18

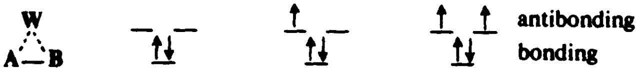
REARRANGEMENTS

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), but some are over

$$\overset{\displaystyle W}{\underset{}{\overset{|}{A}}}\text{—}B \longrightarrow A\text{—}\overset{\displaystyle W}{\overset{|}{B}}$$

longer distances. The migrating group (W) may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can 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 that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (**8-29** to **8-38**).

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



1 **Nucleophilic** **Free radical** **Electrophilic**

orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free-radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those on p. 52 (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 that 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 that 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. 1065).

In any rearrangement we can in principle distinguish between two possible modes of reaction: In one of these the group W becomes completely detached from A and may end

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[1] For books, see Mayo *Rearrangements in Ground and Excited States*, 3 vols.; Academic Press: New York, 1980; Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973. For a review of many of these rearrangements, see Collins; Eastham, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 761-821. See also the series *Mechanisms of Molecular Migrations*.

up on the B atom of a different molecule (*intermolecular* rearrangement); 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 inter- or intramolecular. 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 vs. 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.

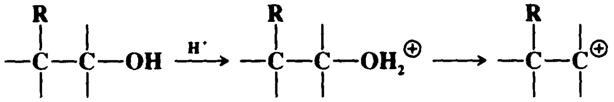
MECHANISMS

Nucleophilic Rearrangements[2]

Broadly speaking, such rearrangements consist of three steps, of which the actual migration is the second:

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 carbocation.* These can be formed in a number of ways (see p. 173), but one of the most common methods when a rearrangement is desired is the acid treatment of an alcohol:

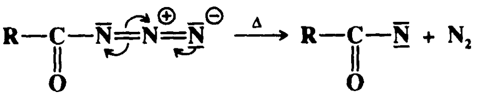


$$-\overset{R}{\underset{|}{\overset{|}{C}}}-\underset{|}{\overset{|}{C}}-OH \xrightarrow{H^+} -\overset{R}{\underset{|}{\overset{|}{C}}}-\underset{|}{\overset{|}{C}}-OH_2^{\oplus} \longrightarrow -\overset{R}{\underset{|}{\overset{|}{C}}}-\underset{|}{\overset{|}{C}}^{\oplus}$$

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. 202):



$$R-\underset{\underset{O}{\|}}{C}-\overline{N}=\overset{\oplus}{N}=\overline{N}^{\ominus} \xrightarrow{\Delta} R-\underset{\underset{O}{\|}}{C}-\overline{N} + N_2$$

3

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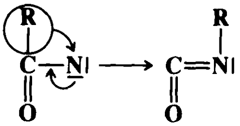
[2] For reviews, see Vogel *Carbocation Chemistry*; Elsevier: New York, 1985, pp. 323-372; Shubin *Top. Curr. Chem.* **1984,** *116/117,* 267-341; Saunders; Chandrasekhar; Schleyer, in Mayo, Ref. 1, vol. 1, pp. 1-53; Kirmse *Top. Curr. Chem.* **1979,** *80,* 89-124. For reviews of rearrangements in vinylic cations, see Shchegolev; Kanishchev *Russ. Chem. Rev.* **1981,** *50,* 553-564; Lee *Isot. Org. Chem.* **1980,** *5,* 1-44.

[3] It was first postulated by Whitmore *J. Am. Chem. Soc.* **1932,** *54,* 3274.

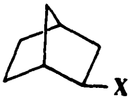
After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step this atom acquires an octet. In the case of carbocations, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination).

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 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 many 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. 1055, 1090), but the difference between the two possibilities is often subtle, and the question is not always easily answered.[4]

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbocations: 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,[5] so that the first step is carbocation formation. The same compound under SN2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. 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 carbocation rearrangement reactions.



4

It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.[6]

We have previously mentioned (p. 166) that stable tertiary carbocations 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

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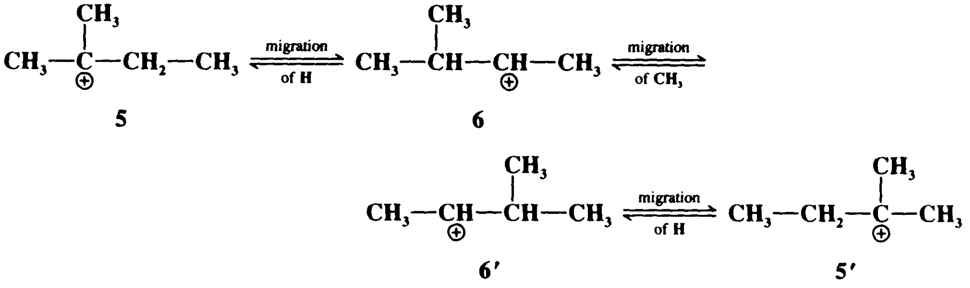
[4] The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie *Pure Appl. Chem.* **1989**, *61*, 23-56, pp. 44-45.

[5] Dostrovsky; Hughes *J. Chem. Soc.* **1946**, 166.

[6] Borodkin; Shakirov; Shubin; Koptyug *J. Org. Chem. USSR* **1976**, *12*, 1293, 1298, **1978**, *14*, 290, 924.

equilibrium mixture of structures.[7] For example, the *t*-pentyl cation (**5**)[8] equilibrates as follows:



$$CH_3-\overset{CH_3}{\underset{\oplus}{C}}-CH_2-CH_3 \underset{\text{of H}}{\overset{\text{migration}}{\rightleftharpoons}} CH_3-\overset{CH_3}{CH}-\underset{\oplus}{CH}-CH_3 \underset{\text{of CH}_3}{\overset{\text{migration}}{\rightleftharpoons}}$$

5 **6**

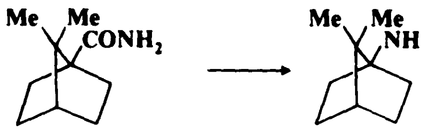
$$CH_3-\underset{\oplus}{CH}-\overset{CH_3}{CH}-CH_3 \underset{\text{of H}}{\overset{\text{migration}}{\rightleftharpoons}} CH_3-CH_2-\overset{CH_3}{\underset{\oplus}{C}}-CH_3$$

6′ **5′**

Carbocations that rearrange to give products of identical structure(e.g., **5** ⇄ **5′**, **6** ⇄ **6′**) are called *degenerate carbocations* and such rearrangements are *degenerate rearrangements*. Many examples are known.[9]

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 (**8-15**), Hofmann (**8-14**), Lossen (**8-16**), and Schmidt (**8-17**) reactions.[10] 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.[11] Another experiment demonstrating



7 **8**

retention was the easy conversion of **7** to **8**.[11] 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.[13] However, this is not the state of affairs at A and B. In

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[7] For reviews, see Brouwer; Hogeveen *Prog. Phys. Org. Chem.* **1972,** *9,* 179-240, pp. 203-237; Olah; Olah, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 751-760, 766-778. For a discussion of the rates of these reactions, see Sorensen *Acc. Chem. Res.* **1976,** *9,* 257-265.

[8] Brouwer *Recl. Trav. Chim. Pays-Bas* **1968,** *87,* 210; Saunders; Hagen *J. Am. Chem. Soc.* **1968,** *90,* 2436.

[9] For reviews, see Ahlberg; Jonsäll; Engdahl *Adv. Phys. Org. Chem.* **1983,** *19,* 223-379; Leone; Barborak; Schleyer, in Olah; Schleyer, Ref. 7, vol. 4, pp. 1837-1939; Leone; Schleyer *Angew. Chem. Int. Ed. Engl.* **1970,** *9,* 860-890 [*Angew. Chem.* *82,* 889-919].

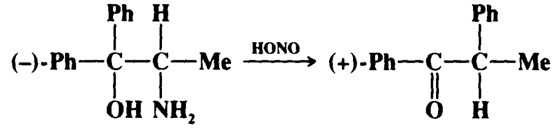
[10] Arcus; Kenyon *J. Chem. Soc.* **1939,** 916; Kenyon; Young *J. Chem. Soc.* **1941,** 263; Campbell; Kenyon *J. Chem. Soc.* **1946,** 25.

[11] For retention of migrating group configuration in the Wagner-Meerwein and pinacol rearrangements, see Beggs; Meyers *J. Chem. Soc. B* **1970,** 930; Kirmse; Gruber; Knist *Chem. Ber.* **1973,** *106,* 1376; Shono; Fujita; Kumai *Tetrahedron Lett.* **1973,** 3123; Borodkin; Panova; Shakirov; Shubin *J. Chem. Soc., Chem. Commun.* **1979,** 354, *J. Org. Chem. USSR* **1983,** *19,* 103.

[12] Barlett; Knox *J. Am. Chem. Soc.* **1939,** *61,* 3184.

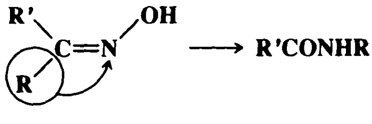
[13] See Cram, in Newman *Steric Effects in Organic Chemistry*; Wiley: New York, 1956; pp. 251-254; Wheland *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1960, pp. 597-604.

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:[14]



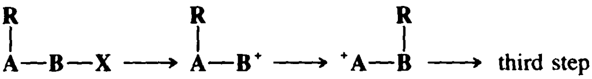
$$(-)\text{-Ph}-\underset{\text{OH}}{\overset{\text{Ph}}{\text{C}}}-\underset{\text{NH}_2}{\overset{\text{H}}{\text{C}}}-\text{Me}\xrightarrow{\text{HONO}}(+)\text{-Ph}-\underset{\text{O}}{\overset{}{\overset{\|}{\text{C}}}}-\underset{\text{H}}{\overset{\text{Ph}}{\text{C}}}-\text{Me}\qquad(8\text{-}2)$$

and inversion at A has been shown in other cases.[15] However, in many other cases, racemization occurs at A or B or both.[16] 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 (**8-18**), only the group trans (usually called *anti*) to the hydroxyl group migrates:



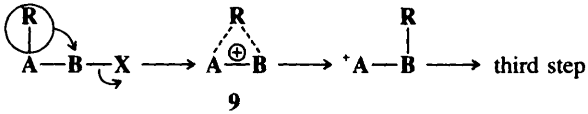
showing inversion at B.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First consider the migration terminus B. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:



$$\overset{\text{R}}{\overset{|}{\text{A}}}-\text{B}-\text{X}\longrightarrow\overset{\text{R}}{\overset{|}{\text{A}}}-\text{B}^+\longrightarrow{}^+\text{A}-\overset{\text{R}}{\overset{|}{\text{B}}}\longrightarrow\text{third step}$$

With respect to B this is an SN1-type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation 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. 309). Indeed, R *is* a neighboring group here. 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

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[14] Bernstein; Whitmore *J. Am. Chem. Soc.* **1939,** *61*, 1324. For other examples, see Tsuchihashi; Tomooka; Suzuki *Tetrahedron Lett.* **1984,** *25*, 4253.

[15] See Meerwein; van Emster *Ber.* **1920,** *53*, 1815, **1922,** *55*, 2500; Meerwein; Gérard *Liebigs Ann. Chem.* **1923,** *435*, 174.

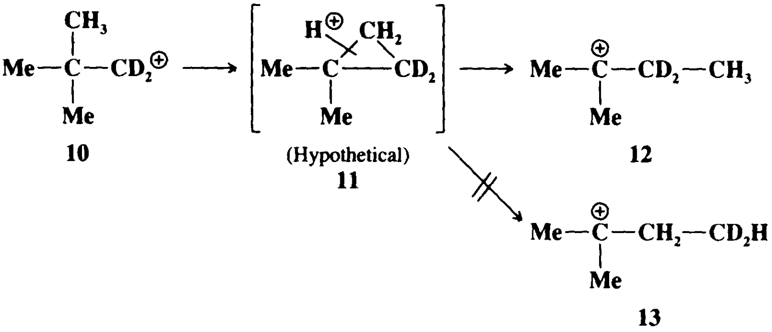
[16] For example, see Winstein; Morse *J. Am. Chem. Soc.* **1952,** *74*, 1133.

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 antiperiplanar). **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 carbocation.[17]

We may summarize a few conclusions:

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 (indicating an SN2-type process) has been shown for a neopentyl substrate by the use of the chiral neopentyl-1-*d* alcohol.[18] On the other hand, there is other evidence that neopentyl systems undergo rearrangement by a carbocation (SN1-type) mechanism.[19]

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[20] (see p. 319 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. 757). 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. 325). 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**).[21] Another experiment that led to the same conclusion was the generation, in several ways, of $\mathrm{Me_3C^{13}CH_2^+}$. In this case the only *t*-pentyl products isolated were labeled in C-3, that is, $\mathrm{Me_2}\overset{\oplus}{\mathrm{C}}\text{—}{}^{13}\mathrm{CH_2CH_3}$ derivatives; no derivatives of $\mathrm{Me_2}\overset{\oplus}{\mathrm{C}}\text{—}\mathrm{CH_2}{}^{13}\mathrm{CH_3}$ were found.[22]



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[17] Benjamin; Collins *J. Am. Chem. Soc.* **1961,** *83,* 3662; Collins; Staum; Benjamin *J. Org. Chem.* **1962,** *27,* 3525; Collins; Benjamin *J. Org. Chem.* **1972,** *37,* 4358.

[18] Sanderson; Mosher *J. Am. Chem. Soc.* **1966,** *88,* 4185; Mosher *Tetrahedron* **1974,** *30,* 1733. See also Guthrie, *J. Am. Chem. Soc.* **1967,** *89,* 6718.

[19] Nordlander; Jindal; Schleyer; Fort; Harper; Nicholas *J. Am. Chem. Soc.* **1966,** *88,* 4475; Shiner; Imhoff *J. Am. Chem. Soc.* **1985,** *107,* 2121.

[20] For example, see Rachon; Goedkin; Walborsky *J. Org. Chem.* **1989,** *54,* 1006. For an opposing view, see Kirmse; Feyen *Chem. Ber.* **1975,** *108,* 71; Kirmse; Plath; Schaffrodt *Chem. Ber.* **1975,** *108,* 79.

[21] Skell; Starer; Krapcho *J. Am. Chem. Soc.* **1960,** *82,* 5257.

[22] Karabastos; Graham *J. Am. Chem. Soc.* **1960,** *82,* 5250; Karabatsos; Orzech; Meyerson *J. Am. Chem. Soc.***1964,** *86,* 1994.

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.[23] Among this evidence is the isolation of 10 to 15% cyclopropanes (mentioned on p. 325). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($CH_3CH_2CD_2^+$, $CH_3CD_2CH_2^+$, $CH_3CH_2{}^{14}CH_2^+$), 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.,[24]

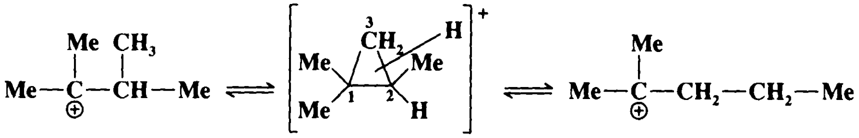
$$CH_3CH_2CD_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D{-}CHD{-}OH$$

$$CH_3CD_2CH_2NH_2 \xrightarrow{HONO} \sim 1\%\ C_2H_4D{-}CHD{-}OH$$

$$CH_3CH_2{}^{14}CH_2NH_2 \xrightarrow{HONO} \sim 2\%\ {}^{14}CH_3CH_2CH_2OH + \sim 2\%\ CH_3{}^{14}CH_2CH_2OH$$

Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-^{14}C-mercuric perchlorate.[25] However, protonated cyclopropane intermediates accounted for less than 1% of the products from diazotization of labeled isobutylamine[26] and from formolysis of labeled 1-propyl tosylate.[27]

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 ions **14** and **16** are in equilibrium. It is not possible for these to interconvert solely by 1,2 alkyl or hydride shifts unless primary carbocations (which are highly unlikely) are intermediates. However, the reaction can be explained[28] 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 that 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 that opens).



14 **15** **16**

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 or is not a true intermediate, though both positions have been argued (see p. 325).

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[23] For reviews, see Saunders; Vogel; Hagen; Rosenfeld *Acc. Chem. Res.* **1973,** *6*, 53-59; Lee *Prog. Phys. Org. Chem.* **1970,** *7*, 129-187; Collins *Chem. Rev.* **1969,** *69*, 543-550. See also Cooper; Jenner; Perry; Russell-King; Storesund; Whiting *J. Chem. Soc., Perkin Trans. 2* **1982,** 605.

[24] Lee; Kruger; Wong *J. Am. Chem. Soc.* **1965,** *87*, 3985; Lee; Kruger *J. Am. Chem. Soc.* **1965,** *87*, 3986, *Tetrahedron* **1967,** *23*, 2539; Karabatsos; Orzech; Meyerson *J. Am. Chem. Soc.* **1965,** *87*, 4394; Lee; Wan *J. Am. Chem. Soc.* **1969,** *91*, 6416; Karabatsos; Orzech; Fry; Meyerson *J. Am. Chem. Soc.* **1970,** *92*, 606.

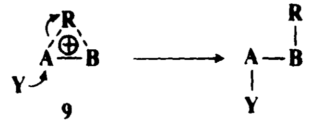
[25] Lee; Cessna; Ko; Vassie *J. Am. Chem. Soc.* **1973,** *95*, 5688. See also Lee; Chwang *Can. J. Chem.* **1970,** *48*, 1025; Lee; Law *Can. J. Chem.* **1971,** *49*, 2746; Lee; Reichle *J. Org. Chem.* **1977,** *42*, 2058.

[26] Karabatsos; Hsi; Meyerson *J. Am. Chem. Soc.* **1970,** *92*, 621. See also Karabatsos; Anand; Rickter; Meyerson *J. Am. Chem. Soc.* **1970,** *92*, 1254.

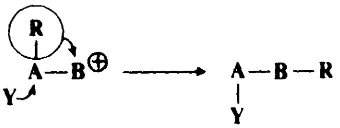
[27] Lee; Kruger *Can. J. Chem.* **1966,** *44*, 2343; Shatkina; Lovtsova; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967,** 2616; Karabatsos; Fry; Meyerson *J. Am. Chem. Soc.* **1970,** *92*, 614. See also Lee; Zohdi *Can. J. Chem.* **1983,** *61*, 2092.

[28] Brouwer; Oelderik *Recl. Trav. Chim. Pays-Bas* **1968,** *87*, 721; Saunders; Jaffe; Vogel *J. Am. Chem. Soc.* **1971,** *93*, 2558; Saunders; Vogel *J. Am. Chem. Soc.* **1971,** *93*, 2559, 2561; Kirmse; Loosen; Prolingheuer *Chem. Ber.* **1980,** *113*, 129.

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:



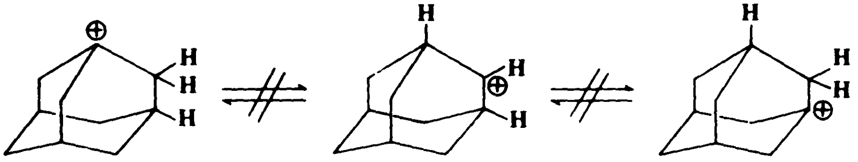
inversion at A and B



inversion at A only

In some cases it has been found that, when H is the migrating species, the configuration at A may be *retained.*[29]

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,[30] though open-chain (e.g., **5** ⇄ **5'**) and cyclic tertiary carbocations undergo such equilibration at 0°C



17 **17'**

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,[30] which is not possible for **17.**

Migratory Aptitudes[31]

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 (**8-18**) provides an example. As we have seen, only the group

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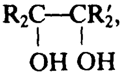
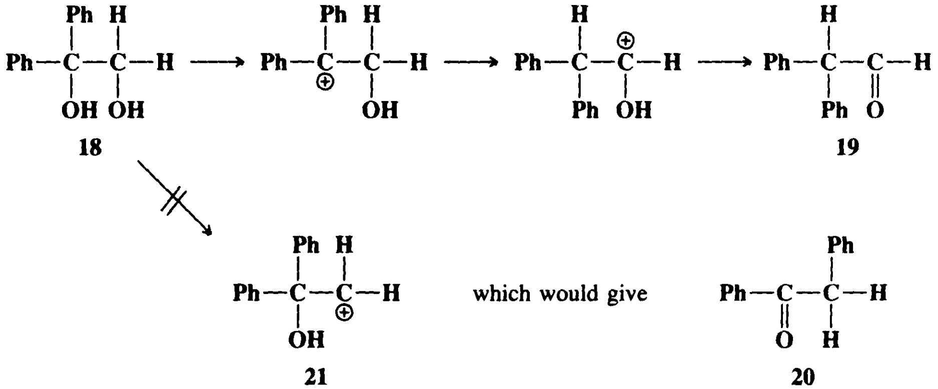
[29] Winstein; Holness *J. Am. Chem. Soc.* **1955,** *77*, 5562; Cram; Tadanier *J. Am. Chem. Soc.* **1959,** *81*, 2737; Bundel'; Pankratova; Gordin; Reutov *Doklad. Chem.* **1971,** *199*, 700; Kirmse; Arold *Chem. Ber.* **1971,** *104*, 1800; Kirmse; Ratajczak; Rauleder *Chem. Ber.* **1977,** *110*, 2290.

[30] Brouwer; Hogeveen *Recl. Trav. Chim. Pays-Bas* **1970,** *89*, 211; Majerski; Schleyer; Wolf *J. Am. Chem. Soc.* **1970,** *92*, 5731.

[31] For discussions, see Koptyug; Shubin *J. Org. Chem. USSR* **1980,** *16*, 1685-1714; Wheland, Ref. 13, pp. 573-597.

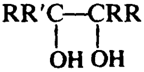
trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 1002), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.[32] However, in some reactions, especially the Wagner–Meerwein (**8-1**) and the pinacol (**8-2**) rearrangements, the molecule may contain several groups that, 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  $R_2\underset{\displaystyle OH}{\underset{|}{C}}\text{—}\underset{\displaystyle OH}{\underset{|}{C}}R'_2$, 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 that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (**18**) gives diphenylacetaldehyde (**19**), not phenylacetophenone (**20**).



18 **19** **21** **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 know, carbocation 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 **41,** p. 1073).

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is  $RR'\underset{\displaystyle OH}{\underset{|}{C}}\text{—}\underset{\displaystyle OH}{\underset{|}{C}}RR'$, since the same carbocation 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 that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.[33] Thus, migration of R gives rise to the cation

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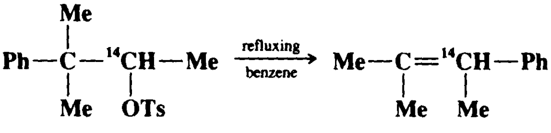
[32] For a discussion, see Cram, Ref. 13, pp. 270-276. For an interesting example, see Nickon; Weglein *J. Am. Chem. Soc.* **1975,** 97, 1271.

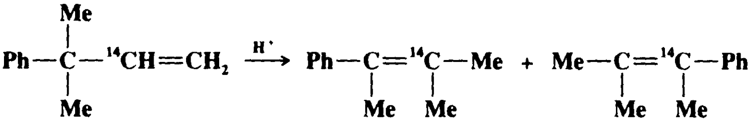
[33] For example, see Howells; Warren *J. Chem. Soc., Perkin Trans. 2* **1973,** 1645; McCall; Townsend; Bonner *J. Am. Chem. Soc.* **1975,** 97, 2743; Brownbridge; Hodgson; Shepherd; Warren *J. Chem. Soc., Perkin Trans. 1* **1976,** 2024.

$R'\overset{\oplus}{C}(OH)CR_2R'$, while migration of R′ gives the cation $R\overset{\oplus}{C}(OH)CRR_2'$ 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 corresponding



$$\mathrm{Ph{-}\overset{Me}{\underset{Me}{C}}{-}\underset{OTs}{^{14}CH}{-}Me} \xrightarrow[\text{benzene}]{\text{refluxing}} \mathrm{Me{-}\underset{Me}{C}{=}\underset{Me}{^{14}CH}{-}Ph}$$

22



$$\mathrm{Ph{-}\overset{Me}{\underset{Me}{C}}{-}^{14}CH{=}CH_2} \xrightarrow{H^+} \mathrm{Ph{-}\underset{Me}{C}{=}\underset{Me}{^{14}C}{-}Me} + \mathrm{Me{-}\underset{Me}{C}{=}\underset{Me}{^{14}C}{-}Ph}$$

23

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).[34] **22** and **23** give the same carbocation; 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 terminus and one that proceeds with the migrating group lending anchimeric assistance.[35]

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 that 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.[36] 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:[37] *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

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[34] Grimaud; Laurent *Bull. Soc. Chim. Fr.* **1967,** 3599.

[35] A number of studies of migratory aptitudes in the dienone-phenol rearrangement (**8-5**) are in accord with the above. For a discussion, see Fischer; Henderson *J. Chem. Soc., Chem. Commun.* **1979,** 279, and references cited therein. See also Palmer; Waring *J. Chem. Soc,. Perkin Trans. 2* **1979,** 1089; Marx; Hahn *J. Org. Chem.* **1988,** *53,* 2866.

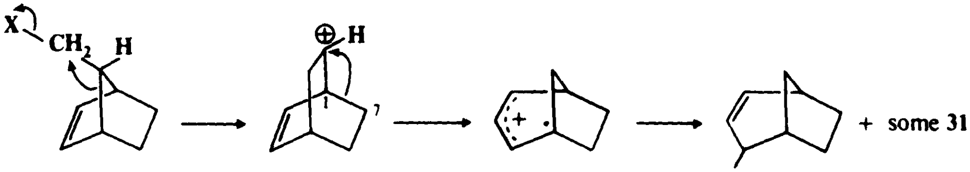
[36] For examples, see Cram; Knight *J. Am. Chem. Soc.* **1952,** *74,* 5839; Stiles; Mayer *J. Am. Chem. Soc.* **1959,** *81,* 1497; Heidke; Saunders *J. Am. Chem. Soc.* **1966,** *88,* 5816; Dubois; Bauer *J. Am. Chem. Soc.* **1968,** *90,* 4510, 4511; Bundel'; Levina; Reutov *J. Org. Chem. USSR* **1970,** *6,* 1; Pilkington; Waring *J. Chem. Soc., Perkin Trans. 2* **1976,** 1349; Korchagina; Derendyaev; Shubin; Koptyug *J. Org. Chem. USSR* **1976,** *12,* 378; Wistuba; Rüchardt *Tetrahedron Lett.* **1981,** *22,* 4069; Jost; Laali; Sommer *Nouv. J. Chim.* **1983,** *7,* 79.

[37] Bachmann; Ferguson *J. Am. Chem. Soc.* **1934,** *56,* 2081.

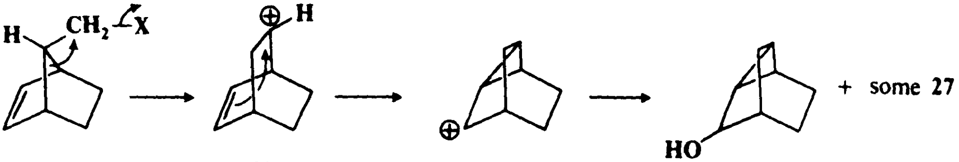
steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.[38]

Memory Effects[39]

Solvolysis of the endo bicyclic compound **24** (X = ONs, p. 353, or Br) gave mostly the bicyclic allylic alcohol **27**, along with a smaller amount of the tricyclic alcohol **31**, while

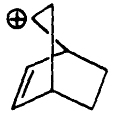


24 **25** **26** **27**

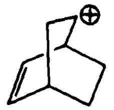


28 **29** **30** **31**

solvolysis of the exo isomers **28** gave mostly **31**, with smaller amounts of **27**.[40] Thus the two isomers gave entirely different ratios of products, though the carbocation 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** what follows is an intramolecular addition of the positive carbon to the double bond. 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 known.[41] 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 that are twisted in opposite senses (e.g., a twisted **29** might have its positive carbon



Twisted **29**



Twisted **25**

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[38] Le Drian; Vogel *Helv. Chim. Acta* **1987**, *70*, 1703, *Tetrahedron Lett.* **1987**, *28*, 1523.

[39] For a review, see Berson *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 779-791 [*Angew. Chem. 80*, 765-777].

[40] Berson; Poonian; Libbey *J. Am. Chem. Soc.* **1969**, *91*, 5567; Berson; Donald; Libbey *J. Am. Chem. Soc.* **1969**, *91*, 5580; Berson; Wege; Clarke; Bergman *J. Am. Chem. Soc.* **1969**, *91*, 5594, 5601.

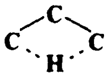
[41] For examples of memory effects in other systems, see Berson; Gajewski; Donald *J. Am. Chem. Soc.*, **1969**, *91*, 5550; Berson; Luibrand; Kundu; Morris *J. Am. Chem. Soc.* **1971**, *93*, 3075; Collins *Acc. Chem. Res.* **1971**, *4*, 315-322; Collins; Glover; Eckart; Raaen; Benjamin; Benjaminov *J. Am. Chem. Soc.* **1972**, *94*, 899; Svensson *Chem. Scr.* **1974**, *6*, 22.

closer to the double bond than a twisted **25**); (2) that ion pairing is responsible;[42] and (3) that nonclassical carbocations are involved.[43] 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 some **27** along with **31**. This means that some of the **25** and **29** ions interconvert, a phenomenon known as *leakage*.

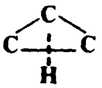
Longer Nucleophilic Rearrangements

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, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that 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, 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.[44] 1,3 Migration of bromine has been reported.[45]

However, most of the debate over the possibility of 1,3 migrations has concerned not methyl or bromine but 1,3 hydride shifts.[46] There is no doubt that *apparent* 1,3 hydride shifts take place (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. 1057). 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 **B**. The evidence is that most reported 1,3 hydride shifts are actually the result of successive 1,2 migrations,[47] 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 **32**:[48]



A



B

$$CH_3-CH_2-\overset{\displaystyle CH_3}{\overset{|}{C}H}-CH_2-OH \xrightarrow{KOH} 1.2\%\ CH_2{=}CH-\overset{\displaystyle CH_3}{\overset{|}{C}H}-CH_3$$

32

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[42] See Collins *Chem. Soc. Rev.* **1975**, *4*, 251-262.

[43] See, for example, Seybold; Vogel; Saunders; Wiberg *J. Am. Chem. Soc.* **1973**, *95*, 2045; Kirmse; Günther *J. Am. Chem. Soc.* **1978**, *100*, 3619.

[44] Skell; Reichenbacher *J. Am. Chem. Soc.* **1968**, *90*, 2309.

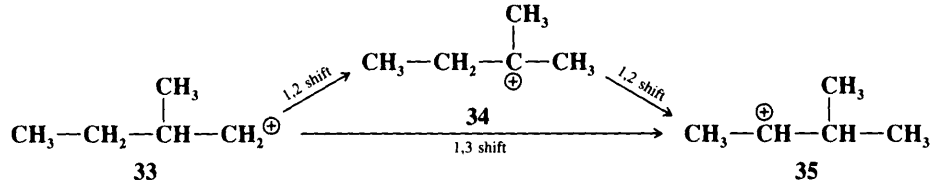
[45] Reineke; McCarthy *J. Am. Chem. Soc.* **1970**, *92*, 6376; Smolina; Gopius; Gruzdneva; Reutov *Doklad. Chem.* **1973**, *209*, 280.

[46] For a review, see Fry; Karabatsos, in Olah; Schleyer, Ref. 7, vol. 2, pp. 527-566.

[47] For example, see Bundel'; Levina; Krzhizhevskii; Reutov *Doklad. Chem.* **1968**, *181*, 583; Fărcaşiu; Kascheres; Schwartz *J. Am. Chem. Soc.* **1972**, *94*, 180; Kirmse; Knist; Ratajczak *Chem. Ber.* **1976**, *109*, 2296.

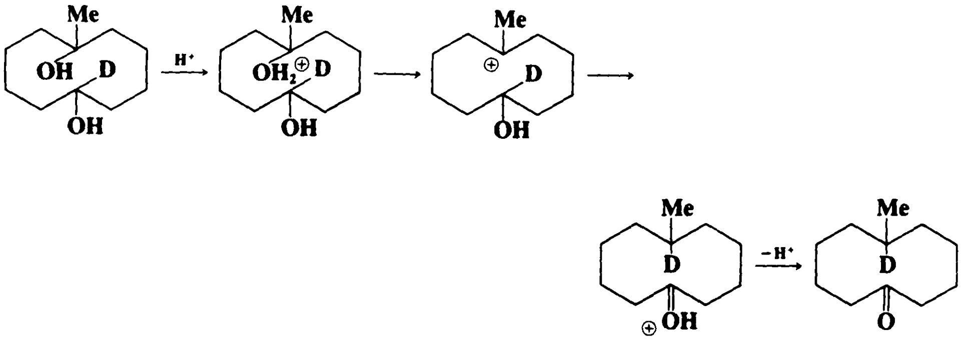
[48] Skell; Maxwell *J. Am. Chem. Soc.* **1962**, *84*, 3963. See also Skell; Starer *J. Am. Chem. Soc.* **1962**, *84*, 3962.

Hypothetically, **32** could have arisen from a 1,3 shift (direct or through a protonated cyclopropane) or from two successive 1,2 shifts:



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[49] 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. 1056, 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.[50]

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.[51] Several examples are given on p. 157. This is the mechanism of one of these:[52]



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.[53] In most cases it is hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.[54]

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[49] For example, see Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1969**, *8*, 573; Dupuy; Goldsmith; Hudson *J. Chem. Soc., Perkin Trans. 2* **1973**, 74; Hudson; Koplick; Poulton *Tetrahedron Lett.* **1975**, 1449; Fry; Karabatsos, Ref. 46.

[50] Saunders; Stofko *J. Am. Chem. Soc.* **1973**, *95*, 252.

[51] For reviews, see Cope; Martin; McKervey *Q. Rev. Chem. Soc.* **1966**, *20*, 119-152. For many references, see Blomquist; Buck *J. Am. Chem. Soc.* **1951**, *81*, 672.

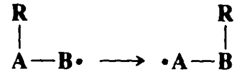
[52] Prelog; Küng *Helv. Chim. Acta* **1956**, *39*, 1394.

[53] For an apparent exception, see Fărcaşiu; Seppo; Kizirian; Ledlie; Sevin *J. Am. Chem. Soc.* **1989**, *111*, 8466.

[54] Cope; Burton; Caspar *J. Am. Chem. Soc.* **1962**, *84*, 4855.

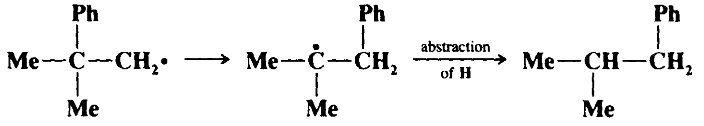
Free-Radical Rearrangements[55]

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned on p. 1051. 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:



$$\overset{\mathrm{R}}{\overset{|}{\mathrm{A}}}-\mathrm{B}\cdot \longrightarrow \cdot\mathrm{A}-\overset{\mathrm{R}}{\overset{|}{\mathrm{B}}}$$

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 carbocation 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 (**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:[56]



$$\mathrm{Me}-\overset{\mathrm{Ph}}{\underset{\mathrm{Me}}{\mathrm{C}}}-\mathrm{CH_2}\cdot \longrightarrow \mathrm{Me}-\underset{\mathrm{Me}}{\dot{\mathrm{C}}}-\overset{\mathrm{Ph}}{\mathrm{CH_2}} \xrightarrow[\text{of H}]{\text{abstraction}} \mathrm{Me}-\underset{\mathrm{Me}}{\mathrm{CH}}-\overset{\mathrm{Ph}}{\mathrm{CH_2}}$$

Many other cases of free-radical migration of aryl groups have been found.[57]

It is noteworthy that the extent of migration is much less than with corresponding carbocations: thus in the example given, there was only about 50% migration, whereas the carbocation 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, even in substrates where the corresponding carbocations undergo facile rearrangement.[58] Another type of migration that is very common for carbocations, but 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.[59]

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[55] For reviews, see Beckwith; Ingold, in Mayo, Ref. 1, vol.1, pp. 161-310; Wilt, in Kochi *Free Radicals*, vol. 1; Wiley: New York, 1973, pp. 333-501; Stepukhovich; Babayan *Russ. Chem. Rev.* **1972,** *41*, 750; Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974, pp. 498-552; Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970, pp. 235-255; Freidlina *Adv. Free-Radical Chem.* **1965,** *1*, 211-278; Pryor *Free Radicals*; McGraw-Hill: New York, 1966, pp. 266-284.

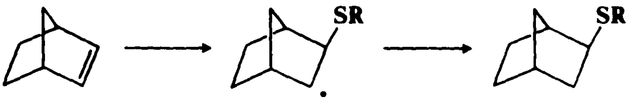
[56] Winstein; Seubold *J. Am. Chem. Soc.* **1947,** *69*, 2916; Seubold *J. Am. Chem. Soc.* **1953,** *75*, 2532. For the observation of this rearrangement by esr, see Hamilton; Fischer *Helv. Chim. Acta* **1973,** *56*, 795.

[57] For example, see Curtin; Hurwitz *J. Am. Chem. Soc.* **1952,** *74*, 5381; Wilt; Philip *J. Org. Chem.* **1959,** *24*, 441, **1960,** *25*, 891; Pines; Goetschel *J. Am. Chem. Soc.* **1964,** *87*, 4207; Goerner; Cote; Vittimberga *J. Org. Chem.* **1977,** *42*, 19; Collins; Roark; Raaen; Benjamin *J. Am. Chem. Soc.* **1979,** *101*, 1877; Walter; McBride *J. Am. Chem. Soc.* **1981,** *103*, 7069, 7074.

[58] For a summary of unsuccessful attempts, see Slaugh; Magoon; Guinn *J. Org. Chem.* **1963,** *28*, 2643.

[59] Seubold *J. Am. Chem. Soc.* **1954,** *76*, 3732.

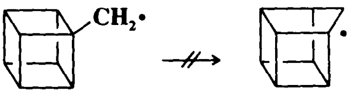
2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **36** is an



36

intermediate, and the corresponding carbocation cannot be formed without rearrangement.[60]

3. The cubylcarbinyl radical did not rearrange to the 1-homocubyl radical, though doing

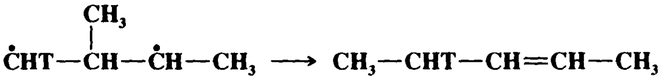


cubylcarbinyl radical 1-homocubyl radical

so would result in a considerable decrease in strain.[60a]

4. It was shown[61] 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.

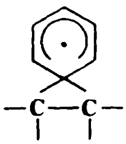
However, 1,2 migration of alkyl groups has been shown to occur in certain *diradicals*.[62] For example, the following rearrangement has been established by tritium labeling.[63]



$$\dot{C}HT-\overset{CH_3}{\underset{|}{\dot{C}H}}-\dot{C}H-CH_3 \longrightarrow CH_3-CHT-CH{=}CH-CH_3$$

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 alkyl groups and hydrogen generally do not, leads to the proposition that **37**, in which the odd electron is not found in the three-membered



37

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, not an intermediate.[64] Among the

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[60] Cristol; Brindell *J. Am. Chem. Soc.* **1954,** *76,* 5699.

[60a] Eaton; Yip *J. Am. Chem. Soc.* **1991,** *113,* 7692.

[61] Brown; Russell *J. Am. Chem. Soc.* **1952,** *74,* 3995. See also Desai; Nechvatal; Tedder *J. Chem. Soc. B.* **1970,** 386.

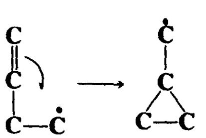
[62] For a review, see Freidlina; Terent'ev *Russ. Chem. Rev* **1974,** *43,* 129-139.

[63] McKnight; Rowland *J. Am. Chem. Soc.* **1966,** *88,* 3179. For other examples, see Greene; Adam; Knudsen *J. Org. Chem.* **1966,** *31,* 2087; Gajewski; Burka *J. Am. Chem. Soc.* **1972,** *94,* 8857, 8860, 8865; Adam; Aponte *J. Am. Chem. Soc.* **1971,** *93,* 4300.

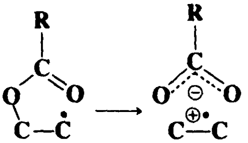
[64] For molecular orbital calculations indicating that **37** is an intermediate, see Yamabe *Chem. Lett.* **1989,** 1523.

evidence is the failure to observe **37** either by esr[65] or CIDNP.[66] Both of these techniques can detect free radicals with extremely short lifetimes (pp. 186-187).[67]

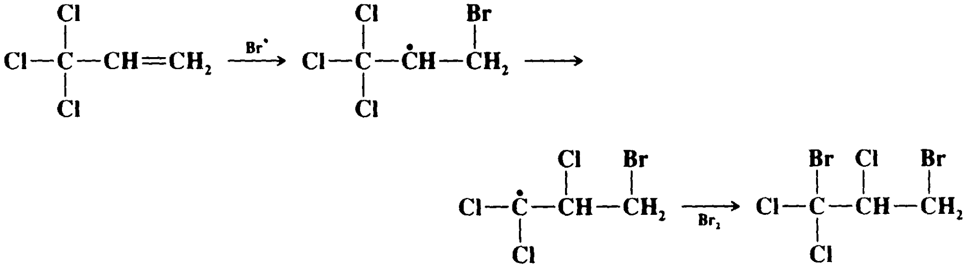
Besides aryl, vinylic[68] and acetoxy groups[69] also migrate. Vinylic groups migrate by way of a cyclopropylcarbinyl radical intermediate,[70] while the migration of acetoxy groups may involve the charge-separated structure shown.[71] In addition, migration has been observed



38



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:



$$\text{Cl}-\overset{\text{Cl}}{\underset{\text{Cl}}{\text{C}}}-\text{CH}=\text{CH}_2 \xrightarrow{\text{Br}^\bullet} \text{Cl}-\overset{\text{Cl}}{\underset{\text{Cl}}{\text{C}}}-\dot{\text{C}}\text{H}-\overset{\text{Br}}{\text{CH}_2} \longrightarrow$$

$$\text{Cl}-\underset{\text{Cl}}{\dot{\text{C}}}-\overset{\text{Cl}}{\text{CH}}-\overset{\text{Br}}{\text{CH}_2} \xrightarrow[\text{Br}_2]{} \text{Cl}-\overset{\text{Br}}{\underset{\text{Cl}}{\text{C}}}-\overset{\text{Cl}}{\text{CH}}-\overset{\text{Br}}{\text{CH}_2}$$

In this particular case the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and co-workers have extensively studied reactions of this sort.[72] It has been shown that the 1,2 migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.[73] 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.

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[65] Kochi; Krusic *J. Am. Chem. Soc.* **1969,** *91*, 3940; Edge; Kochi *J. Am. Chem. Soc.* **1972,** *94*,7695.

[66] Shevlin; Hansen *J. Org. Chem.* **1977,** *42*, 3011; Olah; Krishnamurthy; Singh; Iyer *J. Org. Chem.* **1983,** *48*, 955. **37** has been detected as an intemediate in a different reaction: Effio; Griller; Ingold; Scaiano; Sheng *J. Am. Chem. Soc.* **1980,** *102*, 6063; Leardini; Nanni; Pedulli; Tundo; Zanardi; Foresti; Palmieri *J. Am. Chem. Soc.* **1989,** *111*, 7723.

[67] For other evidence, see Martin *J. Am. Chem. Soc.* **1962,** *84*, 1986; Rüchardt; Hecht *Tetrahedron Lett.* **1962,** 957, *Chem. Ber.* **1965,** *98*, 2460, 2471; Rüchardt; Trautwein *Chem. Ber.* **1965,** *98*, 2478.

[68] For example, see Slaugh; Mullineaux; Raley *J. Am. Chem. Soc.* **1963,** *85*, 3180; Slaugh *J. Am. Chem. Soc.* **1965,** *87*, 1522; Newcomb; Glenn; Williams *J. Org. Chem.* **1989,** *54*, 2675.

[69] Surzur; Teissier *C. R. Acad. Sci., Ser. C* **1967,** *264*, 1981, *Bull. Soc. Chim. Fr.* **1970,** 3060; Tanner; Law *J. Am. Chem. Soc.* **1969,** *91*, 7535; Julia; Lorne *C. R. Acad. Sci., Ser. C* **1971,** *273*, 174; Lewis; Miller; Winstein *J. Org. Chem.* **1972,** *37*, 1478.

[70] For evidence for this species, see Montgomery; Matt; Webster *J. Am. Chem. Soc.* **1967,** *89*, 923; Montgomery; Matt *J. Am. Chem. Soc.* **1967,** *89*, 934, 6556; Giese; Heinrich; Horler; Koch; Schwarz *Chem. Ber.* **1986,** *119*, 3528.

[71] Beckwith; Tindal *Aust. J. Chem.* **1971,** *24*, 2099; Beckwith; Thomas *J. Chem. Soc., Perkin Trans. 2* **1973,** 861; Barclay; Lusztyk; Ingold *J. Am. Chem. Soc.* **1984,** *106*, 1793.

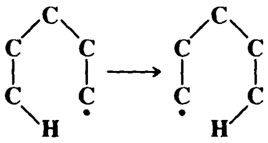
[72] For reviews, see Freidlina; Terent'ev *Russ. Chem. Rev.* **1979,** *48*, 828-839; Freidlina, Ref. 55, pp. 231-249.

[73] See, for example, Skell; Pavlis; Lewis; Shea *J. Am. Chem. Soc.* **1973,** *95*, 6735; Chen; Tang; Montgomery; Kochi *J. Am. Chem. Soc.* **1974,** *96*, 2201.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $RCMe_2CH_2\bullet \rightarrow Me_2\dot{C}CH_2R$. These were found to be in the order R = $H_2C{=}CH_2 > Me_3CC{=}O > Ph > Me_3C{\equiv}C > CN$.[74]

In summary then, 1,2 free-radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.[75]

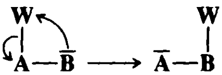
Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known.[76] The most common are 1,5 shifts, but 1,6 and longer shifts have also been found. The possibility of 1,3 hydrogen shifts has been much investigated, but it is not certain if any actually occur. 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 are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for reactions involving them, see **4-8** and **8-42**):



Transannular shifts of hydrogen atoms have also been observed.[77]

Electrophilic Rearrangements[78]

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. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also p. 1072).

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[74] Lindsay; Lusztyk; Ingold *J. Am. Chem. Soc.* **1984**, *106*, 7087.

[75] Slaugh; Raley *J. Am. Chem. Soc.* **1960**, *82*, 1259; Bonner; Mango *J. Org. Chem.* **1964**, *29*, 29; Dannenberg; Dill *Tetrahedron Lett.* **1972**, 1571.

[76] For a discussion, see Freidlina; Terent'ev. *Acc. Chem. Res.* **1977**, *10*, 9-15.

[77] Heusler; Kalvoda *Tetrahedron Lett.* **1963**, 1001; Cope; Bly; Martin; Petterson *J. Am. Chem. Soc.* **1965**, *87*, 3111; Fisch; Ourisson *Chem. Commun.* **1965**, 407; Traynham; Couvillon *J. Am. Chem. Soc.* **1967**, *89*, 3205.

[78] For reviews, see Hunter; Stothers; Warnhoff, in Mayo, Ref. 1, vol. 1, pp. 391-470; Grovenstein *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 313-332 [*Angew. Chem. 90*, 317-336], *Adv. Organomet. Chem.* **1977**, *16*, 167-193; Jensen; Rickborn *Electrophilic Substitution of Organomercurials*; McGraw-Hill: New York, 1968, pp. 21-30; Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 223-243.

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 that cannot be fitted into either of the first two categories.

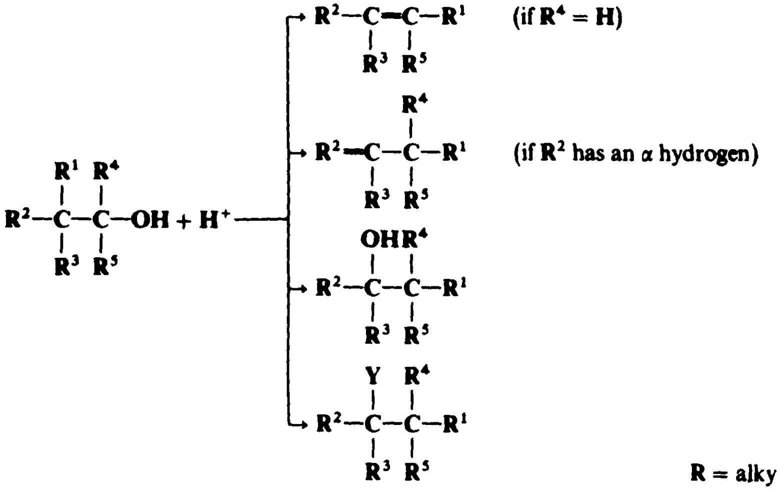
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are **1-30** to **1-36**, **1-40**, **3-25** to **3-28**, and, partially, **1-37**, **1-41**, and **1-42**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. 327, p. 577, and **2-2**). Other reactions that may be regarded as rearrangements are the Pummerer (**9-71**) and Willgerodt (**9-72**) reactions.

1,2 Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

8-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/→1/alkyl)-*migro*-elimination, etc.



R = alkyl, aryl, or hydrogen

When alcohols are treated with acids, simple substitution (e.g., **0-67**) or elimination (**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*. As pointed out previously, the carbocation that 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 the rearrangement product is usually an olefin.[79] 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. 998) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton. Less

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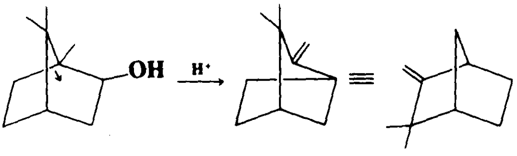
[79] For a review of such rearrangements, see Kaupp *Top. Curr. Chem.* **1988**, *146*, 57-98.

often, the new carbocation 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;[80] under SN1 conditions, carbocations are formed that rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, though, as we have seen (p. 1064), 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.[81] An example is

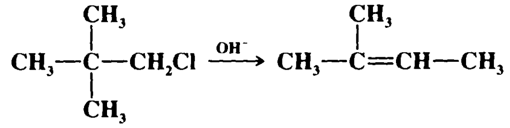
Example *a*



isoborneol camphene

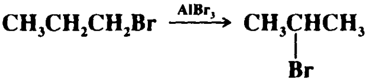
Examples in simpler systems are:

Example *b*



$$CH_3-\underset{CH_3}{\overset{CH_3}{\underset{|}{\overset{|}{C}}}}-CH_2Cl \xrightarrow{OH^-} CH_3-\overset{CH_3}{\overset{|}{C}}=CH-CH_3$$

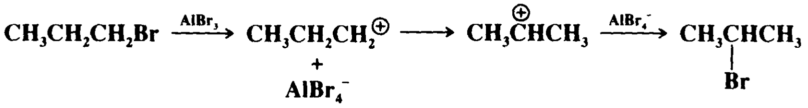
Example *c*



$$CH_3CH_2CH_2Br \xrightarrow{AlBr_3} CH_3\underset{Br}{\underset{|}{C}}HCH_3$$

These examples illustrate the following points:

1. Hydride ion can migrate. In example *c*, it was hydride that shifted, not bromine:



$$CH_3CH_2CH_2Br \xrightarrow{AlBr_3} \underset{\underset{AlBr_4^-}{+}}{CH_3CH_2CH_2^{\oplus}} \longrightarrow CH_3\overset{\oplus}{C}HCH_3 \xrightarrow{AlBr_4^-} CH_3\underset{Br}{\underset{|}{C}}HCH_3$$

2. The leaving group does not have to be H_2O, but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions[82] (see the section on leaving groups in nucleophilic substitution, p. 352). Also, rearrangement may follow when the carbocation 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 some species is initially present to form a carbocation from the alkane.

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[80] See, however, Ref. 248 in Chapter 10.

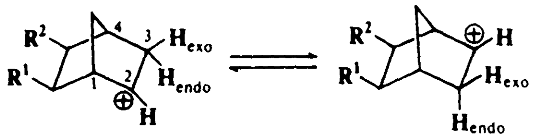
[81] For a review of rearrangements in bicyclic systems, see Hogeveen; van Kruchten *Top. Curr. Chem.* **1979**, *80*, 89-124. For reviews concerning caranes and pinanes see, respectively, Arbuzov; Isaeva *Russ. Chem. Rev.* **1976**, *45*, 673-683; Banthorpe; Whittaker *Q. Rev. Chem. Soc.* **1966**, *20*, 373-387.

[82] For reviews of rearrangements arising from diazotization of aliphatic amines, see, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, the articles by White; Woodcock, pp. 407-497 (pp. 473-483) and by Banthorpe, pp. 585-667 (pp. 586-612).

3. Example *c* illustrates that the last step can be substitution instead of elimination.

4. Example *b* illustrates that the new double bond is formed in accord with Zaitsev's rule.

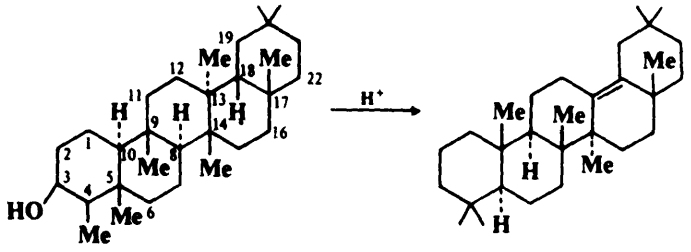
2-Norbornyl cations, besides displaying the 1,2 shifts of a CH_2 group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2 shifts). These 3,2 shifts usually take place from the exo side;[83] that is, the 3-exo hydrogen migrates to the 2-exo position.[84] 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. 321) and that addition to norbornenes is also usually from the exo direction (p. 753).



The direction of rearrangement is usually towards the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,[85] and often the product is a mixture corresponding to an equilibrium mixture of the possible carbocations.

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 ketone found in cork. Reduction gives 3β-friedelanol (**39**). When this compound is treated with acid, 13(18)-oleanene (**40**) is formed.[86] In this case *seven* 1,2 shifts take place. On removal of H_2O from position 3 to leave a positive charge, the following



39 **40**

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

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[83] For example, see Kleinfelter; Schleyer *J. Am. Chem. Soc.* **1961,** *83,* 2329; Collins; Cheema; Werth; Benjamin *J. Am. Chem. Soc.* **1964,** *86,* 4913; Berson; Hammons; McRowe; Bergman; Remanick; Houston *J. Am. Chem. Soc.* **1967,** *89,* 2590.

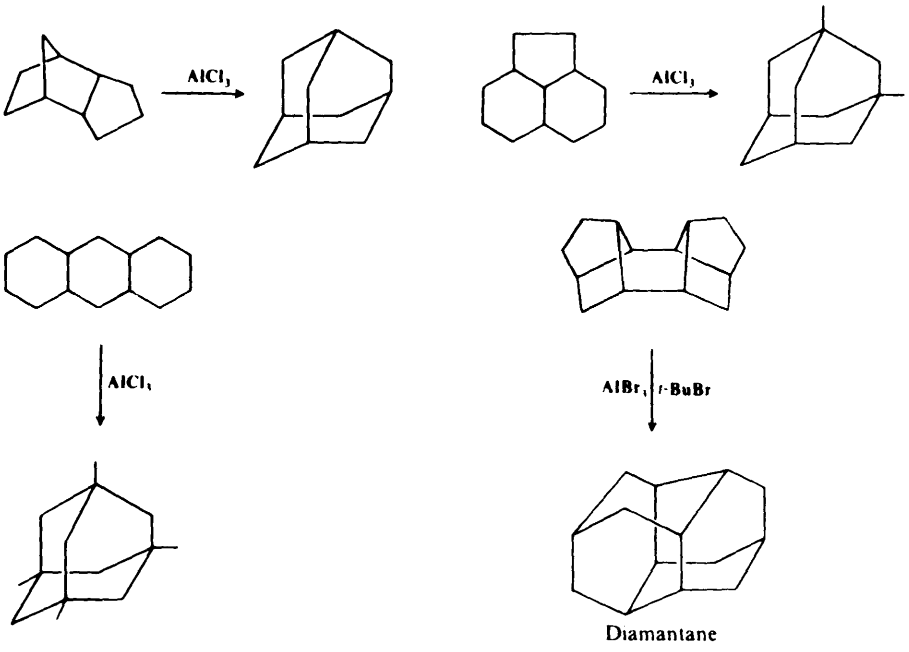
[84] For examples of 3,2 endo shifts, see Bushell; Wilder *J. Am. Chem. Soc.* **1967,** *89,* 5721; Wilder; Hsieh *J. Org. Chem.* **1971,** *36,* 2552.

[85] See, for example, Cooper et al., Ref. 23.

[86] Corey; Ursprung *J. Am. Chem. Soc.* **1956,** *78,* 5041.

positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **40**. 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.[87] As an illustration of point 2 (p. 1069), it may be mentioned that friedelene, derived from dehydration of **39**, also gives **40** on treatment with acid.[88]

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.[89] 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. The IUPAC name for these reactions is **Schleyer adamantization**. Some examples are



If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.[90] These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equi-

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[87] For a discussion, see Whitlock; Olson *J. Am. Chem. Soc.* **1970,** *92*, 5383.

[88] Dutler; Jeger; Ruzicka *Helv. Chim. Acta* **1955,** *38*, 1268; Brownlie; Spring; Stevenson; Strachan *J. Chem. Soc.* **1956,** 2419; Coates *Tetrahedron Lett.* **1967,** 4143.

[89] For reviews, see McKervey; Rooney, in Olah *Cage Hydrocarbons*; Wiley: New York, 1990, pp. 39-64; McKervey *Tetrahedron* **1980,** *36*, 971-992, *Chem. Soc. Rev.* **1974,** *3*, 479-512; Greenberg; Liebman *Strained Organic Molecules*; Academic Press: New York, 1978, pp. 178-202; Bingham; Schleyer, *Fortschr. Chem. Forsch.* **1971,** *18*, 1-102, pp. 3-23.

[90] See Gund; Osawa; Williams; Schleyer *J. Org. Chem.* **1974,** *39*, 2979.

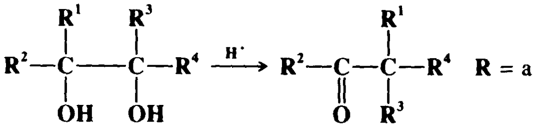
librium.[91] Best yields are obtained by the use of "sludge" catalysts[92] (i.e., a mixture of AlX_3 and *t*-butyl bromide or *sec*-butyl bromide).[93] Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2 shifts, the exact pathways are not easy to unravel because of their complexity.[94] Treatment of adamantane-2-^{14}C with $AlCl_3$ results in total carbon scrambling on a statistical basis.[95]

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.[78] Thus Ph_3CCH_2Cl treated with sodium gave Ph_2CHCH_2Ph along with unrearranged products.[96] This is called the *Grovenstein–Zimmerman rearrangement*. The intermediate is $Ph_3C\bar{C}H_2^-$, and the phenyl moves without its electron pair. Only aryl and vinylic,[97] and not alkyl, groups migrate by the electrophilic mechanism (p. 1051) and transition states or intermediates analogous to **37** and **38** are likely.[98]

OS **V**, 16, 194; **VI**, 378, 845.

8-2 The Pinacol Rearrangement

1/*O*-Hydro,3/hydroxy-(2/→3/alkyl)-*migro*-elimination



$$R^2-\underset{OH}{\overset{R^1}{C}}-\underset{OH}{\overset{R^3}{C}}-R^4 \xrightarrow{H^+} R^2-\underset{O}{\overset{R^1}{\underset{\|}{C}}}-\underset{R^3}{C}-R^4$$

R = alkyl, aryl, or hydrogen

When *vic*-diols (glycols) 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 rearrangement*; the reaction gets its name from the typical compound pinacol $Me_2COHCOHMe_2$, which is rearranged to pinacolone Me_3CCOCH_3.[99] The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (COOEt)[100] 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. 1058 for a discussion of migratory aptitudes). Mixtures are often produced, and which group preferentially migrates

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[91] For a method for the prediction of stabilomers, see Godleski; Schleyer; Ōsawa; Wipke *Prog. Phys. Org. Chem.* **1981,** *13*, 63-117.

[92] Schneider; Warren; Janoski *J. Org. Chem.* **1966,** *31*, 1617; Williams; Schleyer; Gleicher; Rodewald *J. Am. Chem. Soc.* **1966,** *88*, 3862; Robinson; Tarratt *Tetrahedron Lett.* **1968,** 5.

[93] For other methods, see Johnston; McKervey; Rooney *J. Am. Chem. Soc.* **1971,** *93*, 2798; Olah; Wu; Farooq; Prakash *J. Org. Chem.* **1989,** *54*, 1450.

[94] See, for example, Engler; Farcasiu; Sevin; Cense; Schleyer *J. Am. Chem. Soc.* **1973,** *95*, 5769; Klester; Ganter *Helv. Chim. Acta* **1983,** *66*, 1200, **1985,** *68*, 734.

[95] Majerski; Liggero; Schleyer; Wolf *Chem. Commun.* **1970,** 1596.

[96] Grovenstein *J. Am. Chem. Soc.* **1957,** *79*, 4985; Zimmerman; Smentowski *J. Am. Chem. Soc.* **1957,** *79*, 5455; Grovenstein; Williams *J. Am. Chem. Soc.* **1961,** *83*, 412; Zimmerman; Zweig *J. Am. Chem. Soc.* **1961,** *83*, 1196. See also Crimmins; Murphy; Hauser *J. Org. Chem.* **1966,** *31*, 4273; Grovenstein; Cheng *J. Am. Chem. Soc.* **1972,** *94*, 4971.

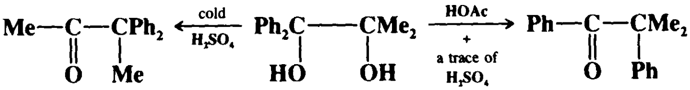
[97] See Grovenstein; Black; Goel; Hughes; Northrop; Streeter; VanDerveer *J. Org. Chem.* **1989,** *54*, 1671, and references cited therein.

[98] Grovenstein; Wentworth *J. Am. Chem. Soc.* **1967,** *89*, 2348; Bertrand; Grovenstein; Lu; VanDerveer *J. Am. Chem. Soc.* **1976,** *98*, 7835.

[99] For reviews, see Bartók; Molnár, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 722-732; Collins; Eastham, Ref. 1, pp. 762-771.

[100] Kagan; Agdeppa; Mayers; Singh; Walters; Wintermute *J. Org. Chem.* **1976,** *41*, 2355. COOH has been found to migrate in a Wagner-Meerwein reaction: Berner; Cox; Dahn *J. Am. Chem. Soc.* **1982,** *104*, 2631.

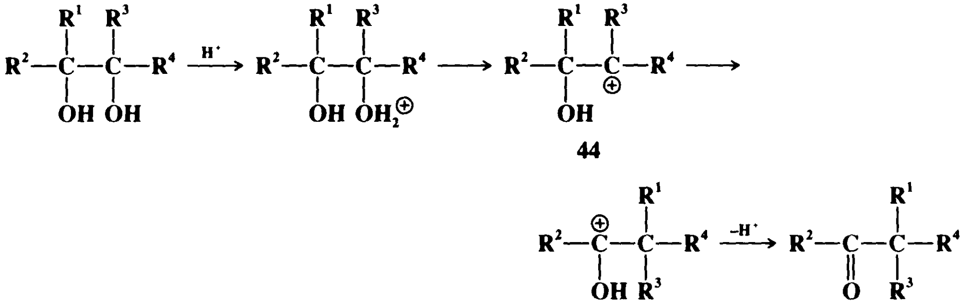
may depend on the reaction conditions as well as on the nature of the substrate. Thus the action of cold, concentrated sulfuric acid on **41** produces mainly the ketone **42** (methyl



42 **41** **43**

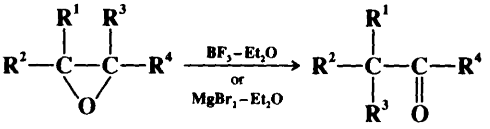
migration), while treatment of **41** with acetic acid containing a trace of sulfuric acid gives mostly **43** (phenyl migration).[101] If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (**8-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with an organic solid acid.[102]

The mechanism involves a simple 1,2 shift. The ion **44** (where all four R groups are Me)



has been trapped by the addition of tetrahydrothiophene.[103] It may seem odd that a migration takes place when the positive charge is already at a tertiary position, but carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (p. 170). There is also the driving force supplied by the fact that the new carbocation 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, β-hydroxyalkyl selenides $R^1R^2C(OH)C(SeR^5)R^3R^4$,[104] and allylic alcohols, which can rearrange on treatment with a strong acid that protonates the double bond. A similar rearrangement is given by epoxides, when treated with acidic[105] reagents such as BF_3–etherate or $MgBr_2$–etherate, or sometimes by heat alone.[106] It has been shown that epoxides are



R = alkyl, aryl, or hydrogen

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[101] Ramart-Lucas; Salmon-Legagneur *C. R. Acad. Sci.* **1928,** *188,* 1301.

[102] Toda; Shigemasa *J. Chem. Soc., Perkin Trans. 1* **1989,** 209.

[103] Bosshard; Baumann; Schetty *Helv. Chim. Acta* **1970,** *53,* 1271.

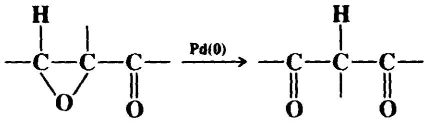
[104] For a review, see Krief; Laboureur; Dumont; Labar *Bull. Soc. Chim. Fr.* **1990,** 681-696.

[105] Epoxides can also be rearranged with basic catalysts, though the products are usually different. For a review, see Yandovskii; Ershov *Russ. Chem. Rev.* **1972,** *41,* 403, 410.

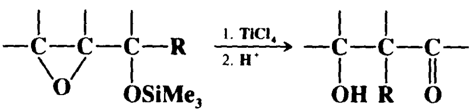
[106] For a list of reagents that accomplish this transformation, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 628.

intermediates in the pinacol rearrangements of certain glycols.[107] 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.[108]

Epoxides can also be rearranged to aldehydes or ketones on treatment with certain metallic catalysts.[109] A good way to prepare β-diketones consists of heating α,β-epoxy ketones at 80-140°C in toluene with small amounts of $(Ph_3P)_4Pd$ and 1,2-bis(diphenylphosphino)ethane.[110]



β-Hydroxy ketones can be prepared by treating the silyl ethers (**45**) of α,β-epoxy alcohols with $TiCl_4$.[111]

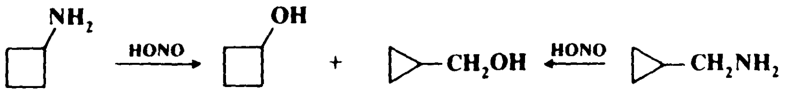


45

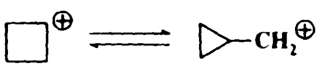
OS **I,** 462; **II,** 73, 408; **III,** 312; **IV,** 375, 957; **V,** 326, 647; **VI,** 39, 320; **VII,** 129. See also OS **VII,** 456.

8-3 Expansion and Contraction of Rings

Demyanov ring contraction; Demyanov ring expansion



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 that is one carbon smaller than the original



Note that this change involves conversion of a secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring

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[107] See, for example, Matsumoto *Tetrahedron* **1968,** *24,* 6851; Pocker; Ronald *J. Am. Chem. Soc.* **1970,** *92,* 3385, *J. Org. Chem.* **1970,** *35,* 3362; Tamura; Moriyoshi *Bull. Chem. Soc. Jpn.* **1974,** *47,* 2942.

[108] Pocker *Chem. Ind.* (*London*) **1959,** 332. See also Herlihy *Aust. J. Chem.* **1981,** *34,* 107.

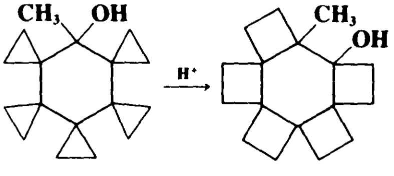
[109] For example, see Alper; Des Roches; Durst; Legault *J. Org. Chem.* **1976,** *41,* 3611; Milstein; Buchman; Blum *J. Org. Chem.* **1977,** *42,* 2299; Prandi; Namy; Menoret; Kagan *J. Organomet. Chem.* **1985,** *285,* 449; Miyashita; Shimada; Sugawara; Nohira *Chem. Lett.* **1986,** 1323; Maruoka; Nagahara; Ooi; Yamamoto *Tetrahedron Lett.* **1989,** *30,* 5607.

[110] Suzuki; Watanabe; Noyori *J. Am. Chem. Soc.* **1980,** *102,* 2095.

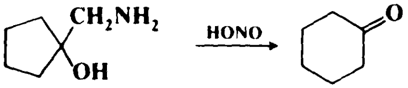
[111] Maruoka; Hasegawa; Yamamoto; Suzuki; Shimazaki; Tsuchihashi *J. Am. Chem. Soc.* **1986,** *108,* 3827. For a different rearrangement of **45,** see Maruoka; Ooi; Yamamoto *J. Am. Chem. Soc.* **1989,** *111,* 6431.

expansion can take place.[112] The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **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 carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,[113] but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C_3 to C_8,[114] 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. 323).

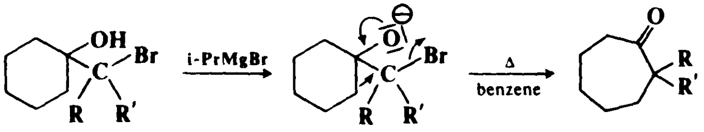
An interesting example of a cascade of ring expansions, similar to the friedelin example described in **8-1,** is the conversion of 16-methylpentaspiro[2.0.2.0.2.0.2.0.2.1]hexadecan-16-ol (**46**) to 2-methylhexacyclo[12.2.0.$0^{2,5}$.$0^{5,8}$.$0^{8,11}$.$0^{11,14}$]hexadecan-1-ol (**47**) on treatment with *p*-toluenesulfonic acid in acetone–water.[115] The student may wish to write out the mechanism as an exercise. Ring expansions of certain hydroxyamines, e.g.,



46 **47**



are analogous to the semipinacol rearrangement (**8-2**). This reaction is called the *Tiffeneau–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



48 **49**

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[112] For monographs on ring expansions, see Hesse *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991; Gutsche; Redmore *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968. For a review of ring contractions, see Redmore; Gutsche *Adv. Alicyclic Chem.* **1971,** *3,* 1-138. For reviews of ring expansions in certain systems, see Baldwin; Adlington; Robertson *Tetrahedron* **1989,** *45,* 909-922; Stach; Hesse *Tetrahedron* **1988,** *44,* 1573-1590; Dolbier *Mech. Mol. Migr.* **1971,** *3,* 1-66. For reviews of expansions and contractions of three- and four membered rings, see Salaün, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 2; Wiley: New York, 1987, pp. 809-878; Conia; Robson *Angew. Chem. Int. Ed. Engl.* **1975,** *14,* 473-485 [*Angew. Chem. 87,* 505-516]. For a list of ring expansions and contractions, with references, see Ref. 106, pp. 630-637.

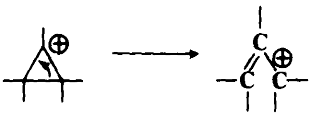
[113] For a review, see Smith; Baer *Org. React.* **1960,** *11,* 157-188.

[114] For a review concerning three-membered rings, see Wong; Hon; Tse; Yip; Tanko; Hudlicky *Chem. Rev.* **1989,** *89,* 165-198, pp. 182-186. For a review concerning three- and four-membered rings, see Breslow, in Mayo *Molecular Rearrangements*, vol. 1; Wiley: New York, 1963, pp. 233-294.

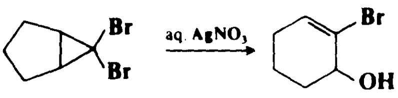
[115] Fitjer; Wehle; Noltemeyer; Egert; Sheldrick *Chem. Ber.* **1984,** *117,* 203. For similar cascade rearrangements, see Giersig; Wehle; Fitjer; Schormann; Clegg *Chem. Ber.* **1988,** *121,* 525, and other papers in this series.

to expand rings of from five to eight members.[116] In this case, a cyclic bromohydrin of the form **48** is treated with a Grignard reagent which, acting as a base, removes the OH proton to give the alkoxide **49**. Refluxing of **49** brings about the ring enlargement. The reaction has been accomplished for **48** in which at least one R group is phenyl or methyl,[117] but fails when both R groups are hydrogen.[118]

A positive charge generated on a three-membered ring gives "contraction" to an allylic cation.[119]

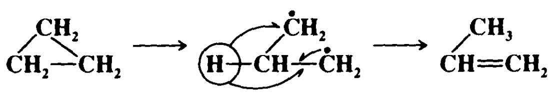


We have previously seen (p. 345) that this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being[120]



The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see p. 1119).

Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (1) On pyrolysis, cyclopropanes can undergo "contraction" to propenes.[121] In the simplest case, cyclopropane gives propene when heated to 400 to 500°C. The mechanism is generally regarded[122] as involving a diradical intermediate[123] (recall that free-radical 1,2 migration is possible for diradicals, p. 1065). (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



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[116] Sisti *Tetrahedron Lett.* **1967**, 5327, *J. Org. Chem.* **1968**, *33*, 453. See also Sisti; Vitale *J. Org. Chem.* **1972**, *37*, 4090.

[117] Sisti *J. Org. Chem.* **1970**, *35*, 2670, *Tetrahedron Lett.* **1970**, 3305; Sisti; Meyers *J. Org. Chem.* **1973**, *38*, 4431; Sisti; Rusch *J. Org. Chem.* **1974**, *39*, 1182.

[118] Sisti *J. Org. Chem.* **1968**, *33*, 3953.

[119] For reviews, see Marvell, Ref. 365, pp. 23-53; Sorensen; Rauk, in Marchand; Lehr *Pericyclic Reactions*, vol. 2; Academic Press: New York, 1977, pp. 1-78.

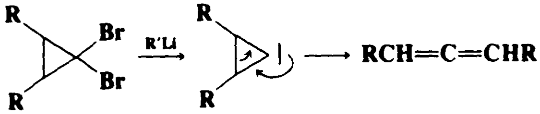
[120] Skell; Sandler *J. Am. Chem. Soc.* **1958**, *80*, 2024.

[121] For reviews, see Berson, in Mayo, Ref. 1, vol. 1, pp. 324-352, *Ann. Rev. Phys. Chem.* **1977**, *28*, 111-132; Bergman, in Kochi, Ref. 55, vol. 1, pp. 191-237; Frey *Adv. Phys. Org. Chem.* **1966**, *4*, 147-193, pp. 148-170.

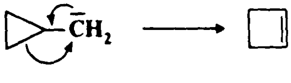
[122] For evidence that diradical intermediates may not be involved, at least in some cases, see Fields; Haszeldine; Peter *Chem. Commun.* **1967**, 1081; Parry; Robinson *Chem. Commun.* **1967**, 1083; Clifford; Holbrook *J. Chem. Soc., Perkin Trans. 2* **1972**, 1972; Baldwin; Grayston *J. Am. Chem. Soc.* **1974**, *96*, 1629, 1630.

[123] We have seen before that such diradicals can close up to give cyclopropanes (**7-46**). Therefore, pyrolysis of cyclopropanes can produce not only propenes but also isomerized (cis → trans or optically active → inactive) cyclopropanes. See, for example, Berson; Balquist *J. Am. Chem. Soc.* **1968**, *90*, 7343; Bergman; Carter *J. Am. Chem. Soc.* **1969**, *91*, 7411.

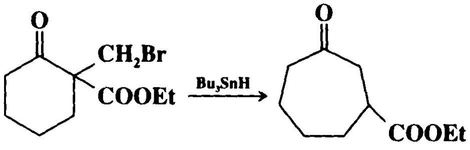
way.[124] One way to generate such a species is treatment of a 1,1-dihalocyclopropane with an alkyllithium compound (**2-39**).[125] In contrast, the generation of a carbene or carbenoid



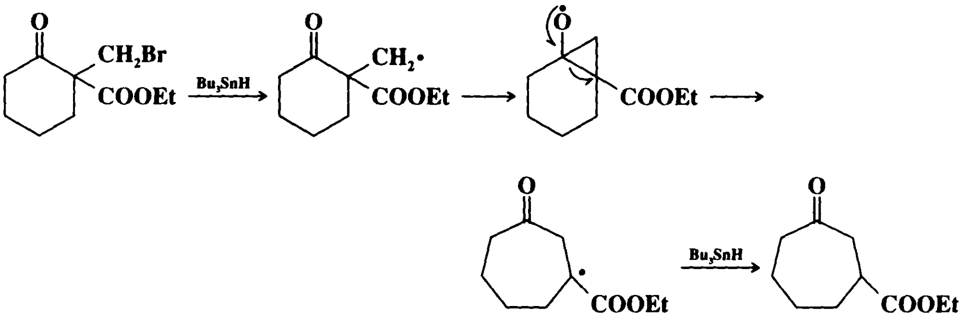
at a cyclopropylmethyl carbon gives ring expansion.[126]



Some free-radical ring enlargements are also known, an example being:[127]



This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is:



This reaction has been extended to the expansion of rings by 3 or 4 carbons, by the use of a substrate containing $(CH_2)_nX$ ($n = 3$ or 4) instead of CH_2Br.[128] By this means, 5-, 6-, and 7-membered rings were enlarged to 8- to 11-membered rings.

OS **III,** 276; **IV,** 221, 957; **V,** 306, 320; **VI,** 142, 187; **VII,** 12, 114, 117, 129, 135; **65,** 17; **67,** 210; **68,** 220; **69,** 220.

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[124] For reviews, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 20-23; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 462-467.

[125] See Baird; Baxter *J. Chem. Soc., Perkin Trans. 1* **1979,** 2317, and references cited therein.

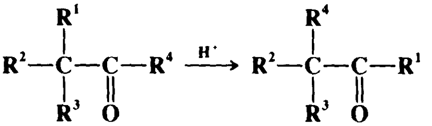
[126] For a review, see Gutsche; Redmore, Ref. 112, pp. 111-117.

[127] Dowd; Choi *J. Am. Chem. Soc.* **1987,** *109*, 3493, *Tetrahedron Lett.* **1991,** *32*, 565, *Tetrahedron* **1991,** *47*, 4847. For a related ring expansion, see Baldwin; Adlington; Robertson *J. Chem. Soc., Chem. Commun.* **1988,** 1404.

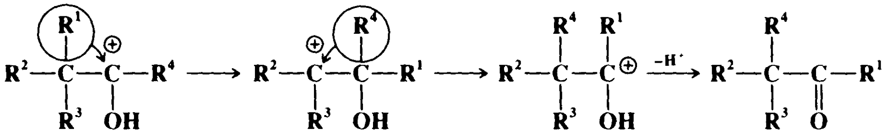
[128] Dowd; Choi *J. Am. Chem. Soc.* **1987,** *109*, 6548, *Tetrahedron Lett.* **1991,** *32*, 565.

8-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones

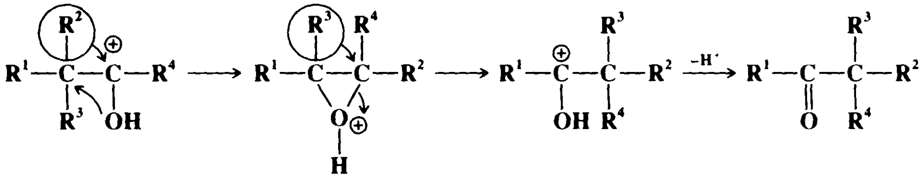
1/Alkyl,2/alkyl-interchange, etc.



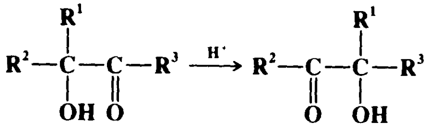
Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.[129] R^2, R^3, and R^4 may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though 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,[130] each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions:[131]



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[132] is one possibility:[133]



If the reaction is carried out with ketone labeled in the C=O group with ^{14}C, 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[134] 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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[129] For reviews, see Fry *Mech. Mol. Migr.* **1971,** *4,* 113-196; Collins; Eastham, in Patai, Ref. 1, pp. 771-790.

[130] Favorskii; Chilingaren *C. R. Acad. Sci.* **1926,** *182,* 221.

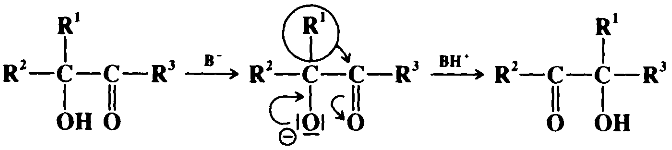
[131] Raaen; Collins *J. Am. Chem. Soc.* **1958,** *80,* 1409; Kendrick; Benjamin; Collins *J. Am. Chem. Soc.* **1958,** *80,* 4057; Rothrock; Fry *J. Am. Chem. Soc.* **1958,** *80,* 4349; Collins; Bowman *J. Am. Chem. Soc.* **1959,** *81,* 3614.

[132] Zook; Smith; Greene *J. Am. Chem. Soc.* **1957,** *79,* 4436.

[133] Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2 shift of an OH group.

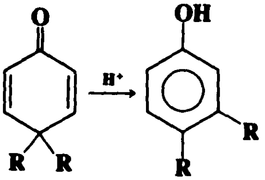
[134] See, for example, Barton; Porter *J. Chem. Soc.* **1956,** 2483; Fry; Carrick; Adams *J. Am. Chem. Soc.* **1958,** *80,* 4743; Zalesskaya; Remizova *J. Gen. Chem. USSR.* **1965,** *35,* 29; Fry; Oka *J. Am. Chem. Soc.* **1979,** *101,* 6353.

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.

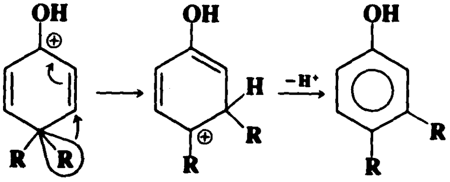


8-5 The Dienone–Phenol Rearrangement

2/C→5/O-Hydro,1/C→2/C-alkyl-*bis*-migration

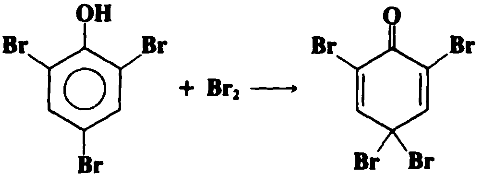


Compounds in which a cyclohexadienone has two alkyl groups in the 4 position undergo, on acid treatment,[135] 1,2 migration of one of these groups:



50 **51**

The driving force in the overall reaction (the *dienone–phenol rearrangement*) is of course creation of an aromatic system.[136] It may be noted that **50** and **51** are arenium ions (p. 502), the same as those generated by attack of an electrophile on a phenol.[137] 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.[138] An example is



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[135] For a reagent that greatly accelerates this reaction, see Chalais; Laszlo; Mathy *Tetrahedron Lett.* **1986,** *27*, 2627.

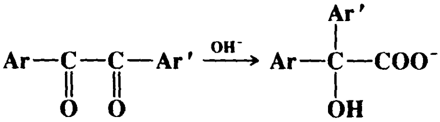
[136] For reviews, see Perkins; Ward *Mech. Mol. Migr.* **1971,** *4*, 55-112, pp. 90-103; Miller *Mech. Mol. Migr.* **1968,** *1*, 247-313; Shine *Aromatic Rearrangements*; Elsevier: New York, 1967, pp. 55-68; Waring *Adv. Alicyclic Chem.* **1966,** *1*, 129-256, pp. 207-223. For a review of other rearrangements of cyclohexadienones, see Miller *Acc. Chem. Res.* **1975,** *8*, 245-256.

[137] For evidence that these ions are indeed intermediates in this rearrangement, see Vitullo *J. Org. Chem.* **1969,** *34*, 224, *J. Org. Chem.* **1970,** *35*, 3976; Vitullo; Grossman *J. Am. Chem. Soc.* **1972,** *94*, 3844; Planas; Tomás; Bonet *Tetrahedron Lett.* **1987,** *28*, 471.

[138] For a review, see Ershov; Volod'kin; Bogdanov *Russ. Chem. Rev.* **1963,** *32*, 75-93.

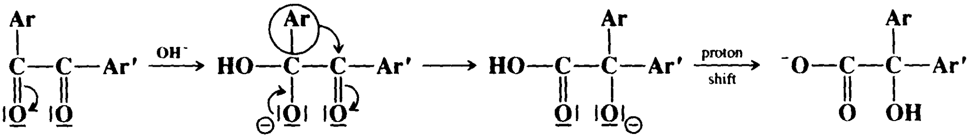
8-6 The Benzil–Benzilic Acid Rearrangement

1/*O*-Hydro,3/oxido-(1/→2/aryl)-*migro*-addition



$$\mathrm{Ar{-}\underset{O}{\underset{\|}{C}}{-}\underset{O}{\underset{\|}{C}}{-}Ar'} \xrightarrow{OH^-} \mathrm{Ar{-}\overset{Ar'}{\overset{|}{\underset{OH}{\underset{|}{C}}}}{-}COO^-}$$

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 $Ph_2COHCOOH$).[139] Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones[140] and to α-keto aldehydes. The use of alkoxide ion instead of OH^- gives the corresponding ester directly,[141] though alkoxide ions that are readily oxidized (such as OEt^- or $OCHMe_2^-$) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in **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 makes room for the migrating group by releasing a pair of π 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. 331) and of many additions to the C=O bond (Chapter 16):

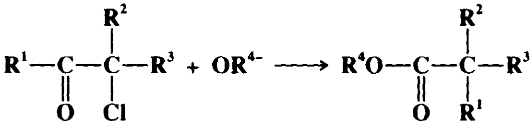


The mechanism has been intensely studied,[139] and there is much evidence for it.[142] The reaction is irreversible.

OS **I**, 89.

8-7 The Favorskii Rearrangement

2/Alkoxy-de-chloro(2/→1/alkyl)-*migro*-substitution



$$\mathrm{R^1{-}\underset{O}{\underset{\|}{C}}{-}\overset{R^2}{\overset{|}{\underset{Cl}{\underset{|}{C}}}}{-}R^3} + \mathrm{OR^{4-}} \longrightarrow \mathrm{R^4O{-}\underset{O}{\underset{\|}{C}}{-}\overset{R^2}{\overset{|}{\underset{R^1}{\underset{|}{C}}}}{-}R^3}$$

The reaction of α-halo ketones (chloro, bromo, or iodo) with alkoxide ions[143] to give rearranged esters is called the *Favorskii rearrangement*.[144] The use of hydroxide ions or amines

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[139] For a review, see Selman; Eastham *Q. Rev. Chem. Soc.* **1960**, *14*, 221-235.

[140] For an example, see Schaltegger; Bigler *Helv. Chim. Acta* **1986**, *69*, 1666.

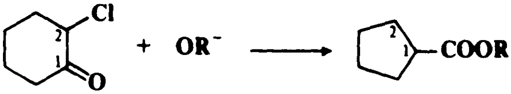
[141] Doering; Urban *J. Am. Chem. Soc.* **1956**, *78*, 5938.

[142] However, some evidence for an SET pathway has been reported: Screttas; Micha-Screttas; Cazianis *Tetrahedron Lett.* **1983**, *24*, 3287.

[143] The reaction has also been reported to take place with BF_3–MeOH and Ag^+: Giordano; Castaldi; Casagrande; Abis *Tetrahedron Lett.* **1982**, *23*, 1385.

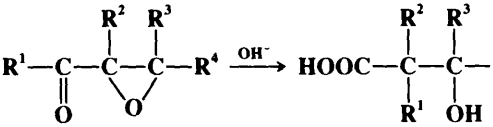
[144] For reviews, see Hunter; Stothers; Warnhoff, in Mayo, Ref. 1, vol. 1, pp. 437-461; Chenier *J. Chem. Educ.* **1978**, *55*, 286-291; Rappe, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 2; Wiley: New York, 1973, pp. 1084-1101; Redmore; Gutsche, Ref. 112, pp. 46-69; Akhrem; Ustynyuk; Titov *Russ. Chem. Rev.* **1970**, *39*, 732-746.

as bases leads to the free carboxylic acid (salt) or amide, respectively, instead of the ester. Cyclic α-halo ketones give ring contraction:



52 **53**

The reaction has also been carried out on α-hydroxy ketones[145] and on α,β-epoxy ketones:[146]



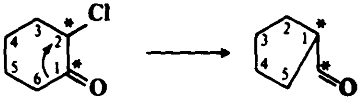
The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.

Through the years, the mechanism[147] of the Favorskii rearrangement has been the subject of much investigation; at least five different mechanisms have been proposed. However, the finding[148] that **54** and **55** *both* give **56** (this behavior is typical) shows that any mechanism

$$\mathrm{PhCH_2}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH_2}} \longrightarrow \underset{\mathbf{56}}{\mathrm{PhCH_2CH_2COOH}} \longleftarrow \mathrm{Ph}\underset{\underset{\mathrm{Cl}}{|}}{\mathrm{CH}}-\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{CH_3}$$

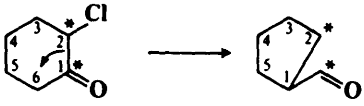
54 **55**

where the halogen leaves and R^1 takes its place is invalid, since in such a case **54** would be expected to give **56** (with $PhCH_2$ migrating), but **55** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **55**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **52**, in which C-1 and C-2 were equally labeled with ^{14}C, was converted to **53**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.[149] Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect *it*. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:



52

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:



52

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[145] Craig; Dinner; Mulligan *J. Org. Chem.* **1972,** *37*, 3539.

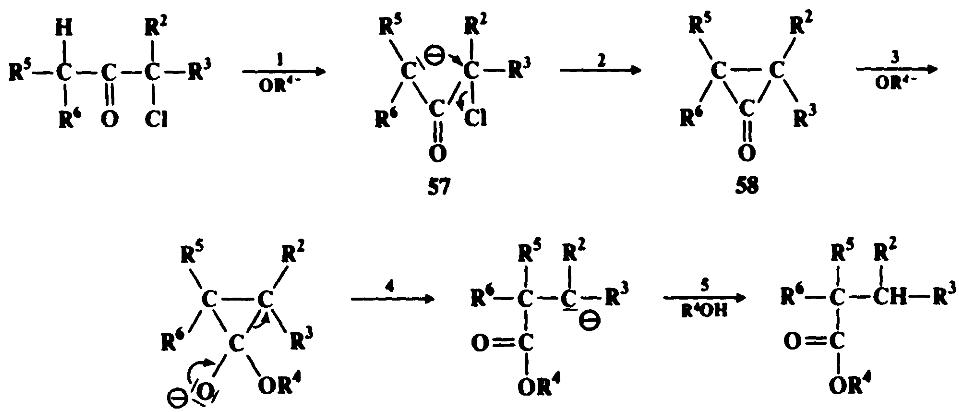
[146] See, for example, House; Gilmore *J. Am. Chem. Soc.* **1961,** *83*, 3972; Mouk; Patel; Reusch *Tetrahedron* **1975,** *31*, 13.

[147] For a review of the mechanism, see Baretta; Waegell *React. Intermed.* (*Plenum*) **1982,** *2*, 527-585.

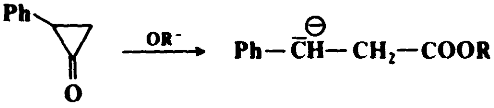
[148] McPhee; Klingsberg *J. Am. Chem. Soc.* **1944,** *66*, 1132; Bordwell; Scamehorn; Springer *J. Am. Chem. Soc.* **1969,** *91*, 2087.

[149] Loftfield *J. Am. Chem. Soc.* **1951,** *73*, 4707.

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **52** are not equivalent, this means that there must be a symmetrical intermediate.[150] The type of intermediate that best fits the circumstances is a cyclopropanone,[151] and the mechanism (for the general case) is formulated (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):



The intermediate corresponding to **58** in the case of **52** 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, **58** is not symmetrical and should open on the side that gives the more stable carbanion.[152] This accounts for the fact that **54** and **55** give the same product. The intermediate in both cases is **59**, which always opens to



59

give the carbanion stabilized by resonance. The cyclopropanone intermediate (**58**) has been isolated in the case where $R^2 = R^5 = t\text{-Bu}$ and $R^3 = R^6 = H$,[153] and it has also been trapped.[154] Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[155]

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 that do not have

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[150] A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **52** had the same isotopic distribution as the starting **52**.

[151] Although cyclopropanones are very reactive compounds, several of them have been isolated. For reviews of cyclopropanone chemistry, see Wasserman; Clark; Turley *Top. Curr. Chem.* **1974,** *47,* 73-156; Turro *Acc. Chem. Res.* **1969,** *2,* 25-32.

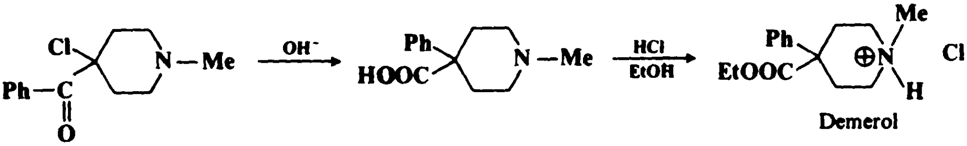
[152] Factors other than carbanion stability (including steric factors) may also be important in determining which side of an unsymmetrical **58** is preferentially opened. See, for example, Rappe; Knutsson *Acta Chem. Scand.* **1967,** *21,* 2205; Rappe; Knutsson; Turro; Gagosian *J. Am. Chem. Soc.* **1970,** *92,* 2032.

[153] Pazos; Pacifici; Pierson; Sclove; Greene *J. Org. Chem.* **1974,** *39,* 1990.

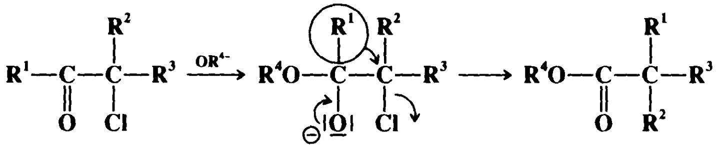
[154] Fort *J. Am. Chem. Soc.* **1962,** *84,* 4979; Cookson; Nye *Proc. Chem. Soc.* **1963,** 129; Breslow; Posner; Krebs *J. Am. Chem. Soc.* **1963,** *85,* 234; Baldwin; Cardellina *Chem. Commun.* **1968,** 558.

[155] Turro; Hammond *J. Am. Chem. Soc.* **1965,** *87,* 3258; Crandall; Machleder *J. Org. Chem.* **1968,** *90,* 7347; Turro; Gagosian; Rappe; Knutsson *Chem. Commun.* **1969,** 270; Wharton; Fritzberg *J. Org. Chem.* **1972,** *37,* 1899.

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:[156]



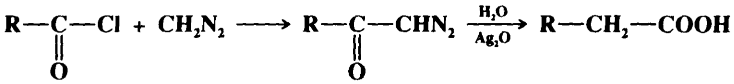
The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*[157])



is a base-catalyzed pinacol rearrangement-type mechanism similar to that of **8-6**. This mechanism requires inversion at the migration terminus and this has been found.[158] It has been shown that even where there *is* an appropriately situated α hydrogen, the semibenzilic mechanism may still operate.[159]

OS **IV**, 594; **VI**, 368, 711.

8-8 The Arndt–Eistert Synthesis



$$R-\underset{\underset{O}{\|}}{C}-Cl + CH_2N_2 \longrightarrow R-\underset{\underset{O}{\|}}{C}-CHN_2 \xrightarrow[Ag_2O]{H_2O} R-CH_2-COOH$$

In the *Arndt–Eistert synthesis* an acyl halide is converted to a carboxylic acid with one additional carbon.[160] The first step of this process is reaction **0-112**. 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 (**0-101** and **6-34** 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.[161] The photolysis method[162] often gives better results than the silver catalysis

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[156] Smissman; Hite *J. Am. Chem. Soc.* **1959,** *81*, 1201.

[157] Tchoubar; Sackur *C. R. Acad. Sci.* **1939,** *208*, 1020.

[158] Baudry; Bégué; Charpentier-Morize *Bull. Soc.Chim. Fr.* **1971,** 1416, *Tetrahedron Lett.* **1970**, 2147.

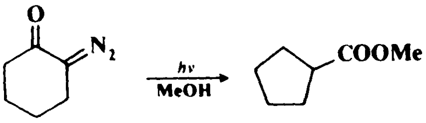
[159] For example, see Conia; Salaun *Tetrahedron Lett.* **1963,** 1175, *Bull. Soc. Chem. Fr.* **1964,** 1957; Salaun; Garnier; Conia *Tetrahedron* **1973,** *29*, 2895; Rappe; Knutsson *Acta Chem. Scand.* **1967,** *21*, 163; Warnhoff; Wong; Tai *J. Am. Chem. Soc.* **1968,** *90*, 514.

[160] For reviews, see Meier; Zeller *Angew. Chem. Int. Ed. Engl.* **1975,** *14*, 32-43 [*Angew. Chem. 87*, 52-63]; Kirmse, Ref. 124, pp. 475-493; Rodina; Korobitsyna *Russ. Chem. Rev.* **1967,** *36*, 260-272; For a review of rearrangements of diazo and diazonium compounds, see Whittaker, in Patai *The Chemistry of Diazonium and Diazo Compounds*, pt. 2; Wiley: New York, 1978, pp. 593-644.

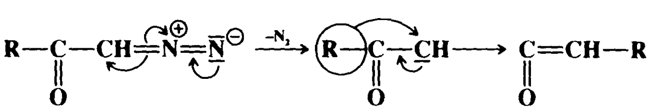
[161] For a list of methods, with references, see Ref. 106, p. 933.

[162] For reviews of the photolysis method, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 185-195; Ando, in Patai, Ref. 160, pp. 458-475.

method. Of course, diazo ketones prepared in any other way also give the rearrangement.[163] 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., **0-5** and **0-26**). Sometimes the reaction is performed with other diazoalkanes (that is, $R'CHN_2$) to give RCHR'COOH. The reaction has often been used for ring contraction of cyclic diazo ketones,[164] e.g.,[165]

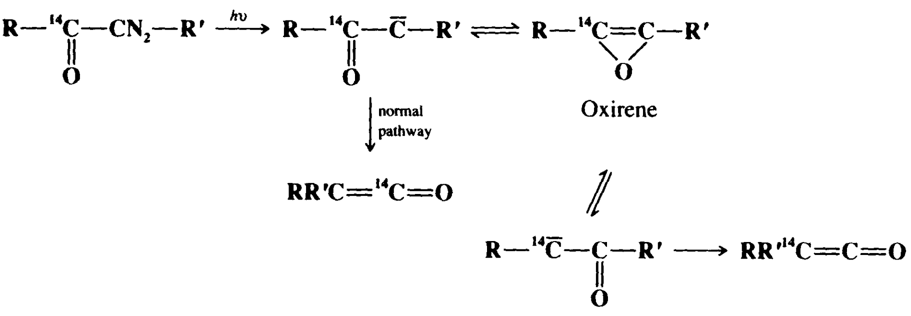


The mechanism is generally regarded as involving formation of a carbene. It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**5-2**), an alcohol (**5-4**), or ammonia or an amine (**5-7**). Particularly stable ketenes (e.g., $Ph_2C{=}C{=}O$) have been isolated and others have been trapped in other ways (e.g., as β-lactams,[166] **6-64**). 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 (**8-15**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,[167] 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,[162] but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene–carbene rearrangement, through an oxirene intermediate.[168] This was shown by ^{14}C labeling experiments, where diazo ketones labeled in the carbonyl group



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[163] For a method of conducting the reaction with trimethylsilyldiazomethane instead of CH_2N_2, see Aoyama; Shioiri *Tetrahedron Lett.* **1980**, *21*, 4461.

[164] For a review, see Redmore; Gutsche, Ref. 112, pp. 125-136.

[165] Korobitsyna; Rodina; Sushko *J. Org. Chem. USSR* **1968**, *4*, 165; Jones; Ando *J. Am. Chem. Soc.* **1968**, *90*, 2200.

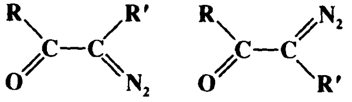
[166] Kirmse; Horner *Chem. Ber.* **1956**, *89*, 2759; also see Horner; Spietschka *Chem. Ber.* **1956**, *89*, 2765.

[167] For a summary of evidence on both sides of the question, see Kirmse, Ref. 124, pp. 476-480. See also Torres; Ribo; Clement; Strausz *Can J. Chem.* **1983**, *61*, 996; Tomoika; Hayashi; Asano; Izawa *Bull. Chem. Soc. Jpn.* **1983**, *56*, 758.

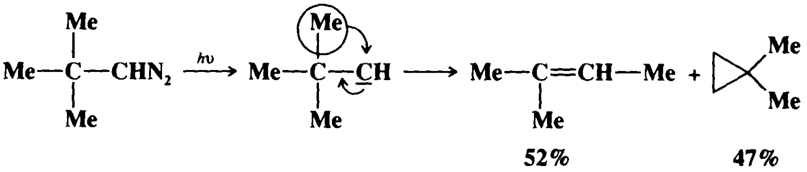
[168] For a review of oxirenes, see Lewars *Chem. Rev.* **1983**, *83*, 519-534.

gave rise to ketenes that bore the label at both C=C carbons.[169] In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when R′ = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.[170] 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.[171] In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by uv-visible, ir, and esr spectra.[172] These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.

The diazo ketone can exist in two conformations, called *s-E* and *s-Z*. Studies have shown that Wolff rearrangement takes place preferentially from the *s-Z* conformation.[173]

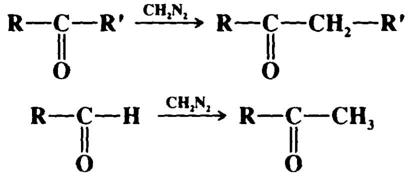

s-Z *s-E*

Other 1,2 alkyl migrations to a carbene or carbenoid terminus are also known,[174] e.g.,[175]



OS **III,** 356; **VI,** 613, 840.

8-9 Homologation of Aldehydes and Ketones
Methylene-insertion



$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{CH_2N_2} R-\underset{\underset{O}{\|}}{C}-CH_2-R'$$

$$R-\underset{\underset{O}{\|}}{C}-H \xrightarrow{CH_2N_2} R-\underset{\underset{O}{\|}}{C}-CH_3$$

Aldehydes and ketones[176] can be converted to their homologs[177] with diazomethane.[178] Formation of the epoxide (**6-61**) is a side reaction. Although this reaction appears super-

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[169] Csizmadia; Font; Strausz *J. Am. Chem. Soc.* **1968,** *90,* 7360; Fenwick; Frater; Ogi; Strausz *J. Am. Chem. Soc.* **1973,** *95,* 124; Zeller *Chem. Ber.* **1978,** *112,* 678. See also Thornton; Gosavi; Strausz *J. Am. Chem. Soc.* **1970,** *92,* 1768; Russell; Rowland *J.Am. Chem. Soc.* **1970,** *92,* 7508; Majerski; Redvanly *J. Chem. Soc. Chem. Commun.* **1972,** 694.

[170] Tanigaki; Ebbesen *J. Am. Chem. Soc.* **1987,** *109,* 5883. See also Bachmann; N'Guessan; Debû; Monnier; Pourcin; Aycard; Bodot *J. Am. Chem. Soc.* **1990,** *112,* 7488.

[171] Csizmadia; Gunning; Gosavi; Strausz *J. Am. Chem. Soc.* **1973,** *95,* 133.

[172] McMahon; Chapman; Hayes; Hess; Krimmer *J. Am. Chem. Soc.* **1985,** *107,* 7597.

[173] Kaplan; Mitchell *Tetrahedron Lett.* **1979,** 759; Tomioka; Okuno; Izawa *J. Org. Chem.* **1980,** *45,* 5278.

[174] For a review, see Kirmse, Ref. 124, pp. 457-462.

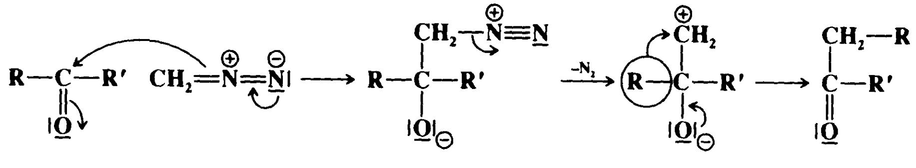
[175] Kirmse; Horn *Chem. Ber.* **1967,** *100,* 2698.

[176] For a homologation of carboxylic esters RCOOEt → RCH_2COOEt, which goes by an entirely different pathway, see Kowalski; Haque; Fields *J. Am. Chem. Soc.* **1985,** *107,* 1429.

[177] Other homologation reagents have also reported: See Taylor; Chiang; McKillop *Tetrahedron Lett.* **1977,** 1827; Villieras; Perriot; Normant *Synthesis* **1979,** 968; Hashimoto; Aoyama; Shioiri *Tetrahedron Lett.* **1980,** *21,* 4619; Aoyama; Shioiri *Synthesis* **1988,** 228.

[178] For a review, see Gutsche, *Org. React.* **1954,** *8,* 364-429.

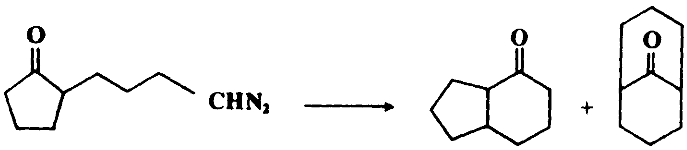
ficially to be similar to the insertion of carbenes into C—H bonds, **2-20** (and IUPAC names it as an insertion), the mechanism is quite different. This is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:



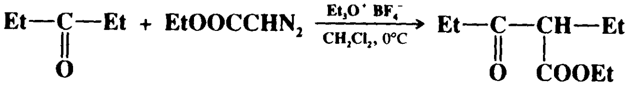
60

The betaine **60** can sometimes be isolated. As shown in **6-61**, **60** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.[178] It may be noted that this mechanism is essentially the same as in the apparent "insertions" of oxygen (**8-20**) and nitrogen (**8-17**) into ketones.

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 BF_3[179] or $AlCl_3$[180] increases the yield of ketone.[181] Cyclic ketones,[182] three-membered[183] and larger, behave particularly well and give good yields of ketones with the ring expanded by one.[184] Aliphatic diazo compounds ($RCHN_2$ and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.[185] An interesting example is the preparation of bicyclic compounds from alicyclic compounds with a diazo group in the side chain, e.g.,[186]



Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,[187] e.g.,



$$\underset{\displaystyle O}{\overset{}{Et{-}\underset{\|}{C}{-}Et}} + EtOOCCHN_2 \xrightarrow[CH_2Cl_2,\ 0°C]{Et_3O^+\ BF_4^-} Et{-}\underset{\underset{\displaystyle O}{\|}}{C}{-}\underset{\underset{\displaystyle COOEt}{|}}{CH}{-}Et$$

---

[179] House; Grubbs; Gannon *J. Am. Chem. Soc.* **1960,** *82*, 4099.

[180] Müller; Heischkeil *Tetrahedron Lett.* **1964,** 2809.

[181] For a review of homologations catalyzed by Lewis acids, see Müller; Kessler; Zeeh *Fortschr. Chem. Forsch* **1966,** *7*, 128-171, pp. 137-150.

[182] For other methods for the ring enlargement of cyclic ketones, see Krief; Laboureur *Tetrahedron Lett.* **1987,** *28*, 1545; Krief; Laboureur; Dumont *Tetrahedron Lett.* **1987,** *28*, 1549; Abraham; Bhupathy; Cohen *Tetrahedron Lett.* **1987,** *28*, 2203; Trost; Mikhail *J. Am. Chem. Soc.* **1987,** *109*, 4124.

[183] For example, see Turro; Gagosian *J. Am. Chem. Soc.* **1970,** *92*, 2036.

[184] For a review, see Gutsche; Redmore, Ref. 112, pp. 81-98. For a review pertaining to bridged bicyclic ketones, see Krow *Tetrahedron* **1987,** *43*, 3-38.

[185] For example, see Smith *J. Org. Chem.* **1960,** *25*, 453; Warner; Walsh; Smith *J. Chem. Soc.* **1962,** 1232; Loeschorn; Nakajima; Anselme *Bull. Soc. Chim. Belg.* **1981,** *90*, 985.

[186] Gutsche; Bailey *J. Org. Chem.* **1963,** *28*, 607; Gutsche; Zandstra *J. Org. Chem.* **1974,** *39*, 324.

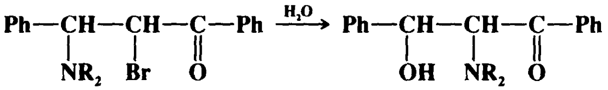
[187] Mock; Hartman *J. Org. Chem.* **1977,** *42*, 459, 466; Baldwin; Landmesser *Synth. Commun.* **1978,** *8*, 413.

When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.[188] The reaction can be made regioselective by applying this method to the α-halo ketone, in which case only the other carbon migrates.[189] The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β-unsaturated aldehydes and ketones.[190]

OS **IV,** 225, 780.

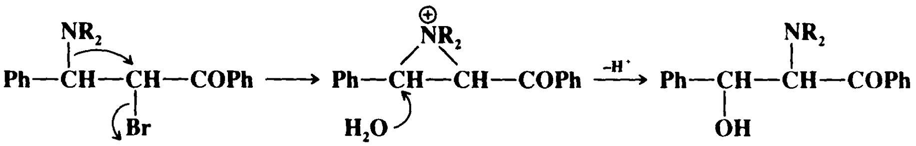
B. Carbon-to-Carbon Migrations of Other Groups

8-10 Migrations of Halogen, Hydroxyl, Amino, etc.
Hydroxy-de-bromo-*cine*-substitution, etc.

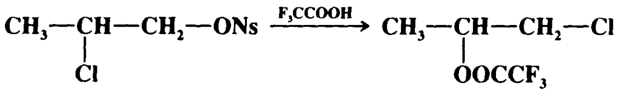


$$\underset{NR_2}{Ph-CH}-\underset{Br}{CH}-\underset{O}{C}-Ph \xrightarrow{H_2O} Ph-\underset{OH}{CH}-\underset{NR_2}{CH}-\underset{O}{C}-Ph$$

When a nucleophilic substitution is carried out on a substrate that has a neighboring group (p. 309) on the adjacent carbon, 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),[191] the reaction took place as follows:

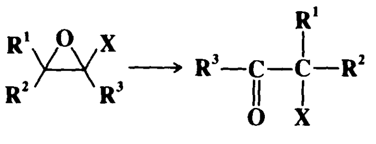


Another example is[192] (ONs = nosylate, see p. 353):



$$CH_3-\underset{Cl}{CH}-CH_2-ONs \xrightarrow{F_3CCOOH} CH_3-\underset{OOCCF_3}{CH}-CH_2-Cl$$

α-Halo and α-acyloxy epoxides undergo ready rearrangement to α-halo and α-acyloxy ketones, respectively.[193] These substrates are very prone to rearrange, and often do so on



X = F, Cl, Br, or OCOR

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[188] Liu; Majumdar *Synth. Commun.* **1975,** *5,* 125.

[189] Dave; Warnhoff *J. Org. Chem.* **1983,** *48,* 2590.

[190] Doyle; Trudell; Terpstra *J. Org. Chem.* **1983,** *48,* 5146.

[191] Southwick; Walsh *J. Am. Chem. Soc.* **1955,** *77,* 405. See also Suzuki; Okano; Nakai; Terao; Sekiya *Synthesis* **1983,** 723.

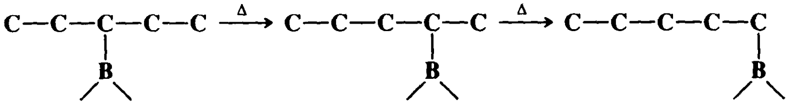
[192] For a review of Cl migrations, see Peterson, *Acc. Chem. Res.* **1971,** *4,* 407-413. See also Loktev; Korchagina; Shubin; Koptyug *J. Org. Chem. USSR.* **1977,** *13,* 201; Dobronravov; Shteingarts *J. Org. Chem. USSR.* **1977,** *13,* 420. For examples of Br migration, see Gudkova; Uteniyazov; Reutov *Doklad. Chem.* **1974,** *214,* 70; Brusova; Gopius; Smolina; Reutov *Doklad. Chem.* **1980,** *253,* 334. For a review of F migration (by several mechanisms) see Kobrina; Kovtonyuk *Russ. Chem. Rev.* **1988,** *57,* 62-71. For an example OH migration, see Cathcart; Bovenkamp; Moir; Bannard; Casselman *Can. J. Chem.* **1977,** *55,* 3774. For a review of migrations of ArS and $Ar_2P(O)$, see Warren *Acc. Chem. Res.* **1978,** *11,* 403-406. See also Aggarwal; Warren *J. Chem. Soc., Perkin Trans. 1* **1987,** 2579.

[193] For a review, see McDonald *Mech. Mol. Migr.* **1971,** *3,* 67-107.

standing without a catalyst, though in some cases an acid catalyst is necessary. The reaction is essentially the same as the rearrangement of epoxides shown in **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).

8-11 Migration of Boron

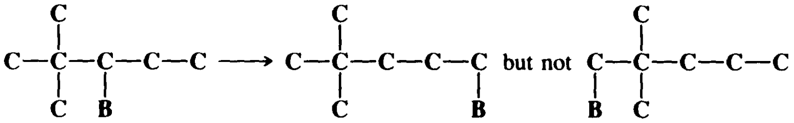
Hydro,dialkylboro-interchange, etc.



When a nonterminal borane is heated at temperatures ranging from 100 to 200°C, the boron moves toward the end of the chain.[194] 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.,

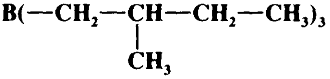
$$\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}-\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}-\mathrm{C}-\mathrm{C} \longrightarrow \mathrm{C}-\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}-\mathrm{C}-\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}$$

but not past a double branch, e.g.,



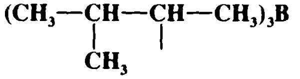
$$\mathrm{C}-\overset{\substack{\mathrm{C}\\|}}{\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}}-\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}-\mathrm{C}-\mathrm{C} \longrightarrow \mathrm{C}-\overset{\substack{\mathrm{C}\\|}}{\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}}-\mathrm{C}-\mathrm{C}-\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}} \text{ but not } \mathrm{C}-\overset{\substack{\mathrm{C}\\|}}{\underset{\substack{|\\ \mathrm{B}}}{\mathrm{C}}}-\underset{\substack{|\\ \mathrm{C}}}{\mathrm{C}}-\mathrm{C}-\mathrm{C}$$

The reaction is an equilibrium: **61, 62,** and **63** each gave a mixture containing about 40% **61,** 1% **62,** and 59% **63.** The migration can go quite a long distance. Thus



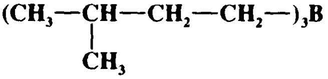
$$\mathrm{B}(-\mathrm{CH_2}-\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_3})_3$$

61



$$(\mathrm{CH_3}-\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}-\underset{|}{\mathrm{CH}}-\mathrm{CH_3})_3\mathrm{B}$$

62



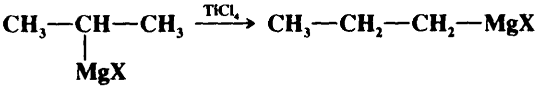
$$(\mathrm{CH_3}-\underset{\substack{|\\ \mathrm{CH_3}}}{\mathrm{CH}}-\mathrm{CH_2}-\mathrm{CH_2}-)_3\mathrm{B}$$

63

$(C_{11}H_{23}CHC_{11}H_{23})_3B$ was completely converted to $(C_{23}H_{47})_3B$, involving a migration of 11 positions.[195] If the boron is on a cycloalkyl ring, it can move around the ring; if any 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.[196] The reaction is useful for the migration of double bonds in a controlled way (see **2-2**). The mechanism may involve a π complex, at least partially.[197]

8-12 Rearrangement of Grignard Reagents

Hydro,magnesio-interchange



$$\mathrm{CH_3}-\underset{\substack{|\\ \mathrm{MgX}}}{\mathrm{CH}}-\mathrm{CH_3} \xrightarrow{\mathrm{TiCl_4}} \mathrm{CH_3}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{MgX}$$

---

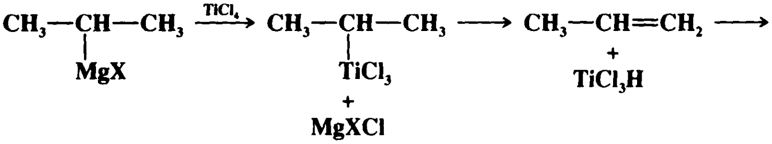
[194] Brown *Hydroboration*; W. A. Benjamin: New York, 1962, pp. 136-149, Brown; Zweifel *J. Am. Chem. Soc.* **1966,** *88*, 1433. See also Brown; Racherla *J. Organomet. Chem.* **1982,** *241*, C37.

[195] Logan *J. Org. Chem.* **1961,** *26*, 3657.

[196] Brown; Zweifel *J. Am. Chem. Soc.* **1967,** *89*, 561.

[197] See Wood; Rickborn *J. Org. Chem.* **1983,** *48*, 555; Field; Gallagher *Tetrahedron Lett.* **1985,** *26*, 6125.

The MgX of Grignard reagents[198] can migrate to terminal positions in the presence of small amounts of $TiCl_4$.[199] The proposed mechanism consists of metal exchange (**2-35**), elimination–addition, and metal exchange:

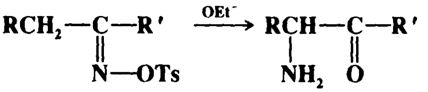


$$\underset{\displaystyle MgX}{CH_3—CH—CH_3} \xrightarrow{TiCl_4} \underset{\displaystyle \underset{MgXCl}{TiCl_3 +}}{CH_3—CH—CH_3} \longrightarrow \underset{\displaystyle TiCl_3H}{CH_3—CH{=}CH_2 +} \longrightarrow$$

$$CH_3—CH_2—CH_2—TiCl_3 \xrightarrow{MgXCl} CH_3—CH_2—CH_2—MgX + TiCl_4$$

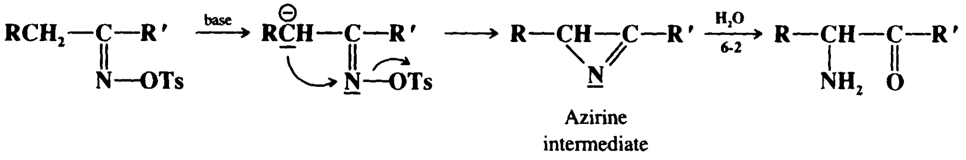
The addition step is similar to **5-12** or **5-13** and follows Markovnikov's rule, so the positive titanium goes to the terminal carbon.

8-13 The Neber Rearrangement
Neber oxime tosylate-amino ketone rearrangement



$$\underset{\displaystyle \| \atop N—OTs}{RCH_2—C—R'} \xrightarrow{OEt^-} \underset{\displaystyle NH_2\ \ O}{RCH—\underset{\|}{C}—R'}$$

α-Amino ketones can be prepared by treatment of ketoxime tosylates with a base such as ethoxide ion or pyridine.[200] 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 (**8-18**) and the abnormal Beckmann reaction (elimination to the nitrile, **7-38**) 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 $RCH(NH_2)COR'$.[201] The mechanism of the Neber rearrangement is as follows:[202]



The best evidence for this mechanism is that the azirine intermediate has been isolated.[203] In contrast to the Beckmann rearrangement, this one is sterically indiscriminate:[204] Both a syn and an anti ketoxime give the same product. The mechanism as shown above consists of three steps. 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

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[198] For reviews of rearrangements in organomagnesium chemistry, see Hill *Adv. Organomet. Chem.* **1977,** *16*, 131-165, *J. Organomet. Chem.* **1975,** *91*, 123-271.

[199] Cooper; Finkbeiner *J. Org. Chem.* **1962,** *27*, 1493; Fell; Asinger; Sulzbach *Chem. Ber.* **1970,** *103*, 3830. See also Ashby; Ainslie *J. Organomet. Chem.* **1983,** *250*, 1.

[200] For a review, see Conley; Ghosh *Mech. Mol. Migr.* **1971,** *4*, 197-308, pp. 289-304.

[201] Baumgarten; Petersen *J. Am. Chem. Soc.* **1960,** *82*, 459, and references cited therein.

[202] Cram; Hatch *J. Am. Chem. Soc.* **1953,** *75*, 33; Hatch; Cram *J. Am. Chem. Soc.* **1953,** *75*, 38.

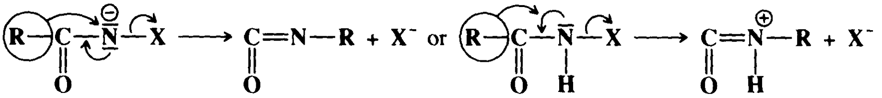
[203] Neber; Burgard *Liebigs Ann. Chem.* **1932,** *493*, 281; Parcell *Chem. Ind.* (*London*) **1963,** 1396; Ref. 202.

[204] House; Berkowitz *J. Org. Chem.* **1963,** *28*, 2271.

give $RCH_2C(=NCl)R'$, which then behaves analogously.[205] N-Chloroimines prepared in other ways also give the reaction.[206]

OS **V**, 909; **VII**, 149.

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. 1053). Reactions **8-14** to **8-17** are used to prepare amines from acid derivatives. Reactions **8-17** and **8-18** are used to prepare amines from ketones. The mechanisms of **8-14, 8-15, 8-16,** and **8-17** (with carboxylic acids) are very similar and follow one of two patterns:



Some of the evidence[207] is: (1) configuration is retained in R (p. 1054); (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[208] or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.[209] It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

8-14 The Hofmann Rearrangement

Bishydrogen-(2/→1/*N*-alkyl)-*migro*-detachment (formation of isocyanate)

$$RCONH_2 + NaOBr \longrightarrow R—N{=}C{=}O \xrightarrow[6\text{-}3]{\text{hydrolysis}} RNH_2$$

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 that has one carbon fewer than the starting amide.[210] The actual product is the isocyanate, but this compound is seldom isolated[211] since it is usually hydrolyzed under the reaction conditions (**6-3**). 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 (**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 (**6-17**). If acylureas are desired, they can be made the main products by using only half the

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[205] For example, see Oae; Furukawa *Bull. Chem. Soc. Jpn.* **1965,** *38,* 62; Nakai; Furukawa; Oae *Bull. Chem. Soc. Jpn.* **1969,** *42,* 2917.

[206] Baumgarten; Petersen; Wolf *J. Org. Chem.* **1963,** *28,* 2369.

[207] For a discussion of this mechanism and the evidence for it, see Smith, in Mayo, Ref. 114, vol. 1, pp. 258-550.

[208] For a review of rearrangements involving nitrene intermediates, see Boyer *Mech. Mol. Migr.* **1969,** *2,* 267-318. See also Ref. 221.

[209] The question is discussed by Lwowski, in Lwowski *Nitrenes*; Wiley: New York, 1970, pp. 217-221.

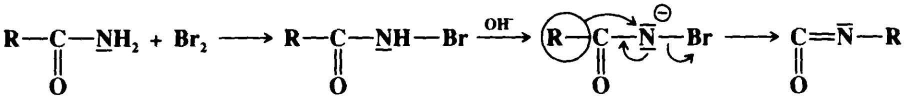
[210] For a review, see Wallis; Lane *Org. React.* **1946,** *3,* 267-306.

[211] If desired, the isocyanate can be isolated by the use of phase transfer conditions: see Sy and Raksis *Tetrahedron Lett.* **1980,** *21,* 2223.

[212] For an example of the use of this method at low temperatures, see Radlick; Brown *Synthesis* **1974,** 290.

usual quantities of Br_2 and NaOH. Another side product, though only from primary R, is the nitrile derived from oxidation of RNH_2 (**9-5**). 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.

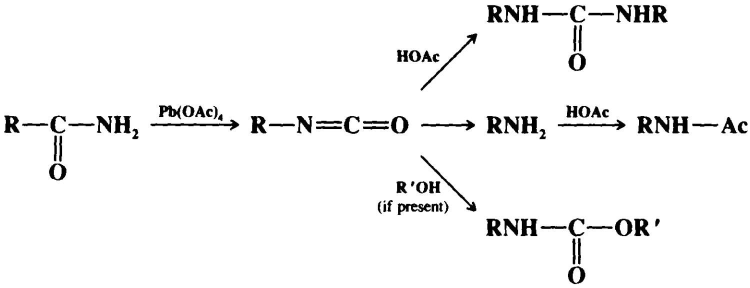
The mechanism follows the pattern outlined on p. 1090.



64

The first step is an example of **2-54** and intermediate N-halo amides (**64**) have been isolated. In the second step, **64** lose a proton to the base. **64** are 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 (**6-8**).



Among other reagents that convert $RCONH_2$ to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) $PhI(OCOCF_3)_2$[215] and hydroxy(tosyloxy)iodobenzene PhI(OH)OTs.[216] A mixture of N-bromosuccinimide, $Hg(OAc)_2$, and R'OH is one of several reagent mixtures that convert an amide $RCONH_2$ to the carbamate RNHCOOR' (R = primary, secondary, or tertiary alkyl or aryl) in high yield.[217]

OS **II**, 19, 44, 462; **IV**, 45; **65**, 173; **66**, 132.

8-15 The Curtius Rearrangement

Dinitrogen-(2/→1/*N*-alkyl)-*migro*-detachment

$$RCON_3 \xrightarrow{\Delta} R{-}N{=}C{=}O$$

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[213] See, for example, Imamoto; Tsuno; Yukawa *Bull. Chem. Soc. Jpn.* **1971,** *44,* 1632, 1639, 1644; Imamoto; Kim; Tsuno; Yukawa *Bull. Chem. Soc. Jpn.* **1971,** *44,* 2776.

[214] Acott; Beckwith *Chem. Commun.* **1965,** 161; Baumgarten; Staklis *J. Am. Chem. Soc.* **1965,** *87,* 1141; Acott; Beckwith; Hassanali *Aust. J. Chem.* **1968,** *21,* 185, 197; Baumgarten; Smith; Staklis *J. Org. Chem.* **1975,** *40,* 3554.

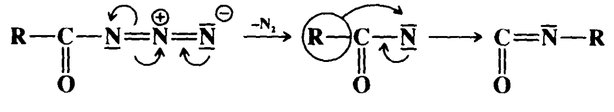
[215] Loudon; Radhakrishna; Almond; Blodgett; Boutin *J. Org. Chem.* **1984,** *49,* 4272; Boutin; Loudon *J. Org. Chem.* **1984,** *49,* 4277; Pavlides; Chan; Pennington; McParland; Whitehead; Coutts *Synth. Commun.* **1988,** *18,* 1615.

[216] Lazbin; Koser *J. Org. Chem.* **1986,** *51,* 2669; Vasudevan; Koser *J. Org. Chem.* **1988,** *53,* 5158.

[217] Jew; Park; Park; Park; Cho *Tetrahedron Lett.* **1990,** *31,* 1559.

The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.[218] 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 **8-14.**[219] 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 **0-61** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to **2-50**). 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 **8-14:**

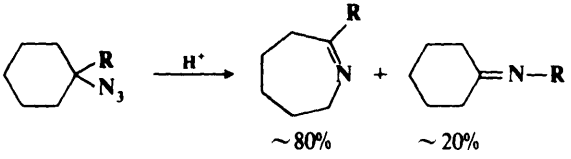


Also note the exact analogy between this reaction and **8-8.** However, in this case, there is no evidence for a free nitrene and it is probable that the steps are concerted.[220]

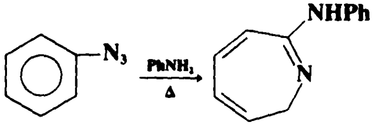
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:[221]

$$R_3CN_3 \xrightarrow{\Delta} R_2C{=}NR$$

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.[222] 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 (**6-2**). Cycloalkyl azides give ring expansion.[223]



Aryl azides also give ring expansion on heating, e.g.,[224]



OS **III,** 846; **IV,** 819; **V,** 273; **VI,** 95, 910. Also see OS **VI,** 210.

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[218] For a review, see Banthorpe, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 397-405.

[219] For a variation that conveniently produces the amine directly, see Pfister; Wyman *Synthesis* **1983,** 38. See also Capson; Poulter *Tetrahedron Lett.* **1984,** *25,* 3515.

[220] See, for example, Lwowski *Angew. Chem. Int. Ed. Engl.* **1967,** *6,* 897-906 [*Angew. Chem. 79,* 922-932]; Linke; Tissue; Lwowski *J. Am. Chem. Soc.* **1967,** *89,* 6308; Smalley; Bingham *J. Chem. Soc. C* **1969,** 2481.

[221] For a treatise on azides, which includes discussion of rearrangement reactions, see Scriven *Azides and Nitrenes*; Academic Press: New York, 1984. For a review of rearrangements of alkyl and aryl azides, see Stevens; Watts, Ref. 1, pp. 45-52. For reviews of the formation of nitrenes from alkyl and aryl azides, see, in Lwowski, Ref. 209, the chapters by Lewis; Saunders, pp. 47-97, pp. 47-78 and by Smith, pp. 99-162.

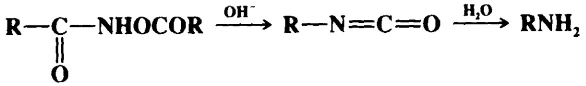
[222] Abramovitch; Kyba *J. Am. Chem. Soc.* **1974,** *96,* 480; Montgomery; Saunders *J. Org. Chem.* **1976,** *41,* 2368.

[223] Smith; Lakritz, cited in Smith, in Mayo, Ref. 114, vol. 1, p. 474.

[224] Huisgen; Vossius; Appl *Chem. Ber.* **1958,** *91,* 1, 12.

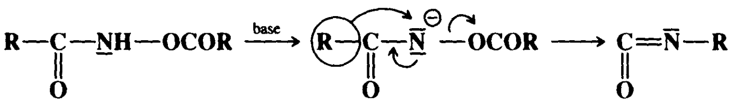
8-16 The Lossen Rearrangement

Hydro,acetoxy-(2/→1/*N*-alkyl)-*migro*-detachment

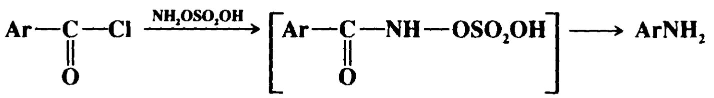


$$R{-}\underset{\underset{O}{\|}}{C}{-}NHOCOR \xrightarrow{OH^-} R{-}N{=}C{=}O \xrightarrow{H_2O} RNH_2$$

The O-acyl derivatives of hydroxamic acids[225] give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*. The mechanism is similar to that of **8-14** and **8-15**:



In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-O-sulfonic acid.[226]



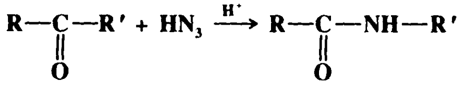
$$Ar{-}\underset{\underset{O}{\|}}{C}{-}Cl \xrightarrow{NH_2OSO_2OH} \left[Ar{-}\underset{\underset{O}{\|}}{C}{-}NH{-}OSO_2OH\right] \longrightarrow ArNH_2$$

8-17 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.[227] The most common is the reaction with carboxylic acids, illustrated above.[228] 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 **8-14** and **8-15** that it is just one laboratory step from the acid to the amine, but conditions are more drastic.[229] Under the acid conditions employed, the isocyanate is virtually never isolated.

The reaction between a ketone and hydrazoic acid is a method for "insertion" of NH between the carbonyl group and one R group, converting a ketone into an amide.[230]



$$R{-}\underset{\underset{O}{\|}}{C}{-}R' + HN_3 \xrightarrow{H^+} R{-}\underset{\underset{O}{\|}}{C}{-}NH{-}R'$$

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

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[225] For a review of hydroxamic acids, see Bauer; Exner *Angew. Chem. Int. Ed. Engl.* **1974,** *13*, 376-384 [*Angew. Chem. 86*, 419-428].

[226] Wallace; Barker; Wood *Synthesis* **1990,** 1143.

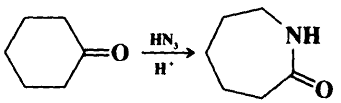
[227] For a review, see Banthorpe, Ref. 218, pp. 405-434.

[228] For a review, see Koldobskii; Ostrovskii; Gidaspov *Russ. Chem. Rev.* **1978,** *47*, 1084-1094.

[229] For a comparision of reactions **8-14** to **8-17** as methods for converting an acid to an amine, see Smith, *Org. React.* **1946,** *3*, 337-449, pp. 363-366.

[230] For reviews, see Koldobskii; Tereschenko; Gerasimova; Bagal *Russ. Chem. Rev.* **1971,** *40*, 835-846; Beckwith, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 137-145.

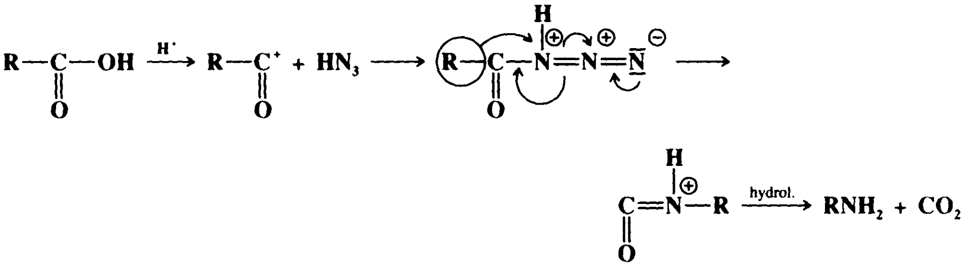
latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones—or carboxylic acids or alcohols—that these functions may be present in the same molecule without interference. Cyclic ketones give lactams:[231]



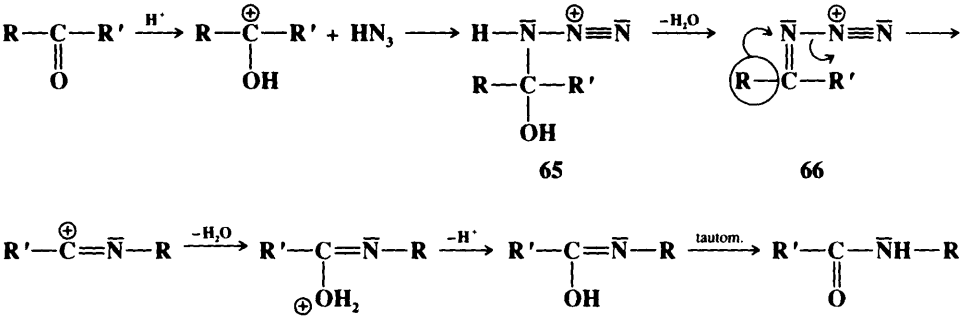
With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.[232] The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (**6-22**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **7-38.**

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 **8-15.**[221]

There is evidence that the mechanism with carboxylic acids[228] is similar to that of **8-15,** except that it is the protonated azide that undergoes the rearrangement:[233]



The first step is the same as that of the AAc1 mechanism (**0-10**), which explains why good results are obtained with hindered substrates. The mechanism with ketones is[234]



65 **66**

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[231] For a review with respect to bicyclic ketones, see Krow, *Tetrahedron* **1981,** *37,* 1283-1307.

[232] Exceptions to this statement have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in ortho and para positions: Bhalerao; Thyagarajan *Can. J. Chem.* **1968,** *46,* 3367; Tomita; Minami; Uyeo *J. Chem. Soc. C.* **1969,** 183.

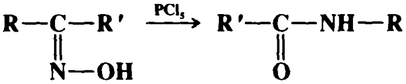
[233] There has been some controversy about this mechanism. For a discussion, see Vogler; Hayes *J. Org. Chem.* **1979,** *44,* 3682.

[234] Smith *J. Am. Chem. Soc.* **1948,** *70,* 320; Smith; Antoniades *Tetrahedron* **1960,** *9,* 210. A slightly different mechanism, involving direct rearrangement of **65,** has been shown in certain cases: Fikes; Shechter *J. Org. Chem.* **1979,** *44,* 741. See also Bach; Wolber *J. Org. Chem.* **1972,** *47,* 239.

The intermediates **66** have been independently generated in aqueous solution.[235] Note the similarity of this mechanism to those of "insertion" of CH_2 (**8-9**) and of O (**8-20**). The three reactions are essentially analogous, both in products and in mechanism.[236] Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (**8-18**).

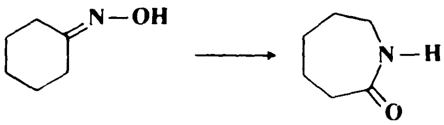
OS **V**, 408; **VI**, 368; **VII**, 254. See also OS **V**, 623.

8-18 The Beckmann Rearrangement
Beckmann oxime–amide rearrangement



$$\underset{\textstyle \text{N—OH}}{\text{R—}\overset{}{\underset{\|}{\text{C}}}\text{—R}'} \xrightarrow{PCl_5} \underset{\textstyle \text{O}}{\text{R}'\text{—}\underset{\|}{\text{C}}\text{—NH—R}}$$

When oximes are treated with PCl_5 or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement.*[237] Among other reagents used have been concentrated H_2SO_4, formic acid, liquid SO_2, HMPA,[238] $SOCl_2$,[239] silica gel,[240] P_2O_5–methanesulfonic acid,[241] HCl–HOAc–Ac_2O, and polyphosphoric acid.[242] The group that migrates is generally the one anti 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 syn 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 syn group actually undergoes migration. In most cases the oxime undergoes isomerization under the reaction conditions *before* migration takes place.[243] The scope of the reaction is quite broad. R and R′ may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates*, so 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[244] or by heating the aldoxime for 60 hr at 100°C after it has been adsorbed onto silica gel.[245] As in the case of the Schmidt rearrangement, when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates. The oximes of cyclic ketones give ring enlargement,[246] e.g.,



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[235] Amyes; Richard *J. Am. Chem. Soc.* **1991,** *113*, 1867.

[236] For evidence for this mechanism, see Koldobskii; Enin; Naumov; Ostrovskii; Tereshchenko; Bagal *J. Org. Chem. USSR* **1972,** *8*, 242; Ostrovskii; Koshtaleva; Shirokova; Koldobskii; Gidaspov *J. Org. Chem. USSR* **1974,** *10*, 2365; Ref. 230.

[237] For reviews, see Gawley *Org. React.* **1988,** *35*, 1-420; McCarty, in Patai *The Chemistry of the Carbon–Nitrogen Double Bond*; Wiley: New York, 1970, pp. 408-439.

[238] Monson; Broline *Can. J. Chem.* **1973,** *51*, 942; Gupton; Idoux; Leonard; DeCrescenzo *Synth. Commun.* **1983,** *13*, 1083.

[239] Butler; O'Donoghue *J. Chem. Res. (S)* **1983,** 18.

[240] Costa; Mestres; Riego *Synth. Commun.* **1982,** *12*, 1003.

[241] Eaton; Carlson; Lee *J. Org. Chem.* **1973,** *38*, 4071.

[242] For a review of Beckmann rearrangements with polyphosphoric acid, see Beckwith, in Zabicky, Ref. 230, pp. 131-137.

[243] Lansbury; Mancuso *Tetrahedron Lett.* **1965,** 2445 have shown that some Beckmann rearrangements are *authentically* nonstereospecific.

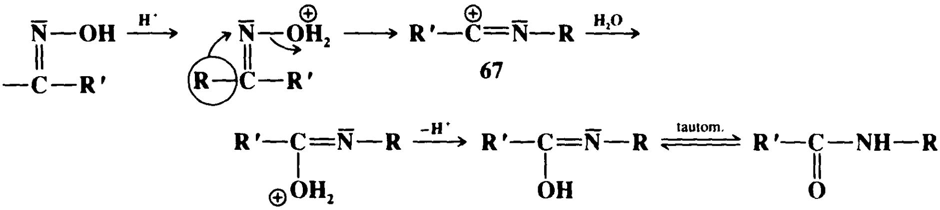
[244] Field; Hughmark; Shumaker; Marshall *J. Am. Chem. Soc.* **1961,** *83*, 1983. See also Leusink; Meerbeek; Noltes *Recl. Trav. Chim. Pays-Bas* **1976,** *95*, 123, **1977,** *96*, 142.

[245] Chattopadhyaya; Rama Rao *Tetrahedron* **1974,** *30*, 2899.

[246] For a review of such ring enlargements, see Vinnik; Zarakhani *Russ. Chem. Rev.* **1967,** *36*, 51-64. For a review with respect to bicyclic oximes, see Ref. 231.

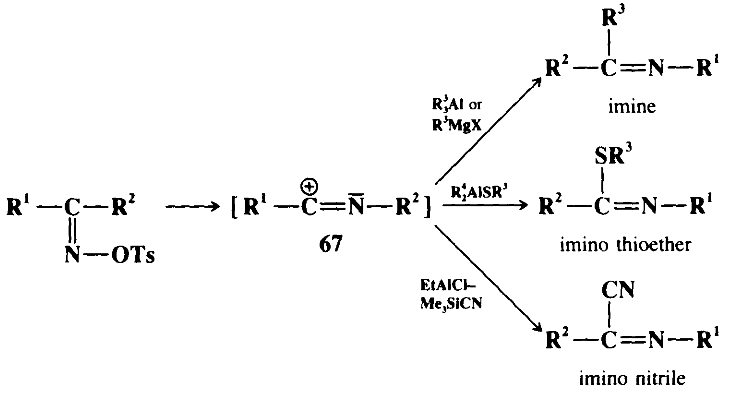
Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, **7-38**). Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with NH_2OSO_2OH and formic acid (**6-20** takes place first, then the Beckmann rearrangement).[247]

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, e.g., proton acids convert it to OH_2^+. After that, the mechanism follows a course analogous to that for the Schmidt reaction of ketones (**8-17**) from the formation of **66** on:[248]



The other reagents convert OH to an ester leaving group (e.g., $OPCl_4$ from PCl_5 and OSO_2OH from concentrated H_2SO_4[249]). Alternatively, the attack on **67** can be by the leaving group, if different from H_2O. Intermediates of the form **67** have been detected by nmr and uv spectroscopy.[250] 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 (**6-55**).[251] Beckmann rearrangements have also been carried out photochemically.[252]

If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,[253] the intermediate **67** is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether, or an imino nitrile[254] (in the



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[247] Olah; Fung *Synthesis* **1979**, 537. See also Novoselov; Isaev; Yurchenko; Vodichka; Trshiska *J. Org. Chem. USSR* **1981**, *17*, 2284.

[248] For summaries of the considerable evidence for this mechanism, see Donaruma; Heldt *Org. React.* **1960**, *11*, 1-156, pp. 5-14; Smith, in Mayo, Ref. 114, vol. 1, 483-507, pp. 488-493.

[249] Gregory; Moodie; Schofield *J. Chem. Soc. B* **1970**, 338; Kim; Kawakami; Ando; Yukawa *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1115.

[250] Gregory; Moodie; Schofield, Ref. 249.

[251] Hill; Conley; Chortyk *J. Am. Chem. Soc.* **1965**, *87*, 5646; Palmere; Conley; Rabinowitz *J. Org. Chem.* **1972**, *37*, 4095.

[252] See, for example, Izawa; Mayo; Tabata *Can. J. Chem.* **1969**, *47*, 51; Cunningham; Ng Lim; Just *Can. J. Chem.* **1971**, *49*, 2891; Suginome; Yagihashi *J. Chem. Soc., Perkin Trans. 1* **1977**, 2488.

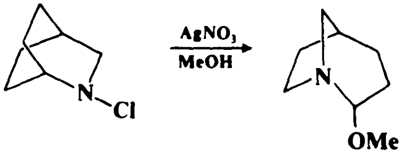
[253] For a review, see Maruoka; Yamamoto *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 668-682 [*Angew. Chem.* 97, 670-683].

[254] Maruoka; Miyazaki; Ando; Matsumura; Sakane; Hattori; Yamamoto *J. Am. Chem. Soc.* **1983**, *105*, 2831; Maruoka; Nakai; Yamamoto *Org. Synth. 66*, 185.

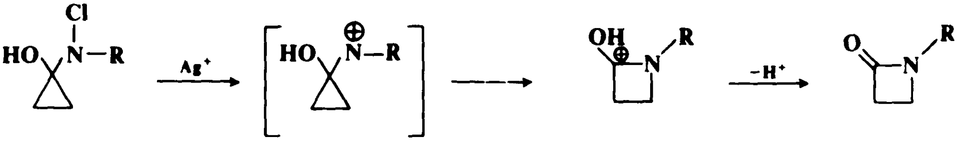
last case, the nucleophile comes from added trimethylsilyl cyanide). The imine-producing reaction can also be accomplished with a Grignard reagent in benzene or toluene.[255]

OS **II,** 76, 371; **66,** 185.

8-19 Stieglitz and Related Rearrangements
Methoxy-de-*N*-chloro-(2/→1/*N*-alkyl)-*migro*-substitution, etc.



Besides the reactions discussed at **8-14** to **8-18,** 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 (above), undergo rearrangement when solvolyzed in the presence of silver nitrate.[256] This reaction is similar to the Wagner–Meerwein rearrangement (**8-1**) and is initiated by the silver-catalyzed departure of the chloride ion.[257] Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **8-3.**[258] An example is the conversion of 1-(N-chloroamino)cyclopropanols to β-lactams.[259]



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

$$Ar_3CNHX \xrightarrow{\text{base}} Ar_2C{=}NAr$$

$$Ar_3CNHOH \xrightarrow{PCl_5} Ar_2C{=}NAr$$

azides (**8-15**), 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:[260]

$$Ar_3CNH_2 \xrightarrow{Pb(OAc)_4} Ar_2C{=}NAr$$

D. Carbon-to-Oxygen Migrations of R and Ar

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[255] Hattori; Maruoka; Yamamoto *Tetrahedron Lett.* **1982,** *23,* 3395.

[256] Gassman; Fox *J. Am. Chem. Soc.* **1967,** *89,* 338. See also Schell; Ganguly *J. Org. Chem.* **1980,** *45,* 4069; Davies; Malpass; Walker *J. Chem. Soc., Chem. Commun.* **1985,** 686; Hoffman; Kumar; Buntain *J. Am. Chem. Soc.* **1985,** *107,* 4731.

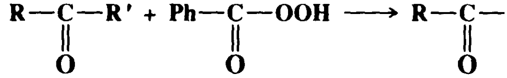
[257] For C → N rearrangements induced by $AlCl_3$, see Kovacic; Lowery; Roskos *Tetrahedron* **1970,** *26,* 529.

[258] Gassman; Carrasquillo *Tetrahedron Lett.* **1971,** 109; Hoffman; Buntain *J. Org. Chem.* **1988,** *53,* 3316.

[259] Wasserman; Adickes; Espejo de Ochoa *J. Am. Chem. Soc.* **1971,** *93,* 5586; Wasserman; Glazer; Hearn *Tetrahedron Lett.* **1973,** 4855.

[260] Sisti *Chem. Commun.* **1968,** 1272; Sisti; Milstein *J. Org. Chem.* **1974,** *39,* 3932.

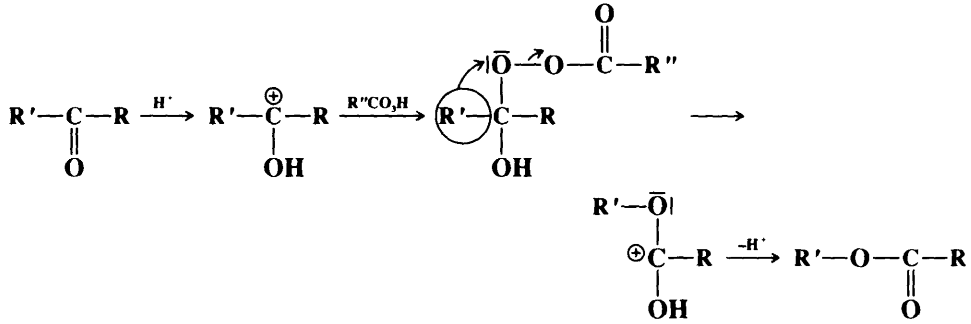
8-20 The Baeyer–Villiger Rearrangement
Oxy-insertion



$$R-\underset{\underset{O}{\|}}{C}-R' + Ph-\underset{\underset{O}{\|}}{C}-OOH \longrightarrow R-\underset{\underset{O}{\|}}{C}-OR'$$

The treatment of ketones with peracids such as perbenzoic or peracetic acid, or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by "insertion" of oxygen.[261] The reaction is called the *Baeyer–Villiger rearrangement*.[262] 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.[263] Enantioselective synthesis of chiral lactones from achiral ketones has been achieved by the use of enzymes as catalysts.[264] For acyclic compounds, R′ must usually be secondary, tertiary, or vinylic, although primary R′ has been rearranged with peroxytrifluoroacetic acid,[265] with BF_3–H_2O_2,[266] and with $K_2S_2O_8$–H_2SO_4.[267] 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). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.[268] Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides.[269] With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing **4-6.** Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H_2O_2 and a selenium compound[270] (see also the Dakin reaction in **9-12**).

The mechanism[271] is similar to those of the analogous reactions with hydrazoic acid (**8-17** with ketones) and diazomethane (**8-8**):



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[261] For a list of reagents, with references, see Ref. 106, p. 843.

[262] For reviews, see Hudlický *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 186-195; Plesničar, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 254-267; House *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: New York, 1972, pp. 321-329; Lewis, in Augustine *Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 237-244; Lee; Uff *Q. Rev. Chem. Soc.* **1967**, *21*, 429-457, pp. 449-453. For a review of enzyme-catalyzed Baeyer–Villiger rearrangements, see Walsh; Chen *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 333-343 [*Angew. Chem. 100*, 342-352].

[263] For a review of the reaction as applied to bicyclic ketones, see Krow *Tetrahedron* **1981**, *37*, 2697-2724.

[264] See Taschner; Black *J. Am. Chem. Soc.* **1988**, *110*, 6892.

[265] Emmons; Lucas *J. Am. Chem. Soc.* **1955**, *77*, 2287.

[266] McClure; Williams *J. Org. Chem.* **1962**, *27*, 24.

[267] Deno; Billups; Kramer; Lastomirsky *J. Org. Chem.* **1970**, *35*, 3080.

[268] For a report of substituent effects in the α, β, and γ positions of alkyl groups, see Noyori; Sato; Kobayashi *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2661.

[269] For a study of the mechanism of this conversion, see Cullis; Arnold; Clarke; Howell; DeMira; Naylor; Nicholls *J. Chem. Soc., Chem. Commun.* **1987**, 1088.

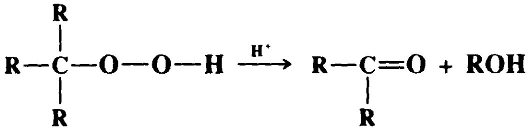
[270] Syper *Synthesis* **1989**, 167. See also Godfrey; Sargent; Elix *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

[271] Proposed by Criegee *Liebigs Ann. Chem.* **1948**, *560*, 127.

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.[272] Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,[273] demonstrating that migration of Ar is concerted with departure of OCOR″.[274] (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.)

8-21 Rearrangement of Hydroperoxides

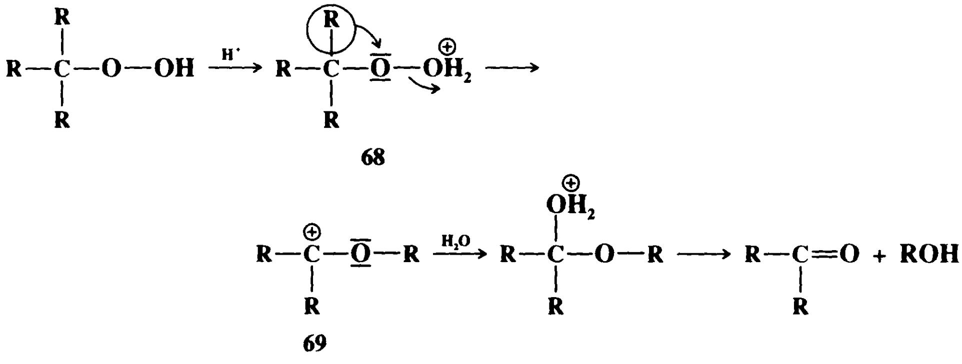
C-Alkyl-O-hydroxy-elimination



$$R_3C{-}O{-}O{-}H \xrightarrow{H^+} R_2C{=}O + ROH$$

Hydroperoxides (R = alkyl, aryl, or hydrogen) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.[275] 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. 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 ($RCH_2OOH \rightarrow CH_2{=}O + ROH$).

The mechanism is as follows:[276]



The last step is hydrolysis of the unstable hemiacetal. Alkoxycarbocation intermediates (**69**, R = alkyl) have been isolated in super-acid solution[277] at low temperatures, and their structures proved by nmr.[278] The protonated hydroperoxides (**68**) could not be observed in these solutions, evidently reacting immediately on formation.

OS **V**, 818.

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[272] Doering; Dorfman *J. Am. Chem. Soc.* **1953**, *75*, 5595. For summaries of the other evidence, see Smith, Ref. 248, pp. 578-584.

[273] Palmer; Fry *J. Am. Chem. Soc.* **1970**, *92*, 2580. See also Mitsuhashi; Miyadera; Simamura; *Chem. Commun.* **1970**, 1301. For secondary isotope-effect studies, see Winnik; Stoute; Fitzgerald *J. Am. Chem. Soc.* **1974**, *96*, 1977.

[274] In some cases the rate-determining step has been shown to be the addition of peracid to the substrate [see, for example, Ogata; Sawaki *J. Org. Chem.* **1972**, *37*, 2953]. Even in these cases it is still highly probable that migration is concerted with departure of the nucleofuge.

[275] For reviews, see Yablokov *Russ. Chem. Rev.* **1980**, *49*, 833-842; Lee; Uff, Ref. 262, 445-449.

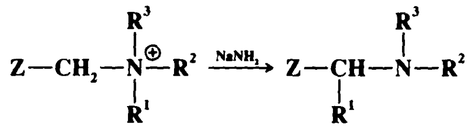
[276] For a discussion of the transition state involved in the migration step, see Wistuba; Rüchardt *Tetrahedron Lett.* **1981**, *22*, 3389.

[277] For a review of peroxy compounds in super acids, see Olah; Parker; Yoneda *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 909-931 [*Angew. Chem.* *90*, 962-984].

[278] Sheldon; van Doorn *Tetrahedron Lett.* **1973**, 1021.

E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

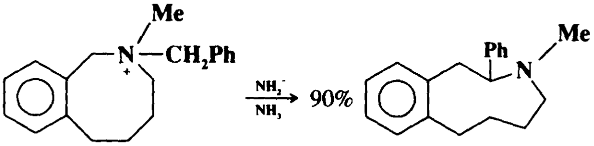
8-22 The Stevens Rearrangement
Hydron-(2/*N*→1/alkyl)-*migro*-detachment



$$Z—CH_2—\overset{R^3}{\underset{R^1}{\overset{|}{\underset{|}{N^{\oplus}}}}}—R^2 \xrightarrow{NaNH_2} Z—\underset{R^1}{\underset{|}{CH}}—\overset{R^3}{\overset{|}{N}}—R^2$$

70

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.[279] The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center.[280] When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see **8-37**), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,[281] e.g.:



The mechanism has been the subject of much study.[282] That the rearrangement is intramolecular was shown by crossover experiments, by ^{14}C labeling,[283] and by the fact that retention of configuration is found at R^1.[284] The first step is loss of the acidic proton to give the ylide **71**, which has been isolated.[285] The finding[286] that CIDNP spectra[287] 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:[288]

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[279] For reviews of the Stevens rearrangement, see Lepley; Giumanini *Mech. Mol. Migr.* **1971,** *3*, 297-440; Pine *Org. React.* **1970,** *18*, 403-464. For reviews of the Stevens and the closely related Wittig rearrangement (**8-23**), see Stevens; Watts, Ref. 1, pp. 81-116; Wilt, in Kochi, Ref. 55, pp. 448-458; Iwai *Mech. Mol. Migr.* **1969,** *2*, 73-116, pp. 105-113; Stevens *Prog. Org. Chem.* **1968,** *7*, 48-74.

[280] Migration of aryl is rare, but has been reported: Heaney; Ward *Chem. Commun.* **1969,** 810; Truce; Heuring *Chem. Commun.* **1969,** 1499.

[281] Elmasmodi; Cotelle; Barbry; Hasiak; Couturier *Synthesis* **1989,** 327.

[282] For example, see Pine *J. Chem. Educ.* **1971,** *48*, 99-102.

[283] Stevens *J. Chem. Soc.* **1930,** 2107; Johnstone; Stevens *J. Chem. Soc.* **1955,** 4487.

[284] Brewster; Kline *J. Am. Chem. Soc.* **1952,** *74*, 5179; Schöllkopf; Ludwig; Ostermann; Patsch *Tetrahedron Lett.* **1969,** 3415.

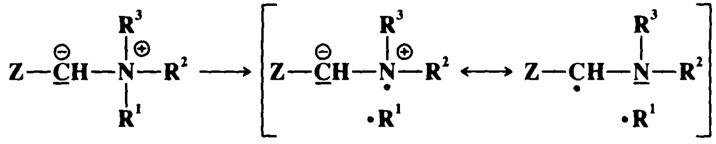
[285] Jemison; Mageswaran; Ollis; Potter; Pretty; Sutherland; Thebtaranonth *Chem. Commun.* **1970,** 1201.

[286] Lepley *J. Am. Chem. Soc.* **1969,** *91*, 1237, *Chem. Commun.* **1969,** 1460; Lepley; Becker; Giumanini *J. Org. Chem.* **1971,** *36*, 1222; Baldwin; Brown; *J. Am. Chem. Soc.* **1969,** *91*, 3646; Jemison; Morris *Chem. Commun.* **1969,** 1226; Ref. 285; Schöllkopf et al., Ref. 284.

[287] For a review of the application of CIDNP to rearrangement reactions, see Lepley, in Lepley; Closs *Chemically Induced Magnetic Polarization*; Wiley: New York, 1973, pp. 323-384.

[288] Schöllkopf; Ludwig *Chem. Ber.* **1968,** *101*, 2224; Ollis; Rey; Sutherland *J. Chem. Soc., Perkin Trans 1.* **1983,** 1009, 1049.

Mechanism *a*

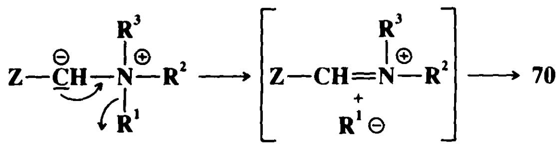


$$Z-\overset{\ominus}{\underline{C}}H-\overset{R^3}{\underset{R^1}{N^{\oplus}}}-R^2 \longrightarrow \left[Z-\overset{\ominus}{\underline{C}}H-\overset{R^3}{\underset{\bullet}{N^{\oplus}}}-R^2 \ \cdot R^1 \longleftrightarrow Z-\overset{\bullet}{C}H-\overset{R^3}{\underline{N}}-R^2 \ \cdot R^1 \right]$$

71 Solvent cage

The radicals do not drift apart because they are held together by the solvent cage. 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,[289] which would be expected if some $\bullet R^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.[290] 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. A third

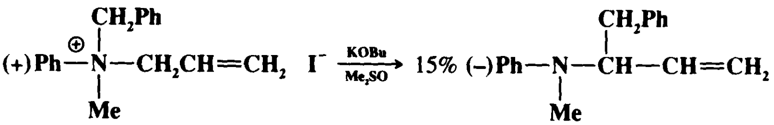
Mechanism *b*



$$Z-\overset{\ominus}{\underline{C}}H-\overset{R^3}{\underset{R^1}{N^{\oplus}}}-R^2 \longrightarrow \left[Z-CH=\overset{R^3}{N^{\oplus}}-R^2 \ + \ R^1\ominus \right] \longrightarrow 70$$

71 Solvent cage

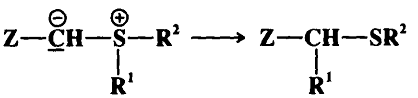
possible mechanism would be a concerted 1,2-shift,[291] but the orbital symmetry principle requires that this take place with inversion at R^1.[292] (See p. 1126.) Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism. However, in the case where the migrating group is allylic, a concerted mechanism can also operate (**8-37**). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 98) gave an optically active product:[293]



$$(+)Ph-\overset{CH_2Ph}{\underset{Me}{\overset{\oplus}{N}}}-CH_2CH=CH_2 \ I^- \xrightarrow[Me_2SO]{KOBu} 15\% \ (-)Ph-\underset{Me}{N}-\overset{CH_2Ph}{CH}-CH=CH_2$$

The Sommelet-Hauser rearrangement competes when Z is an aryl group (see **3-26**). Hofmann elimination competes when one of the R groups contains a β hydrogen atom (**7-6** and **7-7**).

Sulfur ylides containing a Z group give an analogous rearrangement, often also referred to as a Stevens rearrangement.[294] In this case too, there is much evidence (including CIDNP)



$$Z-\overset{\ominus}{\underline{C}}H-\underset{R^1}{\overset{\oplus}{S}}-R^2 \longrightarrow Z-\underset{R^1}{CH}-SR^2$$

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[289] Schöllkopf et al., Ref. 284; Hennion; Shoemaker *J. Am. Chem. Soc.* **1970,** *92*, 1769.

[290] See, for example, Pine; Catto; Yamagishi *J. Org. Chem.* **1970,** *35*, 3663.

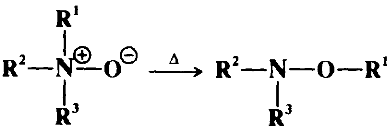
[291] For evidence against this mechanism, see Jenny; Druey *Angew. Chem. Int. Ed. Engl.* **1962,** *1*, 155 [*Angew. Chem. 74*, 152].

[292] Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, p. 131.

[293] Hill; Chan *J. Am. Chem. Soc.* **1966,** *88*, 866.

[294] For a review, see Olsen; Currie, in Patai *The Chemistry of The Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 561-566.

that a radical-pair cage mechanism is operating,[295] except that when the migrating group is allylic, the mechanism may be different (see **8-37**). Another reaction with a similar mechanism[296] is the *Meisenheimer rearrangement*,[297] in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines. The migrating group R^1 is almost



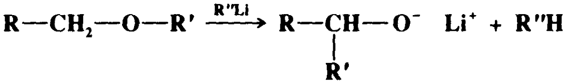
always allylic or benzilic.[298] R^2 and R^3 may be alkyl or aryl, but if one of the R groups contains a β hydrogen, Cope elimination (**7-8**) often competes.

Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the Wittig rearrangement (**8-23**), e.g., $PhCH_2NPh_2 \rightarrow Ph_2CHNHPh$.[299] Only aryl groups migrate in this reaction.

Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles: $RNC \rightarrow RCN$.[300] In polar solvents the mechanism is different.[301]

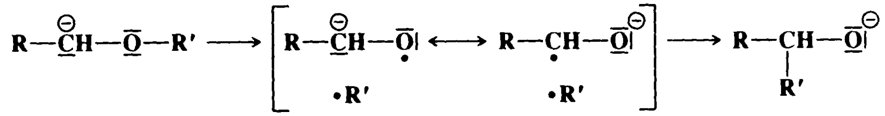
8-23 The Wittig Rearrangement

Hydron-(2/*O*→1/alkyl)-*migro*-detachment



$$R{-}CH_2{-}O{-}R' \xrightarrow{R''Li} R{-}\underset{R'}{CH}{-}O^- \; Li^+ + R''H$$

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 **8-22**.[279] However, a stronger base is required (e.g., phenyllithium or sodium amide). R and R′ may be alkyl, aryl, or vinylic.[302] 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 allylic, benzylic > ethyl > methyl > phenyl.[303] The following radical-pair mechanism[304] (similar to



Solvent cage

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[295] See, for example, Baldwin; Erickson; Hackler; Scott *Chem. Commun.* **1970,** 576; Schöllkopf; Schossig; Ostermann *Liebigs Ann. Chem.* **1970,** *737,* 158; Iwamura; Iwamura; Nishida; Yoshida; Nakayama *Tetrahedron Lett.* **1971,** 63.

[296] For some of the evidence, see Schöllkopf; Ludwig *Chem. Ber.* **1968,** *101,* 2224; Ostermann; Schöllkopf *Liebigs Ann. Chem.* **1970,** *737,* 170; Lorand; Grant; Samuel; O'Connell; Zaro *Tetrahedron Lett.* **1969,** 4087.

[297] For a review, see Johnstone *Mech. Mol. Migr.* **1969,** *2,* 249-266.

[298] Migration of aryl and of certain alkyl groups has also been reported. See Khuthier; Al-Mallah; Hanna; Abdulla *J. Org. Chem.* **1987,** *52,* 1710, and references cited therein.

[299] Eisch; Dua; Kovacs *J. Org. Chem.* **1987,** *52,* 4437; Eisch; Kovacs; Chobe *J. Org. Chem.* **1989,** *54,* 1275.

[300] See Meier; Rüchardt *Chem. Ber.* **1987,** *120,* 1; Meier; Müller; Rüchardt *J. Org. Chem.* **1987,** *52,* 648; Pakusch; Rüchardt *Chem. Ber.* **1991,** *124,* 971.

[301] Meier; Rüchardt *Chimia* **1986,** *40,* 238.

[302] For migration of vinyl, see Rautenstrauch; Büchi; Wüest *J. Am. Chem. Soc.* **1974,** *96,* 2576.

[303] Wittig *Angew. Chem.* **1954,** *66,* 10; Solov'yanov; Ahmed; Beletskaya; Reutov *J. Chem. Soc., Chem. Commun.* **1987,** *23,* 1232.

[304] For a review of the mechanism, see Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1970,** *9,* 763-773 [*Angew. Chem.* *82,* 795-805].

mechanism *a* of **8-22**) is likely, after removal of the proton by the base. One of the radicals in the radical pair is a ketyl. Among the evidence for this mechanism is (1) the rearrangement is largely intramolecular; (2) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities[305] (which rules out an ion-pair mechanism similar to mechanism *b* of **8-22**); (3) aldehydes are obtained as side products;[306] (4) partial racemization of R′ has been observed[307] (the remainder of the product retained its configuration); (5) crossover products have been detected;[308] and (6) when ketyl radicals and R• radicals from different precursors were brought together, similar products resulted.[309] 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.[310] 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.[311] When R′ is allylic a concerted mechanism can operate (**8-37**).

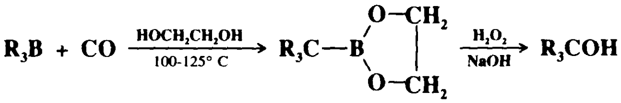
When R is vinylic it is possible, by using a combination of an alkyllithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde:[312]

$$\mathrm{CH_2{=}CH{-}CH_2{-}OR'} \longrightarrow \mathrm{R'CH_2{-}CH{=}CH{-}OLi} \longrightarrow \mathrm{R'CH_2CH_2CHO}$$

There are no OS references, but see OS **66**, 14, for a related reaction.

F. Boron-to-Carbon Migrations.[313] For another reaction involving boron-to-carbon migration, see **0-99**.

8-24 Conversion of Boranes to Tertiary Alcohols



72

Trialkylboranes (which can be prepared from olefins by **5-12**) react with carbon monoxide[314] at 100 to 125°C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes **72**, which

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[305] Lansbury; Pattison; Sidler; Bieber *J. Am. Chem. Soc.* **1966,** *88*, 78; Schäfer; Schöllkopf; Walter *Tetrahedron Lett.* **1968,** 2809.

[306] For example, see Hauser; Kantor *J. Am. Chem. Soc.* **1951,** *73*, 1437; Cast; Stevens; Holmes *J. Chem. Soc.* **1960,** 3521.

[307] Schöllkopf; Fabian *Liebigs Ann. Chem.* **1961,** *642*, 1; Schöllkopf; Schäfer *Liebigs Ann. Chem.* **1963,** *663*, 22; Felkin; Frajerman *Tetrahedron Lett.* **1977,** 3485; Hebert; Welvart *J. Chem. Soc., Chem. Commun.* **1980,** 1035, *Nouv. J. Chim.* **1981,** *5*, 327.

[308] Lansbury; Pattison *J. Org. Chem.* **1962,** *27*, 1933, *J. Am. Chem. Soc.* **1962,** *84*, 4295.

[309] Garst; Smith *J. Am. Chem. Soc.* **1973,** *95*, 6870.

[310] Garst; Smith *J. Am. Chem. Soc.* **1976,** *98*, 1526. For evidence against this, see Hebert; Welvart; Ghelfenstein; Szwarc *Tetrahedron Lett.* **1983,** *24*, 1381.

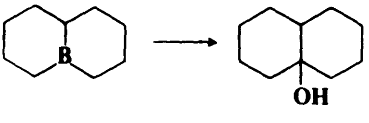
[311] Eisch; Kovacs; Rhee *J. Organomet. Chem.* **1974,** *65*, 289.

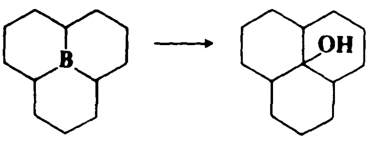
[312] Schlosser; Strunk *Tetrahedron* **1989,** *45*, 2649.

[313] For reviews, see Matteson, in Hartley *The Chemistry of the Metal-Carbon Bond*, vol. 4; Wiley: New York, 1984, pp. 307-409, pp. 346-387; Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 256-301; Negishi; Idacavage *Org. React.* **1985,** *33*, 1-246; Suzuki *Top. Curr. Chem.* **1983,** *112*, 67-115; Pelter, in Mayo, Ref. 1, vol. 2, pp. 95-147, *Chem. Soc. Rev.* **1982,** *11*,191-225; Cragg; Koch *Chem. Soc. Rev.* **1977,** *6*, 393-412; Weill-Raynal *Synthesis* **1976,** 633-651; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 249-300; Paetzold; Grundke *Synthesis* **1973,** 635-660.

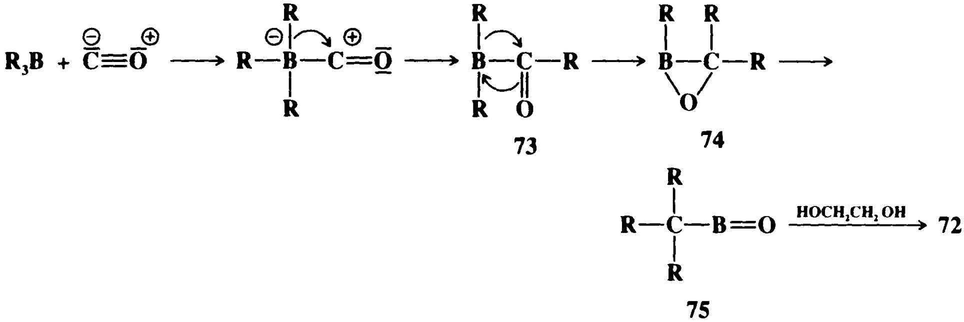
[314] For discussions of the reactions of boranes with CO, see Negishi *Intra-Sci. Chem. Rep.* **1973,** 7(1), 81-94; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 343-371, *Acc. Chem. Res.* **1969,** *2*, 65-72.

are easily oxidized (**2-28**) to tertiary alcohols.[315] The R groups may be primary, secondary, or tertiary, and may be the same or different.[316] 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 **6-29.** 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.[317] The preparation of such heterocyclic boranes was discussed at **5-12.** 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.[318] The following scheme, involving three boron-to-carbon migrations, has been suggested.



The purpose of the ethylene glycol is to intercept the boronic anhydride **75**, which otherwise forms polymers that are difficult to oxidize. As we shall see in **8-25** and **8-26**, 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

$$\text{Method 1} \qquad R_3B + CHCl_2OMe \xrightarrow[2.\,H_2O_2\text{-}NaOH]{1.\,LiOCEt_3\text{-}THF} R_3COH$$

$$\text{Method 2} \qquad R_3B + CN^- \xrightarrow{THF} \underset{\textbf{76}}{R_3\overset{\ominus}{B}\text{—}CN} \xrightarrow[2.\,NaOH\text{-}H_2O_2]{1.\,\text{excess }(CF_3CO)_2O} R_3COH$$

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[315] Hillman *J. Am. Chem. Soc.* **1962,** *84*, 4715, **1963,** *85*, 982; Brown; Rathke *J. Am. Chem. Soc.* **1967,** *89*, 2737; Puzitskii; Pirozhkov; Ryabova; Pastukhova; Eidus *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972,** *21*, 1939, **1973,** *22*, 1760; Brown; Cole; Srebnik; Kim *J. Org. Chem.* **1986,** *51*, 4925.

[316] Brown; Negishi; Gupta *J. Am. Chem. Soc.* **1970,** *92*, 6648; Brown; Gupta *J. Am. Chem. Soc.* **1971,** *93*, 1818; Negishi; Brown *Synthesis* **1972,** 197.

[317] Brown; Negishi *J. Am. Chem. Soc.* **1967,** *89*, 5478; Knights; Brown *J. Am. Chem. Soc.* **1968,** *90*, 5283; Brown; Negishi; Dickason *J. Org. Chem.* **1985,** *50*, 520.

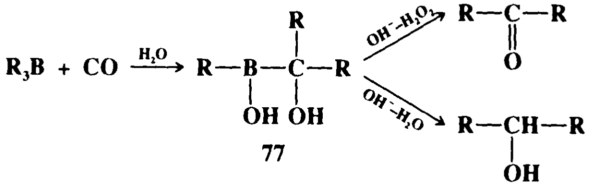
[318] Brown; Rathke *J. Am. Chem. Soc.* **1967,** *89*, 4528.

triethylcarboxide;[319] (2) treatment with a suspension of sodium cyanide in THF followed by reaction of the resulting trialkylcyanoborate **76** with an excess (more than 2 moles) of trifluoroacetic anhydride.[320] All the above migrations take place with retention of configuration at the migrating carbon.[321]

Several other methods for the conversion of boranes to tertiary alcohols are also known.[322]

OS **VII,** 427.

8-25 Conversion of Boranes to Secondary Alcohols or Ketones



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If the reaction between trialkylboranes and carbon monoxide (**8-24**) 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.[323] Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,[324] 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).[318]

The reaction follows the mechanism shown in **8-24** until formation of the borepoxide **74.** In the presence of water the third boron → carbon migration does not take place, because the water hydrolyzes **74** to the diol **77.**

Trialkylboranes can also be converted to ketones by the cyanoborate procedure, mentioned in **8-24.** In this case the procedure is similar, but use of an equimolar amount of

$$R_3\overset{\ominus}{B}—CN \xrightarrow[2.\ H_2O_2\text{-}OH^-]{1.\ (CF_3CO)_2O} RCOR$$

76

trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.[325] By this procedure thexylboranes RR′R″B (R″ = thexyl) can be converted to unsymmetrical ketones RCOR′.[326] Like the carbon monoxide procedure, this method tolerates the presence of

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[319] Brown; Carlson *J. Org. Chem.* **1973,** *38,* 2422; Brown; Katz; Carlson *J. Org. Chem.* **1973,** *38,* 3968.

[320] Pelter; Hutchings; Smith *J. Chem. Soc., Chem. Commun.* **1973,** 186; Pelter; Hutchings; Smith; Williams *J. Chem. Soc., Perkin Trans. 1* **1975,** 145; Pelter *Chem. Ind. (London)* **1973,** 206-209, *Intra-Sci. Chem. Rep.* **1973,** 7(1), 73-79.

[321] See however Pelter; Maddocks; Smith *J. Chem. Soc., Chem. Commun.* **1978,** 805.

[322] See, for example, Lane; Brown *J. Am. Chem. Soc.* **1971,** *93,* 1025; Brown; Yamamoto *Synthesis* **1972,** 699; Brown; Lane *Synthesis* **1972,** 303; Yamamoto; Brown *J. Chem. Soc., Chem. Commun.* **1973,** 801, *J. Org. Chem* **1974,** *39,* 861; Zweifel; Fisher *Synthesis* **1974,** 339; Midland; Brown; *J. Org. Chem.* **1975,** *40,* 2845; Levy; Schwartz *Tetrahedron Lett.* **1976,** 2201; Hughes; Ncube; Pelter; Smith; Negishi; Yoshida *J. Chem. Soc., Perkin Trans. 1* **1977,** 1172; Avasthi; Baba; Suzuki *Tetrahedron Lett.* **1980,** *21,* 945; Baba; Avasthi; Suzuki *Bull. Chem. Soc. Jpn.* **1983,** *56,* 1571; Pelter; Rao *J. Organomet. Chem.* **1985,** *285,* 65; Junchai; Weike; Hongxun *J. Organomet. Chem.* **1989,** *367,* C9; Junchai; Hongxun *J. Chem. Soc., Chem. Commun.* **1990,** 323.

[323] Brown; Rathke *J. Am. Chem. Soc.* **1967,** *89,* 2738.

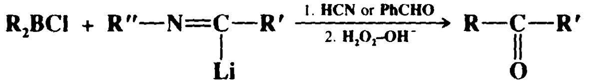
[324] Brown; Kabalka; Rathke *J. Am. Chem. Soc.* **1967,** *89,* 4530.

[325] Pelter; Smith; Hutchings; Rowe *J. Chem. Soc., Perkin Trans. 1* **1975,** 129; Ref. 320. See also Pelter; Hutchings; Smith *J. Chem. Soc., Perkin Trans. 1* **1975,** 142; Mallison; White; Pelter; Rowe; Smith *J. Chem. Res. (S)* **1978,** 234.

[326] This has been done enantioselectively: Brown; Bakshi; Singaram *J. Am. Chem. Soc.* **1988,** *110,* 1529.

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.[327] This method does not waste an R group, is carried out under mild conditions, and has been made enantioselective.[328] A closely related method uses boronic esters $RB(OR')_2$ and $LiCHCl_2$. By the use of chiral R', this method has been used to prepare optically active alcohols.[329] In still another procedure ketones are prepared by the reaction between dialkylchloroboranes and lithium aldimines[330] (which can be prepared by **6-69**).

$$R_2BCl + R'OH \longrightarrow R_2BOR' \xrightarrow[2.\ H_2O_2-OH^-]{1.\ CHCl_2OMe,\ LiOCEt_3 \\ THF,\ 25°C} R_2CO$$



$$R_2BCl + R''{-}N{=}\underset{\displaystyle Li}{\underset{|}{C}}{-}R' \xrightarrow[2.\ H_2O_2-OH^-]{1.\ HCN\ or\ PhCHO} R{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}R'$$

For another conversion of trialkylboranes to ketones, see **8-28**.[331] Other conversions of boranes to secondary alcohols are also known.[332]

OS **VI,** 137.

8-26 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids

$$R_3B + CO \xrightarrow[2.\ H_2O_2-OH^-]{1.\ LiBH_4} RCH_2OH$$

$$R_3B + CO \xrightarrow[2.\ H_2O_2-NaH_2PO_4-Na_2HPO_4]{1.\ LiAl(OMe)_3} RCHO$$

When the reaction between a trialkylborane and carbon monoxide (**8-24**) is carried out in the presence of a reducing agent such as lithium borohydride or potassium triisopropoxyborohydride, the reduction agent intercepts the intermediate **73,** so that only one boron-to-carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.[333] 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. 785). Since only the 9-alkyl group

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[327] Carlson; Brown *J. Am. Chem. Soc.* **1973,** *95,* 6876, *Synthesis* **1973,** 776.

[328] Brown; Srebnik; Bakshi; Cole *J. Am. Chem. Soc.* **1987,** *109,* 5420; Brown; Gupta; Vara Prasad; Srebnik *J. Org. Chem.* **1988,** *53,* 1391.

[329] For reviews, see Matteson *Mol. Struct. Energ.* **1988,** *5,* 343-356, *Acc. Chem. Res.* **1988,** *21,* 294-300, *Synthesis* **1986,** 973-985, pp. 980-983.

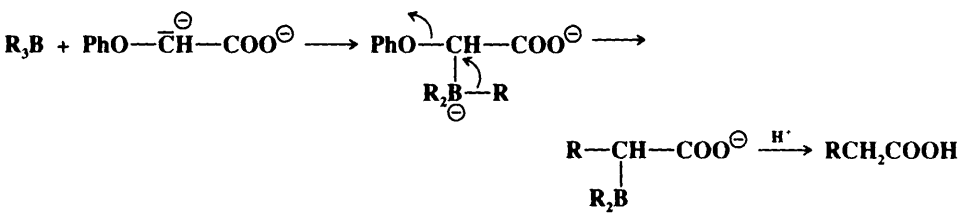
[330] Yamamoto; Kondo; Moritani *Tetrahedron Lett.* **1974,** 793; *Bull. Chem. Soc. Jpn.* **1975,** *48,* 3682. See also Yamamoto; Kondo; Moritani *J. Org. Chem.* **1975,** *40,* 3644.

[331] For still other methods, see Brown; Levy; Midland *J. Am. Chem. Soc.* **1975,** *97,* 5017; Ncube; Pelter; Smith *Tetrahedron Lett.* **1979,** 1893; Pelter; Rao, Ref. 322; Yogo; Koshino; Suzuki *Chem. Lett.* **1981,** 1059; Kulkarni; Lee; Brown *J. Org. Chem.* **1980,** *45,* 4542, *Synthesis* **1982,** 193; Brown; Bhat; Basavaiah *Synthesis* **1983,** 885; Narayana; Periasamy *Tetrahedron Lett.* **1985,** *26,* 6361.

[332] See for example, Zweifel; Fisher, Ref. 322; Brown; Yamamoto *J. Am. Chem. Soc.* **1971,** *93,* 2796, *Chem. Commun.* **1971,** 1535, *J. Chem. Soc., Chem. Commun.* **1972,** 71; Brown; DeLue *J. Am. Chem. Soc.* **1974,** *96,* 311; Hubbard; Brown *Synthesis* **1978,** 676; Uguen *Bull. Soc. Chim. Fr.* **1981,** II-99.

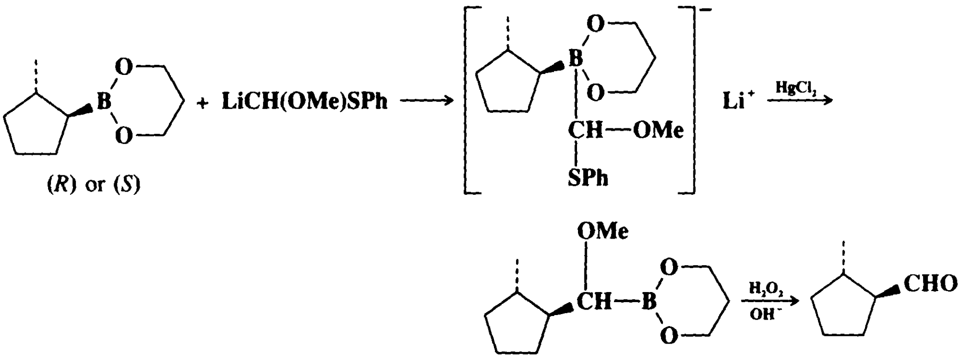
[333] Brown; Rathke *J. Am. Chem. Soc.* **1967,** *89,* 2740; Brown; Coleman; Rathke *J. Am. Chem. Soc.* **1968,** *90,* 499; Brown; Hubbard; Smith *Synthesis* **1979,** 701. For discussions of the mechanism, see Brown; Hubbard *J. Org. Chem.* **1979,** *44,* 467; Hubbard; Smith *J. Organomet. Chem.* **1984,** *276,* C41.

migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.[334] When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*t*-butoxyaluminum hydride,[335] other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.[336] Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxyacetic acid.[337]

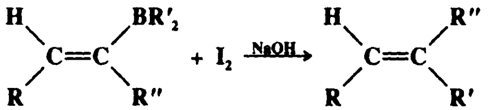


$$R_3B + PhO-\overset{\ominus}{C}H-COO^{\ominus} \longrightarrow PhO-\underset{R_2\overset{\ominus}{B}-R}{CH}-COO^{\ominus} \longrightarrow R-\underset{R_2B}{CH}-COO^{\ominus} \xrightarrow{H^+} RCH_2COOH$$

Boronic esters $RB(OR')_2$ react with methoxy(phenylthio)methyllithium LiCH(OMe)SPh to give salts, which, after treatment with $HgCl_2$ and then H_2O_2, yield aldehydes.[338] This synthesis has been made enantioselective, with high ee values (> 99%), by the use of an optically pure boronic ester,[339] e.g.:



8-27 Conversion of Vinylic Boranes to Alkenes



78 79

The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at 2-30. When the substrate contains a vinylic group, the reaction takes a different course,[340]

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[334] Brown; Knights; Coleman *J. Am. Chem. Soc.* **1969**, *91*, 2144.

[335] Brown; Coleman *J. Am. Chem. Soc.* **1969**, *91*, 4606.

[336] For other methods of converting boranes to aldehydes, see Yamamoto; Shiono; Mukaiyama *Chem. Lett.* **1973**, 961; Negishi; Yoshida; Silveira; Chiou *J. Org. Chem.* **1975**, *40*, 814.

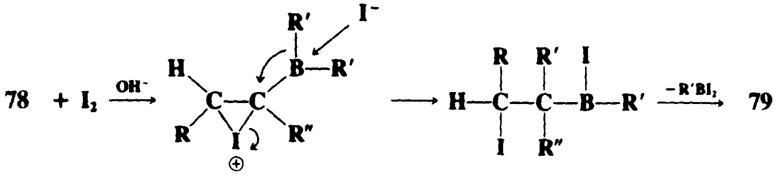
[337] Hara; Kishimura; Suzuki; Dhillon *J. Org. Chem.* **1990**, *55*, 6356. See also Brown; Imai *J. Org. Chem.* **1984**, *49*, 892.

[338] Brown; Imai *J. Am. Chem. Soc.* **1983**, *105*, 6285. For a related method that produces primary alcohols, see Brown; Imai; Perumal; Singaram *J. Org. Chem.* **1985**, *50*, 4032.

[339] Brown; Imai; Desai; Singaram *J. Am. Chem. Soc.* **1985**, *107*, 4980.

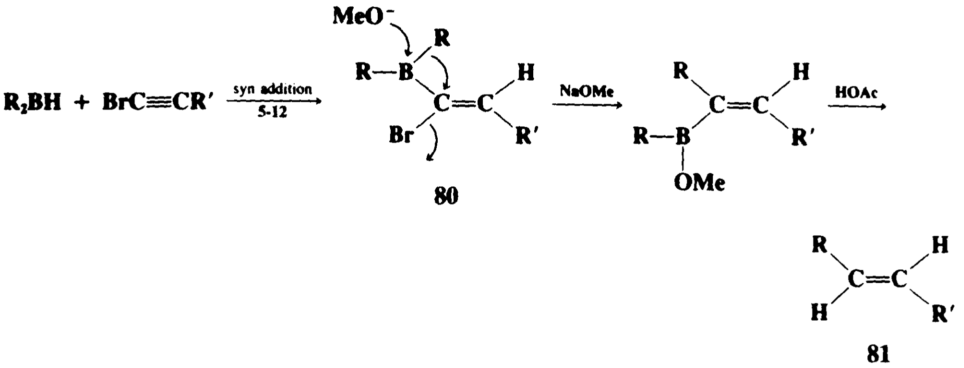
[340] Zweifel; Arzoumanian; Whitney *J. Am. Chem. Soc.* **1967**, *89*, 3652; Zweifel; Fisher *Synthesis* **1975**, 376; Brown; Basavaiah; Kulkarni; Bhat; Vara Prasad *J. Org. Chem.* **1988**, *53*, 239.

with one of the R′ groups migrating to the carbon, to give alkenes **79**.[341] 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′.[342] Since vinylic boranes can be prepared from alkynes (**5-12**), this is a method for the addition of R′ and H to a triple bond. If R″ = H, the product is a *Z* alkene. The mechanism is believed to be



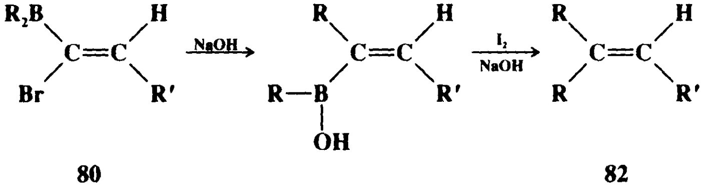
When R′ is vinylic, the product is a conjugated diene.[343]

In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α-halo vinylic borane (**80**).[344] Treatment of this with NaOMe gives the rearrangement shown,



and protonolysis of the product produces the *E*-alkene **81**.[342] If R is a vinylic group the product is a 1,3-diene.[345] If one of the groups is thexyl, the other migrates.[346] 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.[347] The entire conversion of haloalkyne to **82** can be carried out in one



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[341] For a list of methods of preparing alkenes using boron reagents, with references, see Ref. 106, pp. 218-222.

[342] Zweifel; Fisher; Snow; Whitney *J. Am. Chem. Soc.* **1971,** *93*, 6309.

[343] Zweifel; Polston; Whitney *J. Am. Chem. Soc.* **1968,** *90*, 6243; Brown; Ravindran *J. Org. Chem.* **1973,** *38*, 1617; Hyuga; Takinami; Hara; Suzuki *Tetrahedron Lett.* **1986,** *27*, 977.

[344] For improvements in this method, see Brown; Basavaiah; Kulkarni; Lee; Negishi; Katz *J. Org. Chem.* **1986,** *51*, 5270.

[345] Negishi; Yoshida *J. Chem. Soc., Chem. Commun.* **1973,** 606. See also Negishi; Yoshida; Abramovitch; Lew; Williams *Tetrahedron* **1991,** *47*, 343.

[346] Corey; Ravindranathan; *J. Am. Chem. Soc.* **1972,** *94*, 4013; Negishi; Katz; Brown *Synthesis* **1972,** 555.

[347] Zweifel; Fisher *Synthesis* **1972,** 557.

reaction vessel, without isolation of intermediates. An aluminum counterpart of the α-halo vinylic borane procedure has been reported.[348]

E-alkenes **81** can also be obtained[349] by treatment of **78** (R″ = H) with cyanogen bromide or cyanogen iodide in CH_2Cl_2[350] or with $Pd(OAc)_2$–Et_3N.[351]

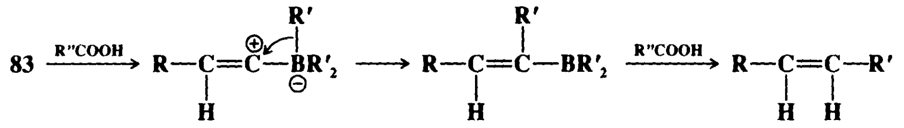
8-28 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides

Alkyl-de-lithio-substitution

$$R'_3B + RC{\equiv}CLi \longrightarrow RC{\equiv}C{-}\overset{\ominus}{B}R'_3\ Li^+ \xrightarrow{I_2} RC{\equiv}CR'$$

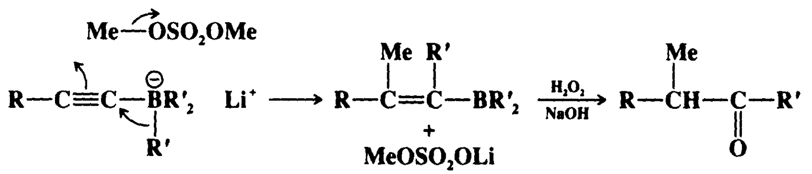
83

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 **83** with iodine.[352] R′ may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **0-100**.[353] 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.[354] Optically active alkynes can be prepared by using optically active thexylborinates RR″BOR′ (R″ = thexyl), where R is chiral, and LiC≡CSiMe$_3$.[355] The reaction can be adapted to the preparation of alkenes[341] by treatment of **83** with an electrophile such as propanoic acid[356] or tributyltin chloride.[357] The reaction with Bu_3SnCl produces the *Z* alkene stereoselectively.



$$83 \xrightarrow{R''COOH} R{-}\underset{H}{C}{=}\overset{R'}{\underset{\ominus}{\overset{\oplus}{C}}}{-}BR'_2 \longrightarrow R{-}\underset{H}{C}{=}\overset{R'}{C}{-}BR'_2 \xrightarrow{R''COOH} R{-}\underset{H}{C}{=}\underset{H}{C}{-}R'$$

Treatment of **83** with an electrophile such as methyl sulfate, allyl bromide, or triethyloxonium borofluoride, followed by oxidation of the resulting vinylic borane gives a ketone (illustrated for methyl sulfate):[358]



$$\overset{Me{-}OSO_2OMe}{R{-}C{\equiv}C{-}\underset{R'}{\overset{\ominus}{B}}R'_2\ \ Li^+} \longrightarrow R{-}\overset{Me}{C}{=}\overset{R'}{C}{-}BR'_2 \ \underset{MeOSO_2OLi}{+} \xrightarrow[NaOH]{H_2O_2} R{-}\overset{Me}{CH}{-}\underset{\overset{\|}{O}}{C}{-}R'$$

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[348] Miller *J. Org. Chem.* **1989,** *54,* 998.

[349] For other methods of converting boranes to alkenes, see Pelter; Subrahmanyam; Laub; Gould; Harrison *Tetrahedron Lett.* **1975,** 1633; Utimoto; Uchida; Yamaya; Nozaki *Tetrahedron* **1977,** *33,* 1945; Ncube; Pelter; Smith *Tetrahedron Lett.* **1979,** 1895; Levy; Angelastro; Marinelli *Synthesis* **1980,** 945; Brown; Lee; Kulkarni *Synthesis* **1982,** 195; Pelter; Hughes; Rao *J. Chem. Soc., Perkin Trans. 1* **1982,** 719; Hoshi; Masuda; Arase *Bull. Chem. Soc. Jpn.* **1986,** *59,* 3985; Brown; Bhat *J. Org. Chem.* **1988,** *53,* 6009.

[350] Zweifel; Fisher; Snow; Whitney *J. Am. Chem. Soc.* **1972,** *94,* 6560.

[351] Yatagai *Bull. Chem. Soc. Jpn.* **1980,** *53,* 1670.

[352] Suzuki; Miyaura; Abiko; Itoh; Brown; Sinclair; Midland *J. Am. Chem. Soc.* **1973,** *95,* 3080, *J. Org. Chem.* **1986,** *51,* 4507; Sikorski; Bhat; Cole; Wang; Brown *J. Org. Chem.* **1986,** *51,* 4521. For a review of reactions of organoborates, see Suzuki *Acc. Chem. Res.* **1982,** *15,* 178-184.

[353] For a study of the relative migratory aptitudes of R′, see Slayden *J. Org. Chem.* **1981,** *46,* 2311.

[354] Midland; Sinclair; Brown *J. Org. Chem.* **1974,** *39,* 731.

[355] Brown; Mahindroo; Bhat; Singaram *J. Org. Chem.* **1991,** *56,* 1500.

[356] Pelter; Harrision; Kirkpatrick *J. Chem. Soc., Chem. Commun.* **1973,** 544; Miyaura; Yoshinari; Itoh; Suzuki *Tetrahedron Lett.* **1974,** 2961; Pelter; Gould; Harrison *Tetrahedron Lett.* **1975,** 3327.

[357] Hooz; Mortimer *Tetrahedron Lett.* **1976,** 805; Wang; Chu *J. Org. Chem.* **1984,** *49,* 5175.

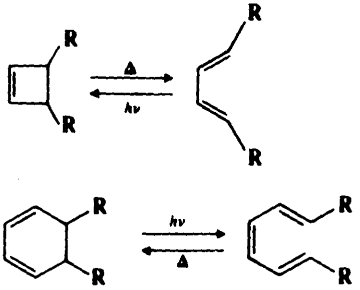
[358] Pelter; Bentley; Harrison; Subrahmanyam; Laub *J. Chem. Soc., Perkin Trans. 1* **1976,** 2419; Pelter; Gould; Harrison *J. Chem. Soc., Perkin Trans. 1* **1976,** 2428; Pelter; Drake *Tetrahedron Lett.* **1988,** *29,* 4181.

Non-1,2 Rearrangements

A. Electrocyclic Rearrangements

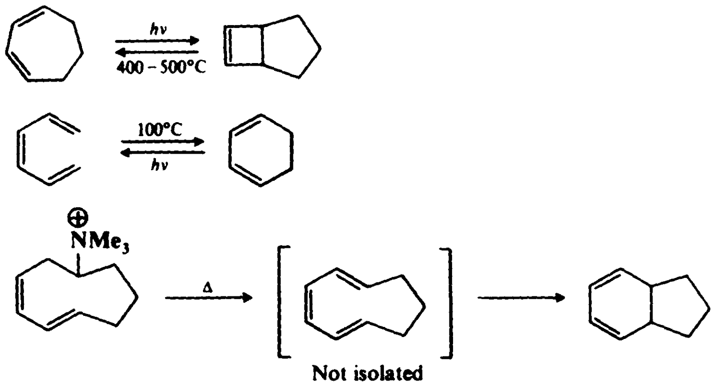
8-29 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes

(4)*seco*-1/4/Detachment; (4)*cyclo*-1/4/Attachment
(6)*seco*-1/6/Detachment; (6)*cyclo*-1/6/Attachment



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[359] are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200°C. 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 wave lengths used.[360] 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.[361]

Some examples are



Ref. 362

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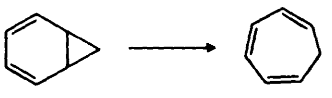
[359] For example; see Shumate; Neuman; Fonken *J. Am. Chem. Soc.* **1965,** *87,* 3996; Gil-Av; Herling *Tetrahedron Lett.* **1967,** 1; Doorakian; Freedman *J. Am. Chem. Soc.* **1968,** *90,* 3582; Brune; Schwab *Tetrahedron* **1969,** *25,* 4375; Steiner; Michl *J. Am. Chem. Soc.* **1978,** *100,* 6413.

[360] For examples of photochemical conversion of a cyclobutene to a 1,3-diene, see Scherer *J. Am. Chem. Soc.* **1968,** *90,* 7352; Saltiel; Lim *J. Am. Chem. Soc.* **1969,** *91,* 5404; Adam; Oppenländer; Zang *J. Am. Chem. Soc.* **1985,** *107,* 3921; Dauben; Haubrich *J. Org. Chem.* **1988,** *53,* 600.

[361] For a review of photochemical rearrangements in trienes, see Dauben; McInnis; Michno, in Mayo, Ref. 1, vol. 3, pp. 91-129.

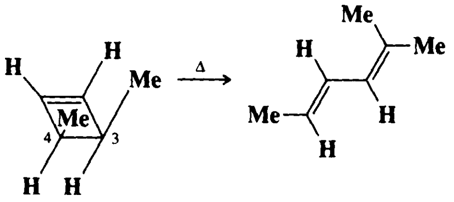
[362] Dauben; Cargill *Tetrahedron* **1961,** *12,* 186; Chapman; Pasto; Borden; Griswold *J. Am. Chem. Soc.* **1962,** *84,* 1220.

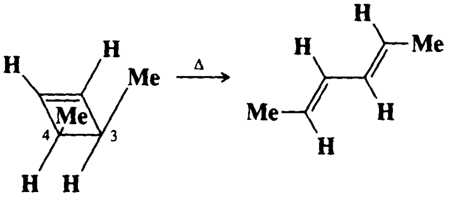
An interesting example of 1,3-cyclohexadiene—1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.[363] Norcaradienes give this reaction so readily (because they are *cis*-1,2-divinylcyclopropanes, see p. 1131) that they cannot generally be isolated, though some exceptions are known[364] (see also p. 869).



Norcaradiene

These reactions, called *electrocyclic rearrangements*,[365] take place by pericyclic mechanisms. The evidence 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:[366]





This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3—C-4 bond. It is called conrotatory because both movements are

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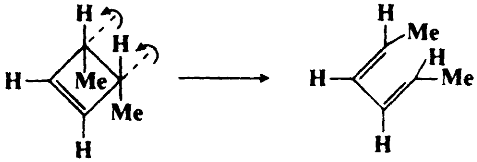
[363] For reviews of the norcaradiene–cycloheptatriene interconversion and the analogous benzene oxide–oxepin interconversion, see Maier *Angew. Chem. Int. Ed. Engl.* **1967,** *6*, 402-413 [*Angew. Chem. 79*, 446-458]; Vogel; Günther *Angew. Chem. Int. Ed. Engl.* **1967,** *6*, 385-401 [*Angew. Chem. 79*, 429-446]; Vogel *Pure Appl. Chem.* **1969,** *20*, 237-262.

[364] See Refs. 1043 and 1044 in Chapter 15.

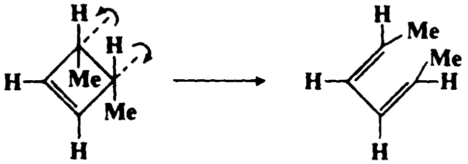
[365] For a monograph on thermal isomerizations, which includes electrocyclic and sigmatropic rearrangements, as well as other types, see Gajewski *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. For a monograph on electrocyclic reactions, see Marvell *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. For reviews, see Dolbier; Koroniak *Mol. Struct. Energ.* **1988,** *8*, 65-81; Laarhoven *Org. Photochem.* **1987,** *9*, 129-224; George; Mitra; Sukumaran *Angew. Chem. Int. Ed. Engl.* **1980,** *19*, 973-983 [*Angew. Chem. 92*, 1005-1014]; Jutz *Top. Curr. Chem.* **1978,** *73*, 125-230; Gilchrist; Storr *Organic Reactions and Orbital Symmetry*; Cambridge University Press: Cambridge, 1972, pp. 48-72; DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973; pp. 461-470; Crowley; Mazzocchi, in Zabicky *The Chemistry of Alkenes*, vol. 2; Wiley: New York, 1970, pp. 284-297; Criegee *Angew. Chem. Int. Ed. Engl.* **1968,** *7*, 559-565 [*Angew. Chem. 80*, 585-591]; Vollmer; Servis *J. Chem. Educ.* **1968,** *45*, 214-220. For a review of isotope effects in these reactions, see Gajewski *Isot. Org. Chem.* **1987,** 7, 115-176. For a related review, see Schultz; Motyka *Org. Photochem.* **1983,** *6*, 1-119.

[366] Winter *Tetrahedron Lett.* **1965,** 1207. Also see Vogel *Liebigs Ann. Chem.* **1958,** *615*, 14; Criegee; Noll *Liebigs Ann. Chem.* **1959,** *627*, 1.

clockwise (or both counterclockwise). Because both rotate in the same direction, the cis isomer gives the cis–trans diene:[367]



The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the cis isomer would have given the cis–cis diene (shown) or the trans–trans diene:



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.[368] 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. 846).[369] As in the case of cycloaddition reactions, we will use the frontier-orbital and Möbius–Hückel approaches.[370]

The Frontier-Orbital Method[371]

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 HOMO of the product in the thermal reaction is the χ_2 orbital (Figure 18.1). Therefore, in a thermal process, the cyclo-

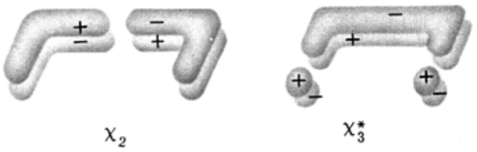


FIGURE 18.1 Symmetries of the χ_2 and χ_3^* orbitals of a conjugated diene.

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[367] This picture is from Woodward; Hoffmann *J. Am. Chem. Soc.* **1965**, *87*, 395, who coined the terms, *conrotatory* and *disrotatory*.

[368] Photochemical ring-opening of cyclobutenes can also be nonstereospecific. See Leigh; Zheng *J. Am. Chem. Soc.* **1991**, *113*, 4019; Leigh; Zheng; Nguyen; Werstiuk; Ma *J. Am. Chem. Soc.* **1991**, *113*, 4993, and references cited in these papers.

[369] Woodward; Hoffmann, Ref. 367. Also see Longuet-Higgins; Abrahamson *J. Am. Chem. Soc.* **1965**, *87*, 2045; Fukui *Tetrahedron Lett.* **1965**, 2009.

[370] For the correlation diagram method, see Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 352-359; Yates *Hückel Molecular Orbital Theory*; Academic Press: New York, 1978, pp. 250-263; Ref. 897 in Chapter 15.

[371] See Ref. 898 in Chapter 15.

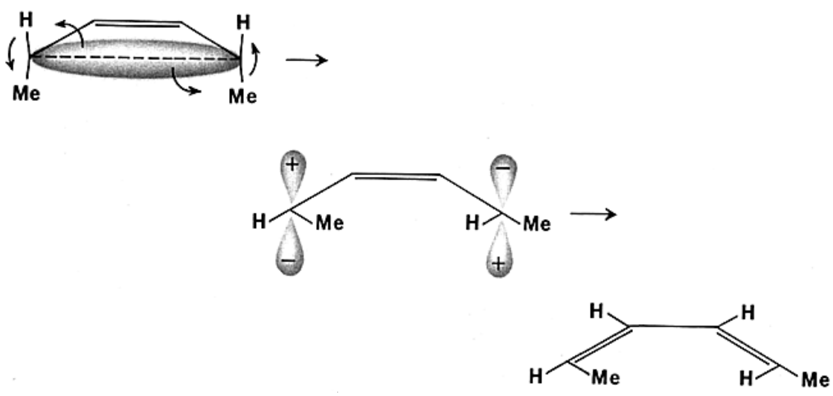

FIGURE 18.2 Thermal ring opening of 1,2-dimethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting *p* orbitals have the symmetry of the HOMO of the diene.

butene 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 (Figure 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Figure 18.1), 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 that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion (Figure 18.3). In the photochemical process the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

The Möbius–Hückel Method[372]

As we saw on p. 848, in this method we choose a basis set of *p* orbitals and look for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Figure 18.4*a*) results in overlap of plus lobes only, while in conrotatory closing (Figure 18.4*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. With zero (or an even number of) sign inversions, the disrotatory transition state is a Hückel

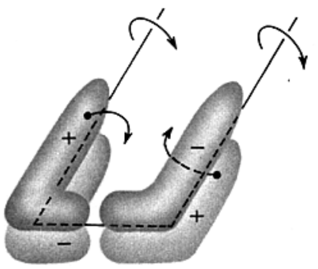

FIGURE 18.3 Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

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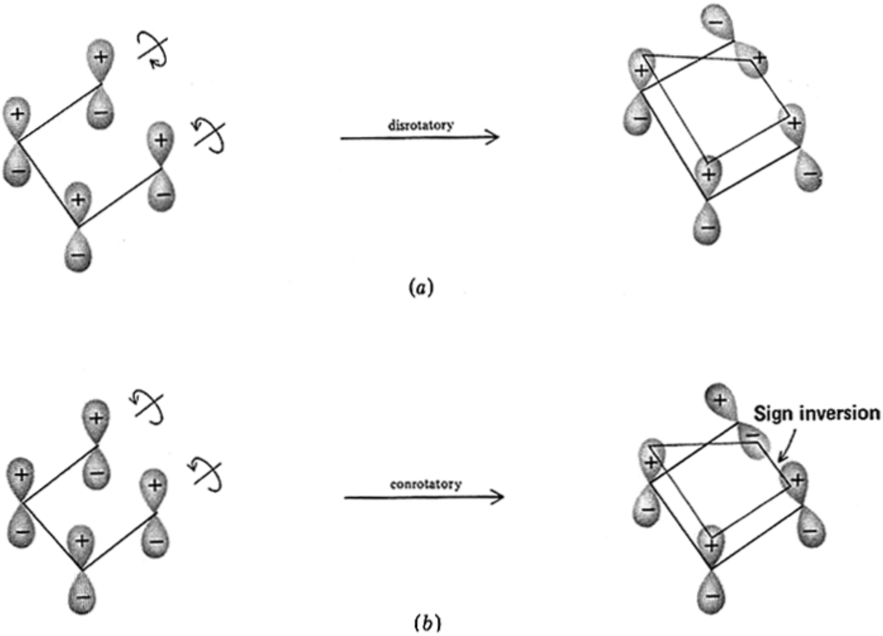
[372] See Ref. 899 in Chapter 15.



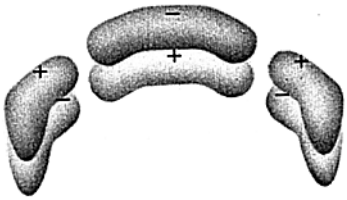
(a)

(b)

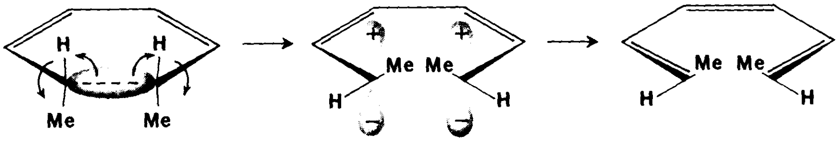
FIGURE 18.4 The 1,3-diene-cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (*a*) Disrotatory ring closure gives zero sign inversions. (*b*) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis 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.

system, and so is allowed thermally only if the total number of electrons is $4n + 2$ (p. 848). Since the total here is 4, the disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a Möbius system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions the rules are reversed: A reaction with $4n$ electrons requires a Hückel system, so only the disrotatory process is allowed.

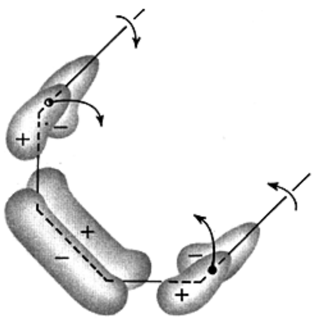
Both the frontier-orbital and the Möbius–Hückel methods can also be applied to the cyclohexadiene—1,3,5-triene reaction; in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for a 1,3,5-triene, the symmetry of the HOMO is



In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



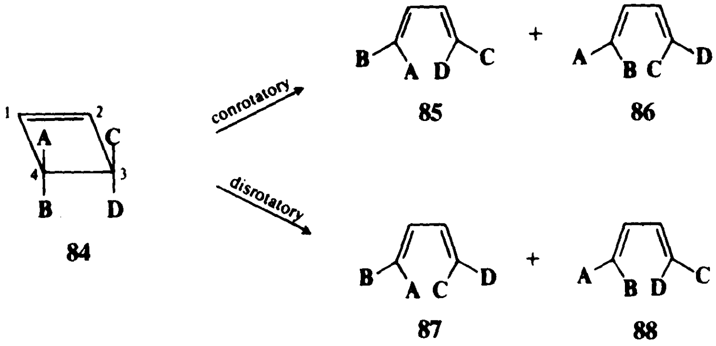
Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals which overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the Möbius–Hückel approach, diagrams similar to Figure 18.4 can be drawn for this case. Here too, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction the Möbius pathway.

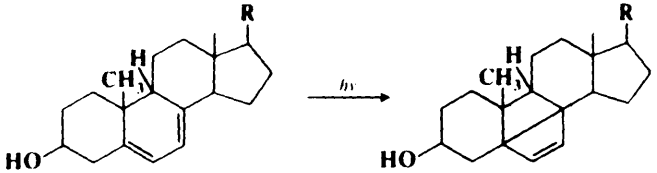
In the most general case, there are four possible products that can arise from a given cyclobutene or cyclohexadiene—two from the conrotatory and two from the disrotatory



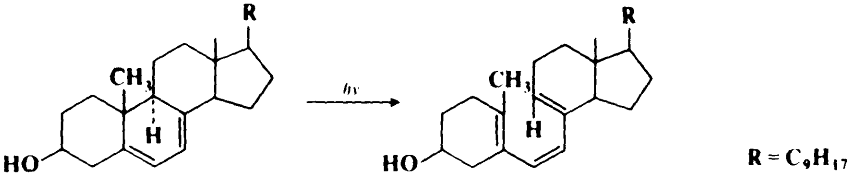
84 **85** **86** **87** **88**

pathway. For example, conrotatory ring opening of **84** gives either **85** or **86**, while disrotatory opening gives either **87** or **88**. 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 **84** by the disrotatory pathway, **87** arises when groups A and C swing in toward each other (clockwise motion around C-4, counterclockwise around C-3), while **88** 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 and C are larger than B and D, the predominant or exclusive product will be **88,** rather than **87.** Predictions of this kind have largely been borne out.[373] There is evidence, however, that steric effects are not the only factor, and that electronic effects also play a role, which may be even greater.[374] An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.[375] The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO (an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.[376]

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.[377] An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer **89** (or of the other syn isomer, not shown)



89



90 **91**

leads to the corresponding cyclobutene,[378] while photolysis of the anti isomers (one of them is **90**) gives the ring-opened 1,3,5-triene **91.** 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 **89** were to react by this pathway, the product would be the triene **91,** 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

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[373] For example, see Baldwin; Krueger *J. Am. Chem. Soc.* **1969,** *91*, 6444; Spangler; Hennis *J. Chem. Soc., Chem. Commun.* **1972,** 24; Gesche; Klinger; Riesen; Tschamber; Zehnder; Streith *Helv. Chim. Acta* **1987,** *70*, 2087.

[374] Kirmse; Rondan; Houk *J. Am. Chem. Soc.* **1984,** *106*, 7989; Dolbier; Koroniak; Burton; Heinze; Bailey; Shaw; Hansen *J. Am. Chem. Soc.* **1987,** *109*, 219; Dolbier; Gray; Keaffaber; Celewicz; Koroniak *J. Am. Chem. Soc.* **1990,** *112*, 363; Hayes; Ingham; Saengchantara; Wallace *Tetrahedron Lett.* **1991,** *32*, 2953.

[375] For theoretical studies, see Rondan; Houk *J. Am. Chem. Soc.* **1985,** *107*, 2099; Buda; Wang; Houk *J. Org. Chem.* **1989,** *54*, 2264; Kallel; Wang; Spellmeyer; Houk *J. Am. Chem. Soc.* **1990,** *112*, 6759.

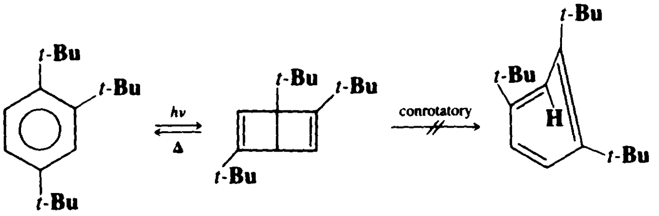
[376] Rudolf; Spellmeyer; Houk *J. Org. Chem.* **1987,** *52*, 3708; Piers; Lu *J. Org. Chem.* **1989,** *54*, 2267.

[377] For a discussion of the factors favoring either direction, see Dauben; Kellogg; Seeman; Vietmeyer; Wendschuh *Pure Appl. Chem.* **1973,** *33*, 197-215.

[378] Dauben; Fonken *J. Am. Chem. Soc.* **1959,** *81*, 4060. This was the first reported example of the conversion of a 1,3-diene to a cyclobutene.

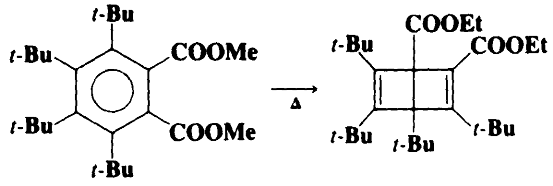
the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **90** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (p. 132) but are very strained. Stable *trans*-cyclohexenes are unknown (p. 158). Thus, **89** and **90** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

The 1,3-diene—cyclobutene interconversion can even be applied to benzene rings. For example,[379] photolysis of 1,2,4-tri-*t*-butylbenzene (**92**) gives 1,2,5-tri-*t*-butyl[2.2.0]hexadiene (**93**, a Dewar benzene).[380] The reaction owes its success to the fact that once **93** is formed,



92 **93** **94**

it cannot, under the conditions used, revert to **92** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **93** to **92** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **93** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**94**), which is of course too strained to exist. **93** cannot revert to **92** by a photochemical pathway either, because light of the frequency used to excite **92** would not be absorbed by **93**. This is thus another example of a molecule that owes its stability to the orbital-symmetry rules (see p. 865). Pyrolysis of **93** does give **92**, probably by a diradical mechanism.[381] In the case of **95** and **96**, the Dewar benzene is actually more stable than the



95 **96**

benzene. **95** rearranges to **96** in 90% yield at 120°.[382] In this case thermolysis of the benzene gives the Dewar benzene (rather than the reverse), because of the strain of four adjacent *t*-butyl groups on the ring.

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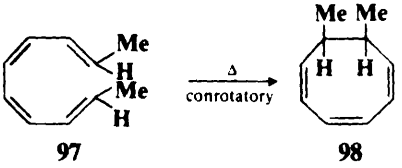
[379] Unsubstituted Dewar benzene has been obtained, along with other photoproducts, by photolysis of benzene: Ward; Wishnok *J. Am. Chem. Soc.* **1968**, *90*, 1085; Bryce-Smith; Gilbert; Robinson *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 745 [*Angew. Chem.* *83*, 803]. For other examples, see Arnett; Bollinger *Tetrahedron Lett.* **1964**, 3803; Camaggi; Gozzo; Cevidalli *Chem. Commun.* **1966**, 313; Haller *J. Am. Chem. Soc.* **1966**, *88*, 2070, *J. Chem. Phys.* **1967**, *47*, 1117; Barlow; Haszeldine; Hubbard *Chem. Commun.* **1969**, 202; Lemal; Staros; Austel *J. Am. Chem. Soc.* **1969**, *91*, 3373.

[380] van Tamelen; Pappas *J. Am. Chem. Soc.* **1962**, *84* 3789; Wilzbach; Kaplan *J. Am. Chem. Soc.* **1965**, *87*, 4004; van Tamelen; Pappas; Kirk *J. Am. Chem. Soc.* **1971**, *93*, 6092; van Tamelen *Acc. Chem. Res.* **1972**, *5*, 186-192. As mentioned on p. 865 (Ref. 1002), Dewar benzenes can be photolyzed further to give prismanes.

[381] See, for example, Oth *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1185; Adam; Chang *Int. J. Chem. Kinet.* **1969**, *1*, 487; Lechtken; Breslow; Schmidt; Turro *J. Am. Chem. Soc.* **1973**, *95*, 3025; Wingert; Irngartinger; Kallfass; Regitz *Chem. Ber.* **1987**, *120*, 825.

[382] Maier; Schneider *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 1022 [*Angew. Chem.* *95*, 1056]. See also Wingert; Maas; Regitz *Tetrahedron* **1986**, *42*, 5341.

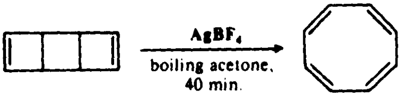
A number of electrocyclic reactions have been carried out with systems of other sizes, e.g., conversion of the 1,3,5,7-octatetraene **97** to the cyclooctatriene **98**.[383] The stereochemistry of these reactions can be predicted in a similar manner. The results of such predictions can be summarized 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).



	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. 849) 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.[384] Furthermore, a "forbidden" reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene—butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis,cis*- and *trans,trans*-1,4-dichloro-1,3-cyclobutadienes, as well as the allowed cis, trans isomer) by the use of ir laser light.[385] This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (p. 232), but not to a higher electronic state.

As is the case for 2 + 2 cycloaddition reactions (**5-49**), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.[386] An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene to cyclooctatetraene:[387]



This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.[388]

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[383] Marvell; Seubert *J. Am. Chem. Soc.* **1967,** *89,* 3377; Huisgen; Dahmen; Huber *J. Am. Chem. Soc.* **1967,** *89,* 7130, *Tetrahedron Lett.* **1969,** 1461; Dahmen; Huber *Tetrahedron Lett.* **1969,** 1465.

[384] For a discussion, see Baldwin; Andrist; Pinschmidt *Acc. Chem. Res.* **1972,** *5,* 402-406.

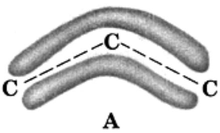
[385] Mao; Presser; John; Moriarty; Gordon *J. Am. Chem. Soc.* **1981,** *103,* 2105.

[386] For a review, see Pettit; Sugahara; Wristers; Merk *Discuss. Faraday Soc.* **1969,** *47,* 71-78. See also Ref. 993 in Chapter 15.

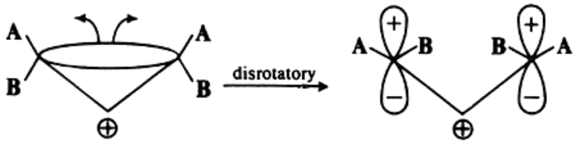
[387] Merk; Pettit *J. Am. Chem. Soc.* **1967,** *89,* 4788.

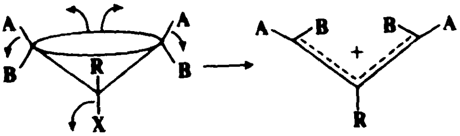
[388] For discussions of how these reactions take place, see Slegeir; Case; McKennis; Pettit *J. Am. Chem. Soc.* **1974,** *96,* 287; Pinhas; Carpenter *J. Chem. Soc., Chem. Commun.* **1980,** 15.

The ring opening of cyclopropyl cations (pp. 345, 1076) is an electrocyclic reaction and is governed by the orbital symmetry rules.[389] For this case we 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. 32). For the cation, with only two electrons, the highest occupied orbital is the one of the lowest energy (**A**). Thus, the cyclopropyl cation must undergo a disrotatory ring opening in order to maintain the symmetry. (Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,[390] since in this case it is the next orbital of the allylic system which is the highest occupied, and this has the opposite symmetry.[391]) However, it is very difficult to generate a free cyclopropyl cation (p. 345), and it is likely that in most 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*, not inward.[392] Thus, the disrotatory pathway that is followed is the one shown in **B**, not the one shown in **C**, because the former puts the electrons of the σ bond on the side opposite that of the leaving group.[393] Strong confirmation of this picture[394] comes from acetolysis of *endo*- (**99**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**100**). The groups

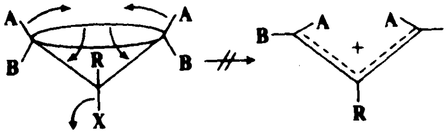


A





B



C

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[389] For discussions, see DePuy *Acc. Chem. Res.* **1968**, *1*, 33-41; Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 588-598 [*Angew. Chem.* *80*, 603-613].

[390] For a review of ring opening of cyclopropyl anions and related reactions, see Boche *Top. Curr. Chem.* **1988**, *146*, 1-56.

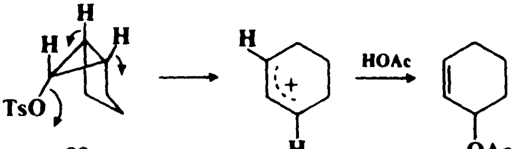
[391] For evidence that this is so, see Newcomb; Ford *J. Am. Chem. Soc.* **1974**, *96*, 2968; Boche; Buckl; Martens; Schneider; Wagner *Chem. Ber.* **1979**, *112*, 2961; Coates; Last *J. Am. Chem. Soc.* **1983**, *105*, 7322. For a review of the analogous ring opening of epoxides, see Huisgen *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 572-585 [*Angew. Chem.* *89*, 589-602].

[392] This was first proposed by DePuy; Schnack; Hausser; Wiedemann *J. Am. Chem. Soc.* **1965**, *87*, 4006.

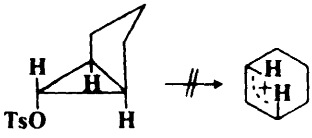
[393] It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser; Grubber *J. Org. Chem.* **1972**, *37*, 2648; Hausser; Uchic *J. Org. Chem.* **1972**, *37*, 4087.

[394] There is much other evidence. For example, see Jefford; Medary *Tetrahedron Lett.* **1966**, 2069; Jefford; Wojnarowski *Tetrahedron Lett.* **1968**, 199; Schleyer; Van Dine; Schöllkopf; Paust *J. Am. Chem. Soc.* **1966**, *88*, 2868; Sliwinski; Su; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 133; Sandler *J. Org. Chem.* **1967**, *32*, 3876; Ghosez; Slinckx; Glineur; Hoet; Laroche *Tetrahedron Lett.* **1967**, 2773; Parham; Yong *J. Org. Chem.* **1968**, *33*, 3947; Reese; Shaw *J. Am. Chem. Soc.* **1970**, *92*, 2566; Dolbier; Phanstiel *Tetrahedron Lett.* **1988**, *29*, 53.

trans to the tosylate must move outward. For **99** this means that the two hydrogens can go outside the framework of the six-membered ring, but for **100** they are forced to go inside.



99



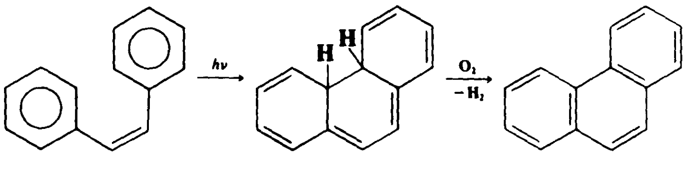
100

Consequently, it is not surprising that the rate ratio for solvolysis of **99:100** was found to be greater than 2.5 x 10^6 and that at 150°C **100** did not solvolyze at all.[395] 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 that is predicted by these rules is in fact formed.[396]

OS **V**, 235, 277, 467; **VI**, 39, 145, 196, 422, 427, 862.

8-30 Conversion of Stilbenes to Phenanthrenes

(6)*cyclo*-De-hydrogen-coupling (overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with uv light[397] in the presence of an oxidizing agent such as dissolved molecular oxygen, $FeCl_3$, Pd–C,[398] or iodine.[398a] The reaction is a photochemically allowed conrotatory[399] 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.[400] 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.,[401]

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[395] Schöllkopf; Fellenberger; Patsch; Schleyer; Su; Van Dine *Tetrahedron Lett.* **1967**, 3639.

[396] Schleyer; Su; Saunders; Rosenfeld *J. Am. Chem. Soc.* **1969**, *91*, 5174.

[397] For reviews, see Mallory; Mallory *Org. React.* **1984**, *30*, 1-456; Laarhoven *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 185-204, 241-254; Blackburn; Timmons *Q. Rev., Chem. Soc.* **1969**, *23*, 482-503; Stermitz; *Org. Photochem.* **1967**, *1*, 247-282. For a review of electrocyclizations of conjugated aryl olefins in general, see Laarhoven *Org. Photochem.* **1989**, *10*, 163-308.

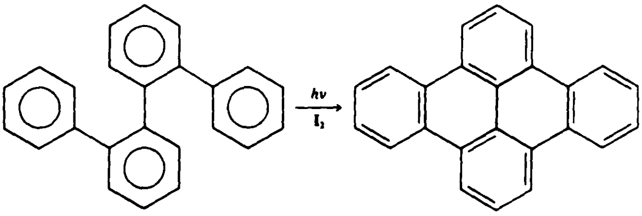
[398] Rawal; Jones; Cava *Tetrahedron Lett.* **1985**, *26*, 2423.

[398a] For the use of iodine plus propylene oxide in the absence of air, see Liu; Yang; Katz; Poindexter *J. Org. Chem.* **1991**, *56*, 3769.

[399] Cuppen; Laarhoven *J. Am. Chem. Soc.* **1972**, *94*, 5914.

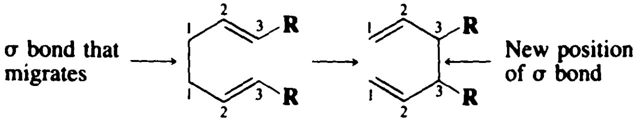
[400] Doyle; Benson; Filipescu *J. Am. Chem. Soc.* **1976**, *98*, 3262.

[401] Sato; Shimada; Hata *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2484.

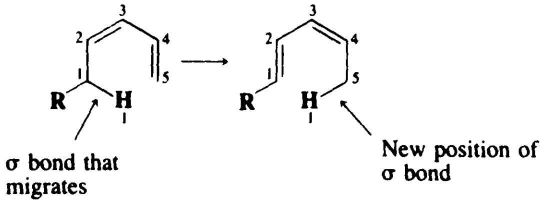


though not all such systems give reaction.[402]

B. Sigmatropic Rearrangements. A sigmatropic rearrangement is defined[403] 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 8-34
A [3,3] sigmatropic rearrangement

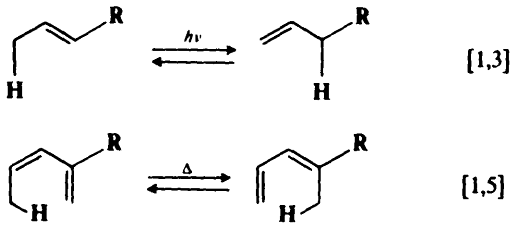


Reaction 8-31
A [1,5] sigmatropic rearrangement

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].

8-31 [1,*j*] Sigmatropic Migrations of Hydrogen

1/→3/Hydrogen-migration; 1/→5/Hydrogen-migration



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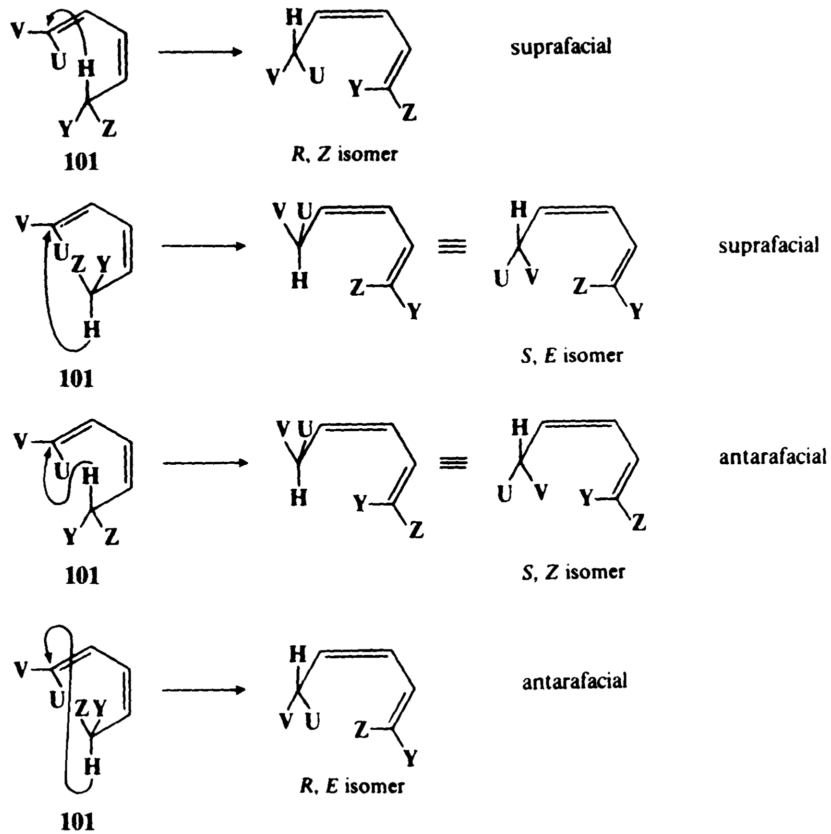
[402] For a discussion and lists of photocyclizing and nonphotocyclizing compounds, see Laarhoven *Recl. Trav. Chim. Pays-Bas*, Ref. 397, pp. 185-204.

[403] Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, p. 114.

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,[404] 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 which any sigmatropic rearrangement can take place, which we illustrate for the case of a [1,5] sigmatropic rearrangement,[405] starting with a substrate of the form **101**, 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 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 **101** 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



101 → *R*, *Z* isomer

101 → *S*, *E* isomer

101 → *S*, *Z* isomer

101 → *R*, *E* isomer

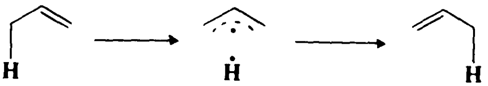
---

[404] For a monograph, see Gajewski, Ref. 365. For reviews, see Mironov; Fedorovich; Akhrem *Russ. Chem. Rev.* **1981**, *50*, 666-681; Spangler *Chem. Rev.* **1976**, *76*, 187-217; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 474-480; Woodward; Hoffmann, Ref. 403, pp. 114-140; Hansen; Schmid *Chimia* **1970**, *24*, 89-99; Roth *Chimia* **1966**, *20*, 229-236.

[405] Note that a [1,5] sigmatropic rearrangement of hydrogen is also an internal ene synthesis (**5-16**).

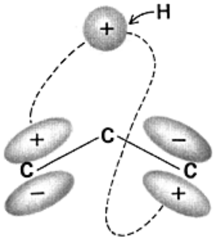
bottom of the π system to give the S,E isomer.[406] The antarafacial migration can similarly lead to two diastereomers, in this case the S,Z and R,E isomers.

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 first use a modified frontier orbital approach.[407] 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.

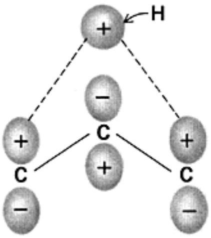


Imaginary transition state for a [1,3] sigmatropic rearrangement

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. 32) has three π orbitals, but the only one that concerns us here is the HOMO which, in a thermal 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 *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.*[408] 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 HOMO; 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 can 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.

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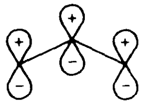
[406] Since we are using the arbitrary designations U, V, Y, and Z, we have been arbitrary in which isomer to call R,Z and which to call S,E.

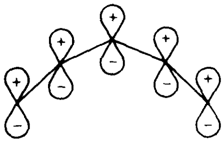
[407] See Woodward; Hoffmann, Ref. 403, pp. 114-140.

[408] 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.

As expected, the Möbius–Hückel method leads to the same predictions. Here we look at the basis set of orbitals shown in **F** and **G** for [1,3] and [1,5] rearrangements, respectively.



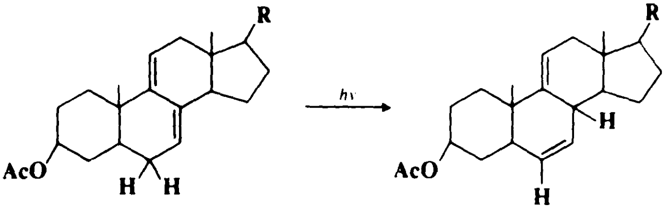
F



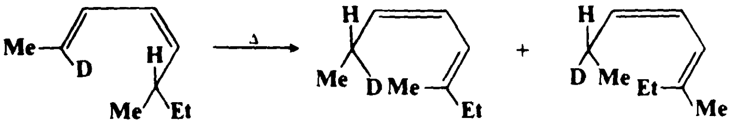
G

A [1,3] shift involves four electrons, so an allowed thermal pericyclic reaction must be a Möbius system (p. 1115) with one or an odd number of sign inversions. As can be seen in **F**, only an antarafacial migration can achieve this. A [1,5] shift, with six electrons, is allowed thermally only when it is a Hückel system with zero or an even number of sign inversions; hence it requires a suprafacial migration.

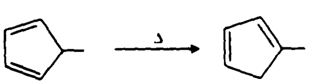
The actual reported results bear out this analysis. Thus a thermal [1,3] migration is allowed to take place only antarafacially, but such a transition state would be extremely strained, and thermal [1,3] sigmatropic migrations of hydrogen are unknown.[409] On the other hand, the photochemical pathway allows suprafacial [1,3] shifts, and a few such reactions are known, an example being[410]



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.[411] Examples of the thermal reaction are



Ref. 412



Ref. 413

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[409] A possible [1,3] migration of hydrogen has been reported. See Yeh; Linder; Hoffman; Barton *J. Am. Chem. Soc.* **1986,** *108,* 7849. See also Parto; Brophy *J. Org. Chem.* **1991,** *56,* 4554.

[410] Dauben; Wipke *Pure Appl. Chem.* **1964,** *9,* 539-553, p. 546. For another example, see Kropp; Fravel; Fields *J. Am. Chem. Soc.* **1976,** *98,* 840.

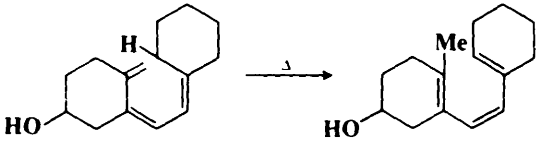
[411] For examples of photochemical [1,5] antarafacial reactions, see Kiefer; Tanna *J. Am. Chem. Soc.* **1969,** *91,* 4478; Kiefer; Fukunaga *Tetrahedron Lett.* **1969,** 993; Dauben; Poulter; Suter *J. Am. Chem. Soc.* **1970,** *92,* 7408.

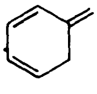
[412] Roth; König; Stein *Chem. Ber.* **1970,** *103,* 426.

[413] McLean; Haynes *Tetrahedron* **1965,** *21,* 2329. For a review of such rearrangements, see Klärner *Top. Stereochem.* **1984,** *15* 1-42.

Note that the first example bears out the stereochemical prediction made earlier. Only the two isomers shown were formed. In the second example, migration can continue around the ring. Migrations of this kind are called *circumambulatory rearrangements*.[414]

With respect to [1,7] hydrogen shifts, the rules predict the thermal reaction to 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.,[415]



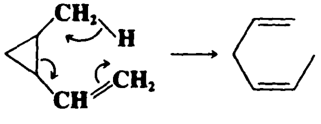


102

Photochemical [1,7] shifts are suprafacial and, not surprisingly, many of these have been observed.[416]

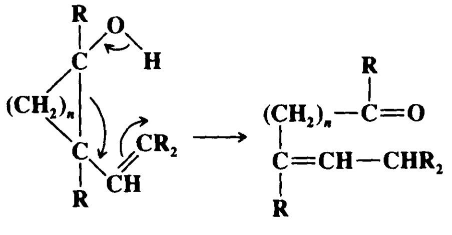
The orbital symmetry rules also help us to explain, as on pp. 865 and 1117, the unexpected stability of certain compounds. Thus, **102** could, by a thermal [1,3] sigmatropic rearrangement, easily convert to toluene, which of course is far more stable because it has an aromatic sextet. Yet **102** has been prepared and is stable at dry ice temperature and in dilute solutions.[417]

Analogs of sigmatropic rearrangements in which a cyclopropane ring replaces one of the double bonds are also known, e.g.,[418]



a homodienyl [1,5] shift

The reverse reaction has also been reported.[419] 2-Vinylcycloalkanols[420] undergo an analogous reaction, as do cyclopropyl ketones (see p. 1138 for this reaction).



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[414] For a review, see Childs *Tetrahedron* **1982,** *38,* 567-608. See also Minkin; Mikhailov; Dushenko; Yudilevich; Minyaev; Zschunke; Mügge *J. Phys. Org. Chem.* **1991,** *4,* 31.

[415] Schlatmann; Pot; Havinga *Recl. Trav. Chim. Pays-Bas* **1964,** *83,* 1173; Hoeger; Johnston; Okamura *J. Am. Chem. Soc.* **1987,** *109,* 4690; Baldwin; Reddy *J. Am. Chem. Soc.* **1987,** *109,* 8051, **1988,** *110,* 8223.

[416] See Murray; Kaplan *J. Am. Chem. Soc.* **1966,** *88,* 3527; ter Borg; Kloosterziel *Recl. Trav. Chim. Pays-Bas* **1969,** *88,* 266; Tezuka; Kimura; Sato; Mukai *Bull. Chem. Soc. Jpn.* **1970,** *43,* 1120.

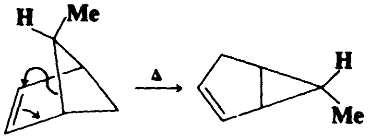
[417] Bailey; Baylouny *J. Org. Chem.* **1962,** *27,* 3476.

[418] Ellis; Frey *Proc. Chem. Soc.* **1964,** 221; Frey; Solly *Int. J. Chem. Kinet.* **1969,** *1,* 473; Roth; König *Liebigs Ann. Chem.* **1965,** *688,* 28; Ohloff *Tetrahedron Lett.* **1965,** 3795; Jorgenson; Thacher *Tetrahedron Lett.* **1969,** 4651; Corey; Yamamoto; Herron; Achiwa *J. Am. Chem. Soc.* **1970,** *92,* 6635; Loncharich; Houk *J. Am. Chem. Soc.* **1988,** *110,* 2089; Parziale; Berson *J. Am. Chem. Soc.* **1990,** *112,* 1650; Pegg; Meehan *Aust. J. Chem.* **1990,** *43,* 1009, 1071.

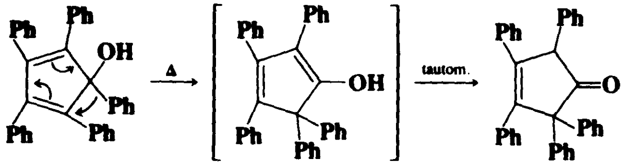
[419] Roth; König, Ref. 418. Also see Grimme *Chem. Ber.* **1965,** *98,* 756.

[420] Arnold; Smolinsky *J. Am. Chem. Soc.* **1960,** *82,* 4918; Leriverend; Conia *Tetrahedron Lett.* **1969,** 2681; Conia; Barnier *Tertahedron Lett.* **1969,** 2679.

8-32 [1,*j*] Sigmatropic Migrations of Carbon



[1,3] migration of alkyl[421]



[1,5] migration of phenyl[422]

Sigmatropic migrations of alkyl or aryl groups[423] are less common than the corresponding hydrogen migrations.[424] When they do take place, there is an important difference. Unlike a hydrogen atom, whose electron is in a 1*s* orbital with only one lobe, a carbon free radical has its odd electron in a *p* orbital that has *two lobes of opposite sign*. Therefore, if we draw the imaginary transition states for this case (see p. 1123), we see that in a thermal suprafacial [1,5] process (Figure 18.5), 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 happen only if configuration is *retained within the migrating group*. On the other hand, thermal suprafacial [1,3] migration (Figure 18.6) *can* take place if the migrating carbon switches lobes. If the migrating 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.

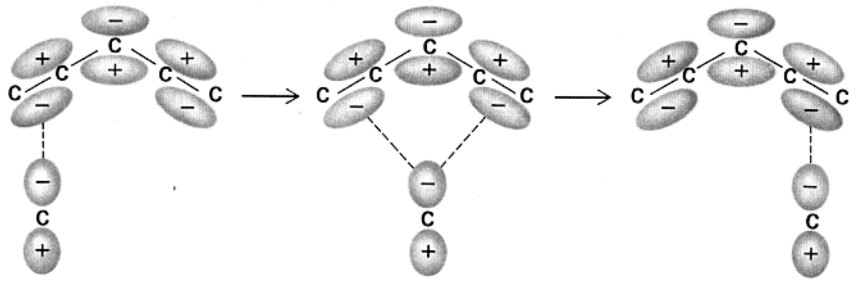


FIGURE 18.5 Hypothetical orbital movement for a thermal [1,5] sigmatropic migration of carbon. To move from one − lobe to the other − lobe, the migrating carbon uses only its own − lobe, retaining its configuration.

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[421] Roth; Friedrich *Tetrahedron Lett.* **1969,** 2607.

[422] Youssef; Ogliaruso *J. Org. Chem.* **1972,** *37*, 2601.

[423] For reviews, see Mironov; Fedorovich; Akhrem, Ref. 404; Spangler, Ref. 404.

[424] It has been shown that methyl and phenyl have lower migratory aptitudes than hydrogen in thermal sigmatropic rearrangements: Shen; McEwen; Wolf *Tetrahedron Lett.* **1969,** 827; Miller; Greisinger; Boyer *J. Am. Chem. Soc.* **1969,** *91*, 1578.

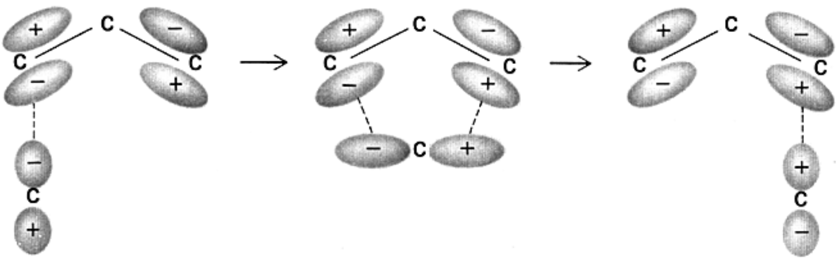
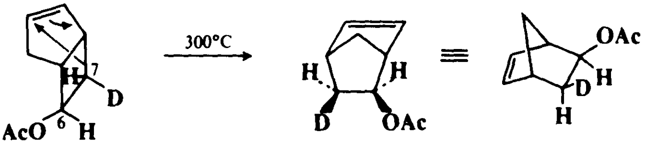


FIGURE 18.6 Hypothetical orbital movement for a thermal [1,3] sigmatropic migration of carbon. The migrating carbon moves from a − to a + lobe, requiring it to switch its own bonding lobe from − to +, inverting its configuration.

More generally, we can 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 (**103**), which gave the *exo*-deuterio-*exo*-norbonyl acetate



103 **104**

104.[425] Thus, as 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.[426] However, similar studies of the pyrolysis of the parent hydrocarbon of **103**, labeled with D at C-6 and C-7, showed that while most of the product was formed with inversion at C-7, a significant fraction (11 to 29%) was formed with retention.[427] Other cases of lack of complete inversion are also known.[428] A diradical mechanism has been invoked to explain such cases.[429] There is strong evidence for a radical mechanism for some [1,3] sigmatropic rearrangements.[430] Photochemical suprafacial [1,3] migrations of carbon have been shown to proceed with retention, as predicted.[431]

[425] Berson; Nelson *J. Am. Chem. Soc.* **1967,** *89,* 5503; Berson *Acc. Chem. Res.* **1968,** *1,* 152-160.

[426] See Ref. 421; Berson *Acc. Chem. Res.* **1972,** *5,* 406-414; Bampfield; Brook; Hunt *J. Chem. Soc., Chem. Commun.* **1976,** 146; Franzus; Scheinbaum; Waters; Bowlin *J. Am. Chem. Soc.* **1976,** *98,* 1241; Klärner; Adamsky *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 674 [*Angew. Chem. 91,* 738].

[427] Baldwin; Belfield *J. Am. Chem. Soc.* **1988,** *110,* 296; Klärner; Drewes; Hasselmann *J. Am. Chem. Soc.* **1988,** *110,* 297.

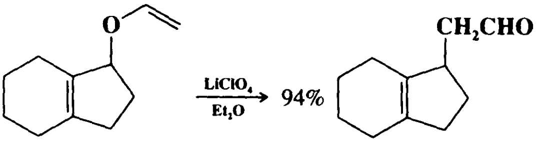
[428] See, for example, Berson; Nelson *J. Am. Chem. Soc.* **1970,** *92,* 1096; Berson; Holder *J. Am. Chem. Soc.* **1973,** *95,* 2037; Pikulin; Berson *J. Am. Chem. Soc.* **1988,** *110,* 8500.

[429] See Newman-Evans; Carpenter *J. Am. Chem. Soc.* **1984,** *106,* 7994; Pikulin; Berson, Ref. 428. See also Berson *Chemtracts: Org. Chem.* **1989,** 2, 213-227.

[430] See, for example, Bates; Ramaswamy *Can. J. Chem.* **1985,** *63,* 745; Dolbier; Phanstiel *J. Am. Chem. Soc.* **1989,** *111,* 4907.

[431] Cookson; Hudec; Sharma *Chem. Commun.* **1971,** 107, 108.

Although allylic vinylic ethers generally undergo [3,3] sigmatropic rearrangements (**8-35**), they can be made to give the [1,3] kind, to give aldehydes, e.g.,

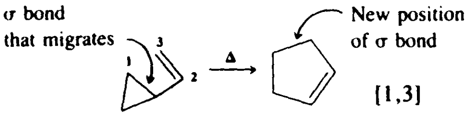


by treatment with LiClO$_4$ in diethyl ether.[431a] In this case the C—O bond undergoes a 1,3 migration from the O to the end vinylic carbon. When the vinylic ether is of the type ROCR'=CH$_2$, ketones RCH$_2$COR' are formed. There is evidence that this [1,3] sigmatropic rearrangement is not concerted, but involves dissociation of the substrate into ions.[431a]

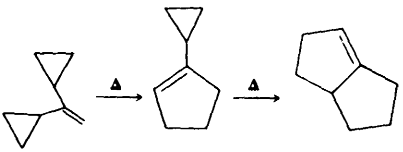
Thermal suprafacial [1,5] migrations of carbon have been found to take place with retention,[432] but also with inversion.[433,434] A diradical mechanism has been suggested for the latter case.[433]

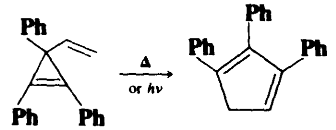
Simple nucleophilic, electrophilic, and free-radical 1,2 shifts can also be regarded as sigmatropic rearrangements (in this case, [1,2] rearrangements). We have already (p. 1051) applied similar principles to such rearrangements to show that nucleophilic 1,2 shifts are allowed, but the other two types are forbidden unless the migrating group has some means of delocalizing the extra electron or electron pair.

8-33 Conversion of Vinylcyclopropanes to Cyclopentenes



The thermal expansion of a vinylcyclopropane to a cyclopentene ring[435] is a special case of a [1,3] sigmatropic migration of carbon, though it can also be considered an internal [$_\pi 2 + {}_\sigma 2$] cycloaddition reaction (see **5-49**). 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[436]





[431a] Grieco; Clarke; Jagoe *J. Am. Chem. Soc.* **1991,** *113,* 5488.

[432] Boersma; de Haan; Kloosterziel; van de Ven *Chem. Commun.* **1970,** 1168.

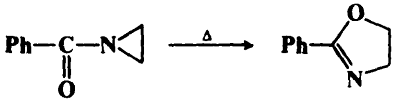
[433] Klärner; Yaslak; Wette *Chem. Ber.* **1979,** *112,* 1168; Klärner; Brassel *J. Am. Chem. Soc.* **1980,** *102,* 2469; Borden; Lee; Young *J. Am. Chem. Soc.* **1980,** *102,* 4841; Gajewski; Gortva; Borden *J. Am. Chem. Soc.* **1986,** *108,* 1083.

[434] Baldwin; Broline *J. Am. Chem. Soc.* **1982,** *104,* 2857.

[435] For reviews, see Wong et al., Ref. 114, pp. 169-172; Goldschmidt; Crammer *Chem. Soc. Rev.* **1988,** *17,* 229-267; Hudlický; Kutchan; Naqvi *Org. React.* **1985,** *33,* 247-335; Mil'vitskaya; Tarakanova; Plate *Russ. Chem. Rev.* **1976,** *45,* 469-478; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 470-474; Gutsche; Redmore, Ref. 112, pp. 163-170; Frey *Adv. Phys. Org. Chem.* **1966,** *4,* 147-193, pp. 155-163, 175-176.

[436] Ketley *Tetrahedron Lett.* **1964,** 1687; Branton; Frey *J. Chem. Soc. A* **1966,** 1342.

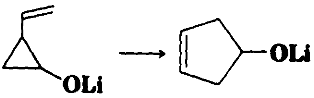
and (both thermally[437] and photochemically[438]) to vinylcyclopropenes. Various heterocyclic analogs[438a] are also known, e.g.,[439]



Two competing reactions are the homodienyl [1,5] shift (if a suitable H is available, see **8-31**), and simple cleavage of the cyclopropane ring, leading in this case to a diene (see **8-3**).

Vinylcyclobutanes can be similarly converted to cyclohexenes,[440] but larger ring compounds do not generally give the reaction.[441] Though high temperatures (as high as 500°C)

are normally required for the thermal reaction, the lithium salts of 2-vinylcyclopropanols rearrange at 25°C.[442]



Salts of 2-vinylcyclobutanols behave analogously.[443]

The reaction rate has also been greatly increased by the addition of a one-electron oxidant tris-(4-bromophenyl)aminium hexafluoroantimonate $Ar_3N^{\bullet +}$ SbF_6^- (Ar = *p*-bromophenyl).[444] This reagent converts the substrate to a cation radical, which undergoes ring expansion much faster.[445]

The mechanisms of these ring expansions are not certain. Both concerted[446] and diradical[447] pathways have been proposed, and it is possible that both pathways operate, in different systems.

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[437] Small; Breslow, cited in Breslow, in Mayo, Ref. 114, vol. 1, p. 236.

[438] Padwa; Blacklock; Getman; Hatanaka; Loza *J. Org. Chem.* **1978,** *43,* 1481; Zimmerman; Aasen *J. Org. Chem.* **1978,** *43,* 1493; Zimmerman; Kreil *J. Org. Chem.* **1982,** *47,* 2060.

[438a] For a review of a nitrogen analog, see Boeckman; Walters *Adv. Heterocycl. Nat. Prod. Synth.* **1990,** *1,* 1-41.

[439] For reviews of ring expansions of aziridines, see Heine *Mech. Mol. Migr.* **1971,** *3,* 145-176; Dermer; Ham *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969, pp. 282-290. See also Wong et al., Ref. 114, pp. 190-192.

[440] See, for example, Overberger; Borchert *J. Am. Chem. Soc.* **1960,** *82,* 1007; Gruseck; Heuschmann *Chem. Ber.* **1990,** *123,* 1911.

[441] For an exception, see Thies *J. Am. Chem. Soc.* **1972,** *94,* 7074.

[442] Danheiser; Martinez-Davila; Morin *J. Org. Chem.* **1980,** *45,* 1340; Danheiser; Bronson; Okano *J. Am. Chem. Soc.* **1985,** *107,* 4579.

[443] Danheiser; Martinez-Davila; Sard *Tetrahedron* **1981,** *37,* 3943.

[444] Dinnocenzo; Conlan *J. Am. Chem. Soc.* **1988,** *110,* 2324.

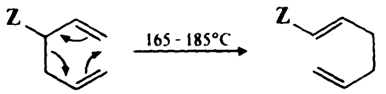
[445] For a review of ring expansion of vinylcyclobutane cation radicals, see Bauld *Tetrahedron* **1989,** *45,* 5307-5363.

[446] For evidence favoring the concerted mechanism, see Shields; Billups; Lepely *J. Am. Chem. Soc.* **1968,** *90,* 4749; Billups; Leavell; Lewis; Vanderpool *J. Am. Chem. Soc.* **1973,** *95,* 8096; Berson; Dervan; Malherbe; Jenkins *J. Am. Chem. Soc.* **1976,** *98,* 5937; Andrews; Baldwin *J. Am. Chem. Soc.* **1976,** *98,* 6705, 6706; Dolbier; Al-Sader; Sellers; Koroniak *J. Am. Chem. Soc.* **1981,** *103,* 2138; Gajewski; Olson *J. Am. Chem. Soc.* **1991,** *113,* 7432.

[447] For evidence favoring the diradical mechanism, see Willcott; Cargle *J. Am. Chem. Soc.* **1967,** *89,* 723; Doering; Schmidt *Tetrahedron* **1971,** *27,* 2005; Roth; Schmidt *Tetrahedron Lett.* **1971,** 3639; Simpson; Richey *Tetrahedron Lett.* **1973,** 2545; Gilbert; Higley *Tetrahedron Lett.* **1973,** 2075; Caramella; Huisgen; Schmolke *J. Am. Chem. Soc.* **1974,** *96,* 2997, 2999; Mazzocchi; Tamburin *J. Am. Chem. Soc.* **1975,** *97,* 555; Zimmerman; Fleming *J. Am. Chem. Soc.* **1983,** *105,* 622; Klumpp; Schakel *Tetrahedron Lett.* **1983,** *24,* 4595; McGaffin; de Meijere; Walsh *Chem. Ber.* **1991,** *124,* 939. A "continuous diradical transition state" has also been proposed: Doering; Sachdev *J. Am. Chem. Soc.* **1974,** *96,* 1168, **1975,** *97,* 5512; Roth; Lennartz; Doering; Birladeanu; Guyton; Kitagawa *J. Am. Chem. Soc.* **1990,** *112,* 1722.

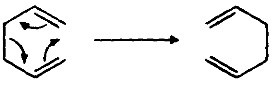
For the conversion of a vinylcyclopropane to a cyclopentene in a different way, see OS **68,** 220.

8-34 The Cope Rearrangement
(3/4/)→(1/6/)-*sigma*-Migration

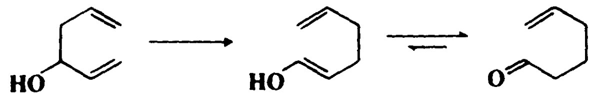


Z = **Ph**, **RCO**, etc.

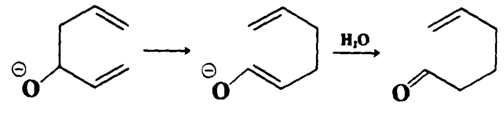
When 1,5-dienes are heated, they isomerize, in a [3,3] sigmatropic rearrangement known as the *Cope rearrangement* (not to be confused with the Cope elimination reaction, **7-8**).[448] When the diene is symmetrical about the 3,4 bond, we have the unusual situation where a reaction gives a product identical with the starting material:[449]



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.[450] 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 is not generally reversible[451] for 3-hydroxy-1,5-dienes, because the product tautomerizes to the ketone or aldehyde:



This reaction, called the *oxy-Cope rearrangement*,[452] has proved highly useful in synthesis.[453] The oxy-Cope rearrangement is greatly accelerated (by factors of 10^{10} to 10^{17}) if the alkoxide is used rather than the alcohol.[454] In this case the direct product is the enolate ion, which is hydrolyzed to the ketone.



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[448] For reviews, see Bartlett *Tetrahedron* **1980,** *36,* 2-72, pp. 28-39; Rhoads; Raulins *Org. React.* **1975,** *22,* 1-252; Smith; Kelly *Prog. Phys. Org. Chem.* **1971,** *8,* 75-234, pp. 153-201; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 455-461.

[449] Note that the same holds true for [1,*j*] sigmatropic reactions of symmetrical substrates (**8-31, 8-32**).

[450] Levy; Cope *J. Am. Chem. Soc.* **1944,** *66,* 1684.

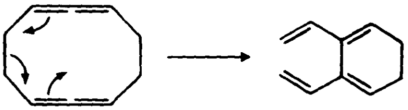
[451] For an exception, see Elmore; Paquette *Tetrahedron Lett.* **1991,** *32,* 319.

[452] Berson; Jones *J. Am. Chem. Soc.* **1964,** *86,* 5017, 5019; Viola; Levasseur *J. Am. Chem. Soc.* **1965,** *87,* 1150; Berson; Walsh *J. Am. Chem. Soc.* **1968,** *90,* 4729; Viola; Padilla; Lennox; Hecht; Proverb *J. Chem. Soc., Chem. Commun.* **1974,** 491; For reviews, see Paquette *Angew. Chem. Int. Ed. Engl.* **1990,** *29,* 609-626 [*Angew. Chem. 102,* 642-660], *Synlett* **1990,** 67-73; Marvell; Whalley, in Patai *The Chemistry of the Hydroxyl Group*, pt. 2; Wiley: New York, 1971, pp. 738-743.

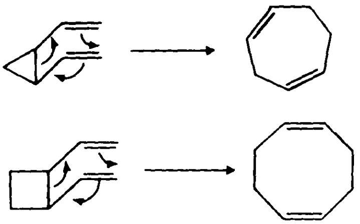
[453] For a list of references, see Ref. 106, pp. 639-640.

[454] Evans; Golub *J. Am. Chem. Soc.* **1975,** *97,* 4765; Evans; Nelson *J. Am. Chem. Soc.* **1980,** *102,* 774; Miyashi; Hazato; Mukai *J. Am. Chem. Soc.* **1978,** *100,* 1008; Paquette; Pegg; Toops; Maynard; Rogers *J. Am. Chem. Soc.* **1990,** *112,* 277; Gajewski; Gee *J. Am. Chem. Soc.* **1991,** *113,* 967. See also Wender; Ternansky; Sieburth *Tetrahedron Lett.* **1985,** *26,* 4319.

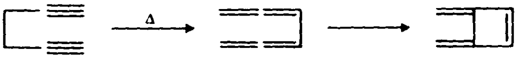
The 1,5-diene system may be inside a ring or part of an allenic system (this example illustrates both of these situations):[455]



but the reaction does not take place when one of the double bonds is part of an aromatic system, e.g., 1-phenyl-1-butene.[456] When the two double bonds are in vinylic groups attached to adjacent ring positions, the product is a ring four carbons larger. This has been applied to divinylcyclopropanes and cyclobutanes:[457]



Indeed, *cis*-1,2-divinylcyclopropanes give this rearrangement so rapidly that they generally cannot be isolated at room temperature,[458] though exceptions are known.[459] When heated, 1,5-diynes are converted to 3,4-dimethylenecyclobutenes.[460] A rate-determining Cope rearrangement is followed by a very rapid electrocyclic (**8-29**) reaction. The interconversion of 1,3,5-trienes and cyclohexadienes (in **8-29**) is very similar to the Cope rearrangement, though in **8-29**, the 3,4 bond goes from a double bond to a single bond rather than from a single bond to no bond.



Like 2 + 2 cycloadditions (p. 863), Cope rearrangements of simple 1,5-dienes can be catalyzed by certain transition-metal compounds. For example, the addition of $PdCl_2(PhCN)_2$ causes the reaction to take place at room temperature.[461] This can be quite useful synthetically, because of the high temperatures required in the uncatalyzed process.

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[455] Harris *Tetrahedron Lett.* **1965,** 1359.

[456] See, for example, Lambert; Fabricius; Hoard *J. Org. Chem.* **1979,** *44,* 1480; Marvell; Almond *Tetrahedron Lett.* **1979,** 2777, 2779; Newcomb; Vieta *J. Org. Chem.* **1980,** *45,* 4793. For exceptions in certain systems, see Doering; Bragole *Tetrahedron* **1966,** *22,* 385; Jung; Hudspeth *J. Am. Chem. Soc.* **1978,** *100,* 4309; Yasuda; Harano; Kanematsu *J. Org. Chem.* **1980,** *45,* 2368.

[457] Vogel; Ott; Gajek *Liebigs Ann. Chem.* **1961,** *644,* 172. For reviews, see Wong et al., Ref. 114, pp. 172-174; Mil'vitskaya et al., Ref. 435, pp. 475-476.

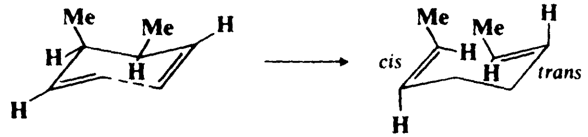
[458] Unsubstituted *cis*-1,2-divinylcyclopropane is fairly stable at −20°: Brown; Golding; Stofko *J. Chem. Soc., Chem. Commun.* **1973,** 319; Schneider; Rebell *J. Chem. Soc., Chem. Commun.* **1975,** 283.

[459] See, for example, Brown *Chem. Commun.* **1965,** 226; Schönleber Chem. Ber. **1969,** *102,* 1789; Bolesov; Ii-hsein; Levina *J. Org. Chem. USSR* **1970,** *6,* 1791; Schneider; Rau *J. Am. Chem. Soc.* **1979,** *101,* 4426.

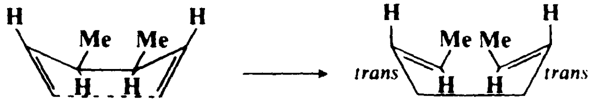
[460] For reviews of Cope rearrangements involving triple bonds, see Viola, Collins, and Filipp *Tetrahedron* **1981,** *37,* 3765-3811; Théron; Verny; Vessière, in Patai *The Chemistry of the Carbon-Carbon Triple Bond,* pt. 1; Wiley: New York, 1978, pp. 381-445, pp. 428-430; Huntsman *Intra-Sci. Chem. Rep.* **1972,** *6,* 151-159.

[461] Overman; Knoll *J. Am. Chem. Soc.* **1980,** *102,* 865; Hamilton; Mitchell; Rooney *J. Chem. Soc., Chem. Commun.* **1981,** 456. For reviews of catalysis of Cope and Claisen rearrangements, see Overman *Angew. Chem. Int. Ed. Engl.* **1984,** *23,* 579-586 [*Angew. Chem.* *96,* 565-573]; Lutz *Chem. Rev.* **1984,** *84,* 205-247. For a study of the mechanism, see Overman; Renaldo *J. Am. Chem. Soc.* **1990,** *112,* 3945.

As we have indicated with our arrows, the mechanism of the uncatalyzed 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 (±) compound gave the trans–trans diene.[462] 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:



There are two possible boat forms for the transition state of the meso isomer. One leads to a trans–trans product;



the other to a cis–cis olefin. For the (±) 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.[463] 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. 1131) can react *only* in the boat form, demonstrating that such reactions are not impossible.[464]

Because of the nature of the transition state in the pericyclic mechanism, optically active substrates with a chiral carbon at C-3 or C-4 transfer the chirality to the product, making this an enantioselective synthesis (see p. 1139 for an example in the mechanistically similar Claisen rearrangement).[465]

Not all Cope rearrangements proceed by the cyclic six-centered mechanism. Thus *cis*-1,2-divinylcyclobutane (p. 1131) 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 **8-33**). This reaction can be rationalized as proceeding by

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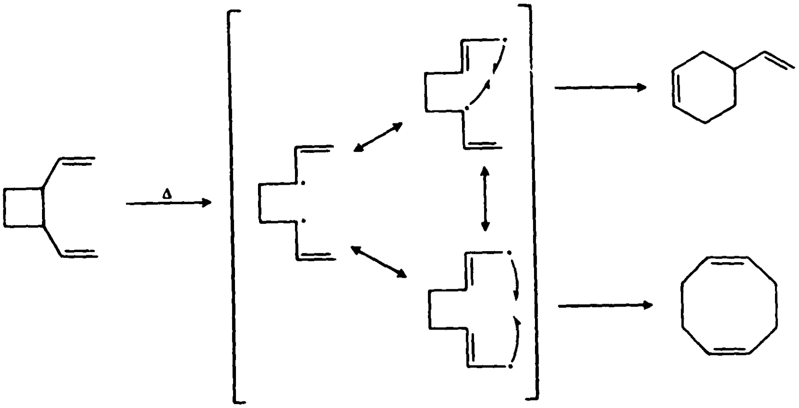
[462] Doering; Roth *Tetrahedron* **1962,** *18,* 67. See also Hill; Gilman *Chem. Commun.* **1967,** 619; Goldstein; DeCamp *J. Am. Chem. Soc.* **1974,** *96,* 7356; Hansen; Schmid *Tetrahedron* **1974,** *30,* 1959; Gajewski; Benner; Hawkins *J. Org. Chem.* **1987,** *52,* 5198; Paquette; DeRussy; Cottrell *J. Am. Chem. Soc.* **1988,** *110,* 890.

[463] Preference for the chair transition state is a consequence of orbital-symmetry relationships: Hoffmann; Woodward *J. Am. Chem. Soc.* **1965,** *87,* 4389; Fukui; Fujimoto *Tetrahedron Lett.* **1966,** 251.

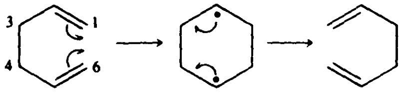
[464] For other examples of Cope rearrangements in the boat form, see Goldstein; Benzon *J. Am. Chem. Soc.* **1972,** *94,* 7147; Shea; Phillips *J. Am. Chem. Soc.* **1980,** *102,* 3156; Wiberg; Matturro; Adams *J. Am. Chem. Soc.* **1981,** *103,* 1600; Gajewski; Jiminez *J. Am. Chem. Soc.* **1986,** *108,* 468.

[465] For a review of Cope and Claisen reactions as enantioselective syntheses, see Hill, in Morrison *Asymmetric Synthesis,* vol. 3; Academic Press: New York, 1984, pp. 503-572, pp. 503-545.

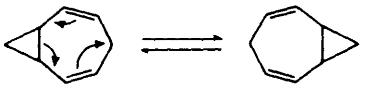


a diradical mechanism,[466] though it is possible that at least part of the cyclooctadiene produced comes from a prior epimerization of the *trans*- to the *cis*-divinylcyclobutane followed by Cope rearrangement of the latter.[467]

It has been suggested that another type of diradical two-step mechanism may be preferred by some substrates.[468] In this pathway,[469] 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 is a *degenerate Cope rearrangement* (p. 1054). Another molecule that undergoes it is bicyclo[5.1.0]octadiene (**105**).[470] At room temperature the nmr spectrum of this com-



105 **105**

pound is in accord with the structure shown on the left. At 180°C it is 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

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[466] Hammond; De Boer *J. Am. Chem. Soc.* **1964,** *86,* 899; Trecker; Henry *J. Am. Chem. Soc.* **1964,** *86,* 902. Also see Dolbier; Mancini *Tetrahedron Lett.* **1975,** 2141; Kessler; Ott *J. Am. Chem. Soc.* **1976,** *98,* 5014. For a discussion of diradical mechanisms in Cope rearrangements, see Berson, in Mayo, Ref. 1, pp. 358-372.

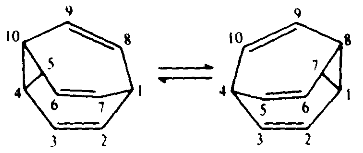
[467] See, for example, Berson; Dervan *J. Am. Chem. Soc.* **1972,** *94,* 8949; Baldwin; Gilbert *J. Am. Chem. Soc.* **1976,** *98,* 8283. For a similar result in the 1,2-divinylcyclopropane series, see Baldwin; Ullenius *J. Am. Chem. Soc.* **1974,** *96,* 1542.

[468] Doering; Toscano; Beasley *Tetrahedron* **1971,** *27,* 5299; Dewar; Wade *J. Am. Chem. Soc.* **1977,** *99,* 4417; Padwa; Blacklock *J. Am. Chem. Soc.* **1980,** *102,* 2797; Dollinger; Henning; Kirmse *Chem. Ber.* **1982,** *115,* 2309; Kaufmann; de Meijere *Chem. Ber.* **1984,** *117,* 1128; Dewar; Jie *J. Am. Chem. Soc.* **1987,** *109,* 5893, *J. Chem. Soc., Chem. Commun.* **1989,** 98. For evidence against this view, see Gajewski; Conrad *J. Am. Chem. Soc.* **1978,** *100,* 6268, 6269, **1979,** *101,* 6693; Gajewski *Acc. Chem. Res.* **1980,** *13,* 142-148; Morokuma; Borden; Hrovat *J. Am. Chem. Soc.* **1988,** *110,* 4474; Berson *Chemtracts: Org. Chem.* **1989,** *2,* 213-227; Halevi; Rom *Isr. J. Chem.* **1989,** *29,* 311; Owens; Berson *J. Am. Chem. Soc.* **1990,** *112,* 5973.

[469] For a report of still another mechanism, featuring a diionic variant of the diradical, see Gompper; Ulrich *Angew. Chem. Int. Ed. Engl.* **1976,** *15,* 299 [*Angew. Chem. 88,* 298].

[470] Doering; Roth *Tetrahedron* **1963,** *19,* 715.

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.[471] The positions of the nuclei are not the same in the two structures. Molecules like **105** that 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. 1131), but in **105** the *cis*-divinylcyclopropane structure is frozen into the molecule in both structures. Several other compounds with this structural feature are also known. Of these, *bullvalene* (**106**) is especially interesting. The Cope rearrangement shown



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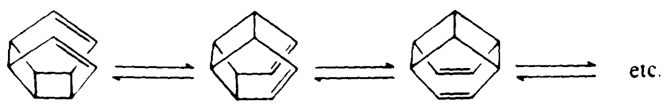
changes the position of the cyclopropane ring from 4,5,10 to 1,7,8. But the molecule could also have undergone rearrangements to put this ring at 1,2,8 or 1,2,7. Any of these could then undergo several Cope rearrangements. In all, there are 10!/3, or more than 1.2 million tautomeric forms, and the cyclopropane ring can be at any three carbons that 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.[472] 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 vinylic 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 unusual situation where the compound rapidly interchanges its structure among 1.2 million equivalent forms.[473] The ^{13}C nmr spectrum of bullvalene also shows only one peak at 100°C.[474]

Another compound for which degenerate Cope rearrangements result in equivalence for all the carbons is *hypostrophene* (**107**).[475] In the case of the compound *barbaralane* (**108**)



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[471] For reviews of valence tautomerizations, see Decock-Le Révérend; Goudmand *Bull. Soc. Chim. Fr.* **1973,** 389-407; Gajewski *Mech. Mol. Migr.* **1971,** *4,* 1-53, pp. 32-49; Paquette *Angew. Chem. Int. Ed. Engl.* **1971,** *10,* 11-20 [*Angew. Chem. 83,* 11-20]; Domareva-Mandel'shtam; D'yakonov *Russ. Chem. Rev.* **1966,** *35,* 559, 568; Schröder; Oth; Merényi *Angew. Chem. Int. Ed. Engl.* **1965,** *4,* 752-761 [*Angew. Chem. 77,* 774-784].

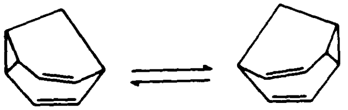
[472] Schröder *Angew. Chem. Int. Ed. Engl.* **1963,** *2,* 481 [*Angew. Chem. 75,* 772], *Chem. Ber.* **1964,** *97,* 3140; Merényi; Oth; Schröder *Chem. Ber.* **1964,** *97,* 3150. For a review of bullvalenes, see Schröder; Oth *Angew. Chem. Int. Ed. Engl.* **1967,** *6,* 414-423 [*Angew. Chem. 79,* 458-467].

[473] A number of azabullvalenes (**106** containing heterocyclic nitrogen) have been synthesized. They also have fluxional structures when heated, though with fewer tautomeric forms than bullvalene itself: Paquette; Barton *J. Am. Chem. Soc.* **1967,** *89,* 5480; Wegener *Tetrahedron Lett.* **1967,** 4985; Paquette; Malpass; Krow; Barton *J. Am. Chem. Soc.* **1969,** *91,* 5296.

[474] Oth; Müllen; Gilles; Schröder *Helv. Chim. Acta* **1974,** *57,* 1415; Nakanishi; Yamamoto *Tetrahedron Lett.* **1974,** 1803; Günther; Ulmen *Tetrahedron* **1974,** *30,* 3781. For deuterium nmr spectra see Poupko; Zimmermann; Luz *J. Am. Chem. Soc.* **1984,** *106,* 5391. For a crystal structure study, see Luger; Buschmann; McMullan; Ruble; Matias; Jeffrey *J. Am. Chem. Soc.* **1986,** *108,* 7825.

[475] McKennis; Brener; Ward; Pettit *J. Am. Chem. Soc.* **1971,** *93,* 4957; Paquette; Davis; James *Tetrahedron Lett.* **1974,** 1615.

(bullvalene in which one CH═CH has been replaced by a CH_2):

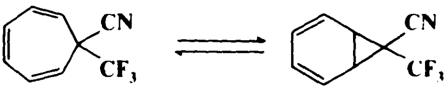


108

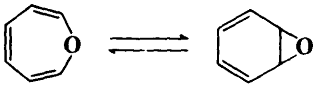
109

there are only two equivalent tautomers.[476] 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. In the case of *semibullvalene* (**109**) (barbaralane in which the CH_2 has been removed), not only is there a rapid interchange at room temperature, but even at −110°C.[477] **109** has the lowest energy barrier of any known compound capable of undergoing the Cope rearrangement.[478]

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 **110** and the norcaradiene **111.**[479] In this case one isomer (**111**) has the *cis*-1,2-divinylcyclopropane structure, while the other does not. In an analogous interconversion, benzene oxide[480] and oxepin exist in a tautomeric equilibrium at room temperature.[481]

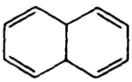


110 **111**

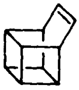


Oxepin **Benzene oxide**

Bullvalene and hypostrophene are members of a group of compounds all of whose formulas can be expressed by the symbol $(CH)_{10}$.[482] Many other members of this group are known, including **112** to **116** and the [10]annulenes (p. 58). All these compounds represent

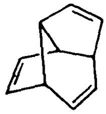


112



basketene

113



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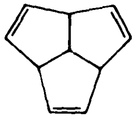
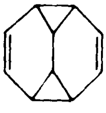


115



116

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[476] Barbaralane was synthesized by Biethan; Klusacek; Musso *Angew. Chem. Int. Ed. Engl.* **1967,** *6*, 176 [*Angew. Chem.* *79*, 152]; by Tsuruta; Kurabayashi; Mukai *Tetrahedron Lett.* **1965,** 3775; by Doering; Ferrier; Fossel; Hartenstein; Jones; Klumpp; Rubin; Saunders *Tetrahedron* **1967,** *23*, 3943; and by Henkel; Hane *J. Org. Chem.* **1983,** *48*, 3858.

[477] Zimmerman; Grunewald *J. Am. Chem. Soc.* **1966,** *88*, 183; Meinwald; Schmidt *J. Am. Chem. Soc.* **1969,** *91*, 5877; Zimmerman; Binkley; Givens; Grunewald; Sherwin *J. Am. Chem. Soc.* **1969,** *91*, 3316.

[478] Cheng; Anet; Mioduski; Meinwald *J. Am. Chem. Soc.* **1974,** *96*, 2887; Moskau; Aydin; Leber; Günther; Quast; Martin; Hassenrück; Miller; Grohmann *Chem. Ber.* **1989,** *122*, 925.

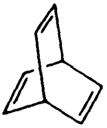
[479] Ciganek *J. Am. Chem. Soc.* **1965,** *87*, 1149. For other examples of norcaradiene–cycloheptatriene valence tautomerizations, see Görlitz; Günther *Tetrahedron* **1969,** *25*, 4467; Ciganek *J. Am. Chem. Soc.* **1965,** *93*, 2207; Dürr; Kober *Chem. Ber.* **1973,** *106*, 1565; Betz; Daub *Chem. Ber.* **1974,** *107*, 2095; Maas; Regitz *Chem. Ber.* **1976,** *109*, 2039; Warner; Lu *J. Am. Chem. Soc.* **1980,** *102*, 331; Neidlein; Radke *Helv. Chim. Acta* **1983,** *66*, 2626; Takeuchi; Kitagawa; Ueda; Senzaki; Okamoto *Tetrahedron* **1985,** *41*, 5455.

[480] For a review of arene oxides, see Shirwaiker; Bhatt *Adv. Heterocycl. Chem.* **1984,** *37*, 67-165.

[481] For reviews, see Ref. 363. See also Boyd; Stubbs *J. Am. Chem. Soc.* **1983,** *105*, 2554.

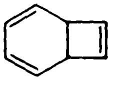
[482] For reviews of rearrangements and interconversions of $(CH)_n$ compounds, see Balaban; Banciu *J. Chem. Educ.* **1984,** *61*, 766-770; Greenberg; Liebman, Ref. 89, pp. 203-215; Scott; Jones *Chem. Rev.* **1972,** *72*, 181-202; Balaban *Rev. Roum. Chim.* **1966,** *11*, 1097-1116. See also Maier; Wiegand; Baum; Wüllner *Chem. Ber.* **1989,** *122*, 781.

positions of minimum energy on the (CH)$_{10}$ energy surface, and many have been interconverted by electrocyclic or Cope rearrangements. Similar groups of (CH)$_n$ compounds exist for other even-numbered values of n.[482] For example, there are 20 possible (CH)$_8$[483] compounds,[484] including semibullvalene (**109**), cubane (p. 154), cuneane (p. 1149), octabisvalene (p. 154), cyclooctatetraene (p. 57), **117** to **119**, and five possible (CH)$_6$ compounds,[485] all of which are known: benzene, prismane (p. 154), Dewar benzene (p. 1117), bicyclopropenyl,[486] and benzvalene.[487]



Barrelene

117



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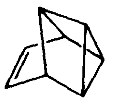
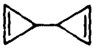


119

Some (CH)$_8$ compounds

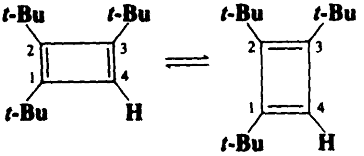


Bicyclopropenyl

Benzvalene

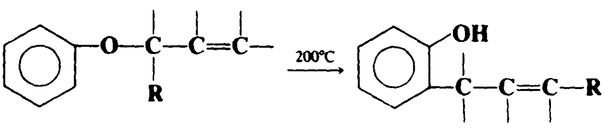
Two (CH)$_6$ compounds

An interesting example of a valence tautomerism is the case of 1,2,3-tri-*t*-butylcyclobutadiene (p. 54). There are two isomers, both rectangular, and ^{13}C nmr spectra show that



they exist in a dynamic equilibrium, even at −185°C.[488]

8-35 The Claisen Rearrangement



Allylic aryl ethers, when heated, rearrange to *o*-allylphenols in a reaction called the *Claisen rearrangement*.[489] If both ortho positions are filled, the allylic group migrates to the para

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[483] For a review of strain in (CH)$_8$ compounds, see Hassenrück; Martin; Walsh *Chem. Rev.* **1989**, *89*, 1125-1146.

[484] The structures of all possible (CH)$_n$ compounds, for n = 4, 6, 8, and 10, are shown in Balaban, Ref. 482. For a review of (CH)$_{12}$ compounds, see Banciu; Popa; Balaban *Chem. Scr.* **1984**, *24*, 28.

[485] For reviews of valence isomers of benzene and some related compounds, see Kobayashi; Kumadaki *Top. Curr. Chem.* **1984**, *123*, 103-150; Bickelhaupt; de Wolf *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 459-478.

[486] For a study of how this compound isomerizes to benzene, see Davis, Shea; Bergman *J. Am. Chem. Soc.* **1977**, *99*, 1499.

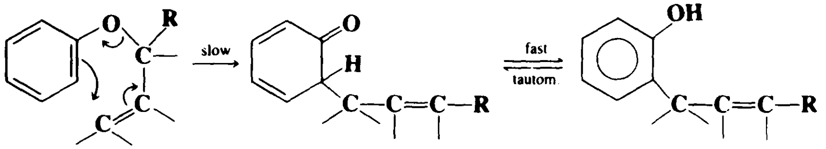
[487] For reviews of benzvalenes, see Christl *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 529-546 [*Angew. Chem.* *93*, 515-531]; Burger *Chimia* **1979**, 147-152.

[488] Maier; Kalinowski; Euler *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 693 [*Angew. Chem.* *94*, 706].

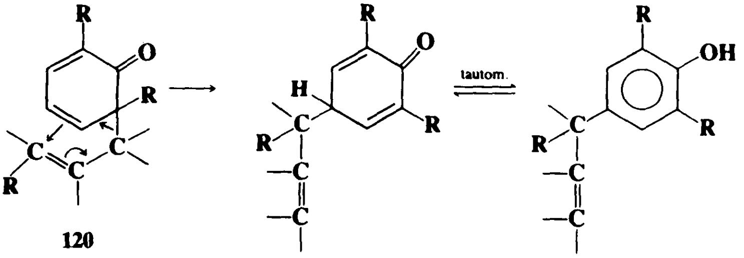
[489] For reviews, see Moody *Adv. Heterocycl. Chem.* **1987**, *42*, 203-244; Bartlett, Ref. 448, pp. 28-39; Ziegler *Acc. Chem. Res.* **1977**, *10*, 227-232; Bennett *Synthesis* **1977**, 589-606; Rhoads; Raulins, Ref. 448; Shine *Aromatic Rearrangements*; Elsevier: New York, 1969, pp. 89-120; Smith; Kelly *Prog. Phys. Org. Chem.* **1971**, *8*, 75-234, pp. 153-201; Hansen; Schmid *Chimia* **1970**, *24*, 89-99, *Chem. Br.* **1969**, *5*, 111-116; Jefferson; Scheinmann *Q. Rev., Chem. Soc.* **1968**, *22*, 391-421; Thyagarajan *Adv. Heterocycl. Chem.* **1967**, *8*, 143-163; Dalrymple; Kruger; White, in Patai *The Chemistry of the Ether Linkage*; Wiley: New York, 1967, pp. 635-660.

position (this is often called the *para-Claisen rearrangement*). 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 allylic 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 allylic group is found exactly as it was in the original ether. Compounds with propargylic groups (i.e., groups with a triple bond in the appropriate position) do not generally give the corresponding products.

The mechanism is a concerted pericyclic [3,3] sigmatropic rearrangement[490] and accounts for all these facts. For the ortho rearrangement:



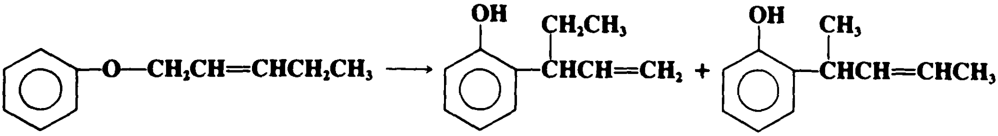
Evidence is the lack of a catalyst, the fact that the reaction is first order in the ether, the absence of crossover products when mixtures are heated, and the presence of the allylic shift, which is required by this mechanism. The allylic shift for the ortho rearrangement (and the absence of one for 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 usually prefers a chairlike transition state.[491] When the ortho positions have no hydrogen, a second [3,3] sigmatropic migration (a Cope reaction) follows:



120

and the migrating group is restored to its original structure. Intermediates of structure **120** have been trapped by means of a Diels-Alder reaction.[492]

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:[493]



Normal product Abnormal product

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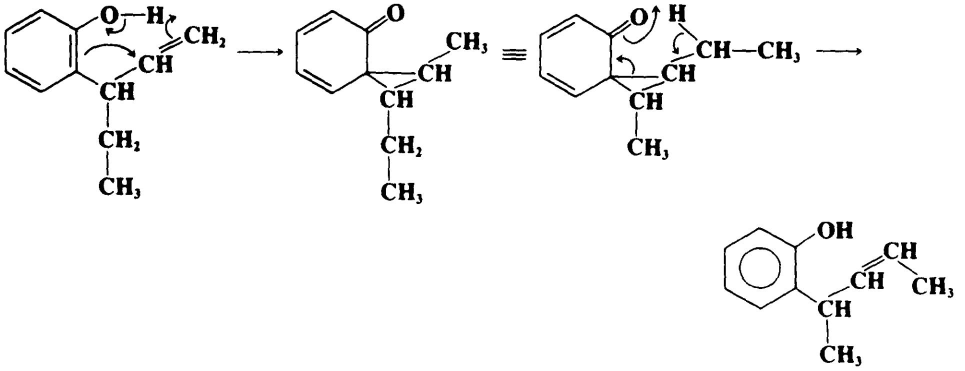
[490] For isotope effect evidence regarding the nature of the concerted transition state, see McMichael; Korver *J. Am. Chem. Soc.* **1979**, *101*, 2746; Gajewski; Conrad *J. Am. Chem. Soc.* **1979**, *101*, 2747; Kupczyk-Subotkowska; Saunders; Shine *J. Am. Chem. Soc.* **1988**, *110*, 7153.

[491] Vittorelli; Winkler; Hansen; Schmid *Helv. Chim. Acta* **1968**, *51*, 1457; Wunderli; Winkler; Hansen *Helv. Chim. Acta* **1977**, *60*, 2436; Copley; Knowles *J. Am. Chem. Soc.* **1985**, *107*, 5306.

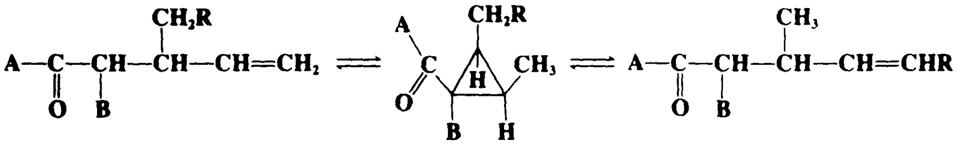
[492] Conroy; Firestone *J. Am. Chem. Soc.* **1956**, *78*, 2290.

[493] For reviews of these abnormal Claisen rearrangements, see Hansen *Mech. Mol. Migr.* **1971**, *3*, 177-236; Marvell; Whalley, in Patai, Ref. 452, pt. 2, pp. 743-750.

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:[494]



This rearrangement, which has been called an *enolene rearrangement*, a *homodienyl* [1,5] *sigmatropic hydrogen shift* (see **8-31**), 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 **121** and **123** through the cyclopropane intermediate **122**.[495]



121 **122** **123**

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.[496] However, solvent effects are greater: rates varied over a 300-fold range when the reaction was run in 17 different solvents.[497] An especially good solvent is trifluoroacetic acid, in which the reaction can be carried out at room temperature.[498] Most Claisen rearrangements are performed without a catalyst, but $AlCl_3$ or BF_3 are sometimes

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[494] Marvell; Anderson; Ong *J. Org. Chem.* **1962,** *27,* 1109; Habich; Barner; Roberts; Schmid *Helv. Chim. Acta* **1962,** *45,* 1943; Lauer; Johnson *J. Org. Chem.* **1963,** *28,* 2913; Fráter; Schmid *Helv. Chim. Acta* **1966,** *49,* 1957; Marvell; Schatz *Tetrahedron Lett.* **1967,** 67.

[495] Roberts; Landolt; Greene; Heyer *J. Am. Chem. Soc.* **1967,** *89,* 1404; Watson; Irvine; Roberts *J. Am. Chem. Soc.* **1973,** *95,* 3348.

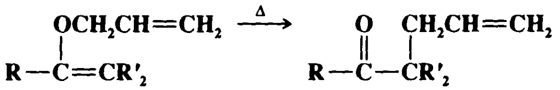
[496] Goering; Jacobson *J. Am. Chem. Soc.* **1958,** *80,* 3277; White; Gwynn; Schlitt; Girard; Fife *J. Am. Chem. Soc.* **1958,** *80,* 3271; White; Slater *J. Org. Chem.* **1962,** *27,* 2908; Zahl; Kosbahn; Kresze *Liebigs Ann. Chem.* **1975,** 1733. See also Desimoni; Faita; Gamba; Righetti; Tacconi; Toma *Tetrahedron* **1990,** *46,* 2165; Gajewski; Gee; Jurayj *J. Org. Chem.* **1990,** *55,* 1813.

[497] White; Wolfarth *J. Org. Chem.* **1970,** *35,* 2196. See also Brandes; Greico; Gajewski *J. Org. Chem.* **1989,** *54,* 515.

[498] Svanholm; Parker *J. Chem. Soc., Perkin Trans. 2* **1974,** 169.

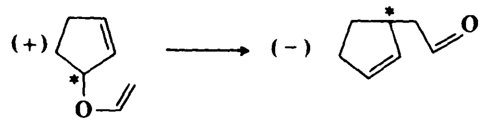
used.[499] In this case it may become a Friedel–Crafts reaction, with the mechanism no longer cyclic,[500] and ortho, meta, and para products may be obtained.

Allylic ethers of enols (allylic vinylic ethers) also undergo the Claisen rearrangement;[501] in fact, it was discovered with these compounds first:[502]



$$\begin{array}{l}\mathrm{OCH_2CH{=}CH_2}\\ \ \ |\\ \mathrm{R{-}C{=}CR'_2}\end{array} \xrightarrow{\Delta} \begin{array}{l}\mathrm{\ \ \ \ O\ \ \ CH_2CH{=}CH_2}\\ \ \ \ \ \|\ \ \ \ |\\ \mathrm{R{-}C{-}CR'_2}\end{array}$$

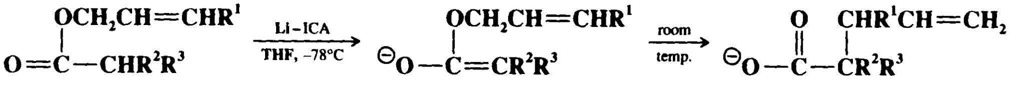
In these cases of course the final tautomerization does not take place even when R′ = H, since there is no aromaticity to restore, and ketones are more stable than enols.[503] The use of water as solvent accelerates the reaction.[504] The mechanism is similar to that with allylic aryl ethers.[505] One experiment that demonstrated this was the conversion of optically active



124 **125**

124 to **125**, which was still optically active.[506] This is another example of asymmetric induction (p. 117).[465]

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 vinylic ethers, and then Claisen rearrangement.[507] In an analogous procedure, the enolates (**126**) of allylic esters [formed by treatment of the esters with lithium isopropylcyclohexylamide (ICA)] rearrange to γ,δ-unsaturated acids.[508]



$$\begin{array}{l}\mathrm{\ \ \ \ OCH_2CH{=}CHR^1}\\ \ \ \ \ \ |\\ \mathrm{O{=}C{-}CHR^2R^3}\end{array} \xrightarrow[\mathrm{THF,\ -78^\circ C}]{\mathrm{Li\text{-}ICA}} \begin{array}{l}\mathrm{\ \ \ \ \ OCH_2CH{=}CHR^1}\\ \ \ \ \ \ \ |\\ \ominus\mathrm{O{-}C{=}CR^2R^3}\end{array} \xrightarrow[\mathrm{temp.}]{\mathrm{room}} \begin{array}{l}\mathrm{\ \ \ \ \ O\ \ \ CHR^1CH{=}CH_2}\\ \ \ \ \ \ \|\ \ \ \ |\\ \ominus\mathrm{O{-}C{-}CR^2R^3}\end{array}$$

126

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[499] For a review, see Lutz, Ref. 461.

[500] For example, crossover experiments have demonstrated that the $ZnCl_2$-catalyzed reaction is intermolecular: Yagodin; Bunina-Krivorukova; Bal'yan *J. Org. Chem. USSR* **1971**, *7*, 1491.

[501] For a review, see Ziegler *Chem. Rev.* **1988**, *88*, 1423-1452

[502] Claisen *Ber.* **1912**, *45*, 3157.

[503] However, it has proved possible to reverse the reaction, with a Lewis acid catalyst. See Boeckman; Flann; Poss *J. Am. Chem. Soc.* **1985**, *107*, 4359.

[504] Grieco; Brandes; McCann; Clark *J. Org. Chem.* **1989**, *54*, 5849.

[505] For discussions of the transition state, see Burrows; Carpenter *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984; Gajewski; Jurayj; Kimbrough; Gande; Ganem; Carpenter *J. Am. Chem. Soc.* **1987**, *109*, 1170. For mo calculations, see Vance; Rondan; Houk; Jensen; Borden; Komornicki; Wimmer *J. Am. Chem. Soc.* **1988**, *110*, 2314; Dewar; Jie *J. Am. Chem. Soc.* **1989**, *111*, 511.

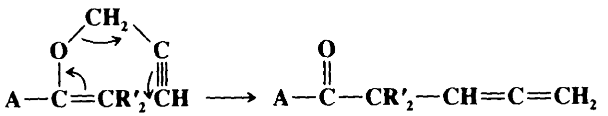
[506] Hill; Edwards *Tetrahedron Lett* **1964**, 3239.

[507] Lorette *J. Org. Chem.* **1961**, *26*, 4855. See also Saucy; Marbet *Helv. Chim. Acta* **1967**, *50*, 2091; Marbet; Saucy *Helv. Chim. Acta* **1967**, *50*, 2095; Thomas *J. Am. Chem. Soc.* **1969**, *91*, 3281; Johnson; Werthemann; Bartlett; Brocksom; Li; Faulkner; Petersen *J. Am. Chem. Soc.* **1970**, *92*, 741; Pitteloud; Petrzilka; *Helv. Chim. Acta* **1979**, *62*, 1319; Daub; Sanchez; Cromer; Gibson *J. Org. Chem.* **1982**, *47*, 743; Bartlett; Tanzella; Barstow *J. Org. Chem.* **1982**, *47*, 3941.

[508] Ireland; Mueller; Willard *J. Am. Chem. Soc.* **1976**, *98*, 2868; Gajewski; Emrani *J. Am. Chem. Soc.* **1984**, *106*, 5733; Cameron; Knight *J. Chem. Soc., Perkin Trans. 1* **1986**, 161. See also Wilcox; Babston *J. Am. Chem. Soc.* **1986**, *108*, 6636.

Alternatively, the silylketene acetal $R^3R^2C{=}C(OSiR_3)OCH_2CH{=}CHR^1$ is often used instead of **126**.[509] This rearrangement also proceeds at room temperature. By either procedure, the reaction is called the *Ireland–Claisen rearrangement*. Note the presence of the negative charge in **126**. As with the oxy-Cope rearrangement (in **8-34**), negative charges generally accelerate the Claisen reaction,[510] though the extent of the acceleration can depend on the identity of the positive counterion.[511] The Ireland–Claisen rearrangement has been made enantioselective by converting **126** to an enol borinate in which the boron is attached to a chiral group.[512]

A number of expected analogs of the Claisen rearrangement are known, e.g., rearrangement of $ArNHCH_2CH{=}CH_2$,[513] of N-allylic enamines $R_2C{=}CRNRCR_2CR{=}CR_2$,[514] of allylic imino esters $RC(OCH_2CH{=}CH_2){=}NR$[515] (these have often been rearranged with transition metal catalysts[516]), and of $RCH{=}NRCHRCH_2CH{=}CH_2$. These rearrangements of nitrogen-containing compounds are often called *aza-Cope rearrangements*.[517] An *azo-Cope* rearrangement: $CH_2{=}CHCR^1_2CR^2_2N{=}NAr \rightarrow R^1_2CH{=}CHCH_2NArN{=}CR^2_2$ has been reported.[518] Propargylic vinylic compounds give allenic aldehydes, ketones, esters, or amides:[519]



A = H, R, OR, NR$_2$

The conversion of allylic aryl thioethers $ArSCH_2CH{=}CH_2$ to *o*-allylic thiophenols (the *thio-Claisen rearrangement*) is not feasible, because the latter are not stable[520] but react to give bicyclic compounds.[521] However, many allylic vinylic sulfides do give the rearrangement.[522] Allylic vinylic sulfones, e.g., $H_2C{=}CRCH_2{-}SO_2{-}CH{=}CH_2$, rearrange, when

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[509] Ref. 508; Ireland; Wipf; Armstrong *J. Org. Chem.* **1991,** *56,* 650.

[510] See, for example, Denmark; Harmata *Tetrahedron Lett.* **1984,** *25,* 1543; Denmark; Harmata; White *J. Am. Chem. Soc.* **1989,** *111,* 8878.

[511] Koreeda; Luengo *J. Am. Chem. Soc.* **1985,** *107,* 5572; Kirchner; Pratt; Hopkins *Tetrahedron Lett.* **1988,** *29,* 4229.

[512] Corey; Lee *J. Am. Chem. Soc.* **1991,** *113,* 4026.

[513] Marcinkiewicz; Green; Mamalis *Tetrahedron* **1961,** *14,* 208; Inada; Ikado; Okazaki *Chem. Lett.* **1973,** 1213; Schmid; Hansen; Schmid *Helv. Chim. Acta* **1973,** *56,* 105; Jolidon; Hansen *Helv. Chim. Acta* **1977,** *60,* 978.

[514] Ficini; Barbara *Tetrahedron Lett.* **1966,** 6425; Hill; Gilman *Tetrahedron Lett.* **1967,** 1421; Ireland; Willard *J. Org. Chem.* **1974,** *39,* 421; Hill; Khatri *Tetrahedron Lett.* **1978,** 4337. For the reverse of this rearrangement, see Wu; Fowler *J. Org. Chem.* **1988,** *53,* 5998.

[515] For examples, see Synerholm; Gilman; Morgan; Hill *J. Org. Chem.* **1968,** *33,* 1111; Black; Eastwood; Okraglik; Poynton; Wade; Welker *Aust. J. Chem.* **1972,** *25,* 1483; Overman *J. Am. Chem. Soc.* **1974,** *96,* 597; Metz; Mues *Tetrahedron* **1988,** *44,* 6841.

[516] See Schenck; Bosnich *J. Am. Chem. Soc.* **1985,** *107,* 2058, and references cited therein.

[517] For a review, see Przheval'skii; Grandberg *Russ. Chem. Rev.* **1987,** *56,* 477-491. For reviews of [3,3] sigmatropic rearrangements with hetero atoms present, see Blechert *Synthesis* **1989,** 71-82; Winterfeldt *Fortschr. Chem. Forsch.* **1970,** *16,* 75-102. For a review of [3,3] rearrangements of iminium salts, see Heimgartner; Hansen; Schmid *Adv. Org. Chem.* **1979,** *9,* pt. 2, 655-731.

[518] Mitsuhashi *J. Am. Chem. Soc.* **1986,** *108,* 2400.

[519] For reviews of Claisen rearrangements involving triple bonds, see Schuster; Coppola, Ref. 124, pp. 337-343; Viola et al., Ref. 460; Théron et al., Ref. 460, pp. 421-428. See also Henderson; Heathcock *J. Org. Chem.* **1988,** *53,* 4736.

[520] They have been trapped: See, for example, Mortensen; Hedegaard; Lawesson *Tetrahedron* **1971,** *27,* 3831; Kwart; Schwartz *J. Org. Chem.* **1974,** *39,* 1575.

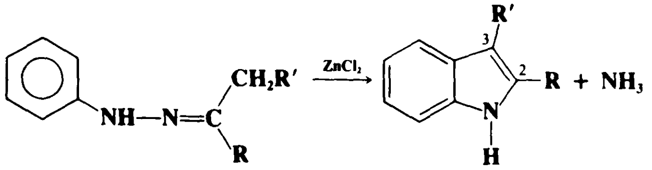
[521] Kwart; Hackett *J. Am. Chem. Soc.* **1962,** *84,* 1754; Meyers; Rinaldi; Banoli *J. Org. Chem.* **1963,** *28,* 2440; Makisumi *Tetrahedron Lett.* **1966,** 6399; Kwart; Cohen *J. Org. Chem.* **1967,** *32,* 3135, *Chem. Commun.* **1968,** 319; Makisumi; Murabayashi *Tetrahedron Lett.* **1969,** 1971, 2449.

[522] See, for example, Schuijl; Brandsma *Recl. Trav. Chim. Pays-Bas* **1968,** *87,* 929, **1969,** *88,* 1201; Corey; Shulman *J. Am. Chem. Soc.* **1970,** *92,* 5522; Kondo; Ojima *Chem. Commun.* **1972,** 62; Meijer; Vermeer; Bos; Brandsma *Recl. Trav. Chim. Pays-Bas* **1974,** *93,* 26; Morin; Paquer; Smadja *Recl. Trav. Chim. Pays-Bas* **1976,** *95,* 179; Schaumann; Grabley *Liebigs Ann. Chem.* **1979,** 1746; Metzner; Pham; Vialle *Tetrahedron* **1986,** *42,* 2025; Beslin; Perrio *Tetrahedron* **1991,** *47,* 6275.

heated in the presence of ethanol and pyridine, to unsaturated sulfonate salts $CH_2{=}CRCH_2CH_2CH_2SO_3^-$, produced by reaction of the reagents with the unstable sulfene intermediates $CH_2{=}CRCH_2CH_2CH{=}SO_2$.[523] Allylic vinylic sulfoxides rapidly rearrange at room temperature or below.[524]

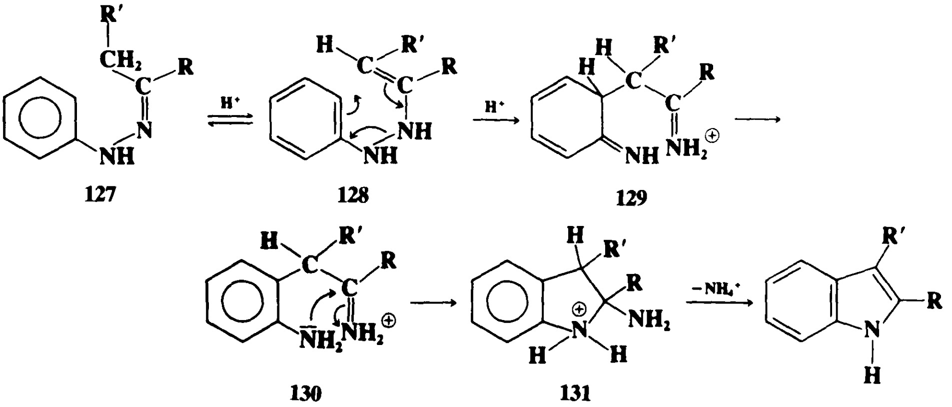
OS **III,** 418; **V,** 25; **VI,** 298, 491, 507, 584, 606; **VII,** 177; **66,** 22, 29.

8-36 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 the *Fischer indole synthesis*.[525] 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 (**6-2**) or by aliphatic diazonium coupling (**2-7**). However, it is not necessary to isolate the arylhydrazone. The aldehyde or ketone can be treated with a mixture of phenylhydrazine and the catalyst; 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).

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:[526]



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[523] King; Harding *J. Am. Chem. Soc.* **1976,** *98,* 3312.

[524] Block; Ahmad *J. Am. Chem. Soc.* **1985,** *107,* 6731.

[525] For a monograph, see Robinson *The Fischer Indole Synthesis*; Wiley: New York, 1983. For reviews, see Grandberg; Sorokin *Russ. Chem. Rev.* **1974,** *43,* 115-128; Shine *Aromatic Rearrangements*, Ref. 489, pp. 190-207; Sundberg *The Chemistry of Indoles*; Academic Press: New York, 1970, pp. 142-163; Robinson *Chem. Rev.* **1969,** *69,* 227-250. For reviews of some abnormal Fischer indole syntheses, see Ishii *Acc. Chem. Res.* **1981,** *14,* 275-283; Fusco; Sannicolo *Tetrahedron* **1980,** *36,* 161-170.

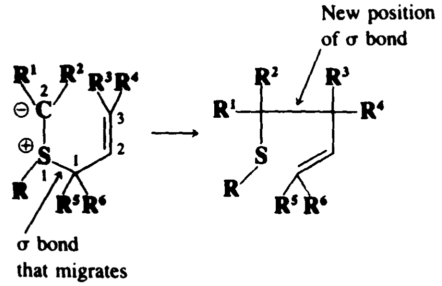
[526] This mechanism was proposed by Robinson; Robinson *J. Chem. Soc.* **1918,** *113,* 639.

There is much evidence for this mechanism, e.g., (1) the isolation of **131**,[527] (2) the detection of **130** by ^{13}C and ^{15}N nmr,[528] (3) the isolation of side products that could only have come from **129**,[529] and (4) ^{15}N labeling experiments that showed that it was the nitrogen farther from the ring that is eliminated as ammonia.[530] The main function of the catalyst seems to be to speed the conversion of **127** to **128**. The reaction can be performed without a catalyst.

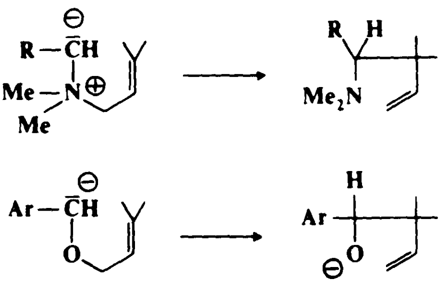
OS **III**, 725; **IV**, 884. Also see OS **IV**, 657.

8-37 [2,3] Sigmatropic Rearrangements

(2/*S*-3/)→(1/5/)-*sigma*-Migration



Sulfur ylides bearing an allylic group are converted on heating to unsaturated sulfides.[531] This is a concerted [2,3] sigmatropic rearrangement[532] and has also been demonstrated for the analogous cases of nitrogen ylides[533] and the conjugate bases of allylic ethers (in the last



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[527] Southwick; McGrew; Engel; Milliman; Owellen *J. Org. Chem.* **1963,** *28,* 3058; Southwick; Vida; Fitzgerald; Lee *J. Org. Chem.* **1968,** *33,* 2051; Forrest; Chen *J. Chem. Soc., Chem. Commun.* **1972,** 1067.

[528] Douglas *J. Am. Chem. Soc.* **1978,** *100,* 6463, **1979,** *101,* 5676.

[529] Robinson; Brown *Can. J. Chem.* **1964,** *42,* 1940; Bajwa; Brown *Can J. Chem.* **1968,** *46,* 1927, 3105, **1969,** *47,* 785, **1970,** *48,* 2293.

[530] Clausius; Weisser *Helv. Chim. Acta* **1952,** *35,* 400.

[531] For example, see Blackburn; Ollis; Plackett; Smith; Sutherland; *Chem. Commun.* **1968,** 186; Trost; LaRochelle *Tetrahedron Lett.* **1968,** 3327; Baldwin; Hackler; Kelly *Chem. Commun.* **1968,** 537, 538, 1083; Bates; Feld *Tetrahedron Lett.* **1968,** 417; Kirmse; Kapps *Chem. Ber.* **1968,** *101,* 994, 1004; Biellmann; Ducep *Tetrahedron Lett.* **1971,** 33; Ceré; Paolucci; Pollicino; Sandri; Fava *J. Org. Chem.* **1981,** *46,* 3315; Kido; Sinha; Abiko; Yoshikoshi *Tetrahedron Lett.* **1989,** *30,* 1575. For a review as applied to ring expansions, see Vedejs *Acc. Chem. Res.* **1984,** *17,* 358-364.

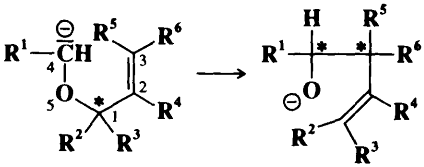
[532] For a review of the stereochemistry of these reactions, see Hoffmann *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 563-572 [*Angew. Chem. 91,* 625-634].

[533] For example, see Jemison; Ollis *Chem. Commun.* **1969,** 294; Rautenstrauch *Helv. Chim. Acta* **1972,** *55,* 2233; Mageswaran; Ollis; Sutherland; Thebtaranonth *J. Chem. Soc., Chem. Commun.* **1973,** 651; Ollis; Sutherland; Thebtaranonth *J. Chem. Soc., Chem. Commun.* **1973,** 657; Mander; Turner *J. Org. Chem.* **1973,** *38,* 2915; Stévenart-De Mesmaeker; Merényi; Viehe *Tetrahedron Lett.* **1987,** *28,* 2591; Honda; Inoue; Sato *J. Am. Chem. Soc.* **1990,** *112,* 1999.

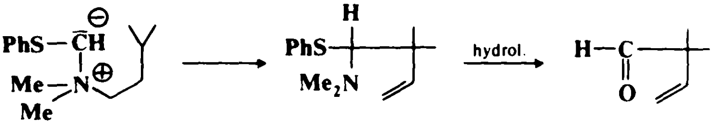
case it is called the [2,3] *Wittig rearrangement*).[534] The reaction has been extended to certain other systems,[535] even to an all-carbon system.[536]

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 (**8-22, 8-23**). However, in this case the migrating group *must* be allylic (in **8-22** and **8-23** other groups can also migrate). Thus, when the migrating group is allylic, there are two possible pathways: (1) the radical-ion or ion-pair mechanisms (**8-22, 8-23**) 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 these reactions, the [2,3] Wittig rearrangement in particular has often been used as a means of transferring chirality. The product of this reaction has potential chiral centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a chiral center at C-1, the product may be optically active as well. Many examples are known in which an optically active ether was converted to a product that was optically active because of chirality at C-3, C-4, or both.[537] If a suitable chiral center is present in R^1 (or if a functional group in R^1 can be so converted), then stereocontrol over three contiguous chiral centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.



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.[538]



Another [2,3] sigmatropic rearrangement converts allylic sulfoxides to allylically rearranged alcohols by treatment with a thiophilic reagent such as trimethyl phosphite.[539] In this

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[534] See, for example, Makisumi; Notzumoto *Tetrahedron Lett.* **1966**, 6393; Schöllkopf; Fellenberger; Rizk *Liebigs Ann. Chem.* **1970**, *734*, 106; Rautenstrauch *Chem. Commun.* **1970**, 4. For a review, see Nakai; Mikami *Chem. Rev.* **1986**, *86*, 885-902. For a list of references, see Ref. 106, pp. 521-522.

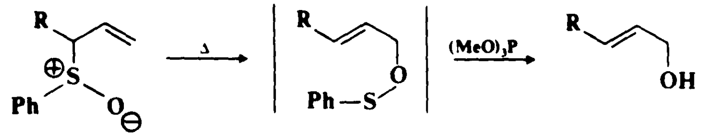
[535] See, for example, Baldwin; Brown; Höfle *J. Am. Chem. Soc.* **1971**, *93*, 788; Yamamoto; Oda; Inouye *J. Chem. Soc., Chem. Commun.* **1973**, 848; Ranganathan; Ranganathan; Sidhu; Mehrotra *Tetrahedron Lett.* **1973**, 3577; Murata; Nakai *Chem. Lett.* **1990**, 2069. For reviews with respect to selenium compounds, see Reich, in Liotta *Organoselenium Chemistry*; Wiley: New York, 1987, pp. 365-393; Reich, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 102-111.

[536] Baldwin; Urban *Chem. Commun.* **1970**, 165.

[537] For reviews of stereochemistry in this reaction, see Mikami; Nakai *Synthesis* **1991**, 594-604; Nakai; Mikami, Ref. 534, pp. 888-895. See also Nakai; Nakai *Tetrahedron Lett.* **1988**, *29*, 4587; Balestra; Kallmerten *Tetrahedron Lett.* **1988**, *29*, 6901; Brückner *Chem. Ber.* **1989**, *122*, 193, 703; Scheuplein; Kusche; Brückner; Harms *Chem. Ber.* **1990**, *123*, 917; Wu; Houk; Marshall *J. Org. Chem.* **1990**, *55*, 1421; Marshall; Wang *J. Org. Chem.* **1990**, *55*, 2995.

[538] Huynh; Julia; Lorne; Michelot *Bull. Soc. Chim. Fr.* **1972**, 4057.

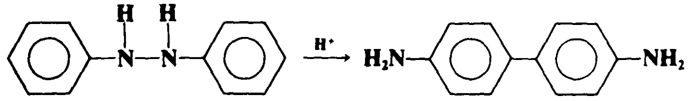
[539] Bickart; Carson; Jacobus; Miller; Mislow *J. Am. Chem. Soc.* **1968**, *90*, 4869; Tang; Mislow *J. Am. Chem. Soc.* **1970**, *92*, 2100; Grieco *J. Chem. Soc., Chem. Commun.* **1972**, 702; Evans; Andrews *Acc. Chem. Res.* **1974**, *7*, 147-155; Isobe; Iio; Kitamura; Goto *Chem. Lett.* **1978**, 541; Hoffmann; Goldmann; Maak; Gerlach; Frickel; Steinbach *Chem. Ber.* **1980**, *113*, 819; Sato; Otera; Nozaki *J. Org. Chem.* **1989**, *54*, 2779.



case the migration is from sulfur to oxygen. [2,3] oxygen-to-sulfur migrations are also known.[540] The Sommelet–Hauser rearrangement (**3-26**) is also a [2,3] sigmatropic arrangement.

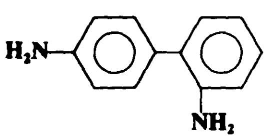
OS **65**, 159.

8-38 The **Benzidine Rearrangement**



Hydrazobenzene **132**

When hydrazobenzene is treated with acids, it rearranges to give about 70% 4,4′-diaminobiphenyl (**132**, benzidine) and about 30% 2,4′-diaminobiphenyl (**133**). This reaction is called the *benzidine rearrangement* and is general for N,N′-diarylhydrazines.[541] Usually, the major product is the 4,4′-diaminobiaryl, but four other products may also be produced. These are the 2,4′-diaminobiaryl (**133**), already referred to, the 2,2′-diaminobiaryl (**134**), and the *o*- and *p*-arylaminoanilines (**135** and **136**), called *semidines*. The **134** and **136** compounds 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 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*′-$PhC_6H_4NHNHC_6H_4Ph$ gives 88% disproportionation products at 25°C.[542]



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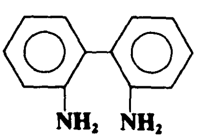

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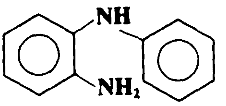

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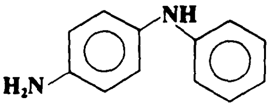

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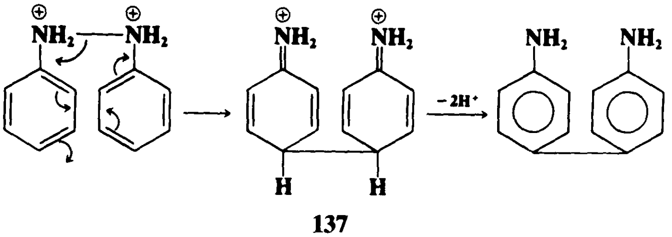
[540] Braverman; Mechoulam *Isr. J. Chem.* **1967,** *5*, 71, Braverman; Stabinsky *Chem. Commun.* **1967,** 270; Rautenstrauch *Chem. Commun.* **1970,** 526; Smith; Stirling *J. Chem. Soc. C* **1971,** 1530; Tamaru; Nagao; Bando; Yoshida *J. Org. Chem.* **1990,** *55*, 1823.

[541] For reviews, see, in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 2; Wiley: New York, 1975, the reviews by Cox; Buncel, pp. 775-807; Koga; Koga; Anselme, pp. 914-921; Williams, in Bamford; Tipper, Ref. 365, vol. 13, 1972, pp. 437-448; Shine *Mech. Mol. Migr.* **1969,** *2*, 191-247, *Aromatic Rearrangements*, Ref. 489, pp. 126-179; Banthorpe *Top. Carbocyclic Chem.* **1969,** *1*, 1-62; Lukashevich *Russ. Chem. Rev.* **1967,** *36*, 895-902.

[542] Shine; Stanley *J. Org. Chem.* **1967,** *32*, 905. For investigations of the mechanism of the disproportionation reactions, see Shine; Habdas; Kwart; Brechbiel; Horgan; San Filippo *J. Am. Chem. Soc.* **1983,** *105*, 2823; Rhee; Shine *J. Am. Chem. Soc.* **1986,** *108*, 1000, **1987,** *109*, 5052.

The mechanism has been exhaustively studied and several mechanisms have been proposed.[543] At one time it was believed that NHAr broke away from ArNHNHAr and became attached to the para position to give the semidine (**136**), 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 (**1-32** to **1-36**). 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 radicals) has been ruled out by many types of crossover experiments, which always showed 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 can be either first[544] or second[545] order in $[H^+]$. 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,[546] 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 $\mathrm{Ar\overset{\oplus}{N}H_2\overset{\oplus}{N}H_2Ar}$.

Most of the proposed mechanisms[547] attempted to show how all five products could be produced by variations of a single process. An important breakthrough was the discovery that the two main products, **132** and **133**, are formed in entirely different ways, as shown by isotope-effect studies.[548] When the reaction was run with hydrazobenzene labeled with ^{15}N at both nitrogen atoms, the isotope effect was 1.022 for formation of **132**, but 1.063 for formation of **133**. This showed that the N—N bond is broken in the rate-determining step in both cases, but the steps themselves are obviously different. When the reaction was run with hydrazobenzene labeled with ^{14}C at a para position, there was an isotope effect of 1.028 for formation of **132**, but essentially no isotope effect (1.001) for formation of **133**. This can only mean that for **132** formation of the new C—C bond *and* breaking of the N—N bond both take place in the rate-determining step; in other words, the mechanism is concerted. The following [5.5] sigmatropic rearrangement accounts for this:[549]



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[543] For a history of the mechanistic investigations and controversies, see Shine *J. Phys. Org. Chem.* **1989,** *2*, 491.

[544] Banthorpe; Hughes; Ingold *J. Chem. Soc.* **1962,** 2386, 2402, 2407, 2413, 2418, 2429; Shine; Chamness *J. Org. Chem.* **1963,** *28*, 1232; Banthorpe; O'Sullivan *J. Chem. Soc. B* **1968,** 627.

[545] Hammond; Shine *J. Am. Chem. Soc.* **1950,** *72*, 220; Banthorpe; Cooper *J. Chem. Soc. B* **1968,** 618; Banthorpe; Cooper; O'Sullivan *J. Chem. Soc. B* **1971,** 2054.

[546] Carlin; Odioso *J. Am. Chem. Soc.* **1954,** *76*, 100; Banthorpe; Ingold; Roy *J. Chem. Soc. B* **1968,** 64; Banthorpe; Ingold; O'Sullivan *J. Chem. Soc. B* **1968,** 624.

[547] For example, see the "polar-transition-state mechanism:" Banthorpe, Hughes; Ingold *J. Chem. Soc.* **1964,** 2864, and the "π-complex mechanism:" Dewar, in Mayo, Ref. 114, vol. 1, pp. 323-344.

[548] Shine; Zmuda; Park; Kwart; Horgan; Collins; Maxwell *J. Am. Chem. Soc.* **1981,** *103*, 955; Shine; Zmuda; Park; Kwart; Horgan; Brechbiel *J. Am. Chem. Soc.* **1982,** *104*, 2501.

[549] This step was also part of the "polar-transition-state mechanism"; see Ref. 547.

The diion **137** was obtained as a stable species in super-acid solution at −78°C by treatment of hydrazobenzene with FSO_3H–SO_2 (SO_2ClF).[550] Though the results just given were obtained with hydrazobenzene, which reacts by the diprotonated pathway, monoprotonated substrates have been found to react by the same [5,5] sigmatropic mechanism.[551] Some of the other rearrangements in this section are also sigmatropic. Thus, formation of the *p*-semidine **136** takes place by a [1,5] sigmatropic rearrangement,[552] and the conversion of 2,2′-hydrazonaphthalene to 2,2′-diamino-1,1′-binaphthyl by a [3,3] sigmatropic rearrangement.[553]

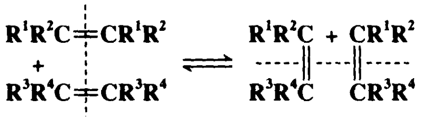
133 is formed by a completely different mechanism, though the details are not known. There is rate-determining breaking of the N—N bond, but the C—C bond is not formed during this step.[554] The formation of the *o*-semidine **135** also takes place by a nonconcerted pathway.[555] Under certain conditions, benzidine rearrangements have been found to go through radical cations.[556]

C. Other Cyclic Rearrangements

8-39 Metathesis of Olefins
Alkene metathesis

$$CH_3CH{=}CHCH_2CH_3 \xrightarrow[WCl_6-EtOH]{EtAlCl_2} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CHCH_2CH_3$$

When olefins are treated with certain catalysts (most often tungsten, molybdenum, or rhenium 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:



$$\begin{matrix} R^1R^2C{=}CR^1R^2 & & R^1R^2C & + & CR^1R^2 \\ + & \rightleftharpoons & \| & & \| \\ R^3R^4C{=}CR^3R^4 & & R^3R^4C & & CR^3R^4 \end{matrix}$$

The reaction is called *metathesis* of olefins.[557] 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.[558] In general, the

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[550] Olah; Dunne; Kelly; Mo *J. Am. Chem. Soc.* **1972,** *94,* 7438.

[551] Shine; Park; Brownawell; San Filippo *J. Am. Chem. Soc.* **1984,** *106,* 7077.

[552] Heesing; Schinke *Chem. Ber.* **1977,** *110,* 3319; Shine; Zmuda; Kwart; Horgan; Brechbiel *J. Am. Chem. Soc.* **1982,** *104,* 5181.

[553] Shine; Gruszecka; Subotkowski; Brownawell; San Filippo *J. Am. Chem. Soc.* **1985,** *107,* 3218.

[554] See Rhee; Shine, Ref. 542.

[555] Rhee; Shine *J. Org. Chem.* **1987,** *52,* 5633.

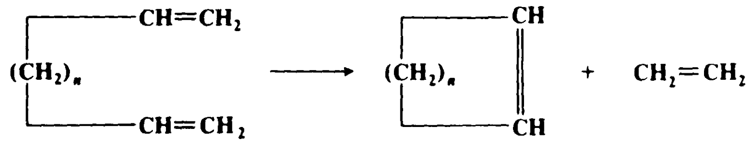
[556] See, for example, Nojima; Ando; Tokura *J. Chem. Soc., Perkin Trans. 1* **1976,** 1504.

[557] For monographs, see Drăguţan; Balaban; Dimonie *Olefin Metathesis and Ring-Opening Polymerization of Cyclo-Olefins*; Wiley: New York, 1985; Ivin *Olefin Metathesis*; Academic Press: New York, 1983. For reviews, see Feast; Gibson, in Hartley, Ref. 313, vol. 5, 1989, pp. 199-228; Streck *CHEMTECH* **1989,** 498-503; Schrock *J. Organomet. Chem.* **1986,** *300,* 249-262; Grubbs, in Wilkinson *Comprehensive Organometallic Chemistry*, vol. 8; Pergamon: Elmsford, NY, 1982, pp. 499-551; Basset; Leconte, *CHEMTECH* **1980,** 762-767; Banks, *CHEMTECH* **1979,** 494-500, *Fortschr. Chem. Forsch.* **1972,** *25,* 39-69; Calderon; Lawrence; Ofstead *Adv. Organomet. Chem.* **1979,** *17,* 449-492; Grubbs *Prog. Inorg. Chem.* **1978,** *24,* 1-50; Calderon, in Patai *The Chemistry of Functional Groups: Supplement A*, pt. 2; Wiley: New York, 1977, pp. 913-964, *Acc. Chem. Res.* **1972,** *5,* 127-132; Katz *Adv. Organomet. Chem.* **1977,** *16,* 283-317; Haines; Leigh *Chem. Soc. Rev.* **1975,** *4,* 155-188; Hocks *Bull. Soc. Chim. Fr.* **1975,** 1893-1903; Mol; Moulijn *Adv. Catal.* **1974,** *24,* 131-171; Hughes *Organomet. Chem. Synth.* **1972,** *1,* 341-374; Khidekel′, Shebaldova; Kalechits *Russ. Chem. Rev.* **1971,** *40,* 669-678; Bailey, *Catal. Rev.* **1969,** *3,* 37-60.

[558] Calderon; Chen; Scott *Tetrahedron Lett.* **1967,** 3327; Wang; Menapace *J. Org. Chem.* **1968,** *33,* 3794; Hughes *J. Am. Chem. Soc.* **1970,** *92,* 532.

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 ten olefins: the original two plus eight new ones. With simple alkenes the proportions of products are generally statistical,[559] 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%.[560]

Many catalysts, both homogeneous[561] and heterogeneous,[562] have been used for this reaction. Some of the former[563] are WCl_6-EtOH-$EtAlCl_2$,[559] $MoCl_2(NO)_2(Ph_3P)_2$-$EtAlCl_2$,[564] WCl_6-BuLi,[565] and WCl_6-$LiAlH_4$,[566] while among the latter are oxides of Mo, W, and Re deposited on alumina or silica gel.[567] 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 $CH_2{=} > RCH_2CH{=} > R_2CHCH{=} > R_2C{=}$.[568] Dienes can react intermolecularly or intramolecularly,[569] e.g.,



Cyclic olefins give dimeric dienes,[570] 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.

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[559] Calderon; Ofstead; Ward; Judy; Scott *J. Am. Chem. Soc.* **1968,** *90,* 4133.

[560] Knoche, Ger. Pat.(Offen.) 2024835, 1970 [*Chem. Abstr.* **1971,** *74,* 44118b]. See also Chevalier; Sinou; Descotes *Bull. Soc. Chim. Fr.* **1976,** 2254; Bespalova; Babich; Vdovin; Nametkin *Doklad. Chem.* **1975,** *225,* 668; Ichikawa; Fukuzumi *J. Org. Chem.* **1976,** *41,* 2633; Baker; Crimmin *Tetrahedron Lett* **1977,** 441.

[561] First reported by Calderon; Chen; Scott, Ref. 558.

[562] First reported by Banks; Bailey *Ind. Eng. Chem., Prod. Res. Dev.* **1964,** *3,* 170. See also Banks *CHEMTECH* **1986,** 112-117.

[563] For a lengthy list, see Hughes *Organomet. Chem. Synth.*, Ref. 557, pp. 362-368. For a homogeneous rhenium catalyst, see Toreki; Schrock *J. Am. Chem. Soc.* **1990,** *112,* 2448.

[564] Zuech; Hughes; Kubicek; Kittleman *J. Am. Chem. Soc.* **1970,** *92,* 528; Hughes, Ref. 558.

[565] Wang; Menapace, Ref. 558.

[566] Chatt; Haines; Leigh *J. Chem. Soc., Chem. Commun.* **1972,** 1202; Matlin; Sammes *J. Chem. Soc., Perkin Trans. 1* **1978,** 624.

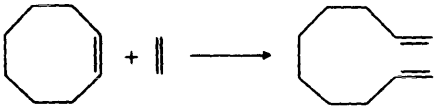
[567] For a list of heterogeneous catalysts, see Banks, *Fortschr. Chem. Forsch.*, Ref. 557, pp. 41-46.

[568] For an explanation for this order, see McGinnis; Katz; Hurwitz *J. Am. Chem. Soc.* **1976,** *98,* 605; Casey; Tuinstra; Saeman *J. Am. Chem. Soc.* **1976,** *98,* 608.

[569] Kroll; Doyle *Chem. Commun.* **1971,** 839; Zuech et al., Ref. 564.

[570] Calderon; Ofstead; Judy *J. Polym. Sci., Part A-1* **1967,** *5,* 2209; Wasserman; Ben-Efraim; Wolovsky *J. Am. Chem. Soc.* **1968,** *90,* 3286; Wolovsky; Nir *Synthesis* **1972,** 134.

The reaction between a cyclic and a linear olefin can give an ring-opened diene:[571]



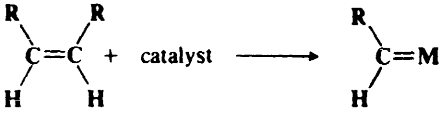
Olefins containing functional groups[572] do not give the reaction with most of the common catalysts, but some success has been reported with WCl_6–$SnMe_4$[573] and with certain other catalysts.

The reaction has also been applied to internal triple bonds:[574]

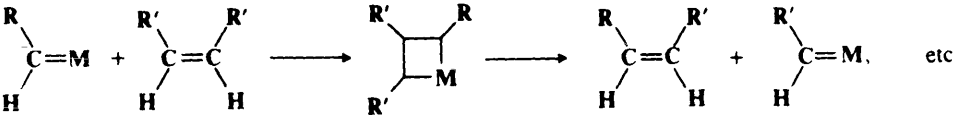
$$2RC{\equiv}CR' \rightleftharpoons RC{\equiv}CR + R'C{\equiv}CR'$$

but it has not been successful for terminal triple bonds.[575] An intramolecular reaction of a double bond with a triple bond has been reported.[576]

The generally accepted mechanism is a chain mechanism, involving the intervention of a metal-carbene complex (**138**)[577] and a four-membered ring containing a metal[578] (**139**).[579]



138



138 **139**

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[571] Wasserman; Ben-Efraim; Wolovsky, Ref. 570; Ray; Crain, Fr. Pat. 1511381, 1968 [*Chem. Abstr.* **1969**, *70*, 114580q]; Mango, U.S. Pat. 3424811, 1969 [*Chem. Abstr.* **1969**, *70*, 106042a]; Rossi; Diversi; Lucherini; Porri *Tetrahedron Lett.* **1974**, 879; Lal; Smith *J. Org. Chem.* **1975**, *40*, 775.

[572] For a review, see Mol *CHEMTECH* **1983**, 250-255. See also Bosma; van den Aardweg; Mol *J. Organomet. Chem.* **1983**, *255*, 159, **1985**, *280*, 115; Xiaoding; Mol *J. Chem. Soc., Chem. Commun.* **1985**, 631; Crisp; Collis *Aust. J. Chem.* **1988**, *41*, 935.

[573] First shown by van Dam; Mittelmeijer; Boelhouwer *J. Chem. Soc., Chem. Commun.* **1972**, 1221.

[574] Pennella; Banks; Bailey *Chem. Commun.* **1968**, 1548; Mortreux; Petit; Blanchard *Tetrahedron Lett.* **1978**, 4967; Devarajan; Walton; Leigh *J. Organomet. Chem.* **1979**, *181*, 99; Wengrovius; Sancho; Schrock *J. Am. Chem. Soc.* **1981**, *103*, 3932; Villemin; Cadiot *Tetrahedorn Lett.* **1982**, *23*, 5139; McCullough; Schrock *J. Am. Chem. Soc.* **1984**, *106*, 4067.

[575] McCullough; Listemann; Schrock; Churchill; Ziller *J. Am. Chem. Soc.* **1983**, *105*, 6729.

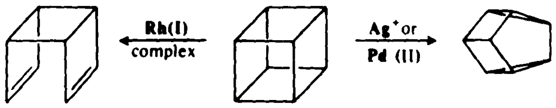
[576] Trost; Trost *J. Am. Chem. Soc.* **1991**, *113*, 1850.

[577] For a review of these complexes and their role in this reaction, see Crabtree *The Organometallic Chemistry of the Transition Metals*; Wiley: New York, 1988, pp. 244-267.

[578] For reviews of metallocycles, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, CA; 1987, pp. 459-520; Lindner *Adv. Heterocycl. Chem.* **1986**, *39*, 237-279.

[579] For reviews of the mechanism, see Grubbs, *Prog. Inorg. Chem.*, Ref. 557; Katz, Ref. 557; Calderon; Ofstead; Judy *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 401-409 [*Angew. Chem.* *88*, 443-442]. See also McLain; Wood; Schrock *J. Am. Chem. Soc.* **1977**, *99*, 3519; Casey; Polichnowski *J. Am.Chem. Soc.* **1977**, *99*, 6097; Mango *J. Am. Chem. Soc.* **1977**, *99*, 6117; Stevens; Beauchamp *J. Am. Chem. Soc.* **1979**, *101*, 6449; Lee; Ott; Grubbs *J. Am. Chem. Soc.* **1982**, *104*, 7491; Levisalles; Rudler; Villemin *J. Organomet. Chem.* **1980**, *193*, 235; Iwasawa; Hamamura *J. Chem. Soc., Chem. Commun.* **1983**, 130; Rappé; Upton *Organometallics* **1984**, *3*, 1440; Kress; Osborn; Greene; Ivin; Rooney *J. Am. Chem. Soc.* **1987**, *109*, 899; Feldman; Davis; Schrock *Organometallics* **1989**, *8*, 2266.

8-40 Metal-Ion-Catalyzed σ-Bond Rearrangements



140 **Cubane** **Cuneane**

Many highly strained cage molecules undergo rearrangement when treated with metallic ions such as Ag$^+$, Rh(I), or Pd(II).[580] The bond rearrangements observed can be formally classified into two main types: (1) 2 + 2 ring openings of cyclobutanes and (2) conversion

Type 1 **Type 2**

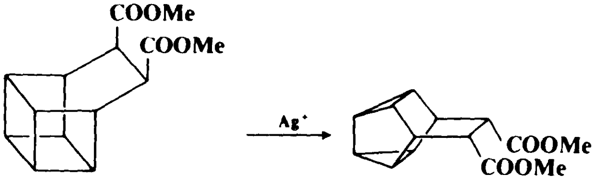
of a bicyclo[2.2.0] system to a bicyclopropyl system. The molecule cubane supplies an example of each type (see above). Treatment with Rh(I) complexes converts cubane to tricyclo[4.2.0.0^{2,5}]octa-3,7-diene (**140**),[581] an example of type 1, while Ag$^+$ or Pd(II) causes the second type of reaction, producing cuneane.[582] Other examples are:

Type 1

Ref. 583

141 **142**

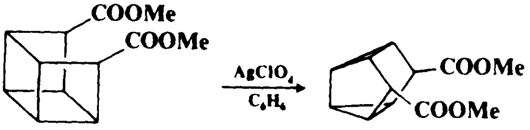
Type 2[584]



143

Ref. 585

Type 2



Ref. 586

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[580] For reviews, see Halpern, in Wender; Pino *Organic Syntheses via Metal Carbonyls*, vol. 2; Wiley: New York, 1977, pp. 705-721; Bishop *Chem. Rev.* **1976,** *76*, 461-486; Cardin; Cetinkaya; Doyle; Lappert *Chem. Soc. Rev.* **1973,** *2*, 99-144, pp. 132-139; Paquette *Synthesis* **1975,** 347-357, *Acc. Chem. Res.* **1971,** *4*, 280-287.

[581] Cassar; Eaton; Halpern *J. Am. Chem. Soc.* **1970,** 92, 3515; Eaton; Chakraborty *J. Am. Chem. Soc.* **1978,** *100*, 3634.

[582] Cassar; Eaton; Halpern *J. Am. Chem. Soc.* **1970,** *92*, 6336.

[583] Paquette; Allen; Henzel *J. Am. Chem. Soc.* **1970,** *92*, 7002; Gassman; Atkins *J. Am. Chem. Soc.* **1971,** *93*, 4579, **1972,** *94*, 7748; Sakai; Westberg; Yamaguchi; Masamune *J. Am. Chem. Soc.* **1972,** *93*, 4611; Paquette; Wilson; Henzel *J. Am. Chem. Soc.* **1972,** *94*, 7771.

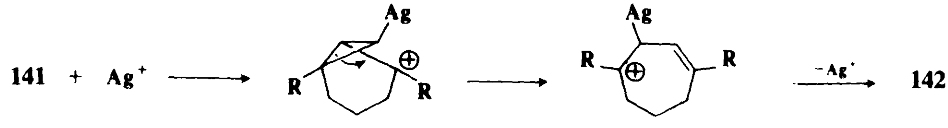
[584] The starting compound here is a derivative of basketane, or 1,8-bishomocubane. For a review of homo-, bishomo-, and trishomocubanes, see Marchand *Chem. Rev.* **1989,** *89*, 1011-1033.

[585] See, for example, Furstoss; Lehn *Bull. Soc. Chim. Fr.* **1966,** 2497; Paquette; Stowell *J. Am. Chem. Soc.* **1970,** *92*, 2584, **1971,** *93*, 2459; Dauben; Kielbania *J. Am. Chem. Soc.* **1971,** *93*, 7345; Paquette; Beckley; Farnham *J. Am. Chem. Soc.* **1975,** *97*, 1089.

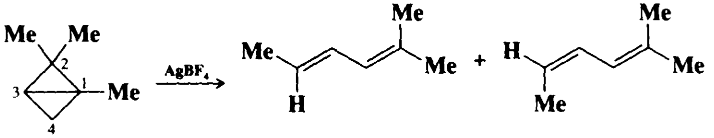
[586] Paquette; Beckley; McCreadie *Tetrahedron Lett.* **1971,** 775; Dauben; Schallhorn; Whalen *J. Am. Chem. Soc.* **1971,** *93*, 1446.

143 is the 9,10-dicarbomethyoxy 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, although 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 **5-49.** The following mechanism, in which Ag^+ attacks one of the edge bonds, has been suggested for the conversion of **141** to **142.**[587]



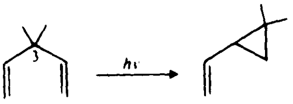
Simpler bicyclobutanes can also be converted to dienes, but in this case the products usually result from cleavage of the central bond and one of the edge bonds.[588] For example, treatment of **144** with $AgBF_4$,[589] $(C_6F_5Cu)_4$,[590] or [(π-allyl)PdCl]$_2$[591] gives a mixture of the two dienes shown, resulting from a formal cleavage of the C_1—C_3 and C_1—C_2 bonds (note that a hydride shift has taken place).



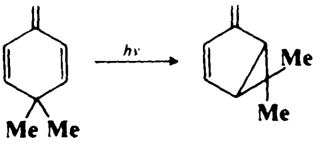
144

8-41 The Di-π-methane and Related Rearrangements

Di-π-methane rearrangement



1,4-Dienes carrying alkyl or aryl substituents on C-3[592] can be photochemically rearranged to vinylcyclopropanes in a reaction called the *di-π-methane rearrangement.*[593] An example is conversion of **145** to **146.**[594] For most 1,4-dienes it is only the singlet excited states that



145 **146**

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[587] Gassman; Atkins, Ref. 583; Sakai et al., Ref. 583.

[588] **141** can also be cleaved in this manner, giving a 3-methylenecyclohexene. See, for example, Gassman; Atkins *J. Am. Chem. Soc.* **1971,** *93,* 1042; Dauben; Kielbania *J. Am. Chem. Soc.* **1972,** *94,* 3669; Gassman; Reitz *J. Am. Chem. Soc.* **1973,** *95,* 3057; Paquette; Zon *J. Am. Chem. Soc.* **1974,** *96,* 203, 224.

[589] Paquette; Henzel; Wilson *J. Am. Chem. Soc.* **1971,** *93,* 2335.

[590] Gassman; Williams *Tetrahedron Lett.* **1971,** 1409.

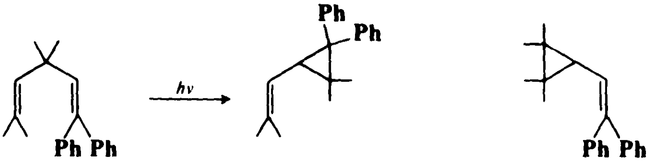
[591] Gassman; Meyer; Williams *Chem. Commun.* **1971,** 842.

[592] Zimmerman; Pincock *J. Am. Chem. Soc.* **1973,** *95,* 2957.

[593] For reviews, see Zimmerman *Org. Photochem.* **1991,** *11,* 1-36; Zimmerman, in Mayo, Ref. 1, vol. 3, pp. 131-166; Hixson; Mariano; Zimmerman *Chem. Rev.* **1973,** *73,* 531-551.

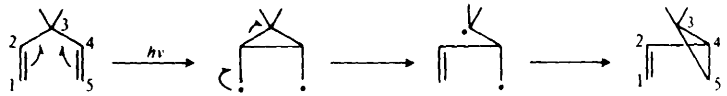
[594] Zimmerman; Hackett; Juers; McCall; Schröder *J. Am. Chem. Soc.* **1971,** *93,* 3653.

give the reaction; triplet states generally take other pathways.[595] For unsymmetrical dienes, the reaction is regioselective. For example, **147** gave **148**, not **149**:[596]



147 **148** **149**
Not formed

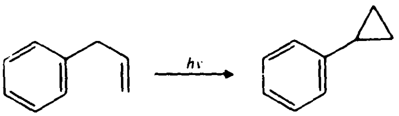
The mechanism can be described by the diradical pathway given[597] (the C-3 substituents act to stabilize the radical), though the species shown are not necessarily intermediates, but

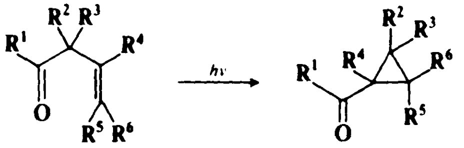


150

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.[598]

The reaction has been extended to allylic benzenes[599] (in this case C-3 substituents are not required), to β,γ-unsaturated ketones[600] (the latter reaction, which is called the *oxa-di-π-methane rearrangement*,[601] generally occurs only from the triplet state), to β,γ-unsaturated imines,[602] and to triple-bond systems.[603]





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[595] However, some substrates, generally rigid bicyclic molecules, (e.g., barrelene, p. 1136, which is converted to semi-bullvalene) give the di-π-methane rearrangement only from triplet states.

[596] Zimmerman; Pratt *J. Am. Chem. Soc.* **1970**, *92*, 6259, 6267; Zimmerman; Baum *J. Am. Chem. Soc.* **1971**, *93*, 3646. See also Zimmerman; Welter *J. Am. Chem. Soc.* **1978**, *100*, 4131; Alexander; Pratt; Rowley; Tipping *J. Chem. Soc., Chem. Commun.* **1978**, 101; Paquette; Bay; Ku; Rondan; Houk *J. Org. Chem.* **1982**, *47*, 422.

[597] See Zimmerman; Werthemann; Kamm *J. Am. Chem. Soc.* **1974**, *96*, 439; Zimmerman; Little *J. Am. Chem. Soc.* **1974**, *96*, 5143; Zimmerman; Boettcher; Buehler; Keck *J. Am. Chem. Soc.* **1975**, *97*, 5635. For an argument against the intermediacy of **150**, see Adam; De Lucchi; Dörr *J. Am. Chem. Soc.* **1989**, *111*, 5209.

[598] Zimmerman; Robbins; McKelvey; Samuel; Sousa *J. Am. Chem. Soc.* **1974**, *96*, 4630.

[599] For example, see Griffin; Covell; Petterson; Dodson; Klose *J. Am. Chem. Soc.* **1965**, *87*, 1410; Hixson *J. Am. Chem. Soc.* **1972**, *94*, 2507; Cookson; Ferreira; Salisbury *J. Chem. Soc., Chem. Commun.* **1974**, 665; Fasel; Hansen *Chimia* **1982**, *36*, 193; Paquette; Bay *J. Am. Chem. Soc.* **1984**, *106*, 6693; Zimmerman; Swafford *J. Org. Chem.* **1984**, *49*, 3069.

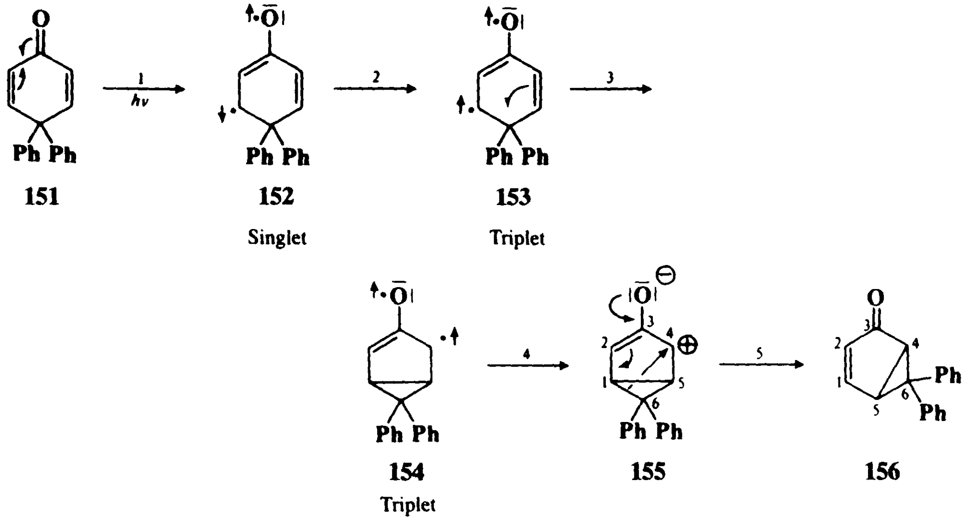
[600] For reviews of photochemical rearrangements of unsaturated ketones, see Schuster, in Mayo, Ref. 1, vol. 3, pp. 167-279; Houk *Chem. Rev.* **1976**, *76*, 1-74; Schaffner *Tetrahedron* **1976**, *32*, 641-653; Dauben; Lodder; Ipaktschi *Top. Curr. Chem.* **1975**, *54*, 73-114.

[601] For a review, see Demuth *Org. Photochem.* **1991**, *11*, 37-109.

[602] See Armesto; Horspool; Langa; Ramos *J. Chem. Soc., Perkin Trans. 1* **1991**, 223.

[603] See Griffin; Chihal; Perreten; Bhacca *J. Org. Chem.* **1976**, *41*, 3931.

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.[604] In this reaction, photolysis of the substrate **151** gives the bicyclo[3.1.0]hexenone **156**. Though the reaction is formally the same (note the conversion of **145** to **146** above), the mechanism is different

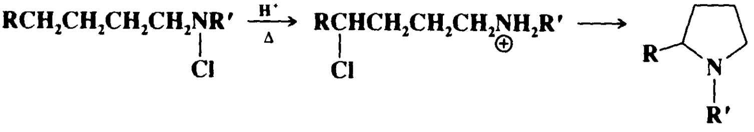


151 **152** Singlet **153** Triplet **154** Triplet **155** **156**

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[605] in this case has been formulated as proceeding through the excited triplet states **153** and **154**. In step 1, the molecule undergoes an $n \rightarrow \pi^*$ excitation to the singlet species **152**, which cross to the triplet **153**. 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. 239). The conversion of **155** to **156** consists of two 1,2 alkyl migrations (a one-step process would be a 1,3 migration of alkyl to a carbocation center, see p. 1062): 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.[606]

2,4-Cyclohexadienones also undergo photochemical rearrangements, but the products are different, generally involving ring opening.[607]

8-42 The Hofmann–Löffler and Related Reactions



$$RCH_2CH_2CH_2CH_2\underset{\displaystyle Cl}{\underset{|}{N}}R' \xrightarrow[\Delta]{H^+} R\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_2CH_2\overset{\oplus}{N}H_2R' \longrightarrow$$

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[604] For reviews of the photochemistry of 2,5-cyclohexadienones and related compounds, see Schaffner; Demuth, in Mayo, Ref. 1, vol. 3, pp. 281-348; Zimmerman *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 1-11 [*Angew. Chem. 81*, 45-55]; Kropp *Org. Photochem.* **1967**, *1*, 1-90; Schaffner *Adv. Photochem.* **1966**, *4*, 81-112. For synthetic use, see Schultz; Lavieri; Macielag; Plummer *J. Am. Chem. Soc.* **1987**, *109*, 3991, and references cited therein.

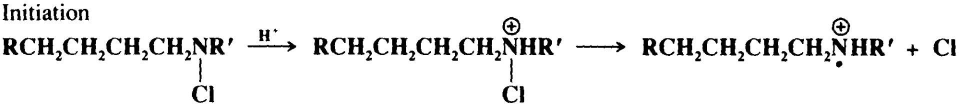
[605] Zimmerman; Schuster *J. Am. Chem. Soc.* **1961**, *83*, 4486; Schuster; Patel *J. Am. Chem. Soc.* **1968**, *90*, 5145; Schuster *Acc. Chem. Res.* **1978**, *11*, 65-73; Zimmerman; Pasteris *J. Org. Chem.* **1980**, *45*, 4864, 4876; Schuster; Liu *Tetrahedron* **1981**, *37*, 3329.

[606] Zimmerman; Crumine; Döpp; Huyffer *J. Am. Chem. Soc.* **1969**, *91*, 434.

[607] For reviews, see Schaffner; Demuth, Ref. 604; Quinkert *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 1072-1087 [*Angew. Chem. 84*, 1157-1173]; Kropp, Ref. 604.

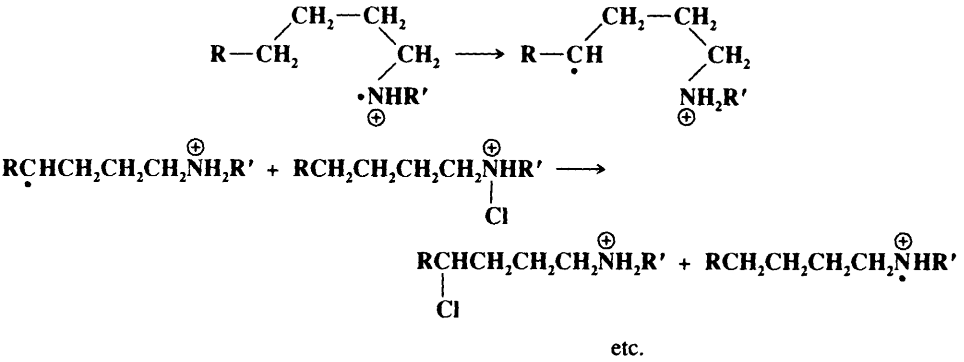
A common feature of the reactions in this section[608] is that they serve to introduce functionality at a position remote from functional groups already present. As such, they have proved very useful in synthesizing many compounds, especially in the steroid field (see also **9-2** and **9-16**). When 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*).[609] R′ is normally alkyl, but the reaction has been extended to R′ = H by the use of concentrated sulfuric acid solution and ferrous salts.[610] 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 (**0-43**), 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.[611]

Initiation

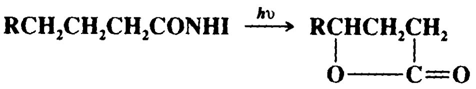


$$RCH_2CH_2CH_2CH_2\underset{\displaystyle Cl}{N}R' \xrightarrow{H^+} RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\displaystyle Cl}{N}}HR' \longrightarrow RCH_2CH_2CH_2CH_2\overset{\oplus}{\underset{\bullet}{N}}HR' + Cl\bullet$$

Propagation



A similar reaction has been carried out on N-halo amides, which give γ-lactones:[612]



$$RCH_2CH_2CH_2CONHI \xrightarrow{h\nu} \begin{array}{l} R\underset{|}{C}HCH_2\underset{|}{C}H_2 \\ \;O\text{——}C{=}O \end{array}$$

Another related reaction is the *Barton Reaction*,[613] by which a methyl group in the δ position to an OH group can be oxidized to a CHO group. The alcohol is first converted

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[608] For a review of the reactions in this section, see Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986, pp. 263-279.

[609] For reviews, see Stella *Angew. Chem. Int. Ed. Engl.* **1983,** *22*, 337-350 [*Angew. Chem.* *95*, 368-380]; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972,** *4*, 203-284, pp. 249-259; Deno *Methods Free-Radical Chem.* **1972,** *3*, 135-154, pp. 136-143.

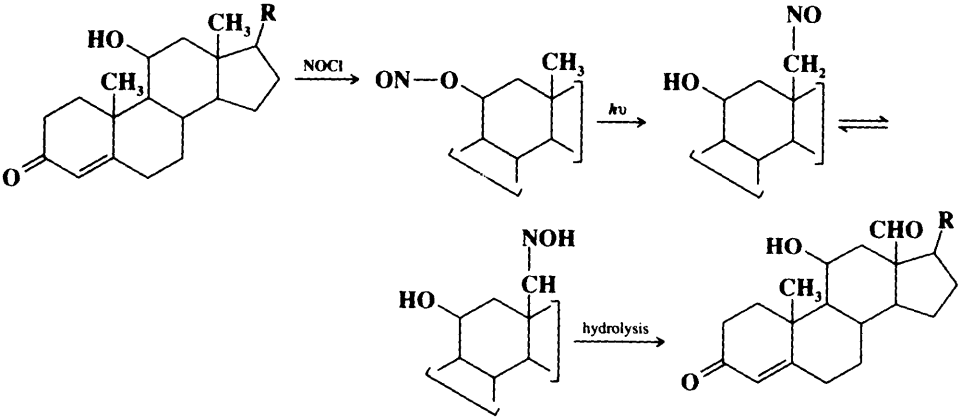
[610] Schmitz; Murawski *Chem. Ber.* **1966,** *99*, 1493.

[611] Wawzonek; Thelan *J. Am. Chem. Soc.* **1950,** *72*, 2118.

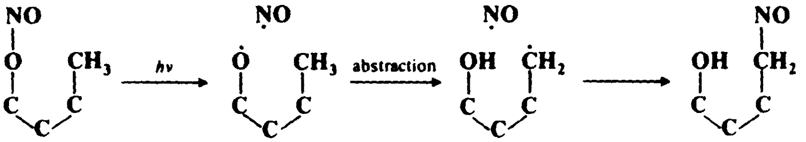
[612] Barton; Beckwith; Goosen *J. Chem. Soc.* **1965,** 181; Petterson; Wambsgans *J. Am. Chem. Soc.* **1964,** *86*, 1648; Neale; Marcus; Schepers *J. Am. Chem. Soc.* **1966,** *88*, 3051. For a review of N-halo amide rearrangements, see Neale *Synthesis* **1971,** 1-15.

[613] For reviews, see Hesse *Adv. Free-Radical Chem.* **1969,** *3*, 83-137; Barton *Pure Appl. Chem.* **1968,** *16*, 1-15.

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.,[614]



This reaction takes place only when the methyl group is in a favorable steric position.[615] The mechanism is similar to that of the Hofmann–Löffler reaction.[616]

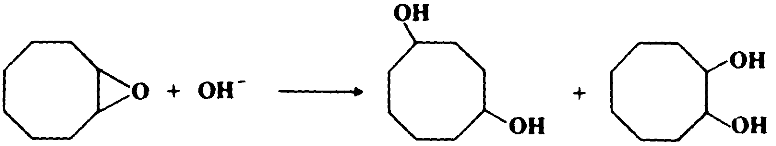


This is one of the few known methods for effecting substitution at an angular methyl group. Not only CH_3 groups but also alkyl groups of the form RCH_2 and R_2CH can give the Barton reaction if the geometry of the system is favorable. An RCH_2 group is converted to the oxime R(C═NOH) (which is hydrolyzable to a ketone) or to a nitroso dimer, while an R_2CH group gives a nitroso compound $R_2C(NO)$. With very few exceptions, the only carbons that 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.[617]

OS **III,** 159.

D. Noncyclic Rearrangements

8-43 Hydride Shifts



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[614] Barton; Beaton *J. Am. Chem. Soc.* **1961,** *83*, 4083. Also see Barton; Beaton; Geller; Pecket *J. Am. Chem. Soc.* **1960,** *82*, 2640.

[615] For a discussion of which positions are favorable, see Burke; Silks; Strickland *Tetrahedron Lett.* **1988,** *29*, 2761.

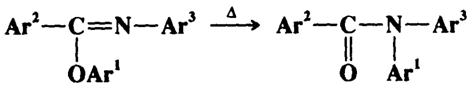
[616] Kabasakalian; Townley *J. Am. Chem. Soc.* **1962,** *84*, 2711; Akhtar; Barton; Sammes *J. Am. Chem. Soc.* **1965,** *87*, 4601. See also Nickon; Ferguson; Bosch; Iwadare *J. Am. Chem. Soc.* **1977,** *99*, 4518; Barton; Hesse; Pechet; Smith *J. Chem. Soc., Perkin Trans. 1* **1979,** 1159; Green; Boyle; Vairamani; Mukhopadhyay; Saunders; Bowen; Allinger *J. Am. Chem. Soc.* **1986,** *108*, 2381.

[617] For a discussion, see Nickon et al., Ref. 616.

The above is a typical example of a transannular hydride shift. The 1,2-diol is formed by a normal epoxide hydrolysis reaction (**0-7**). For a discussion of 1,3 and longer hydride shifts, see p. 1062.

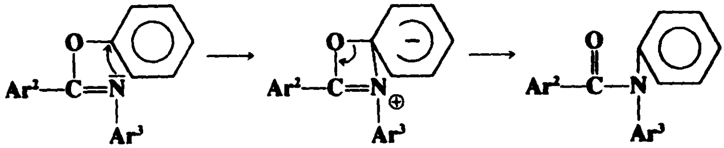
8-44 The Chapman Rearrangement

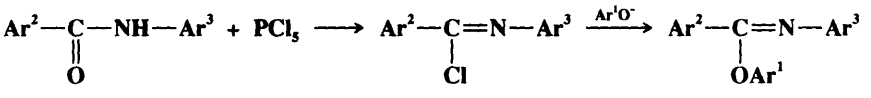
1/*O*→3/*N*-Aryl-migration



$$Ar^2-\underset{\displaystyle OAr^1}{\underset{|}{C}}=N-Ar^3 \xrightarrow{\Delta} Ar^2-\underset{\displaystyle O}{\underset{\|}{C}}-\underset{\displaystyle Ar^1}{\underset{|}{N}}-Ar^3$$

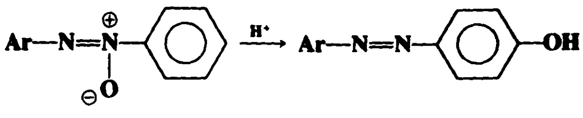
In the *Chapman rearrangement*, N,N-diaryl amides are formed when aryl imino esters are heated.[618] Best yields are obtained in refluxing tetraethylene glycol dimethyl ether (tetraglyme),[619] though the reaction can also be carried out without any solvent at all. Many groups may be present in the rings, e.g., 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 can be hydrolyzed to diarylamines, and this is a method for preparing these compounds. The mechanism probably involves an intramolecular[620] aromatic nucleophilic substitution, resulting in a 1,3 oxygen-to-nitrogen shift. Aryl 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.[621] 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.[622] The mechanism is different, involving an intermolecular process.[623] This is also true for derivatives for formamide (Ar^2 = H).





$$Ar^2-\underset{\displaystyle O}{\underset{\|}{C}}-NH-Ar^3 + PCl_5 \longrightarrow Ar^2-\underset{\displaystyle Cl}{\underset{|}{C}}=N-Ar^3 \xrightarrow{Ar^1O^-} Ar^2-\underset{\displaystyle OAr^1}{\underset{|}{C}}=N-Ar^3$$

8-45 The Wallach Rearrangement



157 **158**

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[618] For reviews, see Schulenberg; Archer *Org. React.* **1965,** *14,* 1-51; McCarty, in Patai, Ref. 237, pp. 439-447; McCarty; Garner, in Patai *The Chemistry of Amidines and Imidates*; Wiley: New York, 1975, pp. 189-240. For a review of 1,3 migrations of R in general, see Landis *Mech. Mol. Migr.* **1969,** *2,* 43-63.

[619] Wheeler; Roman; Santiago; Quiles *Can. J. Chem.* **1969,** *47,* 503.

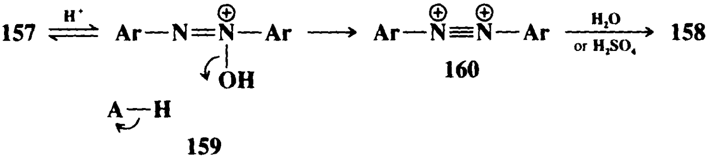
[620] For evidence for the intramolecular character of the reaction, see Wiberg; Rowland *J. Am. Chem. Soc.* **1955,** *77,* 2205; Wheeler; Roman; Rosado *J. Org. Chem.* **1969,** *34,* 966; Kimura *J. Chem. Soc., Perkin Trans. 2* **1987,** 205.

[621] For a review of the formation and reactions of imino chlorides, see Bonnett, in Patai, Ref. 237, pp. 597-662.

[622] Landis, Ref. 618.

[623] See Challis; Frenkel *J. Chem. Soc., Perkin Trans. 2* **1978,** 192.

The conversion of azoxy compounds, on acid treatment, to *p*-hydroxy azo compounds (or sometimes the *o*-hydroxy isomers[624]) is called the *Wallach rearrangement*.[625] When both para positions are occupied, the *o*-hydroxy product may be obtained, but ipso substitution at one of the para positions is also possible.[626] Although the mechanism[627] is not completely settled, the following facts are known: (1) The para rearrangement is intermolecular.[628] (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,[629] 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.[630] The following mechanism,[631] involving the symmetrical intermediate **160**, has been proposed to explain the facts.[632]

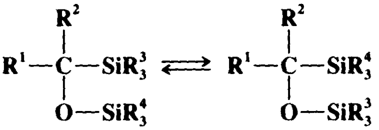


It has proved possible to obtain **159** and **160** as stable species in super-acid solutions.[550] Another mechanism, involving an intermediate with only one positive charge, has been proposed for certain substrates at low acidities.[633]

A photochemical Wallach rearrangement[634] 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.[635]

8-46 Dyotropic Rearrangements

1/*C*-Trialkylsilyl,2/*O*-trialkylsilyl-interchange



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[624] For example, see Dolenko; Buncel *Can. J. Chem.* **1974,** *52*, 623; Yamamoto; Nishigaki; Umezu; Matsuura *Tetrahedron* **1980,** *36*, 3177.

[625] For reviews, see Buncel *Mech. Mol. Migr.* **1968,** 1, 61-119; Shine *Aromatic Rearrangements*, Ref. 489, pp. 272-284, 357-359; Cox; Buncel, Ref. 541, pp. 808-837.

[626] See, for example, Shimao; Oae *Bull. Chem. Soc. Jpn.* **1983,** *56*, 643.

[627] For reviews, see Furin *Russ. Chem. Rev.* **1987,** *56*, 532-545; Williams; Buncel *Isot. Org. Chem.* **1980,** *5*, 184-197; Buncel *Acc. Chem. Res.* **1975,** *8*, 132-139.

[628] See, for example, Oae; Fukumoto; Yamagami *Bull. Chem. Soc. Jpn.* **1963,** *36*, 601.

[629] Shemyakin; Maimind; Vaichunaite *Chem. Ind. (London)* **1958,** 755, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1960,** 808. Also see Behr; Hendley *J. Org. Chem.* **1966,** *31*, 2715.

[630] Buncel; Lawton *Chem. Ind. (London)* **1963,** 1835; Hahn; Lee; Jaffé *J. Am. Chem. Soc.* **1967,** *89*, 4975; Cox *J. Am. Chem. Soc.* **1974,** *96*, 1059.

[631] Buncel; Lawton *Can. J. Chem.* **1965,** *43*, 862; Buncel; Strachan *Can. J. Chem.* **1970,** *48*, 377; Cox, Ref. 630; Buncel; Keum *J. Chem. Soc., Chem. Commun.* **1983,** 578.

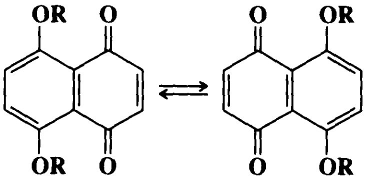
[632] For other proposed mechanisms, see Shemyakin; Maimind; Agadzhanyan *Chem. Ind. (London)* **1961,** 1223; Shemyakin; Agadzhanyan; Maimind; Kudryavtsev *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963,** 1216; Hahn; Lee; Jaffé, Ref. 630; Duffey; Hendley *J. Org. Chem.* **1968,** *33*, 1918; Hendley; Duffey *J. Org. Chem.* **1970,** *35*, 3579.

[633] Cox; Dolenko; Buncel *J. Chem. Soc., Perkin Trans. 2* **1975,** 471; Cox; Buncel *J. Am. Chem. Soc.* **1975,** *97*, 1871.

[634] For a thermal rearrangement (no catalyst), see Shimao; Hashidzume *Bull. Chem. Soc. Jpn.* **1976,** *49*, 754.

[635] For discussions of the mechanism of the photochemical reaction, see Goon; Murray; Schoch; Bunce *Can. J. Chem.* **1973,** *51*, 3827; Squire; Jaffé *J. Am. Chem. Soc.* **1973,** *95*, 8188; Shine; Subotkowski; Gruszecka *Can. J. Chem.* **1986,** *64*, 1108.

A *dyotropic rearrangement*[636] is an uncatalyzed process in which two σ bonds simultaneously migrate intramolecularly.[637] There are two types. The above is an example of Type 1, which consists of reactions in which the two σ bonds interchange positions. In Type 2, the two σ bonds do not interchange positions. An example is

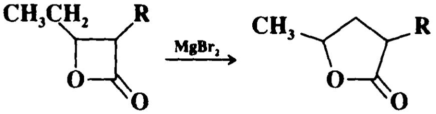


Some other examples are

Type 1 $R{-}C{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{O} \rightleftarrows O{=}C{=}N{-}R$ Ref. 638

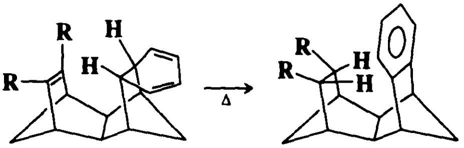
Nitrile oxide Isocyanate

Type 1



Ref. 639

Type 2



Ref. 640

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[636] Reetz *Angew. Chem. Int. Ed. Engl.* **1972,** *11,* 129, 130 [*Angew. Chem. 84,* 161, 163].

[637] For reviews, see Minkin; Olekhnovich; Zhdanov *Molecular Design of Tautomeric Compounds*; D. Reidel Publishing Co.: Dordrecht, 1988, pp. 221-246; Minkin *Sov. Sci. Rev., Sect. B* **1985,** *7,* 51-98; Reetz *Adv. Organomet. Chem.* **1977,** *16,* 33-65.

[638] See, for example, Taylor *J. Chem. Soc., Perkin Trans. 1* **1985,** 1181.

[639] See Black; Hall; Sheu *J. Org. Chem.* **1988,** *53,* 2371; Black; Fields *Synth. Commun.* **1988,** *18,* 125.

[640] See Mackenzie; Proctor; Woodnutt *Tetrahedron* **1987,** *43,* 5981, and references cited therein.