromatic Amines to Quinones



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[65] Kwart and Francis, *J. Am. Chem. Soc.* **81,** 2116 (1959); Stewart and Lee, *Can. J. Chem.* **42,** 439 (1964); Awasthy, Roček, and Moriarty, *J. Am. Chem. Soc.* **89,** 5400 (1967); Kwart and Nickle, *J. Am. Chem. Soc.* **95,** 3394 (1973), **96,** 7572 (1974), **98,** 2881 (1976). See also Müller and Perlberger, *Helv. Chim. Acta* **57,** 1943 (1974).

[66] Westheimer and Nicolaides, *J. Am. Chem. Soc.* **71,** 25 (1949). For other evidence, see Brownell, Leo, Chang, and Westheimer, *J. Am. Chem. Soc.* **82,** 406 (1960); Roček, Westheimer, Eschenmoser, Moldoványi, and Schreiber, *Helv. Chim. Acta* **45,** 2554 (1962); Lee and Stewart, *J. Org. Chem.* **32,** 2868 (1967); Wiberg and Schäfer, *J. Am. Chem. Soc.* **89,** 455 (1967), **91,** 927, 933 (1969); Müller, *Helv. Chim. Acta* **53,** 1869 (1970), **54,** 2000 (1971); Lee and Raptis, *Tetrahedron* **29,** 1481 (1973).

[67] Rahman and Roček, *J. Am. Chem. Soc.* **93,** 5455, 5462 (1971); Roček and Radkowsky, *J. Am. Chem. Soc.* **95,** 7123 (1973); Doyle, Swedo, and Roček, *J. Am. Chem. Soc.* **95,** 8352 (1973); Wiberg and Mukherjee, *J. Am. Chem. Soc.* **96,** 1884, 6647 (1974).

[68] See Barter and Littler, *J. Chem. Soc. B* 205 (1967).

[69] Bonthrone and Reid, *J. Chem. Soc.* 2773 (1959).

[70] Ball, Crutchfield, and Edwards, *J. Org. Chem.* **25,** 1599 (1960); McIsaac and Edwards, *J. Org. Chem.* **34,** 2565 (1969); Bida, Curci, and Edwards, *Int. J. Chem. Kinet.* **5,** 859 (1973); Snook and Hamilton, *J. Am. Chem. Soc.* **96,** 860 (1974).

[71] Littler and Waters, *J. Chem. Soc.* 4046 (1959).

[72] Littler, *J. Chem. Soc.* 2190 (1962).

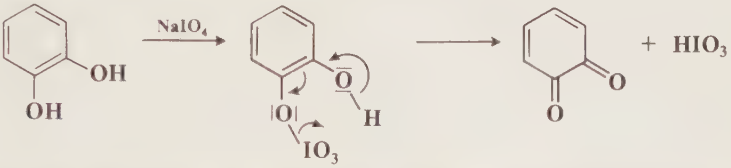
[73] Deno and Potter, *J. Am. Chem. Soc.* **89,** 3550, 3555 (1967). See also Miller, Wolf, and Mayeda, *J. Am. Chem. Soc.* **93,** 3306 (1971); Saigo, Morikawa, and Mukaiyama, *Chem. Lett.* 145 (1975).

[74] Heywood and Phillips, *J. Org. Chem.* **25,** 1699 (1960).

[75] Deslongchamps and Moreau, *Can. J. Chem.* **49,** 2465 (1971); Deslongchamps, Atlani, Fréhel, Malaval, and Moreau, *Can. J. Chem.* **57,** 3651 (1974).

Ortho and para diols are easily oxidized to *ortho-* and *para*-quinones, respectively.[76] Either or both OH groups can be replaced by NH_2 groups to give the same products, though for the preparation of *ortho*-quinones only OH groups are normally satisfactory. The reaction has been successfully carried out with other groups para to OH or NH_2: halogen, OR, Me, *t*-Bu, and even H, though with the last yields are poor. Many oxidizing agents have been used: acid dichromate, lead tetraacetate, HIO_4, and atmospheric oxygen, to name a few. A particularly effective reagent for rings with only one OH or NH_2 group is $(KSO_3)_2N{-}O\cdot$ (dipotassium nitrosodisulfonate; Fremy's salt), which is a stable free radical.[77] The reaction is not exactly analogous to reaction **9-4**, which is an elimination to form a C=O bond. This reaction may be looked on as a 1,6 elimination of two hydrogens.

Less is known about the mechanism than is the case for reaction **9-4** but, as in that case, it seems to vary with the oxidizing agent. For oxidation of catechol with $NaIO_4$, it was found that the reaction conducted in $H_2{}^{18}O$ gave unlabeled quinone,[78] so that the following mechanism, which is an example of category 4 (p. 1075), was proposed:



However, for autoxidations (i.e., with atmospheric oxygen) a free-radical mechanism is known to operate.[79]

OS **I,** 383, 482, 511; **II,** 175, 254, 430, 553; **III,** 633, 753; **IV,** 148; **52,** 83, 88.

9-6 Dehydrogenation of Amines

$$RCH_2NH_2 \xrightarrow[2.\ H_2O]{1.\ IF_5} RCN$$

Primary amines at a primary carbon can be dehydrogenated to nitriles. The reaction has been carried out in a variety of ways: by treatment with IF_5,[80] lead tetraacetate,[81] nickel peroxide,[82] silver(II) picolinate,[83] N-bromosuccinimide and triethylamine,[84] or Cl_2–$NaHCO_3$ followed by CsF,[85] and also catalytically.[86] Secondary amines can sometimes be dehydrogenated to imines.[87] Primary alcohols and aldehydes can be converted directly to nitriles by air oxidation in the presence of ammonia, a strong base (such as OMe^-), and a copper complex.[88] This reaction is a combination of three reactions: oxidation of the alcohol to the aldehyde (reaction **9-4**), formation of the imine (reaction **6-14**), and dehydrogenation of this to the nitrile.

Another reaction which involves dehydrogenation to an imine which then reacts further is the reaction of primary or secondary amines with palladium black.[89] The imine initially formed by

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[76] For reviews, see Thomson, in Patai, Ref. 14, pp. 112–132; Cason, *Org. React.* **4,** 305–361 (1948).

[77] For a review of oxidation with this salt, see Zimmer, Lankin, and Horgan, *Chem. Rev.* **71,** 229–246 (1971).

[78] Adler, Falkehag, and Smith, *Acta Chem. Scand.* **16,** 529 (1962).

[79] Walling, "Free Radicals in Solution," pp. 457–461, John Wiley & Sons, Inc., New York, 1957.

[80] Stevens, *J. Org. Chem.* **26,** 2531 (1961).

[81] Stojiljković, Andrejević, and Mihailović, *Tetrahedron* **23,** 721 (1967).

[82] Nakagawa and Tsuji, *Chem. Pharm. Bull.* **11,** 296 (1963).

[83] Lee, Parkin, Shaw, Hampson, and MacDonald, *Tetrahedron* **29,** 751 (1973).

[84] Gottardi, *Monatsh. Chem.* **104,** 1690 (1973).

[85] Sharts, *J. Org. Chem.* **33,** 1008 (1968).

[86] Peters, Marple, Evans, McAllister, and Castner, *Ind. Eng. Chem.* **40,** 2046 (1948).

[87] For a review, see Dayagi and Degani, in Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," pp. 117–124, Interscience Publishers, New York, 1970.

[88] Brackman and Smit, *Recl. Trav. Chim. Pays-Bas* **82,** 757 (1963); Misono, Osa, and Koda, *Bull. Chem. Soc. Jpn.* **40,** 912 (1967), **41,** 735 (1968).

[89] Yoshimura, Moritani, Shimamura, and Murahashi, *J. Am. Chem. Soc.* **95,** 3038 (1973).

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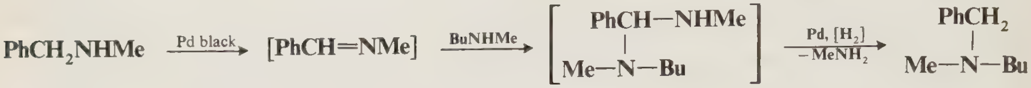
the dehydrogenation reacts with another molecule of the same or a different amine to give an aminal, which loses NH_3 or RNH_2 to give a secondary or tertiary amine. An example is the reaction between N-methylbenzylamine and N-methylbutylamine, which produces 95% N-methyl-N-butylbenzylamine. Another method for the conversion of primary to secondary amines ($2RNH_2 \rightarrow R_2NH$) involves treatment with a catalytic amount of sodium hydride.[90] This reaction also involves an imine intermediate.



$$\mathrm{PhCH_2NHMe} \xrightarrow{\text{Pd black}} [\mathrm{PhCH{=}NMe}] \xrightarrow{\text{BuNHMe}} \begin{bmatrix} \mathrm{PhCH{-}NHMe} \\ | \\ \mathrm{Me{-}N{-}Bu} \end{bmatrix} \xrightarrow[-\mathrm{MeNH_2}]{\mathrm{Pd,\ [H_2]}} \begin{matrix} \mathrm{PhCH_2} \\ | \\ \mathrm{Me{-}N{-}Bu} \end{matrix}$$

9-7 Oxidation of Hydrazines, Hydrazones, and Hydroxylamines

$$\mathrm{Ar{-}NH{-}NH{-}Ar} \xrightarrow{\mathrm{NaOBr}} \mathrm{Ar{-}N{=}N{-}Ar}$$

N,N′-Diarylhydrazines (hydrazo compounds) are oxidized to azo compounds by several oxidizing agents, including NaOBr, HgO, $CuCl_2$, and air and NaOH.[90a] The reaction is also applicable to N,N′-dialkyl- and N,N′-diacylhydrazines. Hydrazines (both alkyl and aryl) substituted on only one side also give azo compounds,[91] but these are unstable and decompose to give nitrogen and the hydrocarbon:

$$\mathrm{Ar{-}NH{-}NH_2} \longrightarrow [\mathrm{Ar{-}N{=}NH}] \longrightarrow \mathrm{ArH + N_2}$$

When hydrazones are oxidized with HgO, Ag_2O, or certain other oxidizing agents, diazo compounds are obtained (see also reaction **7-26**):

$$\mathrm{R_2C{=}N{-}NH_2} \xrightarrow{\mathrm{HgO}} \mathrm{R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}}$$

Diazo ketones have been prepared from glyoxal monohydrazones by oxidation with MnO_2:[92]

$$\mathrm{Ar{-}CO{-}C{=}N{-}NH_2 + MnO_2} \longrightarrow \mathrm{Ar{-}CO{-}CN_2}$$

The glyoxal monohydrazones were synthesized by treatment of phenacyl bromides ($ArCOCH_2Br$) with hydrazine.[92] Hydrazones of the form $ArCH{=}NNH_2$ react with HgO in the solvent diglyme, 1,2-dimethoxyethane, ethanol, or tetrahydrofuran to give nitriles ArCN.[93] Aromatic hydroxylamines are easily oxidized to nitroso compounds, most commonly by acid dichromate.[94]

$$\mathrm{Ar{-}NH{-}OH} \xrightarrow{\mathrm{CrO_3}} \mathrm{Ar{-}N{=}O}$$

OS **II**, 496; **III**, 351, 356, 375, 668; **IV**, 66, 411; **V**, 96, 160, 897; **50**, 6, 27; **51**, 121; **52**, 11, 77. Also see OS **V**, 258.

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[90] Richey and Erickson, *Tetrahedron Lett.* 2807 (1972); Erickson and Richey, *Tetrahedron Lett.* 2811 (1972).

[90a] For a review, see Newbold, in Patai, "The Chemistry of the Hydrazo, Azo, and Azoxy Groups," pt. 1, pp. 543–557, 564–573, John Wiley & Sons, New York, 1975.

[91] See Mannen and Itano, *Tetrahedron* **29**, 3497 (1973).

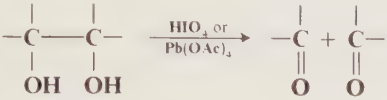
[92] Morrison, Danishefsky, and Yates, *J. Org. Chem.* **26**, 2617 (1961); Hauptmann, Kluge, Seidig, and Wilde, *Angew. Chem. Int. Ed. Engl.* **4**, 688 (1965) [*Angew. Chem.* **77**, 678].

[93] Mobbs and Suschitzky, *Tetrahedron Lett.* 361 (1971).

[94] For a review, see Sandler and Karo, "Organic Functional Group Preparations," vol. 2, pp. 410–416, Academic Press, Inc., New York, 1971.

B. Oxidations Involving Cleavage of Carbon-Carbon Bonds[95]

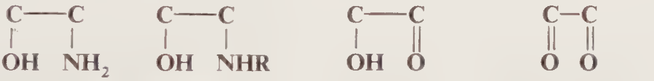
9-8 Oxidative Cleavage of Glycols and Related Compounds



1,2-Glycols are easily cleaved under mild conditions and in good yield with periodic acid or lead tetraacetate.[96] The products are 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the two carbons. The yields are so good that olefins are often converted to glycols (reaction **5-39**) and then cleaved with HIO_4 or $Pb(OAc)_4$ rather than being cleaved directly with ozone (reaction **9-10**) or dichromate or permanganate (reaction **9-11**). A number of other oxidizing agents also give the same products, among them activated MnO_2,[97] thallium(III) salts,[98] and O_2 catalyzed by Co(III) salts.[99] The reaction has also been carried out electrochemically.[100] Permanganate, dichromate, and several other oxidizing agents also cleave glycols, giving carboxylic acids rather than aldehydes, but these reagents are seldom used synthetically.

The two reagents (periodic acid and lead tetraacetate) are complementary, since periodic acid is best used in water and lead tetraacetate in organic solvents. When three or more OH groups are located on adjacent carbons, then the middle one (or ones) is converted to formic acid. This reaction is used a great deal in carbohydrate chemistry, more for structure identification than for preparative purposes.

Similar cleavage is undergone by other compounds which contain oxygens or nitrogens on adjacent carbons:

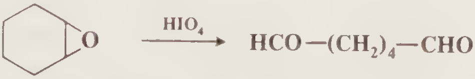


β-Amino alcohols

α-Hydroxy aldehydes and ketones

α-Diketones
α-Keto aldehydes
Glyoxal

α-Diketones are also cleaved by alkaline H_2O_2, to give two molecules of carboxylic acid. HIO_4 has been used to cleave epoxides to aldehydes,[101] e.g.,



α-Hydroxy acids and α-keto acids are not cleaved by HIO_4 but are cleaved by $Pb(OAc)_4$, alkaline H_2O_2, and other reagents. These are oxidative decarboxylations. α-Hydroxy acids give aldehydes or ketones, and α-keto acids give acids:

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[95] For a review, see Bentley, in Bentley and Kirby, Ref. 8, pp. 137–254.

[96] For reviews covering HIO_4, see Sklarz, Ref. 8; Jackson, *Org. React.* **2,** 341–375 (1944). For reviews covering both reagents, see House, Ref. 8, pp. 353–363; Perlin, in Augustine, "Oxidation," vol. 1, pp. 189–212, Marcel Dekker, Inc., New York, 1969; Bunton, in Wiberg, Ref. 2, pp. 367–407; Criegee, *Newer Methods Prep. Org. Chem.* **1,** 12–20 (1948).

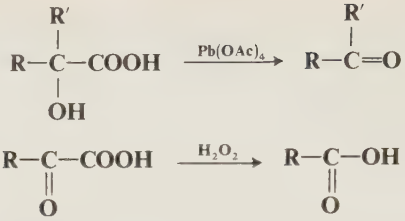
[97] Adler and Becker, *Acta Chem. Scand.* **15,** 849 (1961); Ohloff and Giersch, *Angew. Chem. Int. Ed. Engl.* **12,** 401 (1973) [*Angew. Chem.* **85,** 401].

[98] McKillop, Raphael, and Taylor, *J. Org. Chem.* **37,** 4204 (1972).

[99] de Vries and Schors, *Tetrahedron Lett.* 5689 (1968).

[100] Shono, Matsumura, Hashimoto, Hibino, Hamaguchi, and Aoki, *J. Am. Chem. Soc.* **97,** 2546 (1975).

[101] Nagarkatti and Ashley, *Tetrahedron Lett.* 4599 (1973).

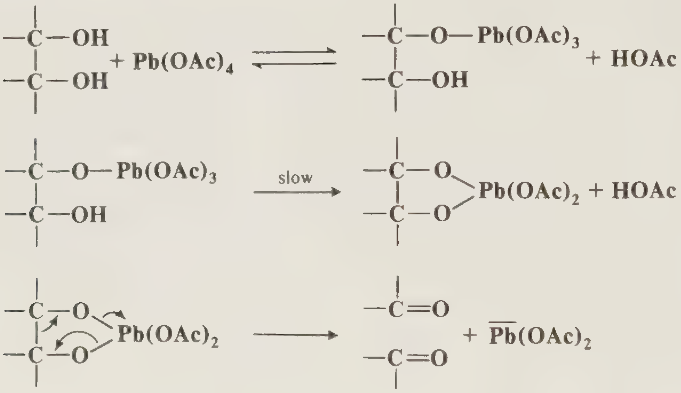


$$\text{R—}\underset{\text{OH}}{\overset{\text{R}'}{\text{C}}}\text{—COOH} \xrightarrow{\text{Pb(OAc)}_4} \text{R—}\overset{\text{R}'}{\text{C}}\text{=O}$$

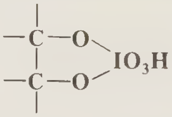
$$\text{R—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—COOH} \xrightarrow{\text{H}_2\text{O}_2} \text{R—}\underset{\text{O}}{\underset{\|}{\text{C}}}\text{—OH}$$

Also see reactions **0-13**, **9-14**, and **9-15**.

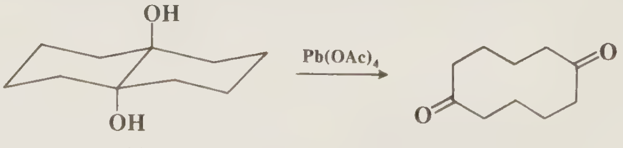
The mechanism of glycol oxidation with $Pb(OAc)_4$ was proposed by Criegee:[102]



This mechanism is supported by these facts: (1) the kinetics are second order (first order in each reactant); (2) added acetic acid retards the reaction (drives the equilibrium to the left); and (3) cis glycols react much more rapidly than trans glycols.[103] For periodic acid the mechanism is similar, with the intermediate[104]



However, the cyclic-intermediate mechanism cannot account for all glycol oxidations, since some glycols which cannot form such an ester (for example, **11**) are nevertheless cleaved by lead tetraacetate (though other glycols which cannot form cyclic esters are *not* cleaved, by either



11

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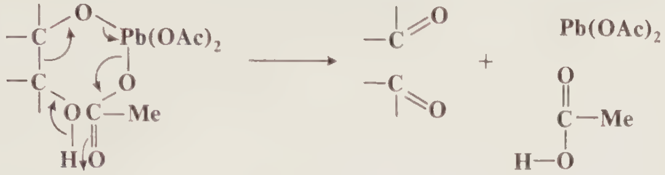
[102] Criegee, Kraft, and Rank, *Justus Liebigs Ann. Chem.* **507**, 159 (1933). For reviews, see Wasserman, in Newman, "Steric Effects in Organic Chemistry," pp. 378–387, John Wiley & Sons, Inc., New York, 1956; Waters, Ref. 2, pp. 72–81; Stewart, Ref. 2, pp. 97–106.

[103] For example, see Criegee, Höger, Huber, Kruck, Marktscheffel, and Schellenberger, *Justus Liebigs Ann. Chem.* **599**, 81 (1956).

[104] Buist, Bunton, and Miles, *J. Chem. Soc.* 743 (1959); Buist and Bunton, *J. Chem. Soc. B* 2117 (1971); Buist, Bunton, and Hipperson, *J. Chem. Soc. B* 2128 (1971).

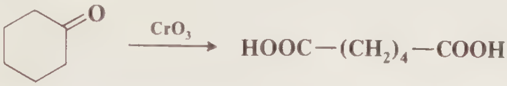
reagent[105]). To account for cases like **11**, a cyclic transition state has been proposed:[103]



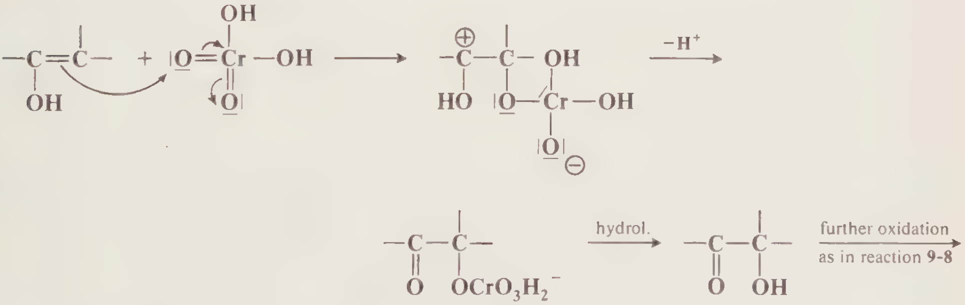
Oxidation by strong oxidizing agents (for example, CrO_3) is probably also through a cyclic intermediate, at least for open-chain and cis cyclic diols,[106] though with some reagents a free-radical mechanism has been demonstrated.[107]

OS **IV**, 124.

9-9 Oxidative Cleavage of Ketones, Aldehydes, and Alcohols



Oxidative cleavage of open-chain ketones or alcohols[108] is seldom a useful preparative procedure, not because these compounds do not undergo oxidation (they do, with the exception of diaryl ketones) but because the result is generally a hopeless mixture. However, the reaction is quite useful for cyclic ketones and the corresponding secondary alcohols, the dicarboxylic acid being prepared in good yield. The formation of adipic acid from cyclohexanone (shown above) is an important industrial procedure. Acid dichromate and permanganate are the most common oxidizing agents, though autoxidation (oxidation with atmospheric oxygen) in alkaline solution has also been used.[109] The mechanism for the cleavage of ketones by strong oxidizing agents is probably through the enol form.[110] The process may be illustrated for chromic acid:



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[105] Angyal and Young, *J. Am. Chem. Soc.* **81**, 5251 (1959).

[106] Roček and Westheimer, *J. Am. Chem. Soc.* **84**, 2241 (1962); Kwart, Ford, and Corey, *J. Am. Chem. Soc.* **84**, 1252 (1962).

[107] Littler, Mallet, and Waters, *J. Chem. Soc.* 2761 (1960).

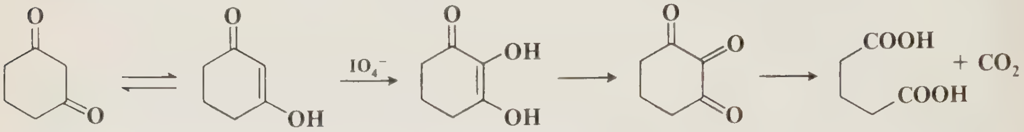
[108] For a review of metal ion-catalyzed oxidative cleavage of alcohols, see Trahanovsky, *Methods Free-Radical Chem.* **4**, 133–169 (1973). For a review of the oxidation of aldehydes and ketones, see Vertler, in Zabicky, "The Chemistry of the Carbonyl Group," vol. 2, pp. 71–156, Interscience Publishers, New York, 1970.

[109] Wallace, Pobiner, and Schriesheim, *J. Org. Chem.* **30**, 3768 (1965).

[110] Best, Littler, and Waters, *J. Chem. Soc.* 822 (1962); Littler, *J. Chem. Soc.* 827, 832 (1962); Roček and Riehl, *J. Org. Chem.* **32**, 3569 (1967); *J. Am. Chem. Soc.* **89**, 6691 (1967).

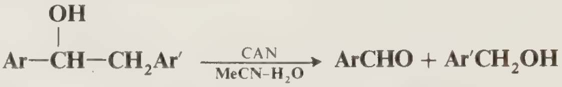
The formation of the chromium ester from the enol is similar to the bromination of ketones (reaction **2-4**). A similar mechanism was demonstrated for nitric acid.[111] However, in some cases, the ketone is attacked directly, and not through the enol.[112]

Cyclic 1,3-diketones, which exist mainly in the monoenolic form, can be cleaved with sodium periodate, with loss of one carbon, e.g.,[113]



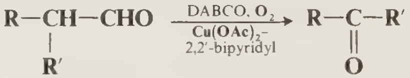
The species which actually undergoes the cleavage is the triketone, so that this is an example of reaction **9-8.**

1,2-Diarylethanols (as well as certain other alcohols) react with ceric ammonium nitrate (CAN) to give cleavage products.[114] The mechanism involves free radicals.



$$\mathrm{Ar{-}\overset{\displaystyle OH}{\overset{|}{C}}H{-}CH_2Ar'} \xrightarrow[\text{MeCN-H}_2\text{O}]{\text{CAN}} \mathrm{ArCHO + Ar'CH_2OH}$$

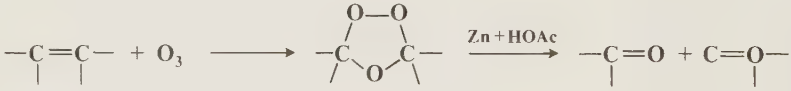
Straight-chain aldehydes can be degraded to lower homologs, one step at a time $[CH_3(CH_2)_n\text{-}CHO \rightarrow CH_3(CH_2)_{n-1}CHO]$, by treatment with O_2 and a cupric acetate–pyridine–triethylamine catalyst.[115] A similar method has been used to cleave branched aldehydes. In this reaction, air is bubbled through a solution of the aldehyde, 1,4-diazabicyclo[2.2.2]octane (DABCO), and a cupric acetate–2,2′-bipyridyl complex in dimethylformamide to give the ketone with one less carbon.[116]



$$\mathrm{R{-}\underset{\underset{\displaystyle R'}{|}}{C}H{-}CHO} \xrightarrow[\text{Cu(OAc)}_2\text{–}\atop \text{2,2'-bipyridyl}]{\text{DABCO, O}_2} \mathrm{R{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}R'}$$

OS **I,** 18; **IV,** 19; **55,** 67.

9-10 Ozonolysis



12

When compounds containing double bonds are treated with ozone, usually at low temperatures, they are converted to compounds called ozonides (**12**) which can be isolated but, because some of them are explosive, are more often decomposed with zinc and acetic acid or catalytic hydrogenation to give 2 moles of aldehyde, or 2 moles of ketone, or 1 mole of each, depending on the groups attached to the olefin.[117] The decomposition of **12** has also been carried out with many other reducing agents, among them trimethyl phosphite[118] and dimethyl sulfide.[119] However, ozonides can also be *oxidized* with oxygen, peracids, or H_2O_2 to give ketones and/or carboxylic acids or *reduced* with $LiAlH_4$, $NaBH_4$, BH_3, or catalytic hydrogenation with excess H_2 to give 2 moles of alcohol.[120] Ozonides can also be treated with ammonia, hydrogen, and a catalyst to give the corresponding amines.[121] Ozonolysis is therefore an important synthetic reaction. In the past it was also very valuable for location of the double bonds in unknown compounds, though with the advent of instrumental methods of structure determination, this usage has declined.

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[111] van Asselt and van Krevelen, *Recl. Trav. Chim. Pays-Bas* **82,** 51 (1963).

[112] Littler, *J. Chem. Soc.* 832 (1962).

[113] Wolfrom and Bobbitt, *J. Am. Chem. Soc.* **78,** 2489 (1956).

[114] Nave and Trahanovsky, *J. Am. Chem. Soc.* **93,** 4536 (1971); Trahanovsky and Macaulay, *J. Org. Chem.* **38,** 1497 (1973). For a review, see Trahanovsky, Ref. 108.

[115] Brackman, Gaasbeek, and Smit, *Recl. Trav. Chim. Pays-Bas* **85,** 437 (1966).

[116] Van Rheenan, *Tetrahedron Lett.* 985 (1969). See also Van Rheenan, *Chem. Commun.* 314 (1969).

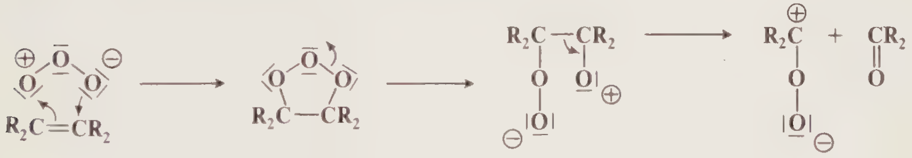
[117] For reviews, see Belew, in Augustine, "Oxidation," Ref. 9, vol. 1, pp. 259–335; Menyailo and Pospelov, *Russ. Chem. Rev.* **36,** 284–294 (1967); Bailey, *Chem. Rev.* **58,** 925–1010 (1958).

[118] Knowles and Thompson, *J. Org. Chem.* **25,** 1031 (1960).

[119] Pappas, Keaveney, Gancher, and Berger, *Tetrahedron Lett.* 4273 (1966).

A wide variety of olefins undergo ozonolysis, including cyclic ones, where cleavage gives rise to one bifunctional product. The reaction has often been carried out on compounds containing more than one double bond; generally the bonds are all cleaved. In some cases, especially when bulky groups are present, conversion of the substrate to an epoxide (reaction **5-40**) becomes an important side reaction and can be the main reaction.[122] Ozonolysis of triple bonds is less common, and the reaction proceeds less easily, since ozone is an electrophilic agent[123] and therefore prefers double to triple bonds (p. 686). Compounds which contain triple bonds generally give carboxylic acids, though sometimes ozone oxidizes them to α-diketones. Acetylenic ethers give α-keto esters:[124] $RC{\equiv}COR' \rightarrow RCOCOOR'$. Aromatic compounds are also attacked less readily than olefins, but they have often been cleaved. Aromatic compounds behave as if the double bonds in the Kekulé structures were really there. Thus benzene gives 3 moles of glyoxal (HCOCHO), and *o*-xylene gives a glyoxal MeCOCHO MeCOCOMe ratio of 3 : 2 : 1, which shows that in this case cleavage is statistical. With polycyclic aromatic compounds the site of attack depends on the structure of the molecule and on the solvent.[125]

Although a large amount of work has been done on the mechanism of ozonization (formation of **12**), not all the details are known. The knowledge we have about the mechanism is largely due to Criegee.[126] The first step of the Criegee mechanism is a 1,3 dipolar addition (reaction **5-50**) of ozone to substrate to give the "initial" or "primary" ozonide **13** (also called *molozonide*[127]).[128] This species is highly unstable and opens up to give the zwitterion **14**, which then cleaves into an aldehyde or ketone (**16**) and a different zwitterion (**15**):[129]



13 **14** **15** **16**

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[120] Sousa and Bluhm, *J. Org. Chem.* **25**, 108 (1960); Diaper and Mitchell, *Can. J. Chem.* **38**, 1976 (1960); Diaper and Strachan, *Can. J. Chem.* **45**, 33 (1967); White, King, and O'Brien, *Tetrahedron Lett.* 3587 (1971).

[121] Diaper and Mitchell, *Can. J. Chem.* **40**, 1189 (1962); Benton and Kiess, *J. Org. Chem.* **25**, 470 (1960); Pollart and Miller, *J. Org. Chem.* **27**, 2392 (1962); White, King, and O'Brien, *Tetrahedron Lett.* 3591 (1971).

[122] See for example, Bailey and Lane, *J. Am. Chem. Soc.* **89**, 4473 (1967); Gillies, *J. Am. Chem. Soc.* **97**, 1276 (1975).

[123] See for example, Wibaut and Sixma, *Recl. Trav. Chim. Pays-Bas* **71**, 761 (1952); Williamson and Cvetanović, *J. Am. Chem. Soc.* **90**, 4248 (1968); Whitworth, Ayoub, Rousseau, and Fliszár, *J. Am. Chem. Soc.* **91**, 7128 (1969); Razumovskii and Zaikov, *J. Org. Chem. USSR* **8**, 468, 473 (1972); Klutsch and Fliszár, *Can. J. Chem.* **50**, 2841 (1972).

[124] Wisaksono and Arens, *Recl. Trav. Chim. Pays-Bas* **80**, 846 (1961).

[125] Dobinson and Bailey, *Tetrahedron Lett.* no. 13, 14 (1960).

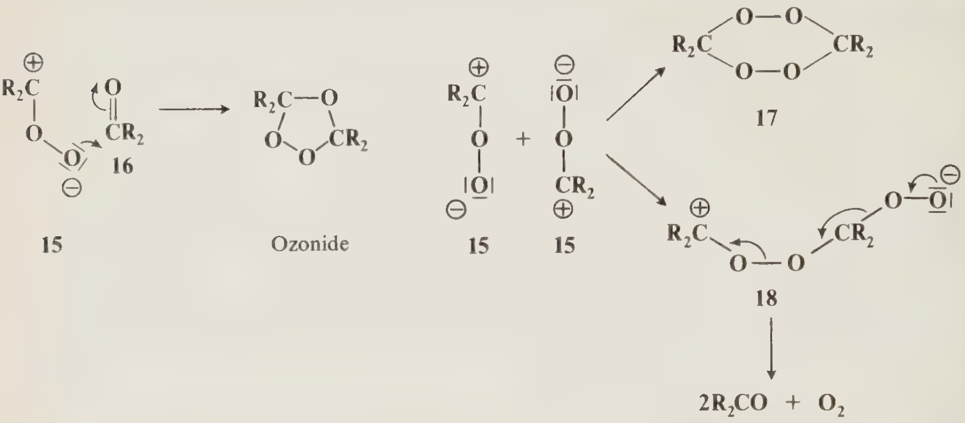
[126] For reviews, see Criegee, *Angew. Chem. Int. Ed. Engl.* **14**, 745–752 (1975) [*Angew. Chem.* **87**, 765–771]; Murray, *Acc. Chem. Res.* **1**, 313–320 (1968).

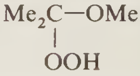
[127] Actually, the name molozonide was coined by Staudinger [*Ber.* **58**, 1088 (1925)] to refer to a different structure, but many authors use this name for **13**.

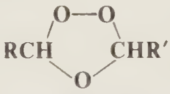
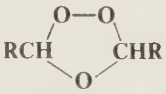
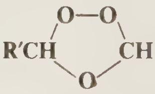
[128] Criegee did not specify the structure of this species, but it has been isolated and observed in solution and seems to have the structure **13**: Criegee and Schröder, *Chem. Ber.* **93**, 689 (1960); Bailey, Thompson, and Shoulders, *J. Am. Chem. Soc.* **88**, 4098 (1966); Durham and Greenwood, *J. Org. Chem.* **33**, 1629 (1968); Bailey, Carter, Fischer, and Thompson, *Can. J. Chem.* **51**, 1278 (1973); Hull, Hisatsune, and Heicklen, *J. Am. Chem. Soc.* **94**, 4856 (1972); Alcock and Mile, *J. Chem. Soc., Chem. Commun.* 575 (1973), 5 (1976).

[129] It has been proposed on the basis of valence bond calculations that the ground state of **15** (R = H) is actually a singlet diradical rather than a zwitterion: Wadt and Goddard, *J. Am. Chem. Soc.* **97**, 3004 (1975).

15 may then undergo various reactions, three of which lead to normal products. One of these is a recombination with **16**, the second a dimerization to the bisperoxide **17**, and the third a kind



of dimerization to the zwitterion **18**.[130] If the first path is taken (this is normally possible only if **16** is an aldehyde; most ketones are not reactive enough[131]), then hydrolysis of the ozonide gives the normal products. If **17** is formed, then hydrolysis of it gives one of the products, and of course **16**, which then does not undergo further reaction, is the other. **18**, if formed, can decompose directly, as shown, to give the normal products and oxygen. In protic solvents, **15** is converted to a hydroperoxide, and these have been isolated, for example,  $Me_2C(OOH)—OMe$ from $Me_2C{=}CMe_2$ in methanol. Further evidence for the mechanism is that **17** can be isolated in some cases, e.g., from $Me_2C{=}CMe_2$. But perhaps the most impressive evidence comes from the detection of cross products. In this mechanism, the two parts of the original olefin break apart and then recombine to form the ozonide. In the case of an unsymmetrical olefin RCH=CHR′ there should then be three ozonides:

since there are two different aldehydes **16** and two different zwitterions **15**, and these can recombine in the three ways shown. Actually *six* ozonides, corresponding to the cis and trans forms of these three, were isolated and characterized for methyl oleate.[132] Similar results have been reported for smaller olefins, e.g., 2-pentene, 2-hexene, 4-nonene, and even 2-methyl-2-pentene.[133] The last-mentioned case is especially interesting, since it is quite plausible that this unsymmetrical olefin would cleave in only one way, so that only one ozonide (in cis and trans versions) would be found; but this is not so, and three were found for this case too. However, terminal olefins give little or no cross ozonide formation.[134] In general, the less alkylated end of the olefin tends to go to **16** and the other to **15**.[135] Still other evidence for the Criegee mechanism is: (1) When $Me_2C{=}CMe_2$ was ozonized in the presence of HCHO, then the ozonide **19** could

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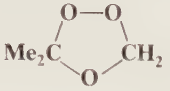
[130] Fliszár, Gravel, and Cavalieri, *Can. J. Chem.* **44**, 67, 1013 (1966); Fliszár and Chylińska, *Can. J. Chem.* **45**, 29 (1967), **46**, 783 (1968).

[131] It follows that tetrasubstituted alkenes do not normally give ozonides. However, they do give the normal cleavage products (ketones) by the other pathways.

[132] Riezebos, Grimmelikhuysen, and van Dorp, *Recl. Trav. Chim. Pays-Bas* **82**, 1234 (1963); Privett and Nickell, *J. Am. Oil Chem. Soc.* **41**, 72 (1964).

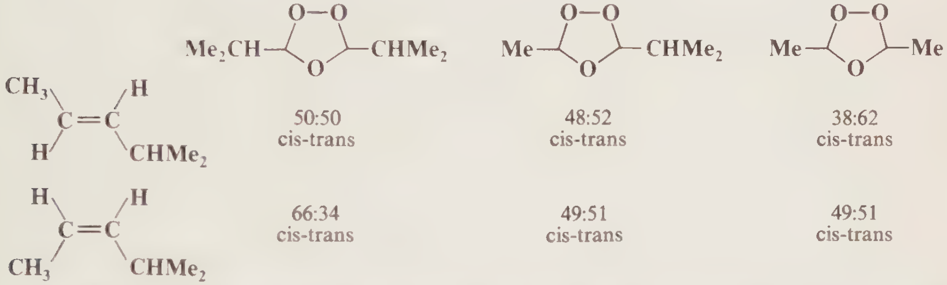
[133] Loan, Murray, and Story, *J. Am. Chem. Soc.* **87**, 737 (1965); Lorenz and Parks, *J. Org. Chem.* **30**, 1976 (1965).

[134] Murray and Williams, *J. Org. Chem.* **34**, 1891 (1969).



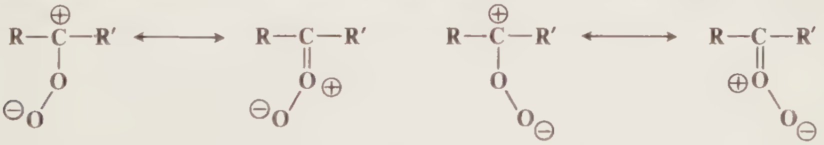
19

be isolated;[136] (2) **15**, prepared in an entirely different manner (photooxidation of diazo compounds), reacted with aldehydes to give ozonides;[137] and (3) cis and trans olefins generally give the same ozonide, which would be expected if they cleave first.[138] However, this was not true for $Me_3CCH{=}CHCMe_3$, where the cis olefin gave the cis ozonide (chiefly), and the trans gave the trans.[139] The latter result is not compatible with the Criegee mechanism. Also incompatible with the Criegee mechanism was the finding that the cis/trans ratios of symmetrical (cross) ozonides obtained from *cis*- and *trans*-4-methyl-2-pentene were not the same:[140]



If the Criegee mechanism operated as shown above, the cis/trans ratio for each of the two cross ozonides would have to be identical for the cis and trans olefins, since in this mechanism they are completely cleaved.

Several mechanistic proposals have been offered to explain the stereochemical results. One proposal[141] is that the Criegee mechanism basically operates, but with the following refinements: (1) The formation of **13** is stereospecific, as expected from a 1,3 dipolar cycloaddition. (2) Once they are formed, **15** and **16** remain attracted to each other, much like an ion pair. (3) **15** exists in



syn-**15** *anti*-**15**

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[135] This is also true when the less alkylated end contains an aryl group: Keaveney, Berger, and Pappas, *J. Org. Chem.* **32,** 1537 (1967); Keaveney and Pappas, *Tetrahedron Lett.* 841 (1969); Fliszár and Granger, *J. Am. Chem. Soc.* **91,** 3330 (1969); **92,** 3361 (1970). See also Fliszár and Renard, *Can. J. Chem.* **48,** 3002 (1970).

[136] Even ketones can react with **15** to form ozonides, provided they are present in large excess: Criegee and Korber, *Chem. Ber.* **104,** 1812 (1971).

[137] Murray and Suzui, *J. Am. Chem. Soc.* **95,** 3343 (1973); Higley and Murray, *J. Am. Chem. Soc.* **96,** 3330 (1974).

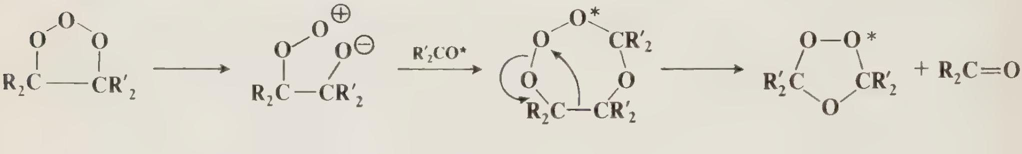
[138] See for example Murray and Williams, *J. Org. Chem.* **34,** 1896 (1969).

[139] Schröder, *Chem. Ber.* **95,** 733 (1962).

[140] Murray, Youssefyeh, and Story, *J. Am. Chem. Soc.* **88,** 3143, 3655 (1966); Story, Murray, and Youssefyeh, *J. Am. Chem. Soc.* **88,** 3144 (1966). Also see Greenwood, *J. Am. Chem. Soc.* **88,** 3146 (1966).

[141] Bauld, Thompson, Hudson, and Bailey, *J. Am. Chem. Soc.* **90,** 1822 (1968); Lattimer, Kuczkowski, and Gillies, *J. Am. Chem. Soc.* **96,** 348 (1974); Bailey, Rustaiyan, and Ferrell, *J. Am. Chem. Soc.* **98,** 638 (1976).

syn and anti forms, which are produced in different amounts and can hold their shapes, at least for a time. This is plausible if we remember that a C=O canonical form contributes to the structure of **15.** (4) The combination of **15** and **16** is also a 1,3 dipolar cycloaddition, so configuration is retained in this step too. Another proposal is entirely different. In this proposal[142] too, the Criegee mechanism basically operates, but there is another pathway which becomes important when large groups are present. In this pathway, the initial ozonide opens up to a zwitterion (**20**), as in the Criegee pathway, *but the charges are reversed.* **20** can now combine



20 **21** **22**

with a molecule of aldehyde or ketone (previously formed by operation of the normal Criegee pathway on another molecule of initial ozonide) to give the seven-membered ring compound **21.** Breakdown of **21** gives the cross ozonide **22.** Since **22** was not formed directly from two independent fragments, the stereochemical behavior can be explained by a consideration of the most favored conformations of **21.** Since in this pathway one of the aldehyde or ketone molecules which was originally present in the initial ozonide has been replaced in **22** by another aldehyde or ketone molecule (it may of course be another molecule of the same compound), the pathway may be called the *aldehyde interchange mechanism.* A number of attempts have been made to distinguish these mechanisms by ^{18}O labeling, making use of the fact, mentioned above, that mixed ozonides (e.g., **19**) can be isolated when an external aldehyde is added. In all three mechanisms a zwitterion reacts with a carbonyl compound to give an ozonide, directly or indirectly, but in the aldehyde interchange mechanism the oxygen atom of the carbonyl group ends up as one of the peroxide oxygens (see the asterisks above), while in either the Criegee or the modified zwitterion mechanism this oxygen appears as the ether oxygen (see the reaction between **15** and **16,** earlier). Several experiments of this kind, wherein ^{18}O-labeled aldehyde is added to the ozonolysis mixture and the resulting ozonide analyzed to determine the position of the ^{18}O label, have been carried out, but unfortunately the results are not entirely unequivocal. With low-molecular-weight alkenes and phenyl alkenes the label appears entirely in the ether oxygen,[143] but with larger alkyl alkenes, where the aldehyde interchange mechanism is predicted[142] to make a substantial contribution, conflicting results have been reported.[144]

Ozonolysis in the gas phase is not generally carried out in the laboratory. However, the reaction is important because it takes place in the upper atmosphere and contributes to air pollution. It has been proposed that mechanisms in the gas phase are different from those in solution.[145]

OS V, 489, 493; **52,** 135. Also see OS **IV,** 554. For the preparation of ozone, see OS **III,** 673.

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[142] Murray, Youssefyeh, and Story, *J. Am. Chem. Soc.* **89,** 2429 (1967).

[143] Bishop, Denson, and Story, *Tetrahedron Lett.* 5739 (1968); Fliszár, Carles, and Renard, *J. Am. Chem. Soc.* **90,** 1364 (1968); Fliszár and Carles, *J. Am. Chem. Soc.* **91,** 2637 (1969); Gillies and Kuczkowski, *J. Am. Chem. Soc.* **94,** 7609 (1972); Gillies, Lattimer, and Kuczkowski, *J. Am. Chem. Soc.* **96,** 1536 (1974).

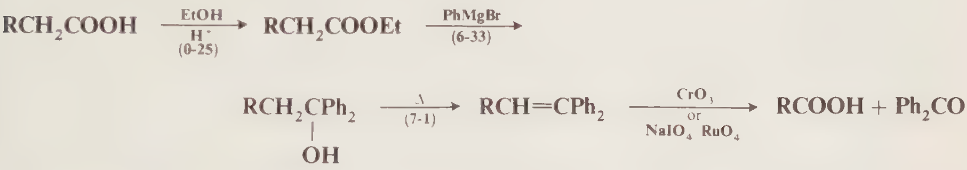
[144] Story, Bishop, Burgess, Murray, and Youssefyeh, *J. Am. Chem. Soc.* **90,** 1907 (1968); Story, Alford, Burgess, and Ray, *J. Am. Chem. Soc.* **93,** 3042 (1971); Murray and Hagen, *J. Org. Chem.* **36,** 1103 (1971); Lattimer and Kuczkowski, *J. Am. Chem. Soc.* **96,** 6205 (1974); Gallaher and Kuczkowski, *J. Org. Chem.* **41,** 892 (1976). See also Klopman and Joiner, *J. Am. Chem. Soc.* **97,** 5287 (1975).

[145] See O'Neal and Blumstein, *Int. J. Chem. Kinet.* **5,** 397 (1973); Becker, Schurath, and Seitz, *Int. J. Chem. Kinet.* **6,** 725 (1974); Williamson and Svetanović, *J. Am. Chem. Soc.* **90,** 4248 (1968).

9-11 Oxidative Cleavage of Double Bonds

$$R_2C{=}CHR \xrightarrow{CrO_3} R_2C{=}O + RCOOH$$

Double bonds can be cleaved by many oxidizing agents, the most common of which are neutral or acid permanganate and acid dichromate. The products are generally 2 moles of ketone, 2 moles of carboxylic acid, or 1 mole of each, depending on what groups are attached to the olefin. With ordinary solutions of permanganate or dichromate yields are generally low, and the reaction is seldom a useful synthetic method; but high yields can be obtained by oxidizing with $KMnO_4$ dissolved in benzene containing the crown ether dicyclohexyl-18-crown-6 (see p. 82).[146] The crown ether coordinates with K^+, permitting the $KMnO_4$ to dissolve in benzene. Another reagent frequently used for synthetic purposes is the *Lemieux-von Rudloff reagent:* HIO_4 containing a trace of MnO_4^-.[147] The MnO_4^- is the actual oxidizing agent, being reduced to the manganate stage, and the purpose of the HIO_4 is to reoxidize the manganate back to MnO_4^-. Another reagent which behaves similarly is $NaIO_4$-ruthenium tetroxide.[148] The *Barbier-Wieland procedure* for decreasing the length of a chain by one carbon involves oxidative cleavage by acid dichromate ($NaIO_4$-ruthenium tetroxide has also been used), but this is cleavage of a 1,1-diphenyl olefin, which generally gives good yields:



$$RCH_2COOH \xrightarrow[\substack{H^+ \\ (0\text{-}25)}]{EtOH} RCH_2COOEt \xrightarrow[(6\text{-}33)]{PhMgBr} \underset{\displaystyle OH}{RCH_2CPh_2} \xrightarrow[(7\text{-}1)]{\Delta} RCH{=}CPh_2 \xrightarrow[\substack{\text{or} \\ NaIO_4\ RuO_4}]{CrO_3} RCOOH + Ph_2CO$$

With certain reagents, the oxidation of double bonds can be stopped at the aldehyde stage, and in these cases the products are the same as in the ozonolysis procedure. Among these reagents are chromyl chloride,[149] chromyl trichloroacetate,[150] and $NaIO_4$–OsO_4.[151]

The mechanism of oxidation probably involves in most cases the initial formation of a glycol (reaction **5-39**), or at least a cyclic ester, and then further oxidation as in reaction **9-8.**[152] In line with the electrophilic attack on the olefin, triple bonds are more resistant to oxidation than double bonds.

Aromatic rings can be cleaved with strong enough oxidizing agents. An important laboratory reagent for this purpose is ruthenium tetroxide along with a cooxidant such as $NaIO_4$ or NaOCl (household bleach may be used).[153] Examples[154] are the oxidation of naphthalene to phthalic acid[155] and, even more remarkably, of cyclohexylbenzene to cyclohexanecarboxylic acid[156] (note

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[146] Sam and Simmons, *J. Am. Chem. Soc.* **94,** 4024 (1972).

[147] Lemieux and Rudloff, *Can. J. Chem.* **33,** 1701, 1710 (1955); Rudloff, *Can. J. Chem.* **33,** 1714 (1955), **34,** 1413 (1956), **43,** 1784 (1965).

[148] For a review, see Lee and van den Engh, in Trahanovsky, Ref. 1, pp. 186–192.

[149] Freeman and Yamachika, *J. Am. Chem. Soc.* **94,** 1214 (1972).

[150] Schildknecht and Föttinger, *Justus Liebigs Ann. Chem.* **659,** 20 (1962).

[151] Pappo, Allen, Lemieux, and Johnson, *J. Org. Chem.* **21,** 478 (1956).

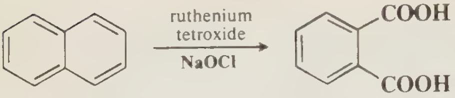
[152] There is evidence that oxidation with Cr(VI) in aqueous acetic acid involves an epoxide intermediate: Awasthy and Roček, *J. Am. Chem. Soc.* **91,** 991 (1969); Roček and Drozd, *J. Am. Chem. Soc.* **92,** 6668 (1970). See also Erickson and Clark, *Tetrahedron Lett.* 3997 (1969).

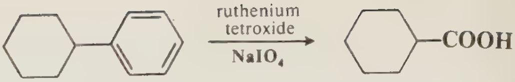
[153] Ruthenium tetroxide is an expensive reagent, but the cost may be greatly reduced by the use of an inexpensive cooxidant such as NaOCl, the function of which is to oxidize RuO_2 back to ruthenium tetroxide.

[154] For other examples, see Piatak, Herbst, Wicha, and Caspi, *J. Org. Chem.* **34,** 116 (1969); Wolfe, Hasan, and Campbell, *Chem. Commun.* 1420 (1970); Ayres and Hossain, *Chem. Commun.* 428 (1972).

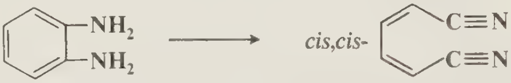
[155] Spitzer and Lee, *J. Org. Chem.* **39,** 2468 (1974).

[156] Caputo and Fuchs, *Tetrahedron Lett.* 4729 (1967).





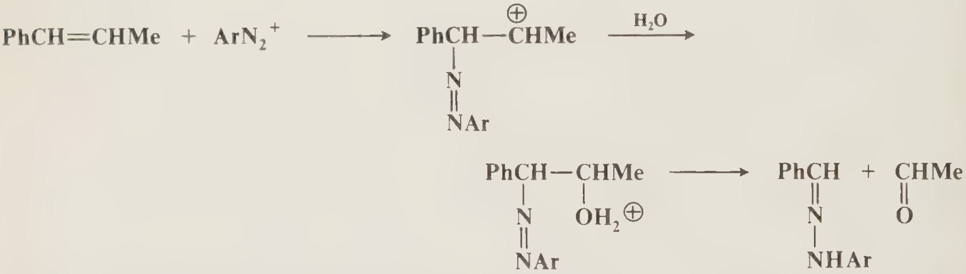
the contrast with reaction **9-12**). Another reagent which oxidizes aromatic rings is air, catalyzed by V_2O_5. The oxidations of naphthalene to phthalic anhydride and of benzene to maleic anhydride (p. 726) by this reagent are important industrial procedures. *o*-Diamines have been oxidized with nickel peroxide and with lead tetraacetate:[157]



Double bonds can be cleaved in other ways. Treatment with NH_2NH^- gives a hydrazone:[158]

$$R_2C{=}CR_2 + NH_2NH^- \longrightarrow R_2CH_2 + R_2C{=}NNH_2$$

Certain olefins can be cleaved with diazonium salts to give aldehydes or ketones and arylhydrazones:[159]



$$PhCH{=}CHMe + ArN_2^+ \longrightarrow \begin{array}{l} \oplus \\ PhCH-CHMe \\ \;\;| \\ \;\;N \\ \;\;\| \\ \;\;NAr \end{array} \xrightarrow{H_2O}$$

$$\begin{array}{l} PhCH-CHMe \\ \;\;|\qquad\;\; | \\ \;\;N \quad\; OH_2^{\oplus} \\ \;\;\| \\ \;\;NAr \end{array} \longrightarrow \begin{array}{l} PhCH \\ \;\;\| \\ \;\;N \\ \;\;| \\ NHAr \end{array} + \begin{array}{l} CHMe \\ \;\;\| \\ \;\;O \end{array}$$

Terminal triple bond compounds can be cleaved to carboxylic acids with thallium(III) nitrate ($RC{\equiv}CH \rightarrow RCOOH$).[160]

OS **II,** 53, 523; **III,** 39, 234, 449; **IV,** 136, 484, 824; **V,** 393; **55,** 67. Also see OS **II,** 551.

9-12 Oxidation of Aromatic Side Chains

$$ArR \xrightarrow{KMnO_4} ArCOOH$$

Alkyl chains on aromatic rings can be oxidized to COOH groups by many oxidizing agents, including permanganate, nitric acid, and acid dichromate. The method is most often applied to the methyl group, though longer side chains can also be cleaved. However, tertiary alkyl groups are resistant to oxidation, and when they *are* oxidized, ring cleavage usually occurs too.[161] It is usually difficult to oxidize an R group on a fused aromatic system without cleaving the ring or oxidizing it to a quinone (reaction **9-19**). However, this has been done (e.g., 2-methylnaphthalene was converted to naphthoic acid) with aqueous $Na_2Cr_2O_7$.[162] Functional groups may be present anywhere on the side chain and, if in the α-position, greatly increase the ease of oxidation.

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[157] Nakagawa and Onoue, *Tetrahedron Lett.* 1433 (1965), *Chem. Commun.* 396 (1966).

[158] Kauffmann, Henkler, Kosel, Rauch, Schultz, and Weber, *Angew. Chem. Int. Ed. Engl.* **1,** 456 (1962) [*Angew. Chem.* **74,** 650].

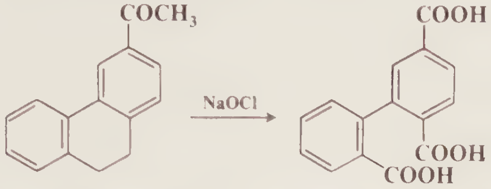
[159] Marxmeier and Pfeil, *Chem. Ber.* **97,** 815 (1964), *Justus Liebigs Ann. Chem.* **678,** 28 (1964).

[160] McKillop, Oldenziel, Swann, Taylor, and Robey, *J. Am. Chem. Soc.* **95,** 1296 (1973).

[161] Brandenberger, Maas, and Dvoretsky, *J. Am. Chem. Soc.* **83,** 2146 (1961).

[162] Friedman, Fishel, and Shechter, *J. Org. Chem.* **30,** 1453 (1965).

However, an exception is an α-phenyl group. In such cases the reaction stops at the diaryl ketone stage. Molecules containing aryl groups on different carbons cleave so that each ring gets one carbon atom, e.g.,

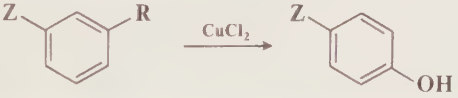


It is possible to oxidize only one alkyl group of a ring that contains more than one. The order of reactivity[163] toward most reagents is $CH_2Ar > CHR_2 > CH_2R > CH_3$.[164] Groups on the ring which are susceptible to oxidation (OH, NHR, NH_2, etc.) must be protected. The oxidation can be performed with oxygen, in which case it is autoxidation, and the mechanism is like that in reaction **4-8**, with a hydroperoxide intermediate. With this procedure it is possible to isolate ketones from $ArCH_2R$.

The mechanism has been studied for the closely related reaction: $Ar_2CH_2 + CrO_3 \rightarrow Ar_2C{=}O$.[165] A deuterium isotope effect of 6.4 was found, indicating that the rate-determining step is either $Ar_2CH_2 \rightarrow Ar_2CH\cdot$ or $Ar_2CH_2 \rightarrow Ar_2CH^+$. Either way this explains why tertiary groups are not converted to COOH and why the reactivity order is $CHR_2 > CH_2R > CH_3$, as mentioned above. Both free radicals and carbonium ions exhibit this order of stability (Chapter 5). The two possibilities are examples of categories 2 and 3 (p. 1075). Just how the free radical or carbonium ion goes on to the product is not known. $Ar{-}\overset{|}{\underset{|}{C}}{-}OH$ may be an intermediate, in which case the further reaction would be like that in reaction **9-4.**

OS **I,** 159, 385, 392, 543; **II,** 135, 428; **III,** 334, 420, 740, 791, 820, 822; **V,** 617, 810.

9-13 Oxidative Cleavage of Alkyl Groups from Rings



It is possible to replace an alkyl group on a ring by an OH group. When the alkyl group is one oxidizable to COOH (reaction **9-12**), then cupric salts are oxidizing agents, and the OH group is found in a position ortho to that occupied by the alkyl group.[166] What happens here is an initial oxidation to COOH, and then an example of reaction **3-20.**[167] This reaction is used industrially to convert toluene to phenol.

In a different kind of reaction, the methyl group of trinitrotoluene can be oxidized to an OH group in the *same* position with $Na_2Cr_2O_7$, H_2SO_4, and HNO_3.[168] The sequence in this case seems to be (1) oxidation to COOH, (2) nucleophilic substitution of the COOH by NO_3^-, and (3) hydrolysis of the nitrate ester.

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[163] Oxidation with Co(III) is an exception. The methyl group is oxidized in preference to the other alkyl groups: Onopchenko, Schulz, and Seekircher, *J. Org. Chem.* **37,** 1414 (1972).

[164] For example, see Foster and Hickinbottom, *J. Chem. Soc.* 680 (1960); Ferguson and Wims, *J. Org. Chem.* **25,** 668 (1960).

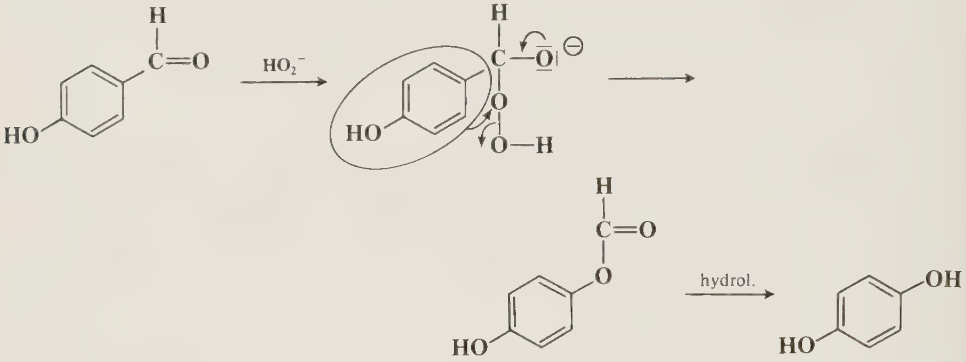
[165] Wiberg and Evans, *Tetrahedron* **8,** 313 (1960).

[166] Kaeding, *J. Org. Chem.* **26,** 3144 (1961).

[167] For a discussion, see Lee and van den Engh, in Trahanovsky, Ref. 1, pp. 91–94.

[168] Dacons, Adolph, and Kamlet, *Tetrahedron* **19,** 791 (1963); Adolph, Dacons, and Kamlet, *Tetrahedron* **19,** 801 (1973).

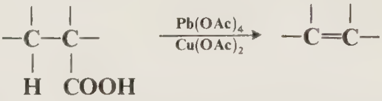
In a third kind of reaction, an aromatic aldehyde ArCHO or ketone ArCOR′ is converted to a phenol ArOH on treatment with alkaline H_2O_2,[169] but there must be an OH or NH_2 group in the ortho or para position. This is called the *Dakin reaction.*[170] The mechanism is probably similar to that of the Baeyer-Villiger reaction **(8-23)**:



OS **I,** 149; **III,** 759.

9-14 Oxidative Decarboxylation

$$RCOOH \xrightarrow{Pb(OAc)_4} ROAc$$



$$\underset{H}{\overset{|}{\underset{|}{-C}}}-\underset{COOH}{\overset{|}{\underset{|}{C-}}} \xrightarrow[Cu(OAc)_2]{Pb(OAc)_4} \overset{|}{-C}=\overset{|}{C-}$$

Carboxylic acids can be decarboxylated with lead tetraacetate[171] to give a variety of products, among them the ester ROAc (formed by replacement of COOH by an acetoxy group), the alkane RH (see reaction **2-39**), and, if a β-hydrogen is present, the alkene formed by elimination of H and COOH, as well as numerous other products arising from rearrangements, internal cyclizations,[172] and reactions with solvent molecules. When R is tertiary, the chief product is usually the alkene, which is often obtained in good yield. High yields of alkenes can also be obtained when R is primary or secondary, in this case by the use of $Cu(OAc)_2$–$Pb(OAc)_4$ instead of $Pb(OAc)_4$.[173] In the absence of $Cu(OAc)_2$, primary acids give mostly alkanes (though yields are generally low), and secondary acids may give esters or alkenes. Esters have been obtained in good yields from some secondary acids, from β,γ-unsaturated acids, and from acids in which R is a benzylic group. γ-Keto acids give good yields of α,β-unsaturated ketones.[174] Other oxidizing agents, including Co(III), Ag(II), Mn(III), and Ce(IV) have also been used to effect oxidative decarboxylation.[175]

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[169] For a convenient procedure, see Hocking, *Can. J. Chem.* **51,** 2384 (1973).

[170] See Schubert and Kintner, in Patai, Ref. 35, pp. 749–752.

[171] For a review, see Sheldon and Kochi, *Org. React.* **19,** 279–421 (1972).

[172] For examples, see Moriarty, Walsh, and Gopal, *Tetrahedron Lett.* 4363 (1966); Davies and Waring, *J. Chem. Soc. C* 1865, 2337 (1968).

[173] Bacha and Kochi, *Tetrahedron* **24,** 2215 (1968); Ogibin, Katzin, and Nikishin, *Synthesis* 889 (1974).

[174] Sane, Divakar, and Rao, *Synthesis* 541 (1973); Mc Murry and Blaszczak, *J. Org. Chem.* **39,** 2217 (1974). See also Hertzler, Berdahl, and Eisenbraun, *J. Org. Chem.* **33,** 2008 (1968).

[175] For references, see Trahanovsky, Cramer, and Brixius, *J. Am. Chem. Soc.* **96,** 1077 (1974). See also Dessau and Heiba, *J. Org. Chem.* **40,** 3647 (1975).

The mechanism with lead tetraacetate is generally accepted to be of the free-radical type.[176] First there is an interchange of ester groups:

$$\text{Pb(OAc)}_4 + \text{RCOOH} \longrightarrow \underset{\textbf{23}}{\text{Pb(OAc)}_3\text{OCOR}} \quad \text{or} \quad \underset{\textbf{24}}{\text{Pb(OAc)}_2\text{(OCOR)}_2}$$

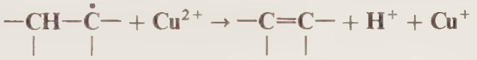
Then follows a free-radical chain mechanism (shown for **23**, though **24** and other lead esters may behave similarly)

$$\text{Initiation} \qquad \underset{\textbf{23}}{\text{Pb(OAc)}_3\text{OCOR}} \longrightarrow \dot{\text{P}}\text{b(OAc)}_3 + \text{R}\cdot + \text{CO}_2$$

$$\text{Propagation} \qquad \text{R}\cdot + \text{Pb(OAc)}_3\text{OCOR} \longrightarrow \text{R}^+ + \dot{\text{P}}\text{b(OAc)}_2\text{OCOR} + \text{OAc}^-$$

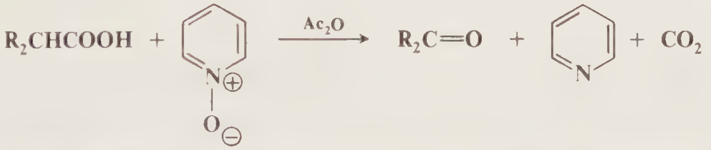
$$\dot{\text{P}}\text{b(OAc)}_2\text{OCOR} \longrightarrow \text{Pb(OAc)}_2 + \text{R}\cdot + \text{CO}_2$$

Products can then be formed either from R· or R^+. Primary R· abstract H from solvent molecules to give RH. R^+ can lose H^+ to give an alkene, react with HOAc to give the ester, react with solvent molecules or with another functional group in the same molecule, or rearrange, thus accounting for the large number of possible products. R· can also dimerize to give R—R. The effect of Cu^{2+} ions[177] is to oxidize the radicals to alkenes, thus producing good yields of alkenes from primary and secondary substrates. Cu^{2+} has no effect on tertiary radicals, because these are efficiently oxidized to alkenes by lead tetraacetate.

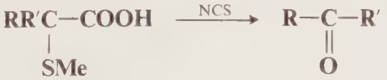


$$-\underset{|}{\text{C}}\text{H}-\underset{|}{\dot{\text{C}}}- + \text{Cu}^{2+} \rightarrow -\underset{|}{\text{C}}=\underset{|}{\text{C}}- + \text{H}^+ + \text{Cu}^+$$

In another type of oxidative decarboxylation, carboxylic acids (or their anhydrides) are converted by pyridine N-oxide in the presence of acetic anhydride to aldehydes or ketones with one less carbon atom.[178]



In still another type, α-methylthio carboxylic acids can be decarboxylated to the corresponding ketones with N-chlorosuccinimide (NCS) in an alcohol solvent containing $NaHCO_3$.[179]



$$\text{RR}'\underset{\underset{\text{SMe}}{|}}{\text{C}}-\text{COOH} \xrightarrow{\text{NCS}} \text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{R}'$$

See also reaction **4-26**.

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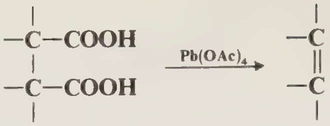
[176] Kochi, *J. Am. Chem. Soc.* **87,** 1811, 3609 (1965); Starnes, *J. Am. Chem. Soc.* **86,** 5603 (1964); Davies and Waring, *Chem. Commun.* 263 (1965); Kochi, Bacha, and Bethea, *J. Am. Chem. Soc.* **89,** 6538 (1967); Cantello, Mellor, and Scholes, *J. Chem. Soc., Perkin Trans. 2* 348 (1974); Beckwith, Cross, and Gream, *Aust. J. Chem.* **27,** 1673, 1693 (1974).

[177] Bacha and Kochi, *J. Org. Chem.* **33,** 83 (1968); Kochi and Bacha, *J. Org. Chem.* **33,** 2746 (1968); Torssell, *Ark. Kemi.* **31,** 401 (1970).

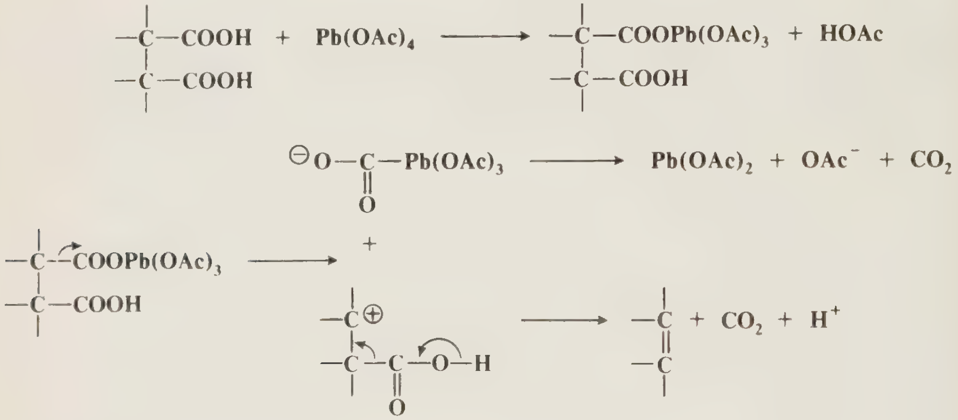
[178] Cohen, Song, Fager, and Deets, *J. Am. Chem. Soc.* **89,** 4968 (1967). For an alternative procedure, see Wasserman and Lipshutz, *Tetrahedron Lett.* 4611 (1975).

[179] Trost and Tamaru, *J. Am. Chem. Soc.* **97,** 3528 (1975).

9-15 Bisdecarboxylation

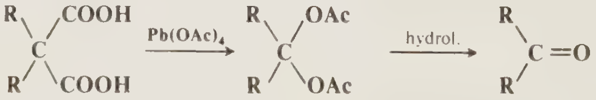


Compounds containing carboxyl groups on adjacent carbons (succinic acid derivatives) can be bisdecarboxylated with lead tetraacetate.[171] The reaction is of wide scope, and many such compounds have successfully given the reaction. The elimination is stereoselective, but not stereospecific (both *meso*- and *dl*-2,3-diphenylsuccinic acid gave *trans*-stilbene),[180] and a concerted mechanism is thus unlikely (see Chapter 15). The following mechanism is not inconsistent with the data:



though a free-radical mechanism seems to hold in some cases.

Compounds containing geminal carboxyl groups (disubstituted malonic acid derivatives) can also be bisdecarboxylated with lead tetraacetate, *gem*-diacetates (acylals) being produced, which are easily hydrolyzable to ketones:[181]



Bisdecarboxylation of succinic acid derivatives to give alkenes has also been carried out by treatment of the corresponding anhydrides with nickel, iron, or rhodium complexes,[182] by decomposition of the corresponding bis peresters,[183] and electrolytically.[184]

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[180] Corey and Casanova, *J. Am. Chem. Soc.* **85**, 165 (1963).

[181] Tufariello and Kissel, *Tetrahedron Lett.* 6145 (1966).

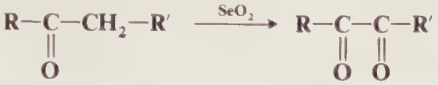
[182] Trost and Chen, *Tetrahedron Lett.* 2603 (1971).

[183] Cain, Vukov, and Masamune, *Chem. Commun.* 98 (1969).

[184] Plieninger and Lehnert, *Chem. Ber.* **100**, 2427 (1967); Radlick, Klem, Spurlock, Sims, van Tamelen, and Whitesides, *Tetrahedron Lett.* 5117 (1968); Westberg and Dauben, *Tetrahedron Lett.* 5123 (1968).

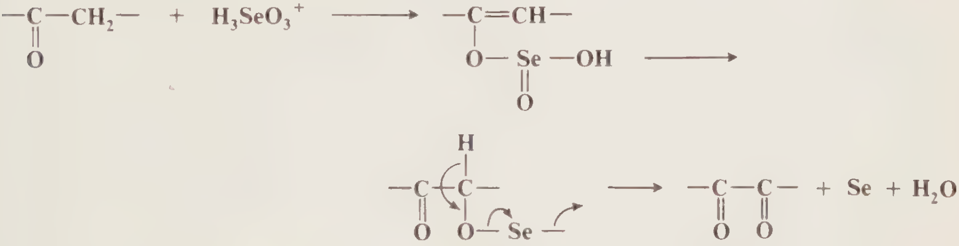
C. Reactions Involving Replacement of Hydrogen by Oxygen

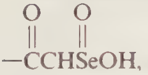
9-16 Oxidation of Methylene to Carbonyl



$$R-\underset{\underset{O}{\|}}{C}-CH_2-R' \xrightarrow{SeO_2} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

Methyl or methylene groups α to a carbonyl can be oxidized with selenium dioxide to give, respectively, α-keto aldehydes and α-diketones.[185] The reaction can also be carried out α to an aromatic ring or to a double bond, though in the latter case hydroxylation (see reaction **4-4**) is the more common result. Although SeO_2 is the reagent most often used, the reaction has also been carried out with N_2O_3 and other oxidizing agents. Substrates most easily oxidized contain two aryl groups on CH_2, and these substrates can be oxidized with many oxidizing agents (see reaction **9-12**). Monoaryl alkanes have been oxidized to alkyl aryl ketones with several oxidizing agents, including CrO_3-acetic acid,[186] ceric ammonium nitrate,[187] and a silver ion–persulfate couple,[188] as well as with SeO_2. With these substrates the oxidation sometimes takes place on the β-carbon (e.g., $PhCH_2CH_3 \rightarrow PhCH_2CHO$). It has been shown for the case where chromyl chloride is the oxidizing agent that there is initial α oxidation followed by rearrangement.[189] Alkenes of the form $C{=}C{-}CH_2$ have been oxidized to α,β-unsaturated ketones by sodium dichromate in $HOAc$-Ac_2O, by *t*-butyl chromate in CCl_4-$HOAc$-Ac_2O,[190] by CrO_3-pyridine complex,[191] and by mercuric salts.[192] CrO_3-pyridine has also been used to convert alkynes of the form $C{\equiv}C{-}CH_2$ to α-keto acetylenes.[193] Two mechanisms have been suggested for the reaction with SeO_2. One of these involves a selenate ester of the enol.[194]



In the other proposed mechanism[194a] the principal intermediate is a β-ketoseleninic acid  $-\overset{\overset{O}{\|}}{C}CH\overset{\overset{O}{\|}}{Se}OH$, and a selenate ester is not involved.

It has proved possible to convert CH_2 to $C{=}O$ groups even if they are not near any functional groups, indirectly, by the remote oxidation method of Breslow (see reaction **9-3**). In a typical

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[185] For reviews of oxidation by SeO_2, see Trachtenberg, in Augustine, Ref. 9, pp. 119–187; Rabjohn, *Org. React.* **5**, 331–386 (1949).

[186] For example, see Harms and Eisenbraun, *Org. Prep. Proced. Int.* **4**, 67 (1972).

[187] Syper, *Tetrahedron Lett.* 4493 (1966).

[188] Daniher, *Org. Prep. Proced.* **2**, 207 (1970).

[189] Wiberg, Marshall, and Foster, *Tetrahedron Lett.* 345 (1962).

[190] Marshall, Ray, Laos, and Riegel, *J. Am. Chem. Soc.* **79**, 6308 (1957); Suga, Sugimoto, Fujita, and Matsuura, *Bull. Chem. Soc. Jpn.* **39**, 2546 (1966).

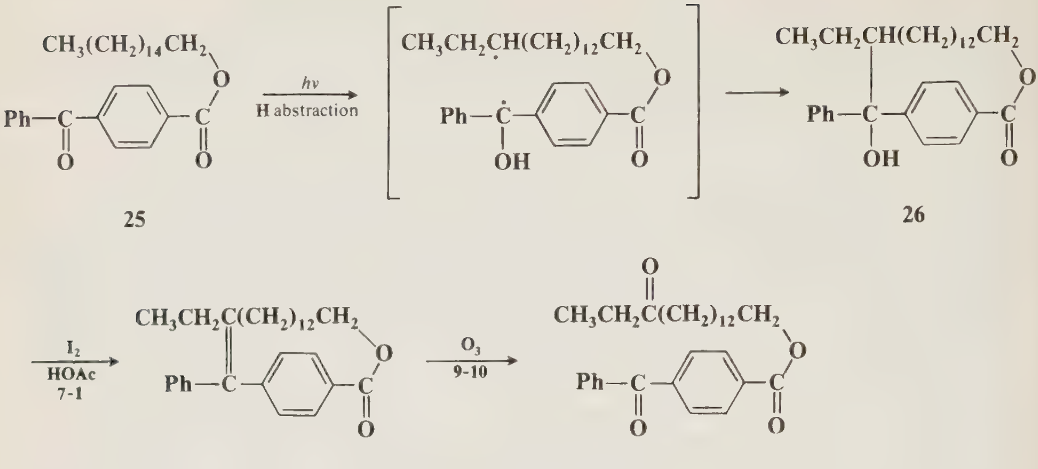
[191] Dauben, Lorber, and Fullerton, *J. Org. Chem.* **34**, 3587 (1969); Fullerton and Chen, *Synth. Commun.* **6**, 217 (1976).

[192] Arzoumanian and Metzger, *Synthesis* 527–536 (1971); Charavel and Metzger, *Bull. Soc. Chim. Fr.* 4102 (1968).

[193] Shaw and Sherry, *Tetrahedron Lett.* 4379 (1971).

[194] Corey and Schaefer, *J. Am. Chem. Soc.* **82**, 918 (1960).

[194a] Sharpless and Gordon, *J. Am. Chem. Soc.* **98**, 300 (1976).



25 **26** **27** **28**

example, the keto ester **25** was irradiated to give the hydroxy lactone **26**, which was dehydrated to **27**. Ozonolysis of **27** gave the diketo ester **28**, in which the C-14 CH_2 group of **25** has been oxidized to a C=O group.[195] The reaction was not completely regiospecific: **28** comprised about 60% of the product, with the remainder consisting of other compounds in which the keto group was located at C-11, C-12, C-15, and other positions along the carbon chain. When longer chains were used (C_{18}, C_{20}), the reaction was less regiospecific, the maximum percentage of any single product being about 20%. The method has also been applied in the steroid series, with greater regiospecificity.[196] In the method so far described, the reaction takes place because one portion of a molecule (the benzophenone moiety) abstracts hydrogen from another portion of the same molecule; that is, the two portions are connected by a series of covalent bonds. However, the reaction can also be carried out where the two reacting centers are actually in different molecules, providing the two molecules are held together by hydrogen bonding. For example, one of the CH_2 groups of *n*-hexadecanol hemisuccinate $CH_3(CH_2)_{14}CH_2OCOCH_2CH_2COOH$ was oxidized to a C=O group by applying the above procedure to a mixture of it and benzophenone-4-carboxylic acid *p*-$PhCOC_6H_4COOH$ in CCl_4.[197]

OS **I**, 266; **II**, 509; **III**, 1, 420, 438; **IV**, 189, 229, 579; **53**, 8. Also see OS **IV**, 23.

9-17 Oxidation of Arylmethanes

$$ArCH_3 \xrightarrow{CrO_2Cl_2} ArCHO$$

Methyl groups on an aromatic ring can be oxidized to the aldehyde stage by several oxidizing agents. The reaction is a special case of reaction **9-16**. When the reagent is chromyl chloride (CrO_2Cl_2), the reaction is called the *Étard reaction*,[198] and the yields are high.[199] Another oxidizing agent is a mixture of CrO_3 and Ac_2O. In this case the reaction stops at the aldehyde stage because the initial product is $ArCH(OAc)_2$ (an acylal), which is resistant to further oxidation. Hydrolysis of the acylal gives the aldehyde.

[195] Breslow and Winnik, *J. Am. Chem. Soc.* **91**, 3083 (1969).

[196] Breslow and Baldwin, *J. Am. Chem. Soc.* **92**, 732 (1970).

[197] Breslow and Scholl, *J. Am. Chem. Soc.* **93**, 2331 (1971).

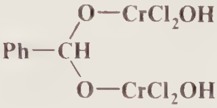
[198] The name Etard reaction is often applied to any oxidation with chromyl chloride, e.g., oxidation of glycols (reaction **9-8**), olefins (reaction **9-11**), etc.

[199] For a review, see Hartford and Darrin, *Chem. Rev.* **58**, 1-61 (1958), pp. 25-53.

Among other oxidizing agents which have been used to accomplish the conversion of $ArCH_3$ to ArCHO are ceric ammonium nitrate[200] and silver(II) oxide.[201] Oxidation of $ArCH_3$ to carboxylic acids is considered at reaction **9-12.**

Conversion of $ArCH_3$ to ArCHO can also be achieved indirectly by bromination to give $ArCHBr_2$ (reaction **4-1**), followed by hydrolysis (reaction **0-2**).

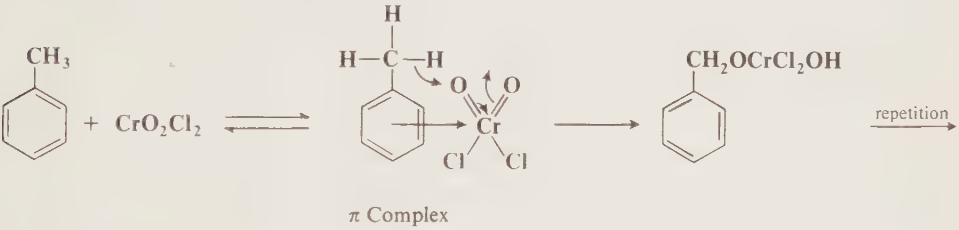
The mechanism of the Étard reaction is not completely known.[202] An insoluble complex is formed on addition of the reagents, which is hydrolyzed to the aldehyde. The complex is probably a kind of acylal, but what the structure is is not fully settled, though many proposals have been made as to its structure and as to how it is hydrolyzed.[199] It is known that $ArCH_2Cl$ is not an intermediate (see reaction **9-20**), since it reacts only very slowly with chromyl chloride. Magnetic susceptibility measurements[203] indicate that the complex from toluene is **29,** a structure first



29

proposed by Étard. According to this proposal the reaction stops after only two hydrogens have been replaced because of the insolubility of **29.** There is disagreement on how **29** is formed, assuming that the complex has this structure. Both an ionic[204] and a free-radical[205] process have been proposed:

Ionic process:



Free-radical process:

$$\mathrm{ArCH_3 + Cl_2CrO_2 \longrightarrow ArCH_2\cdot + HO\dot{C}rOCl_2}$$

$$\mathrm{ArCH_2\cdot + HO\dot{C}rOCl_2 \longrightarrow ArCH_2OCrCl_2OH \xrightarrow{\text{repetition}}}$$

An entirely different structure for the complex was proposed by Nenitzescu and coworkers.[206] On the basis of esr studies they proposed that the complex is $PhCH_2OCrCl_2OCrOCl_2OH$, which is isomeric with **29.** However, this view has been challenged by Wiberg and Eisenthal,[205] who interpret the esr result as being in accord with **29.** Still another proposal is that the complex is composed of benzaldehyde coordinated with reduced chromyl chloride.[207]

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[200] Trahanovsky and Young, *J. Org. Chem.* **31,** 2033 (1966); Radhakrishna Murti and Pati, *Chem. Ind.* (*London*) 702 (1967); Ref. 187.

[201] Syper, *Tetrahedron Lett.* 4193 (1967).

[202] For a review, see Nenitzescu, *Bull. Soc. Chim. Fr.* 1349–1357 (1968).

[203] Wheeler, *Can. J. Chem.* **38,** 2137 (1960). See also Makhija and Stairs, *Can. J. Chem.* **46,** 1255 (1968).

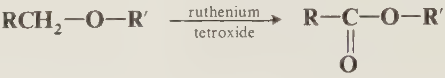
[204] Stairs, *Can. J. Chem.* **42,** 550 (1964).

[205] Wiberg and Eisenthal, *Tetrahedron* **20,** 1151 (1964). See also Gragerov and Ponomarchuk, *J. Org. Chem. USSR* **5,** 1125 (1969).

[206] Necsoiu, Balaban, Pascaru, Sliam, Elian, and Nenitzescu, *Tetrahedron* **19,** 1133 (1963); Necsoiu, Przemetchi, Ghenciulescu, Rentea, and Nenitzescu, *Tetrahedron* **22,** 3037 (1966).

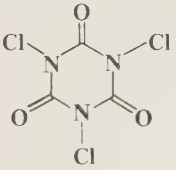
OS **II,** 441; **III,** 641; **IV,** 31, 713.

9-18 Oxidation of Ethers to Esters and Related Reactions



$$RCH_2{-}O{-}R' \xrightarrow[\text{tetroxide}]{\text{ruthenium}} R{-}\underset{\underset{O}{\|}}{C}{-}O{-}R'$$

Ethers in which at least one group is primary alkyl can be oxidized to the corresponding esters in high yields with ruthenium tetroxide.[208] Cyclic ethers give lactones. The reaction, which is a special case of **9-16,** has also been accomplished with CrO_3 in sulfuric acid[209] and with trichloroisocyanuric acid (**30**) in the presence of an excess of water.[210] In a similar reaction, lactams (e.g., **31**) can be converted to cyclic imides by oxidation with a hydroperoxide or peracid and an Mn(II) or Mn(III) salt.[211] Certain tertiary amines containing a methyl group can be oxidized to formamides ($R_2NCH_3 \rightarrow R_2NCHO$) by MnO_2,[212] CrO_3-pyridine,[213] O_2 and platinum,[214] or other oxidizing agents, but the reaction is not general.



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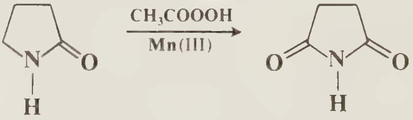

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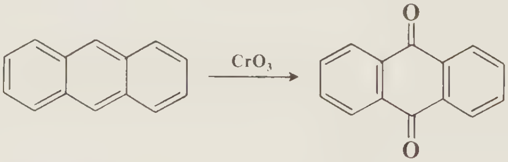
9-19 Oxidation of Aromatic Hydrocarbons to Quinones



Condensed aromatic systems (including naphthalenes) can be directly oxidized to quinones by various oxidizing agents.[215] Yields are generally not high. Benzene cannot be so oxidized by strong oxidizing agents but can be electrolytically oxidized to benzoquinone.

OS **IV,** 698, 757. Also see OS **II,** 554.

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[207] Duffin and Tucker, *Chem. Ind.* (*London*) 1262 (1966); *Tetrahedron* **24,** 6999 (1968).

[208] Berkowitz and Rylander, *J. Am. Chem. Soc.* **80,** 6682 (1958); Lee and van Engh, in Trahanovsky, Ref. 1, pp. 222–225.

[209] Henbest and Nicholls, *J. Chem. Soc.* 221, 227 (1959); Harrison and Harrison, *Chem. Commun.* 752 (1966).

[210] Juenge and Beal, *Tetrahedron Lett.* 5819 (1968); Juenge, Corey, and Beal, *Tetrahedron* **27,** 2671 (1971).

[211] Doumaux, McKeon, and Trecker, *J. Am. Chem. Soc.* **91,** 3992 (1969); Doumaux and Trecker, *J. Org. Chem.* **35,** 2121 (1970).

[212] See for example, Henbest and Thomas, *J. Chem. Soc.* 3032 (1957); Henbest and Stratford, *J. Chem. Soc. C* 995 (1966).

[213] Cavé, Kan-Fan, Potier, Le Men, and Janot, *Tetrahedron* **23,** 4691 (1967).

[214] Davis and Rosenblatt, *Tetrahedron Lett.* 4085 (1968).

[215] For a review, see Thomson, in Patai, Ref. 14, pp. 132–134.

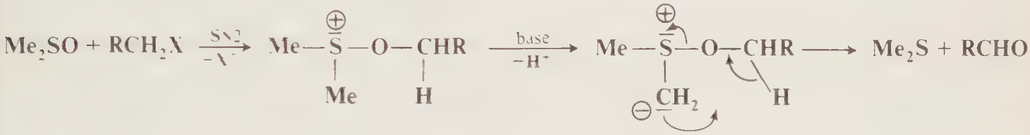
9-20 Oxidation of Primary Halides and Esters of Primary Alcohols to Aldehydes

$$RCH_2Cl \xrightarrow{(CH_3)_2SO} RCHO$$

Primary alkyl halides (chlorides, bromides, and iodides) can be oxidized to aldehydes easily and in good yields with dimethyl sulfoxide.[216] Tosyl esters of primary alcohols can be similarly converted to aldehydes,[217] and epoxides give α-hydroxy ketones or aldehydes.[218] The reaction with tosyl esters represents an indirect way of oxidizing primary alcohols to aldehydes (reaction **9-4**). This type of oxidation can also be carried out without isolation of an intermediate ester: The alcohol is treated with dimethyl sulfoxide, dicyclohexylcarbodiimide (DCC),[219] and anhydrous phosphoric acid.[220] In this way a primary alcohol can be converted to the aldehyde with no carboxylic acid being produced.[221]

Similar oxidation of alcohols has been carried out with dimethyl sulfoxide and other reagents in place of DCC: acetic anhydride,[222] SO_3-pyridine-triethylamine,[223] tosyl chloride,[224] chlorine,[225] mercuric acetate,[226] $AgBF_4$ and Et_3N,[227] $(CF_3SO_2)_2O$,[228] KI and $NaHCO_3$,[229] methanesulfonic anhydride,[224] and cyanuric chloride,[224] among others.

Chloroformate esters RCH_2OCOCl can also be oxidized to aldehydes by treatment with dimethyl sulfoxide followed by Et_3N.[230] The mechanism of these dimethyl sulfoxide oxidations is probably as follows:[231]



32 **33**

though in some cases the base abstracts a proton directly from the carbon being oxidized, in which case the ylide **33** is not an intermediate. Alkoxysulfonium salts **32** have been isolated.[232] This mechanism predicts that secondary compounds should be oxidizable to ketones, and this is the case. In a related procedure for the oxidation of alcohols, the intermediate **32**[233] is formed without the use of dimethyl sulfoxide by treating the substrate with a complex generated from chlorine or N-chlorosuccinimide and dimethyl sulfide.[234]

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[216] Nace and Monagle, *J. Org. Chem.* **24,** 1792 (1959); Kornblum, Jones, and Anderson, *J. Am. Chem. Soc.* **81,** 4113 (1959); Johnson and Pelter, *J. Chem. Soc.* 520 (1964); Traynelis and Hergenrother, *J. Am. Chem. Soc.* **86,** 298 (1964). For reviews, see Durst, *Adv. Org. Chem.* **6,** 285–388 (1969), pp. 343–356; Epstein and Sweat, *Chem. Rev.* **67,** 247–260 (1967).

[217] Kornblum, Jones, and Anderson, Ref. 216.

[218] Cohen and Tsuji, *J. Org. Chem.* **26,** 1681 (1961); Tsuji, *Tetrahedron Lett.* 2413 (1966); Santosusso and Swern, *Tetrahedron Lett.* 4261 (1968), *J. Org. Chem.* **40,** 2764 (1975).

[219] The DCC is converted to dicyclohexylurea, which in some cases is difficult to separate from the product. One way to avoid this problem is to use a carbodiimide linked to an insoluble polymer: Weinshenker and Shen, *Tetrahedron Lett.* 3285 (1972).

[220] Pfitzner and Moffatt, *J. Am. Chem. Soc.* **87,** 5661, 5670 (1965); Fenselau and Moffatt, *J. Am. Chem. Soc.* **88,** 1762 (1966); Albright and Goldman, *J. Org. Chem.* **30,** 1107 (1965).

[221] For a review, see Moffatt, in Augustine and Trecker, Ref. 9, vol. 2, pp. 1–64.

[222] Albright and Goldman, *J. Am. Chem. Soc.* **89,** 2416 (1967).

[223] Parikh and Doering, *J. Am. Chem. Soc.* **89,** 5507 (1967).

[224] Albright, *J. Org. Chem.* **39,** 1977 (1974).

[225] Corey and Kim, *Tetrahedron Lett.* 919 (1973).

[226] Tien, Tien, and Ting, *Tetrahedron Lett.* 1483 (1969).

[227] Ganem and Boeckman, *Tetrahedron Lett.* 917 (1974).

[228] Hendrickson and Schwartzman, *Tetrahedron Lett.* 273 (1975).

[229] Bauer and Macomber, *J. Org. Chem.* **40,** 1990 (1975).

[230] Barton, Garner, and Wightman, *J. Chem. Soc.* 1855 (1964); Barton and Forbes, *J. Chem. Soc., Perkin Trans. 1* 1614 (1975).

[231] Pfitzner and Moffatt, *J. Am. Chem. Soc.* **87,** 5661 (1965); Johnson and Phillips, *J. Org. Chem.* **32,** 1926 (1967); Torssell, *Acta Chem. Scand.* **21,** 1 (1967).

[232] Torssell, *Tetrahedron Lett.* 4445 (1966); Johnson and Phillips, Ref. 231; Khuddus and Swern, *J. Am. Chem. Soc.* **95,** 8393 (1973).

Another way to oxidize primary alkyl halides to aldehydes is by the use of hexamethylenetetramine followed by water. However, this reaction, called the *Sommelet reaction*,[235] is limited to benzylic halides. The reaction is seldom useful when the R in RCH_2Cl is alkyl. The first part of the reaction is conversion to the amine $ArCH_2NH_2$ (reaction **0-47**), which can be isolated. Reaction of the amine with excess hexamethylenetetramine gives the aldehyde. It is this last step which is the actual Sommelet reaction, though the entire process can be conducted without isolation of intermediates. Once the amine is formed, it is converted to an imine ($ArCH_2N{=}CH_2$) with formaldehyde liberated from the reagent. The key step then follows: transfer of hydrogen from another mole of the arylamine to the imine:

$$\mathbf{ArCH_2N{=}CH_2 + ArCH_2NH_2 \longrightarrow ArCH_2NHCH_3 + ArCH{=}NH}$$

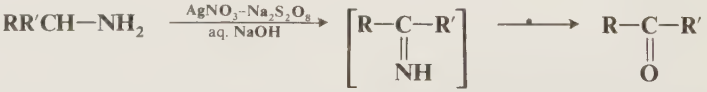
This last imine is then hydrolyzed by water to the aldehyde. Alternatively, the benzylamine may transfer hydrogen directly to hexamethylenetetramine, converting the latter to methylamine. The other product of the reaction is methylamine or $ArCH_2NHCH_3$, depending on whether hexamethylenetetramine is in excess or not. The actual mechanism of the hydrogen-transfer step is in doubt, but it probably begins with a hydride shift. Primary amines (including alkyl RCH_2NH_2) can also be oxidized to imines (and hence hydrolyzed to aldehydes or ketones) by benzophenone and uv light.[236]

Other reagents which convert benzylic halides to aldehydes are 2-nitropropane-NaOEt in EtOH,[237] mercury(I) nitrate followed by ethanolic alkali,[238] and pyridine followed by *p*-nitrosodimethylaniline and then water. The latter procedure is called the *Kröhnke reaction.* Primary halides in general have been oxidized to aldehydes by trimethylamine oxide $Me_3\overset{\oplus}{N}-\overset{\ominus}{O}$,[239] and by K_2CrO_4 in HMPT in the presence of a crown ether.[239a] The former procedure has also been applied to primary tosylates.[239]

Benzyl sulfides $ArCH_2SR$ can be oxidized to aldehydes ArCHO by dimethyl sulfoxide in the presence of certain acyl halides (e.g., benzoyl chloride).[240]

OS **II**, 336; **III**, 811; **IV**, 690, 918, 932; **V**, 242, 668, 825, 852, 872. Also see OS **V**, 689.

9-21 Oxidation of Amines to Aldehydes or Ketones



$$\mathrm{RR'CH{-}NH_2 \xrightarrow[\text{aq. NaOH}]{AgNO_3{-}Na_2S_2O_8} \left[\begin{matrix}R{-}C{-}R'\\ \|\\ NH\end{matrix}\right] \longrightarrow \begin{matrix}R{-}C{-}R'\\ \|\\ O\end{matrix}}$$

Primary aliphatic amines can be oxidized to aldehydes or ketones by reaction with Ag(II), prepared in situ by treatment of silver nitrate with sodium persulfate.[241] The reaction consists of dehydrogenation to the imine (reaction **9-6**), followed by hydrolysis. Other reagents which have been used are nitrosobenzene[242] (for benzylamines), 3,5-di-*t*-butyl-1,2-benzoquinone,[243] certain mesitylglyoxals,[243] and aqueous NaOCl with phase-transfer catalysts.[243a] Benzylic amine salts $PhCH_2CHRNR'_2H^+ \ Cl^-$ (R,R′ = H or alkyl) give benzaldehydes or aryl ketones when heated in dimethyl sulfoxide.[244] The reaction has also been accomplished by conversion of the amine to an oxaziridine and hydrolysis of this:[244a]

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[233] It has been suggested that in the DCC reaction, **32** is not involved, but the ylide **33** is formed directly from a precursor containing DCC and dimethyl sulfoxide: Torssell, Ref. 232; Moffatt, *J. Org. Chem.* **36,** 1909 (1971).

[234] Vilsmaier and Sprügel, *Justus Liebigs Ann. Chem.* **747,** 151 (1971); Corey and Kim, *J. Am. Chem. Soc.* **94,** 7586 (1972), *J. Org. Chem.* **38,** 1233 (1973); McCormick, *Tetrahedron Lett.* 1701 (1974); Crosby, Weinshenker, and Uh, *J. Am. Chem. Soc.* **97,** 2232 (1975).

[235] For a review, see Angyal, *Org. React.* **8,** 197 (1954).

[236] Cohen and Baumgarten, *J. Am. Chem. Soc.* **89,** 3471 (1967); Cohen and Chao, *J. Am. Chem. Soc.* **90,** 165 (1968).

[237] Hass and Bender, *J. Am. Chem. Soc.* **71,** 1767 (1949).

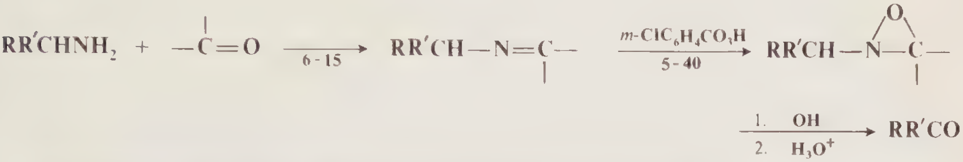
[238] McKillop and Ford, *Synth. Commun.* **4,** 45 (1974).

[239] Franzen and Otto, *Chem. Ber.* **94,** 1360 (1961).

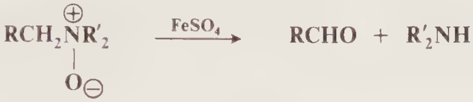
[239a] Cardillo, Orena, and Sandri, *J. Chem. Soc., Chem. Commun.* 190 (1976).

[240] Oda and Hayashi, *Tetrahedron Lett.* 3141 (1967).

[241] Bacon and Stewart, *J. Chem. Soc. C* 1384 (1966). See also Ref. 54.

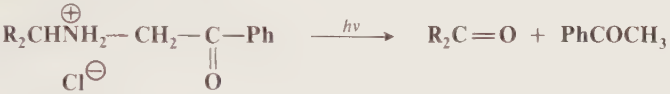


Primary, secondary, and tertiary aliphatic amines have been cleaved to give aldehydes, ketones, or carboxylic acids with aqueous bromine[245] and with neutral permanganate.[246] The other product of this reaction is the amine with one less alkyl group. A similar reaction has been performed on α-amino ketones, with mercuric acetate, to give 1,2-dicarbonyl compounds.[247] Tertiary amine oxides with one primary alkyl group can be cleaved to aldehydes and secondary amines by treatment with iron(III) salts.[248]



$$RCH_2\underset{O^{\ominus}}{\overset{\oplus}{N}}R'_2 \xrightarrow{FeSO_4} RCHO + R'_2NH$$

In still another procedure, phenacyl amides of primary amines are converted to aldehydes or ketones by photolysis of their salts.[249]



$$R_2CH\underset{Cl^{\ominus}}{\overset{\oplus}{N}}H_2-CH_2-\underset{O}{\underset{\|}{C}}-Ph \xrightarrow{h\nu} R_2C{=}O + PhCOCH_3$$

This is a Norrish type II reaction (p. 221).

9-22 Oxidation of Primary Alcohols to Carboxylic Acids

$$RCH_2OH \xrightarrow{CrO_3} RCOOH$$

Primary alcohols can be oxidized to carboxylic acids by many strong oxidizing agents including chromic acid, permanganate, and nitric acid. The reaction may be looked on as a combination of reactions **9-4** and **4-6.** When acid conditions are used, a considerable amount of ester RCOOR is often isolated, though this is probably not formed by a combination of the acid with unreacted alcohol, but by a combination of intermediate aldehyde with unreacted alcohol to give an acetal or hemiacetal, which is oxidized to the ester.[250] Lactones can be prepared by oxidizing diols in which at least one OH is primary.[251] Primary alkyl ethers can be selectively cleaved to carboxylic acids by aqueous Br_2[73] ($RCH_2OR' \rightarrow RCOOH$).

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[242] Suzuki and Weisburger, *Tetrahedron Lett.* 5409 (1966), *J. Chem. Soc. C* 199 (1968).

[243] Corey and Achiwa, *J. Am. Chem. Soc.* **91,** 1429 (1969).

[243a] Lee and Freedman, *Tetrahedron Lett.* 1641 (1976).

[244] Traynelis and Ode, *J. Org. Chem.* **35,** 2207 (1970).

[244a] Dinizo and Watt, *J. Am. Chem. Soc.* **97,** 6900 (1975); Black and Blackman, *Aust. J. Chem.* **28,** 2547 (1975).

[245] Deno and Fruit, *J. Am. Chem. Soc.* **90,** 3502 (1968).

[246] Rawalay and Shechter, *J. Org. Chem.* **32,** 3129 (1967).

[247] Möhrle and Schittenhelm, *Chem. Ber.* **104,** 2475 (1971).

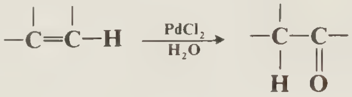
[248] Ferris, Gerwe, and Gapski, *J. Org. Chem.* **33,** 3493 (1968).

[249] Hyatt, *J. Org. Chem.* **37,** 1254 (1972).

[250] Craig and Horning, *J. Org. Chem.* **25,** 2098 (1960).

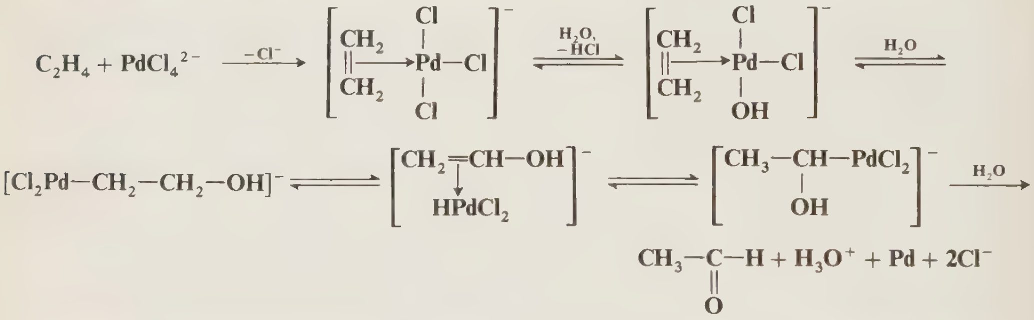
OS **I,** 138, 168; **IV,** 499, 677; **V,** 580. Also see OS **III,** 745.

9-23 Oxidation of Olefins to Aldehydes and Ketones



$$-\overset{|}{C}=\overset{|}{C}-H \xrightarrow[H_2O]{PdCl_2} -\underset{H}{\underset{|}{\overset{|}{C}}}-\underset{O}{\underset{\|}{C}}-$$

Monosubstituted and 1,2-disubstituted olefins can be oxidized to aldehydes and ketones by palladium chloride and similar salts of noble metals.[252] 1,1-Disubstituted olefins generally give poor results. The reaction is used industrially to prepare acetaldehyde from ethylene, but it is also suitable for laboratory preparations. The palladium chloride is reduced to palladium. Because the reagent is expensive, the reaction is usually carried out with a cooxidant, most often $CuCl_2$, whose function is to reoxidize the Pd to Pd(II). The $CuCl_2$ is reduced to Cu(I), which itself is reoxidized to Cu(II) by air, so that atmospheric oxygen is the only oxidizing agent actually used up. Many other cooxidants have been tried, among them O_3, Fe^{3+}, and PbO_2. Aqueous sulfolane is a good solvent for the oxidation of long-chain alkenes.[253] The principal product is an aldehyde only from ethylene: With other olefins Markovnikov's rule is followed, and ketones are formed predominantly. The generally accepted mechanism involves π complexes of palladium.[254]



$$C_2H_4 + PdCl_4^{2-} \xrightarrow{-Cl^-} \left[\begin{matrix} & Cl \\ CH_2 & | \\ \| \longrightarrow & Pd-Cl \\ CH_2 & | \\ & Cl \end{matrix}\right]^- \overset{H_2O,\ -HCl}{\rightleftharpoons} \left[\begin{matrix} & Cl \\ CH_2 & | \\ \| \longrightarrow & Pd-Cl \\ CH_2 & | \\ & OH \end{matrix}\right]^- \overset{H_2O}{\rightleftharpoons}$$

$$[Cl_2Pd-CH_2-CH_2-OH]^- \rightleftharpoons \left[\begin{matrix} CH_2=CH-OH \\ \downarrow \\ HPdCl_2 \end{matrix}\right]^- \rightleftharpoons \left[\begin{matrix} CH_3-CH-PdCl_2 \\ | \\ OH \end{matrix}\right]^- \xrightarrow{H_2O}$$

$$CH_3-\underset{O}{\underset{\|}{C}}-H + H_3O^+ + Pd + 2Cl^-$$

This mechanism accounts for the fact, established by deuterium labeling, that the four hydrogens of the acetaldehyde all come from the original ethylene and none from the solvent.

Similar reactions have been carried out with other oxidizing agents. An example involving migration of an alkyl group instead of hydrogen is oxidation of $Me_2C{=}CMe_2$ with peroxytrifluoroacetic acid–boron trifluoride to give Me_3COMe (pinacolone).[255] This reaction consists of epoxidation (**5-40**) followed by pinacol rearrangement of the epoxide (**8-2**). Other reagents used have

[251] For an example of the preparation of lactones by oxidation of diols with Ag_2CO_3-on-celite, see Fétizon, Golfier, and Louis, *Chem. Commun.* 1118 (1969), *Tetrahedron* **31,** 171 (1975).

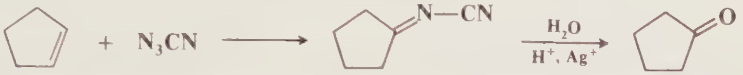
[252] For reviews, see Henry, *Adv. Organomet. Chem.* **13,** 363–452 (1975), pp. 378 388; Jira and Freiesleben, *Organomet. Reac.* **3,** 1–190 (1972), pp. 1-44; Khan and Martell, "Homogeneous Catalysis by Metal Complexes," vol. 2, pp. 77–91, Academic Press, Inc., New York, 1974; Hüttel, *Synthesis* 225–255 (1970), pp. 225–236; Tsuji, *Adv. Org. Chem.* **6,** 109–255 (1969), pp. 119–131; Aguiló, *Adv. Organomet. Chem.* **5,** 321–352 (1967); Bird, "Transition Metal Intermediates in Organic Synthesis," pp. 88–111, Academic Press, Inc., New York, 1967; Smidt, Hafner, Jira, Sieber, Sedlmeier, and Sabel, *Angew. Chem. Int. Ed. Engl.* **1,** 80–88 (1962) [*Angew. Chem.* **74,** 93–102]; Smidt, *Chem. Ind.* (*London*) 54–61 (1962).

[253] Fahey and Zuech, *J. Org. Chem.* **39,** 3276 (1974).

[254] Henry, *J. Am. Chem. Soc.* **88,** 1595 (1966), **94,** 4437 (1972); Jira, Sedlmeier, and Smidt, *Justus Liebigs Ann. Chem.* **693,** 99 (1966); Hosokawa and Maitlis, *J. Am. Chem. Soc.* **95,** 4924 (1973); Moiseev, Levanda, and Vargaftik, *J. Am. Chem. Soc.* **96,** 1003 (1974).

[255] Hart and Lerner, *J. Org. Chem.* **32,** 2669 (1967).

been chromyl chloride[256] (e.g., $Me_3CCH_2CMe{=}CH_2 \rightarrow Me_3CCH_2CHMeCHO$), $Pb(OAc)_4$–F_3CCOOH[257] (e.g., $PhCH{=}CH_2 \rightarrow PhCH_2CHO$), thallium(III) nitrate-methanol[258] (e.g., cyclohexene → cyclopentanecarboxaldehyde), Cl_2 or Br_2 and $AgNO_3$,[259] $HgSO_4$–H_2O,[260] and $Hg(OAc)_2$ followed by $PdCl_2$.[261] An indirect method involves reaction with cyanogen azide to give alkylidene cyanamides, which can be hydrolyzed to ketones,[262] e.g.,



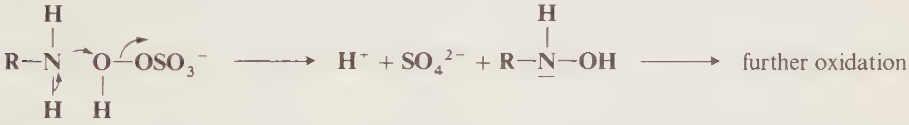
Alkenes have also been converted to more highly oxidized products. Examples are: (1) Treatment with *t*-amyl hydroperoxide and molybdenum salts gives α-hydroxy ketones.[263] (2) 1,2-Disubstituted and trisubstituted alkenes give α-chloro ketones when oxidized with chromyl chloride in acetone: $RCH{=}CR'R'' \rightarrow RCOCClR'R''$.[264] (3) $KMnO_4$ in acetic anhydride oxidizes large-ring cycloalkenes to 1,2-diketones.[265]

OS **51,** 4.

9-24 Oxidation of Primary Amines to Nitroso Compounds

$$ArNH_2 \xrightarrow{H_2SO_5} Ar{-}N{=}O$$

Primary aromatic amines can be oxidized[266] to nitroso compounds. Most often the conversion is accomplished by Caro's acid (H_2SO_5) or with H_2O_2 in HOAc,[267] but the reaction has also been performed with OF_2.[268] Hydroxylamines, which are probably intermediates in most cases, can sometimes be isolated, but under the reaction conditions they are generally oxidized to the nitroso compounds. Primary aliphatic amines can also be oxidized in this manner, but the nitroso compound is stable only if there is no α-hydrogen. If there is an α-hydrogen, the compound tautomerizes to the oxime.[269] The mechanism with H_2SO_5 has been postulated to be an example of category 5 (p. 1076):[270]



$$R{-}\underset{H}{\overset{H}{N}}\;\;\underset{H}{O}{-}OSO_3^- \longrightarrow H^+ + SO_4^{2-} + R{-}\overset{H}{\underline{N}}{-}OH \longrightarrow \text{further oxidation}$$

OS **III,** 334.

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[256] Freeman, Cameron, and DuBois, *J. Org. Chem.* **33,** 3970 (1968); Freeman, DuBois, and Yamachika, *Tetrahedron* **25,** 3441 (1969); Freeman and Arledge, *J. Org. Chem.* **37,** 2656 (1972).

[257] Lethbridge, Norman, and Thomas, *J. Chem. Soc., Perkin Trans. 1,* 35 (1973).

[258] McKillop, Hunt, Kienzle, Bigham, and Taylor, *J. Am. Chem. Soc.* **95,** 3635 (1973). See also Grant, Liau, and Low, *Aust. J. Chem.* **28,** 903 (1975).

[259] Kakis, Brase, and Oshima, *J. Org. Chem.* **36,** 4117 (1971).

[259a] Rogers, McDermott, and Whitesides, *J. Org. Chem.* **40,** 3577 (1975).

[260] Arzoumanian, Aune, Guitard, and Metzger, *J. Org. Chem.* **39,** 3445 (1974).

[261] Rodeheaver and Hunt, *Chem. Commun.* 818 (1971). See also Hunt and Rodeheaver, *Tetrahedron Lett.* 3595 (1972).

[262] Marsh and Hermes, *J. Am. Chem. Soc.* **86,** 4506 (1964).

[263] Dzhemilev, Yur'ev, Tolstikov, Gershanov, and Rafikov, *Doklad. Chem.* **196,** 79 (1971); Tolstikov, Dzhemilev, and Yur'ev, *J. Org. Chem. USSR* **8,** 1204 (1972).

[264] Sharpless and Teranishi, *J. Org. Chem.* **38,** 185 (1973).

[265] Sharpless, Lauer, Repič, Teranishi, and Williams, *J. Am. Chem. Soc.* **93,** 3303 (1971); Jensen and Sharpless, *J. Org. Chem.* **39,** 2314 (1974). See also Haynes, Redmore, and Timmons, *J. Chem. Soc.* 2420 (1963).

[266] For a review on the oxidation of amines, see Challis and Butler, in Patai, "The Chemistry of the Amino Group," pp. 320–338, Interscience Publishers, New York, 1968. For reviews confined to primary aromatic amines, see Hedayatullah, *Bull. Soc. Chim. Fr.* 2957 (1972); Surville, Jozefowicz, and Buvet, *Ann. Chim.* (*Paris*) [14] **2,** 149–157 (1967).

[267] Holmes and Bayer, *J. Am. Chem. Soc.* **82,** 3454 (1960). See also Gorrod, *Tetrahedron Lett.* 6155 (1968).

[268] Merritt and Ruff, *J. Am. Chem. Soc.* **86,** 1392 (1964).

[269] For example, see Kahr and Berther, *Chem. Ber.* **93,** 132 (1960).

[270] Gragerov and Levit, *J. Gen. Chem. USSR* **30,** 3690 (1961).

9-25 Oxidation of Primary Amines, Oximes, or Nitroso Compounds to Nitro Compounds

$$R_3CNH_2 \xrightarrow{KMnO_4} R_3CNO_2$$

$$R_2C{=}NOH \xrightarrow{F_3CCOOOH} R_2CHNO_2$$

Primary amines at a tertiary carbon can be oxidized to nitro compounds in excellent yields with $KMnO_4$.[271] This type of nitro compound is not easily prepared in other ways. Primary amines at a secondary carbon and primary aromatic amines[272] can be oxidized to nitro compounds with various peracids, including peracetic, peroxytrifluoroacetic, and *m*-chloroperbenzoic acids. Primary aromatic amines have also been oxidized to nitro compounds with *t*-butyl hydroperoxide in the presence of certain molybdenum and vanadium compounds.[273] Primary, secondary, and tertiary alkyl primary amines have been oxidized to the corresponding nitro compounds with ozone, but yields are low.[274] Oximes can be oxidized to nitro compounds with peroxytrifluoroacetic acid, among other ways.[271] Aromatic nitroso compounds are easily oxidized to nitro compounds by many oxidizing agents.[275]

OS **III,** 334; **V,** 367, 845; **52,** 77.

9-26 Oxidation of Mercaptans and Other Sulfur Compounds to Sulfonic Acids

$$RSH \xrightarrow{HNO_3} RSO_3H$$

Mercaptans, sulfoxides, sulfones, disulfides,[276] and other sulfur compounds can be oxidized to sulfonic acids with many oxidizing agents, though for synthetic purposes the reaction is most important for mercaptans.[277] Among oxidizing agents used are boiling nitric acid and barium permanganate. Autoxidation (oxidation by atmospheric oxygen) can be accomplished in basic solution.[278] The oxidation of RCH_2SCOR (prepared by reaction **5-7**) to RCH_2SO_3H with H_2O_2–HOAc affords a preparation of aliphatic sulfonic acids from olefins.[279] Aliphatic mercaptans can be oxidized to sulfinic acids with *m*-chloroperbenzoic acid in CH_2Cl_2.[280] Mercaptans can also be oxidized to disulfides (reaction **9-37**).

OS **II,** 471; **III,** 226. Also see OS **V,** 1070.

9-27 Oxidation of Mercaptans and Other Sulfur Compounds to Sulfonyl Halides

$$RSH + Cl_2 \xrightarrow{H_2O} RSO_2Cl$$

Oxidation of mercaptans with chlorine and water gives sulfonyl chlorides directly.[281] Among other sulfur compounds which give the same reaction are sulfides, disulfides, thiocyanates, thio-acetates RSCOMe, Bunte salts (see reaction **0-42**), and isothiuronium salts (see reaction **0-38**). The method has also been used for the preparation of sulfonyl bromides, fluorides, and iodides. R may be primary or secondary alkyl, or aryl, but not tertiary alkyl.

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[271] Larson, in Feuer, "The Chemistry of the Nitro and Nitroso Groups," vol. 1, pp. 306–310, Interscience Publishers, New York, 1969; Kornblum, *Org. React.* **12,** 101–156 (1962), pp. 115–120. See also Barnes and Patterson, *J. Org. Chem.* **41,** 733 (1976).

[272] Emmons, *J. Am. Chem. Soc.* **79,** 5528 (1957).

[273] Howe and Hiatt, *J. Org. Chem.* **35,** 4007 (1970).

[274] Bachman and Strawn, *J. Org. Chem.* **33,** 313 (1968).

[275] See Boyer, in Feuer, Ref. 271, pp. 264–265.

[276] For a review of the oxidation of disulfides, see Savige and Maclaren, in Kharasch and Meyers, "Organic Sulfur Compounds," vol. 2, pp. 367–402, Pergamon Press, New York, 1966.

[277] For a general review of the oxidation of mercaptans, see Capozzi and Modena, in Patai, "The Chemistry of the Thiol Group," pt. 2, pp. 785–839, John Wiley & Sons, Inc., New York, 1974. For a review specifically on the oxidation to sulfonic acids, see Gilbert, "Sulfonation and Related Reactions," pp. 217 239, Interscience Publishers, New York, 1965.

[278] Wallace and Schriesheim, *Tetrahedron* **21,** 2271 (1965).

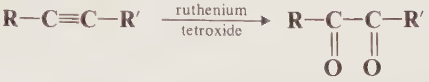
[279] Showell, Russell, and Swern, *J. Org. Chem.* **27,** 2853 (1962).

[280] Filby, Günther, and Penzhorn, *J. Org. Chem.* **38,** 4070 (1973).

[281] For a review, see Gilbert, Ref. 277, pp. 202–214.

D. Reactions in Which Oxygen is Added to the Substrate

9-28 The Oxidation of Alkynes to α-Diketones



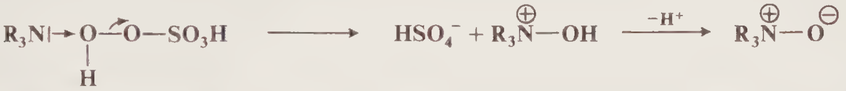
$$R-C\equiv C-R' \xrightarrow[\text{tetroxide}]{\text{ruthenium}} R-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{\|}}{C}-R'$$

Internal alkynes have been oxidized to α-diketones by several oxidizing agents, including ruthenium tetroxide,[282] neutral $KMnO_4$,[283] SeO_2 with a small amount of H_2SO_4,[284] N-bromosuccinimide in anhydrous dimethyl sulfoxide,[285] and thallium(III) nitrate.[160] Ozone generally oxidizes triple-bond compounds to carboxylic acids (reaction **9-10**), but α-diketones are sometimes obtained instead. SeO_2 with a small amount of H_2SO_4 oxidizes arylacetylenes to α-keto acids ($ArC\equiv CH \rightarrow ArCOCOOH$).[284]

9-29 Oxidation of Tertiary Amines to Amine Oxides

$$R_3N \xrightarrow{H_2O_2} R_3\overset{\oplus}{N}-\overset{\ominus}{O}$$

Tertiary amines can be converted to amine oxides by oxidation. Hydrogen peroxide is often used, but peracids are also important reagents for this purpose. Pyridine and its derivatives are oxidized only by peracids.[286] In the attack by hydrogen peroxide there is first formed a trialkylammonium peroxide, a hydrogen-bonded complex represented as $R_3N{\cdot}H_2O_2$, which can be isolated.[287] The decomposition of this complex probably involves an attack by the OH^+ moiety of the H_2O_2. Oxidation with Caro's acid has been shown to proceed in this manner:[288]

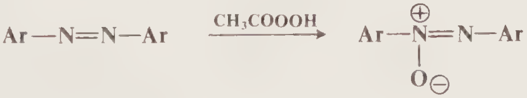


$$R_3N| \rightarrow \underset{\underset{H}{|}}{O}-O-SO_3H \longrightarrow HSO_4^- + R_3\overset{\oplus}{N}-OH \xrightarrow{-H^+} R_3\overset{\oplus}{N}-\overset{\ominus}{O}$$

This mechanism is the same as that of reaction **9-24**, and the products differ only because tertiary amine oxides cannot be further oxidized. The mechanism with other peracids is probably the same. The reaction has also been carried out with hydroperoxides in the presence of V or Mn complexes.[289]

OS **IV**, 612, 704, 828; **50**, 56.

9-30 Oxidation of Azobenzenes to Azoxybenzenes



$$Ar-N=N-Ar \xrightarrow{CH_3COOOH} Ar-\underset{\underset{O^{\ominus}}{|}}{\overset{\oplus}{N}}=N-Ar$$

---

[282] Gopal and Gordon, *Tetrahedron Lett.* 2941 (1971).

[283] Khan and Newman, *J. Org. Chem.* **17**, 1063 (1952).

[284] Sonoda, Yamamoto, Murai, and Tsutsumi, *Chem. Lett.* 229 (1972).

[285] Wolfe, Pilgrim, Garrard, and Chamberlain, *Can. J. Chem.* **49**, 1099 (1971).

[286] For a review, see Katritzky and Lagowski, "Chemistry of the Heterocyclic N-Oxides," pp. 21–72, 539–542, Academic Press, Inc., New York, 1971.

[287] Oswald and Guertin, *J. Org. Chem.* **28**, 651 (1963).

[288] Ogata and Tabushi, *Bull. Chem. Soc. Jpn.* **31**, 969 (1958).

[289] Kuhnen, *Chem. Ber.* **99**, 3384 (1966); Sheng and Zajacek, *J. Org. Chem.* **33**, 588 (1968).

Azo compounds can be oxidized to azoxy compounds by peracids[290] or by hydroperoxides and molybdenum complexes.[291] The mechanism is probably the same as that of reaction **9-29.**[292]

9-31 Oxidation of Isonitriles to Isocyanates

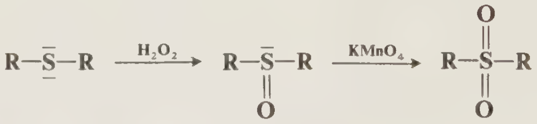
$$R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} \xrightarrow[\text{Me}_2\text{SO}]{\text{Cl}_2} R-N=C=O$$

Isonitriles have been oxidized to isocyanates with HgO and with O_3, as well as with a halogen and dimethyl sulfoxide (or pyridine N-oxide). In the latter case the oxidizing agent is the halogen, which converts the isonitrile to $R-N=CCl_2$ which is hydrolyzed to the isocyanate.[293] Isonitriles can also be oxidized by nitrile oxides, which are thus reduced to nitriles:[294]

$$Ar-C\equiv\overset{\oplus}{N}-\overset{\ominus}{\underline{\bar{O}}}| + R-\overset{\oplus}{N}\equiv\overset{\ominus}{\bar{C}} \longrightarrow Ar-C\equiv N + R-N=C=O$$

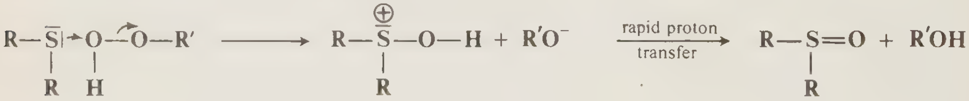
Cyanide ion has been oxidized to cyanate ion with many oxidizing agents. When isonitriles are oxidized by thallium(III) nitrate in the presence of methanol, carbamates are formed, by reaction of the initially formed isocyanate with the methanol (reaction **6-8**).[295]

9-32 Oxidation of Sulfides to Sulfoxides and Sulfones



$$R-\underline{\bar{S}}-R \xrightarrow{H_2O_2} R-\underset{\underset{O}{\|}}{\bar{S}}-R \xrightarrow{KMnO_4} R-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R$$

Sulfides can be oxidized to sulfoxides by 1 mole of 30% H_2O_2 or by many other oxidizing agents,[296] including iodobenzene dichloride $PhICl_2$,[297] $NaIO_4$,[298] *t*-BuOCl,[299] and peracids. Sulfoxides can be further oxidized to sulfones by another mole of H_2O_2, $KMnO_4$, or a number of other agents. If enough oxidizing agent is present, sulfides can be directly converted to sulfones without isolation of the sulfoxides. These reactions give high yields, and many functional groups do not interfere.[300] When the oxidizing agent is a peroxide, the mechanism of oxidation to the sulfoxide is similar to that of reaction **9-29:**[301]



$$\underset{R}{\underset{|}{R-\bar{S}|}}\rightarrow \underset{H}{\underset{|}{O}}-O-R' \longrightarrow R-\underset{\underset{R}{|}}{\overset{\oplus}{S}}-O-H + R'O^- \xrightarrow[\text{transfer}]{\text{rapid proton}} R-\underset{\underset{R}{|}}{S}=O + R'OH$$

---

[290] For a review, see Newbold, Ref. 90a, pp. 557–563, 573–593.

[291] Johnson and Gould, *J. Org. Chem.* **39**, 407 (1974).

[292] Mitsuhashi, Simamura, and Tezuka, *Chem. Commun.* 1300 (1970).

[293] Johnson and Daughhetee, *J. Org. Chem.* **29**, 246 (1964); Johnson and Krutzsch, *J. Org. Chem.* **32**, 1939 (1967).

[294] Finzi and Arbasino, *Tetrahedron Lett.* 4645 (1965).

[295] Kienzle, *Tetrahedron Lett.* 1771 (1972). See also Sawai and Takizawa, *Tetrahedron Lett.* 4263 (1972).

[296] For a review, see Reid, "Organic Compounds of Bivalent Sulfur," vol. 2, pp. 64–66, Chemical Publishing Company, New York, 1960.

[297] Barbieri, Cinquini, Colonna, and Montanari, *J. Chem. Soc. C* 659 (1968).

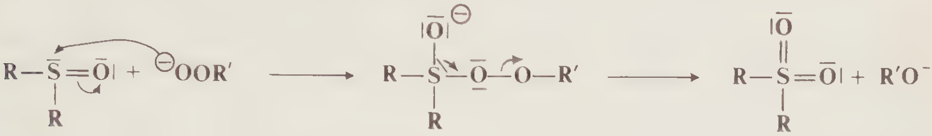
[298] Leonard and Johnson, *J. Org. Chem.* **27**, 282 (1962); Hiskey and Harpold, *J. Org. Chem.* **32**, 3191 (1967).

[299] Walling and Mintz, *J. Org. Chem.* **32**, 1286 (1967); Skattebøl, Boulette, and Solomon, *J. Org. Chem.* **32**, 3111 (1967).

[300] For a review of the oxidation of α-halo sulfides, see Venier and Barager, *Org. Prep. Proced. Int.* **6**, 77–102 (1974), pp. 85–86.

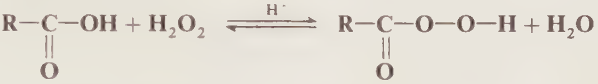
[301] Modena and Todesco, *J. Chem. Soc.* 4920 (1962), and references cited therein. For a review, see Barnard, Bateman, and Cunneen, in Kharasch, "Organic Sulfur Compounds," vol. 1, pp. 229–247, Pergamon Press, New York, 1961.

The second oxidation, which is normally slower than the first[302] (which is why sulfoxides are so easily isolable), has the same mechanism in neutral or acid solution, but in basic solution it has been shown that the conjugate base of the peroxy compound ($R'OO^-$) also attacks the SO group as a nucleophile:[303]



OS V, 791; **50,** 31, 33. Also see OS V, 723.

9-33 Oxidation of Carboxylic Acids to Peroxy Acids

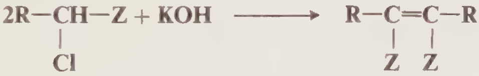


$$\underset{\underset{O}{\|}}{R-C}-OH + H_2O_2 \xrightleftharpoons{H^+} \underset{\underset{O}{\|}}{R-C}-O-O-H + H_2O$$

The oxidation of carboxylic acids with H_2O_2 and an acid catalyst is the best general method for the preparation of peroxy acids.[304] The most common catalyst for aliphatic R is concentrated sulfuric acid. The reaction is an equilibrium and is driven to the right by removal of water or by the use of excess reagents. For aromatic R the best catalyst is methanesulfonic acid, which is also used as the solvent.

E. Oxidative Coupling

9-34 Coupling Involving Carbanions



$$2R-\underset{\underset{Cl}{|}}{CH}-Z + KOH \longrightarrow R-\underset{\underset{Z}{|}}{C}=\underset{\underset{Z}{|}}{C}-R$$

Alkyl halides with an electron-withdrawing group on the halogen-bearing carbon can be dimerized to olefins by treatment with bases. Z may be nitro, aryl, etc. Although carbene intermediates have sometimes been suggested, it is likely that in most cases the mechanism[305] involves nucleophilic substitution followed by elimination[306] (illustrated for benzyl chloride):

$$PhCH_2Cl \xrightarrow{\text{base}} Ph\overset{\ominus}{\bar{C}}HCl \xrightarrow[S_N]{PhCH_2Cl} PhCHClCH_2Ph \xrightarrow{-HCl} PhCH{=}CHPh$$

In a related reaction, diarylmethane dihalides Ar_2CX_2 have been dimerized to tetraaryl alkenes $Ar_2C{=}CAr_2$ with sodium selenide,[307] with copper,[308] and with iron pentacarbonyl.[309] Other dimerizations leading to alkenes have been performed on phosphorus compounds. The ylides $ArCH{=}PPh_3$ and $ArCOCH{=}PPh_3$ have been dimerized to $ArCH{=}CHAr$ and $ArCOCH{=}CHCOAr$ with, respectively, oxygen[310] and selenious acid H_2SeO_3.[311] Phosphonium periodates $RCH_2\overset{+}{P}Ph_3\ \ IO_4^-$ react with bases such as NaOEt or $NaNH_2$ to give alkenes $RCH{=}CHR$.[312] Aryl diazomethanes $ArCHN_2$ are oxidized to $ArCH{=}CHAr$ by ceric ammonium nitrate.[313]

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[302] There are some reagents which oxidize sulfones in preference to sulfoxides, e.g., $NaMnO_4$: see Henbest and Khan, *Chem. Commun.* 1036 (1968).

[303] Curci and Modena, *Tetrahedron Lett.* 1749 (1963), *Tetrahedron* **22,** 1227 (1966); Curci, Giovine, and Modena, *Tetrahedron* **22,** 1235 (1966). See also Ogata and Suyama, *Chem. Ind. (London)* 707 (1971), *J. Chem. Soc., Perkin Trans. 2* 755 (1973).

[304] For a review of the preparation of peroxy acids, see Swern, in Swern, "Organic Peroxides," vol. 1, pp. 313–516, Interscience Publishers, New York, 1970.

[305] For discussion, see Saunders and Cockerill, "Mechanisms of Elimination Reactions," pp. 548–554, John Wiley & Sons, Inc., New York, 1973.

[306] For example, see Hauser, Brasen, Skell, Kantor, and Brodhag, *J. Am. Chem. Soc.* **78,** 1653 (1956); Hoeg and Lusk, *J. Organomet. Chem.* **5,** 1 (1966); Reisdorf and Normant, *Organomet. Chem. Synth.* **1,** 375 (1972); Hanna and Wideman, *Chem. Ind. (London)* 486 (1968).

[307] Okamoto and Yano, *J. Org. Chem.* **34,** 1492 (1969).

[308] Buckles and Matlack, *Org. Synth.* **IV,** 914.

[309] Coffey, *J. Am. Chem. Soc.* **83,** 1623 (1961).

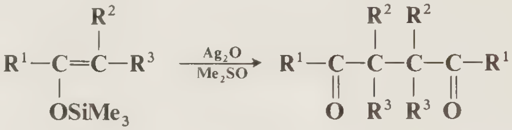
A somewhat different type of coupling is observed when salts of β-keto esters, arylacetonitriles $ArCH_2CN$, and other compounds of the form ZCH_2Z' are treated with an oxidizing agent such as iodine,[314] PbO_2,[315] Cu(II) salts,[316] or a Cu-amine-O_2 system,[317] e.g.,

$$Ar_2CH_2 \xrightarrow[\text{liq. NH}_3]{NaNH_2} Ar\overset{\ominus}{C}H \quad + \quad I_2 \longrightarrow Ar_2CH{-}CHAr_2$$

In this case the product is a substituted alkane rather than an alkene. The reaction with I_2 has been applied to enolates of monoesters to give succinic esters.[317a]

OS **II,** 273; **IV,** 372, 869, 914. Also see OS **I,** 46; **IV,** 877.

9-35 Dimerization of Silyl Enol Ethers or of Lithium Enolates

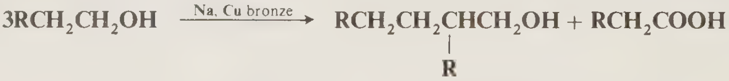


$$R^1-\underset{OSiMe_3}{C}=\overset{R^2}{C}-R^3 \xrightarrow[Me_2SO]{Ag_2O} R^1-\underset{O}{\overset{}{C}}-\underset{R^3}{\overset{R^2}{C}}-\underset{R^3}{\overset{R^2}{C}}-\underset{O}{C}-R^1$$

Silyl enol ethers can be dimerized to symmetrical 1,4-diketones by treatment with Ag_2O in dimethyl sulfoxide or certain other polar aprotic solvents.[318] The reaction has been performed with R^2, R^3 = hydrogen or alkyl, though best yields are obtained when $R^2 = R^3 = H$. In certain cases, unsymmetrical 1,4-diketones have been prepared by using a mixture of two silyl enol ethers.

In a similar reaction, lithium enolates $RC(Li){=}CH_2$ were dimerized to 1,4-diketones $RCOCH_2CH_2COR$ with $CuCl_2$ in dimethylformamide at −78°C.[319]

9-36 The Guerbet Reaction



$$3RCH_2CH_2OH \xrightarrow{\text{Na, Cu bronze}} RCH_2CH_2\underset{R}{C}HCH_2OH + RCH_2COOH$$

Primary alcohols couple in the manner shown when treated with sodium or another base and copper bronze, Raney nickel, or other hydrogenation catalysts. The reaction, called the *Guerbet reaction,* involves three molecules of alcohol, one of which is oxidized to the acid. Yields are about 30 to 50%.[320] The mechanism probably involves conversion of the alcohol to the aldehyde

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[310] Mägerlein and Meyer, *Chem. Ber.* **103,** 2995 (1970).

[311] Shevchuk, Tolochko, and Dombrovskii, *J. Org. Chem. USSR* **7,** 1757 (1971).

[312] Bestmann, Armsen, and Wagner, *Chem. Ber.* **102,** 2259 (1969).

[313] Trahanovsky, Robbins, and Smick, *J. Am. Chem. Soc.* **93,** 2086 (1971).

[314] See for example, Kaiser, *J. Am. Chem. Soc.* **89,** 3659 (1967).

[315] Brettle and Seddon, *J. Chem. Soc. C* 1320 (1970).

[316] Rathke and Lindert, *J. Am. Chem. Soc.* **93,** 4605 (1971).

[317] de Jongh, de Jonge, and Mijs, *J. Org. Chem.* **36,** 3160 (1971).

[317a] Brocksom, Petragnani, Rodrigues, and Teixeira, *Synthesis* 396 (1975).

[318] Ito, Konoike, and Saegusa, *J. Am. Chem. Soc.* **97,** 649 (1975).

[319] Ito, Konoike, and Saegusa, *J. Am. Chem. Soc.* **97,** 2912 (1975).

[320] Weizmann, Bergmann, and Haskelberg, *Chem. Ind.* (*London*) **56,** 587 (1937); Weizmann, Bergmann, and Sulzbacker, *J. Org. Chem.* **15,** 54 (1950).

RCH_2CHO, followed by aldol condensation with loss of water to give $RCH_2CH{=}CRCHO$, and reduction of this by transfer hydrogenation (p. 710) to give the product.[321] The carboxylic acid is formed by disproportionation of some of the aldehyde.

9-37 Oxidation of Mercaptans to Disulfides

$$2RSH \xrightarrow{H_2O_2} RSSR$$

Mercaptans are easily oxidized to disulfides.[322] Hydrogen peroxide is the most common reagent, but many oxidizing agents give the reaction, though strong ones may give reaction **9-26.** Even the oxygen in the air oxidizes mercaptans on standing, if a small amount of base is present. The reaction is reversible (see reaction **9-65**), and the interconversion between cysteine and cystine is an important one in biochemistry. Thiol acids can likewise be coupled:

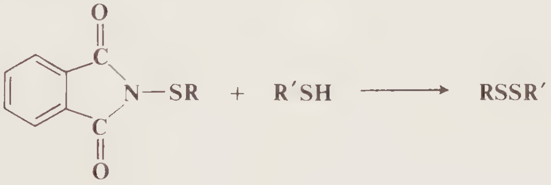
$$2RCOS^- + I_2 \longrightarrow RCOSSCOR$$

The mechanism has been studied for several oxidizing agents and varies with the agent.[323] For oxygen it is[324]

$$\begin{aligned}
RSH + B^- &\rightleftharpoons RS^- + BH\\
RS^- + O_2 &\longrightarrow RS\cdot + \dot{O}_2{}^-\\
RS^- + \dot{O}_2{}^- &\longrightarrow RS\cdot + O_2{}^{2-}\\
2RS\cdot &\longrightarrow RSSR\\
O_2{}^{2-} + BH &\longrightarrow OH^- + B^- + O_2
\end{aligned}$$

With respect to the sulfur, this mechanism is similar to that of reaction **4-15**, involving as it does loss of a proton, oxidation to a free radical, and radical coupling.

Unsymmetrical disulfides can be prepared by treatment of a mercaptan RSH with diethyl azodicarboxylate $EtOOCN{=}NCOOEt$ to give an adduct, to which another mercaptan R′SH is then added, producing the disulfide RSSR′.[325] Another method involves treatment of R′SH with a thiophthalimide (**34**).[326]



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OS **III,** 86, 116.

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[321] Veibel and Nielsen, *Tetrahedron* **23,** 1723 (1967); Gregorio, Pregaglia, and Ugo, *J. Organomet. Chem.* **37,** 385 (1972); Klein, Thömel, and Winkler, *Justus Liebigs Ann. Chem.* 1004 (1973).

[322] For reviews, see Capozzi and Modena, Ref. 277, pp. 785-839; Reid, Ref. 296, vol. 1, pp. 118–126 (1958).

[323] See Tarbell, in Kharasch, Ref. 301, pp. 97–102.

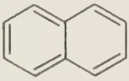
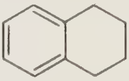
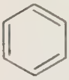
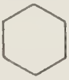
[324] Wallace, Schriesheim, and Bartok, *J. Org. Chem.* **28,** 1311 (1963).

[325] Mukaiyama and Takahashi, *Tetrahedron Lett.* 5907 (1968).

[326] Boustany and Sullivan, *Tetrahedron Lett.* 3547 (1970); Harpp, Ash, Back, Gleason, Orwig, VanHorn, and Snyder, *Tetrahedron Lett.* 3551 (1970).

TABLE 2 The ease of reduction of various functional groups toward catalytic hydrogenation[329]

The groups are listed in approximate order of ease of reduction

Reaction	Substrate	Product	
0-83	RCOCl	RCHO	Easiest
9-49	RNO_2	RNH_2	
5-12	RC≡CR	RCH=CHR	
6-27	RCHO	RCH_2OH	
5-12	RCH=CHR	RCH_2CH_2R	
6-27	RCOR	RCHOHR	
0-80	$ArCH_2OR$	$ArCH_3$ + ROH	
6-29	RC≡N	RCH_2NH_2	
5-13			
9-44	RCOOR′	RCH_2OH + R′OH	
9-41	RCONHR′	RCH_2NHR	
5-13			Most difficult
9-40	$RCOO^-$		Inert

9-38 Oxidation of Amines to Azo or Azoxy Compounds

$$ArNH_2 \xrightarrow{MnO_2} Ar{-}N{=}N{-}Ar$$

Primary aromatic amines have been oxidized to azo compounds by a variety of oxidizing agents, among them MnO_2, lead tetraacetate, O_2 and a base, and sodium perborate in acetic acid. *t*-Butyl hydroperoxide has been used to oxidize certain primary amines to azoxy compounds.[327]

OS **V**, 341.

Reductions: Selectivity

It is often necessary to reduce one group in a molecule without affecting another reducible group. It is usually possible to find a reducing agent which will do this. The most common broad-spectrum reducing agents are the metal hydrides[328] and hydrogen (with a catalyst). Many different metal-hydride systems and hydrogenation catalysts have been investigated in order to find conditions under which a given group will be reduced without reducing another group in the same molecule. In Tables 2, 3, and 4 are listed the reactivity of various functional groups toward catalytic hydrogenation, $LiAlH_4$, and, BH_3, respectively.[329, 330] Table 5 shows which groups can be reduced by catalytic hydrogenation and various metal hydrides.[331] Of course, these tables cannot be exact, for the nature of R and the reaction conditions obviously affect reactivity. Nevertheless, the tables do give a fairly good indication of which reagents reduce which groups.

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[327] Kosswig, *Justus Liebigs Ann. Chem.* **749**, 206 (1971).

[328] For discussions of selectivity with metal hydride reducing agents, see Brown, "Boranes in Organic Chemistry," pp. 209–251, Cornell University Press, Ithaca, N.Y., 1972; Rerick, in Augustine, "Reduction," pp. 1–94, Marcel Dekker, Inc., New York, 1968; Walker, *Chem. Soc. Rev.* **5**, 23–50 (1976).

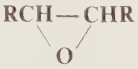
[329] Taken from House, Ref. 8, p. 9.

[330] Tables 3 and 4 are from Brown, Ref. 328, pp. 213 and 232, respectively.

[331] Except for the column on catalytic hydrogenation, these data are from Brown, Ref. 328, p. 251.

TABLE 3 The ease of reduction of various functional groups with $LiAlH_4$ in ether[330]

However, $LiAlH_4$ is a very powerful reagent, and much less selectivity is possible here than with most of the other metal hydrides

Reaction	Substrate	Product	
6-27	RCHO	RCH_2OH	Easiest
6-27	RCOR	RCHOHR	
9-47	RCOCl	RCH_2OH	
9-44	Lactone	Diol	
0-81		RCH_2CHOHR	
9-44	RCOOR′	$RCH_2OH + R'OH$	
9-40	RCOOH	RCH_2OH	
9-40	$RCOO^-$	RCH_2OH	
9-41	$RCONR'_2$	$RCH_2NR'_2$	
6-29	RC≡N	RCH_2NH_2	
9-49	RNO_2	RNH_2	
9-72	$ArNO_2$	ArN=NAr	Most difficult
5-12	RCH=CHR		Inert

$LiAlH_4$ is a very powerful and unselective reagent. Consequently, other metal hydrides are generally used when selectivity is required. As mentioned on p. 833, a number of less reactive (hence more selective) reagents have been prepared by replacing some of the hydrogens of $LiAlH_4$ with alkoxy groups (by treatment of $LiAlH_4$ with ROH).[332] Most of the metal hydrides are nucleophilic reagents and attack the carbon atom of a carbon-hetero single or multiple bond. However, BH_3 [333] and AlH_3 [334] are electrophiles (Lewis acids) and attack the hetero atom. This accounts for the different patterns of selectivity shown in the tables.

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[332] For a review, see Málek and Černý, *Synthesis* 217–234 (1972).

[333] See Brown, Heim, and Yoon, *J. Am. Chem. Soc.* **92,** 1637 (1970); Cragg, "Organoboranes in Organic Synthesis," pp. 319–371, Marcel Dekker, Inc., New York, 1973.

[334] See Brown and Yoon, *J. Am. Chem. Soc.* **88,** 1464 (1966); Yoon and Brown, *J. Am. Chem. Soc.* **90,** 2927 (1968).

TABLE 4 The ease of reduction of various functional groups with borane[330]

It is evident that this reagent and $LiAlH_4$ (Table 3) complement each other

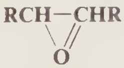
Reaction	Substrate	Product	
9-40	RCOOH	RCH_2OH	Easiest
5-15	RCH=CHR	$(RCH_2CHR)_3B$	
6-27	RCOR	RCHOHR	
6-29	RCN	RCH_2NH_2	
0-81		RCH_2CHOHR	
9-44	RCOOR′	$RCH_2OH + R'OH$	Most difficult
0-83, 9-47	RCOCl		Inert

TABLE 5 Reactivity of various functional groups with some metal hydrides and toward catalytic hydrogenation[331]

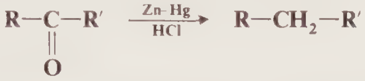
	Reaction	$NaBH_4$ in EtOH	$NaBH_4$ + LiCl in diglyme	$NaBH_4$ + $AlCl_3$ in diglyme	$NaBH_4$ + BF_3 in diglyme	BH_3–THF[333]	Bis-3-methyl-2-butyl-borane (disiamylborane) in THF[335]	LiAlH(O-*t*-Bu)$_3$ in THF	LiAlH(OMe)$_3$ in THF	$LiAlH_4$ in ether	AlH_3 in THF[334]	Catalytic hydrogenation
6-27	$RCHO \to RCH_2OH$	+	+	+	+	+	+	+	+	+	+	+
6-27	$RCOR \to RCHOHR$	+	+	+	+	+	+	+	+	+	+	+
0-83 9-47	$RCOCl \to RCHO$ $RCOCl \to RCH_2OH$	+[336]	+	+	+	−	−	+	+	+	+	+
9-44	Lactone → diol	−	+	+	+	+	+	±[337]	+	+	+	+
0-81	Epoxide → alcohol	−	+	+	+	+	±[337]	±[337]	+	+	+	+
9-44	$RCOOR' \to RCH_2OH + R'OH$	−	+	+	+	±[338]	−	±[337]	+	+	+	+
9-40	$RCOOH \to RCH_2OH$	−	−	+	+	+	−	−	+	+	+	−
9-40	$RCOO^- \to RCH_2OH$	−	−	−	−	−	−	−	+	+	+	−
9-41 0-85	$RCONR'_2 \to RCH_2NR'_2$ $RCONR'_2 \to RCHO$	−	−	+	+	+	+	−	+	+	+	+
6-29	$RC{\equiv}N \to RCH_2NH_2$	−	−	+	+	+	−	−	+	+	+	+
9-49 9-72	$RNO_2 \to RNH_2$ $RNO_2 \to RN{=}NR$	−	−	−	−	−	−	−	+	+	−	+
5-12	$RCH{=}CHR \to RCH_2CH_2R$	−	−	+	+	+	+	−	−	−	−	+

The reactions in this section are grouped into classifications based on bond changes, similar to those used for the oxidation reactions. These sections are: reactions involving replacement of oxygen by hydrogen, reactions in which an oxygen is removed from the substrate, reduction with cleavage, and reductive coupling.

A. Reactions Involving Replacement of Oxygen by Hydrogen.

In reactions **9-39** to **9-43**, a C=O is reduced to a CH_2 group.

9-39 Reduction of Carbonyl to Methylene in Aldehydes and Ketones



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow[HCl]{Zn-Hg} R-CH_2-R'$$

There are various ways of reducing the C=O group of aldehydes and ketones to CH_2.[339] The two most important methods are the *Clemmensen reduction* and the *Wolff-Kishner reduction* (in the Russian literature this is called the *Kizhner reaction*). The Clemmensen reduction consists of heating the aldehyde or ketone with zinc amalgam and aqueous HCl.[340] Ketones are reduced more often than aldehydes. In the Wolff-Kishner reduction,[341] the aldehyde or ketone is heated with hydrazine hydrate and a base (usually NaOH or KOH). The *Huang-Minlon modification*[342] of the Wolff-Kishner reaction, in which the reaction is carried out in refluxing diethylene glycol, has completely replaced the original procedure. The reaction can also be carried out under more moderate conditions (room temperature) in dimethyl sulfoxide with potassium *t*-butoxide as base.[343] The Wolff-Kishner reaction can also be applied to the semicarbazones of aldehydes or ketones. The Clemmensen reduction is usually easier to perform, but it fails for acid-sensitive and high-molecular-weight substrates. For these cases the Wolff-Kishner reduction is quite useful. For high-molecular-weight substrates, a modified Clemmensen reduction, using activated zinc and gaseous HCl in an organic solvent such as ether or acetic anhydride, has proved successful.[344] The Clemmensen and Wolff-Kishner reactions are complementary, since the former uses acidic and the latter basic conditions.

Both methods are fairly specific for aldehydes and ketones and can be carried out with many other functional groups present. However, certain types of aldehydes and ketones do not give normal reduction products. Under Clemmensen conditions,[345] α-hydroxy ketones give either ketones (hydrogenolysis of the OH, reaction **0-79**) or olefins, and 1,3-diones usually undergo rearrangement, e.g.,[346]

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[335] Brown, Bigley, Arora, and Yoon, *J. Am. Chem. Soc.* **92,** 7161 (1970). For reductions with thexylborane, see Brown, Heim, and Yoon, *J. Org. Chem.* **37,** 2942 (1972).

[336] Reacts with solvent, reduced in aprotic solvents.

[337] Slow reaction at variable rate, depending on structure.

[338] Some derivatives react only very slowly; others at a moderate rate.

[339] For a review, see Reusch, in Augustine, Ref. 328, pp. 171–211.

[340] For reviews, see Vedejs, *Org. React.* **22,** 401–422 (1975); Staschewski, *Angew. Chem.* **71,** 726–736 (1959); Martin, *Org. React.* **1,** 155–209 (1942). For a discussion of experimental conditions, see Fieser and Fieser, Ref. 37, pp. 1287–1289.

[341] For a review, see Todd, *Org. React.* **4,** 378–422 (1948).

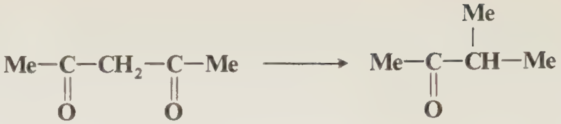
[342] Huang-Minlon, *J. Am. Chem. Soc.* **68,** 2487 (1946), **71,** 3301 (1949).

[343] Cram, Sahyun, and Knox, *J. Am. Chem. Soc.* **84,** 1734 (1962); also see Grundon, Henbest, and Scott, *J. Chem. Soc.* 1855 (1963); Szmant and Román, *J. Am. Chem. Soc.* **88,** 4034 (1966).

[344] Yamamura, Ueda, and Hirata, *Chem. Commun.* 1049 (1967); Yamamura and Hirata, *J. Chem. Soc. C* 2887 (1968); Toda, Hayashi, Hirata, and Yamamura, *Bull. Chem. Soc. Jpn.* **45,** 264 (1972).

[345] For a review of Clemmensen reduction of diketones and unsaturated ketones, see Buchanan and Woodgate, *Q. Rev., Chem. Soc.* **23,** 522–536 (1969).

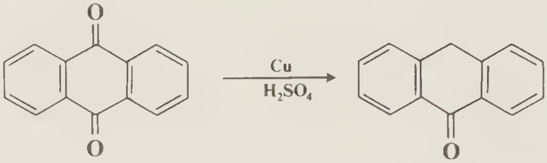
[346] Cusack and Davis, *J. Org. Chem.* **30,** 2062 (1965); Wenkert and Kariv, *Chem. Commun.* 570 (1965); Galton, Kalafer, and Beringer, *J. Org. Chem.* **35,** 1 (1970).



$$\mathrm{Me{-}}\underset{\underset{\displaystyle\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}CH_2{-}}\underset{\underset{\displaystyle\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}Me} \longrightarrow \mathrm{Me{-}}\underset{\underset{\displaystyle\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}}\overset{\overset{\displaystyle\mathrm{Me}}{|}}{\mathrm{CH}}\mathrm{{-}Me}$$

A similar rearrangement is observed on Clemmensen reduction of unsaturated cyclic ketones.[347] Neither method is suitable for α,β-unsaturated ketones. These give pyrazolines[348] under Wolff-Kishner conditions, while under Clemmensen conditions both groups of these molecules may be reduced or if only one group is reduced, it is the C=C bond. Sterically hindered ketones are resistant to both the Clemmensen and Huang-Minlon procedures but can be reduced by vigorous treatment with anhydrous hydrazine.[349] In the Clemmensen reduction, pinacols (reaction **9-67**) are often side products.

Other reagents have also been used to reduce the C=O of aldehydes and ketones to CH_2. Among these are catalytic hydrogenation at 180 to 250°C and, for aryl ketones (ArCOR and ArCOAr), $LiAlH_4$–$AlCl_3$,[350] Li–NH_3,[351] or trialkylsilanes in trifluoroacetic acid.[352] The latter two reagents also reduce aryl aldehydes ArCHO to methylbenzenes $ArCH_3$.[353] Aliphatic aldehydes RCHO can be reduced to RCH_3 with the sandwich compound titanocene dichloride $(C_5H_5)_2TiCl_2$.[354] One carbonyl group of 1,2-diketones can be selectively reduced by H_2S with an amine catalyst[355] or by HI in refluxing acetic acid.[356] One carbonyl group of quinones can be reduced with copper and sulfuric acid or with tin and HCl:[357]



An indirect method of accomplishing the reaction is reduction of tosylhydrazones ($R_2C{=}N{-}NHTs$) to R_2CH_2 with $LiAlH_4$, $NaBH_4$, BH_3, catecholborane, or $NaBH_3CN$.[358] The reduction of α,β-unsaturated tosylhydrazones with $NaBH_3CN$ or with catecholborane proceeds with migration of the double bond to the position formerly occupied by the carbonyl carbon, even if this removes the double bond from conjugation with an aromatic ring.[359] Another indirect method

[347] Davis and Woodgate, *J. Chem. Soc.* 5943 (1965), *Chem. Commun.* 65 (1966).

[348] Pyrazolines can be converted to cyclopropanes; see reaction **7-48.**

[349] Barton, Ives, and Thomas, *J. Chem. Soc.* 2056 (1955).

[350] Nystrom and Berger, *J. Am. Chem. Soc.* **80,** 2896 (1958). See also Volod'kin, Ershov, and Portnykh, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 384 (1967).

[351] Hall, Lipsky, McEnroe, and Bartels, *J. Org. Chem.* **36,** 2588 (1971).

[352] Kursanov, Parnes, and Loim, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 1245 (1966); West, Donnelly, Kooistra, and Doyle, *J. Org. Chem.* **38,** 2675 (1973).

[353] Hall, Bartels, and Engman, *J. Org. Chem.* **37,** 760 (1972) (the Li–NH_3 method); Kursanov, Parnes, Loim, and Bakalova, *Doklad. Chem.* **179,** 328 (1968) (the silane method).

[354] van Tamelen and Gladysz, *J. Am. Chem. Soc.* **96,** 5290 (1974).

[355] Mayer, Hiller, Nitzschke, and Jentzsch, *Angew. Chem. Int. Ed. Engl.* **2,** 370–373 (1963) [*Angew. Chem.* **75,** 1011–1014].

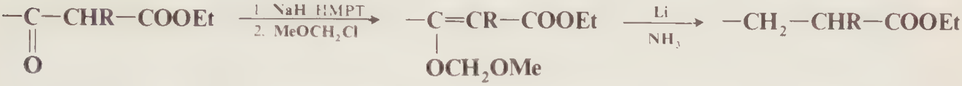
[356] Reusch and LeMahieu, *J. Am. Chem. Soc.* **86,** 3068 (1964).

[357] Meyer, *Org. Synth.* **I,** 60; Macleod and Allen, *Org. Synth.* **II,** 62.

[358] Caglioti and Magi, *Tetrahedron* **19,** 1127 (1963); Caglioti and Grasselli, *Chem. Ind.* (*London*) 153 (1964); Caglioti, *Tetrahedron* **22,** 487 (1966); Fischer, Pelah, Williams, and Djerassi, *Chem. Ber.* **98,** 3236 (1965); Elphimoff-Felkin and Verrier, *Tetrahedron Lett.* 1515 (1968); Hutchins, Milewski, and Maryanoff, *J. Am. Chem. Soc.* **95,** 3662 (1973); Cacchi, Caglioti, and Paolucci, *Bull. Chem. Soc. Jpn.* **47,** 2323 (1974); Lane, *Synthesis* 135–146 (1975), pp. 145–146; Kabalka and Baker, *J. Org. Chem.* **40,** 1834 (1975).

[359] Hutchins, Kacher, and Rua, *J. Org. Chem.* **40,** 923 (1975); Kabalka, Yang, and Baker, *J. Org. Chem.* **41,** 574 (1976); Taylor and Djerassi, *J. Am. Chem. Soc.* **98,** 2275 (1976).

is conversion of the aldehyde or ketone to a dithioacetal or ketal, and desulfurization of this (reaction **4-37**). In still another indirect method, the ketone function of β-keto esters is reduced by conversion to the methoxymethyl enol ether, followed by treatment of this with lithium in liquid NH_3.[360]



$$\underset{\underset{\displaystyle O}{\|}}{-C}-CHR-COOEt \xrightarrow[\text{2. MeOCH}_2\text{Cl}]{\text{1. NaH HMPT}} \underset{\underset{\displaystyle OCH_2OMe}{|}}{-C}=CR-COOEt \xrightarrow[NH_3]{Li} -CH_2-CHR-COOEt$$

The first step in the mechanism[361] of the Wolff-Kishner reaction consists of formation of the hydrazone (reaction **6-21**):

$$R_2C=O \longrightarrow R_2C=N-NH_2$$

It is this species which undergoes reduction in the presence of base, most probably in the following manner:

$$R_2C=N-NH_2 \overset{OH^-}{\rightleftarrows} R_2CH-N=NH + OH^- \longrightarrow R_2CH-N=N^{\ominus} + H_2O$$

$$R_2CH-N=N^{\ominus} \xrightarrow{-N_2} R_2\bar{C}H^{\ominus} \xrightarrow{H_2O} R_2CH_2 + OH^-$$

Regarding the mechanism of the Clemmensen reduction, nothing much can be said. What has been reported in the literature is so contradictory[362] that no conclusions can be drawn, except that the corresponding alcohol is not an intermediate, since alcohols prepared in other ways fail to give the reaction. Note that the alcohol is not an intermediate in the Wolff-Kishner reduction either.

OS **I,** 60; **II,** 62, 499; **III,** 410, 444, 513, 786; **IV,** 203, 510; **V,** 533, 747; **52,** 122; **53,** 77. Also see OS **IV,** 218.

9-40 Reduction of Carboxylic Acids to Alcohols

$$RCOOH \xrightarrow{LiAlH_4} RCH_2OH$$

Carboxylic acids are easily reduced to primary alcohols by $LiAlH_4$.[363] The reaction does not stop at the aldehyde stage (but see reaction **0-84**). The conditions are particularly mild, the reduction proceeding quite well at room temperature. Other hydrides have also been used, but not $NaBH_4$ (see Table 5). Catalytic hydrogenation is also generally ineffective. Borane is particularly good for carboxyl groups (Table 4) and permits selective reduction of them in the presence of many other groups[364] (though the reaction with double bonds takes place at about the same rate).[365] Aluminum hydride reduces COOH groups without affecting carbon-halogen bonds in the same molecule. A particularly mild reduction method consists of treatment of the carboxylic acid with N-ethyl-5-phenylisoxazolium 3-sulfonate, followed by $NaBH_4$ in aqueous solution.[366]

OS **III,** 60.

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[360] Coates and Shaw, *J. Org. Chem.* **35,** 2597, 2601 (1970).

[361] For a review of the mechanism, see Szmant, *Angew. Chem. Int. Ed. Engl.* **7,** 120–128 (1968) [*Angew. Chem.* **80,** 141–149].

[362] See, for example, Poutsma and Wolthius, *J. Org. Chem.* **24,** 875 (1959), Nakabayashi, *J. Am. Chem. Soc.* **82,** 3900, 3906 (1960).

[363] For a review, see Gaylord, Ref. 8, pp. 322–373.

[364] However, a failure to reduce a carboxyl group selectively in the presence of a keto group has been reported: Hirsch and Cross, *Synth. Commun.* **1,** 19 (1971).

[365] Brown and Korytnyk, *J. Am. Chem. Soc.* **82,** 3866 (1960); Batrakov and Bergel'son, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* 348 (1965); Pelter, Hutchings, Levitt, and Smith, *Chem. Commun.* 347 (1970); Yoon, Pak, Brown, Krishnamurthy, and Stocky, *J. Org. Chem.* **38,** 2786 (1973).

[366] Hall and Perfetti, *J. Org. Chem.* **39,** 111 (1974).

9-41 Reduction of Amides to Amines

$$\mathrm{RCONH_2} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2NH_2}$$

Amides can be reduced[367] to amines with $LiAlH_4$ or by catalytic hydrogenation, though high temperatures and pressures are usually required for the latter. Even with $LiAlH_4$ the reaction is more difficult than the reduction of most other functional groups, and often other groups can be reduced without disturbing an amide function. $NaBH_4$ by itself does not reduce amides, though it does so in the presence of $CoCl_2$[368] or of a carboxylic acid such as acetic or trifluoroacetic acid.[368a] Substituted amides can be similarly reduced:

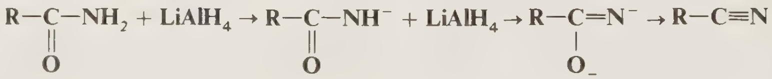
$$\mathrm{RCONHR'} \longrightarrow \mathrm{RCH_2NHR'}$$
$$\mathrm{RCONR'_2} \longrightarrow \mathrm{RCH_2NR'_2}$$

Borane is a good reducing agent for all three types of amides.[369] Another method for the reduction of mono- and disubstituted amides in high yields consists of treatment with triethyloxonium fluoroborate $Et_3O^+\ BF_4^-$ to give the imino ether fluoborate $RC(OEt){=}NR_2^+\ BF_4^-$, followed by reduction of this with $NaBH_4$ in ethanol.[370] Still another reagent which reduces disubstituted amides to amines is trichlorosilane.[371]

With some $RCONR'_2$, $LiAlH_4$ causes cleavage, and the aldehyde (reaction **0-85**) or alcohol is obtained. Thioamides can be reduced with hydrogen and Raney nickel.[372] Lactams are reduced to cyclic amines in high yields with $LiAlH_4$, though cleavage sometimes occurs here too. Imides are generally reduced on both sides, though it is sometimes possible to stop with just one. Both cyclic and acyclic imides have been reduced in this manner, though with acyclic imides cleavage is often obtained, e.g.,[373]

$$\mathrm{PhN(COMe)_2} \longrightarrow \mathrm{PhNHEt}$$

Nitriles have been isolated as intermediates in the treatment of unsubstituted amides with $LiAlH_4$.[374] The following mechanism has been proposed for the conversion of the amide to the nitrile:[374]



$$\mathrm{R-\underset{\underset{\displaystyle O}{\|}}{C}-NH_2 + LiAlH_4 \rightarrow R-\underset{\underset{\displaystyle O}{\|}}{C}-NH^- + LiAlH_4 \rightarrow R-\underset{\underset{\displaystyle O_-}{|}}{C}{=}N^- \rightarrow R-C{\equiv}N}$$

OS **IV**, 339, 354, 564; **54**, 88.

9-42 Reduction of Esters to Ethers

$$\mathrm{RCOOR'} \xrightarrow[\mathrm{LiAlH_4}]{\mathrm{BF_3\text{-}etherate}} \mathrm{RCH_2OR'}$$

Esters and lactones have been reduced to ethers, though the more usual course is the obtention of 2 moles of alcohol (reaction **9-44**). Reduction to ethers has been accomplished with a reagent prepared from BF_3-etherate and either $LiAlH_4$, $LiBH_4$, or $NaBH_4$,[375] with trichlorosilane and uv light,[376] and with catalytic hydrogenation. The reaction with the BF_3 reagent apparently succeeds with secondary R′, but not with primary R′, which give reaction **9-44.** Lactones give cyclic ethers.[377] Thiol esters RCOSR′ have been reduced to sulfides RCH_2SR'.[378]

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[367] For a review, see Challis and Challis, in Zabicky, "The Chemistry of Amides," pp. 795–801, Interscience Publishers, New York, 1970. For a review of the reduction of amides, lactams, and imides with metallic hydrides, see Ref. 363, pp. 544–636.

[368] Satoh, Suzuki, Suzuki, Miyaji, and Imai, *Tetrahedron Lett.* 4555 (1969). See also Rahman, Basha, Waheed, and Ahmed, *Tetrahedron Lett.* 219 (1976); Maki, Kikuchi, Sugiyama, and Seto, *Chem. Ind.* (*London*) 322 (1976).

[368a] Umino, Iwakuma, and Itoh, *Tetrahedron Lett.* 763 (1976).

[369] Brown and Heim, *J. Org. Chem.* **38,** 912 (1973).

[370] Borch, *Tetrahedron Lett.* 61 (1968).

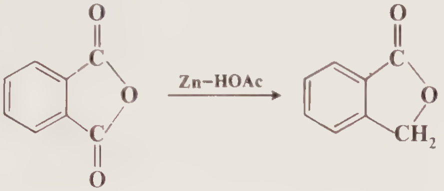
[371] Nagata, Dohmaru, and Tsurugi, *Chem. Lett.* 989 (1972).

[372] Pettit and van Tamelen, *Org. React.* **12,** 356–529 (1962), pp. 385–389.

[373] Witkop and Patrick, *J. Am. Chem. Soc.* **74,** 3861 (1952).

[374] Newman and Fukunaga, *J. Am. Chem. Soc.* **82,** 693 (1960).

9-43 Reduction of Cyclic Anhydrides to Lactones



Cyclic anhydrides can give lactones if reduced with Zn–HOAc, hydrogen and platinum or $RuCl_2(Ph_3P)_3$,[379] $NaBH_4$,[380] or even $LiAlH_4$, although with the last-mentioned reagent diols are the more usual product (reaction **9-46**). Open-chain anhydrides either are not reduced at all (e.g., with $NaBH_4$), or give 2 moles of alcohol.

There are no *Organic Syntheses* references, but see OS **II,** 526, for a related reaction.

9-44 Reduction of Esters to Alcohols

$$\mathbf{RCOOR'} \xrightarrow{LiAlH_4} \mathbf{RCH_2OH + R'OH}$$

$LiAlH_4$ reduces esters to give 2 moles of alcohol.[381] The reaction is of wide scope and has been used to reduce many esters. Where the interest is in obtaining R′OH, this represents a method of "hydrolyzing" esters. Lactones yield diols. $LiBH_4$ also gives the reaction. $NaBH_4$ reduces phenolic esters, especially those containing electron-withdrawing groups,[382] but its reaction with other esters is usually so slow that such reactions are seldom feasible (though exceptions are known[383]), and it is generally possible to reduce an aldehyde or ketone without reducing an ester function in the same molecule. However, $NaBH_4$ reduces esters in the presence of certain compounds (see Table 5). With the reagent $NaBH(OMe)_3$ it is possible to reduce a secondary ester function $R_2CHCOOR'$ in the presence of a tertiary ester function R_3CCOOR'.[384] Esters can also be reduced to alcohols by hydrogenation over copper chromite catalysts,[385] though high pressures and temperatures are required. Ester functions generally survive low-pressure catalytic hydrogenations. Before the discovery of $LiAlH_4$, the most common way of carrying out the reaction was with sodium in ethanol, a method known as the *Bouveault-Blanc procedure*. This procedure is still sometimes used where selectivity is necessary. See also reactions **9-42** and **9-45.**

OS **II,** 154, 325, 372, 468; **III,** 671; **IV,** 834; **53,** 70.

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[375] Pettit, Ghatak, Green, Kasturi, and Piatak, *J. Org. Chem.* **26,** 1685 (1961); Pettit, Green, Kasturi, and Ghatak, *Tetrahedron* **18,** 953 (1962). See also Dias and Pettit, *J. Org. Chem.* **36,** 3485 (1971).

[376] Tsurugi, Nakao, and Fukumoto, *J. Am. Chem. Soc.* **91,** 4587 (1969); Nakao, Fukumoto, and Tsurugi, *J. Org. Chem.* **37,** 76 (1972); Nagata, Dohmaru, and Tsurugi, *J. Org. Chem.* **38,** 795 (1973); Baldwin, Doll, and Haut, *J. Org. Chem.* **39,** 2470 (1974); Baldwin and Haut, *J. Org. Chem.* **40,** 3885 (1975).

[377] See, for example, Pettit, Kasturi, Green, and Knight, *J. Org. Chem.* **26,** 4773 (1961); Edward and Ferland, *Chem. Ind.* (*London*) 975 (1964).

[378] Eliel and Daignault, *J. Org. Chem.* **29,** 1630 (1964); Bublitz, *J. Org. Chem.* **32,** 1630 (1967).

[379] Lyons, *J. Chem. Soc., Chem. Commun.* 412 (1975); Morand and Kayser, *J. Chem. Soc., Chem Commun.* 314 (1976).

[380] Bailey and Johnson, *J. Org. Chem.* **35,** 3574 (1970).

[381] For a review, see Gaylord, Ref. 8, pp. 391–531.

[382] Takahashi and Cohen, *J. Org. Chem.* **35,** 1505 (1970).

[383] For example, see Brown and Rapoport, *J. Org. Chem.* **28,** 3261 (1963).

[384] Bell and Gravestock, *Can. J. Chem.* **47,** 2099 (1969).

[385] For a review, see Adkins, *Org. React.* **8,** 1–27 (1954).

9-45 Reduction of Carboxylic Acids and Esters to Alkanes

$$\mathrm{RCOOR'} \xrightarrow{(\mathrm{C_5H_5})_2\mathrm{TiCl_2}} \mathrm{RCH_3 + R'OH}$$

The reagent titanocene dichloride reduces esters in a manner different from that of reactions **9-42** or **9-44**. The products are the alkane RCH_3 and the alcohol R'OH.[354] The mechanism probably involves an alkene intermediate. Aromatic acids can be reduced to methylbenzenes by a procedure involving refluxing first with trichlorosilane in MeCN, then with tripropylamine added, and finally with KOH and MeOH (after removal of the MeCN).[386] The following sequence has been suggested:[386]

$$\mathrm{ArCOOH} \quad \overset{\mathrm{SiHCl_3}}{} \quad (\mathrm{ArCO})_2\mathrm{O} \xrightarrow[\mathrm{R_3N}]{\mathrm{SiHCl_3}} \mathrm{ArCH_2SiCl_3} \xrightarrow[\mathrm{MeOH}]{\mathrm{KOH}} \mathrm{ArCH_3}$$

Esters of aromatic acids are not reduced by this procedure, so that an aromatic COOH group can be reduced in the presence of a COOR' group.[387] *o*- and *p*-hydroxybenzoic acids and their esters have been reduced to cresols $HOC_6H_4CH_3$ with sodium bis(2-methoxyethoxy)aluminum hydride $NaAlH_2(OC_2H_4OMe)_2$.[388]

Carboxylic acids can also be converted to alkanes, indirectly, by reduction of the corresponding tosylhydrazides $RCONHNH_2$ with $LiAlH_4$ or borane.[389]

9-46 Reduction of Anhydrides to Alcohols

$$\mathrm{RCOOCOR} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{2RCH_2OH}$$

$LiAlH_4$ usually reduces open-chain anhydrides to give 2 moles of alcohol. With cyclic anhydrides the reaction with $LiAlH_4$ can be controlled to give either diols or lactones[390] (see reaction **9-43**).

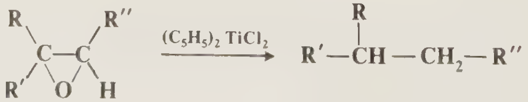
9-47 Reduction of Acyl Halides to Alcohols

$$\mathrm{RCOCl} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{RCH_2OH}$$

Acyl halides are reduced[391] to alcohols by $LiAlH_4$ or $NaBH_4$, as well as by other metal hydrides (Table 5), but not by borane. The reaction may be regarded as a combination of reactions **9-39** and **0-77**.

OS **IV**, 271.

9-48 Complete Reduction of Epoxides



$$\mathrm{R'{-}\overset{\overset{\textstyle R}{|}}{C}H{-}CH_2{-}R''}$$

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[386] Benkeser, Foley, Gaul, and Li, *J. Am. Chem. Soc.* **92,** 3232 (1970).

[387] Benkeser and Ehler, *J. Org. Chem.* **38,** 3660 (1973).

[388] Černý and Málek, *Tetrahedron Lett.* 1739 (1969), *Collect. Czech. Chem. Commun.* **35,** 2030 (1970).

[389] Attanasi, Caglioti, Gasparrini, and Misiti, *Tetrahedron* **31,** 341 (1975), and references cited therein.

[390] Bloomfield and Lee, *J. Org. Chem.* **32,** 3919 (1967).

[391] For a review of the reduction of acyl halides, see Wheeler, in Patai, "The Chemistry of Acyl Halides," pp. 231–251, Interscience Publishers, New York, 1972.

Though the usual product of epoxide reductions is the alcohol (reaction **0-81**), 1,2-epoxides are reduced all the way to the alkane by titanocene dichloride.[354]

9-49 Reduction of Nitro Compounds to Amines

$$\mathbf{RNO_2} \xrightarrow[\text{HCl}]{\text{Zn}} \mathbf{RNH_2}$$

Both aliphatic[392] and aromatic nitro compounds can be reduced to amines, though the reaction has been applied much more often to aromatic nitro compounds, owing to their greater availability. Many reducing agents have been used to reduce aromatic nitro compounds, among them Zn, Sn, or Fe (or sometimes other metals) and acid, catalytic hydrogenation,[393] AlH_3–$AlCl_3$, hydrazine and a catalyst,[394] dodecacarbonyltriiron[$Fe_3(CO)_{12}$]-methanol,[395] $TiCl_3$,[396] and sulfides such as NaHS, $(NH_4)_2S$, or polysulfides. The reaction with sulfides or polysulfides is called the *Zinin reduction.*[397] The reagent sodium dihydro(trithio)borate $NaBH_2S_3$ reduces aromatic nitro compounds to amines,[398] but aliphatic nitro compounds give other products (see reaction **9-62**). In contrast, $LiAlH_4$ reduces aliphatic nitro compounds to amines, but with aromatic nitro compounds the products with this reagent are azo compounds (reaction **9-72**). Most metal hydrides, including $NaBH_4$ and BH_3, do not reduce nitro groups at all, though aromatic nitro compounds have been reduced to amines with $NaBH_4$ and various catalysts, such as $NiCl_2(PPh_3)_2$ or $CoCl_2$.[399] Treatment of aromatic nitro compounds with $NaBH_4$ alone has resulted in reduction of the *ring* to a cyclohexane ring with the nitro group still intact[400] or in cleavage of the nitro group from the ring.[401] With $(NH_4)_2S$ or other sulfides or polysulfides it is often possible to reduce just one of two or three nitro groups on an aromatic ring or on two different rings in one molecule.[402] The nitro groups of N-nitro compounds can also be reduced to amino groups, e.g., nitrourea $NH_2CONHNO_2$ gives semicarbazide $NH_2CONHNH_2$.

With some reducing agents, especially with aromatic nitro compounds, the reduction can be stopped at an intermediate stage, and hydroxylamines (reaction **9-51**), hydrazobenzenes (reaction **9-73**), azobenzenes (reaction **9-72**), and azoxybenzenes (reaction **9-71**) can be obtained in this manner. However, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, if indeed they are intermediates (see however, reaction **9-50**). Reduction by metals in mineral acids cannot be stopped, but always produces the amine. The mechanisms of these reductions have been very little studied, though it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates. Both of these types of compounds give amines when exposed to most of these reducing agents (reaction **9-52**), and hydroxylamines can be isolated (reaction **9-51**). With metals and acid the following path has been suggested:[403]

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[392] For a review of selective reductions of aliphatic nitro compounds without disturbance of other functional groups, see Ioffe, Tartakovskii, and Novikov, *Russ. Chem. Rev.* **35,** 19–32 (1966).

[393] For a review, see Rylander, "Catalytic Hydrogenation over Platinum Metals," pp. 168–202, Academic Press, Inc., New York, 1967.

[394] For a review of the use of hydrazine, see Furst, Berlo, and Hooton, *Chem. Rev.* **65,** 51-68 (1965), pp. 52–60.

[395] Landesberg, Katz, and Olsen, *J. Org. Chem.* **37,** 930 (1972).

[396] Ho and Wong, *Synthesis* 45 (1974).

[397] For a review of the Zinin reduction, see Porter, *Org. React.* **20,** 455–481 (1973).

[398] Lalancette and Brindle, *Can. J. Chem.* **49,** 2990 (1971).

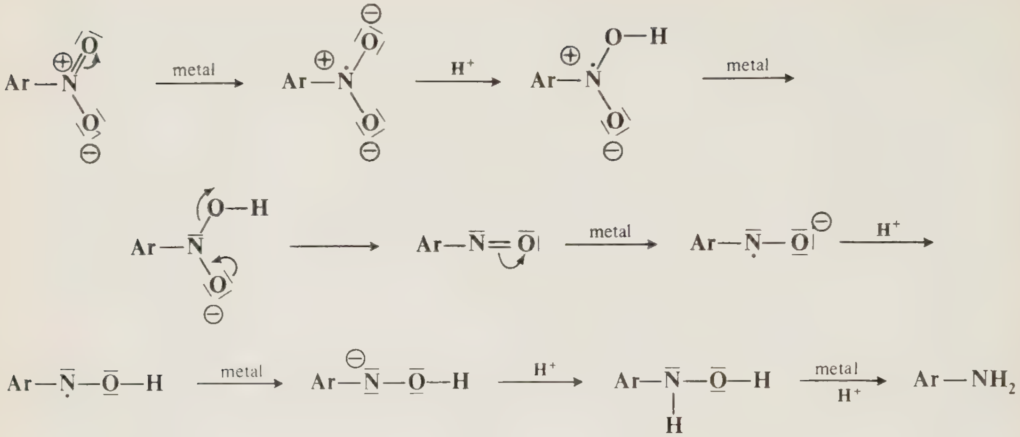
[399] Ref. 368; Jardine and McQuillin, *Chem. Commun.* 626 (1970); Hanaya, Fujita, and Kudo, *Chem. Ind.* (*London*) 794 (1973).

[400] Severin and Schmitz, *Chem. Ber.* **95,** 1417 (1962); Severin and Adam, *Chem. Ber.* **96,** 448 (1963).

[401] Kaplan, *J. Am. Chem. Soc.* **86,** 740 (1964). See also Swanwick and Waters, *Chem. Commun.* 63 (1970).

[402] This result has also been achieved by hydrogenation with Pd–C in 1,2-dimethoxyethane [Lyle and LaMattina, *Synthesis* 726 (1974)] and with the homogeneous catalyst dichlorotris(triphenylphosphine)ruthenium(II) [Knifton, *Tetrahedron Lett.* 2163 (1975)].

[403] House, Ref. 8, p. 211.



OS **I,** 52, 240, 455, 485; **II,** 130, 160, 175, 254, 447, 471, 501, 617; **III,** 56, 59, 63, 69, 73, 82, 86, 239, 242, 453; **IV,** 31, 357; **V,** 30, 346, 552, 567, 829, 1067, 1130.

9-50 Reduction of Nitro Compounds to Nitroso Compounds

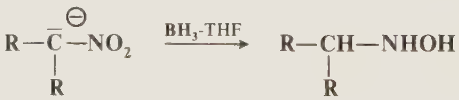
$$ArNO_2 \xrightarrow[H_2O]{h\nu,\ CN^-} ArNO$$

Certain aromatic nitroso compounds can be obtained in good yields by irradiation of the corresponding nitro compounds in 0.1 *M* aqueous KCN with uv light.[404] When nitro compounds are treated with most other reducing agents, nitroso compounds are either not formed or react further under the reaction conditions and cannot be isolated.

9-51 Reduction of Nitro Compounds to Hydroxylamines

$$ArNO_2 \xrightarrow[H_2O]{Zn} ArNHOH$$

When aromatic nitro compounds are reduced with zinc and water under neutral conditions, hydroxylamines are formed. Borane in tetrahydrofuran reduces *aliphatic* nitro compounds (in the form of their salts) to hydroxylamines:[405]



$$R{-}\overset{\ominus}{\underset{R}{C}}{-}NO_2 \xrightarrow{BH_3\text{-}THF} R{-}\underset{R}{CH}{-}NHOH$$

OS **I,** 445; **III,** 668; **IV,** 148; **52,** 77.

9-52 Reduction of Nitroso Compounds and Hydroxylamines to Amines

$$RNO \xrightarrow[HCl]{Zn} RNH_2$$

$$RNHOH \xrightarrow[HCl]{Zn} RNH_2$$

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[404] Petersen and Letsinger, *Tetrahedron Lett.* 2197 (1971); Vink, Cornelisse, and Havinga, *Recl. Trav. Chim. Pays-Bas* **90,** 1333 (1971).

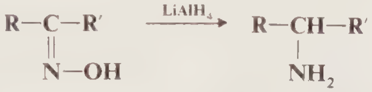
[405] Feuer, Bartlett, Vincent, and Anderson, *J. Org. Chem.* **31,** 2880 (1965).

Nitroso compounds and hydroxylamines can be reduced to amines by the same reagents which reduce nitro compounds (reaction **9-49**). N-Nitroso compounds are similarly reduced to hydrazines:[406]

$$R_2N{-}NO \longrightarrow R_2N{-}NH_2$$

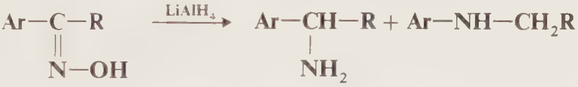
OS **I,** 511; **II,** 33, 202, 211, 418; **III,** 91; **IV,** 247.

9-53 Reduction of Oximes to Primary Amines or Aziridines



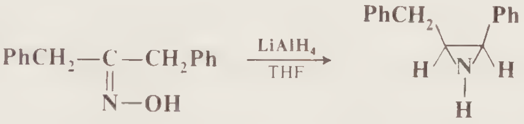
$$\underset{\displaystyle N{-}OH}{\overset{}{R{-}\underset{\|}{C}{-}R'}} \xrightarrow{LiAlH_4} \underset{\displaystyle NH_2}{R{-}\underset{|}{C}H{-}R'}$$

Both aldoximes and ketoximes can be reduced to primary amines with $LiAlH_4$. The reaction is slower than with ketones, so that, for example, $PhCOCH{=}NOH$ gave 34% $PhCHOHCH{=}NOH$.[407] Other reducing agents which give this reduction are zinc and acetic acid, sodium ethoxide, BH_3 at 105 to 110 C,[408] bis(2-methoxyethoxy)aluminum hydride,[409] sodium dihydro(trithio)borate,[410] and sodium and an alcohol.[411] Catalytic hydrogenation is also effective.[412] With some oximes (usually aromatic), secondary amines arising from a rearrangement are side products and sometimes the main products:[413]



$$\underset{\displaystyle N{-}OH}{Ar{-}\underset{\|}{C}{-}R} \xrightarrow{LiAlH_4} \underset{\displaystyle NH_2}{Ar{-}\underset{|}{C}H{-}R} + Ar{-}NH{-}CH_2R$$

With certain oximes (e.g., those of the type $ArCH_2CR{=}NOH$), treatment with $LiAlH_4$ gives aziridines,[414] e.g.,



Hydrazones, arylhydrazones, and semicarbazones can also be reduced to amines with various reducing agents, including Zn–HCl and H_2 and Raney nickel.

Oximes can also be reduced to hydroxylamines (reaction **6-28**).

OS **II,** 318; **III,** 513; **V,** 32, 83, 373, 376.

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[406] For a discussion, see Sandler and Karo, Ref. 94, vol. 1, pp. 374–376 (1968).

[407] Felkin, *C. R. Acad. Sci.* **230,** 304 (1950).

[408] Feuer and Braunstein, *J. Org. Chem.* **34,** 1817 (1969). See also Hassner and Catsoulacos, *Chem. Commun.* 590 (1967).

[409] Černý, Málek, Čapka, and Chvalovský, *Collect. Czech. Chem. Commun.* **34,** 1033 (1969).

[410] Lalancette and Brindle, *Can. J. Chem.* **48,** 735 (1970).

[411] For example, see Sugden and Patel, *Chem. Ind.* (*London*) 683 (1972).

[412] For a review, see Ref. 393, pp. 139–159.

[413] Rerick, Trottier, Daignault, and DeFoe, *Tetrahedron Lett.* 629 (1963); Petrarca and Emery, *Tetrahedron Lett.* 635 (1963); Graham and Williams, *Tetrahedron* **21,** 3263 (1965).

[414] For a review, see Kotera and Kitahonoki, *Org. Prep. Proced.* **1,** 305–324 (1969). For examples, see Shandala, Solomon, and Waight, *J. Chem. Soc.* 892 (1965); Kitahonoki, Kotera, Matsukawa, Miyazaki, Okada, Takahashi, and Takano, *Tetrahedron Lett.* 1059 (1965); Kitahonoki, Takano, Matsuura, and Kotera, *Tetrahedron* **25,** 335 (1969); Landor, Sonola, and Tatchell, *J. Chem. Soc., Perkin Trans. 1* 1294 (1974); Ferrero, Rouillard, Decouzon, and Azzaro, *Tetrahedron Lett.* 131 (1974); Diab, Laurent, and Mison, *Tetrahedron Lett.* 1605 (1974).

9-54 Reduction of Miscellaneous Nitrogen Compounds

$$R{-}N{=}C{=}O \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

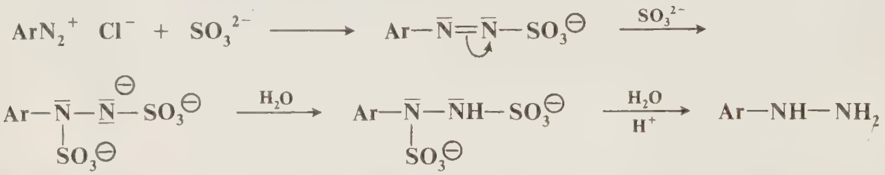
$$R{-}N{=}C{=}S \xrightarrow{LiAlH_4} R{-}NH{-}CH_3$$

$$Ar{-}N{=}N{-}Ar \xrightarrow[\text{catalyst}]{H_2} Ar{-}NH{-}NH{-}Ar$$

$$R{-}N_3 \xrightarrow{LiAlH_4} RNH_2$$

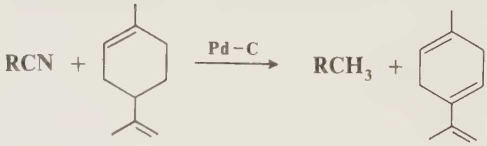
$$ArN_2^+ \ Cl^- \xrightarrow{Na_2SO_3} ArNHNH_2$$

Isocyanates and isothiocyanates are reduced to methylamines, and azides to primary amines, on treatment with $LiAlH_4$. Sulfonyl azides RSO_2N_3 have been reduced to sulfonamides RSO_2NH_2 by irradiation in isopropyl alcohol,[415] and with NaH.[416] $LiAlH_4$ does not usually reduce azo compounds[416a] (indeed these are the products from $LiAlH_4$ reduction of nitro compounds, reaction **9-72**), but these can be reduced to hydrazo compounds by catalytic hydrogenation or with diimide[417] (see reaction **5-12**). Diazonium salts are reduced to hydrazines by sodium sulfite. This reaction probably has a nucleophilic mechanism:[418]



The initial product is a salt of a hydrazinesulfonic acid, which is converted to the hydrazine by acid treatment. Diazonium salts can also be reduced to arenes (reaction **4-24**).

A cyano group can be reduced to a methyl group by treatment with a terpene such as limonene (which acts as reducing agent) in the presence of palladium-charcoal.[419] H_2 is also



Limonene

effective, though higher temperatures are required. R may be alkyl or aryl.

OS **I**, 442; **III**, 475; **V**, 586. Also see OS **V**, 43.

9-55 Reduction of Sulfonyl Halides to Mercaptans

$$RSO_2Cl \xrightarrow{LiAlH_4} RSH$$

Mercaptans can be prepared by the reduction of sulfonyl halides[420] with $LiAlH_4$. Usually, the reaction is carried out on aromatic sulfonyl chlorides. Zinc and acetic acid, and HI, also give the reduction. Disulfides RSSR can also be produced.[421] For the reduction of sulfonyl chlorides to sulfinic acids, see reaction **0-122**.

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[415] Reagen and Nickon, *J. Am. Chem. Soc.* **90**, 4096 (1968).

[416] Lee and Closson, *Tetrahedron Lett.* 381 (1974).

[416a] For a review see Newbold, in Patai, Ref. 90a, pt. 2, pp. 601, 604–614.

[417] For example, see Ioffe, Sergeeva, and Dumpis, *J. Org. Chem. USSR* **5**, 1683 (1969).

[418] Huisgen and Lux, *Chem. Ber.* **93**, 540 (1960).

[419] Kindler and Lührs, *Chem. Ber.* **99**, 227 (1966), *Justus Liebigs Ann. Chem.* **707**, 26 (1967).

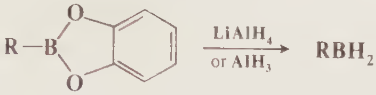
[420] For a review, see Wardell, in Patai, Ref. 277, pp. 216–220.

OS **I**, 504; **IV**, 695; **V**, 843.

9-56 Reduction of Borinates to Boranes

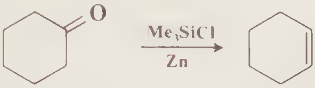
$$R_2BOAr \xrightarrow{LiAlH_4} R_2BH$$

Aryl dialkylborinates can be reduced to dialkylboranes in high yield with $LiAlH_4$.[422] In a similar reaction, monoalkylboranes can be prepared by the reduction of B-alkylcatecholboranes (p. 560) with $LiAlH_4$ or AlH_3.[423]



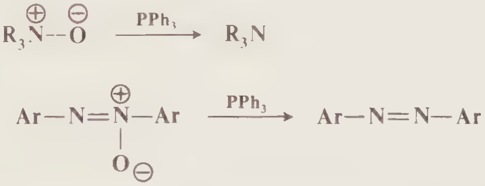
B. Reactions in Which an Oxygen Is Removed from the Substrate

9-57 Reduction of Cyclic Ketones to Cycloalkenes



Cyclic ketones can be directly reduced to cycloalkenes by treatment with chlorotrimethylsilane and zinc.[424] Halogen and ester groups are not affected. Yields are best for six-membered rings. There are many indirect methods for achieving this conversion, among them formation and decomposition of the tosylhydrazone (reaction **7-10**).

9-58 Reduction of Amine Oxides and Azoxy Compounds



$$R_3\overset{\oplus}{N}\text{--}\overset{\ominus}{O} \xrightarrow{PPh_3} R_3N$$

$$Ar\text{—}N{=}\underset{\underset{O^{\ominus}}{|}}{\overset{\oplus}{N}}\text{—}Ar \xrightarrow{PPh_3} Ar\text{—}N{=}N\text{—}Ar$$

Amine oxides[425] and azoxy compounds (both alkyl and aryl) can be reduced practically quantitatively with triphenylphosphine. Other reducing agents, e.g., $LiAlH_4$, H_2–Ni, H_2–Pd, PCl_3, and sulfur, have also been used. Nitrile oxides[426] $R\text{—}C{\equiv}\overset{\oplus}{N}\text{—}\overset{\ominus}{O}$ can be reduced to nitriles with trialkylphosphines.[427]

OS **IV**, 166.

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[421] For example, see Alper, *Angew. Chem. Int. Ed. Engl.* **8**, 677 (1969) [*Angew. Chem.* **81**, 706]; Chan, Montillier, Van Horn, and Harpp, *J. Am. Chem. Soc.* **92**, 7224 (1970).

[422] Brown and Gupta, *J. Organomet. Chem.* **32**, C1 (1971).

[423] Brown and Gupta, *J. Am. Chem. Soc.* **93**, 4062 (1971).

[424] Motherwell, *J. Chem. Soc., Chem. Commun.* 935 (1973).

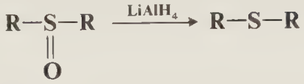
[425] For a review of the reduction of heterocyclic amine oxides, see Katritzky and Lagowski, Ref. 286, pp. 166–231.

[425a] For a review, see Newbold, in Patai, Ref. 90a, pt. 2, pp. 602–603, 614–624.

[426] For a review of the chemistry of nitrile oxides, see Grundmann, *Fortschr. Chem. Forsch.* **7**, 62–127 (1966).

[427] Grundmann and Frommeld, *J. Org. Chem.* **30**, 2077 (1965).

9-59 Reduction of Sulfoxides and Sulfones



$$R{-}\underset{\underset{O}{\|}}{S}{-}R \xrightarrow{LiAlH_4} R{-}S{-}R$$

Sulfoxides can be reduced to sulfides, by $LiAlH_4$ and other reagents, among them HI, dichloroborane $BHCl_2$,[428] trichlorosilane $SiHCl_3$,[429] tributyltin hydride Bu_3SnH,[430] $SnCl_2$–HCl,[431] $TiCl_3$,[432] PCl_3,[433] H_2–Pd–C,[433a] $NaBH_3CN$ and 18-crown-6[434] (see p. 82), acetyl chloride,[435] I_2–SO_2–pyridine,[435a] and Ph_3P.[436] Sulfones, however, are usually stable to reducing agents, though they have been reduced to sulfides with diisobutylaluminum hydride $(i\text{-}Bu)_2AlH$.[437] A less general reagent is $LiAlH_4$, which reduces some sulfones to sulfides, but not others.[438] Both sulfoxides and sulfones can be reduced by heating with sulfur (which is oxidized to SO_2), though the reaction with sulfoxides proceeds at a lower temperature. It has been shown by using substrate labeled with ^{35}S that sulfoxides simply give up the oxygen to the sulfur, but that the reaction with sulfones is more complex, since about 75% of the original radioactivity of the sulfone is lost.[439] This indicates that most of the sulfur in the sulfide product comes in this case from the *reagent*.

9-60 The Conversion of Nitro Compounds to Isocyanates or Isothiocyanates

$$ArNO_2 + CO \xrightarrow[\substack{FeCl_3,\\ 500\text{ atm},\\ 190^\circ C}]{Rh\text{-}C} ArNCO$$

Aromatic nitro compounds can be converted to isocyanates directly by treatment at high pressures with CO and a catalyst consisting of a noble metal (Pd–C or Rh–C) and a Lewis acid.[440] Yields are not high. In a similar reaction, aromatic nitro compounds are converted to isothiocyanates by heating in an autoclave with CS_2 and a base, e.g., NaOMe or NaSPh.[441] In this method pressures are lower and yields are higher.

9-61 Reduction of Hydroperoxides

$$R{-}O{-}O{-}H \xrightarrow{LiAlH_4} ROH$$

Hydroperoxides can be reduced to alcohols with $LiAlH_4$ or Ph_3P,[442] or by catalytic hydrogenation. This functional group is very susceptible to catalytic hydrogenation, as shown by the fact that a double bond may be present in the same molecule without being reduced.[443]

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[428] Brown and Ravindran, *Synthesis* 42 (1973).

[429] Chan, Melnyk, and Harpp, *Tetrahedron Lett.* 201 (1969).

[430] Kozuka, Furumai, Akasaka, and Oae, *Chem. Ind. (London)* 496 (1974).

[431] Ho and Wong, *Synthesis* 206 (1973).

[432] Ho and Wong, *Synth. Commun.* **3**, 37 (1973).

[433] Granoth, Kalir, and Pelah, *J. Chem. Soc. C* 2424 (1969).

[433a] Ogura, Yamashita, and Tsuchihashi, *Synthesis* 385 (1975).

[434] Durst, Zubrick, and Kieczykowski, *Tetrahedron Lett.* 1777 (1974).

[435] Numata and Oae, *Chem. Ind. (London)* 277 (1973).

[435a] Nojima, Nagata, and Tokura, *Bull. Chem. Soc. Jpn.* **48**, 1343 (1975).

[436] Ray, Shaw, and Smith, *Nature* **196**, 372 (1962); Szmant and Cox, *J. Org. Chem.* **31**, 1595 (1966).

[437] Gardner, Kaiser, Krubiner, and Lucas, *Can. J. Chem.* **51**, 1419 (1973).

[438] Bordwell and McKellin, *J. Am. Chem. Soc.* **73**, 2251 (1951); Whitney and Cram, *J. Org. Chem.* **35**, 3964 (1970); Weber, Stromquist, and Ito, *Tetrahedron Lett.* 2595 (1974).

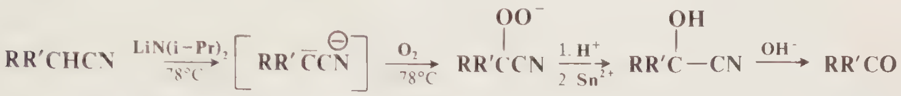
[439] Oae and Kawamura, *Bull. Chem. Soc. Jpn.* **36**, 163 (1963); Kiso and Oae, *Bull. Chem. Soc. Jpn.* **40**, 1722 (1967). See also Oae, Nakai, Tsuchida, and Furukawa, *Bull. Chem. Soc. Jpn.* **44**, 445 (1971); Ašperger, Hegedić, Pavlović, and Stefanović, *J. Org. Chem.* **36**, 3845 (1971).

[440] Hardy and Bennett, *Tetrahedron Lett.* 961 (1967).

[441] Ottmann and Kober, *Angew. Chem. Int. Ed. Engl.* **8**, 760 (1969) [*Angew. Chem.* **81**, 782].

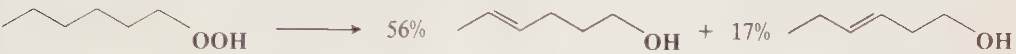
[442] See for example Hiatt, Smythe, and McColeman, *Can. J. Chem.* **49**, 1707 (1971); Hiatt and McColeman, *Can. J. Chem.* **49**, 1712 (1971).

The reaction is an important step in a method for the oxidative decyanation of nitriles containing an α-hydrogen.[444] The nitrile is first converted to the α-hydroperoxy nitrile by treatment with base at −78°C followed by O_2. The hydroperoxy nitrile is then reduced to the cyanohydrin which is cleaved (the reverse of reaction **6-50**) to the corresponding ketone. The method is not successful for the preparation of aldehydes (R′ = H).

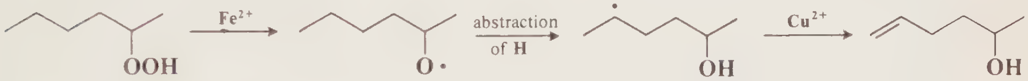


$$\mathrm{RR'CHCN} \xrightarrow[78^\circ\mathrm{C}]{\mathrm{LiN(i\text{-}Pr)_2}} \left[\mathrm{RR'\overset{\ominus}{\bar{C}}CN}\right] \xrightarrow[78^\circ\mathrm{C}]{\mathrm{O_2}} \mathrm{RR'\overset{OO^-}{\overset{|}{C}}CN} \xrightarrow[2\ \mathrm{Sn^{2+}}]{1.\ \mathrm{H^+}} \mathrm{RR'\overset{OH}{\overset{|}{C}}{-}CN} \xrightarrow{\mathrm{OH^-}} \mathrm{RR'CO}$$

When alkyl hydroperoxides are treated with ferrous sulfate and cupric acetate in acetic acid, the OOH group is reduced to OH, but a double bond is also introduced in the 3,4 or 4,5 position,[445] e.g.,



When there is a choice, the double bond is formed in the least substituted position. This reaction can be applied to primary, secondary, or tertiary hydroperoxides. A free-radical mechanism is involved:



9-62 Reduction of Aliphatic Nitro Compounds to Oximes or Nitriles

$$\mathrm{RCH_2NO_2} \xrightarrow{\mathrm{SnCl_2}} \mathrm{RCH{=}NOH}$$

Nitro compounds which contain an α-hydrogen can be reduced to oximes with stannous chloride or with other reagents, among them Co–Cu(II) salts in alkanediamines,[446] Zn dust in HOAc,[447] $CrCl_2$,[448] and (for α-nitro sulfones) $NaNO_2$.[449]

Primary aliphatic nitro compounds can be reduced to nitriles with sodium dihydro(trithio)-borate.[398] Secondary compounds give mostly ketones (e.g., nitrocyclohexane → 45% cyclohexanone,

$$\mathrm{RCH_2NO_2} \xrightarrow{\mathrm{NaBH_2S_3}} \mathrm{RC{\equiv}N}$$

30% cyclohexanone oxime, and 19% N-cyclohexylhydroxylamine). Tertiary aliphatic nitro compounds do not react with this reagent. See also reaction **9-49.**

OS **IV,** 932.

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[443] Rebeller and Clément, *Bull. Soc. Chim. Fr.* 1302 (1964).

[444] Selikson and Watt, *J. Org. Chem.* **40,** 267 (1975).

[445] Kochi, *J. Am. Chem. Soc.* 85, 1958 (1963); Acott and Beckwith, *Aust. J. Chem.* **17,** 1342 (1964); Čeković and Green, *J. Am. Chem. Soc.* **96,** 3000 (1974).

[446] Knifton, *J. Org. Chem.* **38,** 3296 (1973).

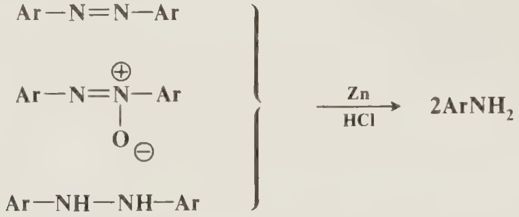
[447] Johnson and Degering, *J. Am. Chem. Soc.* **61,** 3194 (1939).

[448] Hanson and Organ, *J. Chem. Soc. C* 1182 (1970); Hanson, *Synthesis* 1–8 (1974), pp. 7–8.

[449] Zeilstra and Engberts, *Synthesis* 49 (1974).

C. Reduction with Cleavage

9-63 Reduction of Azo, Azoxy, and Hydrazo Compounds to Amines



Azo, azoxy, and hydrazo compounds can all be reduced to amines.[449a] Metals (notably zinc) and acids, and $Na_2S_2O_4$, are frequently used as reducing agents. Borane reduces azo compounds to amines, though it does not reduce nitro compounds.[450] $LiAlH_4$ does not reduce hydrazo compounds or azo compounds, though with the latter, hydrazo compounds are sometimes isolated. With azoxy compounds, $LiAlH_4$ gives only azo compounds (reaction **9-58**).

OS **I,** 49; **II,** 35, 39; **III,** 360. Also see OS **II,** 290.

9-64 Reduction of Peroxides

$$R—O—O—R \xrightarrow{LiAlH_4} 2ROH$$

Peroxides are cleaved to 2 moles of alcohol by $LiAlH_4$ or by catalytic hydrogenation. Peroxides can be reduced to ethers with $P(OEt)_3$:[451]

$$ROOR + P(OEt)_3 \longrightarrow ROR + OP(OEt)_3$$

In a similar reaction, disulfides RSSR′ can be converted to sulfides RSR′ by treatment with tris(diethylamino)phosphine $(Et_2N)_3P$.[452]

9-65 Reduction of Disulfides to Mercaptans

$$RSSR \xrightarrow[H^+]{Zn} 2RSH$$

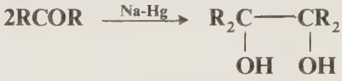
Disulfides can be reduced to mercaptans by mild reducing agents[453] such as zinc and dilute acid or Ph_3P and H_2O.[454] The reaction can also be accomplished simply by heating with alkali.[455] $LiAlH_4$ has also been used.

OS **II,** 580. Also see OS **IV,** 295.

9-66 Reduction of Ozonides. See reaction **9-10**

D. Reductive Coupling

9-67 Bimolecular Reduction of Aldehydes and Ketones to Pinacols



$$2RCOR \xrightarrow{Na\text{-}Hg} \underset{OH}{R_2C}—\underset{OH}{CR_2}$$

[449a] For a review, see Newbold, in Patai, Ref. 90a, pt. 2, pp. 629–637.

[450] Brown and Subba Rao, *J. Am. Chem. Soc.* **82,** 681 (1960).

[451] Horner and Jurgeleit, *Justus Liebigs Ann. Chem.* **591,** 138 (1955).

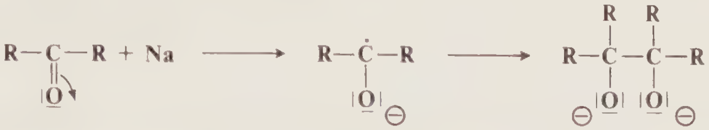
[452] Harpp, Gleason, and Snyder, *J. Am. Chem. Soc.* **90,** 4181 (1968); Harpp and Gleason, *J. Am. Chem. Soc.* **93,** 2437 (1971).

[453] For a review, see Wardell, in Patai, Ref. 277, pp. 220–229.

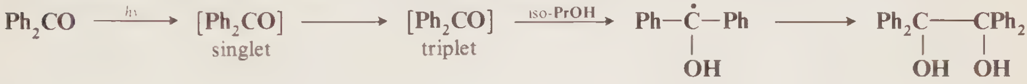
[454] Overman, Smoot, and Overman, *Synthesis* 59 (1974).

[455] For discussions, see Danehy and Hunter, *J. Org. Chem.* **32,** 2047 (1967); Danehy, in Kharasch and Meyers, Ref. 276, pp. 337–349.

Pinacols can be synthesized by reduction of aldehydes and ketones with active metals such as sodium, magnesium, or aluminum.[456] Aromatic ketones give better yields than aliphatic ones. The use of a Mg–MgI_2 mixture has been called the *Gomberg-Bachmann pinacol synthesis*. As with a number of other reactions involving sodium, there is a direct electron transfer here, converting the ketone or aldehyde to a ketyl, which couples:



The dimerization of ketones to pinacols can also be accomplished photochemically; and indeed this is one of the most common photochemical reactions.[457] The substrate, which is usually a diaryl or aryl alkyl ketone (though a few aromatic aldehydes and dialkyl ketones have been dimerized), is irradiated with uv light in the presence of a hydrogen donor such as isopropyl alcohol, toluene, or an amine.[458] In the case of benzophenone, irradiated in the presence of isopropyl alcohol, the ketone molecule initially undergoes $n \rightarrow \pi^*$ excitation, and the singlet species thus formed crosses to the T_1 state with a very high efficiency. The T_1 species abstracts hydrogen from the alcohol (p. 223) and then dimerizes. The iso-PrO• radical, which is formed by this process, donates H• to another molecule of ground-state benzophenone, producing acetone and another molecule of **35**. This mechanism[459] predicts that the quantum yield for the



35

$$\text{iso-PrO}\cdot + Ph_2CO \longrightarrow Me_2CO + \underset{\mathbf{35}}{Ph_2COH}$$

disappearance of benzoquinone should be 2, since each quantum of light results in the conversion of 2 moles of benzophenone to **35**. Under favorable experimental conditions the observed quantum yield does approach 2. Benzophenone abstracts hydrogen with very high efficiency. Other aromatic ketones are dimerized with lower quantum yields, and some (e.g., *p*-aminobenzophenone, *o*-methylacetophenone) cannot be dimerized at all in isopropyl alcohol (though *p*-aminobenzophenone, for example, can be dimerized in cyclohexane[460]). The reaction has also been carried out electrochemically.[461]

Pinacols have also been obtained by treatment of carboxylic acids with butyllithium and $TiCl_3$ (2RCOOH → RCHOH—CHOHR), but yields are low.[462]

OS **I**, 459; **II**, 71.

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[456] For a convenient method, see Schreibmann, *Tetrahedron Lett.* 4271 (1970).

[457] For reviews, see Schönberg, "Preparative Organic Photochemistry," pp. 203–217, Springer-Verlag, New York, 1968; Neckers, "Mechanistic Organic Photochemistry," pp. 163–177, Reinhold, New York, 1967; Calvert and Pitts, "Photochemistry," pp. 532–536, John Wiley & Sons, Inc., New York, 1966; Turro, "Molecular Photochemistry," pp. 139–154, W. A. Benjamin, Inc., New York, 1965; Kan, "Organic Photochemistry," pp. 222–229, McGraw-Hill Book Company, New York, 1966.

[458] For a review of amines as hydrogen donors in this reaction, see Cohen, Parola, and Parsons, *Chem. Rev.* **73**, 141–161 (1973).

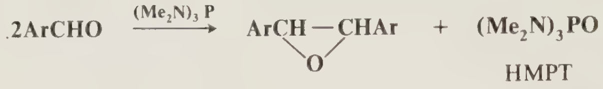
[459] For some of the evidence for this mechanism, see Pitts, Letsinger, Taylor, Patterson, Recktenwald, and Martin, *J. Am. Chem. Soc.* **81**, 1068 (1959); Hammond and Moore, *J. Am. Chem. Soc.* **81**, 6334 (1959); Moore, Hammond, and Foss, *J. Am. Chem. Soc.* **83**, 2789 (1961); Huyser and Neckers, *J. Am. Chem. Soc.* **85**, 3641 (1963). See also Weiner, *J. Am. Chem. Soc.* **93**, 425 (1971); Schuster and Weil, *J. Am. Chem. Soc.* **95**, 4091 (1973).

[460] Porter and Suppan, *Proc. Chem. Soc.* 191 (1964).

[461] For a review, see Baizer and Petrovich, *Prog. Phys. Org. Chem.* **7**, 189–227 (1970).

[462] Axelrod, *Chem. Commun.* 451 (1970).

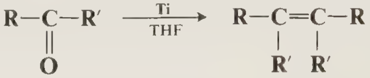
9-68 Bimolecular Reduction of Aldehydes and Ketones to Epoxides



Aromatic aldehydes can be dimerized to epoxides by treatment with hexamethylphosphorus triamide.[463] The reagent[464] is converted to hexamethylphosphoric triamide (HMPT). The reaction can be used for the preparation of mixed epoxides by the use of a mixture of two aldehydes in which the less reactive aldehyde predominates. Epoxides have also been prepared by treatment of aromatic aldehydes or ketones with the anions $(Me_2N)_2\overset{\ominus}{P}{=}O$ and $(EtO)_2\overset{\ominus}{P}{=}O$ (derived, respectively, by treatment with an alkali metal of HMPT or triethyl phosphite).[465]

OS V, 358.

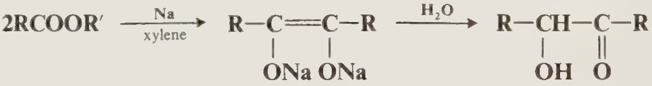
9-69 Bimolecular Reduction of Aldehydes or Ketones to Alkenes



$$\underset{\underset{O}{\|}}{R{-}C{-}R'} \xrightarrow[\text{THF}]{\text{Ti}} R{-}\underset{R'}{\underset{|}{C}}{=}\underset{R'}{\underset{|}{C}}{-}R$$

Aldehydes and ketones, both aromatic and aliphatic (including cyclic ketones), can be converted in high yields to dimeric alkenes by treatment with an active titanium metal powder prepared from $TiCl_3$ and K in dry tetrahydrofuran.[466] The reaction has also been accomplished with Mg and a $TiCl_3$–THF complex,[467] with $TiCl_4$ and zinc,[468] and with certain compounds prepared from WCl_6 and either lithium, lithium iodide, or an alkyllithium[469] (see reaction **7-19**).

9-70 The Acyloin Condensation



$$2RCOOR' \xrightarrow[\text{xylene}]{\text{Na}} R{-}\underset{ONa}{\underset{|}{C}}{=}\underset{ONa}{\underset{|}{C}}{-}R \xrightarrow{H_2O} R{-}\underset{OH}{\underset{|}{CH}}{-}\underset{O}{\underset{\|}{C}}{-}R$$

36

When esters are heated with sodium in refluxing ether or benzene, a bimolecular reduction takes place, and the product is an α-hydroxy ketone (called an acyloin).[470] The reaction, called the *acyloin condensation*, is quite successful when R is alkyl. Acyloins with long chains have been prepared in this way, for example, $R = C_{17}H_{35}$, but for high-molecular-weight esters, toluene or xylene is used as the solvent. The acyloin condensation has been used with great success, in boiling xylene, to prepare cyclic acyloins from diesters.[471] The yields are 50 to 60 % for the preparation of 6- and 7-membered rings, 30 to 40 % for 8- and 9-membered,[472] and 60 to 95 % for rings of 10 to 20 members. Even larger rings have been closed in this manner. This is the best way of closing rings of 10 members or more. The reaction has been used to close 4-membered rings,[473] though this is generally not successful. Small traces of oxygen greatly reduce the yields; hence the reaction must be conducted in an extremely pure nitrogen atmosphere. The presence of double or triple bonds does not interfere.[474] Even a benzene ring may be present, and many paracyclophane derivatives (**37**) with $n = 9$ or more have been synthesized in this manner.[475]

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[463] Mark, *J. Am. Chem. Soc.* **85**, 1884 (1963); Newman and Blum, *J. Am. Chem. Soc.* **86**, 5598 (1964).

[464] For the preparation of the reagent, see Mark, *Org. Synth.* **V**, 602.

[465] Normant, *Bull. Soc. Chim. Fr.* 3601 (1966).

[466] Mc Murry and Fleming, *J. Org. Chem.* **41**, 896 (1976). See also Mc Murry and Fleming, *J. Am. Chem. Soc.* **96**, 4708 (1974).

[467] Tyrlik and Wolochowicz, *Bull. Soc. Chim. Fr.* 2147 (1973).

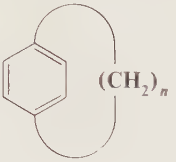
[468] Mukaiyama, Sato, and Hanna, *Chem. Lett.* 1041 (1973).

[469] Sharpless, Umbreit, Nieh, and Flood, *J. Am. Chem. Soc.* **94**, 6538 (1972).

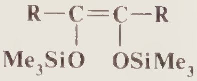
[470] For reviews, see Bloomfield, Owsley, and Nelke, *Org. React.* **23**, 259–403 (1976); McElvain, *Org. React.* **4**, 256–268 (1948).

[471] For a review of cyclizations by means of the acyloin condensation, see Finley, *Chem. Rev.* **64**, 573–589 (1964).

[472] Yields of nine-membered ring products can be increased by adding a homologous diester, e.g., dimethyl tridecanedioate: Finley and Sasaki, *J. Am. Chem. Soc.* **88**, 4267 (1966).



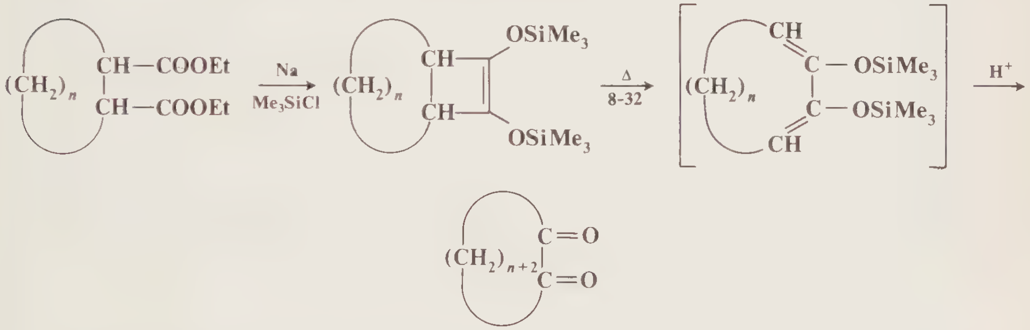
37



$$\begin{array}{c} R-C=C-R \\ \;\;\;\,| \quad\;\; | \\ Me_3SiO \quad OSiMe_3 \end{array}$$

38

Yields in the acyloin condensation can be improved by running the reaction in the presence of chlorotrimethylsilane Me_3SiCl, in which case the dianion **36** is converted to the bis silyl enol ether **38**, which can be isolated and subsequently hydrolyzed to the acyloin with aqueous acid.[476] Among other things, this method inhibits the Dieckmann condensation[477] (**0-111**), which otherwise competes with the acyloin condensation when a five-, six-, or seven-membered ring can be closed (note that the ring formed by a Dieckmann condensation is always one carbon atom smaller than that formed by an acyloin condensation of the same substrate). The Me_3SiCl method is especially good for the closing of four-membered rings,[478] and this reaction has been used in a procedure for ring enlargement of a cyclic diester by two carbons.[479]



The mechanism is not known with certainty, but it is usually presumed that the diketone RCOCOR is an intermediate,[480] since small amounts of it are usually isolated as side products,

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[473] Cope and Herrick, *J. Am. Chem. Soc.* **72,** 983 (1950); Bloomfield and Irelan, *J. Org. Chem.* **31,** 2017 (1966).

[474] Cram and Gaston, *J. Am. Chem. Soc.* **82,** 6386 (1960).

[475] For a review, see Cram, *Rec. Chem. Prog.* **20,** 71 (1959).

[476] Schräpler and Rühlmann, *Chem. Ber.* **97,** 1383 (1964). For a review of the Me_3SiCl method, see Rühlmann, *Synthesis* 236–253 (1971).

[477] Bloomfield, *Tetrahedron Lett.* 591 (1968).

[478] Bloomfield, *Tetrahedron Lett.* 587 (1968); Gream and Worthley, *Tetrahedron Lett.* 3319 (1968); Bloomfield, Irelan, and Marchand, *Tetrahedron Lett.* 5647 (1968); Wynberg, Reiffers, and Strating, *Recl. Trav. Chim. Pays-Bas* **89,** 982 (1970); Bloomfield, Martin, and Nelke, *J. Chem. Soc., Chem. Commun.* 96 (1972). See also Delbaere and Whitham, *J. Chem. Soc., Perkin Trans. 1* 879 (1974).

[479] Mori, Nakahara, and Nozaki, *Can. J. Chem.* **47,** 3266 (1969).

[480] Another mechanism, involving addition of the ketyl to another molecule of ester (rather than a dimerization of two ketyl radicals), in which a diketone is not an intermediate, has been proposed: Bloomfield, Owsley, Ainsworth, and Robertson, *J. Org. Chem.* **40,** 393 (1975).

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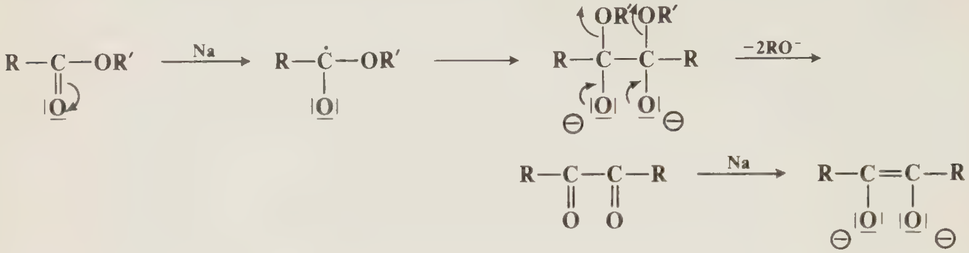
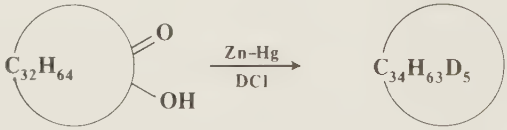
and when it is resistant to reduction (for example, *t*-Bu—CO—CO—*t*-Bu), it is the major product. A possible sequence (analogous to that of reaction **9-67**) is



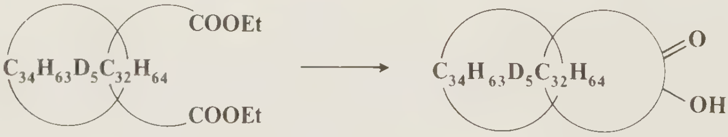
In order to account for the ready formation of large rings, which means that the two ends of the chain must approach each other even though this is conformationally unfavorable for long chains, it may be postulated that the two ends become attached to nearby sites on the surface of the sodium.

The acyloin condensation was used in an ingenious manner to prepare the first reported catenane (see p. 85). The catenane (**41**) was prepared by a statistical synthesis (p. 85) in the following manner: An acyloin condensation was performed on the diethyl ester of the C_{34} dicarboxylic acid (tetratriacontandioic acid) to give the cyclic acyloin **39.** This was reduced by a Clemmensen reduction with DCl in D_2O instead of HCl in H_2O, thus producing a C_{34} cycloalkane containing deuterium (**40**):[481]



39 **40**

40 contained about five atoms of deuterium per molecule. The reaction was then repeated, this time *in a* 1 : 1 *mixture of xylene and* **40** *as solvent.* It was hoped that some of the molecules of ester would be threaded through **40** before they closed:



41

The first thing that was done with the product was to remove by chromatography the **40** which had been used as the solvent. The remaining material still contained deuterium, as determined by infrared spectra, even with all the **40** gone. This was strong evidence that the material consisted not only of **39**, but also of **41.** As further evidence, the mixture was oxidized to open up the acyloin rings (reaction **9-8**). From the oxidation product was isolated the C_{34} diacid (as expected), *containing no deuterium*, and **40,** containing deuterium. The total yield of **41** and **39** was 5 to 20%, but the percentage of **41** in this mixture was only about 1 to 2%.[481] This synthesis of a catenane produced only a small yield and relied on chance, on the probability that a diester molecule would be threaded through **40** before it closed. Another statistical synthesis makes use of the olefin metathesis reaction (**8-41**).[482] When this is applied to large-ring dienes, some of the molecules become twisted (**42**) before the reaction takes place. When such a molecule reacts, the product is the catenane **43.** Mass spectral evidence shows that some catenanes are indeed formed.

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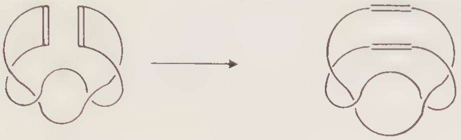
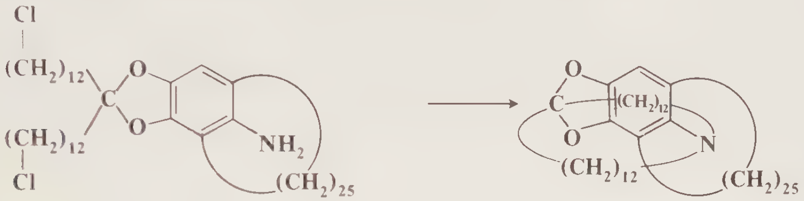
[481] This work was done by Wasserman, *J. Am. Chem. Soc.* **82,** 4433 (1960).



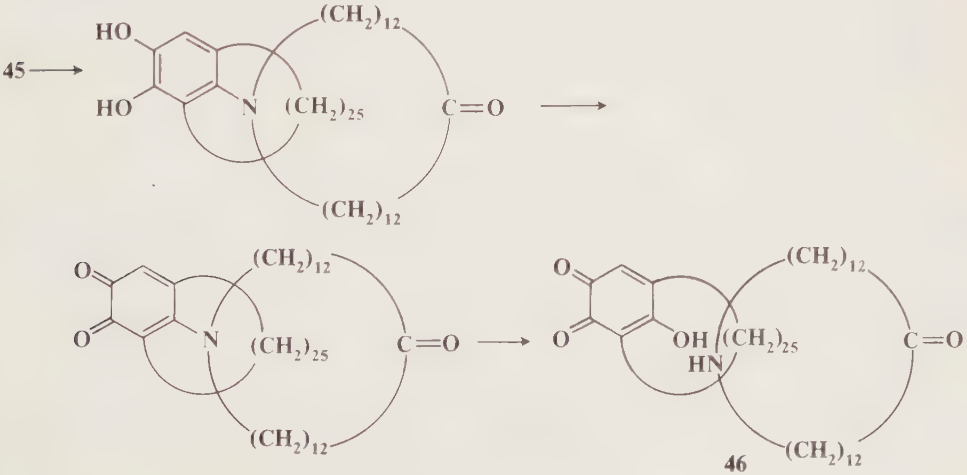
42 **43**

A catenane has also been prepared by a *directed* synthesis.[483] The key step here was formation of a tertiary amine by reaction **0-46.**



44 **45**

Sterically, one of the halide groups of **44** is above the plane, and the other below it, so that ring closure must occur *through* the 28-membered ring. After **45** was formed, the acetal was cleaved (reaction **0-7**). It was then necessary to cleave the remaining bond holding the two rings together, the C—N bond. This was done by oxidation to the *ortho*-quinone (reaction **9-5**), which converted the amine function to an enamine, which was hydrolyzable (reaction **6-2**) with acid to give the catenane (**46**):



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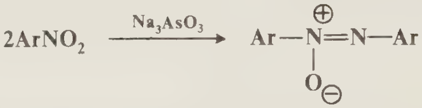
[482] Wolovsky, *J. Am. Chem. Soc.* **92,** 2132 (1970); Ben-Efraim, Batich, and Wasserman, *J. Am. Chem. Soc.* **92,** 2133 (1970).

[483] Schill and Lüttringhaus, *Angew. Chem. Int. Ed. Engl.* **3,** 546 (1964) [*Angew. Chem.* **76,** 567]; Schill, *Chem. Ber.* **98,** 2906 (1965), **99,** 2689 (1966), **100,** 2021 (1967), *Justus Liebigs Ann. Chem.* **695,** 65 (1966). For the preparation of a [3]catenane by a similar approach, see Schill and Zürcher, *Angew. Chem. Int. Ed. Engl.* **8,** 988 (1969) [*Angew. Chem.* **81,** 996 (1969)].

The original large ring (of **44**) was closed by a Thorpe-Ziegler reaction (**6-48**) after an attempted acyloin condensation proved unsuccessful.

OS **II,** 114; **IV,** 840.

9-71 Reduction of Nitro to Azoxy Compounds



$$2ArNO_2 \xrightarrow{Na_3AsO_3} Ar{-}\overset{\oplus}{N}(O^{\ominus}){=}N{-}Ar$$

Azoxy compounds can be obtained from nitro compounds with certain reducing agents, notably sodium arsenite, sodium ethoxide, lead,[484] $NaBH_4$-$CoCl_2$,[485] and glucose.[486] KBF_4 produces azoxy compounds only when there are electron-withdrawing groups on the ring.[487] On the other hand, the reagent thallium produces azoxy compounds only when electron-withdrawing groups (and phenolic and amino groups) are absent.[488] The most probable mechanism with most reagents is that one molecule of nitro compound is reduced to a nitroso compound and another to a hydroxylamine (reaction **9-51**), and these combine (reaction **2-53**). The combination step is rapid compared to the reduction process.[489] Nitroso compounds can be reduced to azoxy compounds with triethyl phosphite or triphenylphosphine[490] or with an alkaline aqueous solution of an alcohol.[491]

OS **II,** 57.

9-72 Reduction of Nitro to Azo Compounds

$$2ArNO_2 \xrightarrow{LiAlH_4} Ar{-}N{=}N{-}Ar$$

Nitro compounds can be reduced to azo compounds with various reducing agents, of which $LiAlH_4$ and zinc and alkali are the most common.[492] With many of these reagents, slight differences in conditions may lead either to the azo or azoxy (reaction **9-71**) compound. Analogously to reaction **9-71,** this reaction may be looked on as a combination of ArN=O and $ArNH_2$ (reaction **2-52**). However, when the reducing agent was $HOCH_2CH_2ONa$[493] or $NaBH_4$,[494] it was shown that azoxy compounds were intermediates. Nitroso compounds can be reduced to azo compounds with $LiAlH_4$.

OS **III,** 103.

9-73 Reduction of Nitro to Hydrazo Compounds

$$2ArNO_2 \xrightarrow[NaOH]{Zn} Ar{-}NH{-}NH{-}Ar$$

Nitro compounds can be reduced to hydrazo compounds with zinc and sodium hydroxide, or electrolytically, or with $LiAlH_4$ mixed with a metal chloride such as $TiCl_4$ or VCl_3.[495] The reduction has also been accomplished with hydrazine hydrate and Raney nickel.[496]

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[484] Azoo and Grimshaw, *J. Chem. Soc. C* 2403 (1968).

[485] Satoh, Suzuki, Kikuchi, and Okada, *Chem. Ind.* (*London*) 1626 (1970).

[486] For a discussion, see Sandler and Karo, Ref. 94, vol. 2, pp. 367–374 (1971).

[487] Shine and Mallory, *J. Org. Chem.* **27,** 2390 (1962).

[488] McKillop, Raphael, and Taylor, *J. Org. Chem.* **35,** 1670 (1970).

[489] Ogata and Mibae, *J. Org. Chem.* **27,** 2048 (1962).

[490] Bunyan and Cadogan, *J. Chem. Soc.* 42 (1963).

[491] See for example, Hutton and Waters, *J. Chem. Soc. B* 191 (1968).

[492] For a discussion, see Sandler and Karo, Ref. 94, vol. 2, pp. 313–317 (1971).

[493] Tadros, Ishak, and Bassili, *J. Chem. Soc.* 627 (1959).

[494] Hutchins, Lamson, Rufa, Milewski, and Maryanoff, *J. Org. Chem.* **36,** 803 (1971).

[495] Olah, *J. Am. Chem. Soc.* **81,** 3165 (1959).

[496] Furst and Moore, *J. Am. Chem. Soc.* **79,** 5492 (1957).

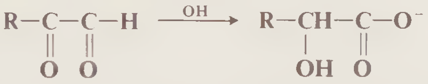
Reactions in Which an Organic Substrate Is Both Oxidized and Reduced

Some reactions which belong in this category have been considered in earlier chapters. Among these are the Tollens' condensation (reaction **6-46**), the benzil-benzilic acid rearrangement (reaction **8-7**), and the Wallach rearrangement (reaction **8-50**).

9-74 The Cannizzaro Reaction

$$2\mathrm{ArCHO} \xrightarrow{\mathrm{NaOH}} \mathrm{ArCH_2OH} + \mathrm{ArCOO^-}$$

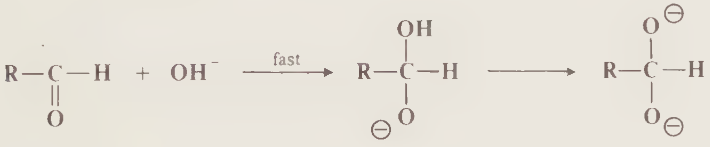
Aromatic aldehydes, and aliphatic ones with no α-hydrogen, give the *Cannizzaro reaction* when treated with NaOH or other strong bases.[497] In this reaction one molecule of aldehyde oxidizes another to the acid and is itself reduced to the primary alcohol. Aldehydes with an α-hydrogen do not give the reaction, because when these compounds are treated with base the aldol condensation (reaction **6-40**) is much faster.[498] Normally, the best yield of acid or alcohol is 50% each, but this can be altered in certain cases. When the aldehyde contains a hydroxide group in the ring, then excess base oxidizes the alcohol formed, and the acid can thus be prepared in high yield (the OH^- is reduced to H_2). On the other hand, high yields of alcohol can be obtained from almost any aldehyde by running the reaction in the presence of formaldehyde. In this case the formaldehyde reduces the aldehyde to alcohol and is itself oxidized to formic acid. In such a case, where the oxidant aldehyde differs from the reductant aldehyde, the reaction is called the *crossed Cannizzaro reaction.* The Tollens' condensation (reaction **6-46**) includes a crossed Cannizzaro reaction as its last step. α-Keto aldehydes give internal Cannizzaro reactions:



$$\mathrm{R{-}C({=}O){-}C({=}O){-}H} \xrightarrow{\mathrm{OH}} \mathrm{R{-}CH(OH){-}C({=}O){-}O^-}$$

This product is also obtained on alkaline hydrolysis of compounds of the formula $RCOCHX_2$. Similar reactions have been performed on α-keto acetals[499] and γ-keto aldehydes.

The mechanism of the Cannizzaro reaction involves a hydride shift (an example of mechanism type 2, p. 1075). First OH^- adds to the C=O to give **47**, which may lose a proton in the basic solution to give the diion **48**.



$$\mathrm{R{-}C({=}O){-}H} + \mathrm{OH^-} \xrightarrow{\text{fast}} \mathrm{R{-}C(OH)(O^-){-}H} \longrightarrow \mathrm{R{-}C(O^-)_2{-}H}$$

47 **48**

The strong electron-donating character of O^- greatly facilitates the ability of the aldehydic hydrogen to leave with its electron pair. Of course this effect is even stronger in **48**. When the hydride does leave it attacks another molecule of aldehyde. The hydride may come from **47** or **48**:

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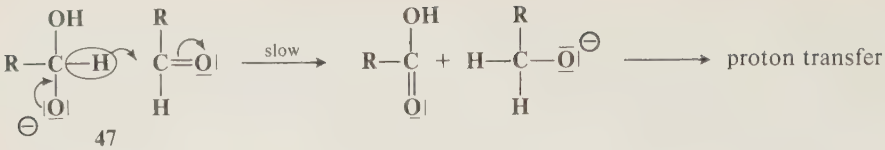
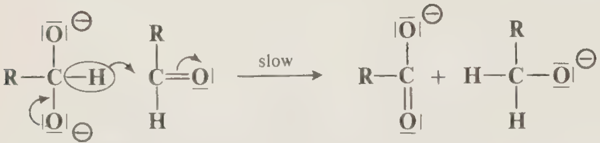
[497] For a review, see Geissman, *Org. React.* **2**, 94–113 (1944).

[498] An exception is cyclopropanecarboxaldehyde: van der Maeden, Steinberg, and de Boer, *Recl. Trav. Chim. Pays-Bas* **91**, 221 (1972).

[499] Thompson, *J. Org. Chem.* **32**, 3947 (1967).



47



48

If the hydride ion comes from **47**, then the final step is a rapid proton transfer. In the other case, the acid salt is formed directly, and the alkoxide ion acquires a proton from the solvent. Evidence for this mechanism is: (1) The reaction may be first order in base and second order in substrate (thus going through **47**) or, at higher base concentrations, second order in each (going through **48**); and (2) when the reaction was run in D_2O, the recovered alcohol contained no α-deuterium, indicating that the hydrogen comes from another mole of aldehyde and not from the medium.[500]

OS **I,** 276; **II,** 590; **III,** 538; **IV,** 110.

9-75 The Tishchenko Reaction

$$2\mathrm{RCHO} \xrightarrow{\mathrm{Al(OEt)_3}} \mathrm{RCOOCH_2R}$$

When aldehydes, with or without α-hydrogen, are treated with aluminum ethoxide, one molecule is oxidized and another reduced, as in reaction **9-74,** but here they are found as the ester. The process is called the *Tishchenko reaction.* Crossed Tishchenko reactions are also possible. With more strongly basic alkoxides, such as magnesium or sodium alkoxides, aldehydes with an α-hydrogen give the aldol condensation. Like reaction **9-74,** this reaction has a mechanism that involves hydride transfer.[501] The Tishchenko reaction can also be catalyzed by boric acid.[502]

OS **I,** 104.

9-76 The Willgerodt Reaction

$$\mathrm{ArCOCH_3} \xrightarrow{\mathrm{(NH_4)_2S_x}} \mathrm{ArCH_2CONH_2} + \mathrm{ArCH_2COO^-}\ \ \mathrm{NH_4^+}$$

In the *Willgerodt reaction* a straight- or branched-chain aryl alkyl ketone is converted to the amide and/or the ammonium salt of the acid by heating with ammonium polysulfide.[503] The carbonyl group of the product is always at the end of the chain. Thus $ArCOCH_2CH_3$ gives the amide and the salt of $ArCH_2CH_2COOH$, and $ArCOCH_2CH_2CH_3$ gives derivatives of $ArCH_2$-CH_2CH_2COOH. However, yields sharply decrease with increasing length of chain. The reaction has also been carried out on vinyl and ethynyl aromatic compounds and on aliphatic ketones, but yields are usually lower in these cases. The use of sulfur and a dry primary or secondary amine (or ammonia) as the reagent is called the *Kindler modification* of the Willgerodt reaction.[504] The product in this case is $Ar(CH_2)_nCSNR_2$, which can be hydrolyzed to the acid.[505] Particularly good results are obtained when morpholine is used as the amine.

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[500] Fredenhagen and Bonhoeffer, *Z. Phys. Chem., Abt. A* **181,** 379 (1938); Hauser, Hamrick, and Stewart, *J. Org. Chem.* **21,** 260 (1956).

[501] See for example, Zakharkin and Sorokina, *J. Gen. Chem. USSR* **37,** 525 (1967); Saegusa, Ueshima, and Kitagawa, *Bull. Chem. Soc. Jpn.* **42,** 248 (1969); Ogata, Kawasaki, and Kishi, *Tetrahedron* **23,** 825 (1967); Ogata and Kishi, *Tetrahedron* **25,** 929 (1969).

[502] Stapp, *J. Org. Chem.* **38,** 1433 (1973).

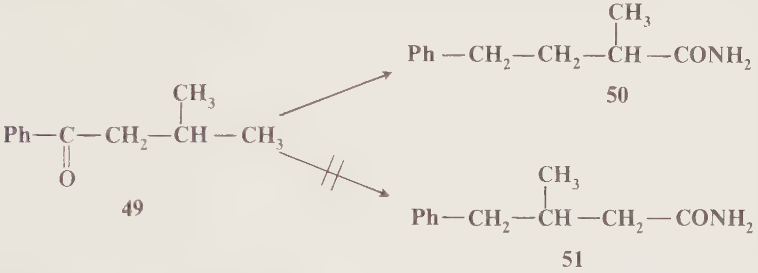
[503] For reviews, see Brown, *Synthesis* 358–375 (1975); Wegler, Kühle, and Schäfer, *Angew. Chem.* **70,** 351-367 (1958), *Newer Methods Prep. Org. Chem.* **3,** 1–51 (1964); Carmack and Spielman, *Org. React.* **3,** 83–107 (1946).

Compounds of the form $ArCOCH_3$ (acetophenones) can be converted to arylacetic acid derivatives in an entirely different manner. The reaction consists of treatment of the substrate with thallium(III) nitrate in acidic methanol, and the product is a methyl arylacetate.[506] Yields

$$\mathrm{ArCOCH_3} \xrightarrow[\mathrm{MeOH-H^+}]{\mathrm{Tl(NO_3)_3}} \mathrm{ArCH_2COOMe}$$

are moderate to high.

The mechanism of the Willgerodt reaction is not completely known, but some conceivable mechanisms can be excluded by the facts which are known. Thus, one might suppose that the alkyl group becomes completely detached from the ring and then attacks it with its other end. However, this possibility is ruled out by experiments such as the following: When isobutyl phenyl ketone (**49**) is subjected to the Willgerodt reaction, the product is **50**, and not **51**, which would arise if the end carbon of the ketone became bonded to the ring in the product:[507]



49 **50** **51**

This also excludes a cyclic-intermediate mechanism similar to that of the Claisen rearrangement (reaction **8-38**). Another important fact is that the reaction is successful for singly branched side chains, such as **49**, but not for doubly branched side chains, as in $PhCOCMe_3$.[507] Still another piece of evidence is that compounds oxygenated along the chain give the same products; thus $PhCOCH_2CH_3$, $PhCH_2COMe$, and $PhCH_2CH_2CHO$ all give $PhCH_2CH_2CONH_2$.[508] All these facts point to a mechanism consisting of consecutive oxidations and reductions along the chain. Just what form these take is not certain, though a number of theories have been proposed. Initial reduction to the hydrocarbon may be ruled out, since alkylbenzenes do not give the reaction. In certain cases imines[509] or enamines[510] have been isolated from primary and secondary amines, respectively, and these have been shown to give the normal products, leading to the suggestion that they may be reaction intermediates.

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[504] For a review, see Asinger, Schäfer, Halcour, Saus, and Triem, *Angew. Chem. Int. Ed. Engl.* **3**, 19–28 (1964) [*Angew. Chem.* **75**, 1050–1059 (1963)].

[505] The reaction between ketones, sulfur, and ammonia may also lead to heterocyclic compounds. For a review, see Asinger and Offermanns, *Angew. Chem. Int. Ed. Engl.* **6**, 907–919 (1967) [*Angew. Chem.* **79**, 953–965].

[506] McKillop, Swann, and Taylor, *J. Am. Chem. Soc.* **95**, 3340 (1973).

[507] King and McMillan, *J. Am. Chem. Soc.* **68**, 632 (1946).

[508] For an example of this type of behavior, see Asinger, Saus, and Mayer, *Monatsh. Chem.* **98**, 825 (1967).

[509] Asinger and Halcour, *Monatsh. Chem.* **95**, 24 (1964).

[510] Mayer, in Janssen, "Organosulfur Chemistry," pp. 229–232, Interscience Publishers, New York, 1967.

Appendix A

The Literature of Organic Chemistry

All discoveries made in the laboratory must be published somewhere if the information is to be made generally available. A new experimental result which is not published might as well not have been obtained, insofar as it benefits the entire chemical world. The total corpus of chemical knowledge (called *the literature*) is located on the combined shelves of all the chemical libraries in the world. If anyone wishes to learn whether the answer to any chemical question is known and, if so, what the answer is, he has only to turn to the contents of these shelves. Indeed the very expressions "is known," "has been done," etc., really mean "has been published." To the uninitiated, the contents of the shelves may appear formidably large, but fortunately the process of extracting information from the literature of organic chemistry is usually not difficult and often not even time-consuming. In this appendix we shall examine the literature of organic chemistry, confining our attention chiefly to the results of laboratory work, rather than those of industrial organic chemistry.[1] The literature can be divided into two broad categories, *primary sources* and *secondary sources*. A primary source publishes the original results of laboratory investigations. Books, indexes, and other publications which cover material which has previously been published in primary sources may be called secondary sources. It is because of the excellence of the secondary sources in the field of organic chemistry (especially *Chemical Abstracts* and Beilstein) that literature searching is comparatively not difficult. The two chief kinds of primary source are journals and patents. There are several types of secondary source.

PRIMARY SOURCES

Journals

For the last hundred years, nearly all new work in organic chemistry (except for that which has been disclosed in patents) has been published in journals. There are thousands of journals which publish chemical papers, in many countries and in many languages. Most are published by chemical and other scientific societies, but some are published by private companies. Some print papers covering all fields of science; some are restricted to chemistry; some to organic chemistry; and there are a few that are still more specialized. Fortunately for the sanity of organic chemists, the vast majority of important papers in "pure" organic chemistry (as opposed to "applied") are published in relatively few journals, perhaps 60 or fewer. Of course, this is still a large number (and it is growing all the time), especially since some are published weekly and some semimonthly, but it is considerably smaller than the total number of journals (perhaps as high as 10,000) which publish chemical articles.

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[1] For monographs on the chemical literature, see Woodburn, "Using the Chemical Literature," Marcel Dekker, Inc., New York, 1974; Mellon, "Chemical Publications," 4th ed., McGraw-Hill Book Company, New York, 1965; Crane, Patterson, and Marr, "A Guide to the Literature of Chemistry," 2d ed., John Wiley & Sons, Inc. New York, 1957. For a three-part article on the literature of organic chemistry, see Hancock, *J. Chem. Educ.* **45,** 193–199, 260–266, 336–339 (1968).

In addition to ordinary papers, there are two other types of publications in which original work is reported: *notes* and *communications*. A note is a brief paper, usually published without a summary (most papers are published with summaries or abstracts prepared by the author). Otherwise, a note is similar to a paper. In recent years, the use of notes has been declining, and some journals no longer publish them. Communications (also called *letters*) are also brief and also usually without summaries (though some journals now publish summaries along with their communications, a welcome trend). However, communications differ from notes and papers in three respects:

1. They are brief, not because the work is of small scope, but because they are condensed. Usually they include only the most important experimental details or none at all.
2. They are of immediate significance. Journals which publish communications make every effort to have them appear as soon as possible after they are received. Some papers and notes are of great importance, and some are of lesser importance; but all communications are supposed to be of high importance.
3. Communications are preliminary reports, and the material in them may be republished as papers or notes, at a later date, in contrast to the material in papers and notes, which cannot be republished.

Although papers (we use the term in its general sense, to cover notes and communications also) are published in many languages, the English-speaking chemist is in a fairly fortunate position. At present more than half of the important papers in organic chemistry are published in English. Not only are American, British, and British Commonwealth journals published almost entirely in English, but so are many others around the world. There are predominantly English-language journals published in Japan, Italy, Czechoslovakia, Sweden, the Netherlands, Israel, and other countries. Most of the articles published in other languages have summaries, or at least titles, printed in English also. Furthermore, the second most important language (in terms of the number of organic chemical papers published) is Russian, and most of these papers are available in English translation, though in most cases 6 months to a year later. A considerable number of important papers are published in German and French, and these are generally not available in translation, so that the organic chemist should have at least a reading knowledge of these languages. An exception is the journal *Angewandte Chemie*, which in 1962 became available in English under the title *Angewandte Chemie International Edition in English*. Of course, a reading knowledge of French and German (especially German) is even more important for the older literature. Before about 1920, more than half of the important chemical papers were in these languages. It must be realized that the original literature is never obsolete. Secondary sources become superseded or outmoded, but nineteenth-century journals may be found in most chemical libraries and are still consulted. Table 1 presents a list of the more important current journals which publish original papers[2] and communications in organic chemistry.[3] Some of them also publish review articles, notes on meetings, book reviews, and other material. Changes in journal title are not infrequent; footnotes to the table indicate some of the more important, but some of the other journals listed have also undergone title changes.

Patents

In many countries, including the United States, it is possible to patent a new compound or a new method for making a known compound (either laboratory or industrial procedures), so long as the compounds are useful. It comes as a surprise to many to learn that a substantial proportion

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[2] In Table 1 notes are counted as papers.

[3] See Mellon and Crane, Patterson, and Marr, Ref. 1, for longer lists of journals, including discontinued ones.

TABLE 1 A list of the more important current journals which publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are indicated in boldface

Also indicated are the principal languages (E = English, G = German, F = French, R = Russian), the number of issues per year as of 1976 (exclusive of issues devoted entirely to indexes), and whether the journal primarily publishes papers (including in some cases notes) (P) or communications (C)

No.	Name	Principal languages	Papers or communications	Issues per year
1	**Acta Chem**ica **Scand**inavica, **Ser**ies **B** (1947)	E	P	10
2	**Angew**andte **Chem**ie (1888)^{4}	G	C^{5}	24
3	**Ann**ales de **Chim**ie **(Paris)** (1789)	F	P	6
4	**Aust**ralian **J**ournal of **Chem**istry (1948)	E	P	12
5	**Bioorg**anic **Chem**istry (1971)	E	P^{5}	4
6	**Bull**etin of the **Chem**ical **Soc**iety of **Japan** (1926)	E	P	12
7	**Bull**etin des **Soc**iétés **Chim**ique **Belg**es (1887)	FE	P	12
8	**Bull**etin de la **Soc**iété **Chim**ique de **Fr**ance (1858)	F	PC^{5}	12
9	**Can**adian **J**ournal of **Chem**istry (1929)^{6}	EF	PC	24
10	**Carbohydr**ate **Res**earch (1965)	EFG	PC	12
11	**Chem**ische **Ber**ichte (1868)^{7}	G	P	12
12	**Chem**istry and **Ind**ustry **(London)** (1923)	E	C	24
13	**Chem**istry **Lett**ers (1972)	E	C	12
14	**Chem**ica **Scr**ipta (1971)	E	P	10
15	**Chimia** (1947)	GEF	C^{5}	12
16	**Collect**ion of **Czech**oslovak **Chem**ical **Commun**ications (1929)	EG	P	12
17	Comptes **R**endus **Hebd**omadaires des **S**eances de l'**Acad**emie des **Sc**iences, **Ser**ie **C** (1835)^{8}	F	C	52
18	**Dokl**ady **Akad**emii **Nauk SSSR** (1922)^{4}	R	C	36
19	**Experientia** (1945)	E	C	12
20	**Gazz**etta **Chim**ica **Ital**iana (1871)	E	P	6
21	**Helv**etica **Chim**ica **Acta** (1918)	GEF	P	8
22	**Int**ernational **J**ournal of **Chem**ical **Kinet**ics (1969)	E	PC	6
23	**Isr**ael **J**ournal of **Chem**istry (1963)	E	P	6
24	**Izv**estiya **Akad**emii **Nauk SSSR, Ser**iya **Khim**icheskaya (1936)^{4}	R	PC	12
25	**J**ournal of the **Am**erican **Chem**ical **Soc**iety (1879)	E	PC	26
26	**J**ournal of the **Chem**ical **Soc**iety, **Chem**ical **Commun**ications (1965)^{9}	E	C	24

TABLE 1 A list of the more important current journals which publish original papers in organic chemistry, listed in alphabetical order of *Chemical Abstracts* abbreviations, which are indicated in boldface *(Continued)*

No.	Name	Principal languages	Papers or communications	Issues per year
27	Journal of the **Chemical Society, Perkin Transactions 1**: Organic and Bio-Organic Chemistry (1841)[10]	E	P	23
28	Journal of the **Chemical Society, Perkin Transactions 2**: Physical Organic Chemistry (1841)[10]	E	P	15
29	Journal of **Fluorine Chemistry** (1971)	E	P	12
30	Journal of **Heterocyclic Chemistry** (1964)	E	PC	6
31	Journal of the **Indian Chemical Society** (1924)	E	P	12
32	Journal of **Medicinal Chemistry** (1958)	E	PC	12
33	Journal of **Molecular Structure** (1967)	EFG	P	12
34	Journal of **Organometallic Chemistry** (1963)	EGF	PC[5]	52
35	Journal of **Organic Chemistry** (1936)	E	PC	26
36	Journal of **Photochemistry** (1972)	E	PC	6
37	Journal für **Praktische Chemie** (1834)	GE	P	6
38	**Justus Liebigs Annalen** der **Chemie** (1832)	G	P	12
39	**Molecular Photochemistry** (1969)	E	P	4
40	**Monatshefte** für **Chemie** (1870)	G	P	6
41	**Naturwissenschaften** (1913)	GE	C[5]	12
42	**Organic Magnetic Resonance** (1969)	EFG	PC	12
43	**Organic Mass Spectrometry** (1968)	EFG	PC	12
44	**Organic Preparations** and **Procedures** International (1969)	E	P[5]	6
45	**Photochemistry** and **Photobiology** (1962)	E	P[5]	12
46	**Pure** and **Applied Chemistry** (1960)	EGF	[11]	12
47	**Recueil** des **Travaux Chimiques** des **Pays-Bas** (1882)	EGF	PC	12
48	**Synthetic Communications** (1971)	E	P	8
49	**Synthesis** (1969)	EG	P[5]	12
50	**Tetrahedron** (1958)	EGF	P	24
51	**Tetrahedron Letters** (1959)	EGF	C	52
52	**Zhurnal Obshchei Khimii** (1869)[4]	R	PC	12
53	**Zhurnal Organicheskoi Khimii** (1965)[4]	R	PC	12
54	Zeitschrift für **Naturforschung, Teil B** (1946)	GE	P	6

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[4] These journals are available in English translation; see Table 2.

[5] These journals also publish review articles.

[6] Former title: **Canadian Journal of Research, Section B.**

[7] Former title: **Berichte der deutschen chemischen Gesellschaft.**

[8] Division of *C. R.* into four sections began in 1966. Series C covers all fields of chemistry. The other series cover physics, geology, etc.

[9] Successor to **Proceedings** of the **Chemical Society**, which appeared from 1957 to 1964.

[10] Beginning with 1966, and until 1971, *J. Chem. Soc.* was divided into three sections, *A*, *B*, and *C*. Starting with 1972, Section *B* became *Perkin Trans. 2*, and Section *C* became *Perkin Trans. 1*. Section *A* (Physical and Inorganic Chemistry) was further divided into *Faraday* and *Dalton Transactions*.

[11] *Pure Appl. Chem.* publishes IUPAC reports and lectures given at IUPAC meetings.

TABLE 2 Journals from Table 1 which are available in English translation
The numbers are keyed to those of Table 1; the year of first translation is given in parentheses

2. Angewandte Chemie, International Edition in English (1962)
18. Doklady Chemistry (English Translation) (1956)
24. Bulletin of the Academy of Sciences of the USSR, Division of Chemical Science (1952)
52. Journal of General Chemistry of the USSR (1949)
53. Journal of Organic Chemistry USSR (1965)

of the patents granted (on the order of 20 to 30%) are chemical patents. Chemical patents are part of the chemical literature, and both U.S. and foreign patents are regularly abstracted by *Chemical Abstracts*. In addition to learning about the contents of patents from this source, chemists may consult the *Official Gazette* of the U.S. Patent Office, which, published weekly and available in most libraries, lists titles of all patents issued that week. Bound volumes of all U.S. patents are kept in a number of large libraries, including the New York Public Library, which also has an extensive collection of foreign patents. Photocopies of any U.S. patent and of most foreign patents can be obtained at low cost from the U.S. Patent Office, Washington, D.C., 20231. In addition, *Chemical Abstracts* lists, in the introduction to the first issue of each volume, instructions for obtaining patents from 26 countries. The same compound or method is often patented in several countries. In such cases, *CA* abstracts only the first patent but relates the numbers of similar patents in a *patent concordance*, carried in each issue.

Although patents are often very useful to the laboratory chemist, and no literature search is complete which neglects relevant patents, as a rule they are not so reliable as papers. There are two reasons for this:

1. It is in the interest of the inventor to claim as much as possible. Therefore he may, for example, actually have carried out a reaction with ethanol and with 1-propanol, but he will claim all primary alcohols, and perhaps even secondary and tertiary alcohols, glycols, and phenols. An investigator repeating the reaction on an alcohol which the inventor did not use may find that the reaction gives no yield at all. In general, it is safest to duplicate the *actual examples* given, of which most chemical patents contain one or more.

2. Although legally a patent gives an inventor a monopoly, it is up to him to protect any alleged infringements in court, and this may cost a good deal of money. Therefore some patents are written so that certain essential details are concealed or entirely omitted. This practice is not exactly cricket, because a patent is supposed to be a full disclosure, but patent attorneys are generally skilled in the art of writing patents, and procedures given are not always sufficient to duplicate the results.

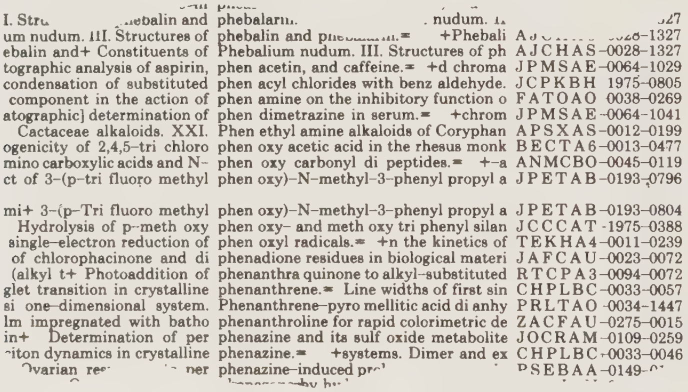
Fortunately, the above statements do not apply to all chemical patents: many make full disclosures and claim only what was actually done. It must also be pointed out that it is not always possible to duplicate the work reported in *every* paper in a journal. In general, however, the laboratory chemist must be more wary of patents than of papers.

SECONDARY SOURCES

Journal articles and patents contain virtually all of the original work in organic chemistry. However, if this were all—if there were no indexes, guides, review articles, and other secondary sources—the literature would be unusable, because it is so vast that no one could hope to find anything in particular. Fortunately, the secondary sources are excellent. They are of various kinds, and the categories tend to merge. Our classification is somewhat arbitrary.

Listings of Titles

The profusion of original papers is so great that publications which merely list the titles of current papers find much use. Such lists are primarily methods of alerting the chemist to useful papers published in journals which he does not normally read. There are two "title" publications covering the whole of chemistry. One of these, *Current Contents Physical and Chemical Sciences,*[12] which began in 1967 and appears weekly, contains the contents pages of all issues of about 700 journals in chemistry, physics, mathematics, and allied sciences. Russian titles are translated into English, but the titles of German and French papers are mostly given in the original. Each issue contains an author index, which, however, lists only the first-named author of each paper. The author's address is also given, so that one may write for reprints. The other "title" publication is *Chemical Titles*, begun in 1961, which is published by Chemical Abstracts Service and is produced by a computer. This biweekly publication lists titles from about 710 chemical journals. All the titles are given in English. The most useful aspect of this publication is the way the titles are given. They are listed in alphabetical order of *every word in the title*, except for such words as "the," "of," "investigation," "synthesis," etc. (each issue contains a list of words prevented from indexing). This means that a title containing seven significant words is listed seven times. Furthermore, at each listing are given the words which immediately precede and follow the alphabetically listed word (called the *keyword*). For example, two short portions of the issue of July 14, 1975, appear thus:



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I. Stru         ebalin and  phebalarn.                 nudum.                     327
um nudum. III. Structures of  phebalin and ph          +Phebali  A                 -1327
ebalin and+ Constituents of  Phebalium nudum. III. Structures of ph  AJCHAS-0028-1327
tographic analysis of aspirin,  phen acetin, and caffeine.= +d chroma  JPMSAE-0064-1029
condensation of substituted  phen acyl chlorides with benz aldehyde.  JCPKBH 1975-0805
 component in the action of  phen amine on the inhibitory function o  FATOAO 0038-0269
atographic] determination of  phen dimetrazine in serum.=  +chrom  JPMSAE-0064-1041
  Cactaceae alkaloids. XXI.  Phen ethyl amine alkaloids of Coryphan  APSXAS-0012-0199
ogenicity of 2,4,5-tri chloro  phen oxy acetic acid in the rhesus monk  BECTA6-0013-0477
mino carboxylic acids and N-  phen oxy carbonyl di peptides.=  +-a  ANMCBO-0045-0119
ct of 3-(p-tri fluoro methyl  phen oxy)-N-methyl-3-phenyl propyl a  JPETAB-0193-0796

mi+ 3-(p-Tri fluoro methyl  phen oxy)-N-methyl-3-phenyl propyl a  JPETAB-0193-0804
  Hydrolysis of p-meth oxy  phen oxy- and meth oxy tri phenyl silan  JCCCAT-1975-0388
 single-electron reduction of  phen oxyl radicals.=  +n the kinetics of  TEKHA4-0011-0239
 of chlorophacinone and di  phenadione residues in biological materi  JAFCAU-0023-0072
 (alkyl t+ Photoaddition of  phenanthra quinone to alkyl-substituted  RTCPA3-0094-0072
glet transition in crystalline  phenanthrene.= Line widths of first sin  CHPLBC-0033-0057
si one-dimensional system.  Phenanthrene-pyro mellitic acid di anhy  PRLTAO-0034-1447
lm impregnated with batho  phenanthroline for rapid colorimetric de  ZACFAU-0275-0015
in+  Determination of per  phenazine and its sulf oxide metabolite  JOCRAM-0109-0259
iton dynamics in crystalline  phenazine.=   +systems. Dimer and ex  CHPLBC-0033-0046
  varian re             per  phenazine-induced pr                  PSEBAA-0149-
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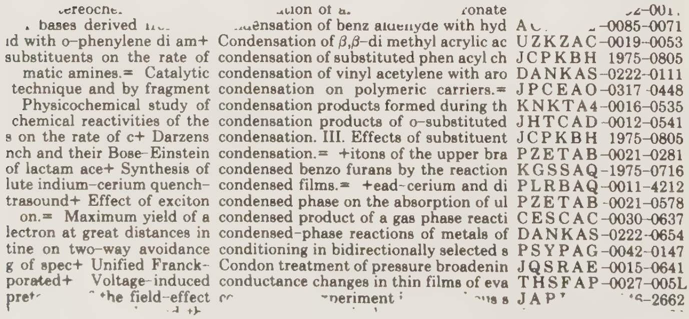

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  ereoche                     tion of                     onate                  -001
   bases derived            ensation of benz aldehyde with hyd  A               -0085-0071
id with o-phenylene di am+  Condensation of β,β-di methyl acrylic ac  UZKZAC-0019-0053
substituents on the rate of  condensation of substituted phen acyl ch  JCPKBH 1975-0805
   matic amines.= Catalytic  condensation of vinyl acetylene with aro  DANKAS-0222-0111
 technique and by fragment  condensation on polymeric carriers.=  JPCEAO-0317-0448
  Physicochemical study of  condensation products formed during th  KNKTA4-0016-0535
 chemical reactivities of the  condensation products of o-substituted  JHTCAD-0012-0541
s on the rate of c+ Darzens  condensation. III. Effects of substituent  JCPKBH 1975-0805
nch and their Bose-Einstein  condensation.=  +itons of the upper bra  PZETAB-0021-0281
of lactam ace+ Synthesis of  condensed benzo furans by the reaction  KGSSAQ-1975-0716
lute indium-cerium quench-  condensed films.=  +ead-cerium and di  PLRBAQ-0011-4212
trasound+ Effect of exciton  condensed phase on the absorption of ul  PZETAB-0021-0578
  on.=  Maximum yield of a  condensed product of a gas phase reacti  CESCAC-0030-0637
lectron at great distances in  condensed-phase reactions of metals of  DANKAS-0222-0654
tine on two-way avoidance  conditioning in bidirectionally selected s  PSYPAG-0042-0147
g of spec+ Unified Franck-  Condon treatment of pressure broadenin  JQSRAE-0015-0641
porated+   Voltage-induced  conductance changes in thin films of eva  THSFAP-0027-005L
pret         he field-effect  c              periment             s s  JAP              -2662
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[12] Title pages of organic chemistry journals are also carried by *Current Contents Life Sciences*, which is a similar publication covering biochemistry and medicine.

Note that a paper entitled "Darzens Condensation. III. Effects of Substituents on the Rate of Condensation of Substituted Phenacyl Chlorides with Benzaldehyde" is listed under *phenacyl* and under *condensation* (twice). It is also listed under *Darzens*, *rate*, *acyl*, *chlorides*, *benzaldehyde*, and *aldehyde*, making nine listings in all. Certain words (e.g., phenacyl, benzaldehyde) are broken into two or more parts so that additional listings may be obtained. The = sign indicates the end of a title. The value of the index is increased by a "wraparound" feature. If the keyword ends (or begins) the title, what would otherwise be empty space is filled by as many words from the *beginning* (or the end) of the title as will fit. For example, at the entry under the keyword *phenanthrene*, in the above example, appears the title "Line Widths of First Singlet Transition in Crystalline Phenanthrene." The computer has room in front of the keyword only for *glet transition in crystalline*. The remainder of the title, *Line widths of first sin* is therefore placed at the end of the line. Where the wraparound feature is used but the entire title still will not fit, the symbol + is given. This type of listing is called a *Keyword-in-Context* (KWIC) index and is obviously highly useful. For example, anyone interested in thiadiazole or any of its derivatives has only to look it up in *Chemical Titles* to find at once all the papers (in that issue) in which this word appears in the title (the July 14, 1975, issue contains eight such listings). The code number given at each entry refers to the source. For example, for the title on the Darzens condensation, mentioned above, the number is JCPKBH-1975-0805. The symbols have the following meanings: JCPKBH means *J. Chem. Soc., Perkin Trans. 2;* 1975 is the volume number (actually in this instance 1975 is the year, because this journal has no volume numbers); and 0805 is the page number (805). In the second section of each issue (called the Bibliography) the complete titles and the authors are given. Incidentally, this Bibliography duplicates, for the journals which they both cover, the listings in *Current Contents Physical and Chemical Sciences*, since the complete contents of journals are given in order of page number. Each issue of *Chemical Titles* has an author index, covering all authors, not just the first author, but addresses are not given.

Abstracts

Listings of titles are valuable, as far as they go, but they do not tell what is in the paper, beyond the implications carried by the titles. From the earliest days of organic chemistry, abstracts of papers have been widely available, often as sections of journals whose principal interests lay elsewhere.[13] At the present time there are only two publications entirely devoted to abstracts covering the whole field of chemistry. One of these, *Referativnyi Zhurnal, Khimiya*, which began in 1953, is published in Russian and is chiefly of interest to Russian-speaking chemists. The other is *Chemical Abstracts*. This publication, which appears weekly, prints abstracts in English of virtually every paper containing original work in pure or applied chemistry published anywhere in the world. Approximately 14,000 journals are covered, in many languages. In addition, *CA* publishes abstracts of every U.S., Austrian, British, Canadian, French, German, and South African patent of chemical interest, as well as of many patents from 19 other countries. *CA* lists and indexes but does not abstract review articles and books. The abstracts currently appear in 80 sections, of which sections 21 to 34 are devoted to organic chemistry, under such headings as Noncondensed Aromatic Compounds, Heterocyclic Compounds (One Hetero Atom), Terpenoids, etc. Each abstract of a paper begins with a heading which gives (1) the abstract number;[14] (2) the title of the paper; (3) the authors' names as fully as given in the paper; (4) the authors' addresses; (5) the abbreviated name of the journal (see Table 1);[15] (6) the year, volume, issue, and page numbers; and (7) the language of the paper. In earlier years *CA* gave the language only if it differed from the language of the journal title. Abstracts of patents begin with the title, inventor and company (if any), patent number, patent class number, date patent issued, date patent applied for, and number of pages in the patent. The body of the abstract is a concise summary of the information in the paper. For certain common journals, e.g., *J. Am. Chem. Soc.*, *J. Org. Chem.*, *J. Chem. Soc.*, the author's summary (if there is one) is used in *CA* as it appears in the original paper, with perhaps some editing and additional information. Each issue of *CA* contains an author index, a patent number index, a patent concordance (see p. 1147), and a keyword index, similar to the KWIC index of *Chemical Titles* (p. 1149). However, the words in the *CA* keyword index are taken from the titles *and* the texts or contexts of the abstracts. No words are given before the keyword and only two or three after. Of course, these additional words are less necessary here, since the user can immediately refer to the abstract, while in *Chemical Titles* no information is given beyond the title.

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[13] For example, *Chem. Ind. (London)* and *Synthesis* publish abstracts of papers which appear in other journals. In the past, such journals as *J. Am. Chem. Soc.*, *J. Chem. Soc.*, and *Ber.* also did so.

[14] Beginning in 1967. See p. 1151.

[15] These abbreviations are changed from time to time. Therefore the reader may notice inconsistencies.

Chemical Abstracts is, of course, highly useful for "current awareness"; it allows one to read, in one place, abstracts of virtually all new work in chemistry, though its large size puts a limit on the extent of this type of usefulness. *CA* is even more useful as a repository of chemical information, a place for finding out what was done in the past. This value stems from the excellent indexes, which enable the chemist in most cases quickly to ascertain where information is located. From the time of its founding in 1907 until 1961, *CA* published annual indexes.[16] Since 1962 there are two volumes published each year, and a separate index is issued for each volume. For each volume there is an index of subjects, authors, formulas, and patent numbers. Beginning in 1972 the subject index has been issued in two parts, a chemical substance index and a general subject index, which includes all entries which are not the names of single chemical substances. However, the indexes to each volume become essentially superseded as collective indexes are issued. The first collective indexes are ten-year (decennial) indexes, but the volume of information has made five-year indexes necessary in recent years. Collective indexes so far published or planned are:

Coll. index	Subject	Chemical substance	Author	Formula	Patent number
1	1907–1916		1907–1916		
2	1917–1926		1917–1926		1907–1936
3	1927–1936		1927–1936	1920–1946	
4	1937–1946		1937–1946		1937–1946
5	1947–1956		1947–1956	1947–1956	1947–1956
6	1957–1961		1957–1961	1957–1961	1957–1961
7	1962–1966		1962–1966	1962–1966	1962–1966
8	1967–1971		1967–1971	1967–1971	1967–1971
9	1972–1976	1972–1976	1972–1976	1972–1976	1972–1976

Thus a user of the indexes at this time would consult the collective indexes through 1971 or 1976 and the semiannual indexes thereafter.

Beginning with the eighth collective index period, *CA* has published an *Index Guide*. This publication gives structural formulas and/or alternate names for thousands of compounds, as well as many other cross references. It is designed to help the user efficiently and rapidly to find *CA* references to his subjects of interest in the general subject, formula, and chemical substance indexes. There is an *Index Guide* for the eighth collective index, covering 1967–1971. Beginning with 1972, a number of changes were introduced into the *CA* indexing practices, including some nomenclature changes, as well as improvements in content, range, and format. The *Index Guide* for vol. 76 (January-June 1972) is a guide to these changes. Annual cumulative supplements have been issued thereafter, and they will all be cumulated in the vol. 85 *Index Guide*. Thus at this time, a user would consult the 1967–1971 *Index Guide* for the eighth collective index period; while for the ninth collective index period one would consult first the most recent annual *Index Guide Supplement* and then the vol. 76 *Index Guide*.

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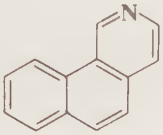
[16] The subject and formula indexes for 1960 and 1961 are each in two parts: January to June, and July to December.

Along with each index (annual, semiannual, or collective) appears an index of ring systems. This valuable index enables the user to ascertain immediately if any ring system appears in the corresponding subject or chemical substance index and under what names. For example, someone wishing to determine whether any compounds containing this ring system



Benz(*h*)isoquinoline

are reported in the 1967–1971 collective index (even if he or she did not know the name) would turn to the listing **6, 6, 6** (since the compound has three rings of six members each), under which he or she would find the sublisting $C_5N—C_6—C_6$ (since one ring contains five carbons and a nitrogen while the others are all-carbon), under which is listed the name benz(*h*)isoquinoline, as well as the names of 37 other systems $C_5N—C_6—C_6$. A search of the subject index under these names will give all references to these ring systems which have appeared in *CA* from 1967 to 1971.

Before 1967, *CA* used a two-column page, with each column separately numbered. A row of letters from *a* to *h* appeared down the center of the page. These letters are for the guidance of the user. Thus an entry 7337*b* refers to the *b* section of column 7337. In early years superscript numbers, e.g., 4327^5, were used in a similar manner. In very early years these numbers were not printed on the page at all, though they are given in the decennial indexes, so that the user must mentally divide the page into nine parts. Beginning with 1967, abstracts are individually numbered, and column numbers are discarded and replaced with page numbers. Therefore, beginning with 1967, index entries give abstract number rather than column number. The abstract numbers are followed by a letter which serves as a check character to prevent miscopying errors in computer handling. To use the *CA* subject, chemical substance, and formula indexes intelligently requires practice, and the student should familiarize himself with representative volumes of these indexes and with the introductory sections to them, as well as with the *Index Guides*.

The indexes today are as complete as the *CA* staff can make them: about one-half of the total *CA* effort goes into indexes. However, in earlier years, especially before 1920, *CA* indexes were not so complete.

CA uses the *Hill system* for its formula indexes: formulas are listed in order of (1) number of carbon atoms; (2) number of hydrogen atoms; and (3) other elements in alphabetical order. Thus, all C_3 compounds are listed before any C_4 compound; all C_5H_7 compounds before any C_5H_8 compound; $C_7H_{11}Br$ before $C_7H_{11}N$; $C_9H_6N_4S$ before C_9H_6O, etc. Deuterium and tritium are represented by D and T and treated alphabetically; e.g., C_2H_5DO after C_2H_5Cl and before C_2H_5F or C_2H_6.

Although *CA* and *Referativnyi Zhurnal, Khimya* are currently the only chemical abstracting publications which cover the entire field of chemistry, there were a number of earlier abstracting publications which have now ceased publication. The most important of these are *Chemisches Zentralblatt* and *British Abstracts*. These publications are still valuable because they began before *CA* and can therefore supply abstracts for papers which appeared earlier than 1907. Furthermore, even for papers published after 1907, *Zentralblatt* and *British Abstracts* are often more detailed. *Zentralblatt* was published, under various names, from 1830 to 1969.[17] *British Abstracts* was a separate publication from 1926 to 1953, but earlier abstracts from this source are available in the *Journal of the Chemical Society* from 1871 to 1925.

Another publication should also be mentioned here. *Current Abstracts of Chemistry and Index Chemicus*, begun in 1960, and appearing weekly, is largely devoted to printing structural formulas of all *new* compounds appearing in about 110 journals, with monthly formula, subject, author, and journal indexes, which are cumulated semiannually and annually.

Beilstein

This publication is so important to organic chemistry that it deserves a section by itself. Beilstein's "Handbuch der organischen Chemie" (in German), usually referred to as *Beilstein*, lists all the known organic compounds which were reported in the literature during its period of coverage. For each compound the following data are given: all names, the molecular formula, the structural formula, all methods of preparation (briefly, e.g., "by refluxing 1-butanol with NaBr and sulfuric acid"), physical constants such as melting point, refractive index, etc., other physical properties, chemical properties including reactions, occurrence in nature (i.e., which species it was isolated from), biological properties if any, derivatives with melting points, analytical data, and any other information which has been reported in the literature. Equally important, for every piece of information, a reference is given to the original literature. Some compounds are discussed in two or three lines, and others require several pages. The value of such a work should be obvious to all.

For many years a degree of training was required in order to use Beilstein, but the publication of a formula index now makes it fairly easy to use. The first three editions are obsolete. The fourth edition (*vierte Auflage*) covers the literature from its beginnings through 1909. This edition, called *das Hauptwerk*, consists of 27 volumes. The compounds are arranged in order of a system which is too elaborate to discuss fully here.[18] The compounds are divided into three divisions which are further subdivided into "systems":

Division	Volumes	System numbers
I. Acyclic compounds	1–4	1–449
II. Carbocyclic compounds	5–16	450–2359
III. Heterocyclic compounds	17–27	2360–4720

Das Hauptwerk is still the basis of Beilstein and has not been superseded. The later literature is covered by supplements, which have been arranged to parallel *das Hauptwerk*. The same system is used, so that the compounds are treated in the same order. The first supplement (*erstes*

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[17] An "obituary" of *Zentralblatt*, by Weiske, which gives its history and statistical data about its abstracts and indexes, was published in the April 1973 issue of *Chem. Ber.* (pp. I–XVI).

[18] An English-language guide to the Beilstein system has recently been published: Weissbach, "A Manual for the Use of Beilstein's Handbuch der Organischen Chemie," Springer-Verlag, New York, 1976. An older work, which many students will find easier to follow, is by Huntress, "A Brief Introduction to the Use of *Beilstein's Handbuch der Organischen Chemie*," 2d ed., John Wiley & Sons, Inc., New York, 1938. For a brief description of the system, see Hendrickson, Cram, and Hammond, "Organic Chemistry," 3d ed., McGraw-Hill Book Company, New York, 1970.

Ergänzungswerk) covers 1910–1919; the second supplement (*zweites Ergänzungswerk*) covers 1920–1929; the third supplement (*drittes Ergänzungswerk*) covers 1930–1949; and the fourth supplement (*viertes Ergänzungswerk*) covers 1950–1959. Like *das Hauptwerk*, each supplement contains 27 volumes,[19] except that supplements 3 and 4 have been combined beginning with vol. 17, so that for vols. 17 to 27 the combined third and fourth supplement covers the years 1930–1959. Each supplement has been divided into volumes in the same way as *das Hauptwerk*, and, for example, compounds found in vol. 3, system number 199, of *das Hauptwerk* will also be found in vol. 3, system number 199, of each supplement.[20] To make cross-referencing even easier, each supplement gives, for each compound, the page numbers at which the same compound may be found in the earlier books. Thus, on page 545 of vol. 6 of the third supplement, under the listing phenetole are found the symbols (H 140; E I 80; E II 142) indicating that earlier information on phenetole is given on page 140 of vol. 6 of *das Hauptwerk*, on page 80 of the first and page 142 of the second supplement. Furthermore, each page of the supplements contains, at the top center, the corresponding page numbers of *das Hauptwerk*. Since the same systematic order is followed in all five series, location of a compound in any one series gives its location in the other four. If a compound is found, for example, in vol. 5 of *das Hauptwerk*, one has but to note the page number and scan vol. 5 of each supplement until that number appears in the top center of the page (of course, the same number may cover several pages). Of course, many compounds are found in only one, two, three, or four of the series, since no work may have been published on that compound during the period covered. Although a given volume of Beilstein is complete to the end of the time period specified, volumes in the second, third, and fourth supplements often contain material which goes considerably beyond that period. For example, p. 3962 of vol. 1 of the fourth supplement (1950–1959) contains references to papers published in 1968 and 1971.

Volumes 28 and 29 of Beilstein are subject and formula indexes, respectively. The most recent complete edition of these volumes is part of the second supplement, and it makes the earlier indexes obsolete, since these indexes are collective: they cover *das Hauptwerk* and the first two supplements. For vol. 1 there is a cumulative subject and a cumulative formula index, which combine *das Hauptwerk* and all four supplements.[20a] It is likely that similar cumulative indexes will be issued for subsequent volumes. For English-speaking chemists (and probably for many German-speaking chemists) the formula indexes are more convenient. Of course, one must still know some German, for most formula listings contain the names of many isomers. If a compound is found only in *das Hauptwerk*, the index listing is merely the volume and page numbers, for example, **1**, 501. Roman numbers are used to indicate the supplements, for example, **26**, 15, I 5, II 7. Thus the subject and formula indexes lead at once to locations in *das Hauptwerk* and the first two supplements (and, for vol. 1, for the third and fourth supplements as well). Locating the compound in the third and fourth supplements is then simple (if that volume has already appeared) by the page-number indication mentioned above. However, the most recent edition of vols. 28 and 29 obviously can contain only compounds which have appeared in the literature before 1930. In order to ascertain if a particular compound which is not listed in vol. 28 or 29 is listed in the third and/or fourth supplements, one can follow one of two procedures. Each separately bound portion of each volume of the third and fourth supplements has its own subject and formula indexes, and several of the volumes have cumulative subject and formula indexes as well (for all the parts of one or two volumes).[21] If one knows (from an approximate knowledge of the system) in which volume the compound is likely to be found, the searcher can turn to the indexes of that volume or (with a little extra labor) can look in all the indexes. The other procedure is to learn the system—which was done by most organic chemists before the appearance of the original formula index.[18] Even an approximate knowledge of the system often helps. Like *CA*, the formula index of Beilstein uses the Hill system for arrangement of formulas (see p. 1151).[22]

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[19] In some cases, to keep the system parallel and to avoid books which are too big or too small, volumes are issued in two or more parts, and, in other cases, two volumes are bound as one.

[20] The fourth supplement (which will eventually cover vols. 1 to 16), and the combined third and fourth supplements (which will cover vols. 17 to 27) are not yet complete. At this writing portions of vol. 2 of the former and vol. 18 of the latter are the latest to have appeared.

[20a] Most page number entries in the combined indexes for vol. 1 contain a letter, e.g., $CHBr_2Cl$ 67f, II 33a, III 87d, IV, 81. These letters tell where on the page to find the compound and are useful because the names given in the index are not necessarily those used in the earlier series. The letter a means the compound is the first on its page, b is the second, etc. No letters are given for the fourth supplement.

There is also a fourth division of Beilstein (systems 4721 to 4877) which covers natural products of uncertain structure: rubbers, sugars, etc. These are treated in vols. 30 and 31, which do not go beyond 1935 and which are covered in the collective indexes. No supplements to them have appeared.

Compendia and Tables of Information

In addition to Beilstein, there are many other reference works in organic chemistry which are essentially compilations of data. These books are very useful and often save the research worker a great deal of time. In this section we discuss some of the more important of such works.

1. Some years ago a work was announced which was to be the English equivalent of Beilstein: Elsevier's "Encyclopedia of Organic Chemistry." Three volumes were published, in more than 15 parts: vol. 12, bicyclic compounds; vol. 13, tricyclic compounds; and vol. 14, tetra- and higher-cyclic compounds. These volumes cover many natural products, especially terpenes and steroids. Although the production of the earlier volumes in the series has now been abandoned, these volumes remain valuable.

2. The fourth edition of the "Dictionary of Organic Compounds" (editorial board: Heilbron, Cook, Bunbury, and Hey), 5 vols., Oxford University Press, New York, 1965, contains brief listings of more than 40,000 organic compounds, giving names, structural formulas (in cases where there might be doubt), physical properties and derivatives, with references. For many entries additional data concerning occurrence and biological activity are also given. The arrangement is alphabetical. Annual supplements have appeared since 1965. The Fifth Cumulative Supplement (1969) combines the first five supplements, and the Tenth Cumulative Supplement (1974) combines the next five. A formula index to the main work and the Fifth Cumulative Supplement appeared in 1971.

3. A multivolume compendium of physical data is Landolt-Börnstein's "Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik, und Technik," 6th ed., Springer-Verlag OHG, Berlin, 1950–. This compendium, which is not yet complete, lists a great deal of data, some of which are of interest to organic chemists, e.g., indexes of refraction, heats of combustion, optical rotations, and spectral data. Literature references are given for all data.

4. "The Handbook of Chemistry and Physics," Chemical Rubber Publishing Company, Cleveland, Ohio (fondly called the "rubber handbook"), which is revised annually (55th ed., 1974–1975), is a valuable repository of data quickly found. For organic chemists the most important table is "Physical Constants of Organic Compounds," which lists names, formulas, color, solubilities, and physical properties of thousands of compounds and occupies nearly half of the volume. However, there are many other useful tables. A similar work is Lange's "Handbook of Chemistry," 11th ed., McGraw-Hill Book Company, New York, 1973.

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[21] The third supplement has cumulative indexes for vol. 5, vol. 6, vols. 7–8, vols. 9–10, and vols. 12–14. The subject indexes for vols. 7–8, 9–10, 11, and 12–14 are in English as well as German.

[22] The now obsolete formula index to the first supplement (which included *das Hauptwerk*) uses another system, called the *Richter system*, in which formulas are listed according to how many different elements they contain.

5. A list of most of the known natural compounds, e.g., terpenes, alkaloids, carbohydrates, to which structures have been assigned, along with structural formulas, melting points, optical rotations, and references, is provided in Devon and Scott, "Handbook of Naturally Occurring Compounds," 3 vols., Academic Press, Inc., New York, 1972–. Supplements are planned.

6. Dreisbach, "Physical Properties of Chemical Compounds," Advances in Chemistry Series nos. 15, 22, 29, American Chemical Society, Washington, D.C., 1955–1961, lists many physical properties of more than 1000 organic compounds.

7. Physical properties of thousands of organometallic compounds, with references, are collected in three large compendia: Dub, "Organometallic Compounds," 2d ed., 3 vols. with supplements and index, Springer-Verlag, New York, 1966–1975; Hagihara, Kumada, and Okawara, "Handbook of Organometallic Compounds," W. A. Benjamin, Inc., New York, 1968; and Kaufman, "Handbook of Organometallic Compounds," D. Van Nostrand Company, Inc., Princeton, N.J., 1961.

8. "The Merck Index of Chemicals and Drugs," 9th ed., Merck and Company, Rahway, N.J., 1976, is a good source of information about chemicals of medicinal importance. Many drugs are given three types of name: *chemical name* (which is the name an organic chemist would give it; of course, there may well be more than one); *generic name*, which must be placed on all containers of the drug; and *trade names*, which are different for each company which markets the drug. For example, the generic name for 1-(4-chlorobenzhydryl)-4-methylpiperazine dihydrochloride is chlorcyclazine hydrochloride. Among the trade names for this drug, which is an antihistamine, are Trihistan, Perazil, and Diparalene. The "Merck Index" is especially valuable because it gives all known names of all three types for each compound, and the names are cross-indexed. The index also gives, for each compound, the structural formula, physical properties, medicinal and other uses, toxicity indications, and references to methods of synthesis. The "Merck Index" also includes a lengthy list of organic name reactions, with references, as well as miscellaneous tables.

9. There are two publications which list properties of azeotropic mixtures. Timmermans, "The Physico-Chemical Constants of Binary Systems in Concentrated Solutions," 4 vols., Interscience Publishers, Inc., New York, 1959–1960, with supplements beginning 1965, is by far the more comprehensive. The other is "Azeotropic Data," 2 vols., Advances in Chemistry Series no. 6 and no. 35, American Chemical Society, Washington, D.C., 1952, 1962.

10. Calculated boiling points at many pressures are given for many compounds in Dreisbach, "Pressure-Volume-Temperature Relationships of Organic Compounds," McGraw-Hill Book Company, New York, 1952.

11. A useful source of derivative melting points is "Handbook of Tables for Organic Compound Identification," 3d ed., Chemical Rubber Publishing Company, Cleveland, Ohio, 1967.

12. Thousands of dipole moments, with references, are collected in McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Company, San Francisco, 1963.

13. "Tables of Interatomic Distances and Configurations in Molecules and Ions," London Chemical Society Special Publication no. 11, 1958, and its supplement, Special Publication no. 18, 1965, include bond distances and angles for hundreds of compounds, along with references.

14. "The Ring Index," American Chemical Society, Washington, D.C., 1960, with supplements beginning 1963, lists, in a systematic order, names and formulas of all ring systems in the literature. References are given for each system.

15. The Sadtler Research Laboratories publish large collections of ir, uv, nmr, and other spectra, in loose-leaf form. Indexes are available.

16. Infrared, uv, nmr, Raman, and mass spectral data, as well as melting-point, boiling-point, solubility and density data, for 21,000 organic compounds are collected in the "Atlas of Spectral Data and Physical Constants for Organic Compounds," 2d ed., 6 vols., CRC Press, Cleveland, Ohio, 1973, edited by Grasselli and Ritchey. It differs from the Sadtler collection in that the data are given in tabular form (lists of peaks) rather than reproductions of the actual spectra, but this book has the advantage that all the spectral and physical data for a given compound appear on one line. References are given to the Sadtler and other collections of spectra. Volumes 5 and 6 contain indexes of spectral peaks for ir, uv, nmr, ^{13}C nmr, mass, and Raman spectra, as well as formula and physical constant indexes.

17. The "Aldrich Library of Infrared Spectra," 2d ed., Aldrich Chemical Company, Milwaukee, Wis., 1975, by Pouchert, contains more than 10,000 ir spectra so arranged that the user can readily see the change which takes place in a given spectrum when a slight change is made in the structure of a molecule.

18. An extensive list of visible and uv peaks is given in "Organic Electronic Spectral Data," Interscience Publishers, New York. Ten volumes have appeared so far, covering the literature through 1968.

19. A collection of 500 ^{13}C nmr spectra is found in Johnson and Jankowski, "Carbon-13 NMR Spectra," John Wiley & Sons, Inc., New York, 1972.

Reviews

A review article is an intensive survey of a rather narrow field; e.g., the titles of some recent reviews are "Advances in Oxazole Chemistry,"[23] "Synthesis of Cyclic Compounds via Copper-Isonitrile Complexes,"[24] and "Chemical Shift Nonequivalence in Prochiral Groups."[25] A good review article is of enormous value, because it is a thorough survey of all the work done in the field under discussion. Review articles are printed in review journals and in certain books. The most important review journals in organic chemistry (though none except *Synthesis* is exclusively devoted to organic chemistry) are, with the year of founding, principal languages, and issues per year:

Accounts of Chemical Research (1968)	E	12
Angewandte Chemie (1888)	G	24
and its English translation:		
Angewandte Chemie, International Edition in English (1962)	E	12
Chemical Reviews (1924)	E	6
Chemical Society Reviews (1947)[26]	E	4
Synthesis (1969)	EG	12
Topics in Current Chemistry (1949)[27]	EG	Irreg.
Uspekhii Khimii (1932)	R	12
and its English translation: **Russian Chemical Reviews** (1960)	E	12

Some of the journals listed on p. 1145, notably the *Bull. Soc. Chim. Fr.*, *Tetrahedron*, and *J. Organomet. Chem.* also publish occasional review articles.

There are several open-ended serial publications which are similar in contents to the review journals but are published irregularly (seldom more often than once a year) and are hardbound. Some of these publish reviews in all fields of chemistry; some cover only organic chemistry; and some specialize further. The coverage is indicated by the titles. When referring to these references, some chemists treat them as books and some as journals (as does *Chemical Abstracts*). In this book we have followed the latter course. Some of the more important such publications, with *CA* abbreviations, are

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[23] Lakhan and Ternai, *Adv. Heterocycl. Chem.* **17**, 99–211 (1974).

[24] Saegusa and Ito, *Synthesis* 291–300 (1975).

[25] Jennings, *Chem. Rev.* **75**, 307–322 (1975).

[26] Successor to *Quarterly Reviews* (abbreviated as *Q. Rev., Chem. Soc.*).

[27] Formerly called **Fortschritte der Chemischen Forschung**.

Advances in **Alicyclic Chem**istry
Advances in **Carbohydr**ate **Chem**istry
Advances in **Catal**ysis
Advances in **Fluorine Chem**istry
Advances in **Free-Radical Chem**istry
Advances in **Heterocycl**ic **Chem**istry
Advances in **Organomet**allic **Chem**istry
Advances in **Org**anic **Chem**istry
Advances in **Photochem**istry
Advances in **Phys**ical **Org**anic **Chem**istry
Advances in **Protein Chem**istry
Essays in **Chem**istry
Fluorine Chemistry **Rev**iews
Fortschritte der **Chem**ie **Org**anischer **Naturst**offe
Mechanisms of **Mol**ecular **Migr**ations
Methods in **Free-Radical Chem**istry
Newer Methods of **Prep**arative **Org**anic **Chem**istry[28]
Organic **Photochem**istry
Organometallic **React**ions
Organic **React**ions
Perspectives in **Struct**ural **Chem**istry
Progress in **Org**anic **Chem**istry
Progress in **Phys**ical **Org**anic **Chem**istry
Progress in **Stereochem**istry
Selective **Org**anic **Transform**ations
Survey of **Prog**ress in **Chem**istry
Topics in **Nonbenzenoid Aromat**ic **Chem**istry
Topics in **Phosphorus Chem**istry
Topics in **Stereochem**istry

There are several publications which provide listings of review articles. One, "Index of Reviews in Organic Chemistry," compiled by Lewis, Chemical Society, London, 1971, is a classified listing of review articles from about 1960 (in some cases much earlier) to about 1970, in alphabetical order of topic. Thus four reviews are listed under "Knoevenagel condensation," five under "Inclusion compounds," and one under "Vinyl ketones." There is no index. Annual supplements have appeared beginning in 1972. Another list of review articles (unclassified, but with author and subject indexes) is found in Kharasch, Wolf, and Harrison, "Index to Reviews, Symposia Volumes, and Monographs in Organic Chemistry," Pergamon Press, New York. Three volumes have so far appeared, covering 1940–1960 (published 1962); 1961–1962 (published 1964); and 1963–1964 (published 1966). Classified lists of review articles on organometallic chemistry are found in articles by Smith and Walton[29] and by Bruce.[30] A similar list for heterocyclic chemistry is found in an article by Katritzky and Weeds.[31]

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[28] This series ceased publication with vol. 6.
[29] Smith and Walton, *Adv. Organomet. Chem.* **13**, 453–558 (1975).
[30] Bruce, *Adv. Organomet. Chem.* **10**, 273–346 (1972), **11**, 447–471 (1973), **12**, 380–407 (1974).
[31] Katritzky and Weeds, *Adv. Heterocycl. Chem.* **7**, 225–299 (1966).

Annual Reviews

The review articles discussed in the previous section are each devoted to a narrow topic covering the work done in that area over a period of years. An annual review is a publication which covers a broad area but limits the period covered, usually to 1 or 2 years.

1. The oldest annual review publication which is still publishing is *Annual Reports on the Progress of Chemistry*, published by the Chemical Society (London), which began in 1905, and which covers the whole field of chemistry. Since 1967, it has been divided into two sections. Organic chemistry is found in Section B.

2. Because the number of papers in chemistry has become so large, the Chemical Society has recently begun to publish annual-review-type volumes of smaller scope, called *Specialist Periodical Reports*. Among those of interest to organic chemists are "Aliphatic Chemistry" (vol. 2 covers 1972); "Aromatic and Heteroaromatic Chemistry" (vol. 2 covers 1972–1973); "Photochemistry" (vol. 5 covers 1972–1973); "Alicyclic Chemistry" (vol. 2 covers 1972); "Carbohydrate Chemistry" (vol. 7 covers 1973); "The Alkaloids" (vol. 4 covers 1972–1973); and "Terpenoids and Steroids" (vol. 4 covers 1972–1973).

3. An annual-review-type publication devoted to the broad field of organic chemistry is the "MTP International Review of Science, Organic Chemistry," published by Butterworth and Company, London, and University Park Press, Baltimore. *Series One*, consisting of 10 volumes plus an index volume, was published in 1973, and covers 1970–1971. Further series are planned, each to cover a 2-year period. The same publishers also publish similar series of volumes devoted to physical and to inorganic chemistry.

4. "Organic Reaction Mechanisms," published by John Wiley & Sons, Inc., New York, is an annual survey which covers the latest developments in the field of mechanisms. The first volume, covering 1965, appeared in 1966.

5. There are two annual reviews devoted to progress in organic synthesis. Theilheimer, "Synthetic Methods of Organic Chemistry," S. Karger Verlag, Basel, is an annual compilation, beginning in 1946, of new methods for the synthesis of organic compounds, arranged according to a system based on bond closings and bond breakings. Equations, brief procedures, yields, and literature references are given. Volume 28 was issued in 1974. Volumes 3 and 4 are available only in German, but all the rest are in English. There is an index to each volume. Cumulative indexes appear in every fifth volume. Beginning with vol. 8, each volume includes a short summary of trends in synthetic organic chemistry. A more recent series is "Annual Reports in Organic Synthesis," Academic Press, Inc., New York, which has covered the literature of each year since 1970. Equations are listed, with yields and references, according to a fairly simple system.

6. The *Journal of Organometallic Chemistry* several times a year publishes annual surveys arranged according to metallic element. For example, vol. 95, published in August 1975, contains annual surveys for 1973 of organic compounds containing Li, Mg, Pb, Cu, Ag, and Au; and for 1974 of organic compounds containing V, Nb, Ta, and the lanthanides and actinides. These annual reviews formerly appeared in *Organometallic Chemistry Reviews, Section B*, which was a separate journal published from 1968 to 1974. Still earlier (for 1964–1966), these reviews were published in book form.

General Treatises

There are a number of large-scale multivolume treatises which cover the whole field of organic chemistry or large areas of it.

1. "Rodd's Chemistry of Carbon Compounds," edited by Coffey, Elsevier Publishing Company, Amsterdam, is a treatise consisting of five main volumes, each of which contains several parts.

Publication began in 1964 and is not yet complete. The organization is not greatly different from most textbooks, but the coverage is much broader and deeper. Supplements to some of the volumes have already appeared. An earlier edition, called "Chemistry of Carbon Compounds," edited by Rodd, was published in 10 parts from 1951 to 1962.

2. Houben-Weyl's "Methoden der organischen Chemie," Georg Thieme Verlag KG, Stuttgart, is a major treatise in German devoted to laboratory methods. The fourth edition, which was begun in 1952 and consists of 16 volumes, some in several parts, is edited by E. Muller. The first four volumes contain general laboratory methods, analytical methods, physical methods, and general chemical methods. The later volumes are devoted to the synthesis of specific types of compounds, e.g., hydrocarbons, oxygen compounds, nitrogen compounds, etc.

3. Grignard's "Traité de chimie organique," 23 vols., Masson et Cie, 2d ed., Paris, 1947–1955, is another treatise which covers the whole field of organic chemistry. The coverage, which is by functional groups, is broad and deep.

4. A major treatise devoted to experimental methods of chemistry is "Techniques of Chemistry," edited by Weissberger, John Wiley & Sons, Inc., New York. This publication, which began in 1970, so far consists of eight volumes, most of them in several parts, covering such topics as electrochemical and spectral methods, kinetic methods, photochromism, and organic solvents. "Techniques of Chemistry" is a successor to an earlier series, called "Techniques of Organic Chemistry," which appeared in 14 volumes, some of them in more than one edition, from 1945 to 1969. The later volumes of this series have not yet been superseded.

5. "Comprehensive Chemical Kinetics," edited by Bamford and Tipper, 1969–, Elsevier Publishing Company, Amsterdam, is a multivolume treatise covering the area of reaction kinetics. Six of these volumes (not all published at the time of writing) deal with the kinetics and mechanisms of organic reactions in a thorough and comprehensive manner.

6. Three multivolume treatises which cover specific areas are Elderfield, "Heterocyclic Compounds," John Wiley & Sons, Inc., New York, 1950–; Manske and Holmes, "The Alkaloids," Academic Press, Inc., New York, 1950–; and Simonson, Owen, Barton, and Ross, "The Terpenes," Cambridge University Press, London, 1947–1957.

Monographs and Treatises on Specific Areas

Organic chemistry is blessed with a large number of books devoted to a thorough coverage of a specific area. Many of these are essentially very long review articles, differing from ordinary review articles only in size and scope. Some of the books are by a single author, and others have chapters by different authors but all are carefully planned to cover a specific area. Many of these books have been referred to in footnotes in appropriate places in this book. Several companies have published series of monographs of which we shall mention four of the most notable.

1. A series of unrelated monographs covering various areas of organic chemistry is published by Academic Press, Inc., New York. Thirty-one titles have been published so far. Typical books in the series are Johnson, "Ylid Chemistry," 1966; Ugi, "Isonitrile Chemistry," 1971; Trost and Melvin, "Sulfur Ylides," 1975; Cram, "Fundamentals of Carbanion Chemistry," 1965; Shamma, "The Isoquinoline Alkaloids," 1972; and Rochester, "Acidity Functions," 1970.

2. Wiley-Interscience publishes a series called "The Chemistry of Functional Groups," under the general editorship of Patai. Each volume deals with the preparation, reactions, and physical and chemical properties of compounds containing a given functional group. Volumes covering 16 functional groups have appeared so far, including books on alkenes, cyano compounds, amines, carboxylic acids and esters, quinones, etc. Several more are planned.

3. A series of monographs on reaction mechanisms is published by the Elsevier Publishing Company. Among the books so far published in this series are Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," 1963; Norman and Taylor, "Electrophilic Substitution in Benzenoid Compounds," 1965; Miller, "Nucleophilic Aromatic Substitution," 1968; Shine, "Aromatic Rearrangements," 1967; and Buncel, "Carbanions," 1974.

4. A series of monographs on "Reactive Intermediates in Organic Chemistry," under the general editorship of Olah, is published by Wiley-Interscience. One or more volumes each on carbonium ions, carbenes, nitrenes, halonium ions, free radicals, and radical ions have already appeared. Other volumes are planned.

Textbooks

There are many excellent textbooks in the field of organic chemistry. We restrict ourselves to listing only a few of those published since 1969. Some of these are first-year texts, and some are advanced (advanced texts generally give references; first-year texts do not, though they may give general bibliographies, suggestions for further reading, etc.); some cover the whole field, and others cover reactions, structure, and/or mechanism only. All the books listed here are not only good textbooks but valuable reference books for graduate students and practicing chemists.

Alder, Baker, and Brown: "Mechanism in Organic Chemistry," Wiley-Interscience, New York, 1971.
Allinger, Cava, De Jongh, Johnson, LeBel, and Stevens: "Organic Chemistry," 2d ed., Worth Publishers, Inc., New York, 1976.
Breslow: "Organic Reaction Mechanisms," 2d ed., W. A. Benjamin, Inc., New York, 1969.
Brown: "Organic Chemistry," Wadsworth Publishing Company, Belmont, Calif., 1975.
Carruthers: "Some Modern Methods of Organic Synthesis," Cambridge University Press, London, 1971.
Ferguson: "Organic Molecular Structure," Willard Grant Press, Boston, 1975.
Gutsche and Pasto: "Fundamentals of Organic Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N.J., 1975.
Harris and Wamser, "Fundamentals of Organic Reaction Mechanisms," John Wiley & Sons, Inc., New York, 1976.
Hendrickson, Cram, and Hammond: "Organic Chemistry," 3d ed., McGraw-Hill Book Company, New York, 1970.
Hirsch: "Concepts in Theoretical Organic Chemistry," Allyn and Bacon, Inc., Boston, 1974.
House: "Modern Synthetic Reactions," 2d ed., W. A. Benjamin, Inc., New York, 1972.
Ingold: "Structure and Mechanism in Organic Chemistry," 2d ed., Cornell University Press, Ithaca, N.Y., 1969.
Le Noble: "Highlights of Organic Chemistry," Marcel Dekker, Inc., New York, 1974.
Lowry and Richardson: "Mechanism and Theory in Organic Chemistry," Harper & Row, New York, 1976.
Morrison and Boyd: "Organic Chemistry," 3d ed., Allyn and Bacon, Inc., Boston, 1973.
Roberts, Stewart, and Caserio: "Organic Chemistry: Methane to Macromolecules," W. A. Benjamin, Inc., New York, 1971.
Solomons: "Organic Chemistry," John Wiley & Sons, Inc., New York, 1976.
Streitwieser and Heathcock: "Introductory Organic Chemistry," The Macmillan Company, New York, 1976.
Sykes: "A Guidebook to Mechanism in Organic Chemistry," 4th ed., John Wiley & Sons, Inc., New York, 1975.
Ternay: "Contemporary Organic Chemistry," W. B. Saunders Company, Philadelphia, 1976.

Other Books

In this section we mention several books which do not fit conveniently into the previous categories. All have to do with laboratory synthesis.

1. *Organic Syntheses*, published by John Wiley & Sons, Inc., New York, is a collection of procedures for the preparation of specific compounds. The thin annual volumes have appeared each year since 1921. The procedures for each 10- (or 9-) year period are collected in cumulative volumes, in this manner:

Annual volumes	Collective volumes
1–9	**I**
10–19	**II**
20–29	**III**
30–39	**IV**
40–49	**V**

The advantage of the procedures in *Organic Syntheses*, compared with those found in original journals, is that these procedures are *tested*. Each preparation is carried out first by its author and then by a member of the *Organic Syntheses* editorial board, and only if the yield is essentially duplicated is the procedure published. While it is possible to repeat most procedures given in journals, this is not always the case. All *Organic Syntheses* preparations are noted in Beilstein and in *CA*. In order to locate a given reaction in *Organic Syntheses*, the reader may use the OS references given in the present volume (through OS **55**); the indexes in *Organic Syntheses* itself; Sugasawa and Nakai; "Reaction Index of Organic Syntheses," John Wiley & Sons, Inc., New York, 1967 (through OS **45**); or Shriner and Shriner, "Organic Syntheses Collective Volumes I, II, III, IV, V Cumulative Indices," John Wiley & Sons, Inc., New York, 1976. A similar publication is *Organic Photochemical Syntheses*, also published by John Wiley & Sons, Inc.; vol. 1 appeared in 1971.

2. Volume 1 of "Reagents for Organic Synthesis," by Fieser and Fieser, John Wiley & Sons, Inc., New York, 1967, is a 1457-page volume which discusses, in separate sections, some 1120 reagents and catalysts. It tells how each reagent is used in organic synthesis (with references) and, for each, tells which companies sell it, or how to prepare it, or both. The listing is alphabetical. Four additional volumes have so far been published, which continue the format of vol. 1, and add more recent material.

3. "Survey of Organic Synthesis," by Buehler and Pearson, John Wiley & Sons, Inc., New York, 1970, discusses hundreds of reactions used to prepare the principal types of organic compounds. The arrangement is by chapters, each covering a functional group, e.g., ketones, acyl halides, amines, etc. Each reaction is thoroughly discussed and brief synthetic procedures are given. There are many references.

4. A similar publication is Sandler and Karo, "Organic Functional Group Preparations," 3 vols., Academic Press. Inc., 1968–1972 (part of the series of Academic Press monographs mentioned on p. 1159). This publication covers more functional groups than Buehler and Pearson.

5. An older book of a similar type is "Synthetic Organic Chemistry," by Wagner and Zook, John Wiley & Sons, Inc., New York, 1953, which discusses, in separate numbered sections, the scope and limitations of 576 reactions, divided into 39 chapters, each of which covers the preparation of a specific type of compound, e.g., olefins, cyanides, lactones. An important and useful feature of the book is the large number of tables which list the best method of preparation, the yield, and physical constants, for thousands of compounds containing no more than two functional groups. References are given for all data.

6. "Compendium of Synthetic Methods," by Harrison and Harrison, John Wiley & Sons, Inc., New York, contains equations describing the preparation of about 4000 monofunctional and difunctional compounds, with references. Two volumes have been published so far (1971, 1974).

7. Two books which are rich in experimental procedures, both translated from the German, are Weygand and Hilgetag, "Preparative Organic Chemistry," edited by Hilgetag and Martini, John Wiley & Sons, Inc., New York, 1972; and Becker et al., "Organicum," translated by Hazzard, Addison-Wesley Publishing Company, Inc., Reading, Mass., 1973.

LITERATURE SEARCHING

Information about a Specific Compound

Most organic chemists find it necessary, occasionally or frequently, to search the literature for information concerning specific compounds. They may need to know if a compound has ever been prepared and if so, how, and/or they may be seeking a melting point, an ir spectrum, or some other property. The directions for this particular type of literature search are so much more specific than for other searches that we discuss them first. Someone who wants all the information that has ever been published on any compound begins by consulting the formula index to the second supplement of Beilstein (p. 1153), which quickly shows whether the compound is mentioned in the literature through 1929. If it is there, the searcher turns to the pages indicated, where all methods used to prepare the compound are given, as well as all physical properties, with references. If the compound is in a volume of Beilstein of which the third and/or fourth supplement has been published, it may be found there, by the method described on p. 1153. If the compound is not listed in the cumulative formula index (and is thus absent from the literature through 1929), the next step is to ascertain whether it is in the third or fourth supplement, which is done as described on p. 1154. If the compound is in vol. 1, for which a cumulative formula index is already available, much of this labor is unnecessary, since this index will give, in one place, the Beilstein locations in *das Hauptwerk* and all four supplements. At this point the investigator will know (1) all information published through 1959,[32] 1949,[33] or 1929,[34] or (2) that the compound is not mentioned in the literature through 1959,[32] 1949,[33] or 1929.[34] In some cases, scrutiny of Beilstein will be sufficient, perhaps if only a boiling point or a refractive index is required. In other cases, especially where specific laboratory directions are needed, the investigator will have to turn to the original papers.

To carry the search past 1929 (or 1949 or 1959), the chemist next turns to the collective formula indexes of *Chemical Abstracts:* 1920–1946; 1947–1956 (if these periods were not covered by Beilstein); 1957–1961; 1962–1966; 1967 1971; 1972–1976; such later collective indexes as have appeared; and the semiannual indexes thereafter. If a given formula index contains only a few references to the compound in question, the pages or abstract numbers will be given directly in the formula index. However, if there are many references, the reader will be directed to see the chemical substance index or (before 1972) the subject index for the same period; and here the number of page or abstract numbers may be very large indeed. Fortunately, numerous subheadings are given, and these often help the user to narrow the search to the more promising entries. Nevertheless, one will undoubtedly turn to many abstracts which do not prove to be helpful. In many cases, the information in the abstracts will be sufficient. If not, the original references must be consulted. In some cases (the index entry is marked by an asterisk or a double asterisk) the compound is not mentioned in the abstract, though it is in the original paper or patent. Incidentally, all entries in the *CA* indexes which refer to patents are prefixed by the letter P. Since 1967, the prefixes B and R have also been used, to signify books and reviews, respectively. Since 1965, each compound listed in any index of *CA* has carried a *CAS registry number*. This is a number, generated by a computer, which is assigned to each distinctly definable chemical entity and remains invariant, no matter what names are used in the literature. The registry numbers greatly facilitate computer searching. So far registry numbers have been assigned to more than 3 million substances.

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[32] For compounds which would naturally belong to a volume for which the fourth or combined third-fourth supplement has already been published.

[33] For compounds which would naturally belong to a volume for which the third supplement has been published but not the fourth.

[34] For compounds which would naturally belong to a volume for which the combined third-fourth supplement has not yet been published.

By the procedure outlined above, all information regarding a specific compound which has been published up to about a year before the search can be found by a procedure which is always straightforward and which in many cases is rapid (if the compound has been reported only a few times). Equally important, if the compound has not been reported, the investigator will know that, too. It should be pointed out that, for common compounds, such as benzene, ether, acetone, etc., trivial mentions in the literature are not indexed (so that they will not be found by this procedure), only significant ones. Thus, if acetone is converted to another compound, an index entry will be found, but not if it is used as a solvent or an eluent in a common procedure.

There are several methods for learning whether a compound is mentioned in the literature after the period covered by the latest semiannual formula index of *CA*. One may consult *Chemical Titles* and the KWIC index (p. 1150) at the end of each issue of *CA*. In these cases, of course, it is necessary to know what name might be used for the compound. The name is not necessary for *Current Abstracts of Chemistry and Index Chemicus* (p. 1152); one consults the monthly formula indexes. However, these methods are far from complete. *Current Abstracts of Chemistry and Index Chemicus* lists primarily *new* compounds, those which would not have been found in the earlier search. As for *Chemical Titles*, the compound can be found only if it is mentioned in the title. The KWIC indexes in *CA* are more complete, being based on internal subject matter as well as title, but they are by no means exhaustive. Furthermore, all three of these publications lag some distance behind the original journals, though *Chemical Titles* is very close. There is no method for the *complete* location of all references to a compound after the period covered by the latest semiannual formula index of *CA*.

The complete procedure described above may not be necessary in all cases. Often all the information one needs about a compound will be found in one of the handbooks (p. 1154), in the "Dictionary of Organic Compounds" (p. 1154), or in one of the other compendia listed in this chapter, most of which give references to the original literature.

Other Searches[35]

There is no definite procedure for making other literature searches. If a chemist wishes to know all that is known about the mechanism of the reaction between aldehydes and HCN, or which compounds of the general formula Ar_3CR have been prepared, or which are the best catalysts for Friedel-Crafts acylation of naphthalene derivatives with anhydrides, or where the group $C(NH_2){=}NH$ absorbs in the ir, he or she is dependent on his or her ingenuity and knowledge of the literature. If a specific piece of information is needed, he or she may be able to find it in one of the compendia mentioned previously. If the topic is more general, it is often the best procedure to begin by consulting one or more monographs, treatises, or textbooks, which will give general background information and often provide references to review articles and to original papers. For example, Olah's treatise on Friedel-Crafts reactions (Ref. 166 in Chapter 11) should certainly be consulted on the Friedel-Crafts topic mentioned above. In many cases this is sufficient, but when a complete search is required, it is necessary to consult the *CA* subject and/or chemical substance indexes, where the ingenuity of the investigator is most required, for now it must be decided which words to look under. If one is interested in the mechanism of the reaction between aldehydes and HCN, one might look under "aldehydes," or "hydrogen cyanide"; or even under "acetaldehyde" or "benzaldehyde," etc., but then the search is likely to prove long. A better choice in this case would be "cyanohydrin," since these are the normal products, and references there would be fewer. It would probably be a waste of time to look under "mechanism." In any case, many of the abstracts would prove not to be helpful. Literature searching of this kind is necessarily a wasteful process. Of course, the searcher would not consult the *CA* annual indexes but only the collective indexes as far as they go and the semiannual indexes thereafter. If it is necessary to search before 1907 (and even before 1920, since *CA* was not very complete from 1907 to about 1920), recourse may be made to *Chemisches Zentralblatt* (p. 1152) and to the abstracts in the *Journal of the Chemical Society* (p. 1152).

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[35] This discussion is necessarily short. For much more extensive discussions, see Mellon, Ref. 1, pp. 218–229; Crane, Patterson, and Marr, Ref. 1, pp. 297–325.

Science Citation Index

A publication which can greatly facilitate literature searching is the computer-produced *Science Citation Index* (*SCI*), begun in 1961. This publication, which is quite different from any other mentioned in this chapter, gives a list of all papers in a given year which have cited a given paper, patent, or book. Its utility lies in the fact that it enables the user to search *forward* from a given paper or patent, rather than backward, as is usually the case. For example, suppose a chemist is familiar with a paper by Corey, Weinshenker, Schaaf, and Huber [*J. Am. Chem. Soc.* **91,** 5675 (1969)] entitled "Stereo-controlled Synthesis of Prostoglandins $F_{2\alpha}$ and E_2 (*dl*)." The chemist is easily able to begin a search for earlier papers by using references supplied in this paper and can then go further backward with the aid of references in those papers, etc. But for obvious reasons the paper itself supplies no way to locate *later* papers. *SCI* is designed to make up for this gap. The citation index of *SCI* lists all papers, patents, or books cited in a given year or quarter (by first author only) and then gives a list of papers which have done the citing. The index is published quarterly and cumulated annually. For example, column 7226 of the 1974 *Citation Index* shows that the Corey paper mentioned above was cited as a footnote in 19 papers published in 1974 or late 1973. It is reasonable to assume that most of the papers which cited the Corey paper were on closely related subjects. For each of the 19 papers are listed the first author, journal abbreviation, volume and page numbers, and year. In a similar manner, if one consulted *SCI* for all the years from 1969 on, one would have a complete list of all papers which cited that paper. One could obviously broaden the search by then consulting *SCI* (from 1974 on) for papers which cited these 19 papers and so on. Papers, patents, or books listed, for example, in the 1974 *SCI* may go back many years; e.g., a paper published by Einstein in 1906 is included. The only requirement is that a paper published in 1974 (or late 1973) has mentioned the earlier paper in a footnote. The arrangement of cited papers or books is alphabetical by cited first author and then by cited year. The arrangement of patents is by country and then by patent number.

SCI covers about 2500 journals in the physical and biological sciences, as well as in medicine, agriculture, technology, and the behavioral sciences. In addition to the Citation Index, each quarterly and annual *SCI* also includes three other indexes. One of these, called *Source Index*, is similar to the *CA* author index. It lists the titles, journal abbreviations, column and page numbers, and year, of all papers published by a given author during that quarter or year. All authors are listed; not just first authors. The second, called the *Corporate Index*, lists all publications which have been published from a given institution during that period, by first author. Thus the *Corporate Index* for 1974 lists 25 papers by 21 different first authors emanating from the Saratov State University, Saratov, USSR. However, it is necessary to be careful in using the *Corporate Index*, since slight differences in the way the addresses were originally given in the journals cause the institution to be listed in different places. Thus, the 1974 *Corporate Index* has separate listings for Univ. Massachusetts, Chem. Dept., Amherst, Mass., 01002, USA; Univ. Massachusetts, Dept. Chem., Amherst, Mass., 01002, USA, and Univ. Massachusetts, Dept. Chem., Amherst, Mass., USA. The third index included in *SCI* is the *Permuterm*[36] *Subject Index*. This index alphabetically lists every significant word in the titles of all papers published in that year or quarter, paired with all other significant words in the same title. Thus, for example, a title with 7 significant words will appear at 42 separate places in the index. Each of the 7 words appears 6 times as the main word, each time paired with a different word as the co-word. The user is then led to the *Source Index*, where the full reference is given.

The publishers of *SCI* also produce another publication, called *Index to Scientific Reviews*, which appears semiannually (the second issue of each year cumulates the first). This publication, which began in 1974, is very similar to *SCI*, but confines itself to listing citations to review articles. The citations come from about 2500 journals in the same general areas as are covered by *SCI*. The review articles cited appeared in about 150 review journals and books, as well as in those journals which publish occasional review articles. Like *SCI*, the *Index to Scientific Reviews* contains citation, source, corporate, and Permuterm indexes.

How to Locate Journal Articles

Having obtained a reference from Beilstein, *SCI*, *CA*, a treatise, or some other source, one often needs to consult the original journal (the location of patents is discussed on p. 1147). The first step is to ascertain the full name of the journal, since it is the abbreviation which is generally given. Of course, everyone should be familiar with the abbreviations of the very important journals, such as *J. Org. Chem.*, *Chem. Ber.*, etc., but references are often found to journals whose titles are not at all familiar (e.g., *K. Skogs Lantbruksakad. Tidskr.* or *Nauchn. Tr. Mosk. Lesotekh. Inst.*). In such cases, one consults the *Chemical Abstracts Service Source Index* (*CASSI*), which contains the names of all of the journals covered by *CA* from 1907 to 1974 (even those which are no longer published), with the most recent abbreviations in bold print. The journals are listed in alphabetical order of the *abbreviations*, not of the titles. Journal title changes have not been infrequent, and *CASSI* also contains all former names, with cross references to the current names. Quarterly supplements to *CASSI* have appeared since 1975, listing new journals and recent changes in journal titles. It should be pointed out that, while many publications use the *CA* abbreviations, not all do. The student will find that usages vary from country to country, and even from journal to journal within a country. Furthermore, the *CA* abbreviations change from time to time.

Once the complete title is known, the journal can easily be obtained if it is in the library customarily used by the chemist. If not, one must use another library, and the next step is to find out which libraries carry the journal. *CASSI* answers this question too, since it carries a list of some 398 libraries in the United States and foreign countries, and *for each journal it tells which of these libraries carries it*, and furthermore, if the holdings are incomplete, which volumes of that journal are carried by each library. It may be possible to visit the closest library personally. If not, many of these libraries maintain one or more of the following services: lending, microfilms, photocopying; and a copy of the article may be obtained in one of these ways, photocopying being most common. Photocopies of original Russian articles can be obtained from Chemical Abstracts Service, The Ohio State University, Columbus, Ohio, 43210.

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[36] Registered trade name.

Appendix B

Classification of Reactions by Type of Compound Synthesized

Acetals and Ketals

0-14 Reaction between alkoxides and *gem*-dihalides (Williamson)
0-19 Transetherification
0-80 Reduction of ortho esters
0-84 Reduction of mesylate esters
0-92 Reaction between Grignard reagents and ortho esters
5-5 Addition of alcohols or phenols to triple bonds
5-48 Addition of acetals to vinyl ethers
6-4 Alcoholysis of nitro compounds
6-6 Addition of alcohols to aldehydes or ketones
6-54 Addition of aldehydes to olefins (Prins)
6-60 Trimerization and polymerization of aldehydes

Acetylenes (*see* Alkynes)

Acids (*see* Carboxylic Acids, Sulfonic Acids)

Acylals

5-6 Addition of acids to alkynes
6-58 Acylation of aldehydes or ketones
9-15 Bisdecarboxylation of malonic acids
9-17 Oxidation of arylmethanes with CrO_3 and Ac_2O

Acyl Halides

0-75 Reaction between acids and inorganic acid halides
0-76 Conversion of acid derivatives to acyl halides
4-3 Halogenation of aldehydes
4-23 Chlorocarbonylation of alkanes
5-1 Addition of hydrogen halides to ketenes
5-23 Free-radical addition of acyl halides to olefins
5-38 Reaction between olefins, carbon monoxide, and $PdCl_2$

Acyloins (*see* Hydroxy Aldehydes and Ketones)

Alcohols (*see also* Diols, Hydroxy Esters, etc.)

0-1 Hydrolysis of alkyl halides
0-4 Hydrolysis of inorganic esters
0-5 Diazotization of primary aliphatic amines
0-7 Hydrolysis of vinyl ethers, acetals, or ortho esters
0-11 Hydrolysis of esters
0-13 Decarbonylation of acids
0-19 Transetherification
0-25 Transesterification
0-30 Reaction between acids and esters
0-54 Ammonolysis of esters
0-68 Cleavage of ethers with concentrated acids
0-80 Reduction of acetals or ortho esters
0-81 Reduction of epoxides
0-92 Cleavage of acetals or ortho esters with Grignard reagents
0-93 Reaction between Grignard reagents and epoxides
0-118 Hydrolysis of sulfonic esters
1-13 Alkylation of aromatic rings with ethylene oxide
1-25 Hydroxyalkylation of aromatic rings
2-22 Reaction between Grignard reagents and oxygen
4-4 Hydroxylation at an aliphatic carbon
5-2 Hydration of olefins
5-15 Hydroboration-oxidation of alkenes
5-16 Oxidation of alanes
5-20 Addition of organometallic compounds to unsaturated alcohols
5-23 Free-radical addition of alcohols to olefins
6-27 Reduction of aldehydes or ketones
6-31 Addition of Grignard reagents to aldehydes or ketones
6-34 Addition of Grignard reagents to esters or acyl halides

6-54 Reaction between aldehydes, olefins, and sodium
7-2 Alkaline cleavage of ethers
7-41 Reaction of N-substituted amides with certain catalysts
8-1 Rearrangement of alcohols or olefins (Wagner-Meerwein)
8-3 Expansion and contraction of rings (Demyanov)
8-23 Cleavage of methyl ketones with peracids (Baeyer-Villiger)
8-24 Cleavage of hydroperoxides
8-26 Rearrangement of ethers upon treatment with alkyllithiums (Wittig)
8-27 From boranes and CO, or CN^-, or $CHCl_2$-OMe; from boranes and bromine
8-28 From boranes, CO, water, and NaOH
8-29 From boranes, CO, and $LiAlH_4$
8-40 [2,3] sigmatropic rearrangements of allylic ethers or allylic sulfoxides
8-46 Photolysis of hypohalites
9-9 Oxidative cleavage of certain alcohols
9-10 Reduction of ozonides
9-36 Coupling of primary alcohols (Guerbet)
9-40 Reduction of carboxylic acids
9-44 Reduction of esters
9-45 Reduction of carboxylic esters with titanocene dichloride
9-46 Reduction of anhydrides
9-47 Reduction of acyl halides
9-61 Reduction of hydroperoxides
9-64 Reduction of peroxides
9-74 Reaction between aldehydes and base (Cannizzaro)

Aldehydes (*see also* Dicarbonyl Compounds, Unsaturated Carbonyl Compounds, etc.)

0-2 Hydrolysis of *gem*-dihalides
0-4 Hydrolysis of vinyl esters of inorganic acids
0-7 Hydrolysis of vinyl ethers, acetals, thioacetals, etc.
0-11 Hydrolysis of vinyl esters
0-83 Reduction of acyl halides
0-84 Reduction of carboxylic acids, esters, or anhydrides
0-85 Reduction of amides
0-97 Alkylation and hydrolysis of imines
0-99 Alkylation and hydrolysis of dithianes
0-100 Alkylation and hydrolysis of oxazines and similar compounds
0-101 Reaction of diazo aldehydes with boranes
0-104 Carbonylation of alkyl halides
0-107 Reaction between formates or formamides and organometallic compounds
0-113 Formylation of carboxylic acid salts
0-117 Reaction between formic acid, another acid, and thorium oxide
1-16 Formylation of aromatic rings with formamides and $POCl_3$ (Vilsmeier)
1-17 Formylation of aromatic rings with carbon monoxide and HCl (Gatterman-Koch)
1-18 Formylation of aromatic rings with HCN and HCl (Gatterman)
1-19 Formylation of aromatic rings with formyl fluoride
1-20 Formylation of aromatic rings with dichloromethyl methyl ether
1-21 Formylation of aromatic rings with chloroform (Reimer-Tiemann)
1-45 Reaction between arylcarbinols and diazonium salts (Stiles-Sisti)
2-31 Carbonylation of organometallic compounds
2-39 Decarboxylation of α-keto or glycidic acids
3-17 Alkylation of aromatic aldehydes
3-27 Rearrangement of aromatic amino sulfides (Sommelet-Hauser)
4-18 Arylation of allylic alcohols
4-21 Formylation of nitrogen heterocycles
4-30 Reaction of diazonium salts with oximes, followed by hydrolysis
5-3 Hydration of acetylene
5-15 Hydrolysis of unsaturated boranes
5-19 Addition of aldehydes to activated olefins (Michael)
5-20 Addition of organometallic compounds to unsaturated aldehydes
5-21 Addition of boranes to unsaturated aldehydes
5-26 Hydroformylation of olefins (oxo process)
6-2 Hydrolysis of imines, oximes, hydrazones, or other C═N compounds
6-4 Hydrolysis of primary nitro compounds (Nef)
6-30 Reduction of nitriles
6-34 Addition of Grignard reagents to formamides
6-36 Reaction of alkyllithium compounds with oxazines and oxazolines
6-42 Reaction of aldehydes or ketones with boron methides
6-76 Hydrolysis of metalated aldimines
7-1 Dehydration of 1,2-diols
7-2 Pyrolysis of vinyl ethers
7-32 Fragmentation of γ-amino or γ-hydroxy halides
7-35 Fragmentation of 1,3-diols or γ-amino alcohols

7-40 Fragmentation of certain ketoximes
7-44 Alkaline hydrolysis of nitrates
7-45 Pyrolysis of β-hydroxy olefins
7-46 Pyrolysis of allyl ethers
8-2 Rearrangements of diols (pinacol)
8-10 Homologization of aldehydes
8-17 Reaction between α-hydroxy or α-halo amides and NaOBr (Hofmann)
8-24 Cleavage of hydroperoxides
8-29 Treatment of boranes with CO and LiAl(OMe)$_3$ or α-lithiated thioacetals
8-46 Photolysis of nitrites, followed by hydrolysis (Barton)
9-4 Oxidation of primary alcohols
9-8 Oxidative cleavage of glycols or related compounds
9-9 Oxidative cleavage of certain alcohols; degradation of aldehydes
9-10 Ozonolysis of olefins
9-11 Oxidative cleavage of certain olefins
9-14 Oxidative cleavage of carboxylic acids
9-16 Oxidation of activated methyl groups
9-17 Oxidation of arylmethanes (Étard)
9-20 Oxidation of primary halides or esters of primary alcohols
9-21 Oxidation of amines
9-23 Oxidation of olefins with noble-metal salts

Alicyclic Compounds

0-86 Internal coupling (Wurtz)
0-94 Reaction between epoxides and phosphorus ylides
0-96 Internal malonic ester synthesis
0-100 Cyclization of halogen-containing oxazines
0-101 Cyclization of haloboranes
0-111 Internal condensation of diesters (Dieckmann)
0-117 Ketonic decarboxylation of dicarboxylic acids
1-13 Intramolecular Friedel-Crafts alkylation
1-14 Scholl ring closure
1-15 Intramolecular Friedel-Crafts acylation
1-26 Cyclodehydration of aldehydes and ketones
2-17 The reaction of ethyl α-(bromomethyl)-acrylate with enamines
2-18 Intramolecular insertion of carbenes
3-16 Cyclization of dihalobiphenyls
4-15 Coupling of terminal diynes (cycloalkynes)
4-16 Intramolecular arylation (Pschorr)
4-35 Coupling of dienes through borane intermediates
5-6 Cyclization of olefinic acids
5-13 Reduction of aromatic rings
5-17 Cyclization of dienes
5-18 Internal ene reactions
5-20 Cyclization of unsaturated Grignard reagents
5-25 Hydrocarboxylation of dienes
5-50 Cycloaddition of allylic anions or cations to olefins
5-51 Addition of olefins to dienes (Diels-Alder)
5-52 Dimerization of olefins
5-53 Addition of carbenes or carbenoids to olefins or alkynes
5-54 Tetramerization of alkynes
5-55 Other cycloaddition reactions
6-31 Ring closure of halo carbonyl compounds
6-40 Internal aldol condensation
6-47 Internal Wittig reactions
6-48 Cyclization of dinitriles (Thorpe-Ziegler)
7-48 Extrusion of N$_2$ from pyrazolines or pyrazoles
7-49 Extrusion of CO from cyclic ketones
7-50 Extrusion of SO$_2$ from cyclic sulfones
7-51 Decarboxylation of cyclic peroxides (Story)
8-1 Wagner-Meerwein rearrangements to give cyclic products
8-3 Expansion and contraction of rings (Demyanov)
8-5 Ring expansion of amino ketones
8-8 Ring contraction of halo ketones (Favorskii)
8-9 Ring contraction of cyclic diazo ketones (Wolff)
8-27 Treatment of cyclic boranes with CO
8-28 Treatment of cyclic boranes with CO, H$_2$O, NaOH, and H$_2$O$_2$
8-32 Cyclization of conjugated dienes and trienes
8-35 $[1,j]$ sigmatropic migrations of carbon
8-36 Ring expansion of vinylcyclopropenes and cyclobutenes
8-37 Ring expansion of vinylcycloalkanes; cyclization of diynes
8-41 Metathesis of dienes
8-42 Metal-ion-catalyzed σ-bond rearrangements
8-43 The di-π-methane rearrangement
9-57 Reduction of cyclic ketones to cycloalkenes
9-70 Condensation of diesters (acyloin)

Alkanes (*see also* Alicyclic Compounds)

0-77 Reduction of alkyl halides
0-78 Reduction of tosylates and similar compounds
0-79 Hydrogenolysis of alcohols
0-82 Reduction of primary amines or quaternary ammonium or phosphonium salts
0-86 Coupling of alkyl halides (Wurtz)

0-87 Coupling of alkyl halides with organometallic reagents
0-89 Reaction between organometallic reagents and alkyl sulfates or sulfonates
0-90 Coupling of alcohols
0-92 Reaction between Grignard reagents and ethers
0-99 Reduction of dithianes
1-46 Reduction of aromatic ethers
2-16 Alkylation of alkanes
2-18 Insertion of carbenes
2-21 Reaction between organometallic compounds and acids
2-39 Decarboxylation of carboxylic acids
2-40 Cleavage of tertiary alkoxides
2-44 Cleavage of nonenolizable ketones
2-45 Cleavage of ketones with amide ion (Haller-Bauer)
2-46 Cleavage of alkanes
2-47 Decyanation of nitriles
4-14 Coupling of alkanes
4-34 Coupling of Grignard reagents
4-35 Coupling of boranes
4-36 Coupling of other organometallic compounds
4-37 Desulfurization of sulfur compounds
4-38 Decarboxylative dimerization (Kolbe)
4-41 Decarbonylation of aldehydes
5-12 Reduction of olefins and alkynes
5-13 Reduction of aromatic rings
5-14 Reductive cleavage of cyclopropanes
5-16 Hydrolysis of alanes
5-17 Addition of alkanes to olefins
5-24 Reductive coupling of olefins
6-31 Reaction of ketones with trimethylaluminum
6-34 Reaction of carboxylic acids with trimethylaluminum
6-47 From unsaturated sulfones and organometallic compounds
9-7 Oxidation of hydrazines
9-11 Cleavage of olefins with hydrazinium ion
9-14 Oxidative decarboxylation of carboxylic acids
9-39 Reduction of aldehydes or ketones (Wolff-Kishner; Clemmensen)
9-45 Reduction of carboxylic acids or esters
9-48 Reduction of epoxides
9-54 Reduction of cyano to methyl groups

Alkenes (*see also* Alicyclic Compounds, Unsaturated Acids, Unsaturated Alcohols, etc.)

0-7 Acid cleavage of *t*-butyl ethers
0-69 Reduction of α-keto epoxides
0-77 Reduction of unsaturated halides
0-82 Reductive cleavage of enamines
0-86 Coupling of vinyl halides
0-87 Coupling of unsaturated halides with organometallic reagents
0-88 Coupling of allylic halides, tosylates, or acetates
0-90 Coupling of allylic alcohols with organometallic reagents
0-91 Coupling of allylic esters with organometallic reagents
2-2 Migration of double and triple bonds
2-21 Hydrolysis of vinylsilanes
2-31 Reaction of Grignard reagents or nickel complexes with CO
2-39 Decarboxylation of unsaturated acids
4-17 Arylation of olefins (Meerwein)
4-18 Arylation of olefins by organopalladium compounds
4-32 Dimerization of allylic iodides
4-34 Dimerization of allylic Grignard reagents
4-36 Dimerization of vinyl organometallic reagents
4-37 Desulfurization of thiophenes
4-38 Additive dimerization of olefins and carboxylic acids
5-12 Selective reduction of alkynes or allenes
5-13 Reduction of aromatic rings
5-17 Dimerization of olefins
5-18 The ene synthesis
5-21 Addition of triallylboranes to triple bonds
5-51 Addition of olefins to dienes (Diels-Alder)
5-53 Addition of carbenes to aromatic rings
5-54 Tetramerization of alkynes
5-55 Dimerization of dienes
5-56 Addition of two alkyl groups to an alkyne
5-59 Reaction of diphenylacetylene with methylsulfinyl carbanion
6-31 Reaction of *gem*-dimetallic compounds with aldehydes or ketones
6-42 Addition to aldehydes or ketones of α-sulfinyl carbanions
6-44 Reaction between anhydrides and aldehydes
6-47 Reaction between phosphorus ylides and aldehydes or ketones (Wittig)
6-66 Reaction of sulfonyl halides with tertiary amines and diazoalkanes
7-1 Dehydration of alcohols
7-2 Alkaline cleavage of ethers
7-3 Pyrolysis of carboxylic esters
7-4 Pyrolysis of xanthates (Chugaev)
7-5 Cleavage of inorganic esters and sulfonates

7-6	Cleavage of quaternary ammonium hydroxides (Hofmann)
7-7	Cleavage of quaternary ammonium salts
7-8	Cleavage of amine oxides (Cope)
7-9	Cleavage of aliphatic diazonium salts
7-10	Decomposition of tosylhydrazones
7-11	Cleavage of sulfonium compounds
7-12	Cleavage of sulfoxides, selenoxides, and sulfones
7-13	Dehydrohalogenation of alkyl halides
7-14	Reaction of sulfonyl halides with tertiary amines
7-15	Elimination of boranes
7-16	Decarbonylation of acyl halides
7-17	Cleavage of Michael adducts
7-18	Pyrolysis of alkali organometallic compounds
7-19	Deoxygenation of *vic*-diols
7-20	Cleavage of cyclic thionocarbonates
7-21	Deoxidation of epoxides
7-22	Desulfurization of episulfides
7-23	Reaction of α-halo sulfones with bases (Ramberg-Bäcklund)
7-24	Reaction of aziridines with nitrous acid
7-25	Denitration of *vic*-dinitro compounds
7-27	Dehalogenation of *vic*-dihalides
7-29	Elimination of a halo and a hetero group (Boord)
7-30	Pyrolysis of hydroxy sulfinamides
7-31	Fragmentation of γ-branched alcohols or halides
7-32	Fragmentation of γ-amino or γ-hydroxy halides
7-34	Decarbonylation of β-hydroxy carboxylic acids and of β-lactones
7-35	Fragmentation of 1,3-diols or γ-amino alcohols
7-38	Elimination of CO and CO_2 from bridged bicyclic compounds
7-45	Pyrolysis of β-hydroxy olefins
7-46	Pyrolysis of allyl ethers
7-53	Twofold extrusion from certain cyclic molecules
8-1	Rearrangement of alcohols and olefins (Wagner-Meerwein)
8-3	Expansion and contraction of rings (Demyanov)
8-9	Rearrangement of carbenes or carbenoids
8-12	Rearrangement of α-haloboronic acids
8-30	Reaction between vinylboranes and iodine or NaOMe
8-31	Reaction of lithium alkynyltrialkylborates with carboxylic acids
8-32	Electrocyclic rearrangements of cyclobutenes and cyclohexadienes
8-34	[1,*j*] sigmatropic migrations of hydrogen
8-35	[1,*j*] sigmatropic migrations of carbon
8-36	Rearrangement of 1,5-dienes (Cope)
8-40	[2,3] sigmatropic rearrangements of unsaturated sulfones
8-41	Metathesis of olefins
8-42	Cyclobutane reversions
8-43	The di-π-methane rearrangement
9-3	Dehydrogenation of diarylalkanes; remote dehydrogenation
9-14	Oxidative decarboxylation of carboxylic acids
9-15	Bisdecarboxylation of succinic acids
9-34	Oxidative coupling of halides
9-39	Reduction of α-hydroxy ketones; of unsaturated tosylhydrazones
9-57	Reduction of cyclic ketones
9-69	Bimolecular reduction of aldehydes or ketones

Alkyl Halides (*see also* Dihalides, Halohydrins, etc.)

0-65	Halide exchange (Finkelstein)
0-66	Reaction between inorganic esters and halide ions
0-67	Reaction between alcohols and hydrogen halides or inorganic acid halides
0-68	Cleavage of ethers with HI or HBr
0-70	Cleavage of esters with LiI
0-72	Cleavage of tertiary amines (von Braun)
0-73	Cleavage of amines with hydrohalic acids
0-74	Conversion of sulfur compounds to halides
0-77	Reduction of dihalides
0-87	Coupling of dihalides with Grignard reagents
0-99	Homologization of primary halides
1-13	Reaction between aromatic rings and carbon tetrachloride
1-27	Haloalkylation of aromatic rings
2-28	Halogenation of organometallic compounds
2-38	Exchange between halides and organometallic compounds
4-1	Free-radical halogenation
4-2	Allylic halogenation
4-32	Reaction of boranes with allyl iodide and O_2
4-39	Decarboxylative halogenation (Hunsdiecker)
4-42	Decomposition of tertiary hypochlorites
5-1	Addition of hydrogen halides to olefins

5-23 Free-radical addition of alkyl halides to olefins
5-30 Addition of halogens to olefins or alkynes
5-37 Addition of alkyl or aryl halides to olefins
7-41 Reaction of N-substituted amides with PCl_5 (von Braun)

Alkynes (*see also* Alkynyl Halides, Alkynyl Ethers)

0-88 Propargylation of alkyl halides
0-92 Alkylation of alkynyl ethers
0-102 Alkylation at an acetylenic carbon
2-2 Triple-bond migration
2-39 Decarboxylation of acetylenic acids
2-45 Cleavage of α,β-acetylenic acid derivatives with amide ion
3-14 Reaction between aryl iodides and copper acetylides
4-15 Coupling of alkynes (Eglinton)
4-20 Arylation of alkynyl iodides
4-34 Dimerization of alkynyl organometallic compounds
7-6 Pyrolysis of bisquaternary ammonium hydroxides
7-13 Dehydrohalogenation of dihalides or vinyl halides
7-23 Decomposition of thiiren-1,1-dioxides
7-26 Reaction of bistosylhydrazones with metallic oxides
7-27 Dehalogenation of tetrahalides
7-33 Fragmentation of β-halo acrylic acid salts or α-chloroacroleins
8-11 Rearrangement of vinyl halides (Fritsch-Buttenberg-Wiechell)
8-31 From boranes and lithium acetylides
8-41 Metathesis of alkynes

Alkynyl Halides

2-28 Reaction of acetylide ions with halogens

Alkynyl Ethers

7-13 Reaction between vinylidine dihalides and amide ion

Allenes

0-77 Reduction of propargyl halides
0-91 Reaction between propargyl esters and organometallic reagents
2-2 Rearrangement of alkynes
6-47 Reaction of phosphoranes with ketenes or CO_2
7-13 Dehydrohalogenation of dihalides
7-27 Dehalogenation of tetrahalides or dihaloalkenes
7-45 Pyrolysis of β-hydroxy alkynes
8-3 Contraction of three-membered rings
8-38 Rearrangement of propargyl vinyl compounds

Amidals (*see* Bisamides)

Amides (*see also* Bisamides)

0-12 Cleavage of an alkyl group from N-*t*-butyl amides
0-53 Reaction between secondary amines and chloroform
0-54 Amination of acyl halides
0-55 Amination of anhydrides
0-56 Amination of acids
0-57 Amination of esters
0-58 Amination of amides
0-59 Amination of other acid derivatives
0-60 N-Alkylation of amides
0-105 Carbonylation of alkyl halides
1-6 Amidation of aromatic rings with hydroxamic acids
1-22 Carbamoylation of aromatic rings (Gatterman)
1-24 Amidation of aromatic rings with isocyanates
1-39 Rearrangement of N-halo-N-acyl aromatic amines (Orton)
2-11 Insertion by nitrenes
2-31 Carbamoxylation of organometallic compounds
2-45 Cleavage of ketones with amide ion (Haller-Bauer)
2-47 Decyanation of cyano amides
2-55 Carbonylation of amines
3-6 N-Arylation of amides
4-13 Reaction of aldehydes with ammonia
4-22 Carbamidation of nitrogen heterocycles
5-3 Hydration of ynamines
5-9 Addition of amides to olefins; addition of amines to ketenes
5-23 Free-radical addition of amides to olefins
5-25 Hydrocarboxylation of olefins in the presence of amines
6-5 Partial hydrolysis of nitriles
6-16 Reductive alkylation of amines (Leuckart)
6-37 Addition of Grignard reagents to isocyanates
6-57 Addition of alcohols or other carbonium-ion sources to nitriles (Ritter)
6-71 Addition of water to isonitriles

7-4	Pyrolysis of O-alkyl imidates
8-8	Rearrangement of α-halo ketones in the presence of amines (Favorskii)
8-9	Rearrangement of diazo ketones in the presence of amines (Arndt-Eistert)
8-17	Reaction between amides, lead tetraacetate, and acetic acid
8-20	Reaction between ketones and hydrazoic acid (Schmidt)
8-21	Rearrangement of oximes (Beckmann)
8-49	Rearrangement of aryl imidates (Chapman)
9-18	Oxidation of tertiary amines
9-76	Oxidation of aryl ketones with ammonium polysulfide (Willgerodt)

Amidines

0-36	Reaction of N-alkylimino esters with secondary amines
0-57	Amination of imino esters
5-9	Addition of amines to ketenimines
6-19	Addition of ammonia or amines to nitriles or nitrilium salts
6-72	Reaction of amines with isocyanides

Aminals

6-15	Addition of amines to aldehydes or ketones

Amine Oxides

9-29	Oxidation of tertiary amines

Amines (*see also* Cyanoamines, Amino Acids, etc.)

0-12	Hydrolysis of amides
0-36	Reduction of N-alkylimino esters
0-39	Cleavage of quaternary ammonium salts
0-46	Alkylation of ammonia or amines
0-47	Reaction between alkyl halides and hexamethylenetetramine
0-48	Indirectly, from alcohols
0-49	Transamination
0-50	Alkylation of amines with diazo compounds
0-52	Amination of alkanes
0-60	Hydrolysis of phthalimides (Gabriel)
0-73	Cleavage of aromatic amines or quaternary ammonium salts
0-82	Reduction of quaternary ammonium salts or aziridines; monomethylation of arylamines
0-92	Cleavage of amine ethers with Grignard reagents
0-99	Alkylation and hydrolysis of N-nitro compounds
0-118	Hydrolysis of sulfonamides
1-6	Direct amination of aromatic rings
1-28	Aminoalkylation of aromatic rings
1-36	Rearrangement of N-nitroamines
1-37	Rearrangement of N-nitrosoamines (Fischer-Hepp)
1-38	Rearrangement of triazenes
1-40	Rearrangement of aryl alkyl ammonium salts (Hofmann-Martius)
2-10	Amination at an activated position
2-29	Conversion of organometallic compounds to amines
2-47	Decyanation of cyanoamines
3-6	Arylation of ammonia or amines
3-7	Reaction between naphthols, bisulfite ion, and ammonia or amines (Bucherer)
3-18	Amination of heterocyclic nitrogen compounds (Chichibabin)
3-19	Direct amination of activated aromatic rings
3-20	Amination of aromatic acids
3-27	Rearrangement of benzyl quaternary ammonium salts (Sommelet-Hauser)
3-28	Rearrangement of aryl hydroxylamines
4-37	Desulfurization of thioamides
5-9	Addition of ammonia or amines to olefins
5-20	Addition of organometallic compounds to allylic amines
5-23	Free-radical addition of amines to olefins
5-27	Aminomethylation of alkenes
5-44	Bisamination of alkenes
6-2	Hydrolysis of imines, enamines, and iminium ions
6-3	Hydrolysis of isocyanates or isothiocyanates
6-5	Hydrolysis of cyanamides
6-10	Reduction of N-alkylimino esters
6-14	Addition of ammonia to aldehydes
6-16	Reductive alkylation of ammonia or amines
6-17	Reaction between aldehydes, ammonia or amines, and an active hydrogen compound (Mannich)
6-28	Reduction of imines, hydrazones, or other compounds containing the C=N bond
6-29	Reduction of nitriles or nitrilium ions
6-34	Addition of Grignard reagents to formamides
6-36	Addition of Grignard reagents to imines
6-73	Reduction of isonitriles
7-6	Cleavage of quaternary ammonium hydroxides (Hofmann)
7-7	Cleavage of quaternary ammonium salts

7-30 Pyrolysis of hydroxysulfinamides
7-40 Fragmentation of certain ketoximes
8-17 Reaction between amides and NaOBr (Hofmann)
8-18 Rearrangement of acyl azides in the presence of water (Curtius)
8-19 Rearrangement of hydroxamic acids (Lossen)
8-20 Addition of hydrazoic acid to carboxylic acids (Schmidt)
8-22 Rearrangement of N-haloamines
8-25 Rearrangement of quaternary ammonium salts (Stevens)
8-40 [2,3] sigmatropic rearrangements of quaternary ammonium salts
8-44 Rearrangement of benzidines
9-6 Conversion of primary to secondary amines by dehydrogenation
9-10 Reaction between ozonides, ammonia, and hydrogen
9-21 Oxidative cleavage of amines
9-41 Reduction of amides
9-49 Reduction of nitro compounds
9-52 Reduction of nitroso compounds or hydroxylamines
9-53 Reduction of oximes
9-54 Reduction of isocyanates, isothiocyanates, or azides
9-58 Reduction of amine oxides
9-63 Reduction of azo, azoxy, or hydrazo compounds

Amino Acids and Esters

0-12 Hydrolysis of lactams
0-46 Amination of halo acids
0-57 Ammonolysis of β-lactones
0-96 Alkylation of N-acetylaminomalonic ester (Sorensen)
2-8 Nitrosation at a carbon bearing an active hydrogen and reduction of the resulting oxime or nitroso compound
6-5 Hydrolysis of cyanohydrins
6-17 Reaction between aldehydes, ammonia, and carboxylic acids
6-32 Reaction of imines, zinc, and halo esters
6-44 Reduction of azlactones
6-51 Addition of cyanide and ammonium ions to aldehydes or ketones, followed by hydrolysis (Strecker)
8-16 Rearrangement of N-halo imino esters
8-17 Reaction between imides and NaOBr (Hofmann)
8-45 Rearrangement of hydroxy amides

Amino Carbonyl Compounds

0-48 Amination of α-hydroxy ketones
0-49 Transamination of Mannich bases
1-40 Photolysis of acylated arylamines
6-17 Reaction between aldehydes, ammonia, and aldehydes, ketones, or esters (Mannich)
6-36 Reaction of iminium ions with enol borinates
8-5 Rearrangement of amino ketones or aldehydes
8-16 Rearrangement of ketoxime tosylates (Neber)
8-25 Rearrangement of quaternary ammonium salts (Stevens)

Amino Ethers

0-20 Alcoholysis of aziridines

Amino Mercaptans

0-51 Amination of episulfides
1-9 Sulfurization of aromatic amines (Herz)

Anhydrides

0-29 Reaction of acyl halides with acid salts
0-30 Dehydration of acids
0-34 Reaction of acid derivatives with inorganic acids
4-10 Acyloxylation of aldehydes
5-6 Addition of acids to ketenes
5-23 Free-radical addition of anhydrides to olefins
8-23 Reaction between α-diketones and peroxy compounds (Baeyer-Villiger)
9-11 Oxidation of aromatic rings

Arenes

0-77 Reduction of aryl and benzylic halides
0-79 Hydrogenolysis of benzyl alcohols
0-80 Reduction of benzylic ethers
0-86 Coupling of halides containing aryl groups
0-87 Coupling of aryl halides with organometallic reagents
0-90 Coupling of benzylic alcohols
1-13 Alkylation of aromatic rings (Friedel-Crafts)
1-14 Arylation of aromatic rings (Scholl)
1-25 Diarylation of ketones
1-26 Ring closure of aryl-substituted carbonyl compounds
1-41 Cleavage or rearrangement of alkyl arenes
1-42 Decarbonylation of aromatic aldehydes
1-43 Decarboxylation of aromatic acids

1-46	Reduction of aromatic ethers
1-47	Desulfonation of aromatic sulfonic acids
1-48	Dehalogenation of aryl halides
1-50	Hydrolysis of organometallic compounds
2-39	Decarboxylation of α-aryl acids
2-40	Cleavage of tertiary alkoxides
2-44	Cleavage of aryl ketones
2-45	Cleavage of aryl ketones with amide ions (Haller-Bauer)
2-47	Decyanation of aryl nitriles
3-9	Reduction of phenols, phenolic ethers, or phenolic esters
3-10	Reduction of aromatic nitro compounds
3-13	Coupling of organometallic compounds with aryl ethers
3-16	Coupling of aryl iodides (Ullmann)
3-17	Alkylation with organolithium compounds
4-16	Free-radical arylation by diazonium salts (Gomberg-Bachmann, Pschorr)
4-19	Free-radical arylation by peroxides
4-20	Photochemical arylation
4-24	Reduction of diazonium salts
4-29	Dimerization of diazonium salts
4-34	Dimerization of Grignard reagents
4-35	Dimerization of arylboranes
4-36	Dimerization of other organometallic compounds
4-37	Reduction of sulfur compounds
4-41	Decarbonylation of aromatic aldehydes
5-24	Reductive coupling of olefins
5-54	Trimerization of alkynes
6-31	Alkylation-reduction of aromatic aldehydes and ketones
6-42	Addition of nitro compounds to pyrylium ions
6-47	Reaction between ylides and pyrylium salts
7-38	Diels-Alder reactions of cyclopentadienones with alkynes
8-33	Photolysis of stilbenes to phenanthrenes
9-1	Aromatization of six-membered rings
9-2	Cyclodehydrogenation of aliphatic chains
9-7	Oxidation of hydrazines
9-34	Dimerization of arenes
9-39	Reduction of aromatic aldehydes
9-45	Reduction of aromatic acids

Aryl Halides

1-12	Halogenation of aromatic compounds
1-39	Rearrangement of N-haloamines (Orton)
1-43	Replacement of aromatic COOH by halogen
1-47	Replacement of aromatic SO_2Br by halogen
1-48	Migration of halogen
2-28	Reaction of aryl organometallic compounds with halogens
3-8	Aryl halide exchange
3-24	Reaction between diazonium salts and iodide ion
3-25	Heating of diazonium fluoborates (Schiemann)
4-25	Reaction between diazonium salts and CuCl or CuBr (Sandmeyer)
4-39	Decarboxylative halogenation (Hunsdiecker)
4-41	Decarbonylation of acyl halides

Azides

0-63	Alkylation or acylation of azide ion
2-30	Reaction of Grignard reagents with tosyl azide
2-49	Reaction between hydrazines and nitrous acid
2-51	Reaction of amine anions with tosyl azide
3-23	Reaction of diazonium salts with azide ion
4-39	Reaction of acyl peroxides with copper azide
5-10	Addition of hydrazoic acid to double bonds
5-35	Addition of halogen azides to double bonds
5-43	Treatment of olefins with sodium azide, ferrous ion, and hydrogen peroxide
8-18	Reaction between hydrazides and nitrous acid
8-20	Reaction between alcohols or olefins and hydrazoic acid

Azines

6-21	Addition of hydrazine to aldehydes or ketones

Aziridines

0-46	Cyclization of haloamines
0-48	Cyclization of amino alcohols
5-35	From β-iodo azides
5-45	Reaction of alkenes with azides
6-36	Reaction between Grignard reagents and oximes
6-45	Reaction of imines with α-halo carbonyl compounds
6-67	Addition of divalent carbon to C=N bonds
7-48	Extrusion of N_2 from triazolines
9-53	Reduction of oximes

Azlactones

6-44	Condensation between aldehydes and N-acylglycines (Erlenmeyer)

Azo Compounds

1-4 Coupling of diazonium salts with aromatic rings
1-38 Rearrangement of aryl triazenes
1-45 Reaction between aromatic alcohols and diazonium salts (Stiles-Sisti)
1-50 Reaction between organometallic compounds and diazonium ions
2-7 Aliphatic diazonium coupling
2-52 Reaction of amines with nitroso compounds (Mills)
4-29 Coupling of aryl diazonium salts
8-50 Rearrangement of azoxy compounds (Wallach)
9-7 Oxidation of hydrazines
9-38 Oxidation of amines
9-58 Reduction of azoxy compounds
9-72 Reduction of nitro compounds

Azoxy Compounds

2-53 Reaction of nitroso compounds with hydroxylamines
9-30 Oxidation of azo compounds
9-38 Oxidation of amines
9-71 Reduction of nitro or nitroso compounds; reaction between nitroso compounds and hydroxylamines

Benzoins (*see* Hydroxy Aldehydes and Ketones)

Bisamides

6-15 Addition of amides to aldehydes or ketones
6-61 Addition of nitriles to aldehydes
6-74 Reaction between isonitriles, acids, amines, and aldehydes or ketones (Ugi)

Bisulfite Addition Compounds (*see* Hydroxy Sulfonic Acids)

Boranes

2-34 Reaction between boron halides and Grignard reagents
5-15 Hydroboration of olefins or alkynes
7-15 Exchange reaction between boranes and olefins
8-14 Migration of boron
9-56 Reduction of borinates

Bunte Salts

0-42 Reaction between alkyl halides and thiosulfate ion

Carbamates

0-48 Heating of N-carbalkoxylsulfamate salts of alcohols
0-54 Reaction between chloroformates and primary amines
0-64 Reaction between alkyl halides, ethanol, and thiocyanate ion
0-73 Cleavage of tertiary amines with ClCOOPh
2-11 Insertion by nitrenes
2-45 Cleavage of α,β-acetylenic esters with amide ion
5-9 Addition of carbamates to olefins
6-8 Addition of alcohols to isocyanates
6-10 Reaction of alcohols with ClCN
6-75 Addition of alkyl hypochlorites to isonitriles
8-17 Reaction between amides, bromine, and alkoxides (Hofmann); reaction between amides, lead tetraacetate, and acetic acid
8-18 Rearrangement of acyl azides in the presence of alcohols (Curtius)
9-31 Oxidation of isonitriles in the presence of alcohols

Carbodiimides

6-62 Addition of isocyanates to isocyanates
6-72 Reaction of azides with isocyanides
7-43 Dehydration of ureas and thioureas

Carbonates

0-22 Alcoholysis of phosgene
4-10 Reaction of aromatic compounds with peroxycarbonate

Carboxylic Acids

0-3 Hydrolysis of 1,1,1-trihalides
0-7 Hydrolysis of ortho esters
0-9 Hydrolysis of acyl halides
0-10 Hydrolysis of anhydrides
0-11 Hydrolysis of esters
0-12 Hydrolysis of amides
0-23 Alcoholysis of anhydrides
0-55 Amination of anhydrides
0-70 Cleavage of esters with LiI
0-75 Exchange between acids and acyl halides
0-96 Malonic ester synthesis
0-98 Alkylation of carboxylic acid salts
0-100 Hydrolysis of oxazines
0-105 Carbonylation of alkyl halides and other substrates
1-22 Carboxylation of aromatic rings with carbonyl halides

1-23 Carboxylation of aromatic rings with carbon dioxide (Kolbe-Schmitt)
1-43 Rearrangement of aromatic carboxylate ions
2-39 Decarboxylation of dicarboxylic acids
2-42 Basic cleavage of β-keto esters or β-diketones
2-43 The haloform reaction
2-44 Cleavage of nonenolizable ketones
3-15 Carboxylation of aryl bromides
3-26 Rearrangement of aromatic nitro compounds upon treatment with cyanide ion (von Richter)
4-6 Oxidation of aldehydes
5-2 Addition of water to ketenes
5-3 Hydrolysis of alkynyl halides
5-15 Oxidation of 1,1-diboranes
5-17 Addition of carbonium ions to 1,1-dichloroethene; addition of carboxylates to olefins
5-23 Free-radical addition of acids to olefins
5-25 Hydrocarboxylation of olefins
6-4 Hydrolysis of primary nitro compounds
6-5 Hydrolysis of nitriles
6-35 Addition of Grignard reagents to carbon dioxide
6-42 Reaction of ketones with tosylmethyl azide, followed by hydrolysis
6-47 Reaction of phosphoranes with CO_2
7-3 Pyrolysis of carboxylic esters
7-40 Fragmentation of certain ketoximes
8-8 Rearrangement of α-halo ketones (Favorskii)
8-9 Rearrangement of diazo ketones (Arndt-Eistert)
9-8 Oxidative cleavage of α-diketones and α-keto acids
9-9 Oxidative cleavage of ketones and secondary alcohols
9-10 Oxidation of ozonides; ozonolysis of alkynes
9-11 Oxidative cleavage of olefins, terminal alkynes, or aromatic rings
9-12 Oxidation of aromatic side chains
9-21 Oxidation of amines
9-22 Oxidation of primary alcohols or ethers
9-74 Reaction between aldehydes and base (Cannizzaro)
9-76 Oxidation of aryl ketones by ammonium polysulfide (Willgerodt)

Carboxylic Esters (*see also* Dicarbonyl Compounds, Unsaturated Esters, etc.)

0-7 Hydrolysis of ortho esters
0-13 Decarbonylation of α-keto esters
0-22 Alcoholysis of acyl halides
0-23 Alcoholysis of anhydrides
0-24 Esterification of acids
0-25 Transesterification
0-26 Alkylation of acid salts
0-27 Cleavage of ethers with anhydrides
0-28 Alkylation of acids with diazo compounds
0-97 Alkylation of esters
0-100 Alkylation and alcoholysis of oxazines
0-101 Reaction of halo esters or diazo esters with boranes
0-105 Carbonylation of alkyl halides and other substrates
0-106 Reaction between Grignard reagents and chloroformates
0-107 Reaction between Grignard reagents and carbonates
0-114 Reduction of β-carbalkoxyphosphoranes
1-33 Acyloxylation of aromatic rings
2-25 Esterification of enolates with acyl peroxides
2-31 Carbonylation of organometallic compounds
2-42 Base cleavage of β-keto esters
3-4 Reaction between aryl halides and acid salts
3-14 Arylation of esters
3-15 Carbalkoxylation of aryl iodides
4-10 Free-radical acyloxylation
4-22 Carbalkoxylation of nitrogen heterocycles
4-39 Reaction between silver salts and iodine (Simonini)
5-3 Hydration of acetylenic ethers
5-5 Addition of alcohols or phenols to ketenes
5-6 Addition of acids or acyl peroxides to olefins
5-19 Addition of esters to activated olefins (Michael)
5-23 Free-radical addition of esters to olefins
5-25 Hydrocarboxylation of olefins in the presence of alcohols
5-39 Addition of acid salts to olefins
5-57 Dicarbalkoxylation of olefins and acetylenes
6-7 Reductive acylation of ketones
6-10 Alcoholysis of nitriles
8-8 Rearrangement of α-halo ketones (Favorskii)
8-9 Rearrangement of diazo ketones in the presence of alcohols (Arndt-Eistert)
8-23 Reaction between ketones and peroxy compounds (Baeyer-Villiger)
9-4 Oxidation of acetals
9-14 Reaction between carboxcylic acids and lead tetraacetate

9-18 Oxidation of ethers
9-22 Oxidation of primary alcohols
9-75 Reaction between aldehydes and aluminum ethoxide (Tishchenko)
9-76 Reaction of acetophenones with $Tl(NO_3)_3$

Catenanes

9-70 Acyloin condensation or other methods

Cyanamides

0-72 Cleavage of tertiary amines with cyanogen bromide (von Braun)

Cyanates

0-14 Reaction of aroxides and cyanogen halides

Cyano Acetals

0-103 Reaction between ortho esters and HCN

Cyanoamines

0-48 Amination of cyanohydrins
6-17 Reaction between aldehydes, ammonia, and nitriles (Mannich)
6-51 Addition of cyanide and ammonium ions to aldehydes or ketones (Strecker)
6-52 Addition of HCN to C=N or C≡N bonds

Cyano Carbonyl Compounds

0-96 Alkylation of cyano carbonyl compounds
0-103 Reaction between lactones and cyanide ion
0-109 Acylation of nitriles by acyl halides
0-112 Acylation of nitriles by esters
0-115 Reaction between acyl halides and CuCN
2-17 Cyanoethylation of enamines; reaction of enamines with cyanogen chloride
3-14 Arylation of cyano carbonyl compounds
5-19 Addition to olefins (Michael)
5-22 Acylation of unsaturated nitriles
5-24 Mixed coupling of unsaturated nitriles and esters
5-28 Addition of HCN to unsaturated aldehydes, ketones, or esters
6-42 Addition of cyano carbonyl compounds to aldehydes or ketones (Knoevenagel)
6-48 Condensation of nitriles (Thorpe)
9-34 Dimerization of cyano carbonyl compounds

Cyanohydrins (*see* Hydroxy Nitriles)

Cycloalkanes and Alkenes (*see* Alicyclic Compounds)

Dialdehydes (*see* Dicarbonyl Compounds)

Diazo Compounds

0-116 Reaction between acyl halides and diazomethane
2-9 Reaction of active-hydrogen compounds with tosyl azide
2-48 Diazotization of α-amino esters and similar compounds
6-42 Addition of diazo esters to aldehydes
7-47 Elimination from N-nitroso-N-alkyl compounds
9-7 Oxidation of hydrazones

Diazonium Salts

1-5 Direct diazotization of aromatic rings
2-48 Diazotization of primary amines

1,2-Dicarbonyl Compounds

0-55 Reaction between α-amino acids and trifluoroacetic anhydride
0-108 Dimerization of acyl halides
0-111 Condensation between esters and ethyl oxalate
0-112 Acylation of 1,3-dithianes, followed by hydrolysis
3-15 Carbalkoxylation of aryl iodides
6-2 Treatment of acyl azides successively with Ph_3P, water, and nitrous acid
6-44 Hydrolysis of azlactones
6-57 Hydrolysis of α-keto amides
6-76 Reaction of metalated aldimines with CO_2
6-77 Hydrolysis of diiminooxetanes
9-10 Ozonization of alkynes or aromatic rings
9-16 Oxidation of ketones with selenium dioxide
9-21 Oxidative cleavage of α-amino ketones
9-23 Oxidation of olefins
9-28 Oxidation of alkynes
9-70 Ring enlargement of cyclic diesters

1,3-Dicarbonyl Compounds

0-96 Alkylation at a carbon bearing an active hydrogen
0-109 Acylation at a carbon bearing an active hydrogen
0-110 Acylation of ketones by anhydrides
0-111 Acylation of esters by esters (Claisen; Dieckmann)
0-112 Acylation of ketones by esters
0-113 Acylation of carboxylic acid salts
2-15 Acylation of acetals or ketals followed by hydrolysis
2-17 Acylation of enamines followed by hydrolysis (Stork)
2-25 Esterification of enolates with acyl peroxides

3-14 Arylation at a carbon bearing an active hydrogen
5-19 Addition of active-hydrogen compounds to olefins (Michael)
5-23 Free-radical addition of 1,3-dicarbonyl compounds to olefins
6-32 Reaction between nitriles, zinc, and α-halo esters (Reformatsky)
6-35 Addition of CO_2 to *gem*-dimetallic compounds
6-42 Addition of 1,3-dicarbonyl compounds to aldehydes or ketones (Knoevenagel)
6-43 Carboxylation of ketones and esters
7-17 Cleavage of Michael adducts
7-52 Extrusion of sulfur from β-keto thiol esters
8-9 Rearrangement of diacyldiazomethanes
8-10 Reaction of ketones with ethyl diazoacetate
9-34 Dimerization of β-keto esters or similar compounds

1,4-Dicarbonyl Compounds

0-7 Cleavage of furans
0-86 Coupling of α,α′-dibromo ketones
1-15 Acylation of aromatic rings by succinic anhydride
5-19 Addition of active-hydrogen compounds to olefins (Michael)
5-22 Acylation of unsaturated ketones or alkynes
5-50 Reaction between ketene and diazo ketones
5-57 Dicarbalkoxylation of olefins and acetylenes
5-58 Reaction between alkynes, alkyl halides, and alcohols
9-35 Dimerization of silyl enol ethers or of lithium enolates

Dicarboxylic Acids (*see* Dicarbonyl Compounds, Carboxylic Acids)

Dicyano Compounds

0-96 Alkylation of malononitriles
3-14 Arylation of malononitriles
5-19 Addition of nitriles to unsaturated nitriles (Michael)
5-24 Reductive coupling of acrylonitrile
6-42 Addition of malononitriles to aldehydes or ketones (Knoevenagel)
6-52 Addition of HCN to nitriles
9-11 Oxidation of *o*-diamines

Diesters (*see* Dicarbonyl Compounds)

Dihalides and Polyhalides

0-69 Treatment of epoxides with $SOCl_2$ or Ph_3P and CCl_4
0-77 Reduction of trihalides
2-39 Decarboxylation of trihalo acids
2-43 The haloform reaction
4-1 Free-radical halogenation
5-1 Addition of hydrogen halides to alkynes
5-30 Addition of halogens to olefins or alkynes
5-37 Free-radical addition of polyhalides to olefins
6-26 Reaction of PCl_5, SF_4, or other reagents with aldehydes, ketones, or other C=O compounds

Diketones (*see* Dicarbonyl Compounds)

Dinitro Compounds

0-62 Reaction between salts of nitro compounds and silver nitrate
4-12 Nitration of paraffins
5-43 Addition of N_2O_4 to olefins

gem-Diols (Hydrates)

6-1 Hydration of aldehydes

1,2-Diols

0-8 Hydrolysis of epoxides
5-39 Hydroxylation of olefins
9-67 Bimolecular reduction of aldehydes or ketones

1,3-Diols

6-46 Condensation between formaldehyde and aldehydes or ketones (Tollens)
6-54 Addition of aldehydes to olefins (Prins)

Disulfides

0-41 Reaction between alkyl halides and disulfide ion
3-5 Reaction between aryl halides and disulfide ion
3-29 The Smiles rearrangement
9-37 Oxidation of mercaptans
9-55 Reduction of sulfonyl halides

Dithiols

6-12 Addition of H_2S to carbonyl compounds or imines

Enamines

5-9 Addition of amines to triple-bond compounds
6-15 Addition of amines to aldehydes or ketones

6-17 Reaction between formic acid, secondary amines, and active-hydrogen compounds (Mannich)
6-34 Reaction between Grignard reagents and formamides
6-76 Reaction of isonitriles with active-hydrogen compounds
9-3 Dehydrogenation of tertiary amines

Enolate Ions

2-3 Treatment of aldehydes or ketones with base
2-20 Treatment of active-hydrogen compounds with base

Enol Ethers and Esters

0-17 O-Alkylation of carbonyl compounds with diazo alkanes
0-19 Transetherifications
0-22 Reaction between acyl halides and active-hydrogen compounds
0-25 Transesterifications
0-26 Acylation of vinyl halides
0-96 Alkylation with ortho esters
0-109 O-Acylation of 1,3-dicarbonyl compounds
5-5 Addition of alcohols or phenols to alkynes; addition of aldehydes or ketones to ketene
5-6 Addition of acids to alkynes
6-6 Addition of alcohols to aldehydes or ketones
6-47 Reaction of α-alkoxy phosphoranes with aldehydes or ketones
7-2 Cleavage of acetals
7-29 Elimination from β-halo acetals

Enol Thioethers

5-7 Addition of mercaptans to alkynes
6-12 Reaction of aldehydes or ketones with mercaptans

Enynes

5-17 Dimerization of acetylenes

Episulfides

0-39 Reaction between epoxides and phosphine sulfides
5-32 Cyclization of β-halo disulfides
6-66 Reaction of diazoalkanes with sulfur or thioketones

Epoxides

0-15 Cyclization of halohydrins
0-18 Cyclization of 1,2-glycols
5-40 Epoxidation of olefins
6-31 Reaction of carbonyl compounds with *gem*-dihalides and Li or BuLi
6-45 Condensation between aldehydes and α-halo esters, ketones, or amides (Darzens)
6-65 Addition of sulfur ylides or diazomethane to aldehydes or ketones
9-68 Bimolecular reduction of aldehydes or ketones

Esters (*see* Carboxylic Esters, Inorganic Esters)

Ethers (*see* also Hydroxy Ethers, etc.)

0-7 Cleavage of oxonium ions
0-11 Reaction between esters and alkoxide ion
0-14 Reaction between alkoxides or aroxides and alkyl halides (Williamson)
0-16 Reaction between alkoxides or aroxides and inorganic esters
0-17 Alkylation of alcohols or phenols with diazo compounds
0-18 Dehydration of alcohols
0-19 Transetherification
0-21 Alkylation of alcohols with onium salts
0-31 Exchange of ethers and oxonium salts
0-68 Cleavage of oxonium salts
0-80 Reduction of acetals or ketals
0-92 Reaction between Grignard reagents and acetals or ketals
2-24 Reaction between Grignard reagents and *t*-butyl peresters
3-4 Reaction between aryl halides and alkoxides or aroxides
4-7 Cyclization of alcohols with lead tetraacetate
4-37 Desulfurization of hemithioacetals
5-5 Addition of alcohols or phenols to olefins
5-15 Hydroboration-reduction of acetylenic acetals
5-23 Free-radical addition of ethers to olefins
5-48 Addition of acetals to vinyl ethers
6-7 Reductive alkylation of alcohols
9-42 Reduction of esters
9-64 Reduction of peroxides

Formazans

2-7 Coupling of diazonium salts with arylhydrazones

Fulvenes

6-42 Condensation between cyclopentadiene and aldehydes or ketones

Glycidic Esters

5-40 Epoxidation of α,β-unsaturated esters
6-45 Condensation between aldehydes or ketones and α-halo esters (Darzens)

Grignard Reagents (*see* Organometallic Compounds)

Halo Acids, Esters, Aldehydes, Ketones (*see* Halo Carbonyl Compounds)

Haloamines

5-33 Addition of N-haloamines to unsaturated compounds

N-Haloamines and Amides

2-54 Halogenation of amines or amides

Halo Carbonyl Compounds

0-71 Reaction of diazo ketones with hydrohalic acids
2-4 Halogenation of aldehydes or ketones
2-5 Halogenation of acids (Hell-Volhard-Zelinskii) and acid derivatives
5-30 Addition of halogens to ketenes
5-31 Addition of HOBr or HOCl to triple bonds; addition of chlorine acetate or $PdCl_2$–$CuCl_2$–HOAc to olefins
5-37 Reaction of enol borinates with bromine, followed by hydrolysis
5-38 Addition of acyl halides to olefins
6-42 From ketones, lithiocyclopropyl phenyl sulfide, and bromine
6-58 Reaction between acyl bromides and aldehydes or ketones
8-13 Rearrangement of halo epoxides
9-23 Oxidation of certain alkenes with chromyl chloride

Halo Ethers and Acetals

2-4 Halogenation of acetals or ketals
5-31 Addition of hypohalites to double bonds; reaction of Br_2 and NaOMe with alkenyl boronic acids
6-25 Addition of alcohols and hydrogen halides to aldehydes or ketones

Haloformic Esters

0-22 Alcoholysis of phosgene

Halohydrins

0-69 Cleavage of epoxides with hydrogen halides
5-31 Addition of hypohalous acids to olefins

Halo Sulfoxides and Sulfones

2-6 Halogenation of sulfoxides and sulfones
5-32 Addition of sulfonyl halides to olefins

Hemiacetals

6-6 Addition of alcohols to aldehydes or ketones

Hemiaminals

6-14 Reaction between aldehydes or ketones and ammonia
6-15 Reaction between aldehydes or ketones and amines

Hemihydrates

6-1 Hydration of aldehydes

Hemimercaptals

6-12 Addition of mercaptans to aldehydes or ketones

Heterocyclic Compounds (*see also* Epoxides, Episulfides, Aziridines, Lactams, Lactones, Anhydrides, Imides)

0-15 Cyclization of halohydrins (cyclic ethers)
0-18 Cyclization of glycols (cyclic ethers; furans)
0-19 Reaction of diols with acetals (cyclic acetals)
0-39 Reaction of dihalides with sulfide ion (cyclic sulfides)
0-46 Cyclization of haloamines (cyclic amines)
0-56 Dimerization of amino acids (diketopiperazines)
0-61 Reaction between ureas and malonic esters or between carbonates and malonamides (cyclic ureides)
1-9 Sulfurization of aromatic rings (cyclic sulfides)
1-15 Intramolecular acylation
1-24 Intramolecular amidation of aromatic rings
1-26 Cyclization of amides with $POCl_3$ (isoquinolines); reaction between aromatic amines, glycerol, sulfuric acid, and nitro compounds (quinolines); reaction between phenols and β-keto esters (coumarins)
2-7 Intramolecular aliphatic diazonium coupling (pyridazines)
2-11 Intramolecular nitrene insertion
3-6 Intramolecular arylation of amines (cyclic amines)
3-14 Intramolecular arylation of active-hydrogen compounds

3-17	Arylation of heterocyclic nitrogen compounds
3-18	Amination of heterocyclic nitrogen compounds
4-7	Cyclization of alcohols with lead tetraacetate (tetrahydrofurans)
4-16	Intramolecular arylation (Pschorr)
4-21	Alkylation and arylation of nitrogen heterocycles
4-22	Carbalkoxylation and carboamidation of nitrogen heterocycles
5-7	Addition of H_2S to conjugated diynes (thiophenes)
5-9	Addition of ammonia or primary amines to conjugated diynes (pyrroles)
5-13	Hydrogenation of heterocyclic aromatic rings
5-15	Addition of boranes to dienes (cyclic boranes)
5-32	Addition of sulfur dichloride to dienes
5-40	Epoxidation of C=N compounds (oxaziranes)
5-41	Photooxidation of dienes (cyclic peroxides)
5-45	Addition of aminonitrenes to triple bonds (1-azirines); addition of nitrenoids to C=N or C=O bonds (diaziridines, oxaziranes)
5-46	Photolysis or thermolysis of vinyl azides (1-azirines)
5-50	1,3-Dipolar addition to double or triple bonds
5-51	Diels-Alder addition involving hetero atoms
5-53	Expansion of heterocyclic rings upon treatment with carbenes
5-55	Other cycloaddition reactions
6-6	Formation of cyclic acetals; reaction between diketones and acids (furans, pyrans)
6-12	Addition of H_2S to aldehydes or ketones (cyclic mercaptals)
6-14	Reaction between aldehydes and ammonia (cyclic amines)
6-15	Intramolecular addition of amines to carbonyl groups (cyclic imines)
6-19	Reaction of dinitriles with ammonia (cyclic imidines)
6-21	Reaction between hydrazines and β-diketones or β-keto esters (pyrazoles; pyrazolones)
6-28	Reduction of N-alkylpyridinium salts (dihydropyridines)
6-36	Alkylation of salts of nitrogen heterocyclic compounds (cyclic amines)
6-42	Reaction of ketones with tosylmethylisocyanide (oxazolines)
6-54	Reaction between alcohols and aldehydes (dioxanes)
6-60	Trimerization of aldehydes (trioxanes)
6-62	Dimerization or trimerization of C=N compounds
6-64	Trimerization of nitriles (triazines)
6-68	Addition of olefins to aldehydes or ketones (oxetanes)
6-69	Reaction of sulfenes and enamines (thietane-1,1-dioxides)
6-77	Reaction of isonitriles with aldehydes or ketones (diiminooxetanes)
7-23	Reaction of dichlorobenzyl sulfones with base (thiiren-1,1-dioxides)
7-48	Extrusion of N_2 from tetrazolines (diaziridines)
7-49	Extrusion of CO_2 from benzoxadiazepinones (indazoles)
7-53	Condensation of thiobenzilic acid with aldehydes or ketones (oxathiolan-5-ones)
8-18	Curtius rearrangement of cycloalkyl or aryl azides
8-22	Rearrangement of N-haloamines (cyclic amines)
8-36	Ring expansion of N-acylaziridines (oxazoles)
8-39	Cyclization of arylhydrazones (Fischer indole synthesis)
8-46	Acid-catalyzed rearrangement of N-haloamines (pyrrolidines; piperidines—Hofmann-Löffler)
9-1	Aromatization of heterocyclic rings
9-2	Cyclodehydrogenation
9-39	Reduction of α,β-unsaturated ketones (pyrazolones)
9-41	Reduction of lactams (cyclic amines)
9-42	Reduction of lactones (cyclic ethers)

Hydrates (*see gem*-Diols)

Hydrazides

0-54	Acylation of hydrazines with acyl halides
0-57	Acylation of hydrazines with esters

Hydrazines

3-18	Hydrazination of heterocyclic nitrogen compounds
5-9	Addition of hydrazines to olefins
8-17	Reaction between ureas and NaOBr (Hofmann)
9-52	Reduction of N-nitroso compounds
9-54	Reduction of azo compounds or diazonium salts
9-73	Reduction of nitro compounds

Hydrazo Compounds (*see* Hydrazines)

Hydrazones

2-7	Aliphatic diazonium coupling
6-21	Addition of hydrazines to aldehydes or ketones
9-11	Cleavage of double bonds with hydrazinium ion or diazonium salts

Hydroperoxides

0-32	Reaction between alkyl or acyl halides and hydrogen peroxide
2-22	Reaction between Grignard reagents and oxygen
4-8	Autoxidation; reaction of alkenes with singlet oxygen
5-7	Addition of mercaptans to olefins in the presence of oxygen

Hydroxamic Acids

0-54	Acylation of hydroxylamine with acyl halides
0-57	Acylation of hydroxylamine with esters
6-4	Hydrolysis of aliphatic nitro compounds

Hydroxy Acids

0-11	Hydrolysis of lactones
1-23	Carboxylation of phenols
2-22	Oxidation of dilithiated carboxylic acids
3-20	Hydroxylation of aromatic acids
6-5	Hydrolysis of cyanohydrins
6-32	Reaction between aldehydes or ketones and zinc carboxylates
6-42	Addition of dianions of carboxylic acids to ketones
8-7	Rearrangement of benzils
8-8	Rearrangement of α,β-epoxy ketones (Favorskii)
9-74	Reaction between keto aldehydes and base

Hydroxy Aldehydes and Ketones

0-6	Hydrolysis of diazo ketones
0-99	Reaction between dithiane salts and epoxides
0-100	Alkylation of oxazines with epoxides
1-34	Rearrangement of phenolic esters (Fries)
2-17	Alkylation of enamines with epoxides
4-4	Hydroxylation of ketones
6-27	Monoreduction of α-diketones
6-40	Condensation of aldehydes and/or ketones (aldol)
6-42	Reaction of ketones with tosylmethylazide and thallium ethoxide, followed by hydrolysis; reaction of aldehydes, ketones, or esters with methoxyvinyllithium
6-46	Condensation of formaldehyde with aldehydes or ketones (Tollens)
6-56	Condensation of aromatic aldehydes (benzoin)
6-76	Reaction of metalated aldimines with aldehydes or epoxides
8-4	Rearrangement of α-hydroxy aldehydes or ketones
8-7	Reaction between benzils and Grignard reagents
9-20	Oxidation of epoxides
9-23	Oxidation of alkenes
9-70	Condensation of esters (acyloin)

Hydroxyamines and Amides

0-51	Amination of epoxides
3-28	Rearrangement of aryl hydroxylamines (Bamberger)
4-4	Hydroxylation of amides
4-5	Hydroxylation of amines
5-42	Oxyamination of double bonds
6-14	Addition of ammonia to aldehydes or ketones
6-15	Addition of amines or amides to aldehydes or ketones
6-32	Reaction between aldehydes or ketones, zinc, and halo amides
6-36	Addition of Grignard reagents to oximes
8-45	Rearrangement of amino esters

Hydroxy Esters

0-25	Transesterification of lactones
0-105	Carbonylation of epoxides
4-4	Hydroxylation of esters
6-32	Reaction between aldehydes or ketones, zinc, and α-halo esters (Reformatsky)
6-41	Condensation between esters and aldehydes or ketones
6-42	Addition of α-metalated esters to ketones
6-55	Addition of aldehydes to alkynyl ethers
8-7	Rearrangement of benzils by means of alkoxide ion
8-45	Rearrangement of esters

Hydroxy Ethers

0-20	Alcoholysis of epoxides

Hydroxylamines

5-9	Addition of hydroxylamine to olefins
6-28	Reduction of oximes
7-8	Cleavage of amine oxides (Cope)
8-25	Rearrangement of N-oxides (Meisenheimer)
9-24	Oxidation of primary amines
9-51	Reduction of nitro compounds

Hydroxy Mercaptans and Sulfides

0-38 Reaction between epoxides and NaSH
0-39 Reaction between epoxides and mercaptides
6-12 Addition of H_2S to aldehydes or ketones

Hydroxy Nitriles

0-103 Reaction between epoxides and cyanide ion
6-32 Reaction between aldehydes and ketones, zinc, and halo nitriles
6-42 Addition of nitriles to ketones
6-50 Addition of HCN to aldehydes or ketones

Hydroxy Sulfonic Acids

0-44 Reaction between epoxides and bisulfite ion
6-13 Addition of bisulfite ion to aldehydes or ketones

Imides (including Ureides)

0-54 Reaction between acyl halides and lithium nitride
0-55 Amination of anhydrides
0-60 N-Alkylation of imides
0-61 N-Acylation of amides or imides
5-9 Addition of imides to olefins
5-25 Hydrocarboxylation of unsaturated amides
6-59 Addition of acids to nitriles
6-62 Dimerization and trimerization of isocyanates
6-74 Reaction of isonitriles, carboxylic acids, aldehydes or ketones, and secondary amines (Ugi)
6-75 Addition of N-halo amides to isonitriles
8-17 Reaction between amides and NaOBr (Hofmann)
8-18 Rearrangement of acyl azides in the presence of water (Curtius)
9-18 Oxidation of lactams

Imines

2-8 Reaction between active-hydrogen compounds and nitroso compounds
5-9 Addition of amines to triple-bond compounds
6-14 Addition of ammonia to aldehydes or ketones
6-15 Addition of amines to aldehydes or ketones
6-29 Reduction of nitrilium ions
6-38 Addition of Grignard reagents to nitriles
6-47 Addition of ylides to nitroso compounds
6-76 Reaction of isocyanides with organometallic compounds (metalated imines)
8-18 Pyrolysis of alkyl or aryl azides
8-22 Rearrangement of trityl N-haloamines and hydroxylamines (Stieglitz)
9-6 Dehydrogenation of secondary amines

Imino Esters (Imidates) and Their Salts

0-36 Reaction between oxonium ions and amides
1-30 Reaction of phenols with nitriles
5-72 Reaction of isonitriles with alcohols
6-10 Alcoholysis of nitriles (Pinner)
8-49 From amides

Inorganic Esters

0-33 Reaction of alcohols or alkyl halides with inorganic acids or halides
2-26 Oxidation of trialkylboranes
3-8 Reaction between aryl halides and $POCl_3$
5-4 Addition of inorganic acids to olefins

Isocyanates

0-54 Reaction between amines and phosgene
0-61 Reaction between oxalyl chloride and unsubstituted amides
0-64 Alkylation or acylation of cyanate ion
2-55 Carbonylation of amines
5-11 Addition of cyanic acid to vinyl ethers
5-36 Addition of iodine isocyanate to double bonds
8-17 Reaction between amides and NaOBr (Hofmann)
8-18 Rearrangement of acyl azides (Curtius)
8-19 Rearrangement of hydroxamic acids (Lossen)
8-20 Addition of hydrazoic acid to carboxylic acids (Schmidt)
9-31 Oxidation of isonitriles
9-60 Reaction of nitro compounds with CO

Isonitriles

0-53 Reaction between primary amines and chloroform
0-103 Reaction between alkyl halides and cyanide ion
7-42 Elimination of water from N-alkylformamides

Isothiocyanates

0-54 Reaction between amines and thiophosgene
0-64 Alkylation or acylation of thiocyanate ion
3-22 Reaction between diazonium salts and thiocyanate ion
6-20 Addition of amines to carbon disulfide
9-60 Reaction of nitro compounds with CS_2

Isothiuronium Salts

0-38 Reaction between alkyl halides and thiourea

Ketals (*see* Acetals)

Ketenes

7-1 Pyrolysis of carboxylic acids
7-14 Dehydrohalogenation of acyl halides
7-28 Dehalogenation of α-halo acyl halides
8-9 Rearrangement of diazo ketones (Wolff)

Ketenimines

0-100 Reaction of oxazines with butyllithium
6-47 Reaction between phosphoranes and isocyanates
7-1 Dehydration of amides

Keto Acids, Aldehydes, and Esters (*see* Dicarbonyl Compounds)

Ketones (*see also* Dicarbonyl Compounds, Unsaturated Carbonyl Compounds, etc.)

0-2 Hydrolysis of *gem*-dihalides
0-4 Hydrolysis of enol esters of inorganic acids
0-7 Hydrolysis of enol ethers, ketals, thioketals, etc.
0-11 Hydrolysis of enol esters
0-26 Alcoholysis of enol esters
0-30 Reaction between enol esters and carboxylic acids
0-77 Reduction of halo ketones
0-82 Reduction of diazo ketones
0-88 Coupling of halo ketones with lithium alkylcopper reagents
0-95 Arylation of diazo ketones or diazo esters
0-96 Acetoacetic ester synthesis and similar reactions
0-97 Alkylation of ketones
0-99 Alkylation and hydrolysis of dithianes and similar compounds
0-100 Alkylation and hydrolysis of oxazines
0-101 Reaction of halo ketones or diazo ketones with boranes
0-104 Carbonylation of alkyl halides
0-106 Reaction between acyl halides and organometallic compounds
0-107 Reaction between other acid derivatives and organometallic compounds
0-109 Acylation of active-hydrogen compounds followed by cleavage
0-112 Reduction of β-keto sulfoxides
0-113 Acylation of carboxylic acid salts followed by cleavage
0-114 Reduction of β-keto alkylidene phosphoranes
0-117 Ketonic decarboxylation
1-15 Acylation of aromatic rings (Friedel-Crafts)
1-22 Reaction between aromatic rings and phosgene
1-30 Acylation of aromatic rings with nitriles (Hoesch)
1-34 Rearrangement of phenolic ethers (Fries)
1-40 Photolysis of acylated arylamines
1-45 Reaction between arylcarbinols and diazonium salts (Stiles-Sisti)
1-50 Reaction of aryltrimethylsilanes with acyl chlorides
2-2 Rearrangement of hydroxy olefins
2-17 Alkylation of enamines followed by hydrolysis (Stork)
2-31 Carbonylation of organometallic compounds
2-39 Decarboxylation of β-keto acids or esters
2-40 Cleavage of tertiary alkoxides
2-41 Replacement of a carboxyl group by an acyl group
2-42 Basic cleavage of β-diketones
3-14 Arylation of ketones
4-18 Arylation of allylic alcohols
4-21 Acylation of nitrogen heterocycles
4-23 Free-radical acylation of alkanes
4-30 Reaction of diazonium salts with oximes, followed by hydrolysis
4-42 Decomposition of tertiary hypochlorites
5-3 Hydration of alkynes or allenes
5-6 Cyclization of olefinic acids
5-13 Reduction of phenols
5-15 Oxidation of boranes; hydrolysis of unsaturated boranes
5-19 Addition of ketones to activated olefins (Michael)
5-20 Addition of organometallic compounds to unsaturated ketones
5-21 Addition of boranes to unsaturated ketones
5-23 Free-radical addition of aldehydes or ketones to olefins
5-25 Hydrocarboxylation of dienes
5-26 Hydroacylation of alkenes
5-53 Hydrolysis of bicyclo[4.1.0]heptanes
6-2 Hydrolysis of imines, oximes, hydrazones, and other C=N compounds
6-4 Hydrolysis of secondary aliphatic nitro compounds (Nef)
6-33 Reaction between lithium carboxylates and alkyllithium compounds
6-38 Addition of Grignard reagents to nitriles
6-46 Methylation of ketones with formaldehyde

6-49 Reaction of phosphoranes with nitriles
6-76 Reaction of alkyl halides with metalated aldimines
7-1 Dehydration of 1,2-diols
7-8 Indirect migration of C=O via a Cope elimination
7-12 Pyrolysis of β-hydroxy sulfoxides
7-32 Fragmentation of γ-amino or γ-hydroxy halides
7-35 Fragmentation of 1,3-diols or γ-amino alcohols
7-40 Fragmentation of certain ketoximes
7-44 Alkaline hydrolysis of nitrates
7-45 Pyrolysis of β-hydroxy olefins
7-46 Pyrolysis of allyl ethers
8-2 Rearrangement of glycols and related compounds (pinacol)
8-3 Ring expansion of certain hydroxyamines (Tiffeneu-Demyanov)
8-4 Acid-catalyzed ketone rearrangements
8-10 Homologization of aldehydes or ketones
8-17 Reaction between α-hydroxy or α-halo amides and NaOBr (Hofmann)
8-24 Cleavage of hydroperoxides
8-28 Treatment of boranes with CO and H_2O, followed by NaOH and H_2O_2; or with CN^- followed by trifluoroacetic anhydride; from dialkylchloroboranes
8-31 Treatment of lithium alkynyltrialkylborates with electrophiles
8-48 Rearrangement of enol ethers
9-4 Oxidation of secondary alcohols
9-8 Oxidative cleavage of glycols and related compounds
9-9 Oxidative degradation of aldehydes
9-10 Ozonolysis of olefins
9-11 Oxidative cleavage of olefins
9-12 Oxidation of diarylmethanes
9-14 Oxidative cleavage of carboxylic acids
9-15 Bisdecarboxylation of malonic acids
9-16 Oxidation of activated methylene groups
9-20 Oxidation of secondary alkyl halides and tosylates
9-21 Oxidation of amines
9-23 Oxidation of olefins with noble-metal salts
9-39 Reduction of diketones or quinones
9-61 Oxidative decyanation of nitriles

Lactams

0-56 Cyclization of amino acids
0-57 Reaction between lactones and ammonia or amines
0-60 Cyclization of halo amides
5-9 Addition of lactams to olefins
5-25 Hydrocarboxylation of unsaturated amines
6-32 Reaction between imines, zinc, and halo esters
6-47 Reaction between imides and phosphoranes
6-70 Addition of ketenes to imines; addition of enamines to isocyanates
8-20 Reaction between cyclic ketones and hydrazoic acid (Schmidt)
8-21 Rearrangement of oximes of cyclic ketones (Beckmann)

Lactones

0-24 Cyclization of hydroxy acids
0-26 Cyclization of halo acids
5-6 Cyclization of olefinic acids
5-25 Hydrocarboxylation of unsaturated alcohols
5-47 Reaction of alkenes with manganese(III) acetate
6-47 Reaction of anhydrides with phosphoranes
6-68 Addition of ketenes to aldehydes or ketones
7-49 Extrusion of CO_2 from 1,2-dioxolane-3,5-diones
7-51 Decarboxylation of cyclic peroxides (Story)
8-23 Reaction between cyclic ketones and peroxy compounds (Baeyer-Villiger)
8-46 Rearrangement of N-halo amides
9-18 Oxidation of cyclic ethers
9-22 Oxidation of diols
9-43 Reduction of cyclic anhydrides

Mercaptals

5-7 Addition of mercaptans to alkynes
6-12 Addition of mercaptans to aldehydes or ketones

Mercaptans

0-11 Hydrolysis of thiol esters
0-38 Reaction of alkyl halides with NaSH; cleavage of isothiuronium salts
1-9 Sulfurization of aromatic compounds (Herz)
2-27 Reaction between Grignard reagents and sulfur
3-5 Reaction between aryl halides and NaSH
3-22 Reaction between diazonium salts and NaSH
5-7 Addition of H_2S to olefins
9-55 Reduction of sulfonyl halides
9-65 Reduction of disulfides

Metallocenes

2-34 Reaction between sodium cyclopentadienylide and metal halides

Monoesters of Dicarboxylic Acids

0-23 Alcoholysis of cyclic hydrides
0-25 Equilibration of dicarboxylic acids and esters
0-113 Acylation of carboxylic acid salts with chloroformates or carbonates
6-10 Alcoholysis of cyano acids

Nitriles (*see also* Dicyano Compounds, Cyano Carbonyl Compounds, etc.)

0-97 Alkylation of nitriles
0-101 Reaction of halo nitriles or diazo nitriles with boranes
0-103 Reaction between alkyl halides and cyanide ion
1-31 Direct cyanogenation of aromatic rings
2-32 Cyanogenation of organometallic compounds
2-39 Decarboxylation of α-cyano acids
3-11 Reaction between aryl halides and CuCN (Rosenmund–von Braun)
3-12 Cyanide fusion of sulfonic acid salts
3-14 Arylation of nitriles
4-28 Reaction between diazonium salts and CuCN (Sandmeyer)
4-39 Reaction of acyl peroxides with copper cyanide
4-41 Decarbonylation of aromatic acyl cyanides
5-19 Addition to activated olefins (Michael)
5-21 Addition of boranes to acrylonitrile
5-23 Free-radical addition of nitriles to olefins
5-28 Addition of HCN to olefins
6-5 Exchange of nitriles with carboxylic acids
6-23 From aldehydes
6-42 Reaction of ketones with tosylmethylisocyanide
6-44 From rhodanine
6-52 Reaction of HCN with carbomethoxy hydrazones, followed by treatment with Br_2 and then methoxide ions
6-63 Reaction between acid salts and BrCN
7-39 Dehydration of aldoximes and similar compounds
7-40 Fragmentation of ketoximes
7-41 Dehydration of amides
9-6 Dehydrogenation of amines
9-7 Oxidation of hydrazones
9-58 Reduction of nitrile oxides
9-62 Reduction of nitro compounds with $NaBH_2S_3$

Nitro Compounds

0-62 Reaction between alkyl halides and nitrite ion
0-96 Alkylation of nitro compounds
1-2 Nitration of aromatic rings
1-36 Rearrangement of N-nitro aromatic amines
2-39 Decarboxylation of α-nitro acids
2-50 N-Nitration of amines or amides
3-17 Methylation of aromatic nitro compounds
4-12 Nitration of paraffins
4-26 Reaction between diazonium salts and sodium nitrite
4-40 Decarboxylative nitration
5-19 Addition to activated olefins (Michael)
5-34 Addition of NOCl and other nitrogen compounds to olefins
5-43 Addition of N_2O_4 and other nitrogen compounds to olefins
6-42 Addition of nitro compounds to aldehydes or ketones
6-43 Carboxylation of nitro compounds
9-25 Oxidation of primary amines, oximes, or nitroso compounds

Nitrogen Ylides

2-19 Treatment of quaternary ammonium salts with organometallic compounds

Nitrones

0-35 Alkylation of oximes

Nitroso Compounds

1-3 Nitrosation of aromatic rings
1-37 Rearrangement of N-nitroso aromatic amines (Fischer-Hepp)
1-43 Nitrosative decarboxylation of aromatic acids
2-8 Nitrosation at a carbon bearing an active hydrogen
2-50 Reaction between secondary amines or amides and nitrous acid
5-34 Addition of NOCl to olefins
5-43 Addition of N_2O_3 to olefins
8-46 Photolysis of nitrites (Barton)
9-7 Oxidation of hydroxylamines
9-24 Oxidation of primary amines
9-50 Reduction of nitro compounds

Olefins (*see* Alkenes)

Organometallic Compounds

0-87 Reaction of alkyllithiums with alkylcopper reagents
2-19 Metalation of susceptible positions with organometallic compounds
2-20 Metalation of susceptible positions with metals or strong bases

2-21 Cleavage of alkyl groups from di- or polyvalent organometallic compounds
2-33 Reaction between an organometallic compound and a metal
2-34 Reaction between an organometallic compound and a metal halide
2-35 Reaction between an organometallic compound and an organometallic compound (exchange)
2-37 Metalation of alkyl or aryl halides with metals
2-38 Metalation of alkyl or aryl halides with organometallic compounds
4-31 Reaction of diazonium salts with metals
5-16 Hydrometalation of alkenes
8-15 Rearrangement of Grignard reagents

Ortho Esters

0-14 Reaction of alkoxides with 1,1,1-trihalides (Williamson)
0-19 Transetherification
6-6 Addition of alcohols to formic acid
6-9 Reaction between imino ester salts and alcohols

Osazones

6-21 Addition of hydrazines to α-hydroxy aldehydes or ketones

Oxime Ethers

0-17 Alkylation of oximes with diazo compounds
0-35 Alkylation of oximes with alkyl sulfates

Oximes

2-8 Nitrosation at a carbon bearing an active hydrogen
5-34 Addition of NOCl to olefins
6-22 Addition of hydroxylamine to aldehydes or ketones
8-46 Photolysis of nitrites (Barton)
9-24 Oxidation of aliphatic primary amines
9-62 Reduction of nitro compounds

Oxiranes (*see* Epoxides)

Oxonium Salts

0-31 Reaction between alkyl halides and ethers or ketones

Ozonides

9-10 Ozonolysis of olefins

Peresters

0-32 Reaction of acyl halides with hydroperoxides

Peroxides (*see also* Hydroperoxides, Peresters)

0-32 Reaction of alkyl and acyl halides with sodium or hydrogen peroxide
4-9 Reaction between hydroperoxides and susceptible hydrocarbons
5-5 Oxymercuration-reduction of alkenes in the presence of a hydroperoxide
5-41 Photooxidation of dienes
7-51 Reaction of ketones with H_2O_2

Peroxy Acids

9-33 Oxidation of carboxylic acids

Phenols

0-7 Acid cleavage of alkyl aryl ethers
0-11 Hydrolysis of phenolic esters
0-33 Cleavage of phenolic ethers with sulfonic acids
0-39 Cleavage of phenolic ethers
0-68 Cleavage of phenolic ethers with HI or HBr
0-92 Cleavage of aryl ethers with Grignard reagents
1-32 Electrophilic hydroxylation of aromatic rings
1-34 Rearrangement of phenolic esters (Fries)
1-35 Rearrangement of phenolic ethers
1-48 Debromination of bromophenols
2-22 Oxidation of Grignard reagents
2-23 Oxidation of arylthallium compounds
3-1 Hydrolysis of aryl halides and other compounds
3-2 Reaction between naphthylamines and bisulfite ion (Bucherer)
3-3 Alkali fusion of sulfonates
3-20 Nucleophilic hydroxylation of aromatic acids
3-21 Hydrolysis of diazonium salts
3-28 Rearrangement of N-hydroxylamines
4-5 Free-radical hydroxylation of aromatic rings
6-27 Reduction of quinones
8-6 The dienone-phenol rearrangement
8-23 Cleavage of aryl ketones with peracids (Baeyer-Villiger)
8-38 Rearrangement of allyl aryl ethers (Claisen)
8-50 Rearrangement of azoxy compounds (Wallach)
9-1 Aromatization of cyclic ketones

9-13 Oxidative cleavage of alkylbenzenes or aromatic aldehydes
9-44 Reduction of phenolic esters

Phosphines

0-46 Reaction between alkyl halides and phosphine
0-82 Reduction of quaternary phosphonium salts
2-34 Reaction between phosphorus halides and Grignard reagents

Phosphonates

6-47 Reaction between alkyl halides and phosphites

Phosphoranes

0-114 Acylation of phosphoranes
6-47 Treatment of phosphonium ions with alkyllithiums; addition of halocarbenes to phosphines

Quaternary Ammonium and Phosphonium Salts

0-46 Alkylation of amines (Menschutkin) or phosphines
5-9 Addition of tertiary amines to alkenes
6-47 Reaction of phosphines with Michael olefins or with alkyl halides

Quinones

1-15 Intramolecular Friedel-Crafts acylation of diaryl ketones
9-5 Oxidation of phenols or aromatic amines
9-19 Oxidation of aromatic hydrocarbons

Schiff Bases (*see* Imines)

Selenides

0-39 Selenylation of alkyl halides
2-12 Selenylation of aldehydes, ketones, and esters
2-27 Selenylation of organometallic compounds

Semicarbazones

6-21 Addition of semicarbazide to aldehydes or ketones

Sulfenimides

0-60 Reaction of alkyl halides with $(PhS)_2NLi$

Sulfenyl Chlorides

4-11 Chlorosulfenation

Sulfides

0-39 Reaction between alkyl halides and mercaptides or Na_2S
0-99 Alkylation of sulfides
1-9 Sulfurization of aromatic rings
1-29 Thioalkylation of aromatic rings
2-12 Sulfenylation of ketones and esters
2-27 Reaction between Grignard reagents and sulfur
3-5 Reaction between aryl halides or phenols and mercaptides or Na_2S
3-22 Reaction between diazonium salts and mercaptides or Na_2S
4-33 Reaction of boranes with disulfides
5-7 Addition of mercaptans to olefins
5-32 Addition of sulfenyl chlorides to olefins
7-11 Cleavage of sulfonium compounds
8-25 Rearrangement of sulfonium salts (Stevens)
8-40 [2,3] sigmatropic rearrangements of sulfur ylides
9-42 Reduction of thiol esters
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